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(4*R*,5*S*)-1,5-Dimethyl-4-phenylimidazolidin-2-one as a chiral auxiliary for the diastereoselective alkylation of a new iminic glycine derivative: practical asymmetric synthesis of α-amino acids

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Abstract

The lithium enolate of enantiomerically pure *N*-[bis(methylthio)methylene] glycinate **11** derived from (4*R*,5*S*)-1,5-dimethyl-4-phenylimidazolidin-2-one reacts with alkyl halides giving the alkylated derivatives **12** with a high degree of control of the diastereoselectivity. These alkylated systems are easily hydrolyzed to the corresponding α-amino acids, the chiral auxiliary being recovered.

One of the most important strategies for the asymmetric synthesis of α-amino acids, based on carbon–carbon bond forming reactions, is the α-alkylation of chiral glycine enolates.[1] Imines derived from glycine are very useful reagents because they are easily enolizable under different reaction conditions, either with strong bases or under phase-transfer catalysis (PTC). In addition, the final hydrolysis to the corresponding α-amino acids can be carried out under mild reaction conditions. Several iminic glycine templates derived from different chiral auxiliaries have been reported.[2–8] Some representative examples are: (a) imino esters prepared from chiral carbonyl compounds such as 2-hydroxypinan-3-one (**1**[2] and **2**[3]) and camphor (**3**[4] and **4**[5]); (b) chiral amides prepared from 2,5-bis(methoxymethoxymethyl)pyrrolidine **5**[6] and sultam derivatives **6**[7]; and (c) chiral esters **7**[8] of 8-phenylmenthol and also of menthol,[8a] binaphthol,[8c] and carbohydrates.[8d]

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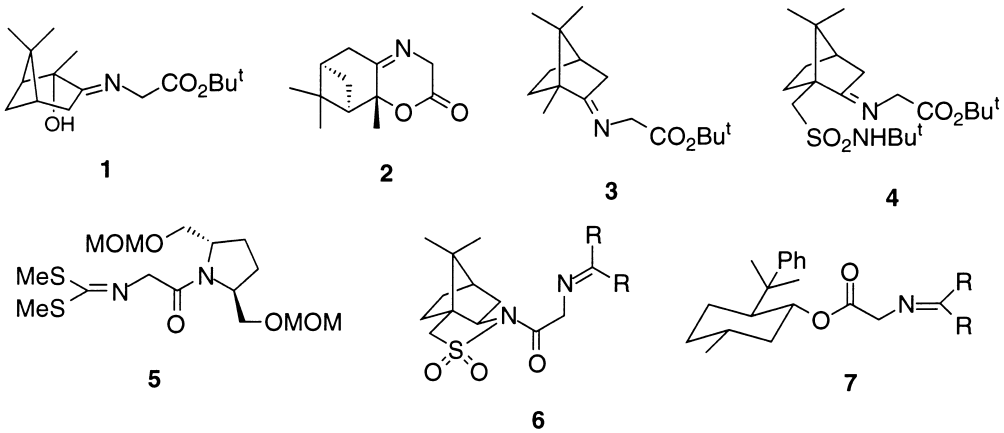
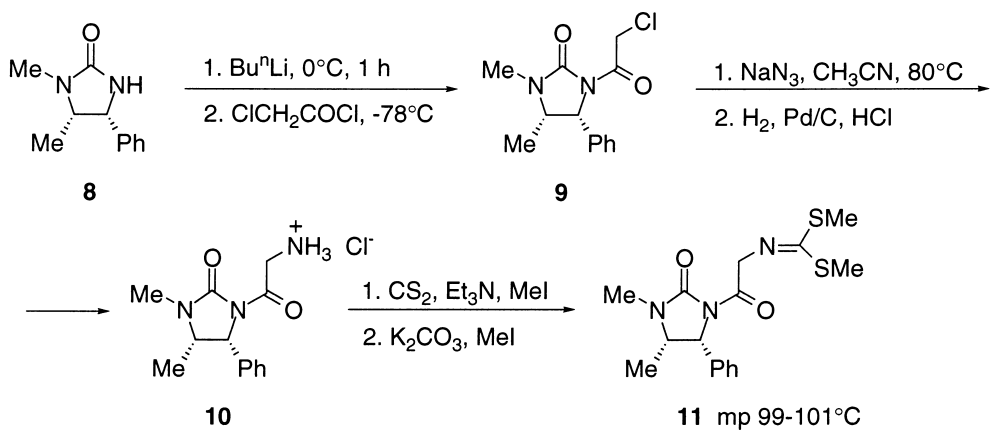


On the other hand, 1,5-dimethyl-4-phenylimidazolidin-2-ones, easily prepared from (+)- or (−)-ephedrinium chloride and urea,[9a] have proved to be good chiral auxiliaries.[9,10] Several *N*-allyl-[9] and *N*-acylimidazolidinones[10] have been used as useful reagents for diastereoselective homoaldol reactions,[9] alkylation of the corresponding enolates,[9b,10a,g] Michael additions,[10b,c,d,e,h] and Diels–Alder cycloaddition reactions.[10f] In the present communication we describe the preparation of a new chiral iminic glycine template derived from (4*R*,5*S*)-1,5-dimethyl-4-phenylimidazolidin-2-one and its application in the asymmetric synthesis of α-amino acids by diastereoselective alkylation of its enolate.

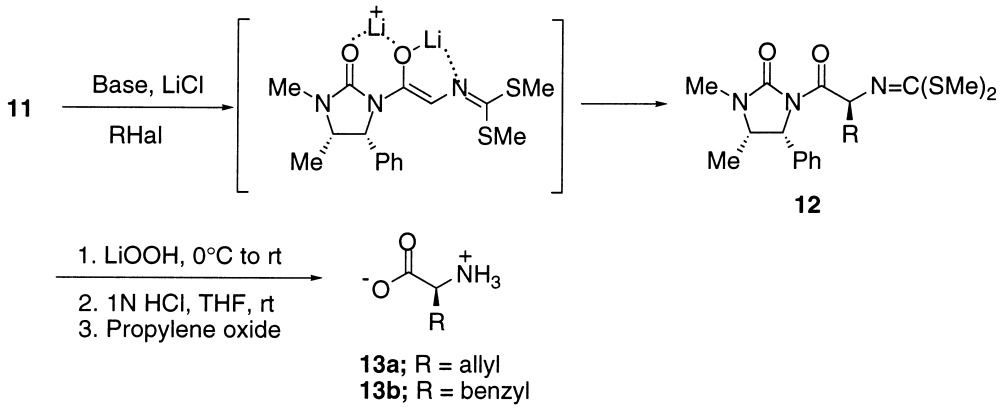
The preparation of the iminic glycine derivative **11** was carried out by acylation of (4*R*,5*S*)-1,5-dimethyl-4-phenylimidazolidin-2-one **8**[9b] with α-chloroacetyl chloride giving compound **9**[11] in 77% yield, which, after substitution with sodium azide[12] and hydrogenation[13] to the amine hydrochloride, afforded product **10** in 85% yield. Final formation of the *N*-[bis(methylthio)methylene]glycinate **11**[14,15] (50% yield) was carried out following a two-step procedure,[16] first by treatment with carbon disulfide and methyl iodide and subsequent reaction with methyl iodide in the presence of potassium carbonate (Scheme 1).



Scheme 1.

The alkylation process (Scheme 2) with allyl bromide was carried out in the presence of several bases, additives and reaction conditions, which have been summarized in Table 1. Since hydrolysis of the *N*-acyl group was mainly observed under solid–liquid PTC conditions (K_2CO_3 or KOH, CH_3CN, TBAB, rt, sonication), strong bases such as n-butyllithium, LDA, LHMDS and KOBu^t were used. The best chemical yields and diastereoselectivities were obtained with LHMDS or KOBu^t in THF and in the presence of

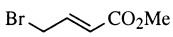
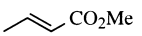
LiCl allowing the temperature to rise from −78 to −20 or 0°C in ca. 2.5 h (Table 1, entries 4 and 6). These reaction conditions were used with other alkyl halides in order to prepare products **12** (Scheme 2 and Table 1). In the case of alkyl bromides it was neccessary to also add LiI in order to prepare in situ the corresponding iodides. When the alkylating agent was not reactive enough we observed cleavage of the acylimidazolidinone bond of starting reagent **11** under the basic reaction conditions.



Scheme 2.

The strong influence of LiCl on the chemical yields of the alkylation process is probably due to the ability of lithium salts to change the degree of aggregation of the enolate, activation of electrophiles by the Lewis acid, Li^+, and also a general salt effect which changes the polarity of the solvent.[17] The

Table 1
Diastereoselective alkylation of imidazolidinone glycine derivative **11**

					Product			
Entry	Base (equiv)	Additive (equiv)	RHal	T (°C)	No.	R	Yield (%)[a]	d.r.[b]
1	n-BuLi (1)	DMPU	ICH_2CHCH_2	-78 to 0	**12a**	$CH_2CH{=}CH_2$	43	86:14
2	LDA (1)	DMPU		-78 to 0	**12a**		53	77:23
3	LHMDS (1)			-78 to 0	**12a**		55	79:21
4	LHMDS (1)	LiCl (6)		-78 to 0	**12a**		86	98:2
5	$KOBu^t$ (1.5)			-78 to -50	**12a**		45	85:15
6	$KOBu^t$ (3)	LiCl (6)		-78 to -20	**12a**		77	93:7
7	LHMDS (1)	LiCl (6)	ICH_2Ph	-78 to 0	**12b**	CH_2Ph	68	95:5
8	LHMDS (1)	LiCl (6)[c]	$BrCH_2Ph$	-78 to 0	**12b**		66	96:4
9	$KOBu^t$ (3)	LiCl (6)[c]		-78 to -20	**12b**		54	91:9
10	LHMDS (1)	LiCl (6)[c]	$BrCH_2C{\equiv}CH$	-78 to 0	**12c**	$CH_2C{\equiv}CH$	58	96:4
11	LHMDS (1)	LiCl (6)	$ICH_2CO_2Bu^t$	-78 to 0	**12d**	$CH_2CO_2Bu^t$	63	87:13
12	$KOBu^t$ (3)	LiCl (6)	ICH_2CO_2Et	-78 to 0	**12d**	CH_2CO_2Et	76	73:27
13	LHMDS (1)	LiCl (6)[c]		-78 to 0	**12e**		70	93:7[d]

[a] Isolated yield after column chromatography (silica gel), based on compound **11**. [b] Determined by HPLC. [c] Lithium iodide (3 equiv) was also added. [d] Determined by ^1H NMR (300 MHz).

increasing effect on the diastereoselectivity can be due to an intramolecular chelation in the intermediate enolate, favouring the attack of the electrophile at the *Si* face (Scheme 2).

When representative alkylated imidazolidinones **12a** (de: 88%) and **12b** (de: 90%) were hydrolyzed with LiOOH in THF/H_2O,[18] the chiral auxiliary was recovered in more than 90% yield. After deprotection of the imine with 1 N HCl and treatment of the resulting chlorhydrate with propylene oxide, (*S*)-allylglycine (**13a**)[19] and (*S*)-phenylalanine (**13b**) were obtained in 56 and 36% yield (based on compound **11**) and in 88 and 90% ee,[20] respectively.

We conclude that the iminic glycine derivative **11**, easily prepared from the recoverable auxiliary (4*R*,5*S*)-1,5-dimethyl-4-phenylimidazolidin-2-one, is an adequate starting chiral template for the asymmetric synthesis of α-amino acids.

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