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Asymmetric alkylation of glycine imines using in situ generated phase-transfer catalysts

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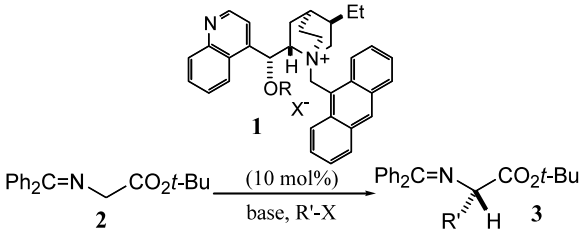
Abstract—In this paper we report an investigation into the possibility of effecting the asymmetric alkylation of glycine imines using chiral quaternary ammonium salt catalysts that are generated in situ. It is demonstrated that *O*-alkyl *N*-alkyldihydrocinchonidinium salts can be assembled from the parent alkaloid under the reaction conditions required for the liquid–liquid phase-transfer alkylation of glycine imines, and that reactions performed in this way give enantioselectivities comparable to those obtained using pre-prepared catalysts. Utilization of this methodolgy in the generation and screening of catalyst libraries is also demonstrated.

The utility of *N*-anthracenylmethyl substituted cinchona alkaloids, e.g. **1** as phase-transfer catalysts for the asymmetric alkylation of glycine imines **2**[1] (Scheme 1) was first reported in 1997. This chemistry can be effected under liquid–liquid,[2] solid–liquid,[3] and micellar phase-transfer conditions,[4] and is also similarly effective under homogeneous reaction conditions involving phosphazene bases.[5]

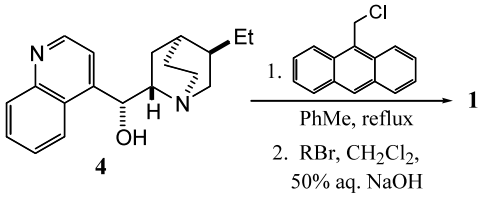
It has also been shown that the same catalysts **1** are effective in a number of other enantioselective C–C bond-forming reactions[6] and also in the highly enantioselective epoxidation of α,β-unsaturated ketones.[7] Cinchona alkaloid derivatives bearing a number of other *N*-alkyl substituents have also been shown to be effective in a variety of asymmetric phase-transfer alkylation processes.[8] These results demonstrate that quaternary ammonium salts of this type have wide utility in asymmetric synthesis, and consequently efficient methods of generating and/or optimizing the catalyst structure are of significant interest.



Scheme 1.

Salts **1** are normally prepared via quaternization of the appropriate cinchona alkaloid, e.g. **4** with 9-chloromethylanthracene, followed (when necessary) by biphasic alkylation of the free hydroxyl group (Scheme 2).[2,3] It has been known for some time that the *O*-alkylation step can be effected in situ during the liquid–liquid phase-transfer alkylation of imine **2**,[2a,f,9] and we have recently been investigating whether it is also possible to effect the initial *N*-quaternization in the same reaction system.

In order to test this, we initially examined the effect of exposing imine **2** to catalytic amounts of dihydrocinchonidine **4** and anthracenylmethyl halides (1.3 equiv.) at room temperature, under typical liquid–liquid phase-transfer conditions (Scheme 3). It was found that when 9-chloromethylanthracene was employed, none of the



Scheme 2.

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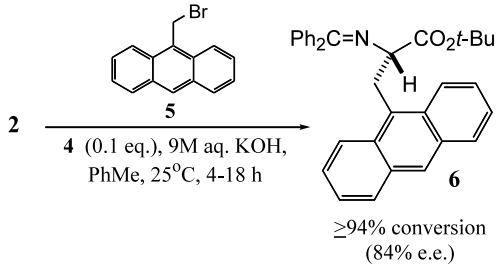
desired alkylation product **6** could be isolated. In addition, no quaternary ammonium salt could be detected in the reaction mixture, which suggests that this reaction failed because quaternization of the cinchonidine did not take place. In contrast, when the more reactive 9-bromomethylanthracene **5** was used, efficient alkylation of the imine **2** was observed (Scheme 3), and HPLC analysis of the corresponding *N*-benzoate derivative[2g] indicated that this process was highly enantioselective.

We also attempted to investigate the use of 9-iodomethylanthracene in this reaction process, however the instability of this material made it impractical for routine use.[10] This initial result established that it is possible to generate an effective asymmetric phase-transfer catalyst in situ, and also provides a highly effective method for accessing anthracenylmethyl glycine derivatives.[11]

Extension of this protocol to allow utilization of two different alkylating agents was then examined. In this case we chose imine **7** as the target since it is straightforward to assess the enantiomeric excess of this material by chiral HPLC. Initial experiments established that the optimal conditions for in situ generation of *N*-anthracenylmethyldihydrocinchonidinium bromide **1** (R = H, X = Br) involved treatment of the starting alkaloid with 1.2–1.5 equiv. 9-bromomethylanthracene **5**, at 60–75°C in toluene for 5 h. After this time a second alkylating agent, in this case benzyl bromide, could be added along with aqueous base and imine **2**. This resulted in rapid formation of the desired phenylalanine imine **7**. None of the corresponding anthracenylmethyl imine **6** appeared to be formed under these conditions, and as far as we could detect, the hydroxyl group of the catalyst had only been alkylated with benzyl bromide. ^{1}H NMR analysis of the reaction mixture indicated that all the starting 9-bromomethylanthracene **5** had been consumed, indicating that the slight excess of this reagent, required to ensure complete quaternization, is degraded during catalyst formation.

The enantioselectivity (93% e.e.) of this process is comparable to that obtained if pre-formed, recrystallized, *N*-anthracenylmethyldihydrocinchonidinium bromide **1** (R = H, X = Br) is employed, suggesting that minor amounts of less selective catalytic elements that could have been generated have minimal effect on reaction selectivity.



Scheme 3.

The final part of this study involved examination of whether three different alkylating agents could be utilized. The first two of these would be involved in generation of the quaternary ammonium catalyst (*N*- then *O*-alkylation), and the third should then participate in the reaction with the imine substrate **2**.

We considered that this type of protocol would be most useful for the automated screening of potential catalyst structures. Consequently, we opted to investigate its application in the parallel synthesis and screening of a small library of catalysts. For this study we chose the alkylation of glycine imine **2** with 3-bromo-2-methylpropene as the assay reaction. This particular alkylation reaction had not previously been optimized in our laboratories and so we considered that this would be a useful test of the methodology. Thus, using a simple robotic system, a library of 20 catalysts were generated in parallel, and the enantioselectivities monitored by HPLC (Fig. 1). Initially we utilized similar reaction conditions to those outlined in Scheme 4. Unfortunately, although the desired transformations took place, a number of the quaternary ammonium salts generated exhibited poor solubility in toluene. This resulted in poor reproducibility in some of the screens. Fortunately this problem was overcome by adding dichloromethane[12] to the reaction mixture after the initial *N*-quaternization had taken place, and using this modification[13] enantioselectivities could be reproduced to ±3% over a number of runs.

Independent synthesis and testing of selected examples of these catalysts confirmed that the screening protocol generated valid results, and utilizing this approach,

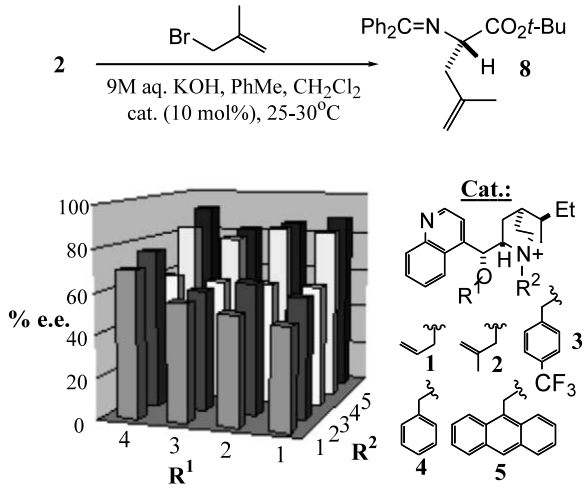
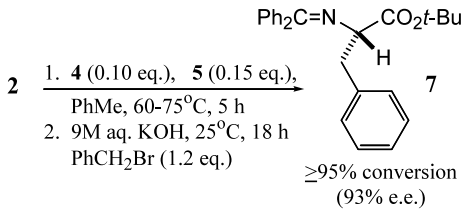
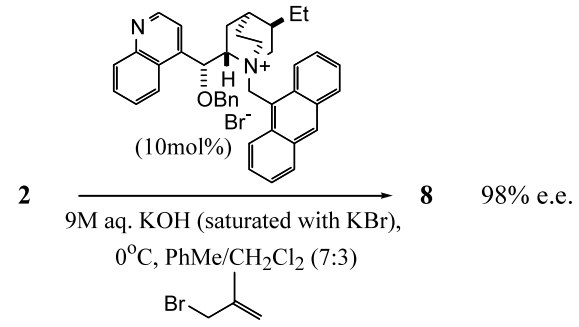


Figure 1.



Scheme 4.



Scheme 5.

quaternary ammonium salt **1** (R = Bn, X = Br) was identified as the most effective catalyst for this transformation, generating the desired imine **8** in 92% e.e.[14]

The results shown in Fig. 1 also demonstrate that both *N*- and *O*-substituents in the catalyst can play a significant role in determining the level of enantioselectivity. This highlights the need to vary both of these substituents when search for optimal catalysts, and emphasizes the utility of the methodology described here.

It is also worth noting that the above reactions were performed at ambient temperature (25–30°C) simply for convenience. If required, it is usually possible to increase the level of enantioselectivity simply by reducing the reaction temperature. For example, by using the optimal catalyst **1** (R = Bn, X = Br) identified in Fig. 1, and reducing the reaction temperature to 0°C,[15] imine **8** can be generated in 98% e.e. (Scheme 5).

In conclusion, this study has demonstrated that cinchona alkaloid-derived quaternary ammonium salts can be generated in situ during the liquid–liquid phase-transfer alkylation of glycine imine **2**, and that this protocol results in enantioselectivities similar to those obtained with pre-prepared catalysts. We believe that his chemistry is likely to be particularly useful for the identification of optimal catalysts structures for a given transformation, and that this approach should be applicable to a wide variety of phase-transfer reaction processes.

Acknowledgements

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12. Sufficent dichloromethane was added so as to give a final toluene:dichloromethane ratio of 7:3. This solvent ratio has previously been reported to be optimal for alkylations of this type, see: Esikova, I. A.; Nahreini, T. S.; O'Donnell, M. J. In *ACS Symposium Series 659: Phase-Transfer Catalysis—Mechanisms and Syntheses*; Halpern, M. E., Ed.; ACS: Washington, DC, 1997; p. 89.

13. **Typical procedure for catalyst screening**: Dihydrocinchonidine (2.5 mg, 0.0085 mmol) in toluene (390 μl) was treated with 9-bromomethylanthracene (110 μl of a 0.085 M solution in toluene, 0.0093 mmol) and the mixture stirred at 75°C for 5 h. After cooling to room temperature, dichloromethane (430 μl) was added, and the mixture stirred for a further 1 h. Benzyl bromide (100 μl of a 0.0085 M solution in toluene, 0.0085 mmol) and 9 M aqueous potassium hydroxide (250 μl, 2.3 mmol) were then added and the mixture stirred for 1 h. 3-Bromo-2-methylpropene (100 μl of a 1.0 M solution in toluene, 0.10 mmol) and imine **2** (300 μl of a 0.28 M solution in toluene, 0.085 mmol) were then added and the mixture stirred vigorously (ca. 1500 rpm) at room temperature until reaction was complete (4–18 h). Enantioselectivities were monitored via HPLC, R_t (Chiralcel OD-H, 99:1, hexane:IPA, 232 nm, 0.5 ml/min) 8.3 min (*S*-isomer), 10.1 min (*R*-isomer). If desired, the product could be isolated by extraction with ethyl acetate (3×1 ml). The combined organic extracts needed to be filtered through a short column of finely-ground anhydrous sodium sulfate, then concentrated under reduced pressure to give the crude alkylated imine **8**. Material isolated in this way was usually sufficiently pure (as judged by ^{1}H NMR) for use in subsequent reactions.
14. This value is the average e.e. (four runs) obtained using catalyst **1** (R = Bn, X = Br) generated in situ. When pre-prepared catalyst was used under similar conditions, imine **8** was obtained in 93% e.e.
15. The aqueous phase was saturated with KBr in order to prevent freezing.