



# Asymmetric synthesis of $\alpha$ -amino acids using polymer-supported *Cinchona* alkaloid-derived ammonium salts as chiral phase-transfer catalysts

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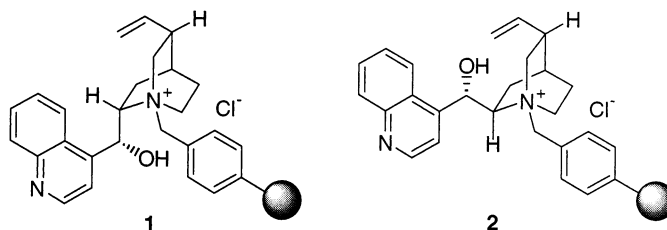
## Abstract

Cinchonidine and cinchonine have been *N*-alkylated with Merrifield resin and employed as chiral phase-transfer catalysts for the enantioselective alkylation of enolates from *N*-(diphenylmethylene)glycine esters with activated electrophiles (up to 90% *ee*). The use of the polymer-supported cinchonidine ammonium salt afforded the corresponding (*S*)-isomers, whereas the (*R*)-isomers were obtained using related cinchonine-supported polymers. © 2000 Elsevier Science Ltd. All rights reserved.

The synthesis of optically active  $\alpha$ -amino acids using a simple and easily scalable procedure remains an important synthetic challenge nowadays.<sup>1</sup> In spite of all the available synthetic methods, frequently based on the alkylation of an array of chiral templates, it is doubtful that the future of the industrial enantioselective preparation of  $\alpha$ -amino acids will follow these routes, the preparation of large-scale amounts of the template being generally rather cumbersome and too expensive. However, the enantioselective synthesis of  $\alpha$ -amino acids employing easily available and re-usable chiral catalysts presents clear advantages for large-scale synthesis. A simple and easily scaleable methodology is phase-transfer catalysis (PTC) using ammonium salts as phase-transfer agents.<sup>2</sup> The use of chiral alkaloid-derived ammonium salts allows the asymmetric synthesis of optically active  $\alpha$ -amino acids. Thus, the *ee*'s obtained by O'Donnell in his pioneering works using tetralkylammonium halides, derived from *Cinchona* alkaloids, as PTC catalysts in a two-phase system<sup>3</sup> were subsequently improved by Corey<sup>4</sup> and Lygo.<sup>5</sup> In addition, chiral spiro ammonium salts with a binaphthyl structure<sup>6</sup> and also TADDOL<sup>7</sup> or NOBIN<sup>8</sup> and derivatives have been used as chiral PTC catalysts in the alkylation of glycine derivatives. With all these antecedents, a further step in the development of this asymmetric PTC methodology would be anchoring the catalysts to a solid support. That method would allow an easy separation from the reaction mixture once the reaction has finished and also the possibility of re-using the same catalysts.

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Supported *Cinchona* alkaloids have previously been used as catalysts. Thus, alkaloid–acrylonitrile copolymers,<sup>9</sup> alkaloid-crosslinked polymers<sup>10</sup> and polymer supported alkaloids<sup>11</sup> have been employed as catalysts for asymmetric Michael additions. In addition, bis-*Cinchona* alkaloid–ethylene glycol dimethacrylate–methyl methacrylate<sup>12a</sup> and bis-*Cinchona* alkaloid–methyl methacrylate<sup>12b</sup> copolymers, as well as PEG,<sup>13</sup> and silica gel<sup>14</sup> supported *Cinchona* alkaloids have been used as catalysts in asymmetric dihydroxylation<sup>12,13</sup> and aminohydroxylation<sup>14</sup> reactions. Moreover, polystyrene-supported quaternary ammonium salts derived from *Cinchona* and *Ephedra* alkaloids have been previously employed as catalysts for asymmetric Michael addition reactions of  $\beta$ -ketoesters to methyl vinyl ketone or thio-*p*-cresol to cyclohex-2-enone,<sup>10a</sup> although with low *ee*'s (up to 27%). In this communication we report the use of these polystyrene-supported ammonium salts derived from cinchonidine **1** and cinchonine **2** as chiral PTC catalysts for the asymmetric synthesis of  $\alpha$ -amino acids.

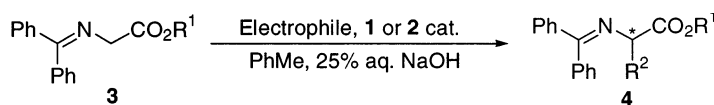


Catalysts **1** and **2** were prepared by reaction of Merrifield resin (crosslinked with 1% of divinylbenzene, 200–400 mesh, 1.7 mmol Cl/g) with an excess (2 equiv.) of cinchonidine or cinchonine, respectively, in refluxing toluene. After filtration and washing thoroughly with ether, polymer-supported quaternary ammonium chlorides **1** and **2** were obtained. The increase in the initial resin weight and the presence of new bands in the IR spectra attributable to the alkaloid structure showed the incorporation of the alkaloid cinchonine to the resin.

Polymer **1** was used as an insoluble PTC catalyst in the triphase alkylation reaction of glycine-derived *N*-(diphenylmethylene)glycine alkyl esters **3** with benzyl bromide in a system formed by toluene and a 25% aqueous NaOH solution at room temperature (Table 1, entries 1–4).<sup>15</sup> The enantioselectivity of the reaction was measured by chiral GLC analysis<sup>16</sup> of the corresponding *N*-trifluoroacetamide amido esters.<sup>17</sup> When the ethyl or isopropyl ester derivatives **3a** or **3b**<sup>18</sup> were employed as starting materials under the same reaction conditions, alkylated compounds **4aa** or **4ba** were obtained in 44 or 66% *ee*, respectively (Table 1, entries 1 and 2). However, when the reaction was carried out with the commercially available *tert*-butyl derivative **3c**, the reaction time was considerably longer (36 h) and product **4ca** was obtained in 58% *ee* (Table 1, entry 4). Thus, derivative **3b** was chosen as the starting material for the alkylation reactions. When the reaction of **3b** was performed at 0°C (bath temperature) a significant increase in the obtained *ee* of **4ba** was observed (90% *ee*, Table 1, entry 3).

In order to determine the absolute configuration of the alkylated products **4**, compound **4ba** was hydrolyzed under refluxing 6N HCl to give phenylalanine in 70% overall yield after treatment of the initially obtained hydrochloride with propylene oxide in refluxing ethanol. The negative sign of the specific rotation of this isolated  $\alpha$ -amino acid compared with the literature<sup>19</sup> allowed assignment of the (*S*)-configuration obtained when using cinchonidine-supported ammonium chloride **1** as catalyst. When the reaction of **3b** was performed employing cinchonine-supported ammonium salt **2** as catalyst, compound **4ba** was obtained with the opposite configuration (Table 1, entry 5), thus allowing the preparation of the corresponding enantiomeric (*R*)-series.

Table 1  
Enantioselective alkylation of glycine derivatives **3**



Entry	R <sup>1</sup> (No.)	Electrophile	Cat.	T (°C)	t (h)	Product No.	Yield <sup>a</sup> (%)	S/R <sup>b</sup> ratio	ee (%)
1	Et ( <b>3a</b> )		<b>1</b>	25	4	<b>4aa</b>	85	72/28	44
2	<i>i</i> Pr ( <b>3b</b> )		<b>1</b>	25	4	<b>4ba</b>	90	83/17	66
3	<i>i</i> Pr ( <b>3b</b> )		<b>1</b>	0	17	<b>4ba</b>	90	95/5	90
4	<i>t</i> Bu ( <b>3c</b> )		<b>1</b>	25	36	<b>4ca</b>	80	79/21	58
5	<i>i</i> Pr ( <b>3b</b> )		<b>2</b>	25	4	<b>4ba</b>	88	30/70	40
6	<i>i</i> Pr ( <b>3b</b> )		<b>2</b>	0	24	<b>4ba</b>	85	30/70	40
7	<i>i</i> Pr ( <b>3b</b> )		<b>1</b>	25	20	<b>4bb</b>	85	73/27	46
8	<i>i</i> Pr ( <b>3b</b> )		<b>1</b>	0	36	<b>4bb</b>	70	78/22	56
9	<i>i</i> Pr ( <b>3b</b> )		<b>1</b>	25	24	<b>4bc</b>	26	68/22	36
10	<i>i</i> Pr ( <b>3b</b> )		<b>1</b>	0	26	<b>4bc</b>	22	82/18	64
11	<i>i</i> Pr ( <b>3b</b> )		<b>1</b>	25	4	<b>4bd</b>	86	75/25	50
12	<i>i</i> Pr ( <b>3b</b> )		<b>1</b>	0	10	<b>4bd</b>	85	82/18	64
13	<i>i</i> Pr ( <b>3b</b> )		<b>1</b>	25	3	<b>4be</b>	95	75/25	50
14	<i>i</i> Pr ( <b>3b</b> )		<b>1</b>	0	6	<b>4be</b>	95	74/26	48
15	<i>i</i> Pr ( <b>3b</b> )		<b>1</b>	25	19	<b>4bf</b>	75	66/34	32
16	<i>i</i> Pr ( <b>3b</b> )		<b>1</b>	25	36	<b>4bg</b>	70	62/38	24

<sup>a</sup> Crude yield determined by <sup>1</sup>H NMR (300 MHz). <sup>b</sup> Determined by chiral GLC (see text).

Different benzyl bromides were employed as electrophiles (Table 1, entries 7–14), some of them with activated or inactivated aromatic rings, although showing no significant influence on the obtained *ee*'s. When other activated electrophiles such as allyl iodide and propargyl bromide were employed with polymer **1** as the catalyst, the corresponding derivatives **4bf** and **4bg** were obtained, respectively, although with low *ee*'s (Table 1, entries 15 and 16). The (*S*)-configuration of **4bf** was assigned by the relative retention times of the (*R/S*)-isomers reported in the literature.<sup>17</sup> When unactivated electrophiles such as butyl iodide were used as electrophiles, no alkylation reaction took place.

Other solvents such as dichloromethane, acetonitrile or *tert*-butyl methyl ether were attempted, but in all cases the obtained *ee*'s were lower. Moreover, the use of other bases such as aqueous solutions of KOH or CsOH lowered the obtained *ee*'s. When compound **4ba** was prepared using LiOH as a base, the obtained *ee*'s were similar to when using NaOH, although the reaction was slower and the yield was only 15%. When catalyst **1** was employed, lowering

the reaction temperature to 0°C (bath temperature) always produced an increase in the obtained *ee*.

The recovered catalysts could be reused without appreciable loss of activity. Thus, once the reaction of **3b** with benzyl bromide was performed at room temperature (Table 1, entry 2) and recycled catalyst **1** was employed again, the preparation of the corresponding alkylated compound **4ba** in almost identical yield and *ee* was allowed. Further studies on the applications of these and related polymer-supported catalysts to other asymmetric synthesis will be reported in due course.

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15. *Representative experimental procedure:* To a mixture of **3** (0.5 mmol) and **1** (50 mg) in toluene (5 mL) was added the electrophile (1.2 mmol) and aqueous 25% solution of NaOH (4 mL). The suspension was vigorously stirred and monitored by GLC. When the reaction was finished, the mixture was filtered and the solid was washed with AcOEt (25 mL). The organics were washed with water, dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated in vacuo.
16. Chirasil-LVal (Chrompack), 1 min 85°C, 2°/min to 180°C. Reference racemic samples were prepared under the same reaction conditions but using tetrabutylammonium bromide as phase-transfer catalyst.
17. Obtained after HCl/Et<sub>2</sub>O hydrolysis of the imine function and further reaction with trifluoroacetic anhydride (Oppolzer, W.; Moretti, R.; Zhou, C. *Helv. Chim. Acta* **1994**, *77*, 2363–2380).
18. Prepared in 80% overall yield by reaction of glycine with thionyl chloride in the presence of isopropanol (Patel, R.; Price, S. *J. Org. Chem.* **1965**, *30*, 3575–3576), followed by treatment of the crude with benzophenone imine (O'Donnell, M. J.; Polt, R. L. *J. Org. Chem.* **1982**, *47*, 2663–2666).
19. (S)-Phenylalanine:  $[\alpha]_{\text{D}}^{20} = -34.5$  (c 1; H<sub>2</sub>O) (*Dictionary of Organic Compounds*; Chapman & Hall: New York, 1982).