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Polymer-Supported *Cinchona* Alkaloid-Derived Ammonium Salts as Recoverable Phase-Transfer Catalysts for the Asymmetric Synthesis of α-Amino Acids†

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† *Dedicated to Prof. Ramón Mestres on the occasion of his 65th anniversary.*

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Abstract: Alkaloids such as cinchonidine, quinine and *N*-methylephedrine have been *N*-alkylated using polymeric benzyl halides or co-polymerized and then *N*-alkylated, thus affording a series of polymer-supported chiral ammonium salts which have been employed as phase-transfer catalysts in the asymmetric benzylation of an *N*-(diphenylmethylene)glycine ester. These new polymeric catalysts can be easily recovered by simple filtration after the reaction and reused. The best *ee*'s were achieved when Merrifield resin-anchored cinchonidinium ammonium salts were employed.

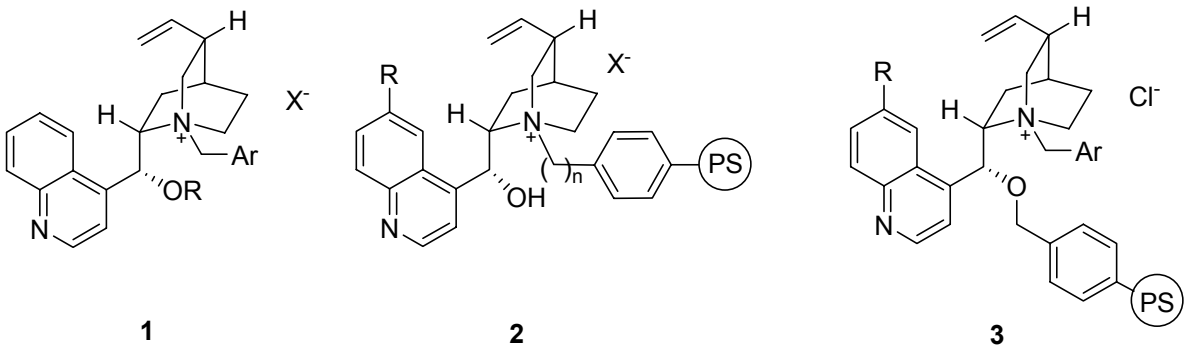
Keywords: Amino acids, asymmetric synthesis, phase-transfer catalysis, chiral ammonium salts.

Introduction

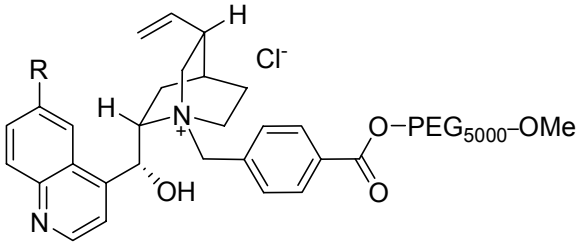
The synthesis of optically active α-amino acids using simple and easily scalable procedures is an important synthetic challenge due to their industrial interest [1]. Amongst all the reported methodologies, the enantioselective synthesis of α-amino acids employing easily available and re-

usable chiral catalysts presents clear synthetic advantages for large-scale procedures. Particularly, the phase-transfer catalysis (PTC) [2] methodology applied to the asymmetric alkylation of glycine and alanine Schiff bases is the most simple and easy to scale up. Thus, *N*-arylmethyl substituted *Cinchona* alkaloid-derived ammonium salts such as cinchonidine derivatives of the type **1** have been employed as chiral phase-transfer catalysts [3] in the asymmetric alkylation of iminic glycinates, first by O'Donnell [4] (**1**, R = H, Ar = Ph, X = Cl) and then by Corey [5] (**1**, R = allyl, Ar = 9-anthryl, X = Br) and Lygo [6] (**1**, R = H, Ar = 9-anthryl, X = Cl). Interestingly, an opposite sense of the asymmetric induction can be observed changing the alkaloid moiety from cinchonidine [(*S*)-enantioselectivity] to its so-called *pseudoenantiomer* cinchonine [(*R*)-enantioselectivity] [7]. Moreover, dimeric [8], trimeric [9] and even dendrimeric [10] *Cinchona* alkaloid-derived catalysts, as well as non-*Cinchona*-derived species such as spiroammonium [11] and phosphonium salts [12], TADDOL [13a,b] and other tartaric acid derivatives [13c,d], guanidinium salts [13e], binaphthyl-derived amines [13b,14] and salen-metal complexes [15] have also been used in these kinds of asymmetric PTC alkylations.

Attaching the chiral catalyst to a solid support can be considered a next step in the development of the PTC methodology due to the resulting ease of separation and possible recycling. As a result, the preparation and uses of all kind of supported reagents is considered nowadays a fast developing topic [16]. Polymeric *Cinchona* alkaloids have been previously used as catalysts [3] in other processes such as asymmetric Michael addition [17], dihydroxylation [18] and aminohydroxylation [19] reactions. However, the use of polymeric *Cinchona* alkaloid-derived ammonium salts as PTC catalysts for the asymmetric synthesis of α-amino acid derivatives is very recent and limited. Thus, *N*-supported Merrifield resin-derived ammonium salts **2** (n = 1, R = H, X = Cl [20]; n = 4, 6 or 8, R = H, OMe, X = I [21]) from cinchonidine and quinine (R = OMe) have been prepared, as well *O*-supported polymeric derivatives such as **3** [22] (R = H, OMe, Ar = 9-anthryl) and *N*- and *O*-alkylated polyethylene glycol (PEG) monomethyl ether ammonium salt derivatives such as **4** [23a] (R = H, OMe, Ar = 9-anthryl) and **5** [R = H, OMe, Ar = 9-anthryl, oblong circle = $MeOPEG_{5000}O_2C$- [23a]; R = H, Ar = 9-anthryl, oblong circle = $MeOPEG_{5000}O$-C_6H_4-$(CH_2)_3O$- [23b]], respectively. In addition, a quinine-derived *N*-methylanthryl ammonium salt attached to a PEG chain at the 6-position of the quinoleine nucleus has been prepared [23b]. All these polymers have being used for the asymmetric alkylation of glycinate imines.



1 **2** **3**



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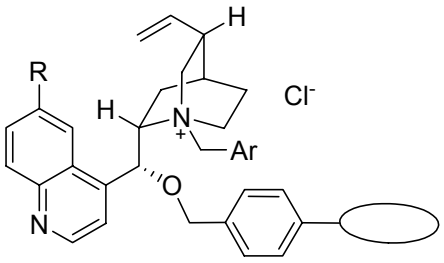

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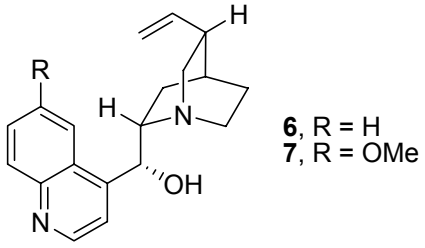
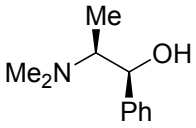
In this context, and as part of our ongoing studies towards the synthesis of easily recoverable and reusable PTC catalysts for the asymmetric synthesis of α-amino acids [8b,10,20c], we describe in this paper the preparation of a series of ammonium salts derived from alkaloids such as cinchonidine (**6**), quinine (**7**) and *N*-methylephedrine (**8**), supported mainly at the nitrogen to an array of commercially available or easily prepared polymers, as well as their use as chiral catalysts in the model asymmetric benzylation reaction of a *N*-(diphenylmethylene)glycine ester under PTC conditions.



6, R = H
7, R = OMe



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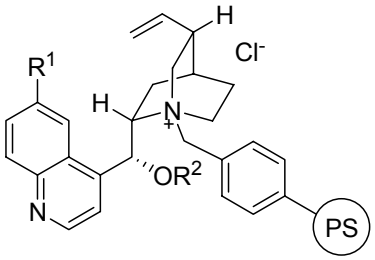
Results and Discussion

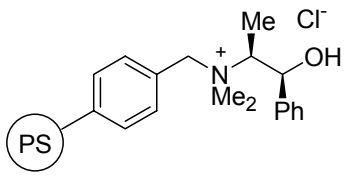
Polymer-supported ammonium salt **2a** was obtained as previously reported [20c] by *N*-alkylation of cinchonidine (**6**) with the Merrifield resin (Fluka, polystyrene crosslinked with 1% divinylbenzene, 1.7 meq Cl/g resin) in refluxing toluene, and is included in this study for comparison. When the *N*-alkylation reaction was carried out on *O*-allyl cinchonidine [5a] using Merrifield resin the *O*-allylated polymer **2b** was obtained, whereas resin **2c** was prepared similarly to resin **2a**, but using quinine (**7**) instead of cinchonidine. Moreover, we also prepared in the same way the (1*R*,*2S*)-*N*-methylephedrine (**8**)-supported resin **9**, which has been previously used in the PTC ethylation of α-cyanotoluene giving rather low *ee*'s [24], although its use in the alkylation of glycinimides was never attempted.

After the preparation of these Merrifield resin-derived chiral ammonium salts, we thought to explore the influence of the support in the performance of the polymeric ammonium salts as PTC catalysts. Thus, we prepare the *N*-tritylated polymer-supported cinchonidine **10a** by reaction of **6** with the corresponding polymer bound triphenylchloromethane (Fluka, 1% DVB, 1.1 mmol Cl/g resin), and also its *O*-allylated counterpart **10b**, similarly to **2b**. In addition, the cinchonidine **6** was *N*-anchored to chloromethylated 1-[4-(4-vinylphenoxy)butoxy]-4-vinylbenzene-crosslinked polystyrene (JandaJel^{TM}-

Cl, Aldrich, 2% crosslinking, 0.45-0.7 mmol Cl/g resin) and to Wang-Br resin (Novabiochem, 1% DVB, 100-200 mesh, 1.19 mmol Br/g resin) to afford polymeric ammonium salts **11** and **12**, respectively. Finally, polymer-supported cinchonidine **13a** was obtained by reaction of **6** with chloromethylated polyethyleneglycol-polystyrene copolymer (ArgoGel^{TM}-Cl, Argonaut Technologies, 1% DVB, 0.4 mmol Cl/g resin), whereas its *O*-allylated analogue **13b** was prepared as above.



2a, R^1 = H, R^2 = H
2b, R^1 = H, R^2 = Allyl
2c, R^1 = OMe, R^2 = H



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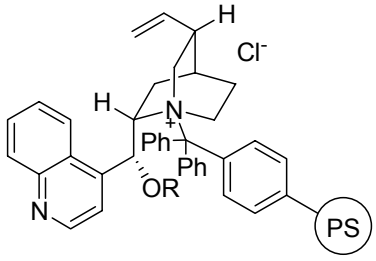
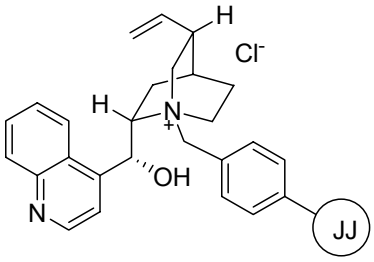


10a, R = H
10b, R = Allyl



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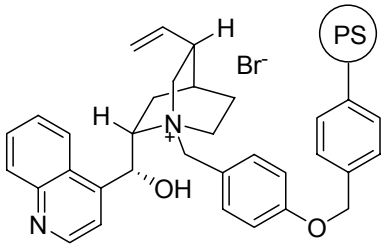

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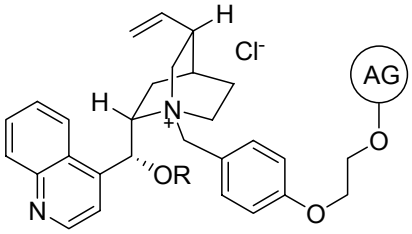
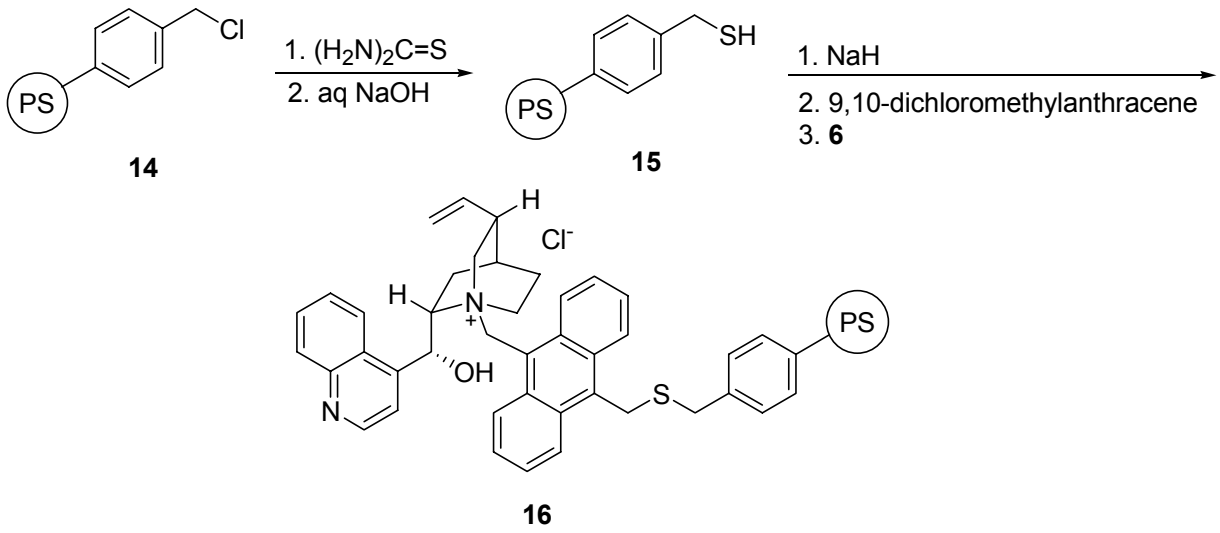


13a, R = H
13b, R = Allyl

PS = polystyrene
JJ = JandaJel^{TM}
AG = ArgoGel^{TM}

After the preparation of all these supported ammonium salts from commercially available polymers, we thought of the synthesis of an anchored cinchonidinium-derived ammonium salt incorporating a 9-anthrylmethyl moiety, which has shown its efficiency as an enantioselectivity-increasing group in *Cinchona*-derived PTC catalysts [5,6]. Thus, we prepared the mercapto resin **15** by treatment of the Merrifield resin (**14**) with thiourea and subsequent hydrolysis (Scheme 1) [25]. This resin was deprotonated with sodium hydride and reacted with 9,10-dichloromethylanthracene [26] (2 equiv) and subsequently with cinchonidine (**6**), affording polymeric salt **16**.

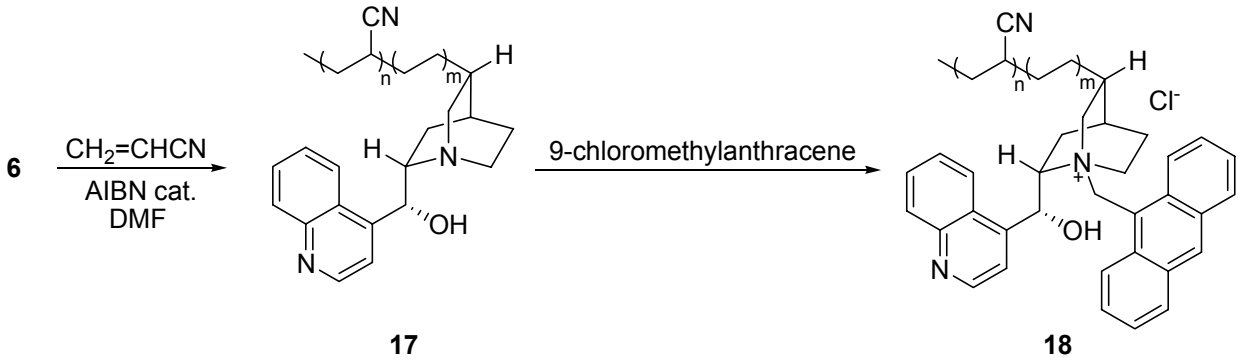
Scheme 1.



The incorporation of the alkaloid in all these obtained catalysts was demosntrated by the presence of new bands in the IR spectra attributable to the alkaloid structure, and also by the increase in the initial resin weight and also the elemental analysis, which also allowed the determination of the loading.

Finally, we also obtained co-polymeric cinchonidine-derived ammonium salt **18** by *N*-alkylation of an acrylonitrile and cinchonidine co-polymer **17** [27]. Thus, a mixture of acrylonitrile and cinchonidine (9:1 molar ratio) and a catalytic amount of azabisisobutyronitrile (AIBN) was heated in degassed DMF at 90ºC affording after precipitation the co-polymer **17** (Scheme 2), which reacted with 9-chloro-methylanthracene to give co-polymeric ammonium salt **18**.

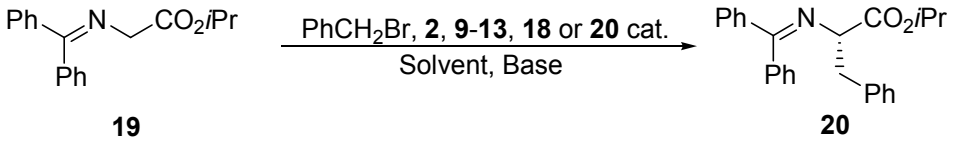
Scheme 2.



Polymers **2**, **9**-**13** as well as **16** and **18** were used as insoluble PTC catalysts (0.1 eq) in the model triphase benzylation reaction of glycine-derived *N*-(diphenylmethylene)glycine isopropyl ester **19** [28] with benzyl bromide in an organic solvent and using an aqueous base (Scheme 3). The isopropyl ester **19** was chosen, instead of the *tert*-butyl derivative usually employed in asymmetric PTC alkylations,

due to preliminary experiments using polymeric ammonium salts such as **2a**, which showed higher *ee*'s and lower reaction times in the alkylation of this glycine derivative [20c]. In addition, toluene was used as solvent and 25% aq NaOH as base when working at r.t. or 0ºC, whereas a mixture of toluene/$CHCl_3$ (7:3 v/v) and 50% aq KOH was used when lower reaction temperatures were employed [8c]. The resulting yields and *ee's* are summarized in Table 1. In all cases the (*S*)-enantiomer **20** was obtained. The *ee* values were determined by chiral GLC analysis from the corresponding trifluoroacetamide, obtained after 2M HCl hydrolysis of the imine **20** and further reaction with trifluoroacetic anhydride [29]. A racemic reference sample of **20** was prepared using tetrabutylammonium bromide as phase-transfer catalyst.

Scheme 3.



19 **20**

From the results shown in Table 1 it can be observed that the Merrifield-anchored cinchonidine-derived ammonium salt **2a** afforded the higher *ee* at 0ºC (90%, Table 1, entry 2), and lowering the reaction temperature further did not produce an increase in the *ee* (entries 3 and 4). However, its allylated counterpart **2b** gave place to considerably lower *ee* values, both at r.t. (entry 5) or 0ºC (entry 6). The analogous polymeric quinine derivative **2c** was clearly less effective as an asymmetric PTC catalyst than its structurally similar cinchonidine-derivative **2a**, giving very low *ee*'s (Table 1, entries 7 and 8). Moreover, the (1*R*,2*S*)-*N*-methylephedrine-derived resin **9** gave a low yield of an almost racemic **20** (Table 1, entry 9).

The polymeric trityl-anchored cinchonidine salt **10a** gave a 44% *ee* of **20** working at r.t. (Table 1, entry 10), which was raised to 70% *ee* when the temperature was lowered to 0ºC (Table 1, entry 11), but showed no further increment when the reaction was carried out at -20ºC (Table 1, entry 12). Similarly to **2a**, when the benzylation reaction was carried out with the *O*-allylated trityl-supported resin **10b** resin, the *ee* dropped remarkably (Table 1, entry 13). In addition, the JandaJel^{TM}-anchored cinchonidine ammonium salt **11** gave a 62% *ee* of **20** at r.t. (Table 1, entry 14) and a slightly lower 56% *ee* at 0ºC, with an observed increase of the reaction time (Table 1, entry 15), whereas the Wang-supported cinchonidinium salt **12** gave *ca.* 55% *ee*, both at r.t. or 0ºC (Table 1, entries 16 and 17). Moreover, ArgoGel^{TM}-supported cinchonidinium salt **13a** afforded up to 68% *ee* from r.t. to -20ºC (Table 1, entries 18-20) and again a tremendous drop in the *ee* was observed using its *O*-allylated counterpart **13b** (Table 1, entry 21).

Furthermore, when the *N*-substituted 9-anthrylmethyl derivative **16** was used as PTC catalyst, up to 74% *ee* of **20** was obtained working at -20ºC (Table 1, entry 23). The use of the co-polymeric cinchonidinium ammonium salt **18** with an anthrylmethyl group at the N gave a 44% *ee* when working

at r.t. (Table 1, entry 25), which increased to 70% *ee*, almost independently of reductions in the temperature to 0ºC or -20ºC (Table 1, entries 26 and 27).

Table 1. Enantioselective PTC benzylation of glycine derivative **19** using polymeric chiral catalysts

Entry	Catalyst	Base	Solvent	T (ºC)	t (h)	Yield[a] (%)	*ee*[b] (%)
1	**2a**	25% NaOH	PhMe	25	4	90	66
2	**2a**	25% NaOH	PhMe	0	17	90	90
3	**2a**	25% KOH	PhMe:$CHCl_3$	-20	10	46	76
4	**2a**	50% KOH	PhMe:$CHCl_3$	-40	9	56	85
5	**2b**	25% NaOH	PhMe	25	10	62	34
6	**2b**	25% NaOH	PhMe	0	140	23	50
7	**2c**	25% NaOH	PhMe	25	8	76	18
8	**2c**	25% NaOH	PhMe	0	96	81	20
9	**9**	25% NaOH	PhMe	0	160	33	2
10	**10a**	25% NaOH	PhMe	25	1	96	44
11	**10a**	25% NaOH	PhMe	0	10	59	70
12	**10a**	50% KOH	PhMe:$CHCl_3$	-20	18	71	69
13	**10b**	25% NaOH	PhMe	0	120	7	2
14	**11**	25% NaOH	PhMe	25	4	76	62
15	**11**	25% NaOH	PhMe	0	10	71	56
16	**12**	25% NaOH	PhMe	25	12	78	56
17	**12**	25% NaOH	PhMe	0	120	63	54
18	**13a**	25% NaOH	PhMe	25	10	75	63
19	**13a**	25% NaOH	PhMe	0	20	91	64
20	**13a**	50% KOH	PhMe:$CHCl_3$	-20	15	90	68
21	**13b**	25% NaOH	PhMe	0	60	28	8
22	**16**	25% NaOH	PhMe	25	2	92	59
23	**16**	25% NaOH	PhMe	0	32	94	70
24	**16**	50% KOH	PhMe:$CHCl_3$	-20	3	86	74
25	**18**	25% NaOH	PhMe	25	1	96	44
26	**18**	25% NaOH	PhMe	0	170	49	70
27	**18**	50% KOH	PhMe:$CHCl_3$	-20	13	74	71

[a] Crude yield determined by ^{1}H NMR (300 MHz). [b] Determined by chiral GLC analysis from the corresponding trifluoroacetamide (see text).

After the benzylation reaction, the polymeric catalysts were filtered off from the reaction mixture and were reused up to three times without any loss of effectivity.

Conclusions

We have prepared chiral polymeric ammonium salts by anchoring a number of alkaloids, mainly from *Cinchona*, to different commercially available halogenated polymers and to a prepared anthryl-containing polystyrene. In addition, we have also obtained a cinchonidinium salt-acrylonitrile co-polymer. All these polymeric ammonium salts have been employed as solid-supported chiral PTC catalysts for the asymmetric benzylation of *N*-(diphenylmethylene)glycine isopropyl ester achieving moderate enantioselectivities. The best results were obtained using a Merrifield resin-supported cinchonidinium salt, the use quinine or ephedrine-derived ammonium salts affording poor results. In all cases higher *ee'*s were obtained when a hydroxyl group was present in the alkaloid moiety, their *O*-allylated counterparts giving lower enantioselectivities. Lowering the reaction temperature usually resulted in higher *ee'*s, although temperatures below 0 ºC generally did not affected remarkably the degree of asymmetric induction. All the supported catalysts could be separated from the reaction mixture by simple filtration and recycled.

Acknowledgments

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Experimental

General

Reagents and solvents from commercial suppliers were of the best grade available and used as provided unless otherwise stated. IR spectra were recorded with a Nicolet 510 P-FT. NMR spectra were measured with a Bruker AC-300 at 300 MHz for ^{1}H- and 75 MHz for ^{13}C- using TMS as internal standard. Elemental analyses were carried out by the Microanalytical Service at the Research Technical Services of the University of Alicante. Chiral GLC analysis were performed using a Chirasil-L-Val column (Chrompack), 1 min 85º, 2º/min to 180º.

General procedure for the preparation of the polymeric ammonium salts **2** *and* **9-13.**

The corresponding halogenated polymer (1 meq) was added to a suspension of the alkaloid **6**, **7** or **8** (2 mmol) in toluene (10 mL) and the mixture was stirred under reflux for 24 h. The reaction mixture was cooled to r.t. and the solid was filtered, washed with AcOEt (3 x 15 mL) and dried in vacuo, affording the polymer-supported ammonium salts **2a**, **2c**, **9**, **10a**, **11**, **12** and **13a**. The *O*-allylated

polymeric ammonium salts **2b**, **10b** and **13b** were obtained following the same procedure, but starting from *O*-allyl cinchonidine [5a].

Polymeric ammonium salt **2a**
IR (KBr) cm^{-1}: 3415 (broad), 3060, 2940, 1596, 1430, 1220, 1100, 750.
Microanalysis: % N = 3.25; loading = 1.7 mmol g^{-1}

Polymeric ammonium salt **2b**
IR (KBr) cm^{-1}: 3080, 2939, 1590, 1440, 1231, 1103, 760.
Microanalysis: % N = 2.03; loading = 1.2 mmol g^{-1}

Polymeric ammonium salt **2c**
IR (KBr) cm^{-1}: 3398 (broad), 3020, 2920, 615, 1497, 1455, 1241, 1012, 757.
Microanalysis: % N = 3.06; loading = 1.6 mmol g^{-1}

Polymeric ammonium salt **9**
IR (KBr) cm^{-1}: 3382 (broad), 3033, 2925, 1596, 1499, 1441, 1011, 756.
Microanalysis: % N = 1.72; loading = 1.6 mmol g^{-1}

Polymeric ammonium salt **10a**
IR (KBr) cm^{-1}: 3241 (broad), 3015, 2925, 1598, 1460, 1100, 763.
Microanalysis: % N = 1.89; loading = 0.9 mmol g^{-1}

Polymeric ammonium salt **10b**
IR (KBr) cm^{-1}: 3054, 2929, 1645, 1448, 1148, 695.
Microanalysis: % N = 0.39; loading = 0.2 mol g^{-1}

Polymeric ammonium salt **11**
IR (KBr) cm^{-1}: 3370 (broad), 3019, 2912, 1602, 1488, 1448, 1233, 1025, 751.
Microanalysis: % N = 1.39; loading = 0.6 mmol g^{-1}

Polymeric ammonium salt **12**
IR (KBr) cm^{-1}: 3351 (broad), 3063, 2919, 1599, 1457, 1221, 1115, 754.
Microanalysis: % N = 2.51%; loading = 1.2 mmol g^{-1}

Polymeric ammonium salt **13a**
IR (KBr) cm^{-1}: 3505 (broad), 3020, 2840, 1602, 1452, 1295, 1240, 1105, 699.
Microanalysis: % N = 0.37; loading = 0.4 mmol g^{-1}

Polymeric ammonium salt **13b**

IR (KBr) cm^{-1}: 2924, 1618, 1460, 1356, 1252, 1110, 695.
Microanalysis: % N = 0.30; loading = 0.4 mmol g^{-1}

Preparation of polymeric ammonium salt **16**

A suspension of Merrifield resin (Fluka, 1% DVB, 1.7 meq. Cl/g resin) (3 meq, 1.76 g) and thiourea (12.78 mmol, 971 mg) in a mixture of THF (20 mL) and EtOH (6 mL) is refluxed for 2 days and the resin thus obtained is filtered and washed successively with water (3 x 20 mL), THF (3 x 20 mL) and benzene (3 x 20 mL). The solid was then suspended in benzene (27 mL) and a mixture of tetrabutylammonium iodide (0.08 mmol, 28 mg) and NaOH (25.95 mmol, 1.038 g) in water (1.4 mL) was added. The reaction mixture was stirred at 80 ºC under nitrogen for 2 days and the resulting solid was filtered and washed successively with THF (3 x 20 mL), water (3 x 20 mL), THF/6M HCl (3:1 v/v, 3 x 20 mL), water (3 x 20 mL), THF, (3 x 20 mL), acetone (3 x 20 mL), CH_2Cl_2 (3 x 20 mL) and MeOH (3 x 20 mL). After drying in vacuo (15 Torr), the resin **15** [25] (1.85 g) was obtained. A suspension of **15** (1 mmol, 654 mg) in toluene (12 mL) was treated with NaH (60% mineral oil, 1.2 mmol, 30 mg) and 9,10-dichloromethylanthracene [26] (2 mmol, 550 mg) was added. The mixture was refluxed 24 h and the resulting solid was filtered, washed with AcOEt (4 x 20 mL) and treated with cinchonidine (**6**) as in the preparation of the former ammonium salts (see above), to give polymeric ammonium salt **16**.

IR (KBr) cm^{-1}: 3399 (broad), 3049, 3015, 2910, 1598, 1499, 1451, 755, 698.
Microanalysis: % N = 2.55; loading = 1.4 mmol g^{-1}

Preparation of co-polymeric ammonium salt **18** [27]

A degassed solution of cinchonidine (**6**) (4 mmol, 1.178 g), acrylonitrile (36.4, 2.4 mL) and AIBN (0.3 mmol, 48 mg) in DMF (12 mL) was heated in a pressure tube at 90 ºC for 48 h. The mixture was cooled to r.t., water (15 mL) and AcOEt (15 mL) were added and the solid was filtered, washed with AcOEt (5 x 15 mL) and dried (15 Torr). To a solution of this solid (606 mg) in DMSO (10 mL) was added 9-chloromethylanthracene (8 mmol, 1.814 g) and the mixture was refluxed for 24 h. The mixture was cooled to r.t. and the solid was filtered, washed with AcOEt (5 x 15 mL) and dried (15 Torr) affording **18** (840 mg).

IR (KBr) cm^{-1}: 3416 (broad), 2939, 2247, 1622, 1448, 1246, 1031, 749.
$[\alpha]_D^{25}$ – 24 (*c* 0.5, DMSO)

General procedure for the benzylation of **19** *using the polymeric ammonium salts as PTC catalysts: Preparation of isopropyl 2-diphenylmethylenamino-3-phenylpropanoate* (**20**).

Benzyl bromide (0.6 mmol, 72 μL) was added to a stirred suspension of **19** [28] (0.5 mmol, 140 mg), the polymeric catalyst (0.1 eq) and the aqueous base (4 mL) in the appropriate solvent (5 mL) and at the selected temperature (see Table 1). When the reaction was considered finished (GLC), the mixture was filtered and the solid was washed with AcOEt (25 mL), thus giving the recovered polymeric catalyst. The filtrate was washed with water (3 x 15 mL) and the organic phase was dried ($MgSO_4$), filtered off and evaporated (15 Torr) to give the title compound: ^{1}H-NMR ($CDCl_3$) δ: 1.19, 1.21 (6H, 2d, J = 6.5), 3.17 (1H, dd, J = 13.1, 9.2), 3.27 (1H, dd, J = 13.1, 4.3), 4.19 (1H, dd, J = 9.2, 4.3), 5.04 (1H, heptet, J = 6.1), 6.62 (1H, m), 7.03-7.60 (13H, m), 7.79 (1H, d, J = 7.9); ^{13}C-NMR ($CDCl_3$) δ: 21.7, 39.5, 67.3, 68.2, 126.1, 127.5, 127.8, 128.2, 128.6, 129.7, 129.9, 130.1, 132.3, 136.1, 138.0, 139.4, 170.5, 171.1; IR (thin film) cm^{-1}: 3063, 3032, 1742, 1629; HRMS (EI) for $C_{22}H_{25}NO_2$ (M^+): Calcd 371.1885; Found 371.1847.

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Sample Availability: Samples of the catalysts are available from the authors.