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Investigation into the enantioselective protonation of enolate Schiff bases with (*R*)-pantolactone

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Abstract—The effect of several factors on the enantioselective protonation of the enolates of α-amino acid derivatives with (*R*)-pantolactone were studied. The highest stereoselectivity (74–76% e.e.) was generally observed by associating lithium chloride with LHMDS and by using the optimum temperature for the formation of the enolate.

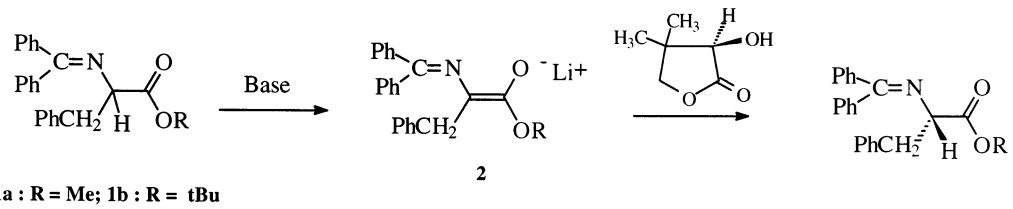
1. Introduction

In the last decade much effort has been devoted to the enantioselective protonation of prochiral enolates as reviewed by Fehr.[1] However this reaction, which provides direct access to chiral compounds, has only rarely been applied to α-amino acids.[2,3] Duhamel et al.[2] have performed an extensive study into the enantioselective protonation of α-amino acid derivatives, which involved deprotonation of the corresponding benzaldehyde Schiff bases using lithium amides, followed by addition of an acyl tartrate derivative as the homochiral proton source. The Duhamel group concluded that the nature of the proton source influenced the selectivity,[2b] the use of aldimino groups with an electron-donating substituent had a beneficial effect,[2c] and that the secondary amine liberated after metalation played a crucial role in proton transfer.[2d]

We have recently developed an efficient method for the synthesis of enantiomerically pure α-amino acids[4] by stereoselective addition of (*R*)-pantolactone to the corresponding prochiral ketenes. We then became interested in using this chiral alcohol for the enantioselective protonation of α-amino acid enolates since hydroxy esters have been reported to be efficient chiral proton sources. To our knowledge, (*R*)-pantolactone has until now been used only for the stereoselective protonation of prochiral ketones[5] and lactones.[6]

2. Results and discussion

We first studied the effect of several factors (type of base, reaction temperature and the presence of salts) which could affect the stereocontrol in the protonation of the benzophenone Schiff base phenylalanine ester



Scheme 1. Enantioselective protonation of the benzophenone Schiff base enolates with (*R*)-pantolactone.

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enolates **2** with (*R*)-pantolactone (Scheme 1). The results are shown in Table 1.

Deprotonation of the methyl ester **1a** at low temperature (−78°C over 30–90 minutes) with lithium diisopropylamide (LDA) or lithium hexamethyldisilazide (LHMDS) and under either kinetic[7a,8] or thermodynamic[7b,8] control, followed by reprotonation at −85°C with (*R*)-pantolactone afforded low to moderate enantiomeric excesses of 2–40% (entries 1–4). However, when the enolate was generated at higher temperatures (−40 to 0°C over 2 hours), a noticeable increase in the enantiomeric excess of the product was often observed (entries 5–9) and the best results were obtained using LHMDS (entries 8 and 9).

In order to control formation of the lithium enolate we first used TMSCl which, because it reacts even at −78°C, can be considered a good enolate trapping agent.[9] Proton NMR analysis after quenching the enolate form at −78°C with TMSCl indicated that only 10–15% of the corresponding silyl ketene actetal was obtained at this temperature instead of 80–85% when using higher temperatures. These experiments did not allow us to determine the (*E*)/(*Z*)-enolate composition. In addition, only a poor percentage of α-deuterated product was obtained using the Seebach method[10] (successive addition of one equivalent of *n*-BuLi and excess CH_3CO_2D deuterating agent) when the enolate was quenched at −78°C. Therefore, it can be assumed that incomplete deprotonation occurs at low temperature probably owing to high steric hindrance[11] and was thus responsible for the observed poor enantiomeric excesses.

Moreover, when using LHMDS or KHMDS as the base and with the same chiral proton source, the amino ester with (*S*)-configuration was predominantly formed (entries 7–10), whereas use of LDA under otherwise identical conditions gave rise to the (*R*)-enantiomer[12] (entries 2, 5 and 6). It is known that the reactivity of the enolate is further complicated by the existence in solution of higher aggregated species.[8e,10c,13] The secondary amine produced by deprotonation of the starting material with metal amide may become part of an aggregate and therefore influence the stereoselectivity in the protonation reaction.[10c,14] Among possible explanations it can be considered that hexamethyldisilazane, generated after deprotonation, ligates poorly to lithium in comparison to diisopropylamine because of its low basicity[10,14] and could promote direct chelation to the carbonyl group of the proton donor, thus giving rise to different stereoselectivity.

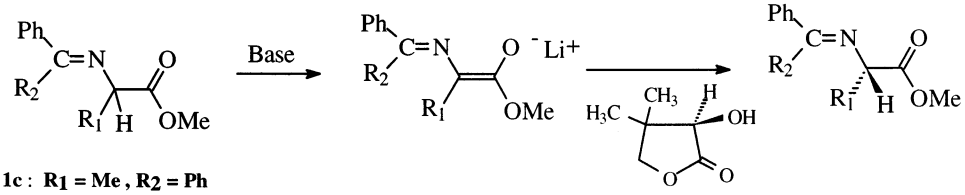
This inversion of selectivity associated only with a structural modification of the achiral base used has not been previously described in enantioselective protonation studies.

The addition of lithium salts (LiCl, LiBr), which must already be present during enolate generation,[13,15a] had no effect when LDA was used as the base (entry 11) whereas a remarkable enhancement of the stereoselectivity was obtained when using LHMDS (entries 12–14). It is known that added salts can change the stereoselectivity of the protonation reaction,[15] mainly by altering the aggregation states of the ion pairs and/or by forming mixed aggregates.

The presence of DMPU[16] as co-solvent had a deleterious effect on the stereoselectivity (entry 15). Furthermore, the enantiomeric excess decreased when the protonation step was conducted at −100°C (entry 16) whereas only a minor effect was observed at 0°C (entry 17). This may be related to the reduced rate of proton transfer occurring at lower temperature.[17] The enan-

Table 1. Enantioselective protonation of phenylalanine derivatives with (*R*)-pantolactone

Entry	Ester	Base	Additive	*T* enolate (°C)	*T* protonation (°C)	Config.	% e.e.
1	**1a**	LDA[7a]	-	−78	−85	(*R*)	10
2	**1a**	LDA[7b]	-	−78	−85	(*R*)	40
3	**1a**	LHMDS[7a]	-	−78	−85	(*S*)	8
4	**1a**	LHMDS[7b]	-	−78	−85	(*S*)	2
5	**1a**	LDA[7a]	-	−78→−40	−85	(*R*)	40
6	**1a**	LDA[7a]	-	−40→0	−85	(*R*)	40
7	**1a**	LHMDS[7a]	-	−78→−40	−85	(*S*)	30
8	**1a**	LHMDS[7a]	-	−40→0	−85	(*S*)	60
9	**1a**	LHMDS[7b]	-	−40→0	−85	(*S*)	58
10	**1a**	KHMDS[7a]	-	−40→0	−85	(*S*)	58
11	**1a**	LDA[7a]	LiCl (3 equiv.)	−40→0	−85	(*R*)	40
12	**1a**	LHMDS[7a]	LiCl (1 equiv.)	−40→0	−85	(*S*)	68
13	**1a**	LHMDS[7a]	LiCl (3 equiv.)	−40→0	−85	(*S*)	76
14	**1a**	LHMDS[7a]	LiBr	−40→0	−85	(*S*)	66
15	**1a**	LHMDS[7a]	DMPU	−40→0	−85	(*S*)	24
16	**1a**	LHMDS[7a]	LiCl (3 equiv.)	−40→0	−100	(*S*)	48
17	**1a**	LHMDS[7a]	LiCl (3 equiv.)	−40→0	0	(*S*)	66
18	**1b**	LDA[7a]	-	−40→0	0	(*S*)	14
19	**1b**	LHMDS[7a]	-	−78	0	(*S*)	2
20	**1b**	LHMDS[7a]	-	−40→0	0	(*S*)	42
21	**1b**	LHMDS[7a]	-	−40→0	0	(*S*)	72



1c : R_1 = Me , R_2 = Ph
1d : R_1 = Ph , R_2 = Ph
1e : R_1 = CH_2Ph , R_2 = H

Scheme 2. Enantioselective protonation of α-amino acid derivatives with (*R*)-pantolactone.

Table 2. Enantioselective protonation of amino acid derivatives with (*R*)-pantolactone

Entry	R_1	R_2	Base[7a,*]	Additive	Config.	% e.e.
1	Me	Ph	LDA	*	(*R*)	18
2	Me	Ph	LHMDS	*	(*S*)	34
3	Me	Ph	LHMDS	LiCl (3 equiv.)	(*S*)	76
4	Ph	Ph	LDA	*	(*R*)	12
5	Ph	Ph	LHMDS	*	(*R*)	20
6	Ph	Ph	LHMDS	LiCl (3 equiv.)	(*R*)	74
7	CH_2Ph	H	LDA	*	(*S*)	38
8	CH_2Ph	H	LHMDS	LiCl (3 equiv.)	(*S*)	54

* Enolate formation at −40 to 0°C; 2 h.

tioselective protonation at −85°C gave the highest enantiomeric excess. No improvement in stereoselectivity resulted from the use of the more sterically hindered *tert*-butyl ester **1b** (entries 18–21).

The same reaction with two other racemic amino acids was then studied (Scheme 2 and Table 2). In all cases as above, the best results were observed by associating LiCl with LHMDS and using the optimal temperature to form the enolate (Table 1, entry 12 and Table 2, entries 3 and 6).

However, it can be noted that in the case of phenylglycine (Table 2, entry 6), the configuration of the newly generated stereogenic center was opposite to that obtained with alkyl amino acids (Table 1, entry 12 and Table 2, entry 3). The importance of phenyl groups in the amino acid derivatives was also demonstrated by using a benzaldehyde Schiff base (Table 2, entries 7 and 8) instead of benzophenone (Table 1, entries 6, 8, 12 and 13) since in the benzaldehyde case neither of the bases used (LDA or LHMDS) caused any inversion of configuration.

In conclusion, we have shown that (*R*)-pantolactone can act as a proton source for the enantioselective protonation of enolate Schiff bases. By a suitable choice of the various parameters, either (*R*)- or (*S*)-α-amino acids can be selectively obtained with modest to high enantiomeric excess.

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