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PTC and organic bases–LiCl assisted alkylation of imidazolidinone–glycine iminic derivatives for the asymmetric synthesis of α-amino acids

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Abstract

Iminic derivatives of (4R,5S)-1,5-dimethyl-4-phenylimidazolidin-2-one and glycine **4** have been highly diastereoselectively alkylated with activated alkyl halides or electrophilic olefins either under PTC conditions or in the presence of the strong organic bases DBU or BEMP at -20° C in the presence of LiCl. Hydrolysis of the alkylated imino imides gave (S)- α -amino acids with recovery of the imidazolidinone chiral auxiliary. © 1998 Elsevier Science Ltd. All rights reserved.

The diasteroselective alkylation of chiral glycine enolates is generally carried out with strong anhydrous bases such as BuⁿLi, LDA or LHMDS and at very low temperatures.¹ Phase transfer catalysis (PTC) is the mildest reaction condition because K_2CO_3 or alkaline metal hydroxides can be used as bases.² However, this methodology requires the use of activated alkyl halides and iminic derivatives. PTC asymmetric alkylation can be carried out (a) with chiral acyclic benzophenone glycinate 1^3 or cyclic 2^4 and 3^5 derivatives or (b) with achiral iminic glycinates and chiral catalyst such as cinchoninium and cinchonidinium salts⁶ or TADDOL.⁷ Recently, strong organic bases such as Schwesinger's⁸ 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP)⁹ and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) have been used for the first time in the highly diastereoselective alkylation of alanine derived oxazine 2 with unactivated alkyl halides at room temperature in the presence of LiI affording, after hydrolysis, highly enantiomerically enriched α -methyl α -amino acids.¹⁰



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In connection with our project on the preparation of synthetically useful chiral glycine and alanine templates for the asymmetric synthesis of α -amino acids, we have found that (4*R*,5*S*)-1,5-dimethyl-4-phenylimidazolidin-2-one¹¹ is a good auxiliary¹² for the diastereoselective alkylation of the corresponding iminic glycine derivative **4a**.¹³ In this case, LHMDS or KOBu^t in the presence of LiCl at -78° C have to be used in the alkylation process, and the use of solid–liquid PTC conditions (K₂CO₃ or KOH, CH₃CN, tetrabutylammonium bromide) at room temperature promoted the cleavage of the *N*-acyl group. In this communication, we describe the diastereoselective alkylation and Michael addition reactions of imidazolidinone–glycine iminic reagents **4** under PTC and strongly basic conditions.

The studies on the alkylation of compounds $4a^{13}$ and $4b^{14,15}$ with allyl iodide (Scheme 1) under different reaction conditions have been summarized in Table 1 (entries 1–8). Both reagents behave in a similar fashion under the different conditions assayed. In the case of the benzophenone derivative 4b, yields for compound 7a are lower than for 6a due to partial deprotection observed during the purification step. For this reason, after the alkylation process the crude product 7a was transformed into amine 8a by extractive work-up with 0.5 N HCl and K₂CO₃ in order to deprotect the amino group. The solid–liquid PTC as well as the organic base-promoted alkylations with allyl iodide were carried out at -20° C in CH₃CN as solvent, thus avoiding hydrolysis of the *N*-acyl group.





The use of an excess of LiCl was found to be crucial in all cases for achieving high diastereoselection. For instance, a ca. 1:1 mixture of diastereomers was obtained when using BEMP as base in the absence of LiCl (Table 1, entry 6). We presume again¹³ that the presence of the lithium ion plays an important role in the structure of the enolate chelating both oxygen atoms and the nitrogen of the imine, thus blocking the conformational motion. LiOH was an adequate inorganic base for PTC conditions (Table 1, entries 1 and 2), again the reaction with K_2CO_3 failed (Table 1, entry 3). BEMP or DBU were used in a small excess (1.5 equiv.)¹⁶ and gave similar yields and diastereoselectivities but the reaction is faster with the later and is also more convenient from an economical point of view.

Reagent **4b** seems to be slightly superior to **4a** and avoids the use of the unpleasant carbon disulphide during the preparation. For these reasons, the reactions with other alkyl halides and the Michael addition with electrophilic olefins were carried out with **4b** (Table 1, entries 9–17). In general, better yields and diastereomeric excesses have been obtained with DBU–LiCl than with PTC conditions, whereas Michael addition with acrylates (Table 1, entries 16 and 17) afforded better diastereoselectivities with *tert*-butyl than with ethyl ester but with lower yield.

Hydrolysis¹⁷ of products **8a** (de: 98%) and **8b** (de: 96%) were carried out with LiOH in THF/H₂O affording the recovered chiral auxiliary imidazolidinones in 83 and 73% yield, respectively. The corres-

Entry	Reagent	\mathbf{E}^{+}	Base (Equiv) ^a		Product				
				t (h)	No.	Х	Yield (%) ^b	d.r ^c .	
1	4a	ICH ₂ CH=CH ₂	LiOH (3)	1	6a	CH ₂ CH=CH ₂	90	92:8	
2	4b	ICH ₂ CH=CH ₂	LiOH (3)	3.5	8a		80	93:7	
3	4b	ICH ₂ CH=CH ₂	$K_2CO_3(3)$	24	_ ^d		-	-	
4	4a	ICH ₂ CH=CH ₂	BEMP (1.5)	4	6a		87	89:11	
5	4 b	ICH ₂ CH=CH ₂	BEMP (1.5)	3.5	7a		60	99:1	
6	4b	ICH ₂ CH=CH ₂	BEMP (1.5) ^e	4	7a		10	50:50	
7	4 a	ICH ₂ CH=CH ₂	DBU (1.5)	1	6a		95	92:8	
8	4 b	ICH ₂ CH=CH ₂	DBU (1.5)	1	8a		86	99:1	
9	4 b	BrCH ₂ Ph	LiOH (3)	15	8b	CH ₂ Ph	57	93:7	
10	4b	(E)-BrCH ₂ CH=CO ₂ Me	LiOH (3)	3.5	8c	(E)-CH ₂ CH=CHCO ₂ Me	76	97:3	
11	4b	CH ₂ =CHCO ₂ Bu ^t	LiOH (3)	72	8d	$CH_2CH_2CO_2Bu^t$	25	97:3	
12	4b	$BrCH_2Ph$	DBU (1.5)	3	8b	CH ₂ Ph	73	98:2	
13	4b	(E)-BrCH ₂ CH=CO ₂ Me	DBU (1.5)	2	8c	(E)-CH ₂ CH=CHCO ₂ Me	78	98:2	
14	4b	BrCH ₂ C≡CH	DBU (1.5)	15	8e	CH ₂ C≡CH	69	99:1	
15	4 b	ICH ₂ CO ₂ Et	DBU (1.5)	3	8f	CH ₂ CO ₂ Et	86	98:2	
16	4b	CH ₂ =CHCO ₂ Et	DBU (1.5)	8	8g	CH ₂ CH ₂ CO ₂ Et	61	90:10	
17	4b	CH ₂ =CHCO ₂ Bu ^t	DBU (1.5)	4	8d	CH ₂ CH ₂ CO ₂ Bu ^t	32	97:3	

Table 1 Reaction conditions for the diastereoselective alkylation of imidazolidinone–glycine derivative **4**

^a All reactions were carried out at -20°C in dry CH₃CN in the presence of 6-8 equiv of LiCl.^b Yields based on starting material **4** after column chromatography (silica gel and silica gel deactivated with hexane/Et₃N 20/1 for **6a** and **7a**, respectively) or isolated crude yield after work-up for compounds **8**.^c Determined by GC for **6a** and by ¹H NMR (300 MHz) for **7** and **8**.^d The starting derivative **4b** was recovered.^e Without LiCl.

ponding α -amino acids **9a** and **9b** were obtained after ion exchange chromatography (Dowex) in 50 and 69% yield (based on starting iminic derivative **4b**, Scheme 1) and with 94 and 87% of ee,¹⁸ respectively.¹⁹

We conclude that PTC conditions or strong organic bases, especially DBU in the presence of LiCl, are very convenient conditions for the diastereoselective alkylation of iminic imidazolidinone–glycine reagents for the asymmetric synthesis of α -amino acids.

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- 13. Guillena, G.; Nájera, C. Tetrahedron: Asymmetry 1998, 9, 1125–1129.
- 14. The new iminic reagent **4b** was prepared in 45% yield by reaction of hydrochloride 5^{15} with benzophenone imine in CH₂Cl₂ at room temperature.



- 15. Prepared from (4R,5S)-1,5-dimethyl-4-phenylimidazolidin-2-one in 65% yield.¹³
- 16. In the case of alkylation of oxazine 2 a fivefold excess of DBU has to be used.¹⁰
- 17. Hydrolysis of **6a** (de: 88%) and **6b** (de: 90%) has been carried out with LiOOH providing α -amino acids **9a** and **9b** in 56 and 36% yield (based on compound **6**) and in 88 and 90% ee,¹⁸ respectively. The auxiliary was also recovered in good yields.¹³
- 18. Ees were analysed by HPLC using a Crownpak CR (+) column.
- 19. Slight partial racemization was observed during the hydrolysis.