Glycine and Alanine Imines as Templates for Asymmetric Synthesis of α-Amino Acids

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Dedicated to Professor José Elguero on the occasion of his 65th birthday

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The present paper is an overview of new methods for the asymmetric synthesis of different types of α-amino acids. These methods are based on alkylation and condensation reactions of glycine and alanine imine derivatives, which can be carried out under very mild and simple reaction conditions. The enolates generated from these types of reagents are very soft and can be alkylated in a highly diastereoselective manner, even at room temperature, by using chiral templates or asymmetric PTC conditions. These methodologies afford monoalkylated and dialkylated α-amino acids as well as heterocyclic derivatives. In the case of cyclic imine derivatives with oxazinone or pyrazinone structures, the condensation reaction under PTC conditions or with Eschenmoser's salt allows the preparation of chiral α,β-didehydro-α-amino acid derivatives which can be hydrogenated, cyclopropanated or submitted to Diels–Alder cycloadditions to afford *N*-methylated and cyclic α-amino acids.

1. Introduction

Proteinogenic and nonproteinogenic α-amino acids are important natural and synthetic products in biology and chemistry as free amino acids and also as components of peptides, proteins and many other natural products. They are used as food additives, agrochemicals, pharmaceuticals and as a source of chiral materials. The increasing number of nonproteinogenic amino acids, nowadays close to 1000, has prompted the development of new methodologies and strategies specially designed for their asymmetric synthesis.[1]

For acyclic mono- and disubstituted α-amino acids, as well as for the heterocyclic ones, the alkylation of chiral glycine and alanine enolates is the most established method. Many types of cyclic glycine and alanine chiral templates

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MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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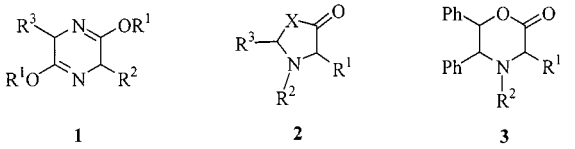
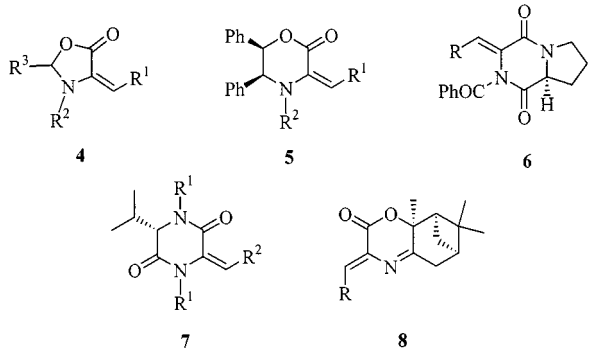
have been described with Schöllkopf's bis-lactim ethers **1**,[2] Seebach's oxa- and imidazolidinones **2**[1k] and Williams' tetrahydro-1,4-oxazin-2-ones **3**[3] being the most traditionally used reagents due to their high diastereofacial enolate bias. In general, these chiral templates need strong bases (BuLi, LDA, LiHMDS, etc.) for deprotonation and, of course, strictly anhydrous conditions, together with very low reaction temperatures.



1 **2** **3**

In the case of cyclic amino acids, the dialkylation of chiral glycine enolates with appropriate dielectrophiles or the cyclopropanation and cycloaddition reactions of chiral α,β-didehydro-α-amino acid (DDAA) derivatives are very efficient methods. Chiral DDAA derivatives have been prepared from glycine templates, usually by Horner–Wadsworth–Emmons olefination of phosphonate derivatives for oxazolidinones **4**[4] and oxazinones **5**,[5] by transformation of (*Z*)-alkylideneoxazolones into chiral diketopiperazines **6**,[6a] and by direct condensation with aldehydes under strongly basic conditions (BuLi, KO*t*Bu) for diketopiperazines **7**[6b,6c] and oxazinones **8**.[7]



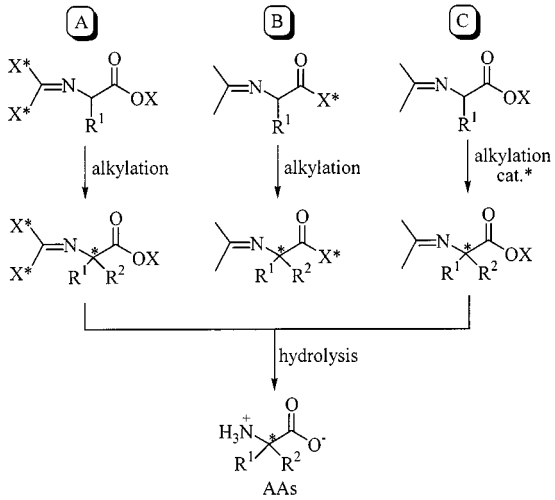
4 **5** **6**

7 **8**

The use of mild reaction conditions such as phase-transfer and palladium-catalysis and even simple organic bases for alkylation of glycine or alanine enolates is especially attractive for the large-scale synthesis of mono- and dialkylated α-amino acids. For the easy generation of these enolates, the imine moiety has to be present in the glycine or alanine templates in order to increase the acidity of their α-hydrogens. This structural feature would also permit condensation reactions of glycine imine templates with carbonyl compounds under phase-transfer catalysis (PTC) conditions in order to prepare DDAA derivatives and, subsequently, cyclic α-amino acids. In this paper, a review of the uses of glycine and alanine imine derivatives for the asymmetric synthesis of α-amino acids under simple and mild reaction conditions, reported mainly in the last five years, is covered.[1f]

2. Alkylation of Acyclic Imine Reagents

Two strategies have been developed for the alkylation of glycine and alanine imine templates: the diastereoselective alkylation of chiral reagents (methods A or B) and the enantioselective alkylation of achiral reagents by means of chiral catalysts (methods C) (Scheme 1). In method A, the auxiliary is at the imine moiety, whereas in method B the chiral auxiliary is present at the carboxylic function. In the case of method C, a chiral phase-transfer catalyst is usually used. In general, when these acyclic derivatives are employed the monoalkylation of glycine systems requires the use of ketone imines, whereas aldehyde imines are the appropriate derivatives in dialkylation reactions due to steric reasons.



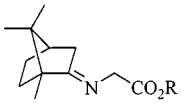
Scheme 1. Asymmetric alkylation strategies of acyclic imines

2.1 Acyclic Chiral Imine Reagents

Glycine- or alanine-derived chiral Schiff bases have been prepared from chiral carbonyl compounds in the imine moiety (strategy A, Scheme 1) or by transformation of the carboxylate function into chiral derivatives (strategy B, Scheme 1). Camphor glycine imines **9**,[8] which belong to the first class of reagents, are prepared from (1*R*,4*R*)-camphor and glycinates. They have been used as nucleophiles in Michael additions to acrylates and crotonates by using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or triethylamine as base in the presence of LiBr[9] in THF as solvent. The combination DBU/LiBr gave the best results, and it even was possible to use catalytic amounts (10 mol-%) of DBU/LiBr with the reaction being finished at 0 °C after only a few minutes in the case of methyl acrylate, affording the adduct in 76% yield and 82:18 *dr*. However, stoichiometric amounts of DBU/LiBr have to be used for crotonates, needing 2–4 h for completion at room temperature and affording the *anti* isomers in 81–83% yield and 74:26 *dr*. The high *anti* selectivity displayed in this Michael addition has been explained by proceeding through the frontier-orbital controlled and chelation-controlled transition states.[8b] Final deprotection with NH_2OH gave the corresponding glutamates or pyroglutamates.[8a]

The chiral auxiliaries (*S*)-2-[*N*-(*N*′-benzylprolyl)amino]-benzophenone [(*S*)-BPB] and -benzaldehyde have been used by Belokon' et al. in the preparation of the nickel(II) complexes of Schiff bases **10** of glycine and alanine.[10a,10b] The benzophenone reagents (*S*)-BPB (**10**, R^1 = Ph) can be alkylated with activated alkyl halides and sodium or potassium hydroxide or carbonate as bases in DMF at room temperature, in general, in high yields and with good diastereoselectivities (up to 95%). A recent new synthetic protocol allows the preparation of the auxiliary BPB and its complexes in bulk quantities.[10c] The easy hydrolysis with dilute HCl allows the isolation of the amino acid and the recovery of the chiral auxiliary. This methodology has been applied to the asymmetric synthesis of monoalkylated α-amino acids[11] and α-methyl(phenyl)alanines.[12] The benzophenone-glycine template **10** (R^1 = Ph, R^2 = H) has been used for the asymmetric synthesis of α-aminophosphonocarboxylic acids by alkylation with α- to γ-phosphorous esters under PTC conditions (KOH, TBAB, MeCN, room temperature) in 30−74% yield and 86−90% *de*.[13] The Michael addition to vinylphosphonate and vinylphosphinate has to be carried out in the presence of DBU as base in DMF at 50−70°C in 61 and 59% yield but with lower *de*'s (36 and 30%, respectively).[13] This complex has been used for the synthesis of 2-substituted glutamic and pyroglutamic acids also by a Michael addition to β-substituted acrylates using a sub-stoichiometric amount of DBU in DMF at room temperature to give, after separation *trans*-3-substituted pyroglutamic acids as the major diastereomers.[14] High diastereoselectivity has been obtained in the case of 3-trifluoromethyl-containing crotonate (>98% *de*) by using an excess of DBU and olefin to afford, after hydrolysis, (2*S*,3*S*)-3-methyl-3-trifluoromethylpyroglutamic acid.[15]

The pyridoxal-derived alanine imines **11** (R^1 = Me),[16a] bearing a chiral side-chain composed of a chiral glycerol structure, have been diastereoselectively alkylated with *p*-nitrobenzyl bromide under PTC conditions (NaOH, CH_2Cl_2, 0 °C) to give the dialkylated derivatives in 32% yield and 26% *ee*.[16b] Better chemical and optical yields (up to 86%) have been obtained with NaH or NaHMDS at low temperature and with activated alkyl halides as electrophiles.



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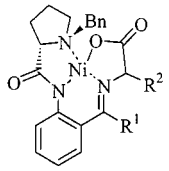
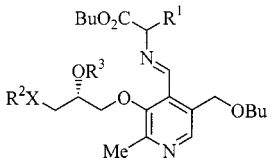
(R = Et, *t*Bu)



10
(R^1 = H, Ph)
(R^2 = H, Me)



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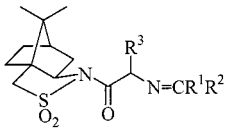
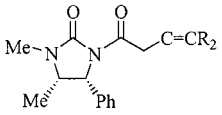
Camphor sultam has been used by Oppolzer et al. as a chiral auxiliary for the diastereoselective alkylation of the glycine imine derivative **12a** using activated alkyl halides and aqueous LiOH as base under PTC conditions. The reaction is rather sluggish and ultrasound has to be used in order to shorten the reaction time and thus avoid the hydrolysis of the *N*-acyl group, the adducts being obtained in 83−99% yield and 75−99% *de*. Monoalkylated (*S*)-α-amino acids have been obtained after hydrolysis in very high *ee* (>99.5%) and the sultam is recovered in 83−100% yield after hydrolysis with LiOH.[17a] More recently, the benzophenone derivative **12b** has been diastereoselectively alkylated at room temperature with ethyl α-bromomethyl acrylate in refluxing acetonitrile with activated alkyl halides such as propargyl and 2-bromoallyl bromides and potassium carbonate under solid-liquid PTC conditions.[17b] A Michael addition also took place using the same reaction conditions with methyl acrylate and methyl vinyl ketone at room temperature. Monoalkylated (*S*)- as well as (*R*)-α-amino acids have been prepared in >97% *de* by using the (2*R*)- or (2*S*)-bornane-10,2-sultam, respectively.[17b] In general, aldimine derivatives are the appropriate reagents for the dialkylation of imine compounds and particularly for the sultam-derived systems **12**. Only in the case of the alanine derivative **12c** (R^3 = Me) has the benzylation been carried out (90:10 *dr*) under PTC conditions with K_2CO_3 as base and tetrabutylammonium bromide (TBAB) as PT catalyst under refluxing acetonitrile for one day. After recrystallization, the pure major diastereomer was isolated in 65% yield and >98% *de*. Final hydrolysis provided enantiomerically pure (*S*)- or (*R*)-α-MePhe depending on the chiral auxiliary employed.[17c]

Recently, our group has found that (−)-(4*R*,5*S*)-1,5-dimethyl-4-phenyl-imidazolidin-2-one is a good chiral auxiliary[18] for the diastereoselective alkylation of the corresponding imine glycine templates **13**.[19] Thus, *N*-[bis(methylthio)methylene]glycinate **13a** and its benzophenone derivative **13b** have been alkylated with activated alkyl halides under solid-liquid PTC conditions with LiOH as base, and also with DBU, in acetonitrile as solvent.[19b] The Michael addition to acrylates, methyl methacrylate, acrylonitrile and methyl vinyl ketone takes place under the same reaction conditions. Moreover, it has been found that in the case of acrylates a sub-stoichiometric amount of DBU (10 mol-%) can be used. The reactions have to be carried out at −20 °C in order to avoid hydrolysis of the *N*-acyl group with subsequent cleavage of the imidazolidinone under the basic reaction conditions. In all cases, the use of an excess of LiCl[9] was found to be crucial for achieving high diastereoselection (up to 98% *de*), probably due to the ability of the lithium salt to chelate both oxygen atoms in the (*Z*)-enolates. In the case of 1,4-dielectrophiles such as α,α′-dibromo-*o*-xylene or (*Z*)-1,4-dibromo-2-butene, *C*- and *N*-alkylation took place and, after hydrolysis, the tetrahydroisoquinoline derivative amino acid and baikiain were isolated.[19c] The final hydrolysis with aqueous LiOH, or LiO_2H for alkylated **13a** derivatives, in THF, allows the recovery of the chiral auxiliary in 73−83% yield and, after ion-exchange chroma-

tography, the isolation of the corresponding (*S*)-α-amino acids in 87−94% *ee*.[19a,19b] A better and simpler reaction pathway involves refluxing the reaction mixture in water for alkylated **13b** derivatives to afford (*S*)-α-amino acids with better *ee*'s. This methodology has also been applied to the synthesis of (*R*)-α-amino acids by using (+)-(4*S*,5*R*)-1,5-dimethyl-4-phenylimidazolidin-2-one as the chiral auxiliary.[19c] Preliminary assays for carrying out the dialkylation of alanine templates, when benzaldehyde, *p*-chlorobenzaldehyde or salicylaldehyde were used as *N*-protecting groups, failed.[19c]



12a, $R^1 = R^2 = MeS$, $R^3 = H$
12b, $R^1 = R^2 = Ph$, $R^3 = H$
12c, $R^1 = H$, $R^2 = 4\text{-}ClC_6H_4$, $R^3 = Me, MeS(CH_2)_2, i\text{Bu}, PhCH_2$



13a, R = MeS
13b, R = Ph

2.2 Asymmetric Phase-Transfer Catalysis

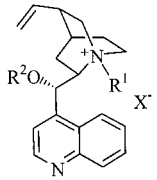
Tetralkylammonium halides, derived from inexpensive and commercially available *cinchona* alkaloids, such as cinchonine **14** (R^1 = Bn, R^2 = H, allyl, Bn) and ψ-enantiomeric cinchonidine **15** (R^1 = Bn, R^2 = H, allyl, Bn) were first used by O'Donnell et al. for the monoalkylation under PTC conditions[20] of the glycine benzophenone derivatives **17** and for the dialkylation of alanine aromatic aldehyde derivatives **18**.[21] The cinchonine catalyst **14** is adequate for the preparation of (*R*)-α-amino acids, and the cinchonidine **15** for the (*S*)-enantiomers. The reaction is carried out in a two-phase system consisting of an organic solvent (toluene, CH_2Cl_2 or acetonitrile) and an aqueous (50% NaOH) or solid base (KOH, KOH/K_2CO_3 or K_2CO_3) with *ee*'s of 42−81%. A new generation of catalysts **14** and **15** (R^1 = 9-anthracenylmethyl, R^2 = H, X = Cl)[22] and **15** (R^1 = 9-anthracenylmethyl, R^2 = allyl, X = Br)[23] have been recently described independently by Lygo's and Corey's groups for the monoalkylation of **17a** and applied to the synthesis of monoalkylated α-amino acids. In the first case, *ee*'s of 82−91% have been obtained working with 50% aqueous KOH in toluene for 3−18 h at room temperature in 40−84% yield.[22a] This methodology has been used for the synthesis of (*S*)- or (*R*)-α-amino acids employing **14** or **15** as catalysts, respectively.

Bis-α-amino acids, which are present in nature as cross-linking agents that help to stabilize structural polymer elements in plants and bacteria or as subunits in bioactive peptides, have also been prepared following this methodology. Unnatural bis-α-amino acids have proved of interest as components of biologically active peptides.[22b,22c]

Corey's catalyst **15** gave high enantioselectivities (92−99.5%) in alkylations and conjugate additions with a variety of alkyl halides and Michael acceptors in 67−91% yield by a solid-liquid PTC reaction with $CsOH{\cdot}H_2O$ in CH_2Cl_2 at −60 to −78 °C for 18−36 h. Unactivated alkyl iodides and activated alkyl bromides as well as α,β-unsaturated ketones and methyl acrylate can be used as electrophiles. In the case of 2-cyclohexenone the *dr* was 21:1 but the enantioselectivity was >99%.[23b] X-ray crystal structures of the catalyst and of the ion-pair of *p*-nitrophenoxide and the cation of **15** (R^1 = 9-anthracenyl, R^2 = allyl, X = Br) led to the proposition of the formation of an ion-pair of the enolate and this cation.[23a] The alkylation of imine **17b** with benzyl bromide at 0 °C with 50% aqueous NaOH in CH_2Cl_2 with the best catalyst **15** afforded a 74.6% *ee* for the *S* enantiomer.[24]

More recently, rigid chiral spiro ammonium salts with a binaphthyl structure **16** (R = H, Ph, β-Np) have been effectively used in the monoalkylation of the glycine iminoester **17a** in toluene and 50% aqueous KOH at 0 °C with activated alkyl bromides in 90−96% *ee* and 60−95% yield (R = β-Np).[25]

Organic soluble nonionic bases such as phosphazene bases BEMP (**20**) or BTPP (**21**) with pK_a = 16.2 or 17.0, respectively, have recently been used in conjunction with chiral ammonium salts **14** or **15** (R^1 = 9-anthracenylmethyl, R^2 = allyl). The alkylation of **17a** in homogeneous conditions at −50 or −78 °C in CH_2Cl_2 as solvent was more effective when using BEMP (**20**) for activated halides and BTPP (**21**) for nonactivated ones, with *ee* between 56−97% and in high chemical yields.[26a] Similar conditions have been used for the enantioselective alkylation of the Wang-resin-bound benzophenone imine of glycine **19** at room temperature affording α-amino acids in 51−89% *ee*.[26b]



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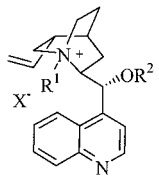

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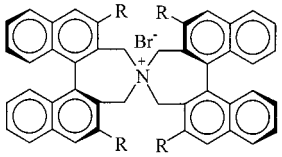

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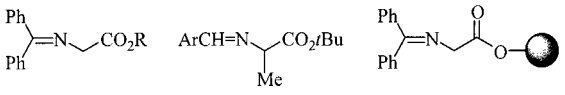
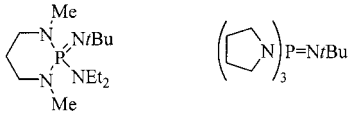


17a, R = *t*Bu
17b, R = Et

18

19



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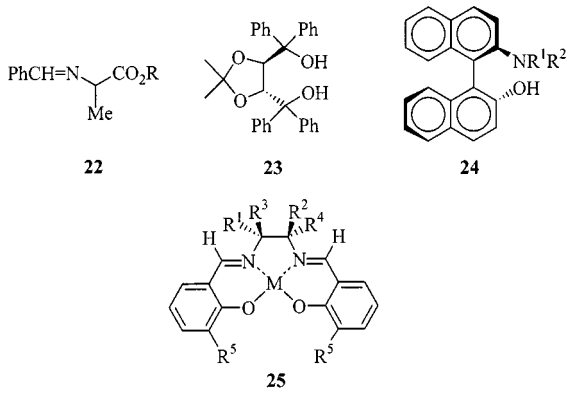
α-Methyl α-amino acids (AMAAs)[11,1m] have been prepared by alkylation of aldimine Schiff bases of alanine esters **22** under PTC conditions by using TADDOL **23**[27a] (up to 82% *ee* and 68−96% yield), NOBIN and its deriva-

tives **24**[27b] (up to 68% *ee* and 50−90% yield) or salen−metal complexes **25**[28] (up to 92% *ee* and 20−99% yield) as chiral catalysts. Activated alkyl bromides, with toluene as solvent and solid NaOH or NaH have been used at room temperature in all cases in the presence of 10% of catalysts **23**−**25**.

Recently, Lygo et al. have carried out the alkylation of the alanine-derived imine **18** (Ar = *p*-ClC_6H_4) in the presence of cinchonidinium bromide **14** (R^1 = 9-anthracenylmethyl, R^2 = H, X = Br)[22d] using solid K_2CO_3/KOH as base in toluene at room temperature with activated alkyl halides in 19−87% *ee* and 58−95% yield.

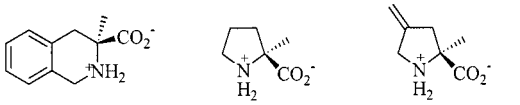


22 **23** **24**

25

3. Alkylation of Cyclic Imine Reagents

The chiral 1,4-oxazin-2-ones **26**, derived from L-alanine, which is also used as the chiral source, can act as very reactive alanine enolate reagents in diastereoselective alkylations under very mild reaction conditions.[29] These cyclic imines, prepared from α-bromoisovalerophenone according to a modification of the method described by Sunjic et al.,[30] have been obtained as a 20:1 *trans*/*cis* mixture of diastereomers and used for the synthesis of (*S*)-AMAAs with acyclic and heterocyclic structures (Scheme 2). Their alkylation took place at room temperature with high diastereoselectivity under different mild reaction conditions. In the case of activated alkyl halides and methyl acrylate, the use of K_2CO_3 as base in acetonitrile under solid-liquid PTC conditions (0.1 equiv. of TBAB) afforded the dialkylated oxazinones **27** in 60−75% yield and 84−96% *de*, whereas paraformaldehyde gave the corresponding aldol in 63% yield and 60% *de*. Unactivated alkyl halides could be employed as electrophiles by using Schwesinger's base BEMP (**20**, 1 equiv.) or DBU (5 equiv.) in *N*-methylpyrrolidone (NMP) as solvent.[29b,29c] In some cases, the presence of LiI avoids competitive *O*-alkylation of the enolate. Alkyl iodides or bromides and allyl or benzyl chlorides are appropriate electrophiles for this alkylation reaction which occurs in ca. 1 h with moderate yields (28−65%) and *de*'s > 96%. Final hydrolysis with 6 M HCl and treatment with propylene oxide allowed the synthesis of free (*S*)-AMAAs. The same strategy, but starting from D-alanine has been used for the preparation of (*R*)-AMAAs.[29c] Dielectrophiles such as α,α′-dibromo-*o*-xylene under PTC conditions and 1,3-dibromopropane or 3-iodo-2-iodomethylprop-1-ene under BEMP conditions afforded, after hydrolysis, the corresponding heterocyclic AMAAs **28**−**30**.

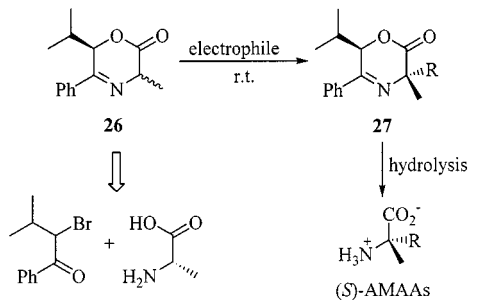


28 (58%, ee>99%) **29** (45%, ee>99%) **30** (47%, ee>99%)

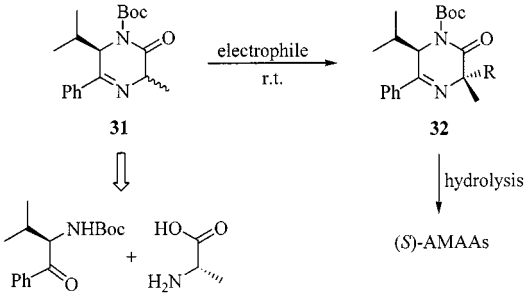
The palladium(0)-catalyzed allylation of oxazinones **27** has been achieved with allylic carbonates as electrophiles at room temperature under neutral conditions in THF as solvent and $Pd(PPh_3)_4$ and 1,2-bis(diphenylphosphanyl)ethane (dppe) as catalyst (5 mol-%).[29a,29c] The corresponding allylated oxazinones **27** have been obtained in 60−69% yield and *de*'s > 96%. When unsymmetrically substituted allylic carbonates were employed, attack at the less-substituted position of the intermediate (η^3-allyl)palladium complexes occurred preferentially in 53−65% yield and 70−88% *de*. A two step hydrolysis for (*S*)-allylalanine has been carried out, as in the case of methyleneprolinate **30**, by treatment with 2 M HCl in THF for 1 h followed by hydrolysis with LiOH at room temperature for 6 h, and final purification by Dowex chromatography.[29a,29c]

Oxazinones **26** and **27** are, in general, sensitive to aqueous acidic and basic media, the yields for purified compounds being moderate in some cases. This inconvenience has been overcome using the corresponding 1,2,3,6-tetrahydro-2-pirazinones **31**.[31] These heterocyclic derivatives[32] were prepared from L-alanine and (*R*)-*N*-Boc-α-aminoisovalerophenone, which is easily accessible from D-valine.[31] The 2-pyrazinones **31** were obtained as a 20:1 *trans*/*cis* mixture of diastereomers as in the case of oxazinones **26** (Scheme 3). This epimerization at C-3 shows the high and similar acidity of these alanine imine templates.

The alkylation of pyrazinones **31** with activated alkyl halides and electrophilic olefins took place under the same solid-liquid PTC conditions as for the oxazinones **26**, but with better yields (62−86%) together with higher *de*'s (94−98%), and, in general, in shorter reaction times.[31] For unactivated alkyl iodides and bromides, as well as for allylic and benzylic chlorides and electrophilic olefins, the combination DBU/LiI (two equiv.) gave better yields than BEMP (**20**) and also using NMP as solvent. In the case of the Michael addition similar yields are obtained using just 0.1 equiv. of DBU. In general, good yields (49−84%), negligible *O*-alkylation and high diastereoselectivity (95−98%)



Scheme 2. Asymmetric synthesis of (*S*)-AMAAs from oxazinones **26**

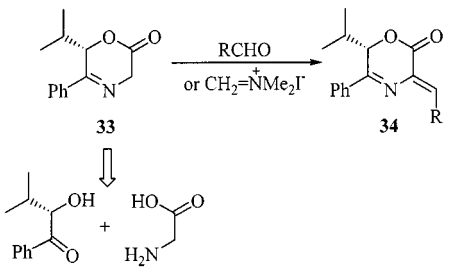


Scheme 3. Asymmetric synthesis of (*S*)-AMAAs from pyrazinones **31**

have been obtained under these organic base conditions.[33] Final hydrolysis of dialkylated pyrazinones **32** with 6 M HCl under reflux gave (*S*)-AMAAs in good yields (72−91%) and high *ee*'s (>96%).[31] The allylation reaction of pyrazinones **31** under palladium(0)-catalysis can be carried out with allylic carbonates and vinyloxirane under neutral conditions at room temperature either with $Pd(OAc)_2$ and PPh_3 or with $Pd(PPh_3)_4$ and dppe as catalysts, to give the corresponding allylated pyrazinones **32** in 56−85% yield and 98% *de*.[31] However, only the dialkylation reaction was observed when glycine-derived oxazinone **33** or pyrazinone **35** were treated with different electrophiles under PTC, palladium(0)-catalysis or organic base conditions.

4. Condensation reactions of Cyclic Imine Reagents

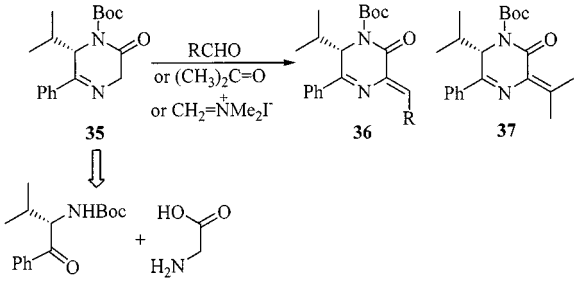
The reaction of chiral glycine templates with aldehydes to afford DDAA derivatives has only been achieved in the case of the diketopiperazines **7**[6b,6c] and the oxazinones **8**[7] using strong anhydrous bases (see above). Only recently has the direct condensation of glycine reagents with oxazinone structure **33** with aldehydes under very mild reaction conditions been achieved.[34] Thus, aliphatic aldehydes react with the cyclic imine reagent **33** under solid-liquid PTC conditions in the presence of K_2CO_3 as base and TBAB as phase-transfer catalyst in acetonitrile at room temperature. In the case of benzaldehyde, the reaction has to be carried out at 0 °C in order to avoid isomerization of the double bond. The crude (*Z*)-DDAA derivatives **34** were obtained in >96% *de*, and were isolated as pure (*Z*)-isomers after flash chromatography in 50−64% yield[34] (Scheme 4). The starting oxazinone **33** has been prepared in 53% overall yield by esterification reaction between the chiral auxiliary (*S*)-2-hydroxyisovalerophenone and *N*-Boc-glycine under DCC/HOBt conditions, followed by Boc-deprotection and base-mediated cyclization.[34]



Scheme 4. Synthesis of oxazinone DDAA derivatives

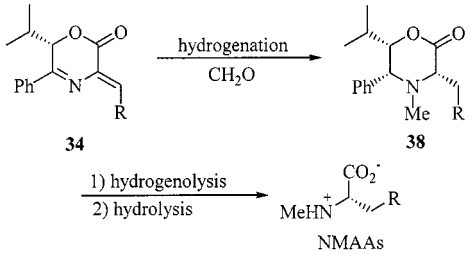
The methylenic derivative **34** (R = H) has been prepared by the direct reaction of oxazinone **33** with *N,N*-dimethyleneammonium iodide (Eschenmoser's salt) in CH_2Cl_2 in 50% yield, based on the ester obtained from (*S*)-2-hydroxyisovalerophenone and *N*-Boc-glycine.[34b,35]

In similar PTC reaction conditions pyrazinone **35**, obtained as previously mentioned[31] from glycine and the amino ketone in 78% overall yield, reacted with aldehydes and acetone to give the corresponding DDAA derivatives **36** and **37** in 47−88% and 51% yields, respectively. In the case of compounds **36**, the (*Z*)-isomers were obtained in >96% *de*[33] (Scheme 5). The reaction with Eschenmoser's salt affords the methylene derivative **36** (R = H) in 88% yield. These chiral pyrazinone DDAA derivatives **36** and **37** are, in general, more stable than the corresponding oxazinones **34**.[31]



Scheme 5. Synthesis of pyrazinone DDAA derivative

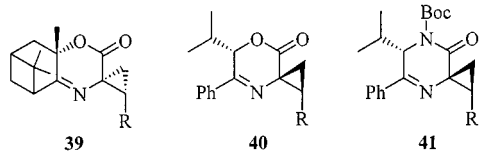
The hydrogenation of the chiral DDAA derivatives **34** in the presence of formaldehyde has been used as a direct methodology for the synthesis of *N*-methyl-α-amino acids (NMAAs). This family of α-amino acids is a constituent of various peptides and depsipeptides isolated from plant strains, microorganisms and marine species. They can also enhance proteolytic stability, increase lipophilicity and cause profound conformational changes of peptides.[36] Thus, when compounds **34** were submitted to hydrogenation with PtO_2 as catalyst in MeOH at room temperature and atmospheric pressure for 30 min in the presence of aqueous formaldehyde, the all-*cis* saturated oxazinones **38** were obtained in 63−75% yield (Scheme 6).[37] Their configuration was determined by ^1H NMR spectroscopy and by an X-ray diffraction analysis of **38** (R = *t*Bu). The saturated oxazinones **38** (R = Me and *i*Pr) were transformed into the corresponding NMAAs in 66−83% overall yield by hydrogenolysis at 3.5 bar with $Pd(OH)_2$ in the presence of trifluo-



Scheme 6. Synthesis of NMAAs from oxazinone DDAA derivatives **34**

roacetic acid in MeOH,[38] followed by hydrolysis with 6 M HCl and final treatment with propylene oxide.

The cyclopropanation reaction of DDAA derivatives is the best strategy for the preparation of 1-aminocyclopropane-1-carboxylic acids (ACCs) because in this way is possible to control the generation of the required two stereogenic centers.[39] These types of 2,3-methanoamino acids constitute an important family of cyclic α-amino acids because of their biological activity and as components of peptides which are present in nature as free amino acids, as simple dipeptides or as components of natural peptides. The cyclopropanation of imine DDAA derivatives such as (*Z*)-oxazinones **34** was performed with Corey's ylide at room temperature similarly to the case of hydroxypinanone oxazinones **8**.[40] Corey's ylide attacked preferentially the less-hindered face of the double bond, and DMSO removal with formation of the spirocyclic adduct occurred prior to bond rotation. In the case of the (*Z*)-DDAA derivatives **8** the cyclopropyl compounds **39** were diastereoselectively obtained in 45−95% yield and, after hydrolysis with 6 M HCl and further treatment with propylene oxide, the ACCs **42** were isolated in 25−40% yield. However, aromatic aldehyde derivatives cannot be hydrolyzed due to ring opening and -formation of α-amino-γ-lactones.[40] In the case of the oxazinones **34**, the cyclopropanation with dimethyl sulfoxonium methylide at room temperature gave mainly spiro derivatives with 9:1 *dr*; the pure stereoisomers **40** were isolated in 52−63% yield after flash chromatography. This methodology has been applied to the synthesis of enantiomerically pure (−)-*allo*-norcoronamic **43** (R = Me) and (−)-*allo*-coronamic **43** (R = Et) acids which were isolated in 60 and 67% yield, respectively, after hydrolysis.[34] Both ACCs play an important role in the control of enzymatic processes for plant growth and fruit ripening.[39] The pyrazinones **36** have also been treated under the same cyclopropanation conditions affording spiro pyrazinones in 11:1 (R = Me) and 23:1 (R = Et) *dr*. The pure major diastereomers **41** have been obtained after purification in 70 and 79% yield, respectively. After hydrolysis with 3 M HCl, (−)-*allo*-norcoronamic acid **43** (R = Me) has been obtained in 24% yield.[33]

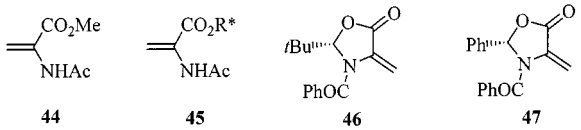


39 **40** **41**

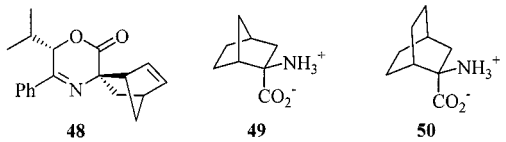
42 **43**

The Diels−Alder reaction of α,β-didehydroalanine derivatives has been used as an adequate strategy for the asymmetric synthesis of cyclohexanic and bicyclic α-amino acids. Previous reports used *N*-acetyl-α,β-didehydroalaninate **44** in the presence of tartaric acid-derived titanium Lewis acids,[41a] or its chiral esters **45** derived from (−)-menthol or (−)-isoborneol.[41] However, oxazolidinones **46** and **47** are the only examples of chiral cyclic α,β-didehydroalaninates used in cycloaddition reactions.[42] They react with cyclopentadiene or cyclohexadiene giving the *exo* adducts after five days at room temperature in the case of the former diene and after 16 days at 130 °C for the latter one. Only recently, have imine DDAA derivatives with oxazinone and pyrazinone structure been used as very reactive dienophiles in cycloaddition reactions.

When the oxazinone dehydroalanine derivative **34** (R = H) is submitted to reaction with cyclopentadiene in toluene as solvent, mainly the *endo* adduct **48** (85% + 15% other diastereomers) was obtained in 3 h at room temperature, which was isolated after chromatography in 55% yield and characterized by X-ray diffraction analysis.[35] Hydrolysis of the imine group with 2 M HCl, followed by hydrogenation and hydrolysis with 6 M HCl, furnished enantiomerically pure 2-aminobicyclo[2.2.1]heptane-2-carboxylic acid **49** in 85% yield.[35] In the case of cyclohexadiene, the reaction occurred in 8 h in toluene at 90 °C with the major isomer being isolated in 49% yield.[43] After the same treatment, the amino acid **50** was obtained in an enantiomerically pure form in 77% yield.[35] The bicyclo[2.2.1]heptane derivatives have been used to study the transport of amino acids with hydrophobic side chains. They also act as insulin-releasing factors and inhibit the flavoprotein amino acid oxidases.[44] The homologous bicyclo[2.2.2]octanes perturb selectively the level of neutral amino acids in the cerebral cortex.[45]



44 **45** **46** **47**



48 **49** **50**

When these Diels−Alder reactions were carried out on dehydroalanine derivatives **36** (R = H) with a pyrazinone structure similar results were obtained.[46] In the case of cyclopentadiene the cycloaddition also took place at room temperature in 3 h and, after hydrogenation and hydrolysis, the amino acid **49** was obtained in 34% overall yield. Cyclohexadiene reacted at room temperature for six days to give the cycloadducts quantitatively and, after hydrogenation and hydrolysis, compound **50** is obtained in enantiomerically pure form in 20% overall yield. It is remarkable that these DDAA derivatives react faster than other cyclic systems such as **46** and **47** and with "normal" kinetic *endo* selectivity with approximation of the diene by the less-hindered face. That could be attributed to a lower steric hindrance close to the nitrogen atom compared to oxazolidinones **46** and **47**. Moreover, the high reactivity of these DDAA derivatives with oxazinone and pyrazinone structures could be justified in terms of the rather low energy of their LUMO, especially in the case of pyrazinone.[47]

Concluding Remarks

This short review shows the usefulness of acyclic and cyclic imine templates in the asymmetric synthesis of amino acids by means of alkylation and condensation reactions. The mild and simple reaction conditions used in the alkylation of glycine and alanine imine enolates make these types of templates very attractive for scalable process in the asymmetric synthesis of mono- and disubstituted α-amino acids. Especially interesting are cyclic templates with oxazinone or pyrazinone structures because they can even be used in direct condensation reactions under simple PTC conditions for the synthesis of reactive DDAA derivatives. These interesting compounds can be employed for the asymmetric synthesis of cyclic α-amino acids such as ACCs as well as bicyclic ones.

Acknowledgments

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