

# From $\alpha$ -Amino Acids to Peptides: All You Need for the Journey

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Received 10 October 2001

**Abstract:** In this account several tools necessary for the synthesis of peptides from  $\alpha$ -amino acids are considered. Different strategies for the asymmetric synthesis of  $\alpha$ -amino acids are studied. New chiral glycine and alanine imines as acyclic and cyclic templates for the asymmetric synthesis of different types of mono as well as dialkylated  $\alpha$ -amino acids with acyclic and heterocyclic structures are reviewed. Their diastereoselective alkylation and final hydrolysis takes place under very mild reaction conditions. New polymer-supported cinchonidine and cinchonine ammonium salts and chiral binaphthol-derived aminoalkoxides (BINOLAMs), have been developed as catalysts for the asymmetric PTC alkylation of imino esters. The use of chiral oxazinone and pyrazinone  $\alpha,\beta$ -dihydroamino acid derivatives in hydrogenation, Heck-arylation, cyclopropanation and Diels–Alder cycloaddition reactions for the asymmetric synthesis of  $\alpha$ -amino acids are also studied. Azomethine ylides derived from saturated oxazinones can also be used in the asymmetric synthesis of prolines by means of diastereoselective dipolar cycloadditions. For the protection of  $\alpha$ -amino acids new efficient reagents, Fmoc-P-OSu and Cbz-P-OSu, derived from poly(styrene-*co*-*N*-hydroxymaleimide) named as polymeric *N*-hydroxysuccinimide (P-HOSu), have been developed. Several new systems such as polymer-supported P-HOSu/DCC and polystyrene-bound P-TBTU or P-HBTU, together with non-polymeric thiouonium salts derived from 2-mercaptopyridine-1-oxide and TMU, such as HOTT and TOTT, and from DMPU, such as HODT and TODT, have been used as peptide coupling reagents, in solution and solid phase peptide synthesis, as well as for the preparation of primary amides, Weinreb amides and other hydroxamates, directly from carboxylic acids.

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**Key words:** amino acids, phase-transfer catalysis, asymmetric catalysis, protecting groups, peptides

## 1 Introduction

The developments in the important field of peptide chemistry<sup>1</sup> is linked to advances in several synthetic methodologies, mainly: (a) the asymmetric synthesis of  $\alpha$ -ami-

no acids, especially for the non-proteinogenic compounds,<sup>2</sup> (b) the discovery of appropriate protecting groups for  $\alpha$ -amino acids<sup>3</sup> and (c) the development of effective coupling techniques either in solution or in solid-phase by means of peptide coupling reagents.<sup>1,4</sup> These areas of interest have attracted the attention of organic chemists and have revolutionized many aspects of organic synthesis. For instance, solid-phase synthesis, introduced by Merrifield for peptides, has expanded into the area of combinatorial chemistry and has encouraged the development of new polymers and linker systems. The asymmetric synthesis of  $\alpha$ -amino acids has brought the discovery of numerous chiral auxiliaries in stoichiometric and substoichiometric versions, together with a plethora of strategies as well as many biotransformations. The structural diversity of  $\alpha$ -amino acids as well as the different reaction conditions for the coupling process requires the use of almost tailor-made synthetic strategies, protecting groups and coupling reagents.

In the last five years our group has been involved in synthetic work related to  $\alpha$ -amino acids and peptides. This account summarizes our work, mainly concerning the design of new chiral glycine and alanine templates and also chiral phase-transfer-catalysts (PTC), for the stoichiometric and substoichiometric asymmetric syntheses, of different types of  $\alpha$ -amino acids via alkylation reactions and other methodologies. Our aim was to find simple and mild reaction conditions, mainly in the alkylation of the corresponding enolates and during the usually tricky final hydrolysis step. More recently, we have entered into the design of new protecting group and peptide coupling reagents searching for effectiveness, but also for scalable syntheses and economically favourable products, moving ourselves to applied green chemistry.

## 2 Asymmetric Synthesis of $\alpha$ -Amino Acids

From recent reviews, mainly published in the last decade,<sup>2</sup> one can deduce that there are five general well-established strategies for the asymmetric synthesis of  $\alpha$ -amino acids: (a) the classic enzymatic synthesis, (b) hydrogenation or cycloaddition reactions of  $\alpha,\beta$ -dihydroamino acid derivatives, (c) Strecker-type synthesis, (d) electrophilic or nucleophilic aminations and (e) electrophilic or nucleophilic alkylations.

The electrophilic alkylation of enolates derived from chiral glycine or alanine templates has become the most versatile and prolific method for the asymmetric synthesis

of acyclic and heterocyclic  $\alpha$ -amino acids. In the last 20 years several types of reagents with acyclic and cyclic structures have been developed. Some of the most efficient and popular templates are the cyclic Schöllkopf's bis(lactim) ethers **1**, Seebach's oxazolidinones and imidazolidinones **2** and Williams' morpholinones **3**. As acyclic systems, Belokon's nickel complexes **4**, Oppolzer's sultam derivatives **5** and Myers' pseudoephedrine glycina-mides **6** can be mentioned (Figure 1). One of the major inconveniences of the use of these systems is that the enolization has to be carried out generally with strong anionic bases (BuLi, LDA, LiHMDS, etc.), very low temperatures, and strict anhydrous conditions. These extreme reaction conditions are not useful for large scale synthesis. Our initial goal was to design easily enolizable chiral glycine and alanine templates with acyclic or cyclic structures. For this purpose we focused our attention on imines derived from aromatic aldehydes or ketones, both as protecting and activating moieties at the nitrogen of glycine and alanine derivatives.<sup>5</sup> These type of reagents are easily enolizable according to their  $pK_a$  values,<sup>6</sup> allowing the use of PTC conditions<sup>7</sup> for the alkylation step, even being alkylated under Pd(0) catalysis.<sup>8</sup> Moreover, this type of compound can be hydrolyzed under very mild conditions and the chiral auxiliary can be located on the glycine or alanine template (Section 2.1) or can be an external reagent, for instance a chiral phase-transfer catalyst<sup>5</sup> (Section 2.2).

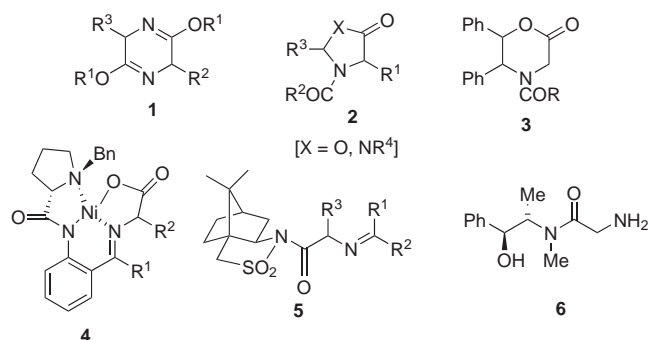


Figure 1

## 2.1 Electrophilic Alkylation of Chiral Glycine and Alanine Templates

The preparation of chiral Schiff bases derived from glycine or alanine is in general very simple, requiring just the condensation with a carbonyl compound or its imine. Another advantage of these systems is that they can be easily hydrolyzed to furnish the corresponding amino acid after the alkylation step. The availability of ephedrine imidazolidinones, which have been proven to be very efficient chiral auxiliaries,<sup>9</sup> and the possibility of their recovery prompted us to prepare the glycinimide derivatives **7** and **8**. For the preparation of these reagents, the imidazolidinone was acylated with  $\alpha$ -chloroacetyl chloride and the glycine structure was completed through the intermediate azide, followed by hydrogenation (Pd/C) and final formation of the imines.<sup>10</sup> They are crystalline compounds stable at room temperature, although the benzophenone derivative **8** is sensitive to acidic media as well as to silica gel. Therefore, they could not be prepared by direct trimethylaluminum-mediated acylation of the imidazolidinones with methyl imino esters as in the case of Oppolzer's sultam-derived glycinimides.<sup>11</sup> The alkylation process, initially studied with *N*-[bis(methylthio)methylene]glycinimide **7**,<sup>10a</sup> was very disappointing. It suffered cleavage of the *N*-acyl group under solid-liquid PTC conditions: potassium carbonate or potassium hydroxide in acetonitrile and tetrabutylammonium bromide (TBAB) as catalyst at room temperature. When aprotic alkylation conditions were assayed with compound **7**, using bases such as lithium hexamethyldisilazide or potassium *tert*-butoxide in THF at low temperatures in the presence of lithium chloride, the alkylation with activated alkyl halides took place diastereoselectively in 58–86% yield and 76–96% de. From these preliminary studies, we deduced not only the crucial influence of lithium chloride in both chemical yield and diastereoselectivity, but also that the temperature was critical in the cleavage of the imide bond. Thus, when the alkylation of compounds **7** and **8** was carried out under PTC conditions at  $-20\text{ }^\circ\text{C}$  with lithium hydroxide in the presence of lithium chloride and TBAB in acetonitrile, the reaction with activated alkyl halides gave

## Biographical Sketch



**Carmen Nájera** was born in Nájera (La Rioja) and graduated from the University of Zaragoza in 1973, obtaining her doctorate in chemistry from the University of Oviedo in 1979. She carried out postdoctoral work with Prof. D. Seebach at the ETH (Zürich), Prof. J. E. Baldwin at the Dyson Perrins Laboratory (Ox-

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products **10** or **11** in 55–90% yield and 84–94% de (Equation 1). The effect of lithium chloride is illustrated in *Z*-enolates **9**, lithium acting as chelating cation changes the degree of aggregation and also its conformation.<sup>12</sup> Lithium chloride is a Lewis acid that can also activate electrophiles and has a general effect on the polarity of the solvent.<sup>13</sup> Reagent **8** gave higher diastereoselectivities than **7** and was preferred in order to avoid unpleasant carbon disulfide. The benzophenone glycinimide **8** was alkylated in the presence of organic bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), tetramethylguanidine (TMG) or 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP)<sup>14</sup> combined with lithium chloride in acetonitrile at –20 °C. DBU was the base of choice because it gave better chemical yields and de in shorter reaction times, even better than under PTC conditions. Activated alkyl halides and electrophilic olefins can be used as electrophiles, working in the last case with 0.1 equivalents of base. Alkylated products **11** were isolated after acid/base extractive work-up in 25–95% yield and 70–98% de.

Two procedures can be employed for the final hydrolysis step. In the case of the *N*-bis(methylsulfanyl)methylene derivatives **10**, the imide cleavage was achieved with lithium hydroperoxide in THF/H<sub>2</sub>O (3:1) to give the chiral auxiliary in 87–90% yield, whereas the imine hydrolysis was performed with 1 M hydrochloric acid. Free amino acids **12** were isolated after treatment with propylene oxide. For products **11** the most convenient conditions involved the use of refluxing in water affording, after simple extractive work-up, recovered (–)-imidazolidinone (95–99%) and (*S*)- $\alpha$ -amino acids **12** such as allylglycine, prenylglycine, phenylalanine, 3,4-(methylenedioxy)-phenylalanine, pyroglutamic and 2-(*tert*-butoxycarbonylamino)-5-oxohexanoic acids in 45–87% yield and 66–96% ee. Other hydrolysis conditions allowed the *N*-Boc- and *N*-Fmoc-protected amino acids and esters to be obtained.<sup>10c</sup>

The alkylation of the glycine template (–)-**8** has been applied to the synthesis of heterocyclic  $\alpha$ -amino acids such as (–)-baikiain **13** and the tetrahydroisoquinoline deriva-

tive **14** by using (*Z*)-1,4-dichloro-2-butene and  $\alpha,\alpha'$ -dibromo-*o*-xylene as dielectrophiles, respectively (Figure 2). Moreover, starting from the (+)-ephedrine-derived imidazolidinone the corresponding benzophenone glycinimide (+)-**8** has been prepared in 54% overall yield, this compound being used for the preparation of (*R*)- $\alpha$ -amino acids by means of DBU–LiCl mediated alkylation followed by hydrolysis in refluxing water.<sup>10c</sup>

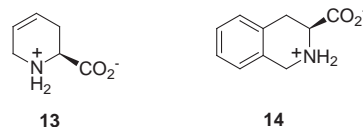
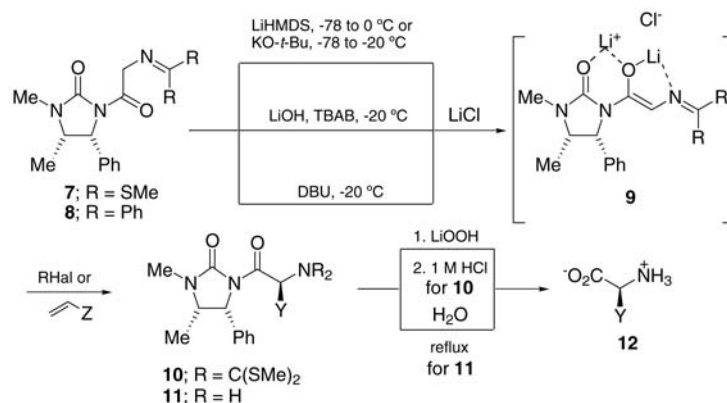


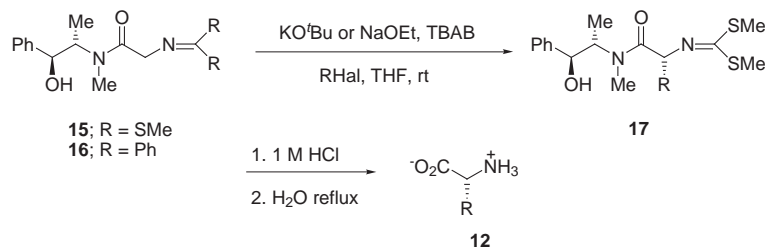
Figure 2

At that point we decided to prepare imines derived from Myers' (+)-pseudoephedrine glycinamide **6**,<sup>15</sup> expecting a higher stability of the amide bond during the basic conditions of the alkylation step. For the synthesis of imine **15**, (+)-pseudoephedrine was deprotonated with BuLi–LiCl and condensed with commercially available *N*-[bis(methylsulfanyl)methylene]glycine methyl ester at 0 °C.<sup>16</sup> Compound **15** could be isolated in 71% yield, but the synthesis of related benzophenone imine **16** took place in low yield (<20%). The alkylation process could only be carried out with glycinamide **15** under PTC conditions, but using strong bases such as sodium hydride, lithium *tert*-butoxide, potassium *tert*-butoxide, or sodium ethoxide in THF at room temperature. Under these conditions, *O*-alkylation at the hydroxy functionality of the chiral auxiliary, observed when potassium hydroxide, caesium hydroxide, or potassium carbonate were used as bases, could be avoided (Equation 2). Activated alkyl halides were employed as electrophiles, alkoxides lithium *tert*-butoxide (1 equiv) or sodium ethoxide (3 equiv), in the presence of TBAB, giving the highest de's (66–94%) and isolated yields (36–72%).

The observed diastereofacial bias was the same as in the case of Myers' glycinamide **6**. In the proposed model the lithium cation of the alkoxide coordinates to two mole-



Equation 1

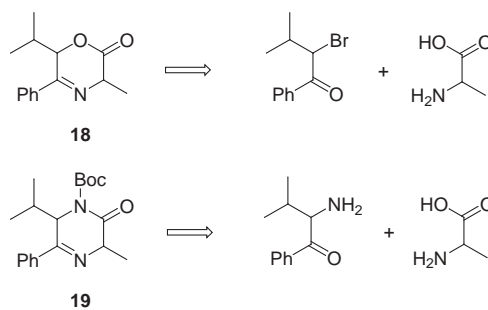


## Equation 2

cules of the solvent (THF) blocking one of the faces of the *Z*-enolate.<sup>15c</sup> We have performed *ab initio* calculations on the enolate<sup>17</sup> at the RHF/6-31G(d) theory level<sup>18</sup> and its optimized geometry confirms the proposed reactive conformation for the enolate of reagent **6**.

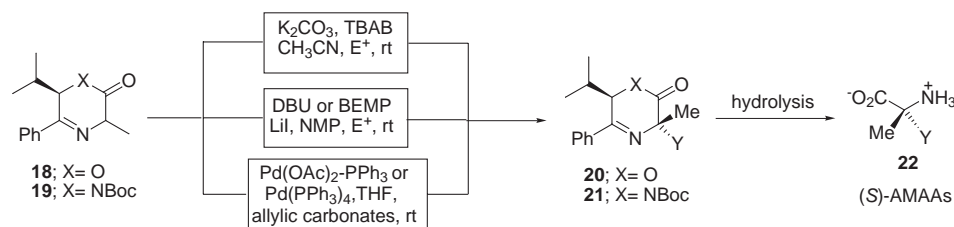
For the synthesis of  $\alpha$ -methyl- $\alpha$ -amino acids (AMAAs), important compounds in medicinal chemistry, the most direct pathway is the alkylation of enolates derived from alanine templates. In the case of alanine acyclic reagents, the imino group should derive from an aldehyde. Very poor results were observed in our initial attempts to alkylate ephedrine-imidazolidinone or pseudoephedrine alanine templates with the amino group protected with benzaldehyde or *p*-chlorobenzaldehyde, probably due to steric reasons. However, we found that cyclic imine templates from alanine, with structure of 3,6-dihydro-2*H*-1,4-oxazin-2-one **18** and 1,2,3,6-tetrahydro-2-pyrazinone **19**, are very efficient substrates for the quaternization of the alanine enolate.<sup>19</sup> These heterocyclic reagents, which bear a phenyl group at the 5-position, have a highly acidic alanine hydrogen at the 3-position, which after deprotonation should give a stabilized azaenolate. Moreover, the isopropyl group at the 6-position can generate 1,4-asymmetric induction through a blocking effect of one of the two diastereotopic faces of the enolate, sterically protecting at the same time the deprotonation of the hydrogen at this position. Our primary studies were dedicated towards investigating the synthesis of oxazinones following a procedure described for the racemic systems.<sup>20</sup> Thus,  $\alpha$ -bromoisovalerophenone was treated with the potassium salt of *N*-Boc-L-alanine in DMF and the resulting diastereomeric esters were separated by recrystallization and/or flash chromatography. After *N*-Boc-deprotection and formation of the imine the (*6R*)-*trans*-oxazinone was obtained and only slight epimerization at C-3 was detected (dr 20:1), which is unimportant because this carbon atom will become planar after the formation of the enolate.<sup>21</sup> Unfortunately, the (*6S*)-*cis*-oxazinone also suffered epimerization at C-6 and could not be used further for the synthesis of (*R*)-AMAAs. Nevertheless, starting from *N*-Boc-D-alanine, the corresponding (*6S*)-*trans*-oxazinone was prepared following the same protocol.<sup>21c</sup> The relative configuration of *trans*-oxazinones was determined by NMR and X-ray diffraction analysis.<sup>21a</sup> The related *trans*-pyrazinone<sup>22</sup> **19** was prepared in 69% overall yield by reaction of (*R*)- $\alpha$ -aminoisovalerophenone hydrochloride, easily accessible from D-valine, with mixed *N*-Boc-L-alanine-pivalic anhydride

followed by cyclization and finally *N*-Boc protection (Scheme 1).<sup>23</sup> Pyrazinone **19** was obtained in the same diastereomeric ratio as oxazinone **18**, what means that both heterocycles have similar acidity at C-3. Semiempirical calculations on the optimised model of lithium enolates of **18**<sup>21c</sup> and **19**<sup>23b</sup> showed the blocking effect of the, almost perpendicular, isopropyl group to the ring in both reagents.



## Scheme 1

These heterocyclic reagents could be alkylated at room temperature under very mild reaction conditions, either with potassium carbonate as base under solid-liquid PTC conditions in acetonitrile or in the presence of organic bases such as DBU or BEMP and lithium iodide in *N*-methylpyrrolidone. Under PTC conditions, activated alkyl halides and electrophilic olefins gave good yields (60–75% for oxazinones and 44–86% for pyrazinones) and diastereoselectivities (84–96% for oxazinones and 95–98% for pyrazinones). Both reagents reacted with formaldehyde under PTC conditions to afford the addition products **20** and **21** (Y = CH<sub>2</sub>OH) in 63% and 71% yield, and with 60% and 81% de, respectively (Equation 3). In general, pyrazinones are more stable than oxazinones towards purification protocols and gave better yields and de, by contrast oxazinones are more readily accessible. BEMP is the base of choice for oxazinones when unactivated alkyl halides were used as electrophiles,<sup>21b,c</sup> the reaction taking place in short times (ca. 1 h), with >96% de and moderate yields (38–65%). For pyrazinones, stoichiometric amounts of DBU should be used for alkyl halides and 10 mol% for Michael additions affording products **21** in 49–84% yield and 95–98% de.<sup>23b</sup> The presence of lithium iodide is important for both systems, since it prevents O-alkylation in the case of oxazinones and the homocoupling of the enolate for pyrazinones.<sup>21b,c</sup> The relative con-



## Equation 3

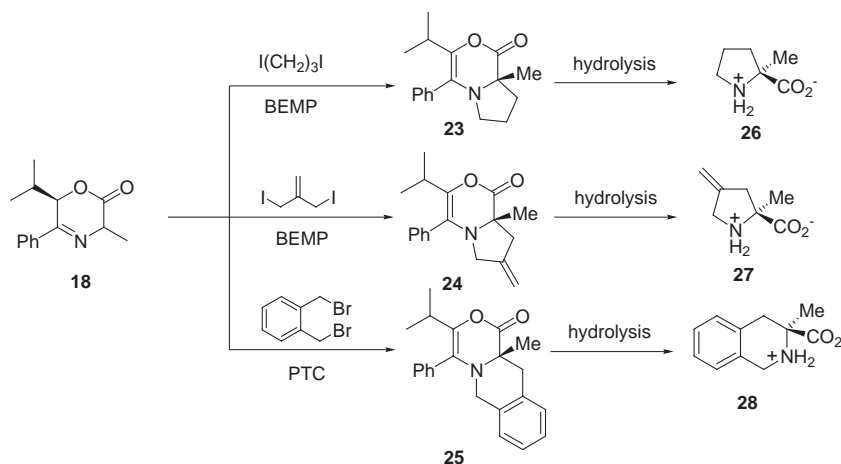
figuration of the obtained alkylated products **20** and **21** was confirmed by NOE experiments and by X-ray diffraction analysis in the case of **20** (Y = CH<sub>2</sub>C≡CH).

The third possibility is the allylation of glycine or alanine enolates under Pd(0)-catalysis. This process has been carried out previously only with LDA-generated enolates from Oppolzer's benzophenone glycinimide **5**.<sup>24</sup> Surprisingly, in the case of oxazinone **18**<sup>21</sup> and pyrazinone **19**<sup>23</sup> the diastereoselective allylation took place under neutral conditions by using allylic carbonates in the presence of Pd(PPh<sub>3</sub>)<sub>4</sub> (5 mol%) and 1,2-bis(diphenylphosphanyl)ethane (dppe) (14 mol%) or Pd(OAc)<sub>2</sub> and PPh<sub>3</sub> (10 mol%) at room temperature in THF. These reaction conditions failed in the case of imidazolidinone glycinimides **8** probably due to steric reasons.<sup>25</sup> The reaction takes place in 53–69% for oxazinones and 64–85% yields for pyrazinones, with 70–96% and 98% de, respectively. When unsymmetrically substituted allylic carbonates were employed, the attack of the enolate took place mainly or exclusively at the less substituted position on the (η<sup>3</sup>-allyl)palladium complex and the resulting double bond was obtained with *E*-configuration. In the case of pyrazinone **19**, the addition of vinyloxirane was regio- and diastereoselective by using Pd(OAc)<sub>2</sub> and dppe, the corresponding (*E*)-allylic alcohol **21** (Y = CH<sub>2</sub>CH=CHCH<sub>2</sub>OH) being obtained in 77% yield and 98% de.<sup>23b</sup>

The most difficult task in the asymmetric synthesis of α,α-dialkylated α-amino acids, such as AMAAs **22**<sup>26</sup> is the final hydrolysis of the corresponding precursors. In the case

of alkylated oxazinones **20** and pyrazinones **21** it was possible to perform the hydrolysis with 6 M aqueous HCl at 150 °C (pressure tube) for 1 d followed by precipitation of the free (S)-AMAAAs **22** by using propylene oxide. Some representative examples such as α-MePhe, α-MeAsp, α-MeTrp, α-MeSer, α-MeGlu, and α-MeLeu were prepared in high enantiomeric excesses and good yields. In the case of the enantiomeric (6*S*)-oxazinone **18**, the corresponding (*R*)-AMAAAs, α-MePhe, α-MeAsp, α-MeGlu, and α-Iva were obtained.<sup>21b</sup> For the hydrolysis to α-allylalanine the use of milder reaction conditions was necessary. Thus, in the case of the oxazinone **20** (Y = allyl) the imine was firstly hydrolysed with 2 M HCl in THF at room temperature for 3 h, followed by the ester hydrolysis with aqueous LiOH in THF at room temperature for 12 h. Finally, the amino acid was purified by Dowex column chromatography and isolated in 57% yield and 93% ee.<sup>21a,b</sup> However, for the pyrazinone derivative **21** (Y = allyl) a mixture of 0.75 M hydrochloric acid, acetic acid, toluene and Dowex was heated at 100 °C during 4 days to give (S)-α-allylalanine in 62% yield and 98% ee (Equation 3).<sup>23b</sup>

The dialkylation of oxazinone **18** and pyrazinone **19** with dihalides was studied for the asymmetric synthesis of heterocyclic AMAAs. Only oxazinone **18** underwent C and N-dialkylation in the presence of BEMP to afford the corresponding products **23** and **24** (55% and 60% yield), or under PTC conditions for **25** (80%) in >98% de. After the appropriate hydrolysis, optically pure cyclic (S)-AMAAAs **26–28** were obtained in 73–81% yield.<sup>21b,c</sup>

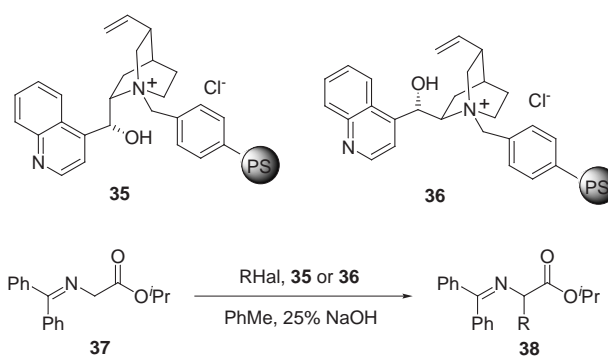


## Equation 4

## 2.2 Electrophilic Alkylation with Chiral Phase-Transfer Catalysts

Other groups in this field were inspired by the pioneering work of O'Donnell's and Grabowski's groups<sup>27</sup> using tetraalkylammonium halides derived from *Cinchona* alkaloids cinchonidine **29** and cinchonine **30** ( $R^1 = \text{Bn}$ ,  $R^2 = \text{H}$ , allyl, Bn), as PTC catalysts in the monoalkylation of benzophenone-imine glycinate for the synthesis of (*R*) and (*S*)- $\alpha$ -amino acids, respectively, with 42–81% ee.<sup>5</sup> Corey's<sup>28</sup> and Lygo's<sup>29</sup> groups could improve the ee up to 99.5% with  $R^1 = \text{anthracenylmethyl}$ . Modified ammonium salts **29** and **30** were used with, cesium hydroxide in dichloromethane at a temperature between  $-78$  and  $-60$  °C<sup>28</sup> and, potassium hydroxide in toluene at room temperature,<sup>29</sup> respectively. Chiral binaphthol derived ammonium salts **31**<sup>30</sup> with KOH in toluene at room temperature or cesium hydroxide at 0 °C have been used for the preparation of (*R*)-AAs or (*R*)-AMAs in ee up to 96% or 99%. NOBIN **32** and TADDOLs,<sup>31</sup> **33** ligands<sup>32</sup> as well as chiral salen-metal complexes **34**<sup>33</sup> have been used for the synthesis of AMAs with ee's up to 93% (Figure 3). Very recently, NOBIN **32** has also been used for the asymmetric synthesis of AAs with high ee.<sup>34</sup> The search for novel chiral PTC catalysts is still an important challenge.<sup>35,36</sup>

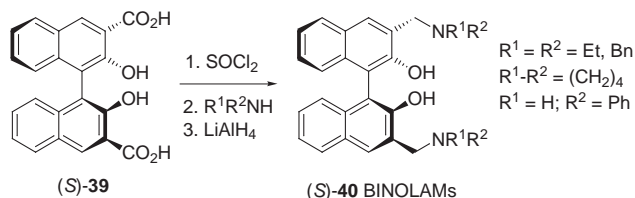
We focused our attention on polymer-supported catalysts derived from *Cinchona* alkaloids, the most accessible ammonium salts,<sup>37</sup> in order to achieve an easy separation and recovery of the PTC catalyst. Cinchonidine and cinchonine were alkylated with Merrifield resin<sup>38</sup> to the corresponding ammonium salts **35** and **36** (Equation 5). The enantioselective alkylation of isopropyl glycinate benzophenone imine **37** was carried out in toluene in the presence of 25% aqueous sodium hydroxide at 0 °C with different activated alkyl halides and with catalysts **35** and **36**.<sup>39</sup> Monoalkylated products **38** were obtained in 70–95% yield and the corresponding (*S*)-AAs in up to 90% ee with catalyst **35** and (*R*)-AAs in up to 40% ee in the case of polymer **36**. The origin of the enantioselectivity is based on the close contact between the enolate and the chiral ammonium salt according to the X-ray structure of *O*-(9)-allyl-*N*-(9)-anthracenylmethylcinchonidinium



Equation 5

*p*-nitrophenoxide.<sup>28a</sup> The model proposed by Corey explains the efficient blocking of one of the faces of the enolate by the ammonium salt.

We have used (aminomethyl)binaphthols **40** related to NOBIN catalysts **32** for the enantioselective alkylation of enolates derived from aldimines of alanines by formation of chiral ion pairs (Equation 6).<sup>33</sup> This type of hydrophobic amino phenols can act as chelating agents for alkali ions and therefore the ion-pairs can be soluble in organic solvents. Different (*S*)-bis(aminomethyl)binaphthols [(*S*)-BINOLAMs] **40** were prepared in 53–58% overall yield from diacid (*S*)-**39**, which was prepared by homocoupling of methyl 3-hydroxy-2-naphthalenecarboxylate<sup>40</sup> and further resolution with *L*-leucine methyl ester.<sup>41</sup>



Equation 6

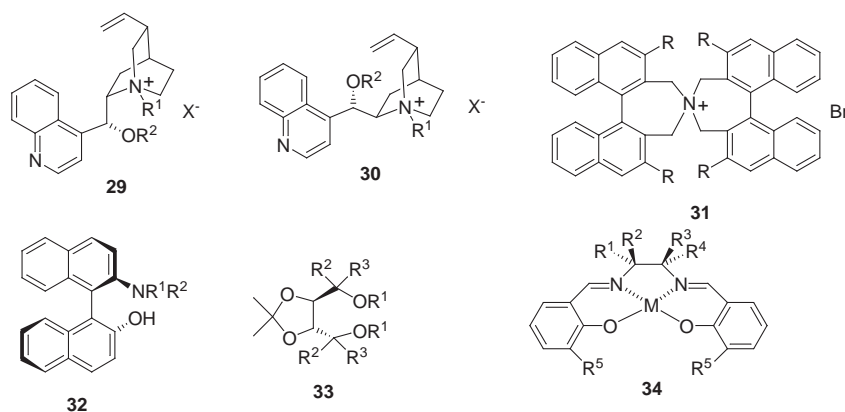
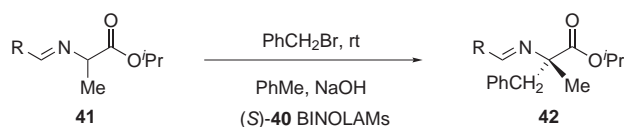


Figure 3

These optically active ligands **40** were used in the alkylation of several aldimines of isopropyl alaninate **41** with benzyl bromide as electrophile and sodium hydroxide (3 equiv) in toluene at room temperature being the best reaction conditions (Equation 7).<sup>42</sup> (*S*)- $\alpha$ -MePhe was isolated in 85% yield and 68% ee after hydrolysis using the diethylamine derivative (*S*)-**40** ( $R^1 = R^2 = \text{Et}$ ) as phase-transfer catalyst (5 mol%).



Equation 7

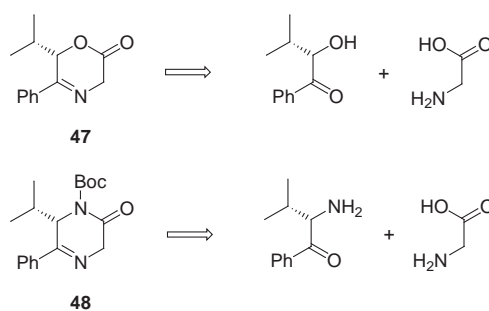
After these preliminary promising results we are now studying further applications of these aminophenols as catalysts in asymmetric synthesis.

### 2.3 Chiral $\alpha,\beta$ -Didehydroamino Acid Derivatives

Chiral  $\alpha,\beta$ -didehydroamino acid (DDAA) derivatives<sup>43</sup> are important building blocks for the synthesis of acyclic amino acids by hydrogenation reactions.<sup>44,2f</sup> Moreover, they are especially suitable compounds for cyclopropanation and cycloaddition reactions affording 1-aminocyclopropane-1-carboxylic acids (ACCs)<sup>21,45</sup> and cyclic and bicyclic  $\alpha$ -amino acids.<sup>21</sup> For the synthesis of chiral cyclic DDAA derivatives **43** and **44**, Horner–Wadsworth–Emmons olefination conditions are used after preparation of the corresponding cyclic glycine phosphonates (Figure 4). In the case of derivatives **45** and **46**, condensation with aldehydes under strong basic conditions must be used. We have developed a preparation of chiral cyclic DDAA derivatives with the structure of oxazinone and pyrazinone bearing an imine function, under mild condensation conditions, in order to study their applications to the asymmetric synthesis of  $\alpha$ -amino acids.

L-Valine-derived (*S*)-2-hydroxy and (*S*)-2-aminoisovalerophenone were used for the preparation of chiral glycine templates oxazinone **47** and pyrazinone **48**, respectively (Scheme 2). In the case of oxazinone **47**, (*S*)-2-hydroxyisovalerophenone was allowed to react with *N*-Boc-glycine under DCC conditions followed by deprotection with hydrogen chloride and subsequent trimethylamine-mediated cyclization affording **47** in 53% overall yield.<sup>46</sup> For the synthesis of pyrazinone **48** the same strategy as for the

alanine derivative **19** was employed, providing the corresponding glycine derivative in 78% overall yield.<sup>47</sup>



Scheme 2

The Knoevenagel-type condensation of these glycine templates with aldehydes took place with potassium carbonate as base and TBAB as phase-transfer catalyst in acetonitrile at room temperature to furnish diastereoselectively (*Z*)-DDAA derivatives **49** (50–64% yield)<sup>46</sup> and **50** (47–88%).<sup>47</sup> Dehydroalanine derivatives **51**<sup>46</sup> and **52**<sup>47</sup> were obtained by simple reaction of glycine templates **47** and **48** with Eschenmoser's salt at room temperature in 50% and 88% yield, respectively (Equation 8). In the case of glycine-derived pyrazinone **48**, it was also possible to carry out the condensation with *tert*-butoxybis(dimethylamino)methane (Bredereck's reagent) or even with inexpensive *N,N*-dimethylformamide dimethylacetal in 1,2-dimethoxyethane (DME) at 75 °C to provide diastereoselectively enaminone (*Z*)-**53** in 96% and 95% yield, respectively.

Pyrazinone DDAA derivatives **50** could also be prepared by Heck reaction of the dehydroalanine derivative **52** and by vinylic substitution onto enaminone **53** (Equation 9).<sup>47b</sup> The coupling of aryl iodides with the methylenepyrazinone **52** took place diastereoselectively under Jeffery's conditions,<sup>48</sup> using palladium(II) acetate (5 mol%) and triphenylphosphine (10 mol%) as catalyst in the presence of tetrabutylammonium bromide and potassium carbonate in refluxing acetonitrile in 54–70% yield. The oxazinone derivative **51** decomposed under similar reaction conditions. Enaminone **53** can act as  $\beta$ -acylvinyl cation equivalent<sup>49</sup> reacting with Grignard reagents or under Barbier conditions<sup>50</sup> affording diastereoselectively (*Z*)-DDAA derivatives **50** in 31–60% yield.

Hydrogenation reaction only took place with oxazinone DDAA derivatives **49**. Higher diastereoselectivities were

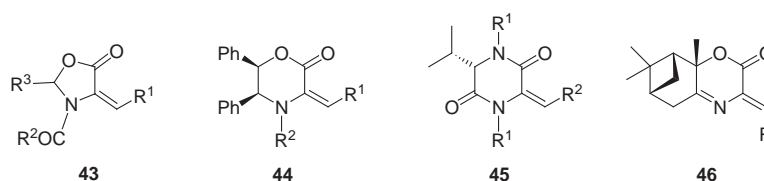
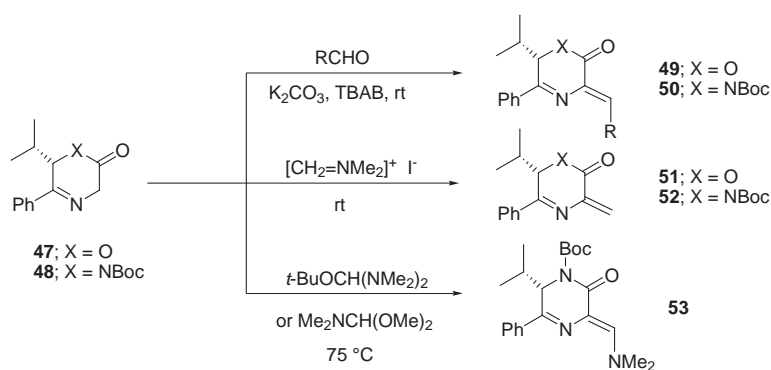
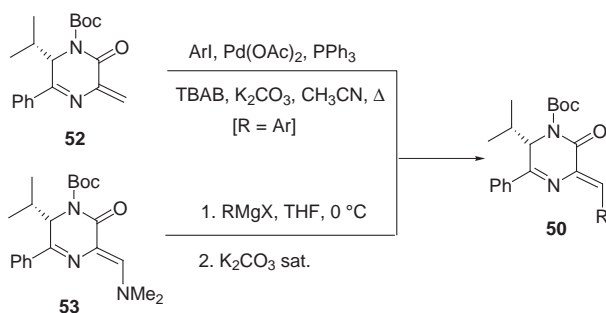


Figure 4



Equation 8

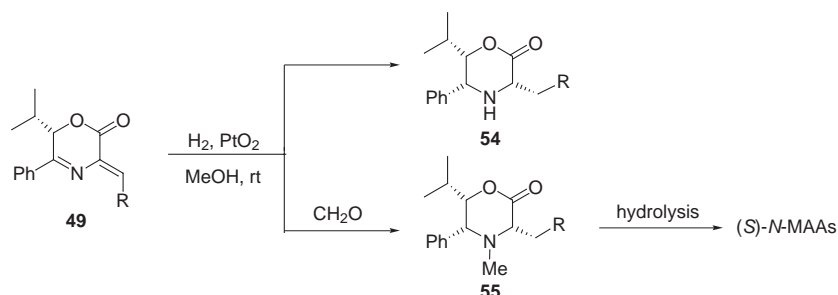


Equation 9

obtained with Pearlman's catalyst in methanol at room temperature and at normal pressure, to give all-*cis*-morpholin-2-ones **54** in 62–95% yield and 92–94% de. When the hydrogenation process was performed in the presence of aqueous formaldehyde, the corresponding *N*-methylmorpholinones **55** were obtained in 70–75% yield and 82–96% de.<sup>47</sup> The easy hydrogenation of the imine group is due to the conjugation of the phenyl group and occurred with total diastereoselectivity. The configuration was assigned by NMR studies as well as by X-ray diffraction analysis on product **55** (R = *t*-Bu). The hydrolysis was studied only in the case of morpholinones **55** in order to obtain *N*-methyl- $\alpha$ -amino acids (*N*-MAAs) because they are important components of peptides and depsipeptides isolated from plant strains, microorganisms and marine species.<sup>51</sup> Hydrogenolytic cleavage of the benzylamine moiety in morpholinones **55** (R = Me, *i*-Pr) was achieved

with Pearlman's catalyst and hydrogen at 3.5 bar in methanol in the presence of trifluoroacetic acid, followed by hydrolysis with 6 M hydrochloric acid at 150 °C and treatment with propylene oxide. Thus, enantiomerically pure (*S*)-2-(methylamino)butanoic acid and (*S*)-*N*-MeLeu were isolated in 63% and 83% overall yield, respectively (Equation 10).

The diastereoselective cyclopropanation<sup>52</sup> of DDAA derivatives **49** and **50** was achieved using Corey's dimethylsulfoxonium methylide,<sup>53</sup> prepared in DMF or DMSO with sodium hydride as base at room temperature. This methodology was applied to the synthesis of (–)-*allo*-nor-coronamic acid **58** and (–)-*allo*-coronamic acid **59**, which play an important role in the control of enzymatic processes for plant growth and fruit ripening. The cyclopropanation was carried out using oxazinone and pyrazinone DDAA derivatives **49** and **50** (R = Me, Et). Spirocyclic compounds **56** and **57** were obtained in 9:1 dr in the case of oxazinones<sup>46a,c</sup> in 11:1 dr (R = Me) and 23:1 dr (R = Et) for pyrazinones.<sup>47</sup> Pure diastereomers could be isolated after flash chromatography in 52% (R = Me) and 63% (R = Et) yield for oxazinones and in 70% (R = Me) and 79% (R = Et) yield for pyrazinones. The configuration of **56** (R = Et) was determined by X-ray diffraction analysis.<sup>46c</sup> The minor diastereomers result probably from attack at the most hindered side; alternatively, a  $\beta,\gamma$ -rotation of the formed enolate adduct prior to the intramolecular displacement of DMSO has to be ruled out. The corresponding 1-aminocyclopropanecarboxylic acids (ACCs) **58** and **59** were obtained from the oxazinones in 60% and



Equation 10



67% yield, respectively in enantiomerically pure form after hydrolysis with 6 M hydrochloric acid at 150 °C and treatment of the hydrochlorides with propylene oxide in the case of oxazinones (Equation 11). However, pyrazinone derivatives **57** decomposed under several hydrolysis conditions, and (–)-*allo*-norcoronamic acid **58** could be isolated in 24% yield after treatment with 3 M hydrochloric acid at 100 °C for 4 days.<sup>47b</sup>

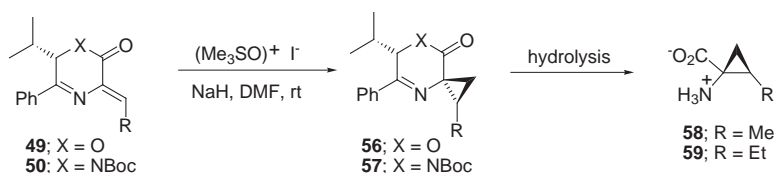
The Diels–Alder cycloaddition reaction was performed with dehydroalanine derivatives **51** and **52**, which behave as better dienophiles<sup>54</sup> than other dehydroalanine related systems,<sup>55</sup> reacting with cyclic dienes under smooth reaction conditions and with *endo*-selectivity. *endo*-Adducts **60**<sup>46</sup> and **61**,<sup>47</sup> were mainly obtained using cyclopentadiene after reaction at room temperature for 3 hours and isolated after purification in 55% and 42% yield, respectively. The configuration of adduct **60** was established by X-ray diffraction analysis.<sup>46b</sup> For cyclohexadiene it was necessary to heat at 90 °C for 6 hours affording oxazinone **62**<sup>46</sup> in 49% yield. In the case of pyrazinone **52** the reaction was carried out at room temperature for 6 days providing adduct **63**<sup>47</sup> in 95% yield, the configuration of which was determined by NMR studies on a reduced derivative of **63**.<sup>47b</sup> The corresponding saturated bicyclic amino acids were isolated after hydrogenation-hydrolysis processes. (–)-(1*R*,2*R*,4*S*)-2-Aminobicyclo[2.2.1]heptane-2-carboxylic acid **64** was obtained in 85% and 61% yield based on oxazinone **62** and pyrazinone **52**, respectively (Equation 12). Related bicyclo[2.2.2]octane **65** was isolated in 85% and 38% overall yield based on oxazinone **63** and pyrazinone **52**, respectively. These type of bicyclic amino acids are very resistant to metabolic attack. Compound **64** inhibits the transport of non polar  $\alpha$ -amino acids across cell membranes, acts as insulin releasing factor, and inhibits fla-

voprotein amino acid oxidases, whereas amino acid **65** perturbs selectively the levels of neutral amino acids in the cerebral cortex.<sup>56</sup>

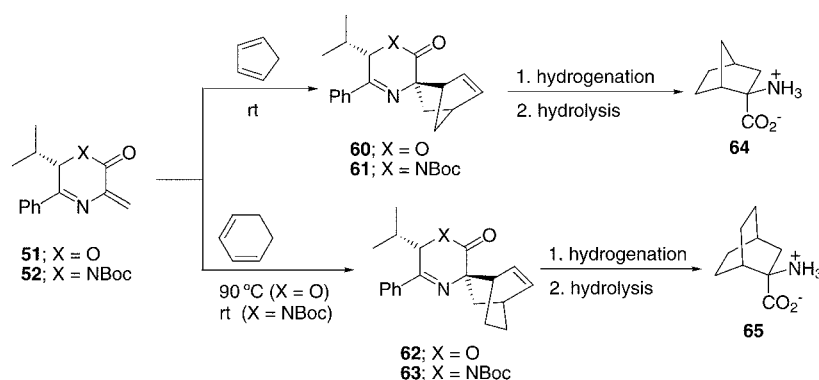
A noticeable feature of these dienophiles **51** and **52** is their high reactivity and the *endo*-selectivity compared to other DDAA derivatives such as **43**,<sup>55</sup> which need days to react with cyclopentadiene and gave *exo*-cycloadducts. The rather low energy of their LUMO<sup>54</sup> and the lower steric hindrance close to the nitrogen atom in compounds **51** and **52** explain the observed difference in reactivity and stereoselectivity.

## 2.4 Chiral Azomethine Ylides

At this point we were interested in studying further applications of chiral saturated oxazinones **69** and **70**, derived from glycine **47** and alanine **18** templates, respectively, as precursors of chiral azomethine ylides. Thus, the most direct strategy for the synthesis of enantiomerically enriched substituted prolines is 1,3-dipolar cycloaddition between chiral azomethine ylides stabilized by a carboxy function and a dipolarophile. Furthermore, it is possible to control the simultaneous formation of four defined stereocenters.<sup>19b,57</sup> Seebach's imidazolidinone-derived ylide **66**,<sup>58</sup> Williams' **67**,<sup>59</sup> and Harwood's morpholin-2-one ylides **68**<sup>60</sup> have been used efficiently as chiral dipoles (Figure 5). Moreover, morpholin-2-ones **69** and **70** derived ylides **71** and **72** bearing bulky groups, such as an isopropyl at C-6 and a phenyl at C-5 could determine the diastereoselection of the cycloaddition reaction.



Equation 11



Equation 12

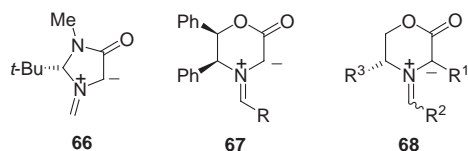
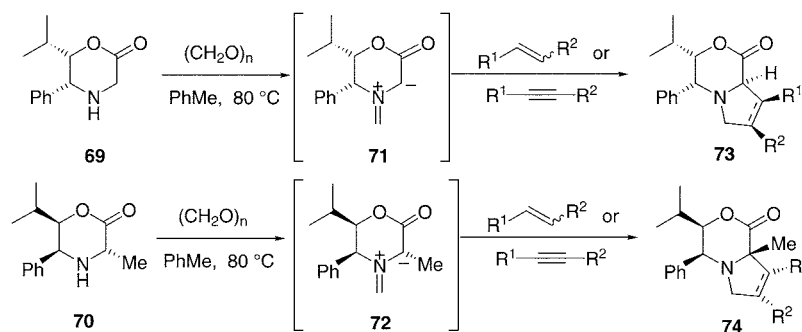


Figure 5

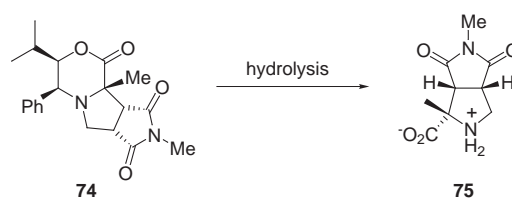
Catalytic hydrogenation of glycine **47** and alanine **18** oxazinones under normal hydrogen pressure in the presence of palladium on carbon afforded diastereoselectively morpholin-2-ones **69** and **70** in 70% and 90% yield, respectively.<sup>61</sup> They reacted with different electron-deficient olefins or acetylenes in the presence of paraformaldehyde in toluene at 80 °C to furnish the corresponding cycloadducts **73** and **74** (22–75% isolated yields) as major products as a consequence of a high *endo*-selectivity (Equation 13). This stereoselectivity is higher than that observed when using dipoles **68**,<sup>60</sup> but slightly lower than employing morpholinone-derived dipoles **67**.<sup>59</sup> Theoretical studies using the PM3 hamiltonian<sup>62,63</sup> on dipole **72** showed a more stable conformation with the phenyl and isopropyl groups in *pseudo*-axial and in *pseudo*-equatorial position, respectively. In the case of using ethyl acetylenecarboxylate, the reaction with ylid **72** was totally regioselective affording unsaturated product **74** ( $R^1 = H$ ,  $R^2 = CO_2Et$ ), according to the frontier orbital coefficients in azomethine ylides and dipolarophiles.<sup>57</sup> The degree of asymmetric induction was fairly high corresponding to attack of the dipolarophile at the less hindered face of dipoles **71** and **72**.

The X-ray diffraction analysis of adduct **74**, derived from *N*-methylmaleimide allowed the configuration of all stereocenters to be assigned. This adduct was hydrolyzed to proline **75** in 60% overall yield by esterification with methanol followed by hydrogenolysis at 3.5 bar with Pearlman's catalyst and hydrolysis and precipitation of the free amino acid (Equation 14).

For the transition structures, the PM3 semi-empirical method<sup>62</sup> and the hybrid Hartree–Fock (HF)/DTF method B3LYP/6-31G(d)<sup>18</sup> revealed that *endo* and *exo* approaches were concerted but asynchronous, with a difference of energies of 0.7 and 2.4 Kcal/mol, respectively, always favouring the former.<sup>61</sup>



Equation 13



Equation 14

### 3 Protecting-group Reagents

The use of benzyloxycarbonyl (Cbz) and 9-fluorenylmethoxycarbonyl (Fmoc) groups for temporary protection of primary and secondary amines, and specially for amino acids, was a key discovery in modern peptide chemistry.<sup>3</sup> These carbamates as well as the *tert*-butoxycarbonyl (Boc) group are very useful for minimizing racemization, generally by formation of oxazolones when *N*-acylated amino acids are prepared. In addition, they can be cleaved under different reaction conditions. For the introduction of the Boc group, di-*tert*-butyldicarbonate is the most useful reagent, while for Cbz and Fmoc the corresponding chloroformate esters are used. However, these chloroformates are unstable, highly toxic and have tendency to promote the formation of undesirable protected dipeptides.<sup>64,65</sup> For these reasons other Cbz-X and Fmoc-X reagents have been developed, *N*-hydroxysuccinimide derivatives Cbz-OSu and Fmoc-OSu being particularly useful, allow *N*-protection to be performed in the absence of a base. We have been working on the preparation of reagents Cbz-OX **76** and Fmoc-OX **77** derived from *N*-hydroxysuccinimide, *N*-hydroxy-5-norbornene-2,3-dicarboxamide, *N*-hydroxyphthalimide and 1-hydroxybenzotriazole (HOBt). Our aims have been to find simple, economical, easily scalable and green processes for the preparation of reagents **76** and **77** (Figure 6). For this purpose, two aspects of the synthesis have been improved. Firstly, the *in situ* preparation of *N*-hydroxyimides HOX by the simple reaction of aqueous hydroxylamine with the corresponding anhydride in water as the solvent. Secondly, the reaction of these aqueous solutions with the corresponding benzyl or 9-fluorenylmethyl chloroformates under PTC conditions.<sup>66</sup> The reaction between these

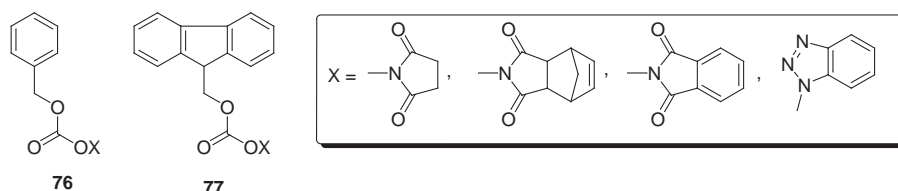


Figure 6

chloroformates and *N*-hydroxyimides or 1-hydroxybenzotriazole hydrate was carried out in a mixture of an organic solvent (toluene, dichloromethane) and water, using potassium carbonate as base and tetrabutylammonium chloride as phase-transfer catalyst. These processes have been carried out in 20 mmol and in some cases in 3 mol scale and with overall yields ranging from 62% to 94%.

In this context we envisaged that the development of polymer supported Cbz-OSu and Fmoc-OSu reagents would allow the easy separation and recycling of the P-XOH reagent. Recent examples of Fmoc, Cbz and Boc-derivatives of a polystyrene-bound HOBt<sup>67</sup> and of a *N*-hydroxysuccinimide (HOSu) ring-opening metathesis polymer<sup>68</sup> have been used as protecting group reagents. We focused our attention on the very inexpensive commercially available poly(styrene-*alt*-maleic anhydride), which, by reaction with aqueous hydroxylamine gave rise to a poly(styrene-*co*-*N*-hydroxymaleimide) **78** (P-HOSu) with an activity of 1.5 mmol g<sup>-1</sup>. The acylation with benzyl or fluorenylmethyl chloroformates, as previously described for reagents **76** and **77**, afforded Cbz-P-OSu **79** and Fmoc-P-OSu **80** as stable white solids soluble in polar solvents such as methanol, acetone, DMSO, and DMF (Figure 7). The protection of amines and amino acids took place with only one equivalent of these reagents in acetone–water in the presence of potassium carbonate. The corresponding products were isolated in good yields 35–90% for Cbz- and 40–95% for Fmoc-derivatives with recovery of the P-HOSu.<sup>69</sup> The synthesis of other P-HOSu-based protecting-group reagents is underway.

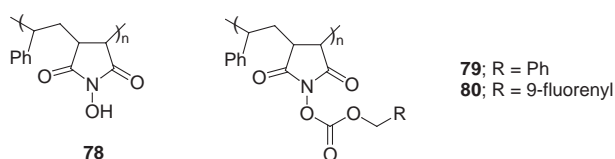


Figure 7

#### 4 Peptide Coupling Reagents

The synthesis of peptides, either in solution or in solid phase, needs the activation of the carboxylic functionality of the amino acid, usually by a peptide coupling reagent.<sup>4</sup> The important requirements for a coupling protocol are: (a) high yields, (b) fast processes and (c) prevention of racemization. Carbodiimides in combination with HOX additives, such as those previously mentioned for the

synthesis of protecting group reagents, is a classical methodology used to generate in situ active esters. Phosphonium and aminium salts as well as other reagents, have become very efficient activating agents in both solution and solid phase peptide synthesis. In this field we have considered the synthesis of new economical reagents based on carbodiimides and aminium salts.

We found out that previously mentioned polymer-supported *N*-hydroxysuccinimide (P-HOSu, **78**)<sup>70</sup> behaves as a nice recoverable additive for dicyclohexylcarbodiimide (DCC)-mediated solution-phase synthesis of simple di- and tri-peptides.<sup>71</sup> These studies have been carried out with both HOSu and P-HOSu by choosing different protected (Boc, Cbz, Fmoc)  $\alpha$ -amino acids at room temperature in the presence of pyridine as a base in acetonitrile for 6 to 7 hours. Yields (83–98%) were similar for both additives, although in some cases P-HOSu was more effective than HOSu. In the case of difficult couplings, for example for  $\alpha,\alpha$ -dialkylamino acids such as  $\alpha$ -aminoisobutyric acid (Aib) or *N*-methyl- $\alpha$ -amino acids, the reaction was performed at 40 °C in 1 day (yields 47–70%). The extent of racemization was examined with Anteunis' test<sup>72</sup> (the coupling of CbzGlyPheOH and ValOMe) affording the corresponding tripeptide in 18:1 and 24:1 diastereomeric ratios with P-HOSu and HOSu, respectively, whereas the dr was 9:1 without the additive. The P-HOSu could be recovered by precipitation with hexanes and simple filtration. This polymer showed good mechanical stability, the cross-linking with diamines as in the case of poly(ethylene-*co*-*N*-hydroxymaleimide),<sup>70a,b</sup> not being necessary.

Aminium salts became very popular reagents owing to their efficiency and low degree of racemization. 1-Hydroxybenzotriazole (HOBt) is the most used HOX system being the leaving group in reagents such as *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU, **81**) and tetrafluoroborate (TBTU, **82**) (Figure 8).<sup>4</sup> These reagents have an aminium structure on the solid state. After the coupling process the peptide has to be carefully washed with water in order to remove all traces of HOBt. We envisaged that the use of a polymer-bound HOBt for the preparation of onium salts would facilitate the separation and recovery of the reagent. Thus, the related polymer-supported reagents P-HBTU **83**<sup>73</sup> and P-TBTU **84**<sup>74</sup> have been prepared from the already described polystyrene-bound HOBt<sup>75</sup> by reaction with the chlorouronium hexafluorophosphate or tetrafluoroborate derived from tetramethylurea (TMU) and oxalyl chloride, in the presence of pyridine.<sup>73,74</sup>

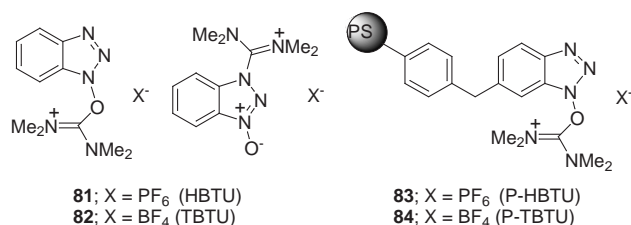
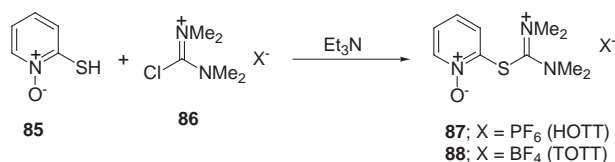


Figure 8

P-TBTU **84** was assayed in di- and tri-peptide synthesis and compared with TBTU **82**.<sup>74</sup> The experiments were carried out in acetonitrile as solvent and pyridine as base for 1 day at room temperature or at 50 °C in the case of hindered amino acids (Aib and *N*-MeVal). In general, the reaction times were longer with the polymeric reagent and yields slightly lower. No racemization was detected when the Anteunis' test<sup>72</sup> was performed. P-TBTU was found to be effective even under aqueous conditions. Thus, the coupling in acetonitrile containing 5% water took place with the same yield as in neat acetonitrile. Polymer-supported P-HOBt was recovered by simple filtration and re-used again for the preparation of P-TBTU. Similar results have been found with P-HBTU.<sup>73</sup>

Our aims in the case of non-supported peptide coupling reagents, were: (a) to find an inexpensive water soluble XOH leaving group, (b) to use a one-pot phosgene-free procedure for the synthesis of aminium salts in order to facilitate its scale-up, and (c) to use non-toxic ureas. As an alternative to already described HOX systems, we focused our attention on the economically favourable 2-mercaptopyridine-1-oxide **85**, which is also very soluble in water and can be easily removed by extractive work-up. The corresponding TMU-derived thiuronium reagents (*S*)-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethylthiuronium hexafluorophosphate **87**, HOTT<sup>76</sup> and tetrafluoroborate **88**, TOTT were prepared in 55% and 75% overall yield following a one-pot procedure by reaction with the chlorouronium salts in the presence of triethylamine (Equation 15).<sup>77</sup> For the synthesis of chlorouronium salts **86** a phosgene-free protocol based on the use of oxalyl chloride and a catalytic amount of DMF, followed by in situ anion interchange was used.



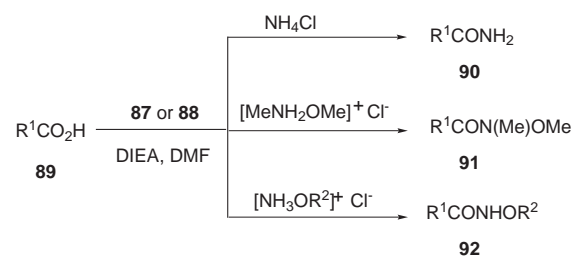
Equation 15

Reagents **87** and **88** were used in the solution-phase synthesis of peptides and compared with other coupling reagents, such as TBTU **82**. In general, good yields (71–97%) were obtained in acetonitrile or DMF with triethyl-

amine as base even coupling Aib and *N*-MeAAs (35–82% yields). Anteunis' test<sup>72</sup> gave 10:1 dr and Young's test (synthesis of BzLeu-Gly-OEt)<sup>78</sup> afforded 7% and 3.7% racemization with HOTT **87** and TOTT **88**, respectively. These values are lower when compared to other HOBt-based uronium salts, for example HBTU **81** gave 12.7% racemization in Young's test.<sup>79</sup>

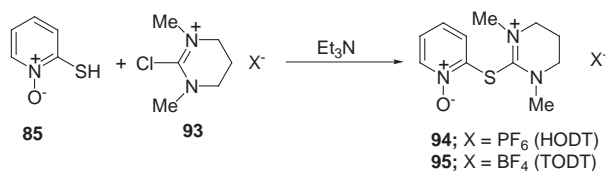
In order to check the efficiency of HOTT **87** and TOTT **88** in solid-phase peptide synthesis (SPPS), the manual step-wise solid-phase assembly of a pentapeptide related to Leu-enkephalinamide, H-Tyr-Aib-Aib-Phe-LeuNH<sub>2</sub>,<sup>80</sup> in which Gly has been substituted by Aib, was performed following a Fmoc/*t*-Bu protection scheme. A poly(ethylene-glycol)-polystyrene (PEG-PS)-resin bearing a peptide amide Rink linker was used as solid support, in DMF as solvent, diisopropylethylamine (DIEA) as base and TBTU **82** as coupling reagent except for the Aib-Aib bond. After 2 hours reaction with HOTT and TOTT, 24% and 19% yield of pentapeptide was obtained, similar to TBTU, which gave 29% of efficiency.<sup>81</sup> The extent of racemization in SPPS was studied with two model tripeptides containing Ser (H-Gly-Ser-Phe-NH<sub>2</sub>)<sup>82</sup> and His (H-Gly-His-Phe-NH<sub>2</sub>),<sup>83</sup> which are especially prone to racemization. The synthesis was performed following the same methodology described above for efficiency studies using HOTT, TOTT and TBTU and we observed in all cases <1% of racemization for the Ser-model and 1.6%, 1.4% and 2.9%, respectively for the His-model.<sup>81</sup>

These thiuronium salts **87** and **88** have also been used as amidation reagents for the synthesis of amides (45–95% yield) derived from aliphatic and aromatic acids **89** and different substituted amines.<sup>77</sup> Moreover, starting from carboxylic acids, primary amides **90** can be easily prepared by reaction with ammonium chloride in DMF as solvent and DIEA as base.<sup>84</sup> The reaction is very fast (30 min) and takes place at room temperature even with hindered substrates. Different functionalised carboxylic acids and protected (Boc, Cbz and Fmoc)  $\alpha$ -amino acids have been transformed successfully into the corresponding pure amides (46–99% yield).<sup>84</sup> These reagents are also very effective for the synthesis of hydroxamates such as Weinreb amides **91**, and *O*-methyl or *O*-benzylhydroxamates **92** under similar reaction conditions (2–3 h, r.t.) described for primary amides (Equation 16). Different carboxylic acids **89**, as well as protected  $\alpha$ -amino acids, were transformed into pure hydroxamates **91** and **92** in high yields (70–95%) without appreciable racemization.<sup>85</sup>



Equation 16

Taking into account the reported embryotoxicity of tetramethylurea (TMU),<sup>86</sup> we have prepared the analogous thiouronium salts **94** (HODT) and **95** (TODT) derived from a non toxic urea, the common solvent 1,3-dimethylpropyleneurea (DMPU).<sup>81</sup> They have been synthesised following the same one-pot phosgene free methodology described for HOTT and TOTT. The chlorouronium **93** as well as the thiouronium salts **94** and **95** are more stable than the corresponding 1,3-dimethylethyleneurea derivatives.<sup>87</sup> We have studied the use of these reagents **94** (HODT) and **95** (TODT) in solution and in solid-phase peptide synthesis, being as efficient as **87** (HOTT) and **88** (TOTT) in solution. However, higher degrees of racemization were obtained with DMPU reagents in the Young's test<sup>78</sup> (39.7% and 41.1%, respectively), whereas Anteunis' test<sup>72</sup> gave similar results (7.4% and 9.0%, respectively).<sup>81</sup> For the SPPS, a lower yield in the synthesis of Leu-enkephalinamide system (10% and 14%) and similar racemization ratios (Ser: <1% and His: 2.0%) were observed.<sup>81</sup>



Equation 17

## 5 Conclusion

This account has shown that chiral acyclic glycine imines derived from ephedrine-imidazolidinones and from pseudoephedrine are appropriate templates for the asymmetric synthesis of monoalkylated cyclic and acyclic  $\alpha$ -amino acids by means of diastereoselective alkylation reaction under mild easily scalable reaction conditions. However, the cyclic chiral alanine imines either with oxazinone or pyrazinone structures are more convenient templates for the synthesis of dialkylated  $\alpha$ -amino acids. For the enantioselective alkylation of acyclic imino glycinates, polymer-supported *Cinchona* alkaloid-derived ammonium salts are recyclable phase-transfer catalysts, whereas for imino alaninates, bis(aminomethyl)binaphthols (BINOLAMs) are the appropriate phase-transfer catalysts. Chiral  $\alpha,\beta$ -didehydroamino acid derivatives with oxazinone and pyrazinone structure have been used successfully in hydrogenation, Heck, cyclopropanation and Diels–Alder reactions for the asymmetric synthesis of NMAAs, ACCs and bicyclic amino acids. Azomethine ylides derived from the morpholinones, prepared by hydrogenation of oxazinones, are excellent dipoles for the 1,3-dipolar cycloaddition with dipolarophiles for the asymmetric synthesis of prolines. In the field of protection of amino acids, Fmoc-P-OSu and Cbz-P-OSu, derived from polymeric *N*-hydroxysuccinimide (P-HOSu) are very effective reagents for the protection of amino groups.

In the case of peptide coupling reagents, polymeric P-HOSu/DCC and P-TBTU and P-HBTU are very efficient for solution-phase synthesis whereas thiouronium salts derived from 2-mercaptopyridine-1-oxide and TMU, such as HOTT and TOTT, and from DMPU, such as HODT and TODT have been used in solution- and solid-phase peptide synthesis with efficiency and racemization rates comparable to other aminium salts. They can also be used for the direct preparation of primary amides, Weinreb amides and other hydroxamates by direct coupling of carboxylic acids and amino acids with ammonium chloride or hydroxylamine derivatives.

## Acknowledgement

First of all I want to thank all my co-workers whose names appear in the references for their fundamental, both experimental and intellectual, contribution to the chemistry described in this account. Continuous financial support by the national and regional administrations through the corresponding institutions (Ministerio de Educación y Ciencia, Ministerio de Ciencia y Tecnología and Generalitat Valenciana) is gratefully acknowledged. I also thank Luxembourg Industries (PAMOL) Ltd. and ASAC Pharmaceuticals International S. A. for generous financial support.

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