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New chiral alanine template with a 1,2,3,6-tetrahydro-2-pyrazinone structure for the asymmetric synthesis of α-methyl α-amino acids †

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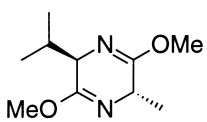
Abstract

(*R*)-6-Isopropyl-5-phenyl-1,2,3,6-tetrahydro-2-pyrazinone, prepared from (*R*)-valine and (*S*)-alanine, reacts with activated alkyl halides and electrophilic olefins under solid–liquid PTC conditions with K_2CO_3 as base, at room temperature and with high diastereoselectivity (>94%). The palladium-catalyzed allylation reaction of this alanine derivative under neutral conditions at room temperature also takes place with a de>96%. Final hydrolysis of alkylated pyrazinones affords enantiomerically pure α-methyl α-amino acids.

The great importance of nonproteinogenic α,α-disubstituted α-amino acids, especially α-methyl α-amino acids (AMAAs), is based on their remarkable influence on the conformation of peptides into which they are incorporated, thus reducing enzymatic and chemical hydrolysis. Moreover, as free amino acids AMAAs act also as enzyme inhibitors and starting building blocks for the synthesis of natural products.[1]

The α-alkylation of suitable chiral alanine enolates is one of the best strategies to create the quaternary stereogenic center.[2] Schöllkopf's bislactim ether **1**, Seebach's oxa- and imidazolidinones **2** and Williams' diphenyl-oxazinones **3** are representative examples of cyclic chiral templates for the asymmetric synthesis of AMAAs. Usually, the enolization of alanine or glycine chiral derivatives requires the use of very strong bases (LDA, LHMDS, ^{n}BuLi) at very low temperatures. These strict reaction conditions are important drawbacks for the industrial use of these systems.



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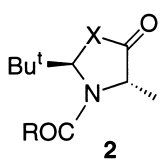

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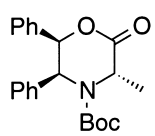

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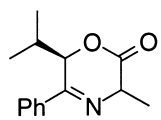

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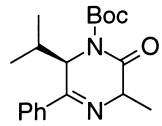

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† Dedicated to Professor Antonio González on the occasion of his 80th birthday.

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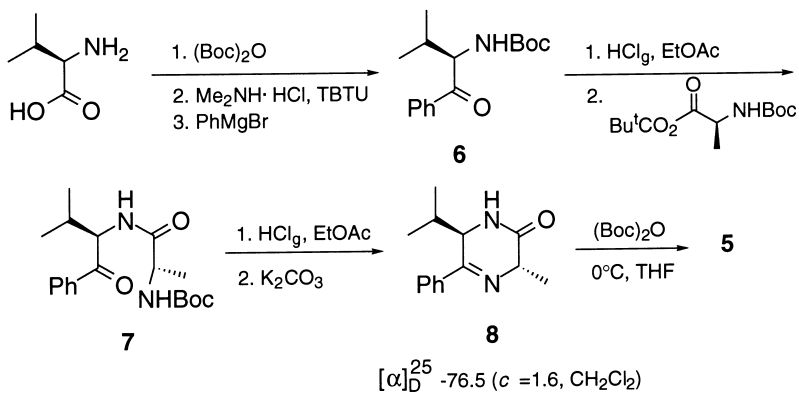
We have recently described the application of a new cyclic iminic alanine template with 3,6-dihydro-2*H*-1,4-oxazin-2-one structure **4**,[3] prepared from α-bromoisovalerophenone and (*S*)-alanine, for the asymmetric synthesis of AMAAs. It can be diastereoselectively alkylated under solid–liquid phase transfer catalysis (PTC) with K_2CO_3 as base or under neutral palladium(0) catalysis at room temperature. In this communication we report the preparation of a new related system with the tetrahydro-2-pyrazinone structure **5**, which can be used also for the asymmetric synthesis of AMAAs under similar reaction conditions. This type of template **5** has similar structural features to oxazinones **4**: (a) the phenyl group at the 5-position should favour the formation of the imine group and the enolization process; (b) the stereogenic center at the 6-position can produce intra-annular 1,4-asymmetric induction at C-3 during the alkylation of the planar enolate; (c) the acidity of the alanine unit should increase with the Boc-protection of the N-1 together with the phenylimino group; (d) it can be prepared from available starting amino acids (*R*)-valine and (*S*)-alanine; and (e) after alkylation they can be easily hydrolyzed.[4]

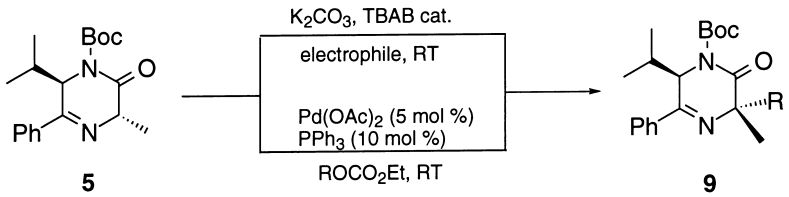
The synthesis of the tetrahydro-2-pyrazinones **5**[5] is based on the coupling of the α-amidoketone **6**, derived from (*R*)-valine, and *N*-Boc-L-alanine in order to prepare the *trans*-diasteromer[6] with the appropriate configuration at the 6-position for L-AMAAs. *N*-Boc-D-Valine was transformed into the *N*,*N*-dimethylamide by reaction with dimethylamine chlorohydrate in the presence of triethylamine and *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(benzotriazol-1-yl)uronium tetrafluoroborate (TBTU) in acetonitrile. The crude amide was allowed to react with phenylmagnesium bromide in THF at room temperature affording the α-amino ketone **6** in 78% overall yield. Deprotection of the amino group and amidation with the *N*-Boc-L-alanine pivalic acid mixed anhydride gave compound **7** (95% yield). The pyrazinone **8** was obtained in 86% yield after deprotection of **7** followed by extractive work-up with aqueous K_2CO_3. Final *N*-Boc-protection with $(Boc)_2O$ at 0°C provided product **5** in 84% yield as *ca*. 20:1 mixture[7] of *trans/cis* diastereomers[8] due to the high acidity of the H-3 of the alanine unit (Scheme 1). The same behaviour was observed in the case of oxazinone **4** but is irrelevant for the diastereoselectivity of the alkylations (see below). The relative configuration for the *trans*-pyrazinone **5** was determined by NOE experiments. Molecular mechanics calculations[9] predict quasi-boat conformation with the isopropyl group in the axial position, as in the case of oxazinone **4**.[3]



Scheme 1.

The alkylation of **5** with a variety of activated alkyl halides and electrophilic olefins took place with K_2CO_3 as base and tetra-*n*-butylammonium bromide (TBAB) in CH_3CN or CH_2Cl_2 at room temperature giving compounds **9** in good yields and high diastereoselectivities (Scheme 2 and Table 1 entries 1–8).

Pyrazinones **5** underwent highly regio- and diastereoselective allylation under neutral conditions with allylic carbonates using $Pd(PPh_3)_4$ (5 mol%) as catalyst in THF at room temperature, the same results have been obtained with $Pd(OAc)_2$ (5 mol%) and PPh_3 (10 mol%) to yield compounds **9a, 9i**



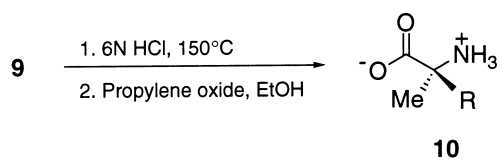
Scheme 2.

Table 1
Synthesis of compounds **9**

entry	electrophile	reaction time	product[a] no.	R	yield (%)[b]	*dr*[c]
1	CH_2=$CHCH_2I$	5 h	**9a**	CH_2CH=CH_2	81	98:2
2	CH≡CCH_2Br	5 h	**9b**	CH_2 C≡CH	86	99:1
3	$PhCH_2Br$	5 h	**9c**	$PhCH_2$	81	98:2
4	EtO_2CCH_2I	5 h	**9d**	CH_2CO_2Et	79	98:2
5	(*E*)-MeO_2CCH=$CHCH_2Br$	5 h	**9e**	(*E*)-CH_2CH=$CHCO_2Me$	75	99:1
6	CH_2=$CHCO_2Me$	19 h	**9f**	$CH_2CH_2CO_2Me$	62[d]	97:3
7	CH_2=CHCN	19 h	**9g**	CH_2CH_2CN	47	98:2
8	CH_2=$CHCOCH_3$	19 h	**9h**	$CH_2CH_2COCH_3$	82	98:2
9	CH_2=$CHCH_2OCO_2Me$	18 h	**9a**	CH_2CH=CH_2	75	99:1
10	CH_2=$CMeCH_2OCO_2Me$	18 h	**9i**	CH_2CMe=CH_2	85	98:2
11	(*E*)-PhCH=$CHCH_2OCO_2Me$	44 h	**9j**	(*E*)CH_2CH=CHPh	78[e]	99:1

[a] All products were pure (TLC, 300MHz ^{1}H NMR) and gave satisfactory spectral data (IR, ^{1}H and ^{13}C NMR, and mass spectra). [b] Isolated yield based on pyrazinone **5**, after column chromatography on silica gel. [c] Determined by HPLC and/or 300MHz ^{1}H NMR. [d] In CH_2Cl_2. [e] A 6% of the other regioisomer was also obtained.

and **9j** (Scheme 2 and Table 1 entries 9–11). The configuration of pyrazinones **9** was confirmed by NOE experiments and diastereomeric ratios were determined by HPLC and/or ^{1}H NMR (300 MHz) spectroscopy. Final hydrolysis of representative alkylated pyrazinones **9** with 6 N aqueous HCl at 150°C (pressure tube) and further treatment of α-amino acid hydrochlorides with propylene oxide in refluxing ethanol for 30 min gave free AMAAs **10** with high *ee* according to their [α] values (Scheme 3 and Table 2).



Scheme 3.

In conclusion, we have found that the new alanine derivative with the 1,2,3,6-tetrahydro-2-pyrazinone structure **5** can be alkylated under very mild and simple reaction conditions, such as solid–liquid PTC and palladium(0) catalysis at room temperature, with high diastereoselectivity. This methodology has been

Table 2
Synthesis of α-methyl α-amino acids (AMAAs) **10**

R	no.	t (h)	yield (%)[a]	$[\alpha]_D^{25}$ [b]	Lit. $[\alpha]_D$[b]	*ee* (%)[c]
$PhCH_2$	**10c**	36	72	-22.1 (*c* = 0.42)	-22.0 (*c* =0.42)[d]	99
CH_2CO_2H	**10d**	36	77	+52.5 (*c* = 0.78)	-52.9[e]	99
$(CH_2)_2CO_2H$	**10f**	48	91	+23.5 (*c* = 1.0)[f]	+23.7 (*c* = 4.0)[f,g]	>97

[a] Based on compound **9**, after recrystallization. [b] In H_2O. [c] Determined by comparing [α] values. [d] See ref. 10.
[e] For the (*R*)-enantiomer, see ref. 11. [f] Measured at 435 nm in 6N HCl, see ref. 11. [g] ≥ 97%.

applied to the synthesis of optically active L-AMAAs. Further applications of these chiral heterocycles in asymmetric synthesis of other α-amino acids are underway.[12]

Acknowledgements

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5. To our knowledge the only example of this type of heterocycle is 1,2,3,6-tetrahydro-6,6-dimethyl-5-phenylpyrazinone, which has been prepared by reaction of 2,2-dimethyl-3-phenyl-2*H*-azirine with glycine ethyl ester: Alvernhe, G.; Laurent, A.; Masroua, A. *Tetrahedron Lett*. **1983**, *24*, 1153–1156.
6. The *cis*-derivative of oxazinones **4** are configurationally unstable at the 3-position.[3]
7. Determined by HPLC and ^{1}H NMR (300 MHz).
8. The chemical shifts for the methyl groups at 3-position of the *trans* and *cis* diastereomers (1.72 and 1.65, respectively) are similar to those observed in the oxazinones (1.74 and 1.70, respectively).
9. PC Model for Windows from Serena Software and Hyperchem 5.0 from Hypercube were used for these calculations.
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