Pergamon

Tetrahedron Letters 40 (1999) 8671–8674

TETRAHEDRON LETTERS

Enantioselective Alkylation Of Alanine-Derived Imines Using Quaternary Ammonium Catalysts.

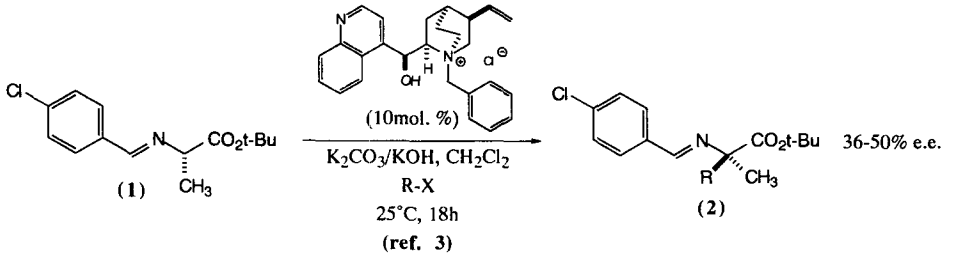
Barry Lygo*[a,1], John Crosby[b] and Justine A. Peterson[a]

Received 6 September 1999; accepted 28 September 1999

a - Department of Chemistry and Applied Chemistry, University of Salford, Salford, M5 4WT, UK.
b - AstraZeneca, Process R&D, Silk Road Business Park, Charter Way, Macclesfield, Cheshire, SK10 2NA, UK.

Abstract: Application of *N*-anthracenylmethyl dihydrocinchonidinium bromide as a catalyst for the enantioselective alkylation of a series of alanine-derived imines is reported. Using solid K_2CO_3/KOH as the stochiometric base such alkylations can be achieved with enantiomeric excesses up to 87% allowing rapid access to α,α-dialkyl-α-amino acid esters.

Chiral α,α-dialkyl-α-amino acids are an important class of non-coded amino acids which have been widely exploited in the design and synthesis of modified peptides. The quaternary chiral centre leads to many of the desirable properties associated with this class of amino acids, but offers a significant challenge with respect to asymmetric synthesis. Although most approaches reported to date involve either the use of chiral auxiliaries or strategies that utilise self-regeneration of stereocentres, there have also been a few reports that involve asymmetric synthesis using chiral catalysts.[2,3] One such approach was reported in 1992 by O'Donnell[4] and involved the asymmetric alkylation of an alanine-derived imine **1** under phase-transfer catalysts (scheme 1). It was shown that using *N*-benzylcinchoninium chloride as the catalyst, alkylation could be achieved in up to 50% e.e. It was also demonstrated that in favourable cases the alkylation products **2** could be obtained in high enantiomeric purity (>97% e.e.) by crystallisation of the racemate, leaving optically enriched material in the filtrate.

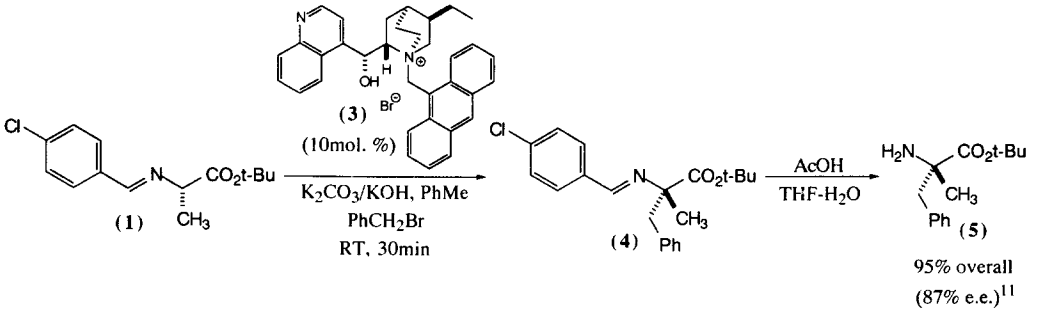


Scheme 1

Obviously if the enantioselectivity of the process outlined in scheme 1 could be significantly improved, it would enhance the utility of this approach to α,α-dialkyl-α-amino acids. We have been investigating the use of *Cinchona* alkaloid derivatives as chiral control elements for synthesis[5,6,7] and recently both ourselves[6] and others[8] have reported that *N*-anthracenylmethyl substituted *Cinchona* alkaloids can be utilised as catalysts for the enantioselective synthesis of α-amino acids *via* the alkylation of glycine imines.[9] Here we report preliminary results on the application of these catalysts to enantioselective alkylation of alanine-derived imines.

0040-4039/99/$ - see front matter
PII: S0040-4039(99)01836-5

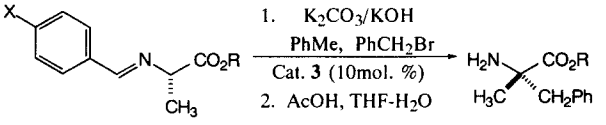
For this study *N*-anthracenylmethyl dihydrocinchonidinium bromide **3** was chosen as the catalyst,[10] since this proved to be the most effective in our earlier studies on the alkylation of glycine imines. After some experimentation, it was found that the optimal conditions for desired alkylation of alanine-derived imine **1** involved the use of toluene as the organic phase, and a finely-ground solid base which was generated by fusing together potassium hydroxide and anhydrous potassium carbonate.[4,11] Under these conditions the reaction of imine **1** with benzyl bromide occurred rapidly at room temperature. Hydrolysis of the resulting imine gave (*S*)-α-methylphenylalanine *tert*-butyl ester **5** in excellent overall yield and with 87% e.e.[12,13] (scheme 2). It should be noted that for reproducible results the base employed in this reaction must be freshly prepared. On storage the base readily absorbs moisture and this significantly reduces its activity in this reaction system, resulting in extended reaction times and reduced enantioselectivity.



Scheme 2

Although the level of enantioselectivity observed here is broadly similar to that obtained in the alkylation of glycine imines under liquid-liquid phase-transfer conditions,[6] studies into optimisation of the reaction revealed that alkylation in the absence of catalyst was relatively fast ($t_{1/2} \leq 1$h). This suggests that, at least for this reaction process, catalyst **3** may not only be acting as a phase-transfer agent, but may also be involved in ion-exchange processes[8c] once interfacial deprotonation has occurred.

In order to test the generality of this reaction we decided to investigate the alkylation of a series of alanine-derived imines with the same electrophile ($PhCH_2Br$) (table 1), and also to investigate the alkylation of imine **1** with a series of different electrophiles (table 2).

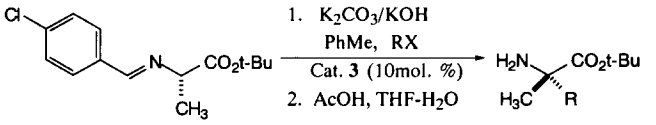


X	R	% E.e.[12]	% Yield
MeO	*t*-Bu	84	85
H	*t*-Bu	84	87
Cl	*t*-Bu	87	95
Cl	*i*-Pr	60	80
Cl	Me	33	80

Table 1

As can be seen from the results depicted in table 1, a number of alanine-derived imines can serve as substrates for the alkylation process, and imines prepared using 4-methoxybenzaldehyde, benzaldehyde, and 4-chlorobenzaldehyde all give similar levels of enantioselectivity (table 1, entries 1-3). As previously observed,[4] benzophenone-derived imines could not be usefully employed in this type of alkylation due to the

reduced acidity of the substrate. Incorporation of ester groups other than *tert*-butyl led to substantially reduced levels of selectivity (table 1, entries 3-5) and this is consistent with earlier observations reported for the alkylation of glycine-derived imines.[9]



RX	% E.e.[12]	% Yield
$PhCH_2Br$	87	95
2-NapthCH_2Br	81	62
4-Cl-$C_6H_4CH_2Br$	77	72
n-BuI	36	n.d.
ICH_2CO_2t-Bu	19	58

Table 2

Variation of the electrophile led to significant changes in the level of enantioselectivity (table 2). Arylmethyl bromides generally gave the highest levels of selectivity (e.g. table 2, entries 1-3), whereas other types of alkyl halide (e.g. table 2, entries 4-5) gave low levels of asymmetric induction. Initial investigations suggest that loss of selectivity with some electrophiles may largely be a consequence of the competing, non-selective, background alkylation. Thus it may be possible to reduce the rate of this competing process, and hence expand the range of electrophiles that can be utilised. Investigations into this are currently underway in our laboratories.

In conclusion, we have identified reaction conditions that employ *N*-anthracenylmethyl dihydrocinchonidinium bromide **3** as a catalyst for the asymmetric alkylation of alanine-derived imines. Reaction with arylmethyl bromides allows the preparation of α,α-dialkyl-α-amino acids with high levels of enantioselectivity. The product amino acids can generally be obtained in optically-pure form either by direct recrystallisation or by crystallisation of simple derivatives,[14] and given the simplicity of the reaction procedures involved[11] this represents an attractive method for the preparation of such materials.

Acknowledgements: We thank Zeneca and the Salford University Science Research Institute for a studentship (to J.A.P.) and Mrs. R. Howard for mass spectra.

References and Notes

1. Current Address: School of Chemistry, Nottingham University, Nottingham, NG7 2RD, UK
2. For recent reviews relating to the synthesis of chiral α,α-dialkyl-α-amino acids see: Cativiela, C; Diaz-de-Villegas, M.D. *Tetrahedron Asymm.*, **1998**, *9*, 3517; Williams, R.M. "*Synthesis of Optically Active α-Amino Acids*", Pergamon Press, Oxford, **1989**; Wirth, T. *Angew. Chem. Int. Ed. Engl.*, **1997**, *36*, 225; Seebach, D; Sting, A.R; Hoffmann, M. *Angew. Chem. Int. Ed. Engl.*, **1996**, *35*, 2708.
3. See for example: Vedejs, E; Fields, S.C; Hayashi, R; Hitchcock, S.R; Powell, D.R; Schrimpf, M.R. *J. Am. Chem. Soc.*, **1999**, *121*, 2460; Belokon, Y.N; Kochetkov, K.A; Churkina, T.D; Ikonnikov, N.S; Chesnokov, A.A; Larionov, O.V; Parmár, V.S; Kumar, R; Kagan, H.B. *Tetrahedron Asymm.*, **1998**, *9*, 851; Belokon, Y.N; North, M; Kublitski, V.S; Ikonnikov, N.S; Krasik, P.E; Maleev, V.I. *Tetrahedron Lett.*, **1999**, *40*, 6105; and references therein.
4. O'Donnell, M.J; Wu, S. *Tetrahedron Asymm.*, **1992**, *3*, 591.
5. For synthetic approaches to substituted hydroxymethyl quinuclidines see: Lygo, B; Crosby, J; Lowdon, T.R; Wainwright, P.G. *Tetrahedron Lett.*, **1997**, *38*, 2343; Lygo, B; Crosby, J; Lowdon, T.R; Wainwright, P.G. *Tetrahedron*, **1999**, *55*, 2795.

6. For the application of *N*-anthracenylmethyl substituted *Cinchona* alkaloids to the asymmetric alkylation of glycine imines see: Lygo, B; Wainwright, P.G. *Tetrahedron Lett.*, **1997**, *38*, 8595; Lygo, B; Crosby J; Peterson, J.A. *Tetrahedron Lett.*, **1999**, *40*, 1385; Lygo, B. *Tetrahedron Lett.*, **1999**, *40*, 1389.
7. For the application of *N*-anthracenylmethyl substituted *Cinchona* alkaloids to the asymmetric epoxidation of enones see: Lygo, B; Wainwright, P.G. *Tetrahedron Lett.*, **1998**, *39*, 1599; Lygo, B; Wainwright, P.G. *Tetrahedron*, **1999**, *55*, 6289.
8. (a) Corey, E.J; Xu, F; Noe, M.C. *J. Am. Chem. Soc.*, **1997**, *119*, 12414; (b) Corey, E.J; Noe, M.C; Xu, F. *Tetrahedron Lett.*, **1998**, *39*, 5347; (c) O'Donnell, M.J; Delgado, F; Hostettler, C; Schwesinger, R. *Tetrahedron Lett.*, **1998**, *39*, 8775; (d) O'Donnell, M.J; Delgado, F; Pottorf, R.S. *Tetrahedron*, **1999**, *55*, 6347; (e) Dehmlow, E.V; Wagner, S; Müller, A. *Tetrahedron*, **1999**, *55*, 6335; (f) Horikawa, M; Busch-Petersen, J; Corey, E.J. *Tetrahedron Lett.*, **1999**, *40*, 3843.
9. For earlier work on the enantioselective alkylation of glycine imines under liquid-liquid phase-transfer conditions see: 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; 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; O'Donnell, M.J; Wu, S; Esikova, I; Mi, A. *U.S. Patent 5,554,753*, September 10, **1996**; O'Donnell, M.J; Wu, S; Huffman, J.C. *Tetrahderon*, **1994**, *50*, 4507; Tohdo, K; Hamada, Y; Shioiri, T. *Synlett*, **1994**, 247; Imperiali, B; Fisher, S.L. *J. Org. Chem.*, **1992**, *57*, 757; Tohdo, K; Hamada, Y; Shioiri, T. *Pept. Chem.*, **1991**, 7; O'Donnell, M.J; Bennett, W.D; Wu, S. *J. Am. Chem. Soc.*, **1989**, *111*, 2353.
10. It is important to note that the catalyst structure is modified by rapid *O*-alkylation under the reaction conditions, however generally the nature of the alkylating group has little influence on the enantioselectivity of the resulting reaction processes.
11. Imine **1** (0.74mmol) in dry toluene (1ml) was added dropwise to a stirred suspension of K_2CO_3/KOH (200mg, see comments in text) and catalyst **3** (0.074mmol) in dry toluene (2ml). The alkyl halide (0.89mmol) in dry toluene (1ml) was then added, and the mixture stirred vigorously (1000-1200rpm) for 0.5-3h at room temperature. The resulting mixture was filtered through a pad of Celite, washing through with more toluene (3ml) and the solvent removed under reduced pressure. The residue was dissolved in THF (1ml) and 50% aqueous acetic acid (2ml) added. After stirring at room temperature for 24h the solution was diluted with diethyl ether (10ml) and extracted with 2M hydrochloric acid (3x7ml). The acid extracts were washed with diethyl ether (2x5ml), then basified (K_2CO_3) and extracted with ethyl acetate (3x10ml). The ethyl acetate extracts were then dried (Na_2SO_4) and concentrated under reduced pressure to give the crude amino acid esters which could be purified by chromatography on silica gel (ethyl acetate) or by crystallisation.
12. Enantiomeric excesses (e.e.'s) were determined to ±3% by conversion of the amino acid *tert*-butyl esters into the corresponding *N*-benzoyl derivatives (PhCOCl, Et_3N, CH_2Cl_2) followed by HPLC analysis (Chiralcel OD-H, *i*-propanol/hexane, 254nm). In all cases the stereochemically enriched samples were compared with statistical mixtures generated using tetra-butylammonium bromide as the catalyst for alkylation.
13. The absolute stereochemistry of this material was determined by cleavage of the *tert*-butyl ester (6M HCl), and comparison of the rotation of the free amino acid with known data (Cativiela, C; Diaz-de-Villegas, M.D; Galvez, J.A. *Tetrahedron Asymm.*, **1994**, *5*, 261).
14. For example the *N*-benzoyl derivative of (*S*)-α-methylphenylalanine **5** (87% e.e.) can be obtained in ≥97% e.e. by a single crystallisation from ethyl acetate / petroleum ether (72% recovery).