Pergamon

Tetrahedron Letters, Vol. 38, No. 49, pp. 8595-8598, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10293-3

A New Class of Asymmetric Phase-Transfer Catalysts Derived From *Cinchona* Alkaloids - Application in the Enantioselective Synthesis of α-Amino Acids.

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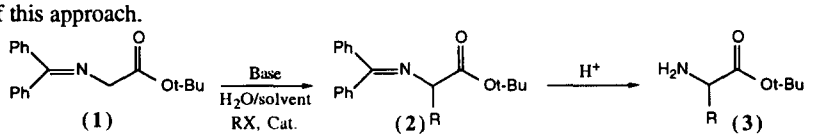
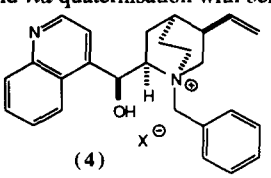
Abstract: A new class of *Cinchona* alkaloid-derived quaternary ammonium phase-transfer catalysts bearing a *N*-anthracenylmethyl function are presented. These catalysts show high stereocontrol in the asymmetric alkylation of a benzophenone-derived glycine-imine, and application of this process to the enantioselective synthesis of a range of α-amino acid esters (e.e. 67-94%) is investigated.

The synthesis of mono-substituted α-amino acid derivatives[1] *via* asymmetric phase-transfer catalysed[2] alkylation of glycine-imine (**1**) has been known for some time[3] (scheme 1). The use of relatively cheap, commercially available starting materials, coupled with the straightforward reaction conditions employed, makes this an attractive method for the synthesis of non-natural α-amino acids. The only drawback of this approach has been that the enantioselectivities obtained are generally moderate (e.e. 42% - 66%)[4]. Although the products (**3**) (or subsequent derivatives) can often be obtained in optically-pure form by recrystallisation, the material losses that inevitably result detract from the overall efficiency of this process. Clearly if the enantioselectivity of the alkylation process could be significantly improved, this would substantially enhance the appeal of this approach.



Scheme 1

To date the most effective asymmetric catalysts for this process reported are *N*-benzylcinchonium chloride (**4, X=Cl**) and *N*-benzylcinchonidinium chloride (**5, X=Cl**), which can be readily derived from the corresponding alkaloid *via* quaternisation with benzylchloride.



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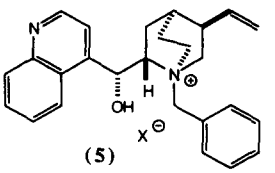
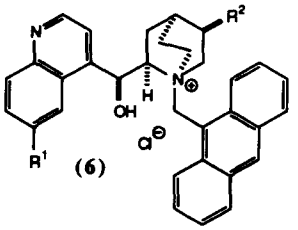


(5)

We have recently been concerned with the development of new chiral control elements for asymmetric synthesis[5], and now wish to report a new class of catalysts (**6**)-(**7**) which are also derived from the *Cinchona* alkaloids, but in this instance have been quaternised using 9-chloromethylanthracene.



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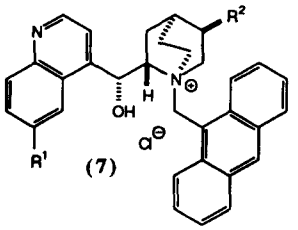
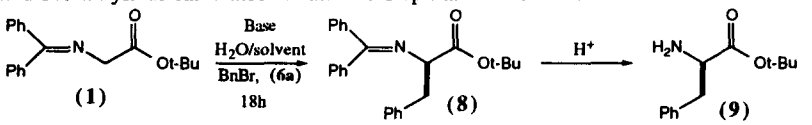


(7)

(a) $R^1 = H$, $R^2 = CH{=}CH_2$
(b) $R^1 = H$, $R^2 = CH_2{-}CH_3$
(c) $R^1 = OCH_3$, $R^2 = CH{=}CH_2$

In order to determine suitable reaction conditions for the asymmetric phase-transfer alkylation of imine **(1)** we initially investigated the reaction system using 10 mol% of catalyst **(6a)**, with benzyl bromide as the alkylating agent (table 1). As can be seen from the results obtained, the use of catalyst **(6a)** results in good enantioselectivity (e.e. 85-90%)[6] for this process. In addition it appears that the reaction can be carried out using a variety of water-imiscible solvents, and gives broadly similar results using either sodium or potassium hydroxide as base. As would be expected, there appears to be a slight variation of enantioselectivity with temperature, with 3-25°C giving best results. Below 3°C problems are encountered as the aqueous phase can freeze, effectively stopping reaction. The stirring rate does not appear to influence the enantioselectivity of these reactions, however it does affect the rate of reaction and substantially decreased reaction times can be achieved with high stirring rates. Because intermediate **(8)** proved unstable to purification by chromatography, this material was treated with aqueous acid to give phenylalanine *tert*-butyl ester **(9)** before purification, and overall yields calculated for the two-step transformation[7].



(1) (8) (9)

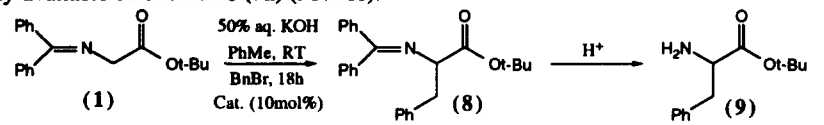
Reaction Solvent	Base	Reaction Temperature	%ee of (8)[6]	Overall Yield of (9)
PhMe	KOH	3°C	90%	85%
		25°C	89%	63%
		40°C	85%	80%
	NaOH	25°C	85%	75%
t-BuOMe	KOH	25°C	88%	67%
CH_2Cl_2	KOH	25°C	86%	73%
	NaOH	25°C	86%	77%

Table 1

For subsequent studies we chose to use toluene as the solvent since this is more environmentally acceptable than dichloromethane, and currently somewhat less expensive than *tert*-butylmethylether. We found that potassium hydroxide was the base of choice since the rate of uncatalysed alkylation (background reaction) was substantially slower with this base when compared with sodium hydroxide. We also chose to carry out all subsequent reactions at room temperature since this was more convenient for prolonged reaction times and little advantage in terms of enantioselectivity was gained by cooling the reaction.

We next examined the effect of the alkaloid component on the reaction selectivity by investigating the reaction using catalysts derived from cinchonine **(6a)**, cinchonidine **(7a)**, dihydrocinchonine **(6b)**, dihydrocinchonidine **(7b)**, quinidine **(6c)**, and quinine **(7c)** (table 2). As would be expected, the *pseudo*-enantiomeric catalyst pairs **(6)** and **(7)** give almost identical, but opposite enantioselectivity in the alkylation reaction. It is also clear that the quinidine and quinine derived catalysts **(6c)** and **(7c)** are the least effective, giving lower selectivity and lower overall yields. The catalyst derived from dihydrocinchonidine **(7b)** gave the

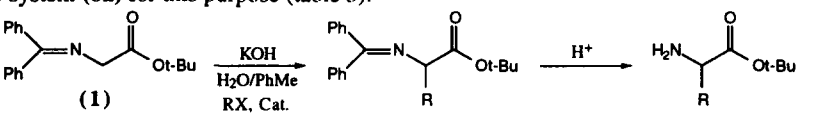
best selectivity (94% ee), however this was not substantially higher than the catalyst derived from commercially-available cinchonidine (**7a**) (91% ee).



Catalyst	%ee[6] of (8) (major isomer)	Overall Yield of (9)
6a	89% (R)	63%
6b	86% (R)	77%
6c	78% (R)	56%
7a	91% (S)	68%
7b	94% (S)	85%
7c	83% (S)	58%

Table 2

We next investigated the range of alkylating agents that would participate in this reaction process. Since dihydrocinchonidine is not widely available from commercial sources, and generally has to be prepared from cinchonidine we chose to utilise catalyst (**7a**), derived from the latter alkaloid, along with the *pseudo*-enantiomeric system (**6a**) for this purpose (table 3).



Entry	R-X	Cat.	Reaction Time	%ee[6] (major isomer)	Overall Yield
1	$PhCH_2Br$	**6a**	18h	89% (R)	63%
2		**7a**	18h	91% (S)	68%
3	$CH_2{=}CHCH_2Br$	**6a**	18h	88% (R)	62%
4		**7a**	18h	88% (S)	76%
5	CH_3I	**6a**	3h	86% (R)	40%
6		**7a**	3h	89% (S)	41%
7	$CH_3(CH_2)_3I$	**6a**	18h	87% (R)	56%
8		**7a**	18h	88% (S)	42%
9	(2-naphthyl)CH_2Br	**6a**	18h	82%[8] (R)	86%
10		**7a**	18h	86%[8] (S)	75%
11	t-BuO_2CCH_2I	**6a**	4h	67%[8] (R)	83%
12		**7a**	4h	72%[8] (S)	84%

Table 3

From the results shown it appears that a wide variety of alkyl halides can be used, generally giving the corresponding amino acid ester in good enantiomeric excess. In all cases the enantiomeric excesses were determined by HPLC analysis[6], however for entries 9-12 it was not possible to do this directly on the imine product, and a two-step conversion into the corresponding *N*-benzoyl derivative was necessary[8]. For simple alkyl groups (entries 5-8) the iodides are generally preferred[9], and yields tend to be lower than for benzyl and allyl bromides (entries 1-4). *tert*-Butyl iodoacetate (entries 9-10) can also be used, providing rapid access to aspartic acid derivatives, although in this instance the enantioselectivity is somewhat lower.

It is worth commenting on the fate of the catalysts employed in these reactions. It has already been observed that rapid alkylation of the hydroxyl group occurs under related reaction conditions when the corresponding *N*-benzyl-*Cinchona* derivatives[3a] are employed in dichloromethane and 50% aqueous sodium hydroxide is used as the base. It was also shown that the pre-formed *O*-alkyl catalysts give similar results suggesting that this is the active form of the catalyst in the reaction. We have observed similar results with the *N*-anthracenylmethyl catalysts, and it appears that the reaction selectivity is largely independent of the nature of the *O*-alkyl substituent. This is fortunate because under the reaction conditions utilised, a different catalyst will be generated every time a different alkylating agent is employed.

In conclusion, we have developed a new class of asymmetric phase-transfer catalysts which show high enantioselectivity in the synthesis of a range of α-amino acids. It should be noted that the aim of this study was to compare different alkylating agents under near-identical reaction conditions. If required, it should be possible to further optimise the efficiency of a particular alkylation process by careful manipulation of temperature (table 1) and catalyst structure (table 2). We are currently involved in the further development of these catalyst systems and in investigating their applicability to other asymmetric phase-transfer processes.

Acknowledgements: We thank the EPSRC-DTI Asymmetric Synthesis Link core program for a studentship (to P.G.W.), Dr. M. Stuckey for n.m.r. spectra and Mrs. R. Howard for mass spectra. We would also like to thank Dr. John Crosby (Zeneca Pharmaceuticals) and Mr. Terence R. Lowdon (Hickson and Welch Ltd.) for helpful discussions.

References and Notes

1. For general discussions on the enantioselective synthesis of α-amino acids see: Williams, R.M; "*Synthesis of Optically Active α-Amino Acids*"; Pergamon Press; New York; 1989.
2. For general discussions on asymmetric phase-transfer catalysis see: O'Donnell, M.J. In "*Catalytic Asymmetric Synthesis*"; Ed. Ojima, I; VCH; New York; 1993.
3. (a) O'Donnell, M.J; Wu, S; Huffman, J.C. *Tetrahderon*, **1994**, *50*, 4507; (b) Tohdo, K; Hamada, Y; Shiori, T. *Synlett*, **1994**, 247; (c) Tohdo, K; Hamada, Y; Shiori, T. *Pept. Chem.*, **1991**, 7; (d) Imperiali, B; Fisher, S.L. *J. Org. Chem.*, **1992**, *57*, 757; (e) O'Donnell, M.J; Bennett, W.D; Wu, S. *J. Am. Chem. Soc.*, **1989**, *111*, 2353; (f) Esikova, I.A; Nahreini, T.S; O'Donnell, M.J. in "ACS Symposium Series 659: Phase-Transfer Catalysis - Mechanisms and Syntheses", Ed. Halpern, M.E., ACS, Washington D.C, 1997, p89; (g) O'Donnell, M.J; Esikova, I.A; Mi, A; Shullenberger, D.F; Wu, S. in "ACS Symposium Series 659: Phase-Transfer Catalysis - Mechanisms and Syntheses", Ed. Halpern, M.E., ACS, Washington D.C, 1997, p124.
4. It has recently been reported[3f] that careful manipulation of the reaction parameters can lead to increased enantioselectivity. In this way the alkylation of glycine-imine **(1)** with benzylbromide using catalyst **(5, X=Br)** has been improved from 66% e.e. to 81% e.e.
5. Lygo, B; Crosby, J; Lowdon, T.R; Wainwright, P.G. *Tetrahedron Lett.*, **1997**, *38*, 2343.
6. Unless otherwise stated, the e.e. values were determined by HPLC of the crude imine on a chiral Baker-Bond DNPG (covalent) column, values reported are reproducible to ±2%.
7. **Typical procedure**: A solution of glycine imine **(1)** (0.5mmol) in toluene (5ml) is treated sequentially with the appropriate catalyst (0.05mmol), alkylating agent (0.6mmol), and 50% aqueous potassium hydroxide (1ml). The resulting mixture is stirred vigorously (*ca.* 1000rpm) at room temperature (25±5°C) for 3-18h (see table 3). The aqueous layer is then extracted with ethyl acetate (3x5ml), and the combined organics dried (Na_2SO_4) and concentrated under reduced pressure to give the crude imine product. This material is dissolved in tetrahydrofuran (3ml) and 15% aqueous citric acid (1.5ml) added. The mixture is stirred vigorously at room temperature for 3h, then diluted with water (5ml). The mixture is extracted with diethyl ether (2x5ml) to remove any excess alkylating agent and benzophenone, then the aqueous layer is basified (K_2CO_3). Extraction with ethyl acetate (3x5ml) followed by drying of the extracts (Na_2SO_4) and concentration under reduced pressure gives the crude amino acid *tert*-butyl ester which can generally be purified by passing through a plug of silica.
8. E.e. values were determined by HPLC of the crude N-benzoylamino acid *tert*-butyl ester on a Chiralcel OD-H column, values reported are reproducible to ±5%.
9. The corresponding alkyl bromides tend to react very slowly. It is also advantageous to use iodine-free alkyl iodides and to carry these reactions out in the dark.

(*Received in UK* 16 *September* 1997; *revised* 30 *September* 1997; *accepted* 2 *October* 1997)