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A Catalytic Enantioselective Synthesis of α-Methyl Amino Acid Derivatives by Phase-Transfer Catalysis

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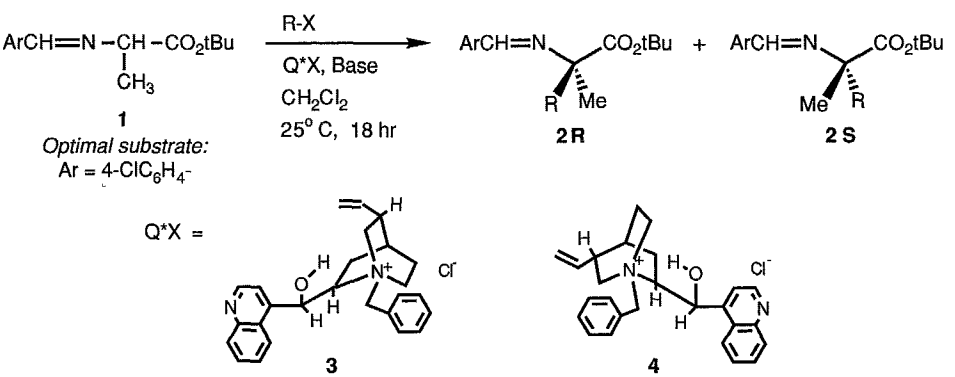
Abstract: *Optically active α-methyl amino acid derivatives are prepared in up to 50% enantiomeric excess by phase-transfer catalytic alkylation of aldimine Schiff bases of alanine t-butyl ester.*

α,α-Disubstituted α-amino acids, especially α-methyl amino acids (AMAA), have been the subject of numerous studies.[1-7] This important class of amino acids is of significance for several reasons: when incorporated into peptides, AMAAs reduce the conformational space available to the resulting peptide chain and also reduce the enzymatic and chemical hydrolysis of such peptides while increasing their lipophilicity. The AMAAs themselves are often effective enzyme inhibitors. Since this class of amino acids contains a quaternary carbon center, asymmetric synthesis is the method of choice for their preparation.

Asymmetric synthesis of α-methyl amino acids by phase-transfer catalytic (PTC) alkylation using a chiral catalyst would provide a particularly attractive method for the preparation of optically active α-methyl amino acids because of the simplicity both in terms of reagents and conditions (room temperature reactions) and the potential for scale-up as well as the need to use only a catalytic amount of the enantiocontrol element.[7] We have previously reported the asymmetric synthesis of monoalkylated amino acids from protected glycine derivatives by liquid-liquid PTC alkylation in the presence of cinchona alkaloid-derived quaternary ammonium salts.[8] We now report the asymmetric synthesis of α-methyl amino acids from the Schiff base derivatives of aromatic aldehydes and alanine *tert*-butyl ester using solid-liquid phase-transfer catalytic alkylation and cinchona-derived optically active catalysts.



Initial studies focused on the effect of different base systems on the PTC alkylation of Schiff base t-butyl ester **1a** (Table 1, A). The best result (48% ee, 87% chemical yield) was obtained by using the mixed base KOH:K_2CO_3.[9] Under the same conditions, no alkylation product was observed when LiOH was used as base. Although the liquid-liquid conditions (50% aqueous NaOH as base)[8] also gave the same level of optical induction (49% ee), the chemical yield was lower than that obtained when the mixed base KOH:K_2CO_3 was used under solid-liquid PTC conditions.

Table 1: Asymmetric PTC Alkylation of Schiff Bases **1** with Alkyl Halides under Various Conditions.[a,b]

Variable	Major Enantiomer	Chemical yield	% ee (%R, %S)
A) Base[c]			
NaOH (50% aq.)	R	72%	49% (74.5, 25.5)
NaOH	R	73%	41% (70.5, 29.5)
KOH	R	70%	46% (73, 27)
KOH:K_2CO_3 (1:1)	R	87%	48% (74, 26)
KOH (melted):K_2CO_3 (1:1)	R	78%	46% (73, 27)
B) Aryl group in **1**[d]			
4-ClC_6H_4- (**1a**)	R	78%	46% (73, 27)
4-$MeOC_6H_4$- (**1b**)	R	80%	42%[e] (71, 29)
Ph- (**1c**)	R	78%	22%[e] (61, 39)
1-Naphthyl- (**1d**)	R	82%	16%[e] (58, 42)
2-Naphthyl- (**1e**)	R	79%	42% (71, 29)
2,4,6-$Cl_3C_6H_2$- (**1f**)	R	68%	24% (62, 38)
C) RBr[f]			
4-$FC_6H_4CH_2Br$	R	84%	50% (75, 25)
4-$ClC_6H_4CH_2Br$[g]	R	87%	48% (74, 26)
4-$BrC_6H_4CH_2Br$	R	80%	44% (72, 28)
$PhCH_2Br$	R	80%	44% (72, 28)
2-NaphthylCH_2Br	R	87%	42% (71, 29)
CH_2=$CHCH_2Br$	R	78%	36% (68, 32)

[a] General Conditions: Substrate prepared from L-alanine; Catalyst, N-benzyl cinchoninium chloride (**3**); Solvent, CH_2Cl_2; 25 °C., 18 hr; % ee determined directly on reaction products (Note 9). [b] All new compounds were characterized by NMR and high-resolution mass spectral data. [c] Substrate, **1a**; RX, 4-$ClC_6H_4CH_2Br$. [d] Base, KOH (melted):K_2CO_3 (1:1); RX, 4-$ClC_6H_4CH_2Br$. [e] % ee obtained from C-18 HPLC of GITC derivative from the hydrolysis product of the Schiff bases **2** (Reference 8). [f] Substrate, **1a**; Base, KOH:K_2CO_3 (1:1). [g] Absolute configuration assigned by preparation and analysis of the GITC derivative by HPLC (Reference 11).

Either enantiomer of the alkylated product can be obtained as the major enantiomer by using the "pseudoenantiomeric catalysts" **3** or **4**. In earlier monoalkylation studies,[8] optical yields for the products from the cinchonine-derived catalyst **3** were only slightly better than for the cinchonidine-derived catalyst **4** (66% ee vs. 64% ee, respectively).[8] In contrast, the alkylation of **1a** with catalysts **3** and **4** gave somewhat different results. Using catalyst **3** the alkylated product was obtained in 48% ee (R) whereas with catalyst **4** a 24% ee (S) was obtained. Interestingly, use of Schiff base t-butyl ester from L-alanine (S absolute configuration) gave slightly higher induction when compared with either D-alanine or D,L-alanine (48% ee vs 44% ee vs 42% ee, respectively).[12,13] Alkylation of optically pure **1** derived from L-alanine with an achiral phase-transfer catalyst (tetrabutylammonium bromide) gave, as expected, only racemic product.

Next the nature of the imine protecting group was changed to study the effect of this variable on the reaction (Table 1, B). Earlier studies demonstrated that the benzophenone imine, which is used for monoalkylation of protected glycine derivatives, does not normally undergo a second alkylation because of the decreased acidity of the α-methine proton in the monoalkylated derivative.[14,15] The complementary aldimines are the protecting group of

choice in cases where a second alkylation is desired.[7b-d,i] As observed previously, the 4-chlorobenzaldehyde imine is the best protecting group in this series. In contrast with **1a** and **1f**, the Schiff bases **1b-1e** are relatively inactive under the KOH:K_2CO_3 (1:1) conditions. In these cases the alkylation reactions were carried out using a more active base system [KOH (melted):K_2CO_3 (1:1)].

Various active alkyl halides such as substituted benzyl bromides or allyl bromide, can be used in the alkylation reaction (Table 1, C). Attempts to use a less active alkyl halide (iBuBr) gave incomplete conversion of starting material to product.

Finally, attention was turned to scale up of the reaction and enantiomer isolation. As previously noted,[8] it is sometimes possible to effect a very simple purification of one enantiomer by crystallization of the racemate, leaving optically enriched product in the filtrate. Thus, stereoselective alkylation of **1a** (7.5 g) with 4-chlorobenzyl bromide and catalyst **3** followed by two recrystallizations to remove racemic product and then deprotection gave 4-chloro-α-methyl-D-phenylalanine (1.4 g, 23% overall from **1a**) in >97% ee.

Research continues in the catalytic enantioselective synthesis of α-amino acid derivatives with the complementary objectives to improve the levels of enantiocontrol for the preparation of product amino acids and to understand the nature of the interactions which control the stereoselectivity in these processes.

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