New Oxazinone and Pyrazinone Derivatives as Chiral Reagents for the Asymmetric Synthesis of α-Amino Acids

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Introduction.

The synthesis of nonproteinogenic α-amino acids in enantiopure form is an important goal nowadays due to their increasing role in biology and chemistry [1]. They are present in natural and pharmacologically active compounds, are enzyme inhibitors, neurotoxins, metal chelators, make peptides resistant to enzymatic degradation and have conformational-inducing properties in designed peptides and proteins. They can also be used as precursors of biologically active compounds and many other synthetic applications [2]. They can be classified as monoalkylated and dialkylated α-amino acids according to the substitution at the α-position. Allylic, arylic and vinylic glycines, heterocyclic and *N*-methyl α-amino acids (NMAAs) are important types of monoalkylated amino acids. Quaternary systems can be acyclic such as allylic, arylic and vinylic alanines as well as heterocyclic, cyclic and bicyclic derivatives (Figure 1). Specially, α-methyl-α-amino acids (AMAAs) are important members of this family, showing a vast array of biological properties. In spite of their importance, there is a lack of commercially available enantiopure AMAAs which is probably due, in part, to the nonexistence of a general and economical large scale synthesis for these compounds.

The established methods for the asymmetric synthesis of α-amino acids affecting carbon-carbon bond formation are electrophilic and nucleophilic alkylations and Strecker synthesis. For the carbon-nitrogen bond formation, nucleophilic and electrophilic amination are used (Scheme 1). Among these methods, the asymmetric alkylation of chiral glycine or alanine anion equivalents is one of the most general strategies used, specially for AMAAs.

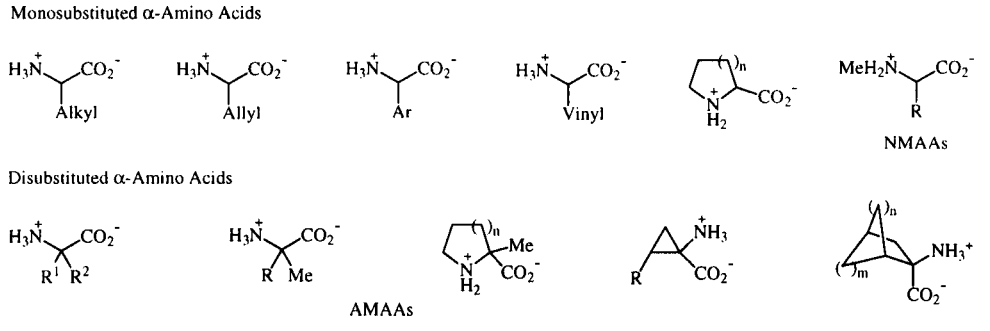
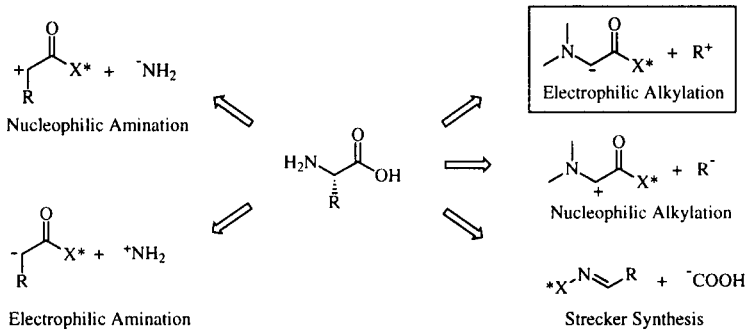
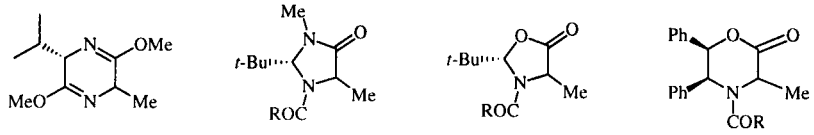


Figure 1. Nonproteinogenic α-Amino Acids.

Scheme 1
Retrosynthetic Analysis of Chiral α-Amino Acids



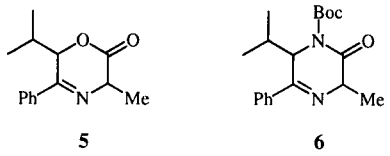
The alkylation of chiral cyclic alanine templates, such as bislactim ethers **1** [3], imidazolidinones **2** [4], oxazolidinones **3** [5] and oxazinones **4** [6] is the most efficient methodology for the preparation of AMAAs with high diastereofacial enolate preference (Figure 2). However, the alkylation step requires the use of strong bases (butyllithium, lithium diisopropylamide, lithium hexamethyldisilazide, potassium *tert*-butoxide, *etc.*), very anhydrous conditions and low temperatures. These strict reaction conditions as well as the difficulties in the hydrolysis of α,α-dialkylated α-amino acids make the development of new alanine templates, which use simpler and milder reaction conditions, highly desirable.



1 **2** **3** **4**

Figure 2.

Phase transfer catalytic (PTC) alkylation has been carried out with alanine-aromatic aldehyde imines using ammonium salts (up to 50% *ee*) [7] or 2,2-dimethyl-α,α,α',α'-tetraphenyl-1,3-dioxolane-4,5-dimethanol (TADDOL) (up to 82% *ee*) [8] as chiral catalysts. Glycine-Schiff base derivatives have also been allylated under mild reaction conditions with allylic carbonates and palladium(0) as catalysts [9]. These mild reaction conditions can only be used with this type of soft enolates. In this context, we focused our attention on heterocyclic alanine derivatives with structure of 3,6-dihydro-2*H*-1,4-oxazin-2-ones **5** and of 1,2,3,6-tetrahydropyrazin-2-ones **6** (Figure 3). These heterocycles have an easily hydrolyzable conjugated phenylimine moiety with a presumably highly acidic C3-hydrogen. They also have a stereogenic center at the C6-position with an isopropyl group, which can block one of the diastereomeric faces of the formed enolate and generate intraannular 1,4-asymmetric induction. These structural features would make these systems appropriate for working under mild, simple, and therefore easily scalable conditions in the synthesis of α-methyl-α-amino acids (AMAAs).



5 **6**

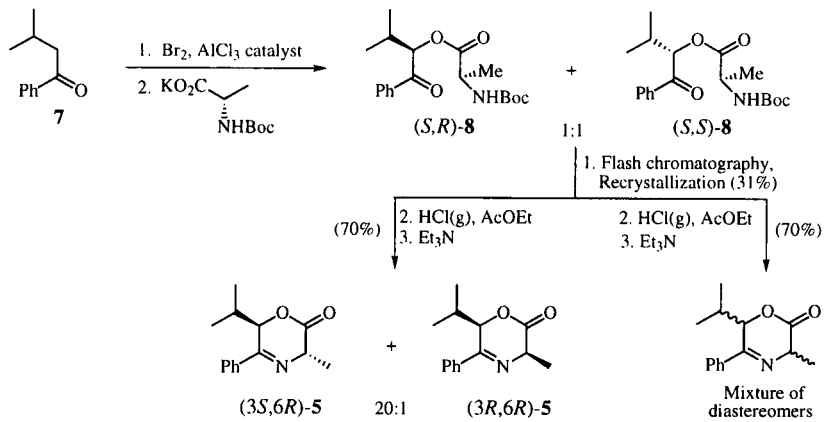
Figure 3.

I. Alanine-Derived Oxazin-2-ones.

For the preparation of alanine-derived oxazin-2-ones, the procedure described by Sunjic *et al.* [10] was modified as described in Scheme 2 [11,12]. α-Bromoisovalerophenone, prepared by $AlCl_3$-catalyzed bromination of isovalerophenone (**7**), was allowed to react with the potas-

Scheme 2

Synthesis of Alanine Derived Oxazinones



sium salt of *N*-Boc-(*S*)-alanine to afford a *ca.* 1:1 mixture of diastereomeric esters **8**. After separation by flash chromatography and crystallization, pure isomer (*R,S*)-**8** and (*S,S*)-**8** were both obtained in 31% yield. Deprotection of ester (*R,S*)-**8** with hydrogen chloride in ethyl acetate (EtOAc) and further treatment with triethylamine (Et_3N) afford oxazin-2-ones (6*R*)-**5** in 70% yield as a 20:1 mixture of *trans:cis* diastereomers. This is a consequence of the tendency of C3 to epimerization due to the predicted high acidity of H3. The configurational stability, which is the key for the 1,4-asymmetric induction on C3 could not be kept in the case of ester (*S,S*)-**8** and epimerization at C6 was also observed during the cyclization step. This fact made oxazinone (6*S*)-**5** unsuitable for the synthesis of (*R*)-α-methyl-α-amino acids.

The *trans* isomer (3*S*,6*R*)-**5** could be isolated in crystalline form and its structure was determined by nOe experiments and X-ray diffraction analysis [11] (Figure 4). From the structure it can be observed that in the boat conformation, the phenyl group forces the isopropyl group into an axial position, thus blocking one of the faces of the oxazinone. Semiempirical calculations (AM1) were carried out on a model lithium enolate of (6*R*)-**5** corroborating the blocking effect of the isopropyl group.

The easiness of enolate formation on oxazinones **5** was demonstrated when the *ca.* 1:20 *cis:trans* mixture of (6*R*)-**5** was diastereomerically alkylated with activated halides under solid-liquid PTC reaction conditions (Scheme 3, Table 1). The cyclic structure of this alanine-ketone Schiff base derivative allowed this PTC-induced alkylation,

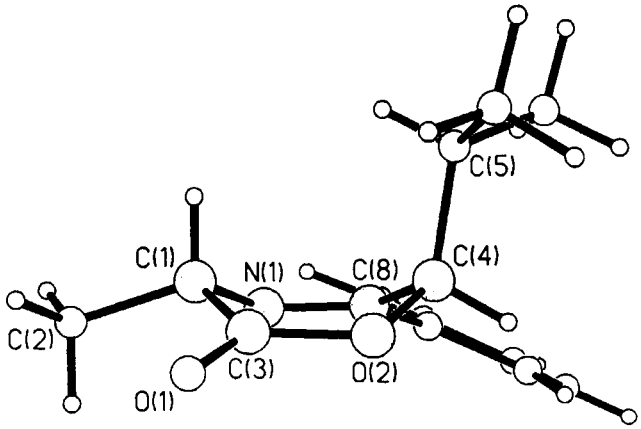
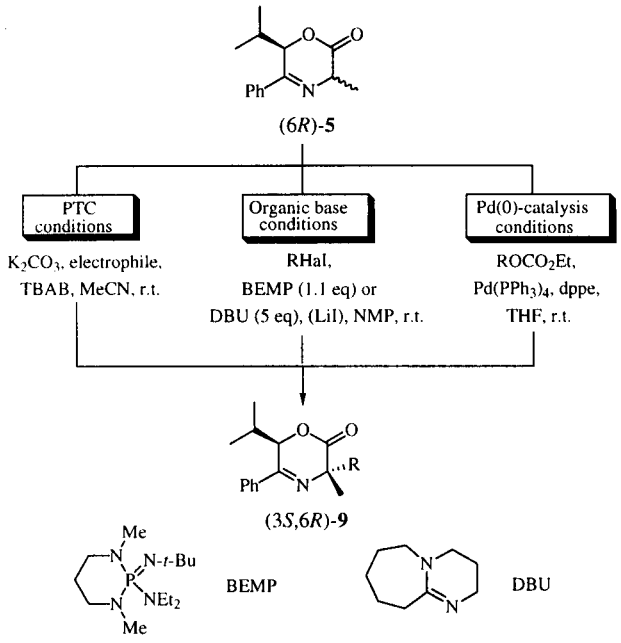


Figure 4. X-Ray Structure of Oxazinone (3*S*,6*R*)-**5**

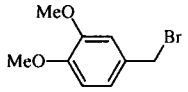
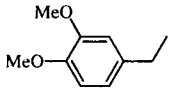
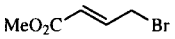
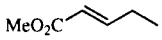
Scheme 3
Alkylation of Alanine Derived (6*R*)-Oxazinones



which has been only previously achieved in the case of racemic alanine-aldehyde Schiff base derivatives [7,8]. Oxazinones (3*S*,6*R*)-**9** such as the precursor of (*S*)-α-methyl-DOPA (Table 1, entry 4) were diastereoselectively obtained at room temperature using potassium carbonate as base and tetrabutylammonium bromide (TBAB) as phase transfer catalyst in acetonitrile as solvent. Allyl, propargyl and benzyl halides and ethyl iodoacetate, as well as paraformaldehyde and methyl acrylate have been used as electrophiles. Yields of isolated oxazinones were in some cases moderate due to the partial decomposition observed during the chromatographic purification. The proposed configuration was confirmed by nOe experiments and in the case of the propargyl derivative **9b** also by X-ray diffraction analysis [11].

In the case of activated alkyl halides, the use of PTC conditions or anhydrous bases (*e.g.*, lithium diisopropylamide, lithium hexamethyldisilazide, potassium *tert*-butoxide, and sodium hydride) at low temperature afforded no alkylation products. However, when strong organic bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and Schwesinger's 2-*tert*-butylimino-2-diethyl-

Table 1
Diastereoselective Alkylation of (6*R*)-**5** under PTC Conditions

Entry	Electrophile	R	Time (hours) [a]	Product **9**, % yield [b]	% *de* [c]
1	CH_2=$CHCH_2I$	CH_2=$CHCH_2$	24	(6*R*)-**9a**, 62	92
2	HC≡CCH_2Br	HC≡CCH_2	12	(6*R*)-**9b**, 70	>96
3	$PhCH_2Br$	$PhCH_2$	8	(6*R*)-**9c**, 75	>96
4			12	(6*R*)-**9d**, 75	90
5			12	(6*R*)-**9e**, 68	84
6	EtO_2CCH_2I	EtO_2CCH_2	24	(6*R*)-**9f**, 60	90
7	$(CH_2O)_n$	$HOCH_2$	12	(6*R*)-**9g**, 63	60
8	CH_2=$CHCO_2Me$	$MeO_2CCH_2CH_2$	12	(6*R*)-**9h**, 60	90

[a] Monitorized by GLC; [b] Isolated yield for the pure major diastereomer after flash chromatography; [c] Determined by ^{1}H nmr (300 MHz) and/or GLC for the reaction crude.

amino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) [12,13] were used at room temperature in 1-methyl-2-pyrrolidinone (NMP) the alkylation took place with *de* higher than 96% (Scheme 3 and Table 2). NMP was the solvent of choice in order to avoid competitive *O*-alkylation of the enolate. The addition of lithium iodide also diminished the amount of the *O*-alkylation by-products (Table 2, entries 6/7, 15/16, or 21/22) and allowed the use of an alkyl bromide as electrophile (Table 2, entry 8). The reaction took place in shorter reaction times than when using PTC conditions but with lower yields. In general, higher yields of (6*R*)-**9** were obtained when using 1.1 equivalents of BEMP as base than with DBU, which needs the use of 5 equivalents for completion [12,13].

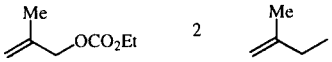
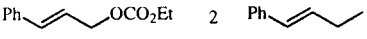
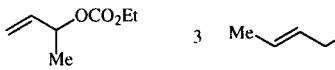
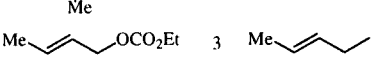
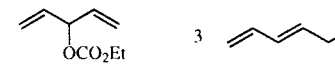
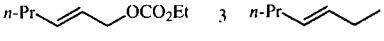
Table 2
Diastereoselective Alkylation of Oxazinones (6*R*)-**5** under Organic Base Conditions

Entry	RHal	Base,LiI (equivalents)	Solvent	Time (hours) [a]	*C*/*O*-Alkylation ratio [b]	Product (6*R*)-**9** [c] % yield [d]
1	EtI	BEMP, LiI (1.2)	NMP	1	25/1	(6*R*)-**9i**, 55
2	*i*-PrI	BEMP, LiI (1.2)	NMP	1	24/1	(6*R*)-**9j**, 48
3	*n*-BuI	BEMP	THF	12	5/3	(6*R*)-**9k**, 38
4	*n*-BuI	BEMP	DMF	1	9/1	(6*R*)-**9k**, 56
5	*n*-BuI	BEMP	MeCN	1	10/1	(6*R*)-**9k**, 58
6	*n*-BuI	BEMP	NMP	1	17/1	(6*R*)-**9k**, 64
7	*n*-BuI	BEMP, LiI (1.1)	NMP	1	50/1	(6*R*)-**9k**, 65
8	*n*-BuBr	BEMP, LiI (2)	NMP	1	1/0	(6*R*)-**9k**, 38
9	*i*-BuI	BEMP, LiI (1.5)	NMP	1	1/0	(6*R*)-**9l**, 45
10	$Ph(CH_2)_2I$	BEMP, LiI (1.5)	NMP	1	1/0	(6*R*)-**9m**, 52
11	$ClCH_2I$	BEMP	NMP	1	1/0	(6*R*)-**9n**, 57 [e]
12	CH_2=$CHCH_2Cl$	BEMP	NMP	1	1/0	(6*R*)-**9a**, 38
13	$PhCH_2Cl$	BEMP	NMP	1	5/1	(6*R*)-**9c**, 44
14	EtI	DBU	NMP	1	50/1	(6*R*)-**9i**, 53
15	*i*-PrI	DBU	NMP	1.75	5/1	(6*R*)-**9j**, 46
16	*i*-PrI	DBU, LiI (1.2)	NMP	1.25	100/1	(6*R*)-**9j** 33
17	*n*-BuI	DBU	NMP	1	25/1	(6*R*)-**9k**, 53
18	*i*-BuI	DBU	NMP	2.5	10/1	(6*R*)-**9l**, 28
19	$ClCH_2I$	DBU	NMP	1.25	1/0	(6*R*)-**9n**, 52
20	CH_2=$CHCH_2Cl$	DBU	NMP	1	1/0	(6*R*)-**9a**, 37
21	$PhCH_2Cl$	DBU	NMP	1	5/1	(6*R*)-**9c**, 43
22	$PhCH_2Cl$	DBU, LiI (1.2)	NMP	1	1/0	(6*R*)-**9c**, 45

[a] Monitored by GLC; [b] Determined by ^{1}H nmr (300 MHz) and/or GLC; [c] Diastereomeric ratio >98:2: determined by ^{1}H nmr (300 MHz) and/or GLC of the reaction crude; [d] Isolated yield of the major diastereomer (6*R*)-**9** after flash chromatography; [e] Neutral silica gel was used.

Oxazinones (6*R*)-**5** were easy and diastereoselectively alkylated using allylic carbonates under mild neutral Pd(0) catalysis [9] at room temperature in THF as solvent (Scheme 3, Table 3). The reaction can be carried out in the presence of catalytic amounts of tetrakis(triphenylphosphine) palladium(0) (5 mol%) and 1,2-bis(diphenylphosphino)ethane (dppe) (14 mol%) or of palladium(II) acetate (5 mol%) and triphenylphosphine (10 mol%) (Table 3, entry 2). In the case of unsymmetrical allylic carbonates a lack of regioselectivity was observed (Table 3, entries 4-7), although the major regioisomer was easily purified by flash chromatography [11,12].

Table 3
Diastereoselective Allylation of (6*R*)-**5** under Pd(0) Catalysis

Entry	$ROCO_2Et$	Time (hours)	R	Product (6*R*)-**9**, % yield [a]	% *de* [b]
1		2		(6*R*)-**9a**, 60	>96
2 [c]		12		(6*R*)-**9a**, 69	>96
3		2		(6*R*)-**9o**, 65	>96
4		2		(6*R*)-**9p**, 53 [d]	82
5		3		(6*R*)-**9q**, 65 [e]	84
6		3		(6*R*)-**9q**, 60 [e]	84
7		3		(6*R*)-**9r**, 56 [f]	70
8		3		(6*R*)-**9s**, 53	88

[a] Isolated yield of the major regio- and diastereomer after flash chromatography; [b] Determined by ^1H nmr (300 MHz) and/or GLC on the reaction crude; [c] A mixture of palladium(II) acetate (5 mol%) and triphenylphosphine (10 mol%) was used as catalyst; [d] A 28% of the other regioisomer was also detected (^1H nmr); [e] A 13% of the other regioisomer was also detected (^1H nmr); [f] A 21% of the other regioisomer was also detected (^1H nmr).

Representative oxazinones (6*R*)-**9** were hydrolyzed by treatment with 6 *M* hydrochloric acid at 150° in a pressure tube and subsequently refluxed with propylene oxide in ethanol affording the corresponding free and highly enantiomerically enriched (*S*)-AMAAs **10** (Scheme 4 and Table 4). In the case of allylated oxazinones, a milder cleavage was used. The imine group of oxazinone **9a** was hydrolyzed with 2 *M* hydrochloric acid in THF and the ester group with lithium hydroxide in aqueous THF. Subsequent Dowex chromatography gave (*S*)-α-allylalanine in 57% yield and 93% *ee*. Attempts to recover the chiral α-hydroxyisovalerophenone failed because of decomposition, in the case of 6 *M* hydrochloric acid hydrolysis, and racemization using the stepwise methodology [11,12].

Scheme 4
Hydrolysis of (6*R*)-Oxazinones: Synthesis of (*S*)-AMAAs

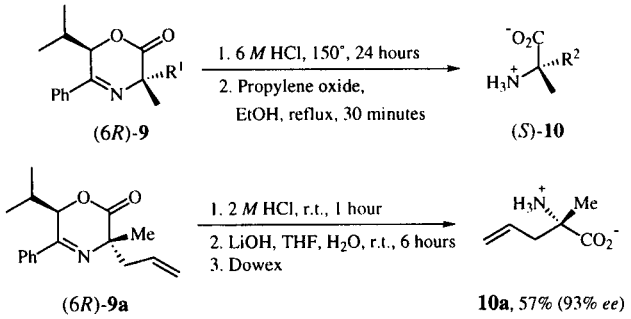


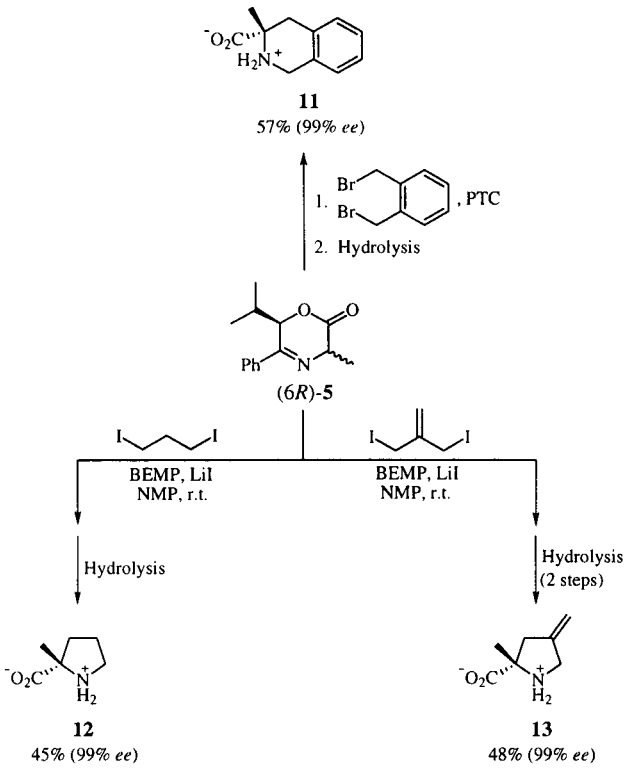
Table 4
Hydrolysis of Oxazinones (6*R*)-**9**.
Synthesis of (*S*)-α-Methyl α-Amino Acids **10**

Entry	R^1	Substrate (6*R*)-**9**	R^2	Product **10**, % yield [a]	% *ee* [b]
1	$PhCH_2$	(6*R*)-**9c**	$PhCH_2$	(*S*)-**10c**, 80	98
2	EtO_2CCH_2	(6*R*)-**9f**	HO_2CCH_2	(*S*)-**10f**, 78	92
3	$HOCH_2$	(6*R*)-**9g**	$HOCH_2$	(*S*)-**10g**, 75	58
4	$MeO_2C(CH_2)_2$	(6*R*)-**9h**	$HO_2C(CH_2)_2$	(*S*)-**10h**, 70	90
5	*i*-Bu	(6*R*)-**9l**	*i*-Bu	(*S*)-**10l**, 72	99

[a] Referred to oxazinone (6*R*)-**9**; [b] Determined by comparison with [α] values reported in the literature.

For the synthesis of cyclic α-methyl-α-amino acids, dihalides were used as alkylating agents. In the case of solid-liquid PTC conditions *o*-dibromomethylbenzene was allowed to react with (6*R*)-**5** affording, after hydrolysis, the tetrahydroisoquinoline amino acid **11** in 58% yield and 99% *ee* (Scheme 5). The reaction with 1,3-diiodopropane or 3-iodo-2-iodomethyl-1-propene was carried out using BEMP as base in the presence of lithium iodide at room temperature. Final hydrolysis of the *N*,α-dialkylated oxazinones gave the corresponding enantiomerically pure prolines **12** or **13** in 45 and 48% yield, respectively (Scheme 5) [12,13].

Scheme 5
Synthesis of Cyclic (*S*)-AMAAs



The corresponding enantiomeric (*R*)-AMAAs were obtained starting from (*R*)-alanine as chiral source. Oxazinones (6*S*)-**5** were prepared following the same synthetic route indicated on Scheme 2 [12]. Their alkylation under PTC or BEMP conditions affords oxazinones (6*R*)-**8** and, after hydrolysis, (*R*)-α-methyl-α-amino acids **10** are generated (Scheme 6 and Table 5).

Scheme 6
Asymmetric Synthesis of (*R*)-AMAAs

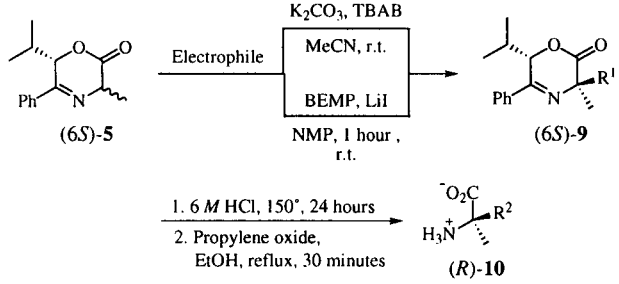


Table 5
Synthesis of (*R*)-α-Methyl-α-Amino Acids from (6*S*)-**5**

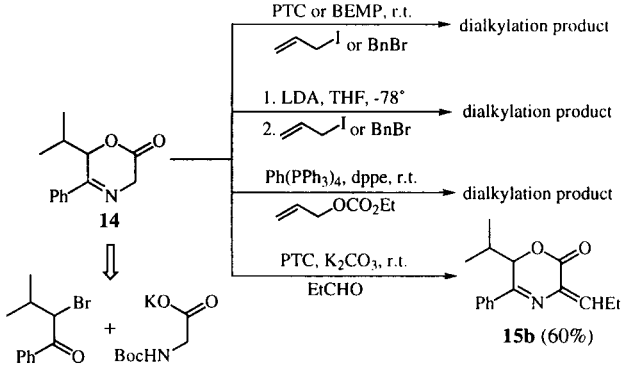
Entry	Electrophile	Product **9**, % yield [a] (% *de*) [b]	R^2	Product **10**, % yield [c] (% *de*) [d]
1 [e]	$PhCH_2Br$	(6*S*)-**9c**, 75 (>96)	CH_2Ph	(*R*)-**10c**, 76 (98)
2 [e]	ICH_2CO_2Et	(6*S*)-**9f**, 65 (90)	CH_2CO_2H	(*R*)-**10f**, 80 (93)
3 [e]	$CH_2{=}CHCO_2Me$	(6*S*)-**9h**, 59 (90)	$CH_2CH_2CO_2H$	(*R*)-**10h**, 66 (92)
4 [f]	EtI	(6*S*)-**9i**, 60 (96)	Et	(*R*)-**10i**, 89 (97)

[a] Isolated yield of pure major diastereomer after flash chromatography; [b] Determined by ^1H nmr (300 MHz) and/or GLC on the reaction crude; [c] Referred to oxazinone **9**; [d] Determined by comparison with [α] values reported in the literature; [e] PTC conditions; [f] Organic base conditions (BEMP).

II. Glycine Derived Oxazin-2-one.

Racemic oxazin-2-one **14** was prepared by reaction of α-bromoisovalerophenone with the potassium salt of *N*-Boc-glycine followed by deprotection with hydrogen chloride and cyclization with triethylamine. Preliminary studies about the reactivity of this oxazinone with allyl iodide or benzyl bromide under PTC, BEMP and LDA conditions as well as with allyl ethyl carbonate under palladium catalysis, afforded 3,3-dialkylated oxazinones. However, when oxazinone **14** was allowed to react with propanal under PTC conditions a condensation reaction took place affording the didehydroamino acid (DDAA) derivative **15b** (Scheme 7) [15].

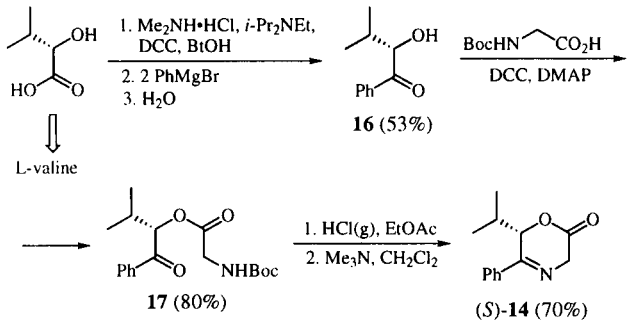
Scheme 7
Reactivity of Glycine Derived Oxazinone



The reactivity of chiral didehydroamino acid (DDAA) derivatives in hydrogenation, cyclopropanation, Michael additions and cycloadditions allows the asymmetric synthesis of different types of α-amino acids [1]. The easy preparation of compound **15b** prompted us to prepare the enantiomerically pure derivative of oxazinone **14** in order to obtain the homochiral DDAA derivatives **15**.

The chiral glycine template (6*S*)-oxazinone **14** was prepared by reaction of (*S*)-2-hydroxyisovalerophenone (**16**) with *N*-Boc-glycine in the presence of 1,3-dicyclohexylcarbodiimide (DCC) providing ester **17**. Final deprotection cyclization sequence gave oxazinone (6*S*)-**14** in 56% overall yield. The synthesis of the chiral auxiliary **16** was carried out from (*S*)-2-hydroxyisovaleric acid, commercially available or easily prepared from L-valine, by addition of phenylmagnesium bromide to its dimethylamide (Scheme 8) [15].

Scheme 8
Synthesis of Chiral Glycine Oxazinone



The reaction of oxazinone (6*S*)-**14** with aldehydes under solid-liquid PTC conditions, using potassium carbonate as base and tetrabutylammonium bromide as the catalyst in acetonitrile at room temperature, provide stereoselectively (*Z*)-DDAA in 96% *de*, the pure (*Z*)-isomers **15** being isolated after flash chromatography (Scheme 9 and Table 6). In the case of benzaldehyde, the reaction was carried out at 0° in order to avoid partial isomerization of the double bond to an *endo* conjugated position.

Scheme 9
Synthesis of Chiral Oxazinone DDAA Derivatives

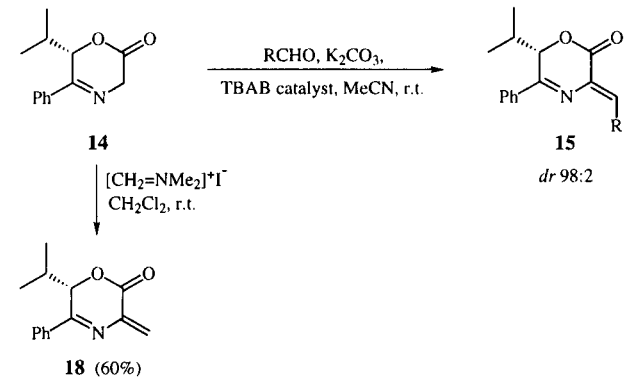


Table 6
Synthesis of Chiral Oxazinone DDAA Derivatives **15**

Entry	R	No.	Time (hours)	% Yield [a]
1	Me	**15a**	12	50
2	Et	**15b**	12	55
3	*i*-Pr	**15c**	12	63
4	*t*-Bu [b]	**15d**	40	62
5	Ph	**15e**	8 [c]	64

[a] Based on compound **14**; [b] 2 Equivalents of pivalaldehyde were used; [c] The reaction was carried out at 0°.

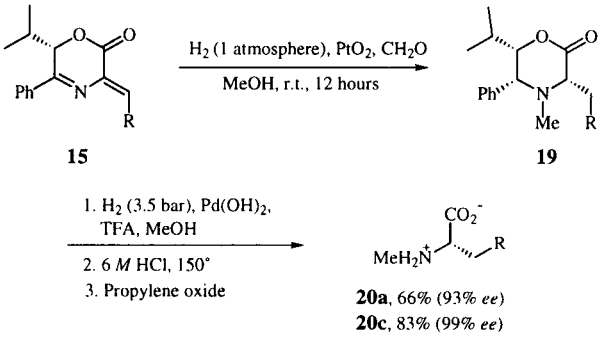
Configurational assignments for compounds **15** were made from ^{1}H nmr spectra of crude *Z*/*E* diastereomeric mixtures, with chemical shifts for the olefinic protons ranging between 6.74 and 7.00 ppm for (*Z*)-isomers and lower values (6.48-6.73 ppm) for (*E*)-isomers. Also the vicinal CH coupling constants are closed to 5 Hz in proton-coupled ^{13}C nmr, which is typical of a *Z*-configuration. The assignment of the *Z* stereochemistry was unequivocally established for **15a** by X-ray crystallographic analysis [15].

The methylene derivative **18** was obtained by reaction of the *in situ* generated (6*S*)-**14** with *N*,*N*-dimethylmethyleneammonium iodide (Eschenmoser's salt) in methylene chloride at room temperature (Scheme 9) in 50% yield based on ester **17**.

The hydrogenation of these DDAA derivatives in the presence of formaldehyde could be a direct strategy for the synthesis of important *N*-methyl α-amino acids. These family of α-amino acids are constituents of various peptides and depsipeptides isolated from plant strains, microorganisms and marine species. They can also be incorporated into strategic positions of peptides leading to enhance proteolytic stability to an increase in lipophilicity and to profound conformational changes [16].

Thus, when DDAA derivatives **15** were submitted to hydrogenation with platinum oxide as catalyst in methanol at room temperature and atmospheric pressure

Scheme 10
Hydrogenation of Oxazinone DDAA Derivatives:
Synthesis of (*S*)-NMAAs



for 30 minutes in the presence of aqueous formaldehyde, all-*cis* oxazinones **19** were stereoselectively obtained (Scheme 10 and Table 7). Their configuration was determined by ^1H nmr and by X-ray diffraction analysis of **19d** [17].

Table 7
Hydrogenation of Oxazinone DDAA Derivatives **15**

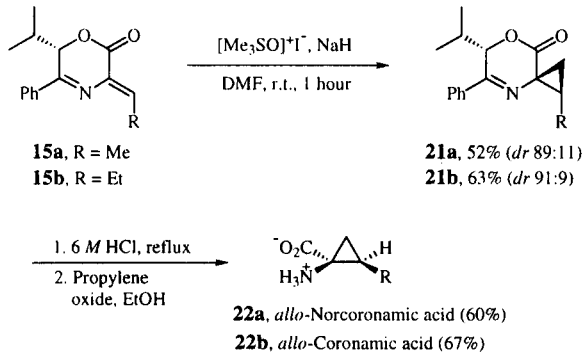
Entry	R	No.	*dr* [a]	% Yield [b]
1	Me	19a	98:2	72
2	*i*-Pr	19c	97:3	70
3	*t*-Bu	19d	95:5	63 [c]
4	Ph	19e	91:9	75

[a] Determined by GC for (3*S*,5*R*,6*S*) and (3*R*,5*R*,6*S*) diastereomers; [b] Isolated yield after flash chromatography based on compound **15**; [c] After crystallization.

Saturated oxazinones **19a** and **19b** were submitted to hydrogenolysis at 3.5 bar with palladium(II) hydroxide as the catalyst in the presence of trifluoroacetic acid (TFA) in aqueous methanol [18] in order to cleave the benzylic amine. Final hydrolysis under refluxing 6 *M* hydrochloric acid and treatment with propylene oxide afforded *N*-methyl α-amino acids **20a** and **20c** in 66 and 83% overall yields, respectively (Scheme 10) [17].

The cyclopropanation reaction of oxazinone DDAA derivatives has been applied to the asymmetric synthesis of 1-aminocyclopropanecarboxylic acids (ACCs). Thus, oxazinones **15** were easily and diastereoselectively cyclopropanated using Corey's dimethylsulfoxonium methylide [15]. After reaction of **15a** and **15b** with this ylide during 1 hour at room temperature, a *ca.* 89:11 and 91:9 mixture of diastereomeric products **21** were obtained (Scheme 11), the major diastereomer being isolated after flash chromatography in 52 and 63% yield, respectively. The facial diastereoselectivity is due to the *anti* attack of the ylide relative to the bulky isopropyl group.

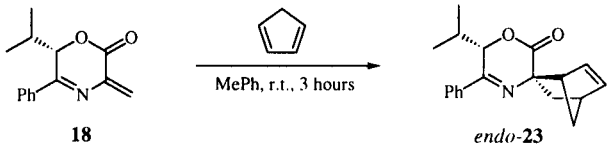
Scheme 11
Cyclopropanation of Oxazinone DDAA Derivatives: Synthesis of ACCs



Hydrolysis of compounds **21** provides enantiomerically pure (-)-*allo*-norcoronamic (**22a**) and (-)-allo-coronamic (**22b**) acids, in 60 and 67% yield respectively, after treatment with 6 *M* hydrochloric acid under reflux and further reaction with propylene oxide (Scheme 11) [15]. These ACCs play an important role in the control of enzymatic processes for plant growth and fruit ripening.

The Diels-Alder reaction was carried out with the methylene derivative **18** and cyclopentadiene or 1,3-cyclohexadiene [19]. In the first case, the cycloaddition took place in 3 hours at room temperature using toluene as solvent, affording mainly the *endo* cycloadduct **23** in 85% and 15% of other diastereomers. The major diastereomer **23** was isolated in 55% yield after chromatography and its configuration determined by X-ray diffraction analysis [19] (Scheme 12). In the case of 1,3-cyclohexadiene the reaction took place in toluene at 90° for 8 hours.

Scheme 12
Diels-Alder Reaction of Chiral DDAA Derivative **18**

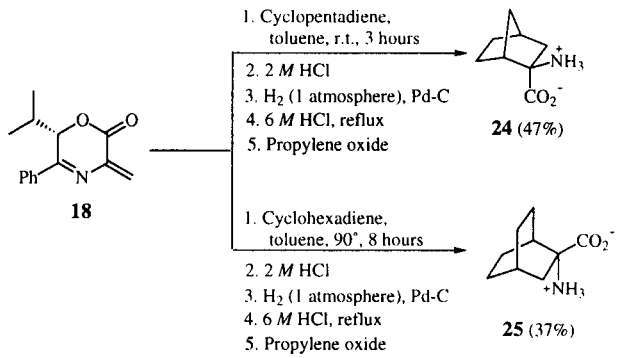


18

endo-**23**
85:15 Other Diastereoisomer
Isolated Yield: 55%

The major cycloadducts were hydrogenated after hydrolysis of the imine. Further hydrolysis of the ester function and treatment with propylene oxide allowed the isolation of the corresponding bicyclic α-amino acids **24** and **25** in 85 and 75% yield, respectively (Scheme 13) [19]. Compound **24** inhibits the transport of nonpolar amino acids across cell membranes, acts as an insulin-releasing factor and also inhibits the flavoprotein amino acid oxidases. Furthermore, amino acid **25** selectively perturbs the level of neutral amino acids in the cerebral cortex [19].

Scheme 13
Synthesis of Bicyclic α-Amino Acids

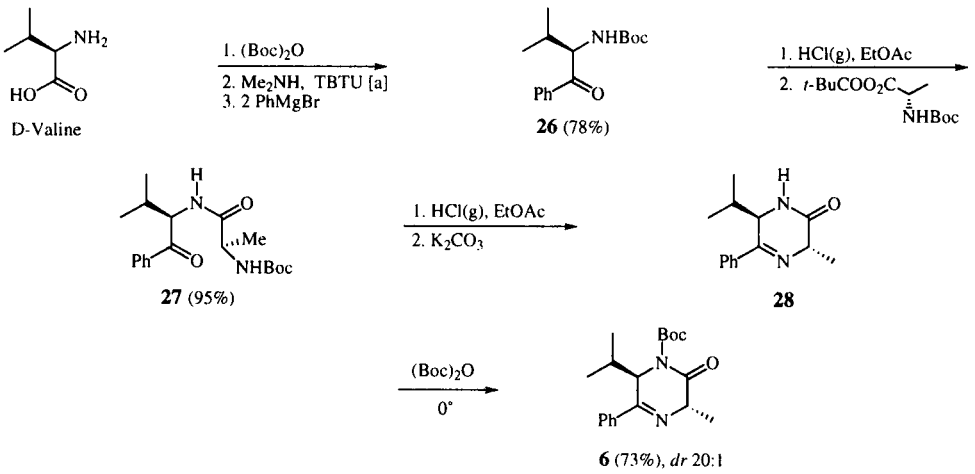


III. Alanine Derived Pyrazin-2-ones.

In this context, we envisaged that 1,2,3,6-tetrahydro-2-pyrazinones also could be appropriate heterocyclic systems for the preparation of new chiral alanine and glycine templates with the same structural features as the oxazinones studied above. In addition, these derivatives could be more stable than oxazinones providing higher yields and also could be possible to recover the chiral auxiliary. For the preparation of these rarely known heterocycles, the same strategy as for the oxazinones was followed, using in this case an α-aminoketone as chiral auxiliary.

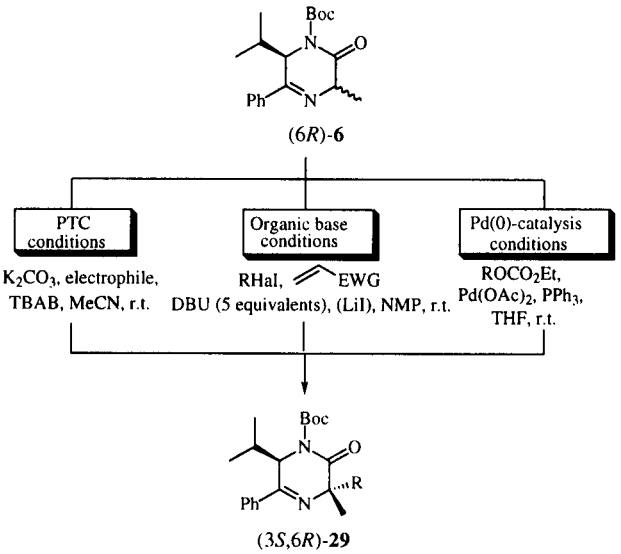
The starting D-valine was transformed into the *N*-Boc-aminoketone **26** in 78% yield by addition of phenylmagnesium bromide to the *N*-Boc-protected dimethylamide. After Boc-deprotection and amidation with *N*-Boc-L-alanine-pivalic acid mixed anhydride, compound **27** was obtained in 95% yield. Cyclization of amide **27** to pyrazinone **28** was carried out by Boc-deprotection with hydrogen chloride in ethyl acetate and workup with aqueous potassium carbonate. Final Boc-protection at 0° with di-*tert*-butyl dicarbonate gave product (6*R*)-**6** in 84% yield as a *ca.* 1:20 mixture of *cis*:*trans* diastereomers [20] (Scheme 14). The relative configuration of **6** was determined by nOe experiments. Molecular mechanics calculations predict a quasi-boat conformation with the isopropyl group perpendicular to the phenyl group as in the case of oxazinones **5** (see Figure 4).

Scheme 14
Synthesis of Alanine Derived Pyrazinones



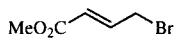
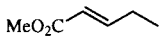
[a] TBTU: *O*-(1*H*-Benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium Tetrafluoroborate.

Scheme 15
Alkylation of Alanine Derived (6*R*)-Pyrazinones



The alkylation of pyrazinones (6*R*)-**6** was carried out with PTC conditions using potassium carbonate and tetrabutylammonium bromide in acetonitrile or methylene chloride at room temperature and activated alkyl halides and electrophilic olefins as alkylating agents. The expected pyrazinones (3*S*,6*R*)-**29** were obtained in good yields and high diastereoselectivities [20] (Scheme 15 and Table 8). When 1,8-diazabicyclo[5.4.0]undec-7-ene was used as base in the presence of lithium iodide in *N*-methylpyrrolidone the alkylation with unactivated alkyl halides and also the Michael addition took place in good chemical yields and diastereoselectivities (Scheme 15 and Table 9). Palladium catalyzed allylation with allylic carbonates using palladium(II) acetate (5 mol%) and triphenylphosphine (10 mol%) as catalyst, in tetrahydrofuran at room temperature, affords products **29** in high yields and *de's* (Scheme 15 and Table 10). In some cases, the obtained yields and *de's* were better for pyrazinones than for oxazinones. The configuration of pyrazinones was confirmed by nOe experiments and the *dr* were determined by HPLC and/or ^{1}H nmr [20].

Table 8
Diastereoselective Alkylation of (6*R*)-**6** under PTC Conditions

Entry	Electrophile	R	Time (hours)	Product **29**, % yield [a]	% *de* [b]
1	CH_2=$CHCH_2I$	CH_2=$CHCH_2$	5	(6*R*)-**29a**, 81	96
2	HC≡CCH_2Br	HC≡CCH_2	5	(6*R*)-**29b**, 86	98
3	$PhCH_2Br$	$PhCH_2$	5	(6*R*)-**29c**, 81	96
4			5	(6*R*)-**29d**, 75	98
5	EtO_2CCH_2I	EtO_2CCH_2	5	(6*R*)-**29e**, 79	96
6	CH_2=$CHCO_2Me$	$MeO_2CCH_2CH_2$	19	(6*R*)-**29f**, 62	94
7	CH_2=CHCN	CH_2CH_2CN	19	(6*R*)-**29g**, 47	96
8	CH_2=$CHCOCH_3$	$CH_2CH_2COCH_3$	19	(6*R*)-**29h**, 82	96

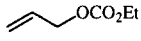
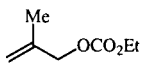
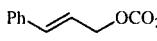
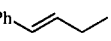
[a] Isolated yield for the pure major diastereomer after flash chromatography; [b] Determined by ^{1}H nmr (300 MHz) and/or HPLC for the reaction crude.

Table 9
Diastereoselective Alkylation of (6*R*)-**6** under DBU Conditions

Entry	Electrophile	R	Time (hours)	Product **29**, % yield [a]	% *de* [b]
1	EtI	Et	1	(6*R*)-**29i**, 84	98
2	*i*-BuI	*i*-Bu	24	(6*R*)-**29j**, 70	98
3	*n*-BuBr	*n*-Bu	22	(6*R*)-**29k**, 64	96
4	BnCl	Bn	23	(6*R*)-**29c**, 71	98
5	CH_2=$CHCO_2Et$	$EtO_2CCH_2CH_2$	17	(6*R*)-**29l**, 49	96
6	CH_2=$CHCOCH_3$	$CH_2CH_2COCH_3$	22	(6*R*)-**29h**, 69	96

[a] Isolated yield for the pure major diastereomer after flash chromatography; [b] Determined by ^{1}H nmr (300 MHz) and/or HPLC for the reaction crude.

Table 10
Diastereoselective Allylation of (6R)-**6** under PD(0)-Catalysis

Entry	$ROCO_2Et$	Time (hours)	R	Product **29**, % Yield [a]	% *de* [b]
1		18		(6*R*)-**29a**, 75	98
2		18		(6*R*)-**29i**, 85	96
3		44		(6*R*)-**29j**, 78 [c]	98

[a] Isolated yield of the major regio- and diastereoisomer after flash chromatography; [b] Determined by ^{1}H nmr (300 MHz) and/or HPLC on the reaction crude; [c] A 6% of the regioisomer was also obtained (^{1}H nmr).

Final hydrolysis of representative alkylated pyrazinones **29** with 6 *M* hydrochloric acid at 150° and final treatment of α-amino acid hydrochlorides with propylene oxide gave free AMAAs **10** in high *ee's* [20] (Scheme 16 and Table 11).

Scheme 16
Hydrolysis of (6*R*)-Pyrazinones: Synthesis of (*S*)-AMAAs

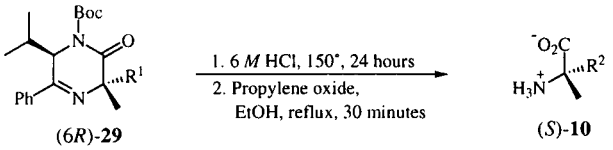


Table 11
Hydrolysis of Pyrazinones (6*R*)-**29**.
Synthesis of (*S*)-α-Methyl α-Amino Acids **10**

Entry	R^1	Substrate (6*R*)-**29**	R^2	Product **10**, % Yield [a]	% *ee* [b]
1	$PhCH_2$	(6*R*)-**29c**	$PhCH_2$	(*S*)-**10c**, 72	99
2	EtO_2CCH_2	(6*R*)-**29d**	HO_2CCH_2	(*S*)-**10f**, 77	99
3	$MeO_2C(CH_2)_2$	(6*R*)-**29f**	$HO_2C(CH_2)_2$	(*S*)-**10h**, 91	>97

[a] Referred to pyrazinone (6*R*)-**29**; [b] Determined by comparison with [α] values in the literature

IV. Glycine Derived Pyrazin-2-ones.

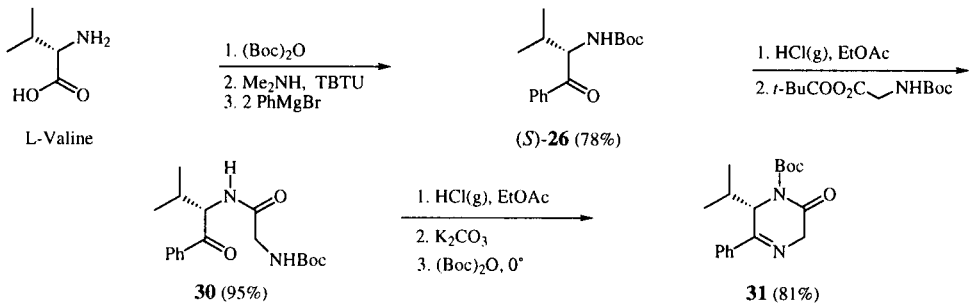
In the case of the synthesis of the glycine template **31**, the same methodology for pyrazinone **6** was followed. L-Valine was used as starting chiral material, which was successively transformed into the (*S*)-aminoketone **26** in 78% yield, amide (*S*)-**30** in 95% yield and finally (6*S*)-**31** in 81% yield (Scheme 17) [21].

The condensation under solid-liquid PTC conditions took place with aldehydes affording (*Z*)-DDAA derivatives **32** in high yields and >96% *de* (Scheme 18 and Table 12). The reaction with acetone under the same PTC conditions provided compound **33** in 51% yield. The methylene derivative **34** was also obtained by reaction with Eschenmoser' salt in 88% yield [21].

Preliminary essays concerning to the reactivity of pyrazinone **32a** (R = Me) with Corey's ylide gave the corresponding cyclopropanated derivative **35** in 81% yield and 92:8 *dr* (Scheme 19) [21].

Cycloaddition reaction of compound **34** with cyclopentadiene at room temperature in toluene for 3 hours gave mainly the *endo* adduct **36** which was isolated by flash chromatography in 42% yield (Scheme 20) [21].

Scheme 17
Synthesis of Glycine Derived Pyrazinone



Scheme 18
Synthesis of Chiral Pyrazinone DDAA Derivatives

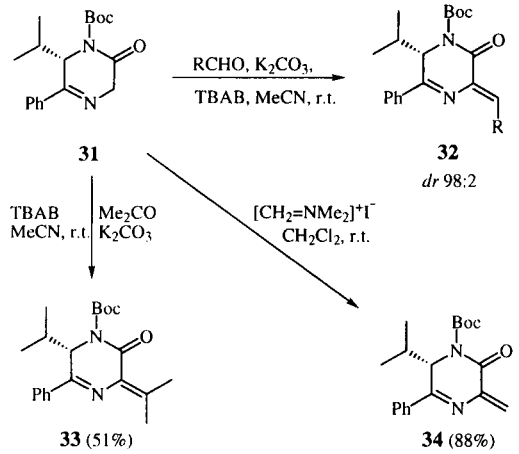
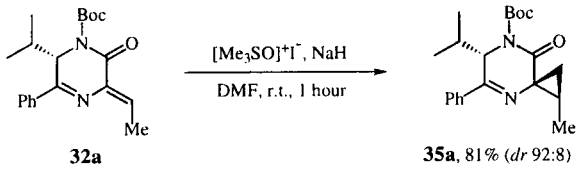


Table 12
Synthesis of Chiral Pyrazinone DDAA Derivatives **32**

Entry	R	No.	Time (hours)	% Yield [a]
1	Me	**32a**	20	88
2	Et	**32b**	20	86
3	*i*-Pr	**32c**	20	83
4	*t*-Bu	**32d**	48	47
5	Ph [b]	**32e**	20	85

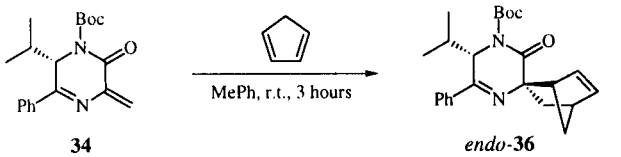
[a] For the pure (*Z*)-isomer based on compund **31**; [b] A 1:1 mixture of potassium and sodium carbonate was used.

Scheme 19
Cyclopropanation of Pyrazinone DDAA Derivatives



32a **35a**, 81% (*dr* 92:8)

Scheme 20
Diels-Alder Reaction of Chiral DDAA Derivative **34**



34 *endo*-**36**
95:5 Other Diastereoisomer
Isolated Yield: 42%

Conclusions.

In conclusion, the above described oxazinones and pyrazinones are appropriate new reagents for the asymmetric synthesis of several types of important α,α-disubstituted α-amino acids working always under very mild reaction conditions with high diastereoselectivity at room temperature (Scheme 21).

Chiral alanine derived oxazinones have been highly diastereoselectively alkylated under solid-liquid PTC, organic bases and also neutral palladium(0) catalysis conditions. This methodology allows the asymmetric synthesis of acylic and heterocyclic α-methyl α-amino acids (AMAAs). The analogous chiral glycine oxazinone can be condensed with aldehydes under solid-liquid PTC conditions to the corresponding chiral DDAA derivatives. Diastereoselective hydrogenation and cyclopropanation of these new DDAA derivatives affords *N*-methyl α-amino acids (NMAAs) and 1-aminocyclopropanecarboxylic acids (ACCs), respectively. The parent methylene DDAA derivative can be used in Diels-Alder cycloaddition reactions for the asymmetric synthesis of bicyclic α-amino acids.

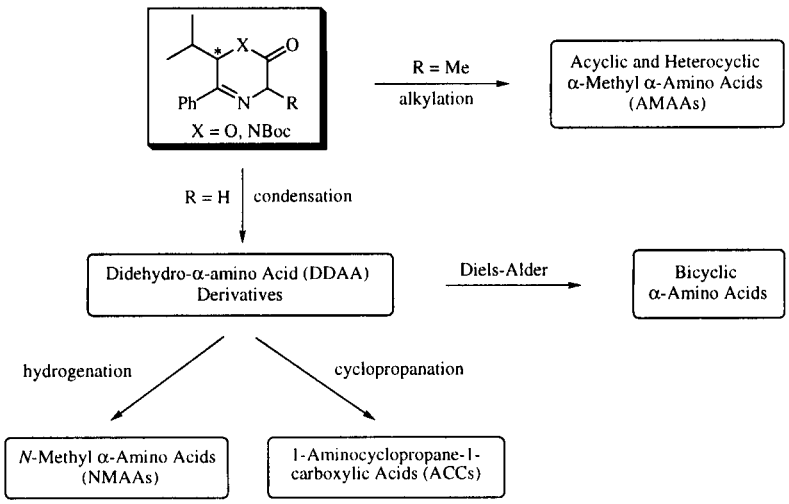
In addition, related pyrazinones can also be used under similar types of reaction conditions. Preliminary results show that they present a higher stability than the corresponding oxazinones and can also be employed as useful reagents for the asymmetric synthesis of these interesting α,α-disubstituted α-amino acids.

REFERENCES AND NOTES

[*] E-mail: cnajera@ua.es

[1a] R. M. Williams, Synthesis of Optically Active Amino Acids, Pergamon Press, Oxford, 1989; [b] C. H. Stammer, *Tetrahedron*, **46**, 2231 (1990); [c] H. Heimgartner, *Angew. Chem. Int. Ed. Engl.*, **30**, 238 (1991); [d] R. O. Duthaler, *Tetrahedron*, **50**, 1540 (1994); [e] K. Burgess, K.-K. Ho and D. Mye-Sherman, *Synlett*, 575 (1994); [f] M.

Scheme 21
Synthetic Applications of Chiral Oxazinones and Pyrazinones



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