Solution- and Solid-Phase Approaches in Asymmetric Phase-Transfer Catalysis by Cinchona Alkaloid Derivatives

Baptiste Thierry, Thierry Perrard, Christophe Audouard, Jean-Christophe Plaquevent,* Dominique Cahard*
UMR 6014 de l’IRCOF (Institut de Recherche en Chimie Organique Fine), Université de Rouen, 76821 Mont Saint Aignan Cedex, France
Fax +33(3)235522971; E-mail: jean-christophe.plaquevent@univ-rouen.fr; dominique.cahard@univ-rouen.fr
Received 15 June 2001

Abstract: The catalytic asymmetric alkylation under phase-transfer conditions of various substrates (enones, α-fluoro ketones, glycine-imines) promoted by chiral quaternary ammonium salts derived from cinchona alkaloids is described. A solvent-free phase-transfer catalysis is presented as well as a new type of polymer-supported phase-transfer catalyst derived from cinchona alkaloids.

Key words: phase-transfer catalysis, polymers, Michael addition, fluorine, asymmetric catalysis

Asymmetric phase-transfer catalysis (PTC) is dominated by cinchona alkaloid derivatives, though, other quaternary ammonium salts and metal catalysis have recently appeared as strong competitors. There are numerous reports on reactions that have been accomplished by enantioselective PTC, especially carbon-carbon bond formation (alkylation, Darzens reaction, Michael addition, aldol reaction, cyclopropanation, epoxidation, α-hydroxylation of ketones). We present herein our contribution on the use of cinchona alkaloids in asymmetric PTC through three different reactions: 1) Michael addition onto enones, 2) construction of quaternary fluorinated carbon centers, 3) alkylation of the benzophenone imine of glycine tert-butyl ester. Both solution and solid-phase approaches were examined.

Our interest in asymmetric PTC began during the synthesis of methyljasmonate in which the asymmetric key-step consisted of an enantioselective Michael addition of dimethyl malonate onto 2-pentylcyclohexenone. The Michael adduct thus obtained was then decarboxylated in a racemization-free process (Scheme 1). This approach was selected among other possibilities, such as generating the malonate ion using chiral bases (magnesium amides or alkali alkoxides) or high pressure condensations in the presence of a chiral tertiary amine. Those two approaches were not efficient from the point of view of asymmetric synthesis, since the adducts were obtained in reasonable yields, but without any asymmetric induction.

A structure-enantioselectivity relationship study allowed us to select the following ammonium salts derived from quinine and quinidine, respectively, as the most efficient chiral catalysts for this transformation (Figure 1).

Figure 1

The best conditions, both in terms of yield and enantioselectivity, required the use of mild conditions: 1) presence of a mineral base (typically potassium carbonate), 2) reaction at mild temperature (room temperature or –20 °C), 3) absence of additional solvent (an excess of dimethyl malonate was used, and eventually recovered after the reaction). In the best case, an enantiomeric excess as high as 90% was obtained. Since the method was both efficient and simple, we then decided to examine the scope and limitations of this system for other Michael additions. In a first set of experiments, we verified that the conditions used were specific for dimethyl malonate. Indeed, other nucleophilic agents were used (AcCH2 COOMe, MeSCH2 COOMe, tert-butyl malonate, methyl-tert-butyl malonate) in the same conditions (solvent-free reaction), with none of them giving the Michael addition. In a second series of experiments, we used the same system with various electrophilic species (Table 1).
As indicated in Table 1, the enantioselectivity was higher for the 2-pentylicyclohexenone, a result consistent with our published models for asymmetric induction. In addition one can observe that moderate ee’s are obtained for cyclopentenone and chalcone, with reasonable yields. By contrast, cyclohexenone failed to give high conversion, especially when $\alpha$-substituted. In all cases, the pseudoenantiomeric effect was observed when switching from catalyst 1 (quinine salt) to catalyst 2 (quinidine salt).

At this stage of our research, we thought that a further useful development in the field of PTC would be the immobilisation of the catalyst on an insoluble polymeric support. Indeed the immobilisation of a chiral catalyst on an insoluble polymer support offers several advantages over the use of the same catalyst in solution. The easy recovery and potential recycling of the catalyst and the greatly simplified product purification are among the main advantages of the solid-phase approach. Grafting cinchona alkaloids onto polymers would give these catalysts a new lease of life in asymmetric PTC. We have introduced new polymer-supported chiral phase-transfer catalysts possessing a spacer between the matrix and the quaternary nitrogen atom of the cinchona alkaloid in the asymmetric synthesis of $\alpha$-amino acids (Figure 2, Type I). We report herein the application of these catalysts to the enantioselective alkylation of $\alpha$-fluorotetralone, as well as the design and the evaluation of a second class of polymer-supported cinchona alkaloids (Figure 2, Type II).

We investigated the alkylation of fluorinated substrates such as 2-fluoro-1-tetralone, and we compared the PTC approach with the electrophilic fluorination of 2-benzyl1-tetralone. Recently, we have succeeded in developing a
new class of electrophilic enantioselective fluorinating agents: the N-fluoro quaternary ammonium salts of cinchona alkaloids (one more contribution to the venerable history of the cinchona alkaloids!). Both routes lead to the enantioselective construction of quaternary fluorinated carbon centers, which is not a trivial problem in modern synthetic organic chemistry (Scheme 2).

The benzylation reaction proceeded smoothly under PTC conditions with the aid of cinchoninium iodide linked to polystyrene with a four-carbon spacer (Type I, 4-CN). The reaction was carried out at –20 °C for 4 days with 21 equivalents of KOH, 5 equivalents of benzyl bromide and 0.1 equivalent of catalyst to afford the 2-benzyl-2-fluoro-1-tetralone in 73% yield and 62% enantiomeric excess. In the second route, enantioselective fluorination with the tetrafluoroborate of N-fluoro cinchonidinium was realised in THF at –40 °C for 24 hours yielding the 2-benzyl-2-fluoro-1-tetralone in 96% yield and 50% enantiomeric excess. Both routes led to moderate enantiomeric excesses with opposite absolute configuration at the quaternary stereogenic center. Indeed, under PTC conditions, an ion-pair is formed between the cinchonine supported salt and the enolate, masking one face of the tetralone; while in the fluorination route, the fluorinating agent derived from the pseudoenantiomeric cinchonidine attacks the silyl enol ether on the other face of the tetralone.

The strategy of attaching the cinchona alkaloid onto a polymer resin through a methylene spacer provides an efficient catalyst, but enantioselectivities still need to be improved. Obviously, the methylene spacer is not as sterically hindered as that of 9-anthracenylmethyl described by Corey or Lygo. Thus, we thought that the enantioselectivity could be possibly improved by attaching the polystyrene matrix elsewhere than on the nitrogen; the hydroxyl function was selected for this purpose, leaving the nitrogen of the quinuclidine moiety free to be quaternarized with the aid of 9-(chloromethyl)-anthracene (Figure 2, Type II). The sequence quaternization / grafting was preferred to the reverse one for reasons of efficiency (Scheme 3).

All four cinchona alkaloids [cinchonidine (CD), cinchonine (CN), quinidine (QD), quinine (QN)] were grafted according to this sequence, and these type II catalysts were evaluated in the alkylation of N-diphenylmethylene glycine tert-butyl ester and compared with type I catalysts (Scheme 4). The enantioselectivity was found to be strongly dependent on the alkaloid and improved when compared to type I catalysts (Table 2).

<table>
<thead>
<tr>
<th>Catalyst Temp (°C) Time (h) Yield (%) ee(%)</th>
<th>(Abs. Config.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I a</td>
<td></td>
</tr>
<tr>
<td>4-CN 0 27 60 81; (R) 7</td>
<td></td>
</tr>
<tr>
<td>6-CN 0 40 73 75; (R) 7</td>
<td></td>
</tr>
<tr>
<td>8-CN 0 48 52 73; (R) 7</td>
<td></td>
</tr>
<tr>
<td>Type II from:</td>
<td></td>
</tr>
<tr>
<td>CN –40 48 48 23; (R)</td>
<td></td>
</tr>
<tr>
<td>CD –40 27 64 93; (S)</td>
<td></td>
</tr>
<tr>
<td>CD –50 30 67 94; (S)</td>
<td></td>
</tr>
<tr>
<td>QN –40 48 49 36; (S)</td>
<td></td>
</tr>
<tr>
<td>QD –40 48 46 26; (R)</td>
<td></td>
</tr>
</tbody>
</table>

a n-CN (n = 4, 6, 8) stands for polystyrene-supported cinchoninium salt tethered by n methylene units.

With type I catalysts bearing a spacer, we have shown that cinchonine produced significantly higher enantiomeric excesses than other diastereomeric alkaloids, and that the four methylene spacer proved the most appropriate means of high enantioselection. It is worth noting that the pseudoenantiomeric effect was not observed with type I catalysts even if cinchonine and cinchonidine are known to behave as pseudoenantiomers, in the sense that the two families normally give rise to opposite enantiomers in PTC reactions. When using type II catalysts, not only the pseudoenantiomeric effect was observed, but also a strong

\[ \begin{align*}
\text{Scheme 3}
\end{align*} \]
preference for cinchonidine with regard to cinchonine was shown in opposition to what was observed with type I catalysts. Moreover, the results obtained with type II catalysts are closely related to those obtained by Corey and Lygo, with respect to the yields and the enantiomeric excesses. The comparison of the two types of catalysts clearly indicated the superiority of the second type, which showed a better behaviour in enantioselection, since ee’s were up to 94% were obtained.

In conclusion, we have shown different aspects of the use of cinchona alkaloids in asymmetric PTC. The polymer-supported approach offers significant advantages and high enantioselectivities. Further developments of these and related polymer-supported catalysts are in progress.

SPECIAL TOPIC
Solution- and Solid-Phase Approaches in Asymmetric Phase-Transfer Catalysis

1H, 13C and 19F NMR spectra were recorded on a Bruker DPX 300 spectrometer in CDCl 3 , and 6 (ppm) is quoted relative to the residual signal of CDCl 3 (1H NMR 6 = 7.27 ppm; 13C NMR, 6 = 77.2 ppm). In the case of 19F NMR, trifluoroacetone methyl served as internal standard (6 = 0 ppm). HPLC was carried out using a Waters 600 apparatus equipped with Chiralcel columns. Flash chromatography was performed on silica gel Merck Kieselgel 60 (230–400 Mesh). Specific rotations were measured with a Perkin–Elmer M 341 polarimeter. THF was dried by heating under reflux over Na and benzophenone followed by distillation. CH 2 Cl 2 and toluene were freshly distilled from CaH 2 under N 2 . All reactions were carried out under an Ar atm in dried glassware.

**Michael Addition of Dimethyl Malonate onto Enone; General Procedure**

To a solution of enone (0.66 mmol) in dimethyl malonate (2.50 mL, 20 mmol, 30 equiv), 40.2 mg of catalyst I (0.07 mmol, 0.11 equiv) and 12.4 mg of K 2 CO 3 (0.09 mmol, 0.14 equiv) were successively added. After magnetic stirring at –20 °C for the indicated time (see Table 1), the reaction mixture was diluted with Et 2 O (20 mL). The organic layer was washed successively with 0.1 N HCl (2 × 5 mL), H 2 O (5 mL), dried (MgSO 4 ), filtered and evaporated. The crude pale yellow oil was distilled in a bulb-to-bulb apparatus (Kugelrohr distillation) to remove and recycle dimethyl malonate. Finally, flash-chromatography on silica gel (heptane–Et 2 O, 9:1) afforded the 2-benzyl-2-fluoro-3-(carboxymethyl-methylacetate)-cyclopentanone. Mp 98 °C. IR (film): 2920, 1736, 1436, 1140 cm –1 .

**Type II Polymer-supported Catalyst: O-(9)-4-Methylpolystyrenyl-V-9-anthracenemethyl Cinchonidinium Chloride.**

To a solution of sodium hydride 95% (5.2 mg, 0.206 mmol, 1.1 equiv) in DMF was added -9-anthracenemethyl cinchonidinim chloride (179.3 mg, 0.370 mmol, 1.1 equiv) at 22 °C, and the resulting mixture was stirred for 10 min. Methylvinyl resin (1% DVB, 200–400 Mesh, 1.7 mmol g –1 , 121 mg, 1 equiv) was then added and the mixture was stirred under N 2 at 22 °C for 5 days. The solution was then filtered and washed successively with MeOH and dried in vacuo (20 mmHg) for 1 d, affording a yellow resin.

Yield: 77%; (ee = 59%).

**Benzylation of 2-Fluoro-1-tetralone**

A mixture of 2-fluoro-1-tetralone (100 mg, 0.609 mmol, 1 equiv), N-(9)-4-butyloxystyrenyl cinchonium iodide (75 mg, 0.061 mmol, 0.1 equiv) and KOH 50% (1 mL, 12.79 mmol, 21 equiv) in toluene was treated with benzyl bromide (5 mL), heated under reflux over Na for 1 d, affording a yellow resin.

Yield: 90%.
Benzylation of 7.58 (m, 1 H), 8.10 (d, 1 H, J = 7.6 Hz), 7.25 (m, 6 H), 7.19–7.15 (m, 3 H), 7.06 (d, 2 H, J = 8.3 Hz), 4.10 (dd, 1 H, J = 13.3, 9.3 Hz), 1.44 (s, 9 H). 13C NMR (75 MHz, CDCl3): δ = 170.8, 170.3, 139.6, 138.4, 136.4, 132.4, 130.1, 129.9, 128.7, 128.2, 128.0, 127.9, 127.7, 127.6, 126.1, 81.1, 67.9, 39.6, 28.0.

Acknowledgement

The authors thank Rhodia Organique Fine, the Ministère de la Recherche et de la Technologie, and the réseau interrégional normand ‘PUNCH Orga’ for supporting these studies.

References


