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# New Polymer-supported Catalysts Derived from *Cinchona* Alkaloids: Their Use in the Asymmetric Michael Reaction

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**Abstract** : New polymer-supported catalysts derived from quinine and quinidine were elaborated and tested in the conjugate addition between enamino ester **13** and methyl vinyl ketone. By employing a 7-atom-length spacer, an excellent enantioselectivity was observed (87%). 

Although *Cinchona* alkaloids have long been recognized as efficient chiral catalysts for a variety of homogeneous asymmetric reactions, their utility is often limited by the difficulty of separating the product from the catalyst. In order to obtain more easy-to-handle catalysts, several groups have elaborated insoluble polymer-supported *Cinchona* alkaloids. An attractive feature of such catalysts is that they are easily removed at the end of the reaction for future reuse. Alkaloid-acrylonitrile copolymers,[1] alkaloid-crosslinked polymers,[2] polymers in which the alkaloid moiety is anchored at C-9 in *O*-acylated form,[3] and silica gel-supported bis-*Cinchona* alkaloids[4] have thus been synthesized. The present paper concerns the design of new polymer-supported catalysts derived from *Cinchona* alkaloids and their use in the asymmetric Michael reaction. Since in almost all cases so far reported, the stereochemistry of the asymmetric reactions induced by these alkaloids is essentially controlled by the configurations at C-8 and C-9, we envisaged to take advantage of the remote vinyl side chain at C-3 as the connecting site to polymers. Moreover, since the reactivity of alkaloid catalysts is generally reduced by being directly attached to a polymer support, spacer groups of various lengths were also inserted between the catalytic scaffold and the polymer matrix.

Central to the success of any solid-phase strategy is a direct and general method for coupling the initial starting materials onto the solid support. In our case we sought to bind *Cinchona* alkaloids to a Merrifield resin *via* a relatively robust ether linkage. With this aim in view, primary alcohols **1** and **2** were prepared from

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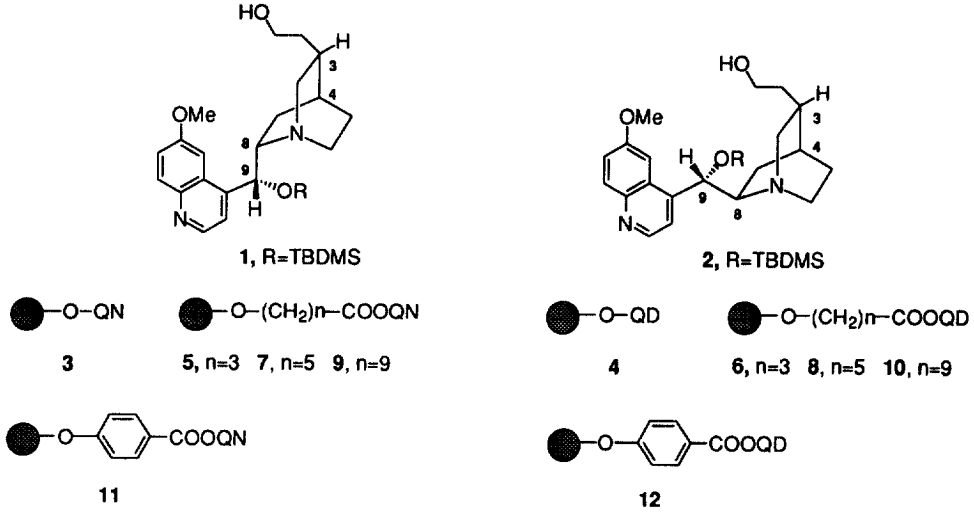
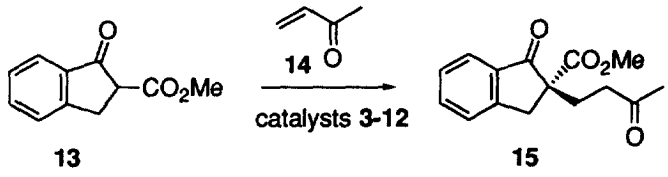
quinine (QN) and quinidine (QD) respectively,[5] according to the methodology reported by Sanders *et al* involving the protection of the hydroxyl group at C-9 with a TBDMS group, followed by hydroboration of the vinyl side chain.[6] Immobilization of alcohols **1**, **2** was next performed, either by direct attachment to the resin, or by means of an adequate spacer. Currently, the choice of available linkers still limits the reaction sequence possible on supports, since these are mostly optimized for biopolymer synthesis. Design of spacers must take into account their compatibility and interplay between resin and catalytic scaffold, and therefore the nature of anchors is one of the most decisive factors. In the present case, we envisaged the use of ω-hydroxy acids as linkers, so they might be bound to the polymer matrix at their OH end *via* a robust ether connection, and at their COOH end to the alkaloid as an ester linkage, ensuring a point of selective detachment for loading determination. A library of ten supported alkaloids (**3** to **12**) was elaborated and tested. Catalysts **3** and **4** were prepared by direct coupling of alcohols **1** and **2** to a Merrifield resin using NaH in DMF at 150 °C, followed by cleavage of the TBDMS group at C-9 by means of *n*-Bu4NF. Catalysts **5** to **12** were synthesized by linking first the ω-hydroxy acid spacers as their corresponding sodium dianions to the Merrifield resin at 120 °C in DMF. The pendent COOH group of resulting anchored linkers was next esterified with alcohols **1** and **2** (DCC, DMAP in DMF), and the TBDMS group at C-9 was finally cleaved with *n*-Bu4NF.




Supported catalysts **3-12** were characterized by (C, H, N, O, Cl) elemental analysis and IR spectroscopy. Loading for resins **5-12** was determined after selective cleavage of the ester group (LiOH in DMF-$H_2O$ at 20 °C). Furthermore, polymeric species **3-12** were efficiently discriminated by near infrared (NIR) spectroscopy. For that purpose, original spectra were transformed by a first-order derivative, and then normalized prior principal component analysis.[7] We next tested the efficiency of resins **3** to **12** to promote the conjugate addition between 2-carbomethoxy-indan-1-one **13** and methyl vinyl ketone **14**, because several polymer-supported *Cinchona* alkaloids have already been used as catalysts in this reaction. [1,2a,3]




The following optimized reaction parameters were applied in all experiments: slow addition (20-24 h) of a 2-fold excess of **14** to a well-stirred solution of **13** in dichloromethane at 20 °C, in the presence of a catalytic amount (10 mol %) of polymer-supported alkaloid. Results are summarized in Table 1.

Table 1. Yields, enantiomeric excesses and absolute configuration of the Michael adduct **15**

| Resin | Loading[a] | Adduct **15** | | |
|---|---|---|---|---|
| | | Yield[b] [%] | ee[c] [%] | abs. conf. |
| **3** | 0.6 | 95 | 12 | *R* |
| **4** | 0.6 | 80 | 45 | *R* |
| **5** | 0.2 | 75 | 13 | *R* |
| **6** | 0.3 | 80 | 21 | *R* |
| **7** | 0.3 | 85 | 87 | *R* |
| **8** | 0.2 | 95 | 39 | *R* |
| **9** | 0.3 | 85 | 31 | *R* |
| **10** | 0.2 | 80 | 24 | *R* |
| **11** | 0.25 | 85 | 10 | *R* |
| **12** | 0.3 | 75 | 12 | *R* |

[a] In mmol of alkaloid per g of resin. [b] Isolated compound. [c] Data are averages from two or more experiments.[8-9]

These outcomes deserve the following comments. Polymer-supported alkaloids **3-12** were found to be good catalysts, the Michael adduct **15** having been obtained with an excellent chemical yield in all cases. The Table also shows that the extent of the asymmetric induction was greatly sensitive to the polymer composition, especially to the length of the spacer, and also to the nature of the alkaloid. Optimum for the best ee (87%) was obtained with resin **7**, in which quinine is fixed to the polymer matrix by means of a 7-atom-length spacer. To our knowledge, this is the highest ee value achieved in the asymmetric reaction between **13** and **14**, catalyzed with "free", [1a, 9] or immobilized *Cinchona* alkaloids.[1,2a,3] It should be pointed out that a dramatic decrease of the ee was observed with other catalysts, in which the alkaloids are directly attached to the Merrifield resin (**3** and **4**), or by means of a 5-atom-spacer (**5** and **6**), a 11-atom-spacer (**9** and **10**), or an "aromatic spacer" (**11** and **12**). Another striking feature of the present results is that all the catalysts used gave predominantly enantiomer (*R*)-**15**, *irrespective of the kind of the alkaloid incorporated* (quinine or quinidine). Other examples of such a phenomenon are scarce. [10] This unusual steric course can be rationalized by invoking that the chiral influence stemming from C-3 and C-4 at the quinuclidine nucleus is strengthened by

the large appendage at C-3 (linker and polymer support) to overshadow the chiral forces originating from the quinoline-carbinol half at C-8.

To conclude, the new polymer-supported *Cinchona* alkaloids we have synthesized were found to be good catalysts to promote the conjugate addition between β-keto ester **13** and methyl vinyl ketone. The length of the spacer arm inserted between the polymer matrix and the alkaloid is critical to obtain good ee. By employing a 7-atom-length spacer, the ee was better than those previously reported with *Cinchona* alkaloids. The steric course of the present Michael addition reaction is not substantially influenced by the configuration at C-8 and C-9 in the alkaloid residue, but is clearly dominated by the nature of the substituent at C-3. Further synthetic applications of these promising supported catalysts are currently under investigation in our laboratories.

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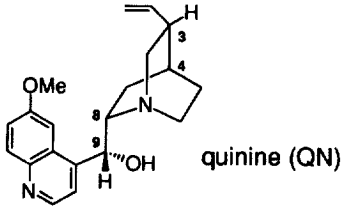
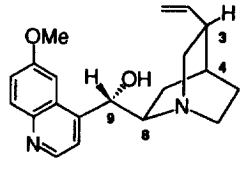
5 - (3*R*, 4*S*, 8*S*, 9*R*)-(-)-Quinine and (3*R*, 4*S*, 8*R*, 9*S*)-(+)-quinidine exhibit a *"mirror-half-image"* relationship.




quinine (QN)




quinidine (QD)

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