Asymmetric PTC Alkylation of Glycine Imines: Variation of the Imine Ester Moiety

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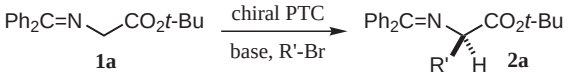
Abstract: Studies into the enantioselective phase-transfer alkylation of a series of glycine imine esters are presented. Using a quaternary ammonium salt catalyst derived from α-methylnaphthylamine, high enantioselectivities were obtained in reactions involving imines containing *tert*-butyl, benzhydryl, and benzyl esters. In contrast, a quaternary ammonium salt catalyst derived from dihydrocinchonidine gave highest enantioselectivities with *tert*-butyl and ethyl esters. Application of the benzhydryl ester alkylation in the preparation of a differentially protected aspartic acid derivative is also presented.

Key words: amino acids, asymmetric alkylation, phase-transfer catalysis, quaternary ammonium salts

In recent years the asymmetric phase-transfer catalyzed alkylation of glycine imines (Scheme 1) has emerged as a highly effective method for the enantioselective synthesis of α-amino acids.[1–4] This chemistry has now been developed to the point that it is regularly being exploited in target synthesis.[5] Throughout the development of this methodology most work has focused on the identification of highly effective phase-transfer catalysts and the optimization of reaction conditions. In contrast, relatively little variation in the nature of the glycine imine ester function has been reported, with the vast majority of studies involving only *tert*-butyl ester **1a**.[3] With this in mind, we have recently examined the enantioselective alkylation of alternative glycine imine esters and in this paper report preliminary results arising from this work.



Scheme 1

We have examined the asymmetric alkylation of four different glycine imine esters **1** (**a**: R = *t*-Bu; **b**: R = $CHPh_2$; **c**: R = CH_2Ph; **d**: R = Et). These particular imines were selected because they are straightforward to prepare[6] and because they incorporate synthetically versatile ester functions. In particular, the benzhydryl and benzyl esters were of interest to us because of they are readily cleaved via hydrogenolyzis, thus offering a useful alternative to the strong acid or base normally employed in the hydrolytic cleavage of esters **2a**.[7]

Pioneering studies by the O'Donnell group included investigations into the C-benzylation of these four imine esters using *N*-(4-trifluoromethylbenzyl)cinchoninium bromide as the phase-transfer catalyst.[8] This work established *tert*-butyl ester **1a** as the optimal substrate for reactions of this type, the product **2a** (R′ = Bn) being generated in 56% ee with this particular catalyst. Interestingly the benzyl and benzhydryl esters gave the lowest levels of enantioselectivity (28% ee and 14% ee respectively) in this study. Similar trends have also been reported for reactions involving C_2-symmetric binaphthyl derived phase-transfer catalysts.[4a]

Our own work in this area[2] has concentrated on the use of phase-transfer catalysts such as *O*-benzyl-*N*-(9-anthracenylmethyl)dihydrocinchonidinium bromide (**3**). Catalysts of this type give very high levels of enantioselectivity in the alkylation of glycine imine **1a**,[1] but their similarity to the catalysts employed in the O'Donnell study suggested that they may not work so well with the alternative esters. Partly because of this, we have recently being developing strategies for the rapid generation and screening of asymmetric phase-transfer catalyst libraries[2b] and this work has established that salt **4** is also capable of delivering very high levels of enantioselectivity in the alkylation of imine **1a**.[2a]

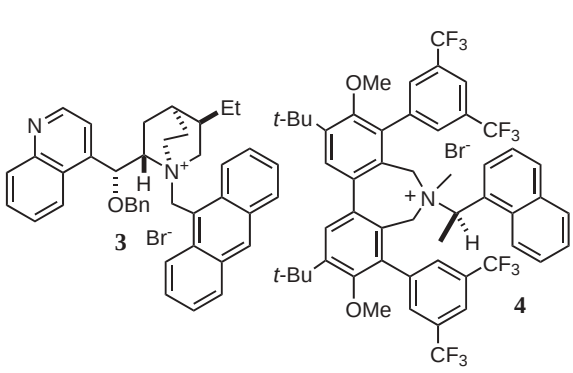


Figure 1

Although quaternary ammonium salts **3** and **4** give similar levels of enantioselectivity in the alkylation of imine **1a**, there is little similarity between the two structures and so it seemed likely that they would perform differently with the imine esters chosen for study. Thus, we initially

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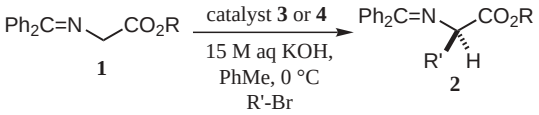
tested the two catalysts in trial experiments involving the alkylation of imine esters **1a**–**d** with benzyl bromide. Several additional alkylation reactions were then performed on each imine ester substrate, using the catalyst that gave the highest enantioselectivity in these initial experiments.

Table 1 Asymmetric PTC Alkylation of Glycine Imine Esters Using Catalysts **3** and **4**[9]



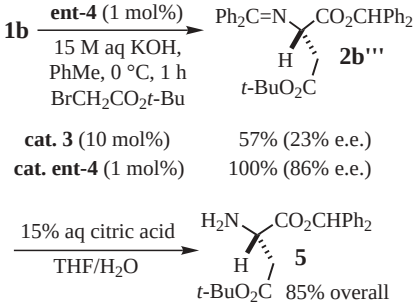
Entry	R	R′-Br	Product	Catalyst (mol%)[a]	Yield (%)	Ee (%)[b,c]
1	*t*-Bu	$PhCH_2Br$	**2a**	**3** (10)	90	93 (*S*)
2		$PhCH_2Br$	**2a**	**4** (1)	89	97 (*R*)
3		$CH_2=CHCH_2Br$	**2a'**	**4** (1)	71	94 (*R*)
4		$CH_2=CBrCH_2Br$	**2a''**	**4** (1)	77	93 (*R*)
5	Ph_2CH	$PhCH_2Br$	**2b**	**3** (10)	96	63 (*S*)
6		$PhCH_2Br$	**2b**	**4** (1)	95	92 (*R*)
7		$CH_2=CHCH_2Br$	**2b′**	**4** (1)	78	98 (*R*)
8		$CH_2=CBrCH_2Br$	**2b″**	**4** (1)	68	94 (*R*)
9	$PhCH_2$	$PhCH_2Br$	**2c**	**3** (10)	68	79 (*S*)
10		$PhCH_2Br$	**2c**	**4** (1)	86	86 (*R*)
11		$CH_2=CHCH_2Br$	**2c′**	**4** (1)	51	90 (*R*)
12		$CH_2=CBrCH_2Br$	**2c″**	**4** (1)	91	80 (*R*)
13	Et	$PhCH_2Br$	**2d**	**4** (1)	88	55 (*R*)
14		$PhCH_2Br$	**2d**	**3** (10)	63	87 (*S*)
15		$CH_2=CHCH_2Br$	**2d′**	**3** (10)	86	81 (*S*)
16		$CH_2=CBrCH_2Br$	**2d″**	**3** (10)	83	73 (*S*)

[a] Catalyst **4** exhibits higher activity than **3** and so can be used at lower loadings. Similar levels of enantioselectivity were obtained if 5 mol% of **4** was used.
[b] All ee's were determined by HPLC comparison with racemic samples.
[c] Stereochemical assignments (in parentheses) of products **2a** were established by comparison with authentic samples. Stereochemical assignments for products **2b**–**d** are assumed, based on those found for **2a**.

The results of this study are shown in Table 1. With the glycine imine *tert*-butyl ester **1a**, both catalysts gave similar levels of enantioselectivity in the reaction with benzyl bromide (entries 1, 2). This result is entirely expected based on previous studies involving these catalysts,[2] and served as a benchmark for the subsequent alkylation studies. With the benzhydryl and benzyl esters **1b** and **1c**, use of catalyst **4** resulted in significantly higher enantioselectivity in the test alkylation (entries 5–6, 9, 10), whereas the ethyl ester **1d** gave higher selectivity with catalyst **3** (entries 13, 14).

Follow up experiments involving alkylation of imine **1b** with allyl and 2-bromoallyl bromide suggest that this substrate, in conjunction with catalyst **4**, should give high enantiomeric excesses with a range of electrophiles. In contrast, benzyl and ethyl esters **1c** and **1d** gave variable results, but again high enantioselectivities could be obtained (80–90% ee and 73–87% ee respectively).

Overall these results suggest that all four glycine imine esters **1a**–**c** could have application in the enantioselective synthesis of α-amino acid derivatives, and that benzhydryl ester **1b** is an excellent alternative to the *tert*-butyl ester **1a**. To further probe this we examined the utility of ester **1b** in the synthesis of a differentially protected L-aspartic acid derivative **5** (Scheme 2). In order to achieve this, alkylation of imine **1b** with *tert*-butyl bromoacetate is required. In our experience, glycine imine alkylations involving this particular electrophile generally result in significantly lower levels of enantioselectivity than those obtained with other types of alkyl halide,[2] consequently this represents a useful test of the limitations of this methodology.



Scheme 2

Since the use of catalyst **4** appears to result in selectivity for the (*R*)-imines **2b**, access to the L-amino acid derivative **5** required use of its enantiomer (**ent-4**). Thus, alkylation of **1b** was investigated using this latter catalyst. Using our standard conditions,[9] the desired product **2b‴** was isolated in excellent yield and high enantiomeric excess (86% ee). The enantioselectivity of this alkylation could be further improved to 90% ee by employing $CsOH·H_2O$ as the base and running the alkylation at –78 °C[10] for 4 hours. In contrast, use of catalyst **3** gave low levels of selectivity (23% ee at 0 °C) illustrating the difficulties associated with obtaining high enantioselectivity in this particular alkylation. Hydrolysis of the imine function in **2b‴** then provided the desired aspartic acid derivative **5** in good overall yield (Scheme 2).

In conclusion, we have studied the asymmetric phase-transfer alkylation of a series of glycine imine esters and found that the benzhydryl esters can serve as a useful alternative to the more commonly employed *tert*-butyl esters. Exploitation of this in target synthesis is currently under investigation and will be reported in due course.

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(9) **Representative Procedure:** A solution of salt **ent-4** (1.2 mg, 1 mol%) and imine **1b** (50 mg, 0.12 mmol) in toluene (4 mL) was cooled to 0 °C, degassed, and placed under an argon atmosphere. *tert*-Butyl bromoacetate (22 μL, 0.14 mmol) was added followed by degassed 15 M aq KOH (1mL). The resulting mixture stirred at 1500 rpm for 45 min, then diluted with H_2O (5 mL) and extracted with EtOAc (3 × 4 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Residual *tert*-butyl bromoacetate was removed under vacuum (1 mm Hg, r.t.) to afford imine **2b‴** as a colourless oil (64 mg, 100%, 86% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62–7.60 (2 H, m, ArH), 7.41–7.23 (16 H, m, ArH), 7.16–7.13 (2 H, m, ArH), 6.89 (1 H, s, $OCHPh_2$), 4.58 (1 H, dd, *J* = 7.5, 5.5 Hz, H-2), 2.99 (1 H, dd, *J* = 15.5, 5.5 Hz, H-3a), 2.85 (1 H, dd, *J* = 15.5, 7.5 Hz, H-3b), 1.35 (9H, s, *t*-Bu). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.8 (C), 170.0 (C), 139.9 (C), 139.9 (C), 139.6 (C), 136.0 (C), 130.5 (CH), 129.0 (CH), 128.8 (CH), 128.5 (CH), 128.0 (CH), 128.0 (CH), 127.9 (CH), 127.4 (CH), 127.1 (CH), 80.8 (C), 77.5 (CH), 62.3 (CH), 39.5 (CH_2), 28.1 (CH_3). HPLC: Chiralpak AD column (150 × 2.1 mm), hexane/*i*-propanol (97.5/2.5), 0.2 mL/min, R_t = 13.9 min (*R*)-isomer, 18.8 min (*S*)-isomer.
Imine **2b‴** (38 mg) was then dissolved in THF (1 mL) and treated with 15% aq citric acid (1 mL). The resulting solution was stirred at r.t. for 3 h, then washed with Et_2O (3 × 2 mL). The aqueous layer was basified (sat. aq K_2CO_3) and extracted with $CHCl_3$ (3 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to afford amine **5** as a colourless oil (22 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.27 (10 H, m, ArH), 6.92 (1 H, s, $OCHPh_2$), 3.84 (1 H, dd, *J* = 6.5, 4.5 Hz, H-2), 2.80 (1 H, dd, *J* = 16.5, 4.5 Hz, H-3a), 2.72 (1 H, dd, *J* = 16.5, 6.5 Hz, H-3b), 1.88 (2 H, s, broad, NH_2), 1.38 (9 H, s, *t*-Bu). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.5 (C), 170.3 (C), 139.8 (C), 128.6 (CH), 128.6 (CH), 128.2 (CH), 128.1 (CH), 127.2 (CH), 127.2 (CH), 81.5 (C), 77.8 (CH), 51.6 (CH), 39.8 (CH_2), 28.1 (CH_3)

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