

Update 1 of: α,β -Diamino Acids: Biological Significance and Synthetic Approaches

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Alma Viso was born in Madrid (Spain) in 1964. She obtained a B.S. degree in Chemistry in 1987 and a Ph.D. in 1992 from Universidad Complutense de Madrid (UCM). In 1992, she moved to Massachusetts Institute of Technology (MIT) as a Fulbright fellow to work with Stephen L. Buchwald for 18 months. She joined the faculty at UCM (Madrid) in 1993 as an Assistant Professor and was promoted to Associate Professor in May 2002. In December 2002, she joined Instituto de Química Orgánica General, CSIC, as a Staff Researcher (Científico Titular) and was promoted to Senior Staff Researcher (Investigador Científico) in 2007. Her current research interests are focused in two main areas, the development of new methodologies in asymmetric synthesis using sulfoxides and sulfonamides and the application of these novel methods to efficient syntheses of therapeutically valuable products.

1. Introduction

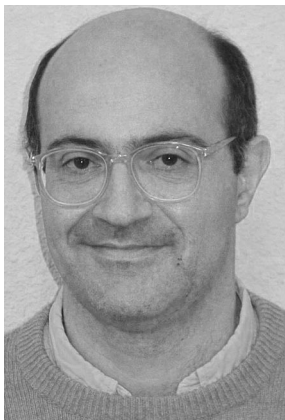
The discovery of nonproteinogenic amino acids among natural products, either in native state or as fragments of complex molecules, has increased the level of interest in this family of molecules from different scientific standpoints. Compounds with valuable biological properties can be found among these atypical amino acids. In addition, they have served as building blocks for the synthesis of new molecules or as surrogates of native amino acids in known peptidic entities to modulate their biological behavior.

In this context, α,β -diamino acids and their derivatives esters and amides, have attracted a great deal of attention among organic chemists and biochemists through the years. This interest has been due to the ubiquitous nature of α,β -diamino acids as key structural fragments of biologically active compounds. Beyond this focus, the simplest compound, 2,3-diaminopropionic acid, has re-

cently found application in the environmentally safe production of hydrogen for fuel cells, as a selective carrier of CO₂ through gel membranes.^{1a} Also, it has served to assemble a molecular device that produces propelling motion upon IR irradiation^{1b} and, lately, in the context of food chemistry, 2,3-diaminopropionic acid has been identified as an inhibitor of polyphenol oxidase, the enzyme responsible for the browning of fruits and vegetables^{1c} and as an enhancer of Maillard browning.^{1d} In spite of the incidence of these molecules in an increasing number of areas, this review will deal with the biological significance, the therapeutic uses, and other interesting applications of α,β -diamino acids and their derivatives found in the existing literature.

Additionally, aside from the above considerations, the structural complexity of these molecules, having two vicinal chiral centers has also represented a challenge for synthetic organic chemists, especially the synthesis of enantiopure materials. Therefore, the aim of this article will also be to provide a deep and general view of the existing methodology for the synthesis of aliphatic α,β - or 2,3-diamino acids and their simple derivatives, esters,

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Roberto Fernández de la Pradilla was born in Logroño (Spain) in 1958. He received his B.S. degree in Chemistry from Universidad Complutense de Madrid (UCM) in 1980 and a Ph.D. degree from The University of Michigan in 1985 under the supervision of Joseph P. Marino. After postdoctoral work at UCM (Madrid), he became Assistant Professor there in 1987. In 1988, he joined Instituto de Química Orgánica General, CSIC, as a Staff Researcher (Científico Titular) and was promoted to Senior Staff Researcher (Investigador Científico) in 2000 and to Research Professor in 2007. In 1992–93, Dr. Fernández de la Pradilla was a Visiting Scientist with Rick L. Danheiser at Massachusetts Institute of Technology (MIT) for 18 months. His current scientific interests involve the development of novel synthetic strategies that rely on chiral sulfoxides with particular emphasis on strategies that allow for multiple asymmetric transformations, as well as pursuing straightforward applications of these methods to the synthesis of bioactive products.



Mariola Tortosa was born in Alcoy (Spain) in 1976. She obtained her B.S. in Chemistry from the Universidad Autónoma de Madrid (UAM) in 1999. She then joined the group of Dr. R. Fernández de la Pradilla at the Instituto de Química Orgánica General, CSIC, to carry out graduate work on the development of new asymmetric methods using chiral vinyl sulfoxides. After receiving her Ph.D. in 2005, she moved to The Scripps Research Institute in Florida to work as a postdoctoral fellow with Dr. William R. Roush for three years. Her research in Florida was directed toward the completion of a total synthesis of the antitumor agent Superstolide A using a transannular Diels–Alder strategy. In 2008 she returned to CSIC to work again with Dr. A. Viso and Dr. R. Fernández de la Pradilla as a Juan de la Cierva fellow. Her research interests include the development of new copper-catalyzed reactions and the synthesis of natural products.

or amides. Among the compounds considered in this review, either of the amino groups can be acylated or contained within a heterocyclic structure. Cyclic analogues such as imidazolidines and piperazines will be included in the article; however, aziridines and 3-amino- β -lactams will be out of the scope of this review and will be only considered as intermediates in the synthesis of acyclic derivatives since extensive revisions of their chemistry already exist in the literature.^{1e–i}



Ana B. García was born in Valladolid (Spain) in 1975. She obtained her B.S. degree in Chemistry from Universidad Autónoma de Madrid (UAM) in 1998. She then joined the group of Dr. A. Viso and Dr. R. Fernández de la Pradilla at Instituto de Química Orgánica General, CSIC, to carry out graduate work on the synthesis of vicinal dinitrogenated compounds from enantiopure sulfinimines. After receiving her Ph.D. in 2003, she spent one year at Universidad de Alcalá de Henares (UAH) working on cationic heteroaromatic systems with DNA intercalating properties under the guidance of Prof. Juan J. Vaquero and then she performed postdoctoral research with Prof. Herbert Waldmann at the Max Planck Institute for Molecular Physiology in Germany, working on the solid phase synthesis of natural product derived libraries first as a Max Planck fellow and then with a European Union contract. She holds a researcher position in the department of Medicinal Chemistry at the Spanish National Cancer Research Center (CNIO) since October 2006.

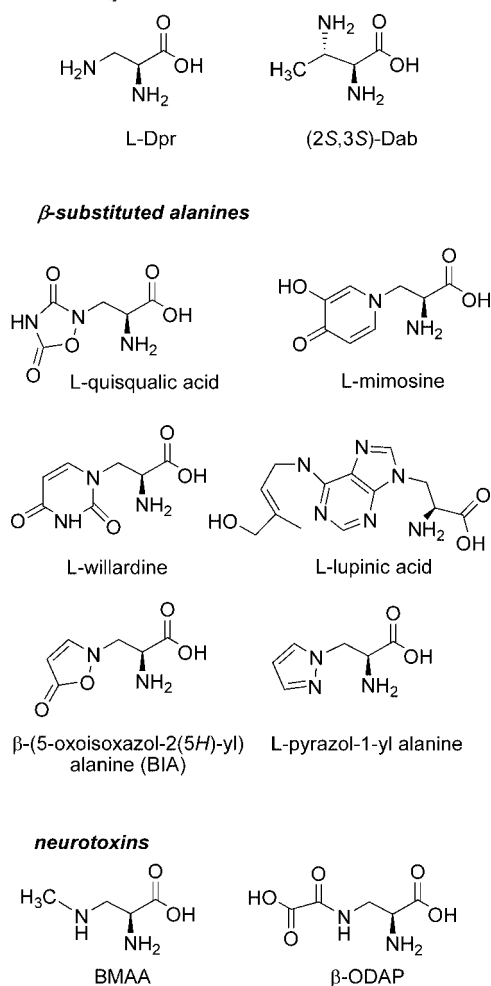


Aida Flores was born in Murcia (Spain) in 1979. She obtained her B.S. degree in Chemistry from Universidad Autónoma de Madrid (UAM) in 2001. She then joined the group of Dr. A. Viso and Dr. R. Fernández de la Pradilla at Instituto de Química Orgánica General, CSIC, to carry out graduate work for her Ph.D. During this period, she spent three months in the laboratories of Gary Molander at the University of Pennsylvania. On completion of her studies, in 2007 she took up her present position as a postdoctoral research assistant with Prof. Timothy Donohoe at the University of Oxford.

2. Relevance of Molecules Containing α,β -Diamino Acids

2.1. Natural Products

Free α,β -diamino acids have been detected as part of living organisms (Chart 1). Indeed, the presence of the simplest member of the family, α,β -diaminopropionic acid (Dpr or A₂pr, frequently referred to in the literature as Dap or DAPA), has been confirmed in protein-free extracts from Bombyx insects (D-Dpr)² and it is a common constituent of the amino acid pool of seeds from various species of *Mimosa* and *Acacia*.³ Among other examples, the two diastereomers

Chart 1. Free α,β -Diamino Acids in Nature

of α,β -diaminobutanoic acid (α,β -Dab) have been identified in the root nodules of *Lotus tenuis* inoculated with *Rhizobium* strain NZP2213.^{4a} Also cucurbitine is a naturally occurring pyrrolidine containing an α,β -diamino acid found in the seeds of *Cucurbitaceae* plants (pumpkin).^{4b,c} Recently, both Dpr and α,β -Dab have been detected in a sample of the Murchison meteorite, and this supports the formation of polypeptide structures under primitive Earth conditions and suggests polycondensation reactions of diamino acids into early peptide–nucleic acid material as one conceivable pathway for prebiotic evolution of DNA and RNA genomes.^{5a,b}

Within the large number of nonproteinogenic amino acids isolated from plants as secondary metabolites, the group of heterocyclic β -substituted alanines is of special interest to biochemistry, ecology, and neurochemistry (Chart 1).^{3,6} L-Quisqualic acid, an amino acid first isolated from the seeds of *Quisqualis indica* L. that has been used in Chinese medicine as a vermicide, is able to function as an agonist at multiple EAA (excitatory amino acid) receptor subtypes in the central nervous system. It has high affinity for the kainate, AMPA, and the metabotropic receptors. It also inhibits the $\text{Ca}^{2+}/\text{Cl}^-$ -dependent glutamic acid uptake system in brain synaptic plasma membrane preparations and an *N*-acetyl α -linked acidic dipeptidase that hydrolyzes the brain dipeptide $\text{Ac}-\text{Asp}-\text{Glu}-\text{OH}$.⁷ Mimosine, another nonproteinogenic plant α,β -diamino acid derived from seeds of *Leucaena leucicephala* or *Mimosa pudica*, has attracted a great deal of attention due to its capacity to act as a specific blocker of the cell cycle. Mimosine may block cell proliferation by

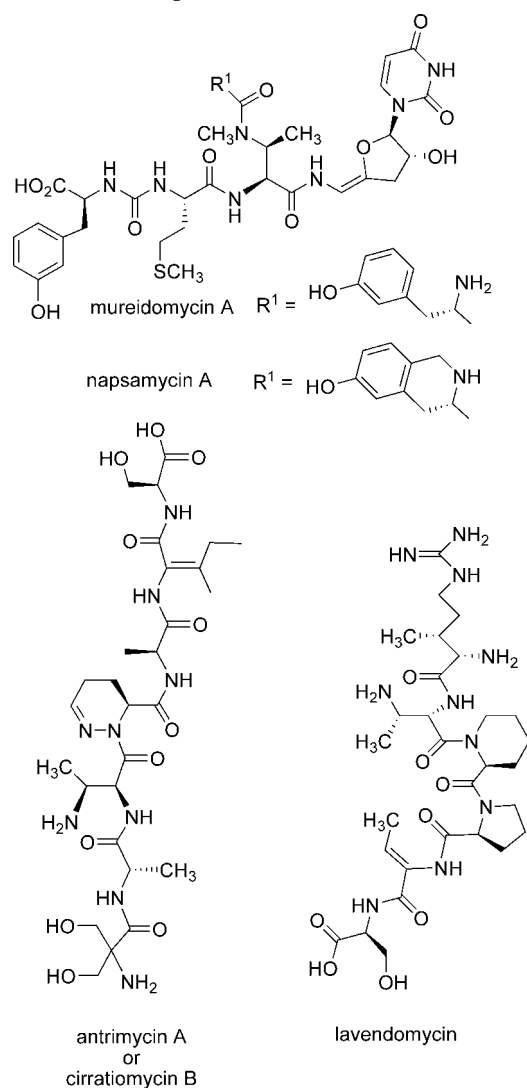
multiple mechanisms, and some mimosine derivatives have been considered as iron(III) chelators with potential activity against β -thalassaemia.⁸ Willardine and isowillardine belong also to this family of heterocyclic β -substituted alanines, and in particular, willardine has been characterized as an agonist of AMPA and kainate receptors.⁹ Among others, lupinic acid, isolated from *Lupinus angustifolius*,¹⁰ β -(5-oxoisoxazol-2(5H)-yl) alanine (BIA, β -isoxazolinone alanine), found in *Lathyrus sativus*, and pyrazol-1-yl alanine, characterized as a hypoglycemic agent and isolated from pressed juice of *Citrullus vulgaris*,¹¹ have been classified within this family and have been the object of different synthetic and biosynthetic studies.¹²

Two of the simplest α,β -diamino acid derivatives occurring in plants are neurotoxic to animals: L- β -methylaminoalanine (BMAA) and 3-(*N*-oxalyl)-L-2,3-diaminopropionic acid (β -ODAP). BMAA is an agonist of the ionotropic glutamate receptors that occurs in the cycad *Cycas micro-nesia* Hill in Guam.¹³ BMAA may have originally played a role as an antiherbivore compound in the plant but is now of great interest because of its link to a neurodegenerative disease with clinical and histological aspects similar to amyotrophic lateral sclerosis, Alzheimer's disease, and parkinsonism dementia (ALS-PDC). Biomagnification of BMAA in the Guam ecosystem has been proposed. Initially produced by a cyanobacterium associated with cycad roots, BMAA is concentrated in cycad seeds that feed flying foxes, a prized food item of the indigenous people. Those who died of ALS-PDC have high amounts of BMAA in their brain tissues, which would explain the incidence of ALS-PDC among this group, 50–100 times higher than elsewhere.^{14a–c}

The mechanism by which BMAA exerts neurotoxicity is little understood and a number of studies have tried to shed light on this issue.^{14d–f} Furthermore, BMAA was recently found to be produced by most cyanobacteria and their wide global distribution raise concerns regarding the long-term effect on human health.^{14g,h} On the other hand, although certain *Lathyrus* species have been found to be suitable as multi-purpose legume crops, their use is limited by the presence, mainly in seeds, of β -ODAP an ionotropic glutamate receptor agonist,^{15a,b,c–e} which causes lathyrisms, a paralysis of the lower limbs, which occurs in humans and to a lesser extent in animals. The presence of β -ODAP is both a public health problem and a barrier to the utility of a very beneficial staple crop, grass-pea. For these reasons, many efforts have been devoted to find food processing methods to eliminate the neurotoxin by solid fermentation^{16a,b} or mild acidic treatment that causes rearrangement of β -ODAP to the nontoxic isomer α -ODAP.^{17a–c,d} Several genotypes of grass pea containing low levels of β -ODAP^{18a,b,c,d} as well as the influence of environmental facts such as water stress and nutrient imbalance, in the biosynthesis of β -ODAP have been reported.^{18e,f} Furthermore, in vivo studies have demonstrated that BIA is the biosynthetic precursor of β -ODAP in *L. sativus*.^{12a,19a} Finally, β -ODAP (named as dencichine) is also found in lower concentrations in *Panax ginseng*, a well-known hemostatic agent in traditional Chinese medicine.^{19b–d}

Bacterial cultures are frequently the source of simple α,β -diamino acids such as (+)-2,3-diaminosuccinic acid,^{20a} antineoplastic agents such as 593A, containing the α,β -diamino acid streptoludin,^{20b,c} and peptidic antibiotics that include α,β -diamino acid residues in their structures such as edeines. Edeines contain a Dpr unit and exist as two isomers (active/inactive) depending on what nitrogen of the

Chart 3. Natural Peptidic Antibiotics III



(Chart 2a). Besides the antibiotic activity, ZwA enhances the insecticidal activity of the protein endotoxins produced by *B. thuringiensis* used against crop pests.^{31k,l}

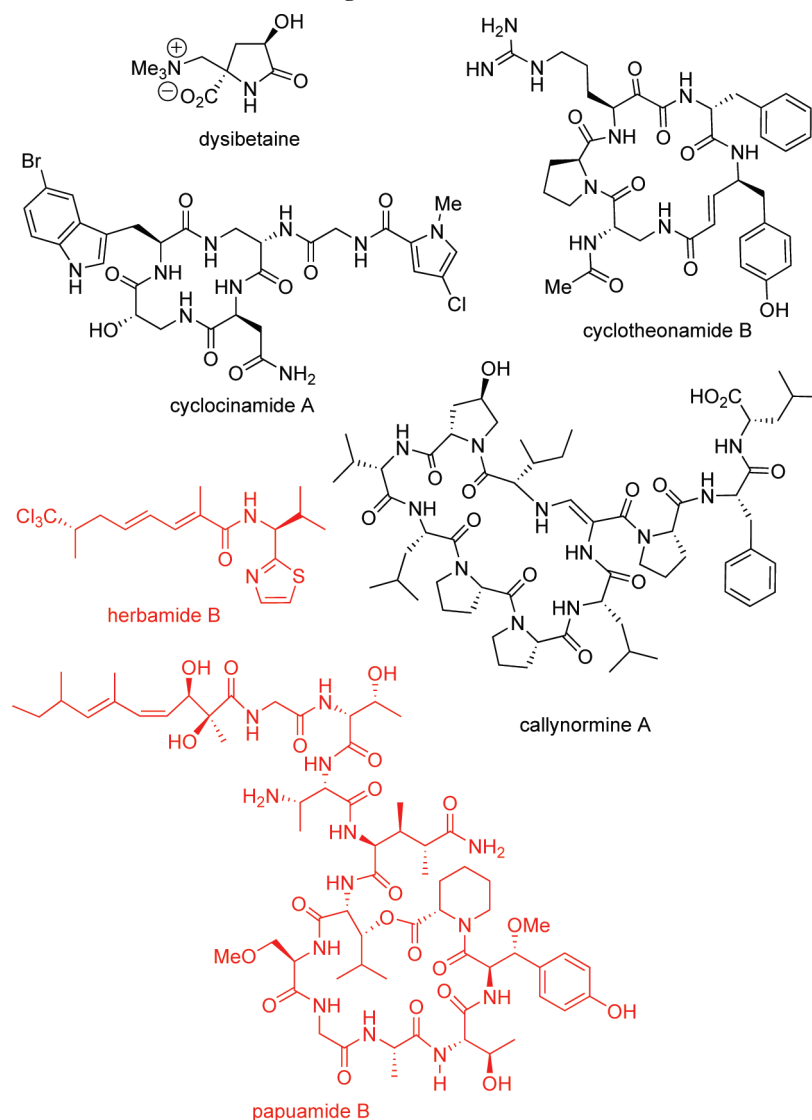
Screening soil microorganisms for the production of antibiotics specifically active against *Pseudomonas aeruginosa* led to structurally related peptidynucleoside antibiotics mureidomycins,^{32a–e,f} napsamycins,³³ and pacidamycins^{34a–c,d} that contain a fragment of α,β -Dab within their structures (Chart 3). These compounds are potent and specific blockers of bacterial peptidoglycan synthesis through inhibition of translocase, showing a low level of toxicity against mammalian cells. α,β -Dab is also contained in a variety of other peptidic antibiotics such as the family of amphomycins and the structurally related friulimycins,^{35a–c,d} aspartocin,³⁶ glumamycin,³⁷ and lavendomycin.³⁸ Furthermore, structurally equivalent antrimycins³⁹ and cirratimycins⁴⁰ are a family of dehydroheptapeptides containing α,β -Dab isolated from different microorganisms. Among them, antrimycin A was characterized as an antitubercular agent. Additionally an α,β -Dab residue is present in FR900490, an immunomodulating peptide isolated from fungus *Discosia* sp.⁴¹

On the other hand, in the past decades, the ocean has become a great source of unique chemical structures, and biologically interesting molecules containing α,β -diamino acid residues within their structure have also been isolated from marine organisms (Chart 4). For example, dysibetaine

was recently isolated from the aqueous extract of the marine sponge *Dysidea herbacea* collected from Yap, Micronesia.⁴² Furthermore, routine screening focused on detecting agents active against solid tumors led to the discovery of cyclo-cinamide A, an unusual halogenated hexapeptide from marine sponge *Psammocinia* sps. that contains a 5-bromoindole, as well as a 4-chloro-*N*-methylpyrrole, within the structure.^{43a–b,c} In addition, cyclotheonamides, a family of cyclic pentapeptides isolated from marine sponge *Theonella swinhoei*, with high activity as inhibitors of serine proteases such as thrombin, have motivated a number of studies focused on their characterization and biological properties, as well as the development of different synthetic approaches.^{44a–c,d} Some marine sponges are the source of structurally similar depsipeptides mirabamides and papuamides with anti-HIV activity that contain an α,β -Dab residue. The total synthesis of the simpler papuamide B has been newly addressed.^{44e,f} Recently, the structure of herbamide B, with the β -nitrogen embedded in a thiazole ring, has been fully elucidated. This compound was isolated from the marine red cyanobacterium *Lyngbya majuscula*.^{44g,h} Finally, recently isolated callynormine A contains an α,β -unsaturated α,β -diamino acid residue as part of this unusual marine peptide structure. It has been proposed that the double bond imposes conformational restrictions to peptides as an alternative to disulfide bridges.^{45a,b}

2.2. Synthetic Peptides and Related Compounds

In some instances, α,β -diamino acids have played a central role in replacing natural amino acids in peptidic structures in the search for modifications of the biological activities and stabilities to peptidases. Within the context of peptide design, Dpr and its derivatives, mono-, di-, and trimethylated at the β -nitrogen atom, have been used as surrogates of Asn residues in a protein matrix. These residues, especially the *N*-alkylated derivatives, would be able to introduce simultaneously specific polar interactions and a nonpolar surface area compatible with hydrophobic environments. In fact, incorporation of the monomethyl amino acid at position 16 of a 33-residue peptide (GCN4-p1) promotes heterodimerization with other helices containing an Asp at the same position by means of formation of a buried salt bridge at the helix/helix interface of the dimer.⁴⁶ Dpr has also been used to build peptide models to study the interaction of a polyleucine-based α -helical transmembrane peptide with phosphatidylcholine bilayers. The presence of terminal Dpr instead of Lys attenuates the hydrophobic mismatched effects of the peptide on the thermotropic phase behavior of the host phosphatidylcholine bilayer, in contrast to the predictions of the snorkel model.^{47a,b} The specific substitution of Lys by Dpr and other diamino acids has been examined in other contexts,^{47c,d} for example, in a 17-residue alanine-lysine peptide, seeking to assess the influence of α -helix propensity using circular dichroism measurements. The results confirmed that helix propensity decreases with the length of the side-chain (Dpr).⁴⁸ Additionally, by means of ¹H NMR spectroscopy, the helicity in water has been determined for a series of template-nucleated alanine-lysine peptides, in which Lys residues have been replaced by Dpr among other diamino acids to assess the role of Lys in stabilizing the helix.⁴⁹ Within a similar context, an α -methyl- α -amino- β -methylamino acid residue was incorporated into a linear heptapeptide with the β -nitrogen as part of the backbone, and conformational studies by NMR spectroscopy and CD measurements did not show indication of helical structures.^{50a}

Chart 4. α,β -Diamino Acid Derivatives from Marine Organisms

In addition, Dpr has also been used as a surrogate of other basic amino acids (Arg, α,γ -Dab) in antimicrobial peptides (AMPs) to understand the role of cationicity in their mechanism of action based on ionic and hydrophobic interactions.^{50b,c}

On the other hand, designing artificial ion-selective channel proteins is an active area of research that could shed light on the understanding of the function of natural ion channels and the transport of ions through the cellular membranes. In this context and focused on the search of anion selective channels, Dpr, among other residues, has been introduced at position 18 of alamethicine channels as a surrogate of Gln. While Lys18 produced high anion selectivity, the presence of Dpr results in a reversal of ion selectivity, probably due to chloride ions compensating for the local charge of the amino side chain in a wide region of the pore.⁵¹ In another recent article, the use of L-Dpr as part of a cyclic peptide capable of forming artificial transmembrane ion channels by self-assembly of planar peptide rings has been reported. The pH dependence of ionic conductance indicated that the amino group of Dpr may play a role in the conductance of the peptide channels.⁵²

Interestingly, in a different context, imidazolyl alanine has been used in a study focused on developing a peptide catalyst

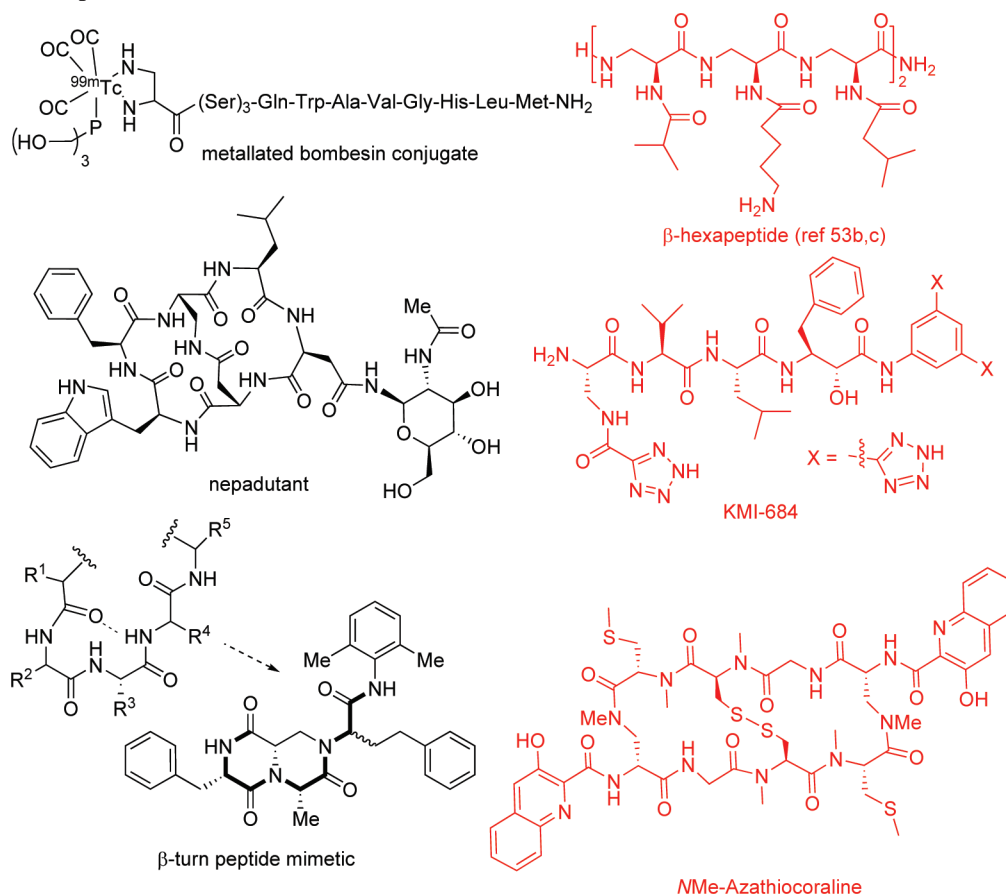
capable of mimicking enzyme activities. Indeed, incorporation of imidazolyl alanine into a peptidic β -turn backbone promotes kinetic resolution of racemic *trans*-*N*-(2-hydroxycyclohexyl)acetamide through *O*-acylation reactions. In the presence of Ac_2O , generation of an enantio-discriminating acylimidazolium intermediate as acylating species has been proposed to explain the different reactivity of each enantiomer.^{53a}

Recently, the solid phase synthesis of β -peptides based on Dpr has been carried out. The CD spectra of these molecules (Chart 5) suggest the presence of a solvent-dependent secondary structure and they exhibit high proteolytic stability and no toxicity. Therefore, they are promising biomimetic oligomers for application in medicinal chemistry.^{53b,c}

In the context of searching methodologies for the chemoselective glycosidation of peptides, a 2-amino-3-methoxyamino propanoic acid residue has been successfully incorporated into a pentapeptide for the ligation of the sugar through the aminoxy pending group.^{53d}

Aside from the above studies, radiolabeled peptides are becoming a potential tool for quantitative in vivo receptor imaging of receptor-expressing tissues. Among the existing methodologies, condensation of a radiolabeled aldehyde (or

Chart 5. Synthetic Peptides



capable of being labeled) and a hydroxylamino derivative provides a chemoselective method to label peptidic compounds. In this context, Dpr has been used as part of a starting initiator unit containing the aminoxy linker for oxime ligation in the solid-phase peptide synthesis of radiolabeled compounds.⁵⁴ In a parallel context, bombesin (BBN), a peptide that binds to gastrin-releasing peptide receptors (GRPs), overexpressed on a variety of human cancer cells, has been modified by introduction of a Dpr residue at the *N*-terminus. The BBN conjugate forms complexes with $^{99\text{m}}\text{Tc}(\text{I})$ and $\text{Re}(\text{I})$ through the Dpr residue, that specifically target GRPs in vitro and in vivo in human tumor cells (Chart 5). These results open new promising perspectives in the use of radiopharmaceuticals in nuclear medicine, fueling the search for new methodologies to build complexes.^{55a,b-d}

Other labeled peptides with a Dpr residue as an appendant unit for fluorine groups, useful in PET imaging,^{55d} as well as fluorescent probes such as pyrene, dansyl, and oxazine groups are helpful to investigate the action of the parent peptides in living cells.^{55e-g}

In addition to the above examples, a number of peptidic molecules containing Dpr residues within their sequence have been studied due to their biological activity and their potential therapeutic value. There are recent examples of this class of compounds such as GR231118, a neuropeptide Y_1 receptor antagonist,^{56a,b} nepadutant, a tachykinin NK_2 receptor antagonist (Chart 5),^{57a,b} degarelix analogues acting as gonadotropin-releasing hormone (GnRH) antagonists,^{57c} nociceptin related peptides,^{57d} arginine vasopressin modified peptides that selectively activate vasopressin receptor V_{1b} ,^{57e} and a series of cyclic peptide analogues of Agouti-related protein

(AGRP) with activity as agonists of the melanocortin-4 receptor.^{58a,b} Potent and small-sized peptides such as KMI-684 have been recently designed as β -secretase inhibitors with a tetrazole group acting as a carboxylic acid bioisostere attached to a Dpr residue (Chart 5).^{58c} Within this context, octanoylated pentapeptides derived from ghrelin have been recently identified as ghrelin *O*-acyltransferase (GOAT) inhibitors, and its potency was dramatically increased when the octanoylated serine-3 was replaced by octanoylated diaminopropionic acid.^{58d} A vancomycin related structure has also been modified by introducing an α,β -diamino acid as the *C*-terminal component in the search for new agents against vancomycin-resistant *Enterococci*.^{58e} Besides, Dpr has been used in designing peptoid-dexamethasone conjugates to carry out cell permeability studies.^{58f} Finally, looking for an increase in stability, Dpr residues have been used to build *N*-Me amide bridges as isosteres for depsi and thiodepsi bonds in thiocoraline, a potent DNA intercalating antitumoral (Chart 5).^{58g}

Especially relevant is the role of Dpr in the design of a cyclic CCK8 analogue selective for the cholecystokinin CCK_A receptor, based on structural information provided by ^1H NMR spectroscopy of the complex $\text{CCK}_8\text{-CCK}_A$. The presence of an intramolecular amide bond between the amino side-chain of Dpr and the carboxyl terminus secures a conformation for the new peptide that mimics the bioactive conformation of CCK8 in the complex.^{59a,b} Conformational restrictions have also been pursued by cyclization through the β -nitrogen of an α,β -diamino acid in the synthesis of cyclic dynorphin analogues,^{59c} cyclic agonists of the secretin receptor,^{59d} and bicyclic oxytocin antagonists.^{59e} In a related context, a bifunctional 2,5-diketopiperazine formed from Dpr

has been recently used as a scaffold to induce a β -hairpin in a peptidomimetic structure.^{59f}

Finally, some of the simplest α,β -diamino acids also offer unique opportunities in combinatorial chemistry.⁶⁰ As a consequence now, a number of orthogonally protected building blocks based on α,β -diaminopropionic acid are commercially available. In fact, amino acids containing an extra amino group result in usefulness as linkers in solid-phase synthesis, allowing for the creation of diversity in chemical libraries.⁶¹ Consequently, focused on β -turn mimetic design, bicyclic diketopiperazine libraries have been synthesized using orthogonally protected piperazine-2-carboxylic acid or α,β -diaminopropionic acid as linkers of hydroxymethyl polystyrene resin (Chart 5).^{62a,b} Also, several libraries of peptides generated via combinatorial modifications of a Dpr residue have been produced in the search for selective PKC α (protein kinase C- α) inhibitors,^{62c} Fyn-selective SH3 domain ligands,^{62d} and peptide borono lectins as sensors of glycoproteins with potential in cancer diagnosis.^{62e} Similarly, α,β -diaminopropionic acid derivatives have been linked to resins for the solid-phase synthesis of cyclic guanidines, hydantoins, and 1,3-azole-based peptides.^{63a–b,c}

α,β -Diamino acids have found application as well in designing molecules with a defined shape. Recent examples are water-soluble spiro-ladder oligomers built from heterocyclic diamino acid monomers,^{63d} globular shape peptide dendrimers synthesized using Drp as branching unit,^{63e–g} and cyclic peptide scaffolds employed to assemble glycoclusters in which the carbohydrates have a well-defined orientation.^{63h}

2.3. Therapeutically Useful Compounds

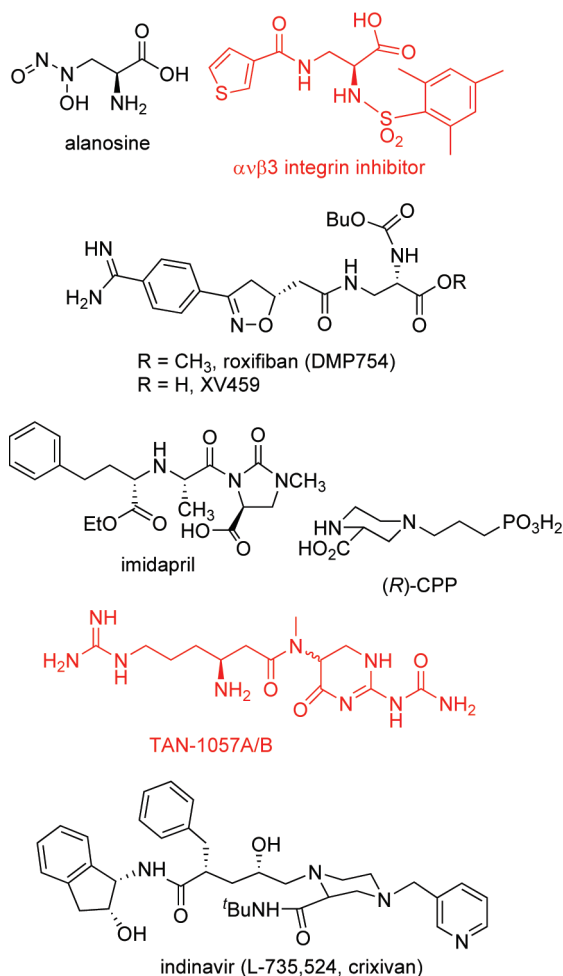
In the context of drug discovery and focused on the assessment of structure–activity relationships (SAR), α,β -diamino acids have been used as building blocks for the synthesis of analogues of nonpeptidic molecules or small peptidomimetics. Certainly, the introduction of α,β -diamino acid residues has not always resulted in compounds with improved biological profiles; however, these observations probably indicate that modifications in crucial points of the molecules have been made, especially when complete loss of bioactivity is observed.⁶⁴ Nevertheless, several other studies have reported molecules with attractive biological profiles, comparable to the lead compounds, such as analogues of antitumor PT523⁶⁵ and analogues of angiotensin-converting enzyme (ACE) inhibitor, enalapril.^{66a,b} Interestingly, the synthesis of a nonpeptidic library of potential VLA-4 antagonists has resulted in the identification of a potent lead compound containing an α,β -diamino acid residue, capable of inhibiting the binding of VLA-4 and fibronectine. This compound provides a good starting point for further optimization.⁶⁷ In addition, the parallel synthesis of a library of side-chain-modified diamino acid hydroxamates has led to the identification of a family of D-diaminopropionic acid hydroxamates as potent inhibitors of procollagen C-terminal proteinase with potential application against fibrotic diseases.^{68a}

On the other hand, in the search to overcome antibiotic resistance, siderophore drug conjugates have been proposed as valuable tools. The nature of the linker between the siderophore and the drug could play a crucial role in releasing the drug and therefore controlling the point of delivery. In this context, a siderophore containing a β -N-hydroxy aceta-

mido alaninate unit as linker has been synthesized to exploit the potential anchimerically assisted drug release inside the cell.^{68b}

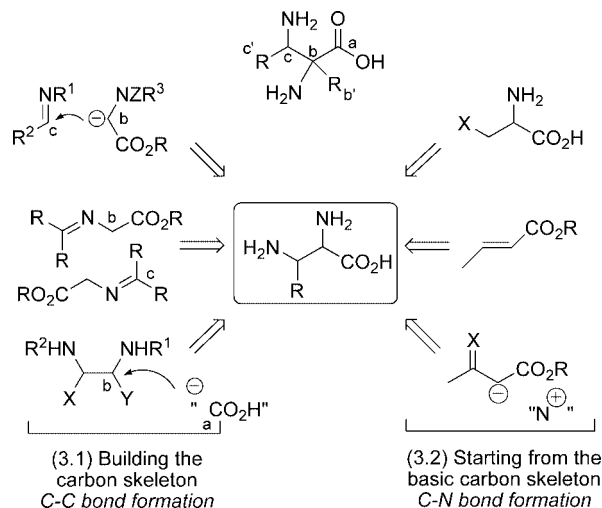
Similarly to vicinal diamines, α,β -diamino acid derivatives have a great capacity to form chelates with different metals and have been used as ligands, either directly implicated in complexation to the metal or as tethers between different moieties of the ligands.^{69a–h,i} Consequently, different research groups have taken advantage of this behavior in the search of new anticancer drugs. Complexes of Pd(II) and diamino succinates have been evaluated for antitumor activity in MDA-MB468 and HL-60 cell lines and DNA binding capacities (pUC8 plasmid).⁷⁰ Similarly, *cis*-dichloro(D,L-diaminopropionate ethyl ester)palladium(II) and *cis*-dichloro-(D,L-diaminopropionate ethyl ester)platinum(II) have been synthesized and their cytotoxic activities in several tumor cell lines have been evaluated. In addition, the interaction of these complexes with DNA, in vitro and in vivo, has been examined.⁷¹ More recently, a group of α,β -diaminopropionamide platinum complexes, bearing groups capable of interacting with DNA at the amide ligands, have been prepared. Unfortunately, the values of cytotoxicity in a number of tumor cell lines were higher than expected (IC₅₀ > 50 μ M). Furthermore, α,β -diaminopropionamide platinum complexes conjugated to neomycin B and guanidinoneomycin B have been found to generate RNA selectivity upon the *cis* platinum moiety.⁷²

Aside from the above studies, there are several α,β -diamino acid derivatives that have been recognized for their therapeutic value and extensive research has been devoted to their development as useful drugs (Chart 6). Among them, alanosine is an antineoplastic agent, produced by fermentation of *Streptomyces alanosinicus*, with a high antitumor activity in L1210 and P388 murine leukemias.^{73a–c,d} Structurally, alanosine is bioisosteric to L-aspartic acid and contains an *N*-nitroso-*N*-oxyalkylamine moiety and therefore is a potential redox-sensitive NO-releasing compound.⁷⁴ Indeed, the use of alanosine for treatment of T-cell acute lymphoblastic leukemia (T-ALL) has been proposed on the basis of its capacity to act as inhibitor of de novo synthesis of AMP and its toxicity for methylthioadenosine phosphorylase (MTAP)-deficient tumor cell lines.⁷⁵ Roxifiban, also referred to as DMP754, is the ester prodrug of XV459, an α,β -diamino acid-derived compound that behaves as a selective oral antagonist of the platelet glycoprotein IIb/IIIa receptor. Potential benefits in cardiovascular disorders such as intravascular thrombosis and unstable angina pectoris have been proposed for this compound.^{76a–f,g} Another interesting compound is imidapril, also known as tanatril, in which the α,β -diamino acid residue is part of an imidazolidinone ring. Imidapril stops the synthesis of angiotensin II by inhibition of ACE and has been used clinically in the treatment of hypertension, chronic congestive heart failure, acute myocardial infarction, and diabetic nephropathy.^{77a–b,c} On the other hand, the simple Dpr skeleton has served as a scaffold to build molecules with interesting properties such as inhibitors of the glutamate transporter EAAT-2,^{77d} inhibitors of the enzymatic degradation of carnosine mediated by carnosinase,^{77e} inhibitors of matrix metalloproteinases (MMP-7 and MMP-9),^{77f} inhibitors of $\alpha\nu\beta$ -3 and $\alpha2\beta1$ integrins,^{77g,h} and inhibitors of GABA transporters mGAT3 and GAT4.⁷⁷ⁱ Recently, *N*-terminal Dpr dipeptides have been examined as methylglyoxal scavengers to prevent the degradation of proteins by reaction with highly reactive α -dicarbonyls.^{77j}

Chart 6. Therapeutically Useful α,β -Diamino Acids

Finally, the natural dipeptide antibiotic TAN-1057A/B, containing a heterocyclic amidinoureia derived from Dpr has been the subject of several SAR studies due to its promising antibiotic activity and unique structure.^{77k-m}

On the other hand, 2-carboxypiperazine analogues constitute a special group within the pharmaceutically interesting α,β -diamino acid derivatives in which the two nitrogen atoms are embedded in an aliphatic six-membered ring, and several studies have included carboxypiperazines as a basic scaffold of SAR studies.⁷⁸ For example, a new family of cyclic matrix metalloproteinase (MMP) inhibitors derived from (\pm)-piperazine-2-carboxylic acid has been described. One of them has shown a high affinity for MMPs 1, 3, 9, and 13, and cocrystallization with MMP-3 has provided X-ray data of one complex.⁷⁹ In another report, the 2-carboxypiperazine skeleton has been employed for the synthesis of a constrained analogue of enkephalin.⁸⁰ In addition, the *R* enantiomer of 4-(3-phosphopropyl)-2-piperazine carboxylic acid (CPP) has been identified as a potent and selective antagonist of the *N*-methyl-D-aspartate (NMDA) subtype glutamate receptors with potential therapeutic utility in the treatment of epilepsy and the amelioration of neuronal damage from cerebral ischemia.^{81a-c,f} Draflazine and mioflazine belong to a family of carboxamide piperazines that have been studied extensively for their capacity to enhance extracellular adenosine concentrations by specific binding to adenosine transporter in cardiac tissue and thereby protect heart tissue against ischemia-induced damage.^{82a-c,d} However, the 2-carboxypiperazine that has caused a major impact in drug discovery is undoubtedly indinavir (also referred to as L-735,524 and

Chart 7. Representative Routes toward α,β -Diamino Acids

crivivan), an orally bioavailable HIV protease inhibitor and one of the most important therapeutic agents to date to treat HIV infection. Nevertheless, the fast emergence of drug-resistant mutants of the HIV virus increases the need for more potent and bioavailable protease inhibitors to achieve sustained viral suppression in vivo, and a number of studies dealing with modifications of the original indinavir structure are emerging.^{83a-c,d}

3. Synthetic Approaches to α,β -Diamino Acids

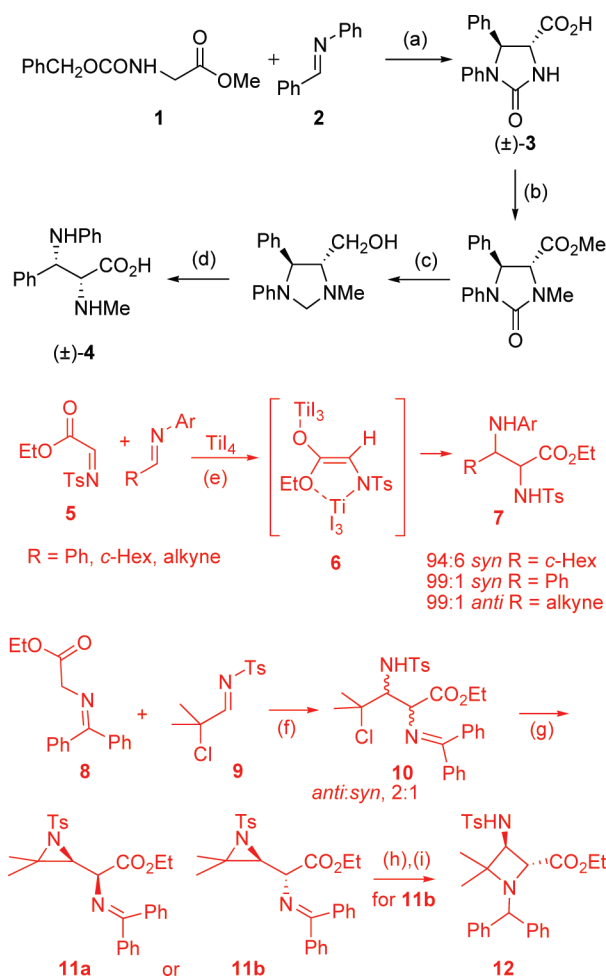
The structural complexity of these diamino acids, with two vicinal nitrogen-bearing chiral centers, has also represented a challenge for synthetic organic chemists, especially the synthesis of enantiopure materials. Within this context, in the past years, a number of synthetic routes of variable length, yield, and complexity have been reported. Chart 7 gathers some representative synthetic routes toward α,β -diamino acid derivatives. The methods found in the literature can be classified essentially in two main categories: (section 3.1) methods that require construction of the carbon backbone and (section 3.2) methods that start from the basic carbon skeleton and modify the nature of the functional groups.

3.1. Construction of the Carbon Backbone

The development of new methodologies to form carbon-carbon bonds is essential for the progress of organic synthesis. In this context, the search of adequate methodologies for the approach to α,β -diamino acids represents a synthetic challenge. Within this category, different groups can be established with respect to the carbon-carbon bond that is formed in the key step, and therefore, the following section has been organized according to methods in which the b-c, a-b, b-b', or c-c' bonds are formed (Chart 7).

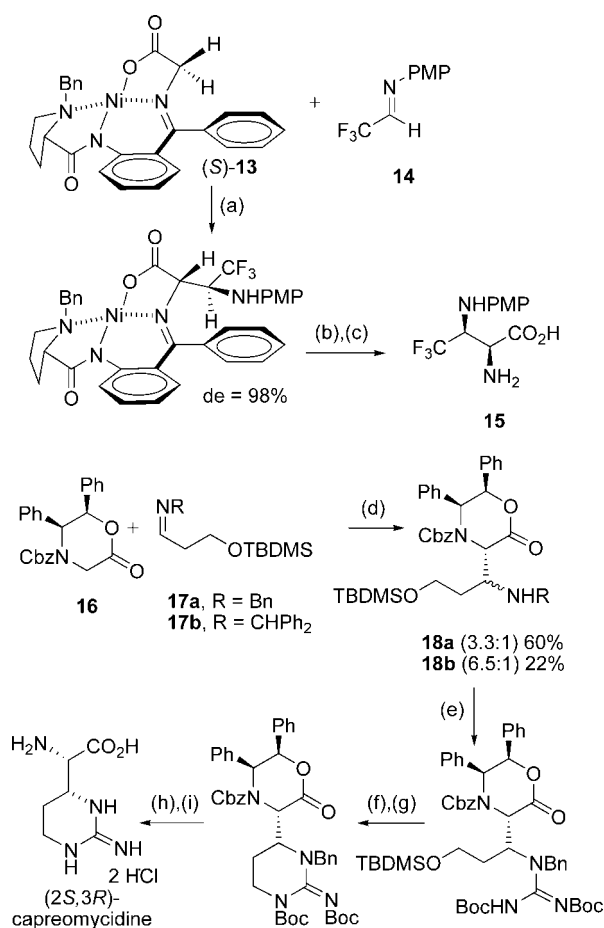
3.1.1. Methods in Which the b-c Bond Is Formed

3.1.1.1. Imines and Related Compounds as Electrophiles. The nucleophilic addition of glycines to imines and related compounds plays a pivotal role within this category. This strategy has been applied in the past to the synthesis of 3-amino- β -lactams through the nucleophilic addition of an α -amino enolate to the imine producing an α,β -diamino ester intermediate that cyclizes to yield the azetidin-2-one ring. However, the use of suitably functionalized precursors can circumvent cyclization to the β -lactam.⁸⁴ An example of this

Scheme 1^a

^a Reagents and conditions: (a) NaNH_2 , HMPT; (b) MeI , Ag_2O , DMF; (c) LiAlH_4 , Et_2O ; (d) CrO_3 , aq. HOAc; (e) MeCN , -40 to -10 °C, 50–85%; (f) LDA , THF, 66%; (g) separation and then K_2CO_3 , acetone; (h) NaCNBH_3 ; (i) Et_3N , CH_3CN .

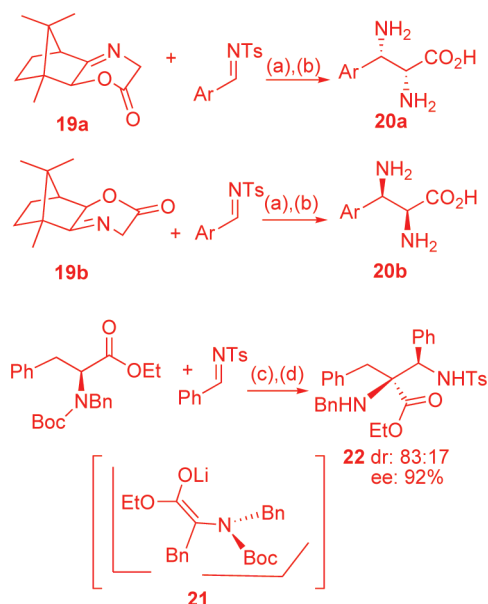
approach is the stereoselective one-pot synthesis of (\pm)-2-oxo-1,5-diphenyl-4-carboxylic acid, **3**, by addition of the enolate derived from *N*-benzyloxycarbonyl glycinate **1** to imine **2**. Carboxyimidazolidinone **3** is transformed into (\pm)-2,3-diamino-3-phenylpropanoic acid, **4**, by reduction of the urea to an aminal followed by oxidation under acidic conditions that allows for the simultaneous removal of the aminal and recovery of the carboxylic moiety (Scheme 1).^{85a,b} A recent example reports high *syn* diastereoselectivities (>90:10) when the glycinate **6** is generated in situ under reductive conditions from an α -iminoester **5** and TiI_4 . In these examples, the relative stereochemistry of the final diamino esters **7** depends on the nature of the substituents of the imine counterpart with a complete reversal to the anti isomer when the imine contains a triple bond.^{85c} In other case within this approach, *N*-(*p*-toluenesulfonyl)- α -chloroaldehydes **9** act as electrophiles, affording racemic γ -chloro- α,β -diamino esters **10** upon reaction with benzophenone imine glycinate **8** with low *syn*/*anti* diastereoselectivity. After separation, both diastereoisomers were efficiently cyclized by treatment with K_2CO_3 to β,γ -aziridino α -amino ester derivatives **11a,b**. After reduction with NaCNBH_3 , the anti isomer **11b** undergoes a regioselective intramolecular ring-opening of the β -aziridine to afford *trans*-azetidine **12**.^{85d,e} Finally, substoichiometric amounts of Lewis acids such as $\text{Zn}(\text{OTf})_2$ allow for the smooth reaction of benzophenone imine glycinate

Scheme 2^a

^a Reagents and conditions: (a) Et_3N , LiCl , DMF, 91%, 1 h; (b) HCl , MeOH ; (c) Dowex-H, NH_4OH ; (d) (i) LiHMDS , (ii) Me_2AlCl , (iii) **18a** or **18b**, THF, -78 °C, 1 h; (e) $\text{BocN}=\text{C}(\text{SMe})\text{NHBoc}$, Et_3N , AgOTf , DMF, rt, 3 h; (f) 1.7% HF, MeCN , 2 h, rt, 81–91%; (g) DIAD, PPh_3 , THF, 0 °C 15 min, rt 1 h; (h) H_2 , PdCl_2 , 115 psi, 4 d; (i) 0.5 M HCl , reflux, 1.5 h, 95%.

and in situ generated imines, thus generating *anti*- α,β -diamino esters with high yields and diastereoselectivities.^{85f,g}

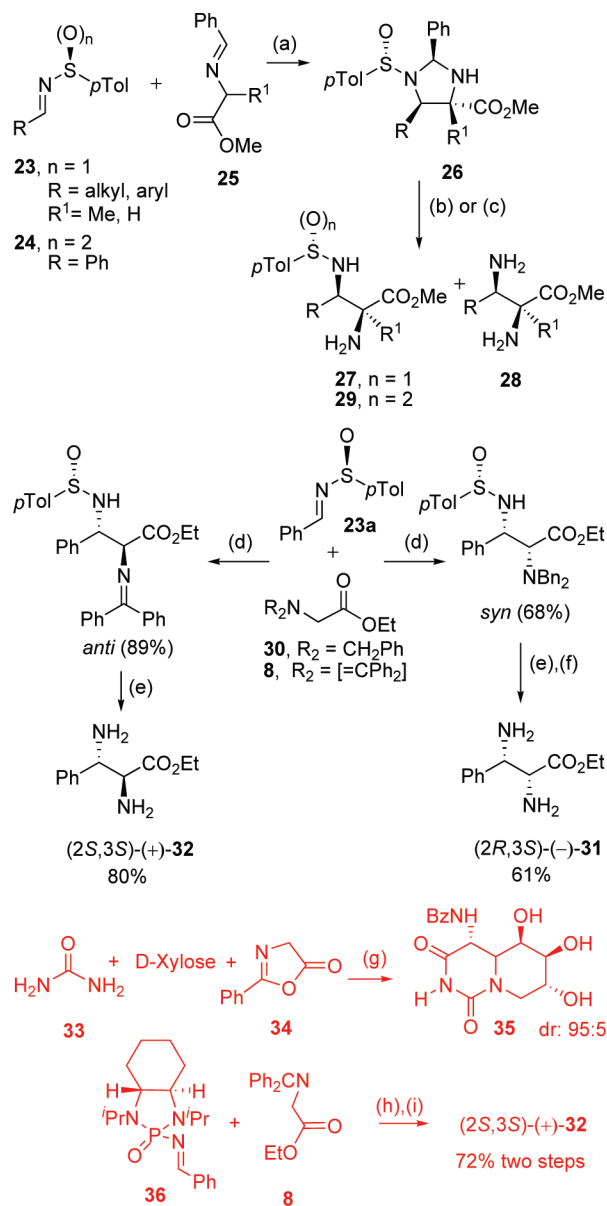
Asymmetric versions of this route involving chiral glycinate can also be found in recent literature. Thus, the addition of an enantiopure $\text{Ni}(\text{II})$ complex of α -imino glycinate **13** to trifluoromethylimine **14** takes place with a high degree of diastereocontrol, giving rise to fluorinated *syn*-3-trifluoromethyl-2,3-diamino acid, **15**, with 98% diastereomeric excess (Scheme 2).^{86a} Recently, α -aminosulfones and α -iminoesters have been successfully employed in this Mannich reaction.^{86b,c} A parallel approach has been used for the asymmetric synthesis of (2*S*,3*R*)-capreomycin within the context of the total synthesis of capreomycin IB. Indeed, the aluminum enolate of a chiral oxazinone derived from glycine **16** reacts with benzylimine **17a** to produce an inseparable 3.3:1 mixture of Mannich products **18a** in 60% yield. A significant improvement in selectivity was achieved using benzhydryl imine **17b** (6.5:1) but with a lower yield (**18b**, 22%). Other attempts to improve the selectivity were unsuccessful. Subsequently, five additional steps, including complete epimerization to the desired (2*S*,3*R*) diastereoisomer, were necessary to transform the diastereomeric mixture of **18a** into capreomycin (Scheme 2).^{87a,b} A recent example of this tactic consists of using camphor-based tricyclic iminolactones **19a,b** as precursors of the chiral enolates. Each

Scheme 2a^a

^a Reagents and conditions: (a) (i) LDA, THF, (ii) ZnCl₂, -78 °C; (b) (i) 6N HCl, 45 °C, (ii) EtOH, propylene oxide; (c) LDA, THF, -78 °C; (d) TFA, CH₂Cl₂, 0 °C.

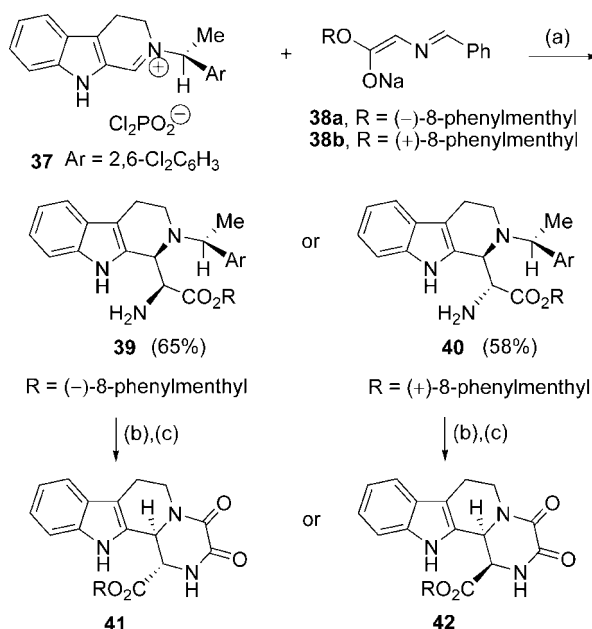
diastereomer of **19** reacts diastereoselectively with sulfonyl imines (>99:1, syn) rendering, after acidic hydrolysis 3-aryl-2,3-diaminopropanoic acids **20a** and **20b** with high enantiomeric purity (ee > 99%).^{87c} The concept of memory of chirality has also been applied for the synthesis of α,β-diamino acids. Thus, a (S)-phenylalanine derivative (ee > 99%) provides upon treatment with LDA an enolate with a chiral C–N axis **21** that reacts with sulfonyl imines affording α,β-diamino esters **22** with a quaternary stereocenter in high yield, 83:17 dr and 92% ee for the major diastereomer (Scheme 2a).^{87d}

Chiral sulfinimines **23** can act as chiral inductors in the highly stereoselective stepwise addition of lithiated α-imino esters **25** in the presence of BF₃·Et₂O to afford enantiopure 2-carbomethoxy-N-sulfinylimidazolidines **26** (Scheme 3). In some cases, this methodology allows for the synthesis of imidazolidines with quaternary centers (R¹ = Me). From **26**, enantiopure *syn*-N-sulfinyl-α,β-diamino esters (**27**) or α,β-diamino esters (**28**) can be selectively produced through fairly general amination cleavage procedures. Acidic conditions for amination cleavage of **26** can be modulated by choosing a nonnucleophilic solvent (THF/H₂O vs MeOH) to preserve the sulfinamide moiety and thus achieve different degrees of functionalization at the amino groups. Interestingly, the reaction of achiral N-sulfonyl imine **24** (R = Ph) and lithiated α-imino glycinate **25** (R¹ = H) provided racemic N-sulfonyl α,β-diamino esters **29** with low diastereoselectivity.^{88a,b} Recently, sulfinamido-sulfonamide esters derived from **27** have been used as ligands for the enantioselective ethylation of aldehydes.^{88c} A parallel strategy has been addressed by the group of Davis in the synthesis of *syn* and *anti* α,β-diamino esters (**31**, **32**) recently used in the total synthesis of (–)-agelastatin A and (+)-CP-99,994. It has been demonstrated that the diastereoselectivity (*syn* or *anti*) in the addition of glycinate derived from **30** and **8** to the sulfinimine **23a** can be completely controlled by proper selection of the nitrogen protecting group in the glycinate. The different stereochemical outcome of these reactions, for *N,N*-dibenzylglycinate **30** or *N*-benzhydrylglycinate **8** was

Scheme 3^a

^a Reagents and conditions: (a) **25** + LDA + **23** (or **24**), then BF₃·Et₂O, -78 °C to rt; (b) H₃PO₄, THF-H₂O, rt, 68–84% for **27**; (c) H₃PO₄, MeOH-H₂O, rt, 59–65% for **28**; (d) LDA, -78 °C, THF then **23a**; (e) TFA, EtOH; (f) Pd(OH)₂, H₂, EtOH; (g) MW irradiation, Ce₂(SO₄)₃, 74%; (h) LDA, THF, -78 °C, 93%; (i) (i) HBr, MeOH, (ii) NaHCO₃, 90%.

attributed to different geometries (*E* vs *Z*, respectively) adopted by the enolates in either transition state. In addition, a thorough study has demonstrated that for the *N*-benzhydrylglycinate **8** a small amount of H₂O is crucial in preventing the retro-Mannich reaction of the kinetic *anti* isomer, thus yielding complete *anti* diastereoselectivity, while in the absence of H₂O the addition provides *syn* isomers exclusively (Scheme 3).^{89a,b,c-e} Recently, Yadav has reported the one-pot synthesis of 4-amino perhydropyrimidines **35** using a Biginelli reaction. Upon MW irradiation and in the presence of a Ce(III) salt, D-xylose and D-glucose react with ureas (**33**) and thioureas generating aldose-derived C=N species that are attacked in situ by an 1,3-oxazol-5-one **34** and finally evolve to the perhydropyrimidine **35** diastereoselectively.^{89f} Finally, chiral *N*-phosphonyl imines **36** have been submitted to addition of lithium glycine

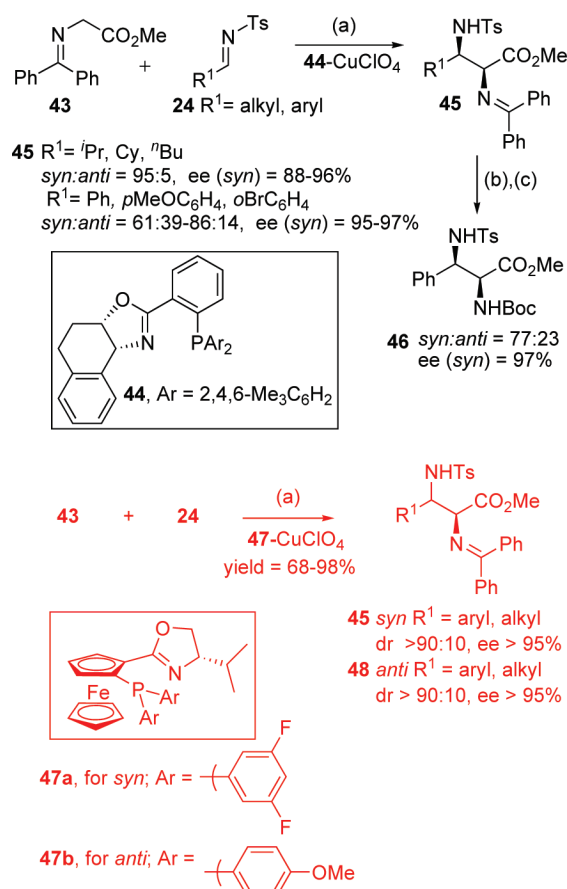
Scheme 4^a

^a Reagents and conditions: (a) THF, –78 °C; (b) DMAP, ClCOCO₂Et; (c) Pd–C (10% mol), (NH₄)HCO₂.

enolates rendering *anti*- α,β -diamino ester (+)-**32** with high diastereoselectivity and high ee (Scheme 3).^{89g,h}

Within the same general approach, an example of double diastereoselection has also been used for the asymmetric synthesis of β -carboline containing α,β -diamino esters (Scheme 4). Indeed, chiral cyclic iminium ion **37** prepared from tryptamine was submitted to addition of (–) and (+)-8-phenylmenthol-derived α -imino glycinate enolates **38a** and **38b**. In both reactions, an enantiomerically pure single adduct was obtained with *syn*-**39** or *anti*-**40** stereochemistry, respectively. Further structural evidence was achieved by NMR analysis of diketopiperazines **41** and **42**.^{90a} In another recent example, chiral *t*-butyl sulfinimines and chiral oxazolidinone enolates provide high double diastereoselection, yielding α,β -diamino acid derivatives in high yield.^{90b}

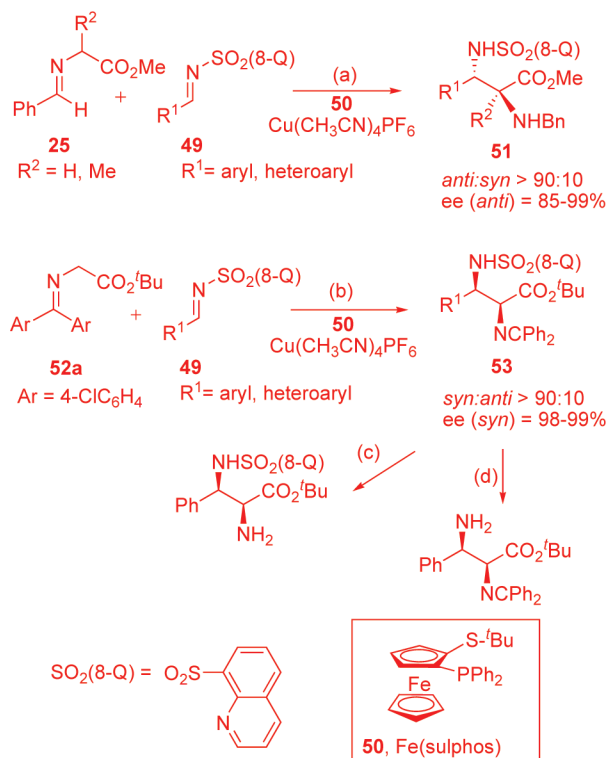
Asymmetric catalysis also constitutes a useful tool in the synthesis of α,β -diamino esters.^{91a–c} In this context, the chiral Lewis acid-stabilized imino glycinate enolate, generated from **43** and Et₃N in the presence of 10% of CuClO₄ and chiral oxazoline **44**, reacts with a group of *N*-sulfonyl imines, **24**, to afford as major products *syn*- α,β -diamino esters **45** with good enantiomeric excesses (88–97%). Interestingly, the aliphatic nature of *N*-sulfonyl imines **24** is crucial to reach a good *syn/anti* diastereoselectivity (95:5). Acidic hydrolysis of the benzhydryl group and introduction of a *t*-butoxycarbonyl group finally yielded **46** (Scheme 5).^{91d} Two similar approaches have been reported using chiral ferrocenyl phosphino oxazolines and copper salts. In the first, developed by Wu, the Mannich reaction between benzophenone imine glycinate **43** and *N*-sulfonyl imines **24** in the presence of CuClO₄ and the chiral ligands **47** provides α,β -diamino esters in good yields and high enantioselectivities. The method is highly versatile because either the *syn*-**45** or the *anti*-**48** diamino esters can be selectively accessed by tuning the nature of the phosphine aromatic groups in the ligand, thus **47a** (Ar = 3,5-F₂C₆H₃) provides *syn*-**45** and **47b** (Ar = 4-MeOC₆H₄) provides *anti*-**48**.^{91e} Similarly, AgOAc can act as a metal template combined with **47c** (Ar = 4-CF₃C₆H₄, not shown) in the synthesis of *syn*-**45** avoiding the use of

Scheme 5^a

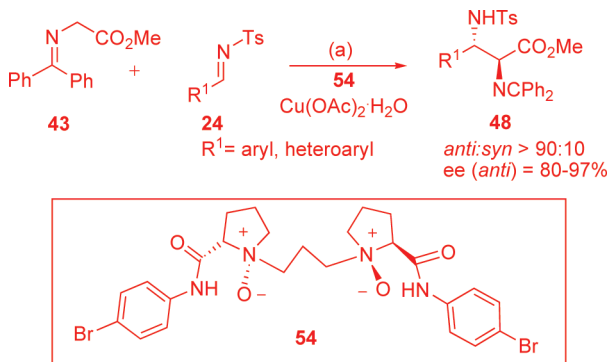
^a Reagents and conditions: (a) Et₃N, THF, 4 Å MS, –78 °C. (b) 2 N HCl, Et₂O; (c) (Boc)₂O, Na₂CO₃.

Et₃N; however, the method lacks generality providing good *syn:anti* diastereoselectivity only for **45** R¹ = *i*Pr.^{91f}

The enantioselective synthesis of *anti*- α,β -diamino esters is also possible using ferrocenyl phosphine (Fesulphos, **50**) and copper(I) salts (Scheme 5a). The group of Carretero and Gómez Arrayás has recently examined the Mannich reaction of imino glycinate **25** and sulfinimines, finding that under these conditions the use of *N*-(8-quinolyl)sulfinimine **49** is crucial to obtain *anti*-**51** with high diastereoselectivity. Reductive treatment of the reaction mixtures with NaBH₄ facilitates the analysis of the results. Diastereomeric ratios are higher than 90:10 in most cases with 90–99% ee for the *anti* isomers. Besides, alaninates can be used in the reaction providing α,β -diamino esters **51** with quaternary stereocenters. Alternatively, this group has found that benzophenone imino glycinate **52a** under the above conditions affords *syn*- α,β -diamino esters **53** in high diastereomeric ratios and enantioselectivities. The predominant *syn* diastereoselectivity is presumably promoted by the presence of the additional phenyl group in the imino glycinate that determines the approach of the sulfinimine in the transition state. An additional advantage of this methodology is the orthogonal protection of the final compounds that allows removal of either of the two amino protecting groups under mild conditions.^{91g,h} In a recent example, copper(II) salts, Cu(OAc)₂, and C-2 symmetric *N*-oxides (**54**) also form a chiral complex that catalyzes the Mannich reaction of glycinate **43** and aryl sulfinimines **24**. The reaction takes place in the absence of an additional base and is fairly

Scheme 5a^a

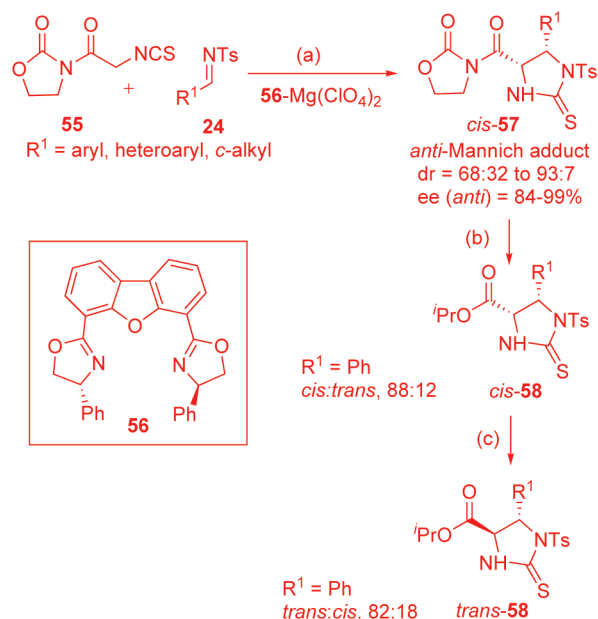
^a Reagents and conditions: (a) (i) **50** 5% mol, Et₃N, THF, 4 Å MS, −78 °C, (ii) NaBH₄, EtOH, 61–92%; (b) **50** 5% mol, Et₃N, THF, 4 Å MS, −20 or −40 °C, 76–85%; (c) HCl 10%, CH₂Cl₂, quant; (d) Mg, MeOH, rt, sonication, 72%.

Scheme 5b^a

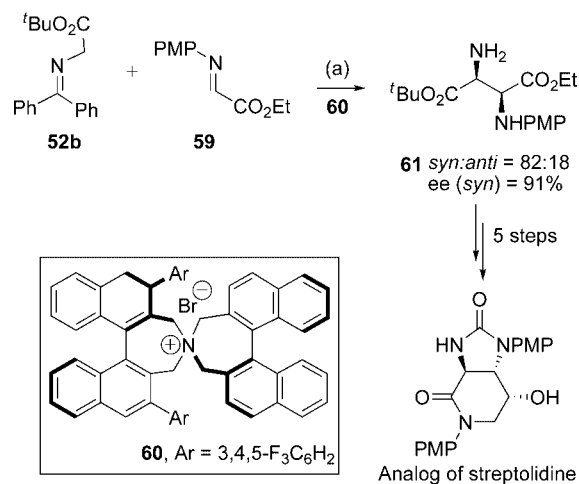
^a Reagents and conditions: (a) **54** 5% mol, THF, 0 °C, 24–48 h.

general, providing *anti*-α,β-diamino esters **48** in good yields, high anti selectivities, and enantiomeric excesses above 90% in most cases (Scheme 5b).⁹¹ⁱ Finally, the enantioselective Mannich reaction of isothiocyanate **55** and aryl and alkyl sulfonimines **24** has been reported using bis-oxazoline **56** and Mg(ClO₄)₂ as catalysts. The nature of the nucleophile allows for the in situ protection of the amines as cyclic thioureas **57**. In most examples, enantiomeric excesses higher than 90% are achieved for the anti major cyclic thiourea diamino acid derivative **57**, however the syn:anti ratios are moderate. Interestingly, after removal of the oxazolidinone in **57** (R¹ = Ph) the resulting *cis*-**58** thiourea (dr = 88:12) can be epimerized to *trans*-**58** (82:18) by treatment with DBU in THF (Scheme 5c).^{91j}

Similarly, enantiomerically enriched syn diaminosuccinate **61** [de, 64%; ee (syn), 91%], a derivative of 3-amino aspartate, has been prepared through phase-transfer-catalyzed

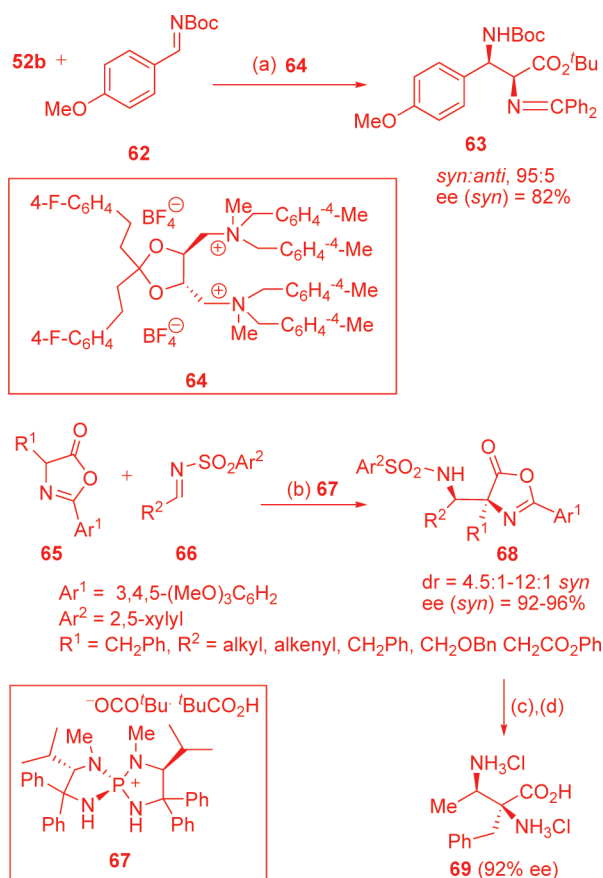
Scheme 5c^a

^a Reagents and conditions: (a) **56** 11% mol, DIPEA, CH₂Cl₂ −78 °C, 63–98%; (b) MeMgBr, THF, ^tPrOH, 72%; (c) DBU, THF, 35 °C, 78%.

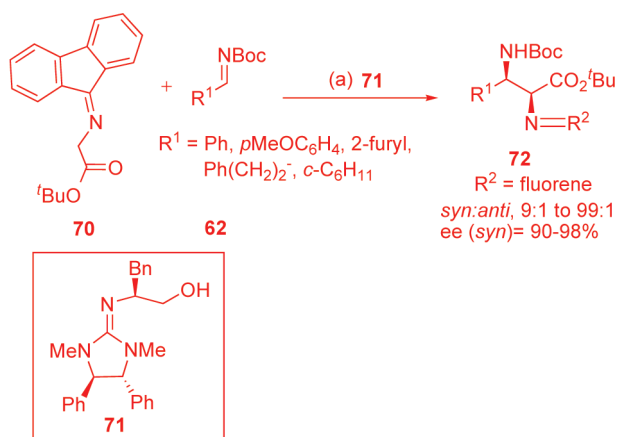
Scheme 5d^a

^a Reagents and conditions: (a) 17% aqueous NaOH, mesitylene, **60** (2% mol) then 1 N HCl, THF.

Mannich reaction of **52b** with imine **59** in the presence of 2% of *N*-spiro C₂-symmetric chiral quaternary ammonium salt **60**. The synthesis of a precursor of streptolidine, constituent of the streptothricin antibiotics was also reported in five linear steps from **61** (Scheme 5d).^{92a} Alternatively, syn-α,β-diamino ester derivatives **63** have been generated from *N*-Boc imines **62** using a tartrate-derived diammonium salt [(*S,S*)-TaDiAS] **64** with excellent syn:anti ratio and moderate enantiomeric excesses (Scheme 5e).^{92b} Another recent example of the use of chiral quaternary onium salts as enantioselective catalysts has been developed by the group of Ooi. The Mannich reaction between oxazol-5-(4*H*)-ones **65** and sulfonyl imines **66** in the presence of *P*-spiro tetraaminophosphonium salt **67** gives adduct **68** with moderate to excellent diastereoselectivities and high enantiomeric excesses for the major isomer. The optimized pivalate counterion in **67** acts as base forming a chiral enolate. Finally, in one particular example a two step hydrolysis provides α,β-

Scheme 5e^a

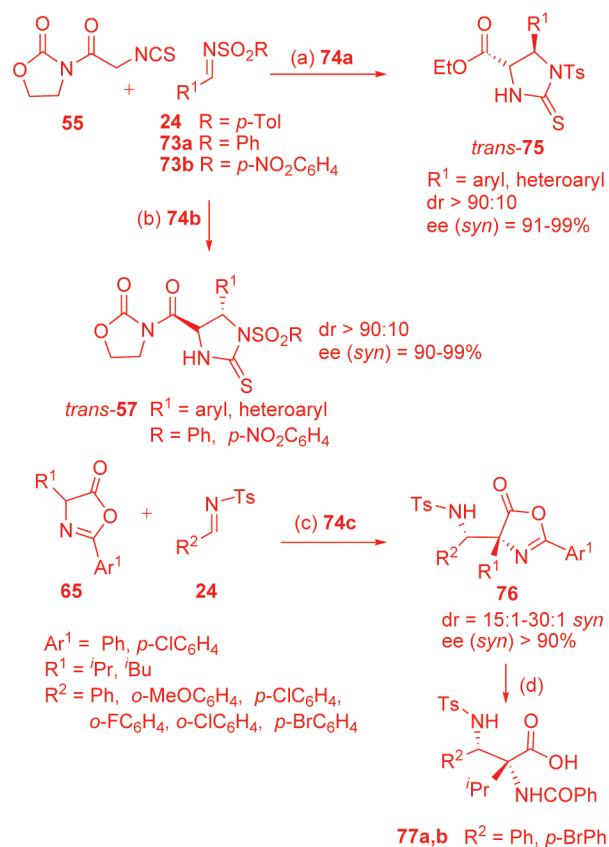
^a Reagents and conditions: (a) Cs₂CO₃, PhF, **64** 10% mol, -45 °C, 95%; (b) **67** 2% mol, THF, -40 or -50 °C, 89–99%; (c) H₂SO₄ aq THF, 0 °C to rt; (d) HCl conc 100 °C, 87% steps c and d.

Scheme 5f^a

^a Reagents and conditions: (a) **71** 10% mol, THF, -45 °C, 84%-quant.

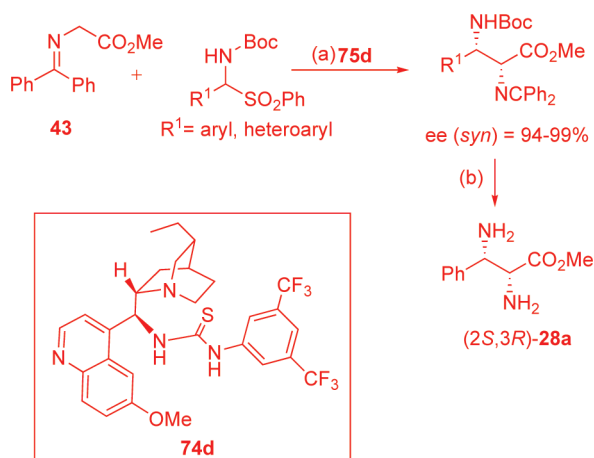
diamino acid dihydrochloride **69** in good yields and with no loss of the enantiopurity.^{92c}

Recently, chiral guanidine catalyst **71** has successfully induced asymmetry in the Mannich reaction between *N*-Boc imines **62** and fluorenone imino glycinate **70** (Scheme 5f). The enolates generated from these glycinate are further stabilized by resonance involving 14π electrons of the fluorene moiety. This procedure provides syn-α,β-diamino esters **72** in high diastereomeric ratios (90:10 to 99:1) and excellent enantiomeric excesses. The methodology has also been applied to the synthesis of syn-α,β-diamino phosphonic

Scheme 5g^a

^a Reagents and conditions: (a) (i) 2.5% mol **74a**, *m*-xylene, rt, (ii) BrMgOEt, THF, 0 °C; (b) 1% mol **74b**, toluene, 0.1 M, rt 87–97%; (c) 20% mol **74c**, Et₂O, rt; (d) HCl conc CH₃CN, rt.

esters.^{92d} Finally, different groups have found that quinidine-derived catalysts **74a–c** induced asymmetry in different Mannich processes (Scheme 5g).^{92e–g} Thus, isothiocyanate **55** reacts with tosyl imines **24** with **74a** as base-catalyst to provide, after cleavage of the oxazolidinone ring, a thiourea diamino ester derivative **trans-75** in good diastereomeric ratios and high enantiomeric excesses. Upon examination of the reaction scope, it was found that R¹ groups such as alkyl and alkenyl lead to a decrease of the diastereoselectivity.^{92e} Simultaneously, the group of Seidel has demonstrated that *N*-benzenesulfonyl imines **73a** and *N*-nosyl imines **73b** also react with **55** in the presence of quinidine **74b**, providing **trans-57** with higher efficiency than the tosyl imines **24**. A relationship between the insolubility of the final thiourea **57** and the turnovers of the catalyst has been invoked to explain this behavior.^{92f} In addition, the Mannich reaction between oxazol-5-(4*H*)-ones **65** and sulfonyl imines **24** using **74c** as a catalyst provides adduct **76** with excellent diastereoselectivities and high enantiomeric excesses for the major syn isomer. Two of the reported examples were transformed into diamino acid derivatives **77a** and **77b** with a quaternary

Scheme 5h^a

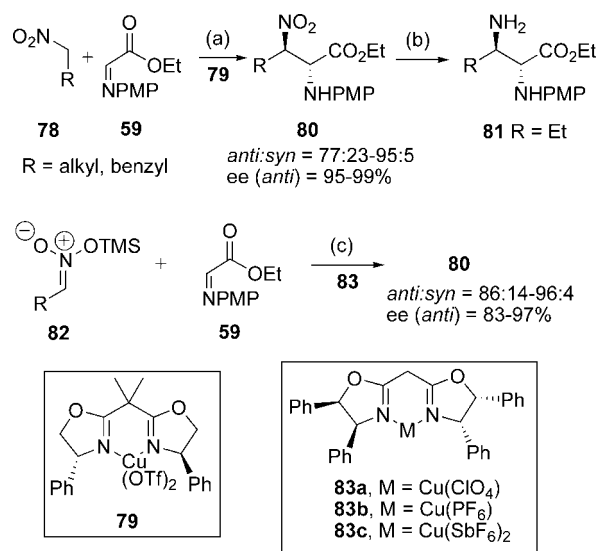
^a Reagents and conditions: (a) **74a** (10% mol), CF₃Ph, satd Na₂CO₃, 4 °C to rt, 62–98%; (b) 4 M HCl–MeOH, rt.

stereocenter by acidic hydrolysis.^{92g} To finish, cinchona alkaloid thiourea **74d** has been examined as a catalyst in the Mannich reaction of glycinate **43** and *N*-Boc protected aryl imines generated from bench stable α -amido sulfones. The reaction has been optimized to provide syn diamino esters in high diastereo- and enantioselectivities (Scheme 5h).^{92h}

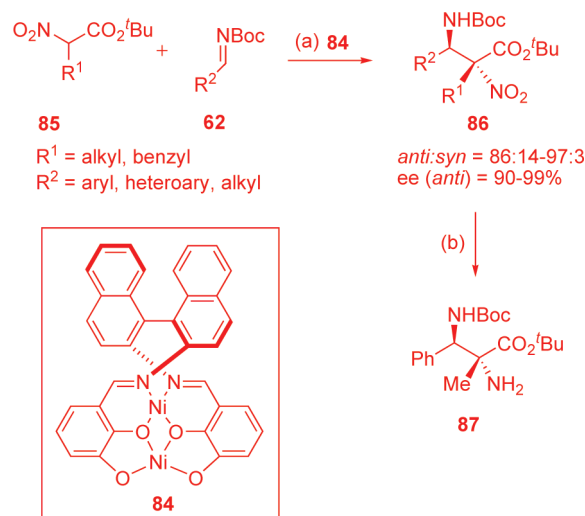
Imines are also susceptible to nucleophilic addition of nitroalkanes.^{93a} Recently, the group of Jørgensen has developed one of the most efficient protocols for the synthesis of α,β -diamino esters, the catalytic enantioselective aza-Henry reaction between imino ester **59** and nitro compounds **78** (**R** = alkyl, benzyl). The reaction proceeds at room temperature with high anti/syn diastereoselectivity (from 77:23 to 95:5) and ee values above 95% for major anti- β -nitro- α -amino esters, **80**, in the presence of base (Et₃N) and a Cu(II) complex based on a chiral bisoxazoline ligand **79**.^{93b} Furthermore, the use of base can be avoided using silyl nitronates **82** (**R** = alkyl) instead of nitro compounds. The reaction gives good conversions either with *N*-*p*-tosyl imino ester or with the more electron rich *N*-*p*-methoxyphenyl or *N*-phenyl imino esters. In this process, the use of chiral copper-bisoxazoline complexes, **83**, secures excellent anti/syn selectivities and high ee values for the final products. In any case, the resulting α -amino- β -nitro ester **80** (**R** = Et) can be readily converted into anti- α,β -diamino ester **81** by hydrogenation with Raney Ni in high yield (Scheme 6).^{94a}

More recently, this group has applied the method to the synthesis of diamino succinates with quaternary centers using simultaneously **79** and quinine as a chiral base.^{94b} Within this context, bimetallic complex **84** (Scheme 6a) induces the enantioselective aza-Henry reaction between nitro esters **85** and *N*-Boc-imine **62**, providing **86** with good anti diastereoselectivities and high enantiomeric excesses. Even for isomerizable aliphatic imines **62** (**R**¹ = *n*-Bu, *i*Bu, Ph(CH₂)₂), the results are fairly good, lowering the reaction temperature from 0 to –40 °C. In one example, reduction of the nitro group yielded α,β -diamino ester **87** with a quaternary center and both nitrogens differentially protected.^{94c}

Recently, Johnston has reported the enantioselective Brønsted acid catalyzed addition of nitro acetates **88** to aromatic *N*-Boc imines **62** using chiral *trans*-1,2-cyclohexane diamine derived quinolinium salts (**89**). After reduction of the resulting nitro compound, the best results are 12:1 anti:syn ratio and 93% ee for the major anti diaminoester **90**.^{94d}

Scheme 6^a

^a Reagents and conditions: (a) Et₃N, **79** (20% mol), rt or 0 °C. (b) Raney Ni, H₂, 80%. (c) THF, **83** (20% mol), –100 °C.

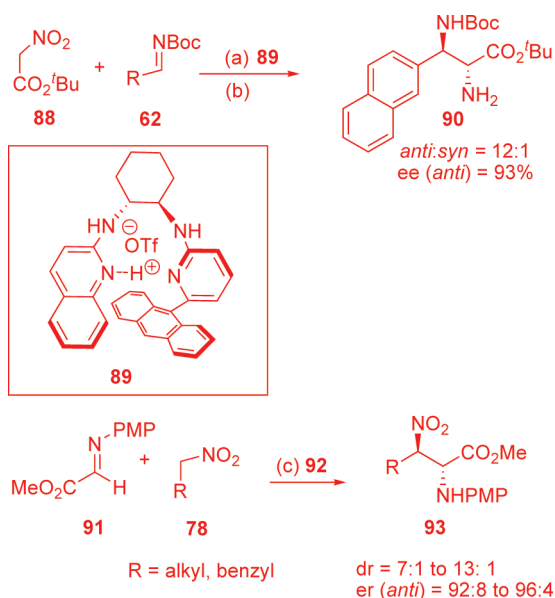
Scheme 6a^a

^a Reagents and conditions: (a) THF, **84** 5% mol, 0 or –40 °C; (b) NaBH₄, NiCl₂, 0 °C, 94%.

Similarly, chiral BINOL phosphoric acid **92** catalyzes the enantioselective aza-Henry reaction to provide anti vicinal nitro amino esters **93** with good diastereo- and enantioselectivities for alkyl and benzyl nitro compounds **78** (Scheme 6b).^{94e}

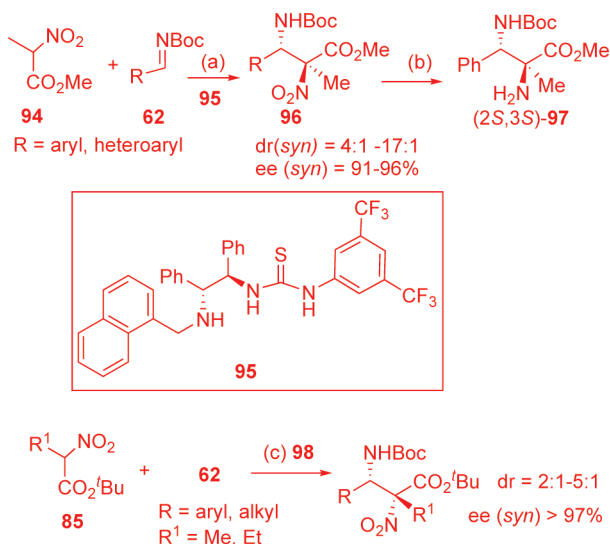
Alternatively, chiral bifunctional ureas have been examined as enantioselective catalysts in the aza-Henry approach (Scheme 6c).^{94f} In particular, **95** containing a secondary amine moiety induces asymmetry in the addition of 2-nitro propionate **94** to *N*-Boc imine **62** (**R** = aryl or heteroaryl), yielding syn amino nitro ester **96** with a quaternary center. The reported syn diastereoselectivities range from moderate to excellent with high enantioselectivities and for one example reduction to α,β -diamino ester **97** has been carried out.^{94g} Finally, the aza-Henry reaction has been carried out with a catalytic amount of chiral ammonium betaines **98** that acts simultaneously as a chiral base (phenoxide) and a chiral onium salt. The synthesis of β -amino α -nitro esters has been

Scheme 6b^a



^a Reagents and conditions: (a) Tol, $-78\text{ }^{\circ}\text{C}$, **35** (5% mol); (b) NaBH_4 , CoCl_2 ; (c) benzene, $30\text{ }^{\circ}\text{C}$, **92** (10% mol).

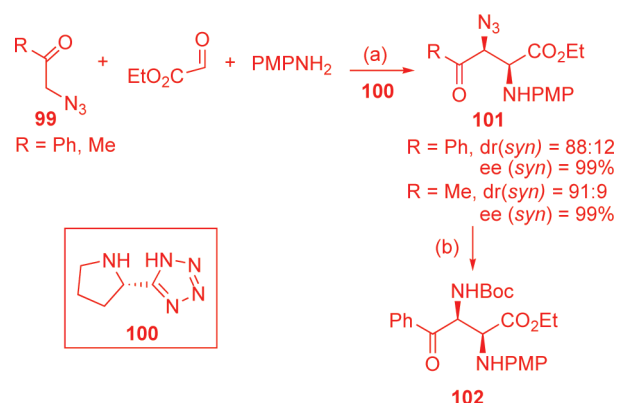
Scheme 6c^a



^a Reagents and conditions: (a) *m*-xylene, 4 Å MS, -20 °C, **95** (10% mol), 75–85%; (b) NiCl₂, NaBH₄, MeOH-THF, 0 °C, 81%; (c) toluene, 0 °C, **98** (1% mol), 91–99%.

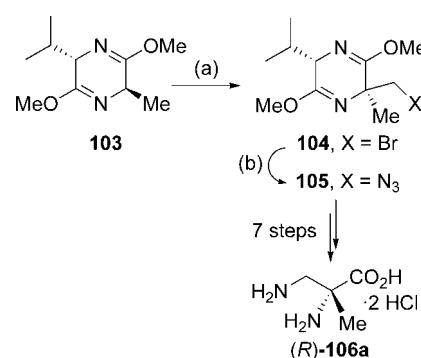
accomplished in high enantiomeric excesses albeit in moderate syn/anti ratios.^{94h}

Scheme 6d^a



^a Reagents and conditions: (a) DMSO, rt, **100** (30% mol), 87–96%; (b) Pd/C, H₂, Boc₂O, EtOAc.

Scheme 7^a



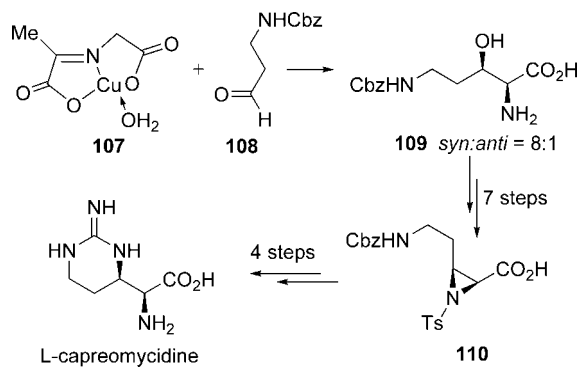
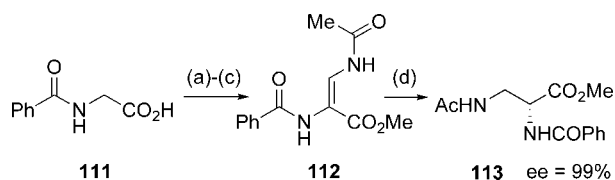
^a Reagents and conditions: (a) BuLi, THF, -78 °C, 15 min, then CH₂Br₂, THF, -70 °C, 30 h, 69%; (b) NaN₃, DMSO, 80 °C, 48 h.

To finish, α -azidoketones have also been used as nucleophiles in the enantioselective Mannich approach to α,β -diamino acids (Scheme 6d). Thus, 30% of a L-proline derived tetrazole **100** catalyzes the three-component Mannich reaction between azidoketones **99** and iminoacetate **59** generated in situ from ethyl glyoxalate and *p*-methoxy aniline. The proposed reaction mechanism involves a chiral enamine from the azido ketone and the L-proline derived catalyst. Furthermore, the azido moiety turns out to be crucial for the regioselective enamine formation. Thus, *syn*-azido amino esters **101** are produced in good diastereoselectivities and high ee. Further hydrogenation and introduction of a Boc protecting group successfully yielded α,β -diamino ester **102**.⁹⁴ⁱ

3.1.1.2. Other Electrophiles. Reactions of glycines and related compounds with electrophiles different from imines have also been employed to build the b–c carbon–carbon bond of α,β -diamino acids and derivatives. In 1991, the group of Mittendorf reported the enantioselective synthesis of α,β -diamino acid **106** by diastereoselective alkylation of bislactim ether **103** with dibromomethane followed by nucleophilic substitution of the bromomethyl bislactim ether **104** with sodium azide. After reduction of azide **105**, a six-step sequence leads to the production of enantiopure α -methyl- α,β -diamino acid **106a** as a hydrochloride salt (Scheme 7).⁹⁵

Following this general strategy, other electrophiles were employed, such as *N*-bromomethylphthalimide, in the context of the synthesis of α,α -disubstituted α,β -diamino acids as fragments of cyclic amidine-containing peptidomimetics⁹⁶

Scheme 8

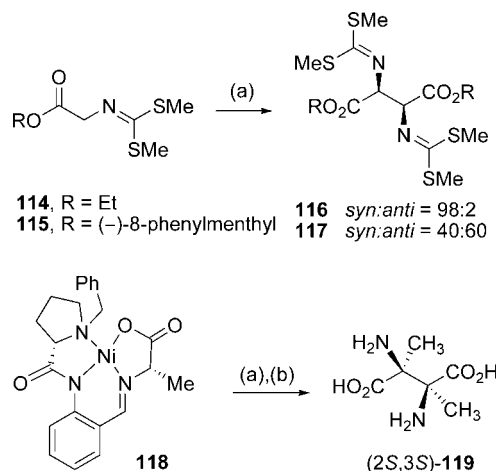
Scheme 9^a

^a Reagents and conditions: (a) $\text{Me}_2\text{NCH(OMe)}_2$, toluene, reflux; (b) NH_4OAc , MeOH, rt; (c) MeCOCl , base, CH_2Cl_2 -Et₂O; (d) (*R,R*)-EtDuPhos-Rh(I), H_2 , 60–90 psi, 15–60 h.

and ethyl formate in the condensation with ethyl hippurate to give (±)-quisqualic acid, further submitted to enzymatic resolution.⁹⁷ In addition, the synthesis of L-capreomycin has also been addressed by construction of the b–c carbon–carbon bond. In this route, the key synthetic intermediate is β-hydroxy-L-ornithine derivative **109**, which was readily prepared by condensation of *N*-piruvylideneglycinate copper(II) complex **107** and β-(benzyloxycarbonylamino) propionaldehyde, **108**, as electrophile as an 8:1 mixture of syn/anti isomers. After separation, the syn (threo) isomer was acylated and resolved by means of an acylase. β-Hydroxy-L-ornithine was finally transformed in L-capreomycin through a synthetic sequence that includes formation and then cleavage of a cis aziridine ring in **110** (Scheme 8).⁹⁸

Amide acetals also have resulted in useful electrophiles in the synthesis of α,β-diamino acids as in the synthesis of piperidino and pyrrolidino diamino acids analogues to streptolutin.⁹⁹ Furthermore, the highly enantioselective synthesis of α,β-diaminopropionic acid derivatives **113** has been achieved following this strategy (Scheme 9). Condensation of hippuric acid, **111**, with dimethylformamide dimethyl acetal, followed by treatment with NH_4OAc in MeOH and then acylation of the resulting enamide produced α,β-dehydro-α,β-diamino ester **112**. The key step for the enantioselective synthesis of **113** is the remarkable asymmetric hydrogenation of **112** using the (*R,R*)-EtDuPhos-Rh(I) complex that provides α,β-diamino esters in yields above 99% and ee's of 99%.¹⁰⁰

3.1.1.3. Dimerization of Glycinates. In some instances, dimerizations of glycinates and related compounds¹⁰¹ have been used for the synthesis of diamino succinates (3-amino aspartates). Early attempts within this approach explored the photodimerization of methyl *N*-acylglycinate and related *N*-acylamino esters to give an equimolecular mixture of diastereomers.^{101b} Besides, free 2,3-diaminosuccinic acids have been obtained as an equimolecular mixture of racemic and meso diastereoisomers by reaction between ethyl *N*-acetyl malonate and 2-acetoxy glycinate in the presence of

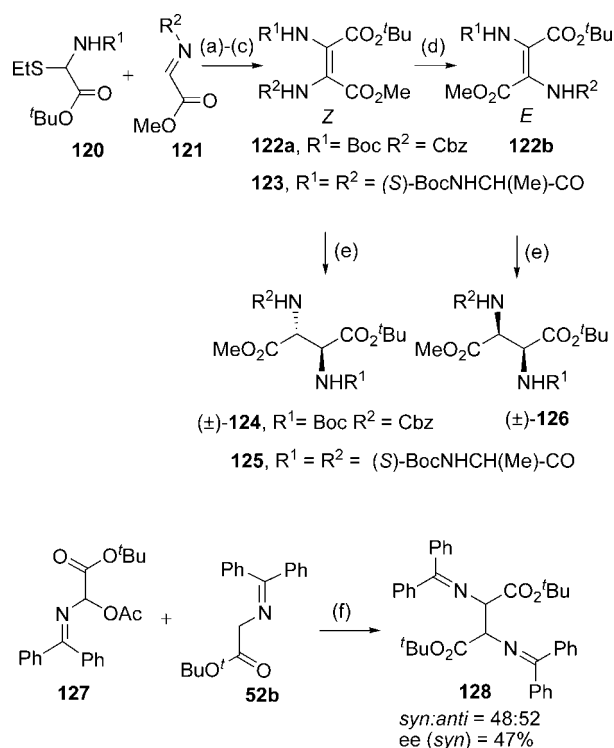
Scheme 10^a

^a Reagents and conditions: (a) BuLi, THF, –78 °C; then I₂, –78 °C to rt, 20 h, 80% for **114**, **115**, and MnO₂, 1 h, 20 °C, 52% for **118**; (b) 2 N HCl, MeOH then Dowex-50, 54%.

sodium hydride followed by removal of protecting groups and hydrolysis.¹⁰² More recently, a highly diastereoselective oxidative dimerization of glycinates **114** has been reported by enolization with BuLi, LDA, or ^tBuLi followed by treatment with iodine to afford racemic syn (threo) diamino succinates **116** (*syn/anti* > 98:2) in high yield. Unfortunately, this dimerization is highly substrate-dependent and efforts to effect the enantioselective oxidative dimerization of (–)-8-phenylmenthyl glycinate **115** produced a 40:60 mixture of syn and anti diamino succinates **117**. The syn and anti isomers were separated and submitted to nonpimerizing hydrolysis to give the enantiopure free (2S,3S)-3-aminoaspartic acid and the meso isomer.¹⁰³ On the other hand, oxidative dimerization of a chiral Ni(II) complex, **118**, derived from α-imino alaninate occurs by treatment with *n*-BuLi followed by addition of pentyl iodide or MnO₂ to afford after acidic hydrolysis (–)-(2S,3S)-2,3-dimethyl-2,3-diaminosuccinic acid, **119**. Interestingly, similar Ni(II) complexes, derived from glycine or valine, do not undergo the above oxidative dimerization (Scheme 10).¹⁰⁴

Very recently, another diastereoselective route toward diaminosuccinic acid derivatives that relies on the dimerization of two fragments obtained by glycinate transformations has been reported. The coupling of α-ethylthioglycinate **120** and α-acyliminoglycinate **121** mediated by PPh₃ afforded a good yield of Z-dehydrodiamino succinate, **122a**, that can be readily converted to the *E* isomer, **122b**, under basic conditions. cis-Selective catalytic hydrogenation of both *Z* and *E* dehydrodiamino acids allowed for the efficient and diastereoselective synthesis of anti and syn orthogonally protected diamino succinates **124** and **126**. Furthermore, the presence of chiral centers in the starting dehydrosuccinate **123** provided enantiopure anti diamino succinate **125** through diastereoselective hydrogenation.¹⁰⁵ Finally, enantioselective catalysis has also been used in the synthesis of diamino succinates **128**. Indeed, 2-acetoxyimino glycinate **127** was submitted to a palladium-mediated π-azaallylic substitution using α-iminoglycinate **52b** derived sodium enolate as nucleophile and several chiral phosphine ligands. Unfortunately, although the yields are fairly good, diastereomeric ratios (D,L/meso) are moderate and ee values for the D,L pair are low (Scheme 11).¹⁰⁶

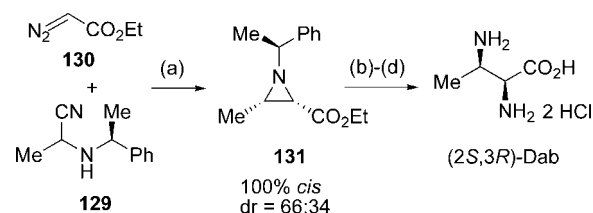
3.1.1.4. Through Cyclic Intermediates. Cycloaddition reactions, one of the most useful tools for the construction

Scheme 11^a

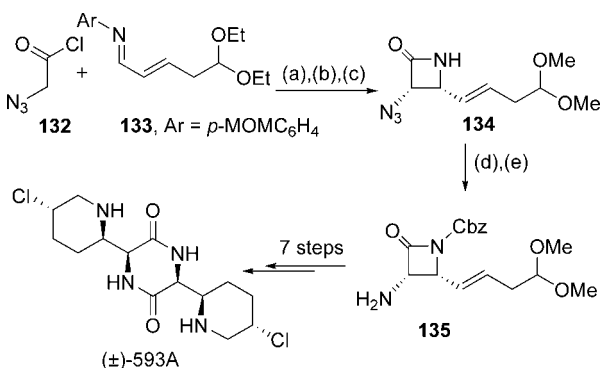
^a Reagents and conditions: (a) 120, SO₂Cl₂, CH₂Cl₂, 0 °C; (b) PPh₃; (c) 121, Et₃N, THF, −78 °C, 61%; (d) Et₃NH, MeOH, 70 °C, 52%; (e) [Rh(COD)Cl]₂dppf, 90 bar, H₂, toluene, 80 °C; (f) Pd(OAc)₂, MeCN, (R)-BINAP, 24 h, NaH, 77%.

of carbon–carbon bonds, have also been used in the synthesis of α,β -diamino acids. In this context, imines and related compounds containing C–N bonds can undergo stereocontrolled cycloaddition with a number of species that render cyclic precursors of α,β -diamino acids. One of these cyclic precursors are 2-alkoxycarbonyl aziridines, readily available by Lewis acid-mediated [2 + 1] cycloaddition of imines and alkyl diazoacetates. Studies on this process comprise the use of Lewis acids,¹⁰⁷ metal complexes based on Cu(I) and chiral oxazolines,¹⁰⁸ Rh(II) and sulfur ylides,¹⁰⁹ boron-based catalyst VAPOL-B,¹¹⁰ prepared from vaulted biphenanthrol, [(S)-VAPOL], and cinchona-derived quaternary ammonium salts as chiral phase-transfer catalysts.¹¹¹

Alternatively, 1,3,5-triazines, *N*-methoxymethylanilines, and 2-amino nitriles can be used as the source of imines in the presence of the Lewis acid.¹¹² In particular, SnCl₄ and 2-amino nitriles derived from 1-(*R* or *S*)-phenylethylamine 129, provide in situ formation of the iminium ion in the reaction with diazoacetate 130. In this example, aziridine 131 is obtained with complete *cis* selectivity and with moderate diastereoselectivity relative to the chiral auxiliary. Further transformation of 2-ethoxycarbonyl aziridine 131 into the corresponding enantiopure free α,β -diamino acid [*syn*-(2*R*,3*S*)-Dab] was reported in three steps (Scheme 12).^{113a} Recently, *N*-sulfonyl trifluoromethyl aziridine-2-carboxylates have been submitted to regio- and diastereoselective opening with amines and azide as nucleophiles providing *syn* trifluoromethyl α,β -diamino esters in good yields.^{113b,c} Other methods are available for the synthesis of 2-carboxyaziridines such as aza-Darzens reaction of imines and α -haloenolates¹¹⁴ and reaction with α -carboxamide sulfonium ylides;¹¹⁵ however, their coverage is out of the scope of this review.

Scheme 12^a

^a Reagents and conditions: (a) SnCl₄, CH₂Cl₂, rt; (b) TMSN₃, BF₃·OEt₂; (c) H₂, Pd-C, (Boc)₂O; (d) 6 NHCl.

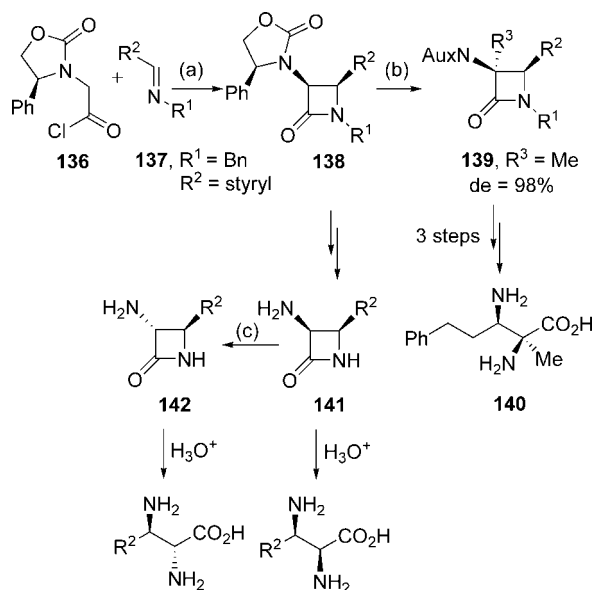
Scheme 13^a

^a Reagents and conditions: (a) Et₃N; (b) HCl, CH(OMe)₃, MeOH, reflux; (c) CAN, THF, H₂O, 0 °C; (d) CbzCl, Et₃N, CH₂Cl₂, −30 °C; (e) Zn, HOAc, Et₂O, CH₂Cl₂, rt.

3-Amino- β -lactams are valuable precursors to α,β -diamino acid derivatives. These intermediates are available by the [2 + 2] ketene–imine cycloaddition, also referred to as Staudinger reaction, using a suitable amino ketene equivalent or another ketene equivalent such as 2-acetoxyacetyl chloride that allows for straightforward introduction of an amino group at C-3 after β -lactam formation.^{116a–d,e} The preparation of amino taxol side-chain precursors has been addressed using this strategy.¹¹⁷ Alternatively, 3-azido β -lactams are available by cycloaddition of imines 133 and azido ketenes 132, and an example of this approach was employed in the total synthesis of antibiotic (±)-593A. In fact, after [2 + 2] cycloaddition, 3-azido β -lactam 134 was transformed into 3-amino β -lactam 135 that spontaneously dimerized to a diketopiperazine then leading to the target antibiotic (Scheme 13).¹¹⁸

A more straightforward route to enantiopure α,β -diamino acids has been reported using the Evans–Sjögren acid chloride 136 with imine 137. The resulting *cis*-3-amido-4-styryl- β -lactam, 138, can be then alkylated diastereoselectively at C-3 (139), furnishing after complete removal of protecting groups and β -lactam cleavage (three steps), free α -methyl- α,β -diamino acid, 140 (Scheme 14).¹¹⁹ The group of Ojima has shown that *cis*-(*S*,*R*)-3-amino- β -lactams 141, readily obtained from 138, can be converted to enantiopure (*S*,*R*)- α,β -diamino acids by acidic hydrolysis in quantitative yield. In addition, *cis* lactam 141 can undergo epimerization to trans isomer 142 by aldimine formation followed by treatment with base. Further acidic hydrolysis afforded (*R*,*R*)- α,β -diamino acids in good yield (Scheme 14).^{116b,120}

More recently, the diastereoselective C-3 alkylations of 4-unsubstituted 3-amido- β -lactam 143 with benzylic and allylic bromides to give 144a,b have served to demonstrate that the oxazolidinone auxiliary alone can exert a high degree of stereocontrol, leading to the opposite relative configuration

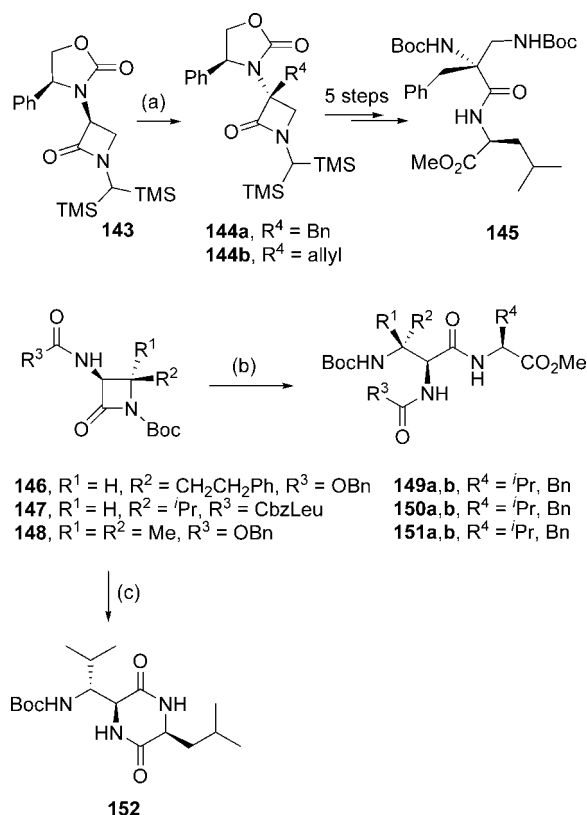
Scheme 14^a

^a Reagents and conditions: (a) Et₃N, CH₂Cl₂, -78 °C to rt; (b) LHMDS, MeI; (c) PhCHO, LHMDS.

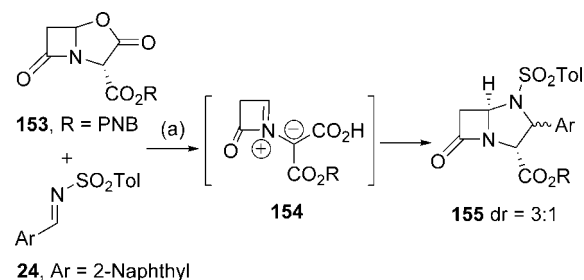
in the alkylation step (see Scheme 14). Finally, β -lactam **144a** was transformed into α,β -diamino acid derivative **145** in five linear steps. The highly efficient transformation of enantiopure Boc-protected 3-amino- β -lactams into α -alkyl- α,β -diamino acid residues incorporated as part of a peptide backbone has been also developed by the group of Palomo.^{116c,121} Indeed, upon treatment with (*S*)-phenylalanine or (*S*)-valine methyl esters and sodium azide, β -lactams **146** and **147** afforded dipeptides **149a,b** and **150a,b**. However, sodium azide failed in promoting peptidic coupling with 4,4-disubstituted β -lactam **148**, and the presence of potassium cyanide was necessary to reach a good yield of the highly substituted dipeptides **151a,b**. Another useful transformation reported by this group is the catalytic hydrogenation of 3-amido β -lactam **147** that promotes β -lactam cleavage followed by ring closure to diketopiperazine **152** (Scheme 15).¹²²

2-Carboxyimidazolines and imidazolidines are cyclic analogues of α,β -diamino acids, easily accessible via [3 + 2] cycloaddition of imines and azomethine ylides. Thermolysis of β -lactam-fused oxazolidinone **153** is an efficient method for the in situ generation of azomethine ylides. The dipole thus generated **154** reacted with aromatic *N*-sulfonyl imines **24** giving racemic *N*-sulfonyl aryloxycarbonyl imidazolidines **155** with low diastereoselectivity (exo/endo = 3:1, Scheme 16). Interestingly, 2*H*-azirines can also act as 1,3-dipolarophiles, trapping the above azomethine ylide (**154**) to give intermediates that can be easily transformed into 1-azacepham analogues.¹²³

Asymmetric [3 + 2] dipolar cycloaddition of azomethine ylides and imines has been addressed using chiral sulfinimines **23** and enolates **156** derived from α -alkyl- α -imino esters (from Phe, Ala, Leu) and LDA. In the absence of any Lewis acid additive, **156** behaves as a dipole, giving enantiopure *N*-sulfinyl methoxycarbonyl imidazolidines **157** with a remarkably high degree of endo stereocontrol and an excellent diastereofacial discrimination of the starting sulfinimine.¹²⁴ Within this context, the group of Harwood reported that chiral azomethine ylides **161** generated in situ from (5*S*)-phenylmorpholin-2-one, **158**, in the presence of aromatic

Scheme 15^a

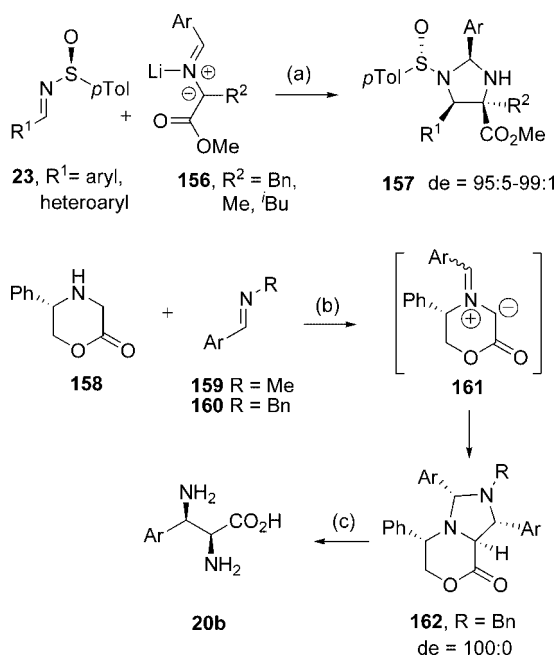
^a Reagents and conditions: (a) LDA, R⁴X, THF, -78 °C to rt, 16 h, 70–90%; (b) (*S*)-H₂NCH(R⁴)CO₂Me, DMF, NaN₃ (for **146**, **147**), or KCN (for **148**), DMF, rt, 10–14 h, 70–89%; (c) H₂, Pd-C, EtOH, rt, 14 h, 90% from **147**.

Scheme 16^a

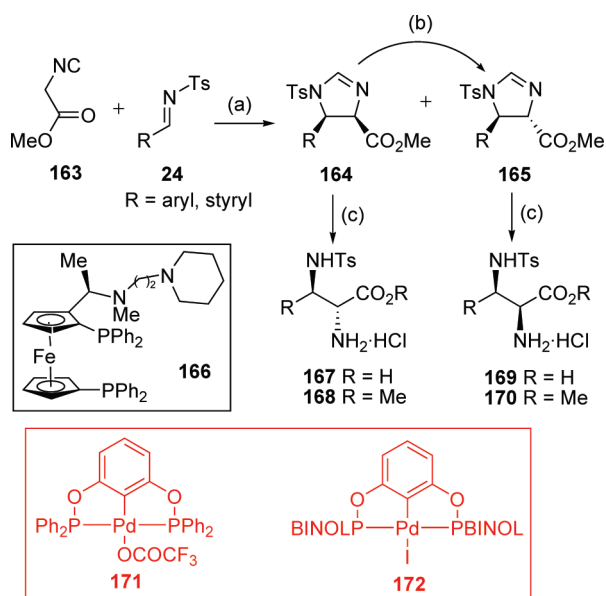
^a Reagents and conditions: (a) MeCN, sealed tube 80 °C, 20 h, 49%.

aldimines **159** and **160** and pyridinium *p*-toluenesulfonate can undergo cycloaddition with excess imine to give imidazolidines **162** as single products. Finally, hydrogenolysis of the adducts under acidic conditions released the corresponding enantiopure *syn*- α,β -diamino acids **20b** in excellent yields (Scheme 17).¹²⁵

A remarkable example within this context is the reaction between lithiated isocynoacetates and Schiff bases to give racemic 2-unsubstituted imidazolidines that undergo acidic hydrolysis to produce racemic α,β -diamino acids.¹²⁶ Furthermore, the reaction of methyl isocynoacetate **163** with *N*-sulfonyl imines **24** (R = aryl, (*E*)-styryl) is catalyzed by transition metal complexes such as AuCl(NC₆H₅-hex) to give racemic *cis* imidazolidines **164** with high diastereoselectivity. The reaction was very slow for other imines (*N*-aryl, *N*-phosphinyl), and other metal complexes [Ag(I), Rh(I), Ru(II)] gave lower *cis* selectivity. Imidazolidines **164** were readily converted into *anti*- α,β -diamino acids **167** or their

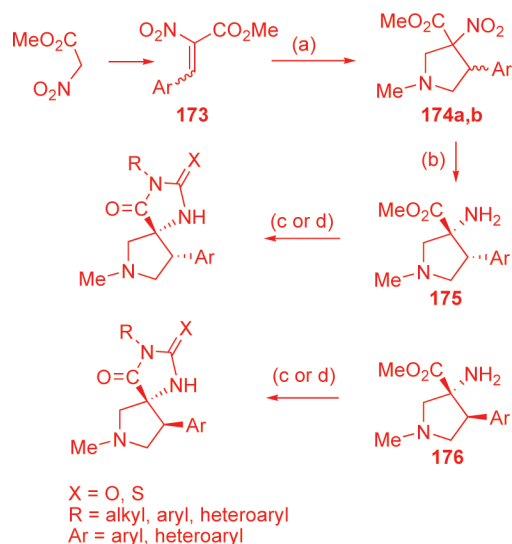
Scheme 17^a

^a Reagents and conditions: (a) THF, LDA, –70 to 4 °C, 37–80%; (b) PPTS, toluene, reflux; (c) TFA, MeOH–H₂O (10:1), Pd(OH)₂, H₂, 5 bar.

Scheme 18^a

^a Reagents and conditions: (a) AuCl (*c*-hexNC); 164:165, 89:11–95:5 RuH₂(PPh₃)₄; 164:165, 13:87–5:95 AuCl·SMe₂; 166; (4*R*,5*R*)-164, ee = 96%–99%; 171; 164:165, 86:14–92:8; (b) Et₃N, CH₂Cl₂, reflux; (c) 6 N HCl for 167 and 169; HCl, MeOH for 168 and 170.

methyl esters **168** by 6 N HCl or HCl–MeOH, respectively. Alternatively, racemic *cis* imidazoline **164** (R = Ph) can be isomerized into the thermodynamically more stable *trans* isomer, **165**, by treatment with Et₃N, and then acidic hydrolysis or methanolysis gives the corresponding *syn*- α,β -diamino acids **169** or esters **170** (Scheme 18).¹²⁷ Interestingly, the group of Lin has observed that RuH₂(PPh₃)₄ as catalyst and CH₂Cl₂–MeOH 1:3 as solvent provides opposite diastereoselectivity for the cycloaddition to *N*-sulfonyl imines **24** (R = aryl, (*E*)-styryl, ^tButyl). Racemic *trans* imidazolines **165** were thus obtained as major products (*trans*/*cis* = 95:5–87:13) in good yields.¹²⁸ Furthermore, an enantiose-

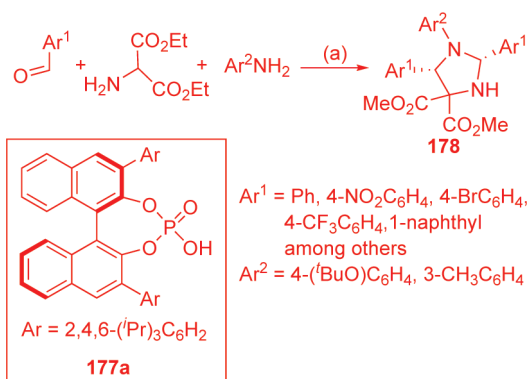
Scheme 18^a

^a Reagents and conditions: (a) MeNHCH₂CO₂H, (CH₂O)_{*m*}, Tol, Δ , 82–90%; (b) (i) chromatographic separation, (ii) H₂, Ra–Ni, Et₃N, MeOH, 61–80%; (c) (i) RNCO, CH₂Cl₂ at rt or DMF at 80 °C (X = O), (ii) KO^tBu, THF, rt; (d) RNCS, DMF, 40 °C (X = S).

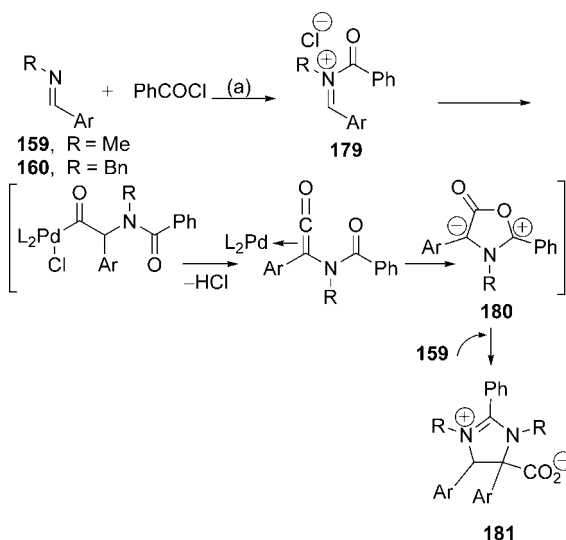
lective cycloaddition can be carried out in the presence of a catalytic amount of Au(I) complex bearing a chiral ferrocenylphosphine ligand, **166**. As above, Au(I) catalysis produces *cis* imidazolines (4*R*,5*R*)-**164** (R = aryl) as optically pure materials (ee: 96–99%) that were converted to anti diamino esters (2*R*,3*R*)-**168** using a parallel procedure.^{129a,b} Also, a number of palladium-pincer complexes have been examined as catalysts in the reaction of methyl isocyanacetate **163** with *N*-sulfonyl imines **24**. In particular, complex **171** provided racemic *cis* imidazolines **164** with high diastereoselectivity (7:1–11:1).^{129c} In a further attempt to improve this process, chiral palladium-pincer complexes based on BINOL units **172** have been used, however low *cis*:*trans* diastereomeric ratios and moderate enantioselectivities were found for the resulting imidazolines.^{129d}

1,3-Dipolar cycloaddition has also been used in the context of the total synthesis of cucurbitine,^{129e} and more recently, a 144-compound library of 4-aryl cucurbitine derivatives has been produced (Scheme 18a).^{129f,g} The methodology that provides this library entails the cycloaddition of an azomethine ylide, in situ generated from *N*-methylglycine, and α -nitro acrylates **173** to provide an equimolecular mixture of pyrrolidine adducts **174a** and **174b**. After a simple chromatographic separation of both adducts and reduction of the nitro groups, *cis* and *trans* 4-aryl cucurbitine esters **175** and **176** were submitted to annulation with isocyanates and isothiocyanates to yield hydantoin and thiohydantoin spiro-fused pyrrolidine library. Also, enantioselective Brønsted acid catalysis of 1,3-dipolar cycloadditions has been applied to the synthesis of α,β -diamino esters. Thus, several BINOL derived phosphoric acids **177** were evaluated as catalysts in the reaction between aldehydes, diethylamino malonate, and anilines via cycloaddition of an aldimine and an azomethine ylide, both generated in situ. Imidazolidine containing α,β -diamino esters **178** are available through this method in moderate to good diastereoselectivities and enantiomeric excesses ranging from 85 to 98% (Scheme 18b).^{129h}

Finally, the synthesis of α -amino acid-derived imidazolines **181** reported by Arndtsen can also be held in this category

Scheme 18b^a

^a Reagents and conditions: (a) toluene, -10°C , 76–99%.

Scheme 19^a

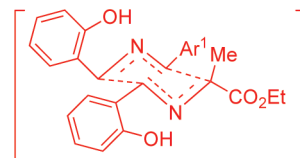
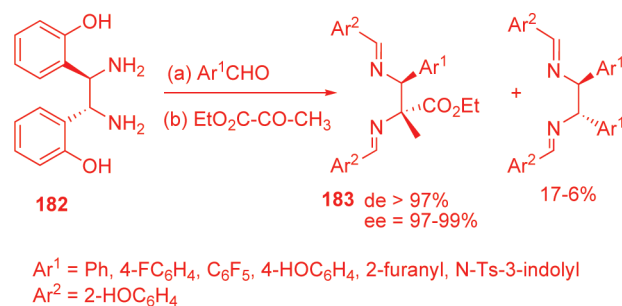
^a Reagents and conditions: (a) $\text{Pd}(\text{dba})_3$ (5% mol), bipy (10% mol), MeCN, 55°C , CO, 62–92%.

(Scheme 19). Palladium-mediated formation of a transient cyclic 1,3-dipole, **180**, has been invoked in this work by insertion of carbon monoxide in an *N*-acyliminium species, **179**, formed in situ followed by dipolar cycloaddition of **180** with a second molecule of imine (**159**, **160**) to afford zwitterionic carboxyimidazoline **181** in good yield.^{130a}

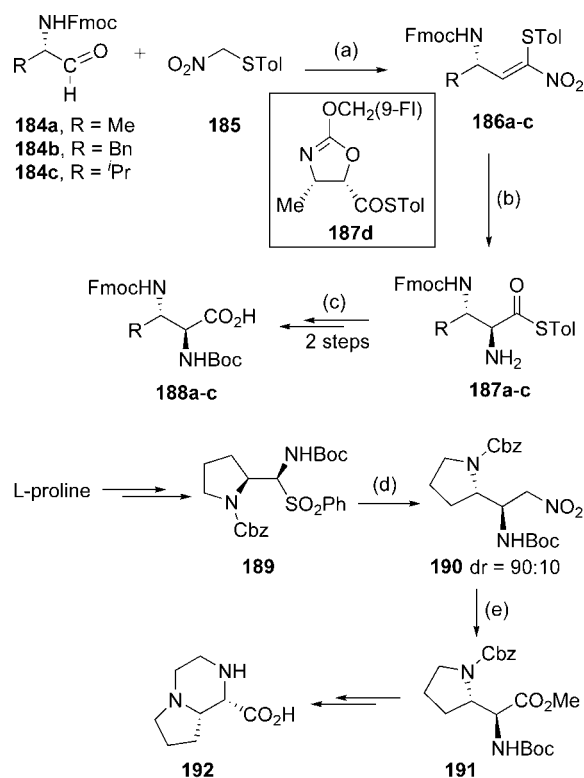
3.1.1.5. Diaza-Cope Rearrangement. This type of sigmatropic rearrangement has been widely used for the synthesis of vicinal diamines from bis-aldimines. Only recently the approach has been applied to the synthesis of α,β -diamino esters involving the use of electron-deficient ketones as ketimine precursors. Thus, (*R,R*)-1,2-bis(2-hydroxyphenyl)-1,2-diaminoethane **182** reacts in a one-pot procedure, with an aromatic aldehyde and then with ethyl pyruvate to yield *syn*- α,β -diamino esters **183** (Scheme 19a). The rearrangement is stereospecific providing only one of the four possible isomers, characterized by X-ray crystallography, with high enantiomeric excesses.^{130b,c}

3.1.2. Methods in Which the *a*–*b* Bond Is Formed3.1.2.1. Nucleophilic Synthetic Equivalents of CO_2R .

Construction of the *a*–*b* carbon–carbon bond is another key approach in the synthesis of α,β -diamino acids. In fact, the carboxylic group is introduced in the molecule by means of a synthetic equivalent as a nucleophile or electrophile and

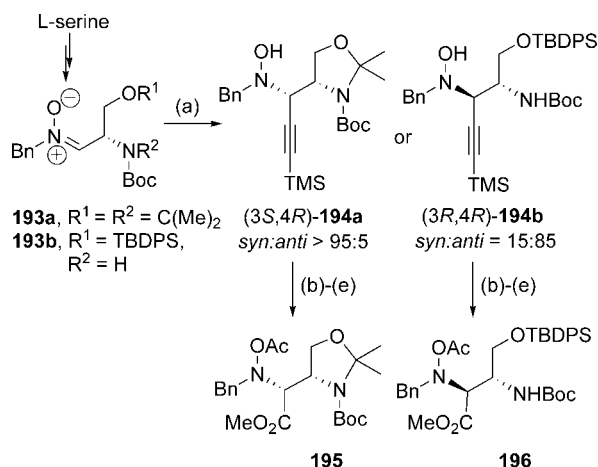
Scheme 19a^a

^a Reagents and conditions: (a) DMSO, rt, 0.5–2 h; (b) rt, 3 h, 58–67%.

Scheme 20^a

^a Reagents and conditions: (a) (i) ^tBuOK, ^tBuOH-THF, (ii) MeSO_2Cl , ⁱPr₂EtN, CH_2Cl_2 , 69–80%; (b) (i) LiOO^tBu , toluene, (ii) NH_3 , 35–57%; (c) (i) Boc_2O , THF, 97–99%, (ii) H_2O_2 , NaOH, 63–91%; (d) MeNO_2 , THF, NaH, rt, 78%; (e) (i) KMnO_4 , KOH- K_2HPO_4 , ^tBuOH, rt, (ii) K_2CO_3 , MeI, DMF, rt (72% for 2 steps).

then additional manipulation to give the carboxylic group is usually needed. Within this context, nitro compounds have been employed as nucleophiles to form the *a*–*b* carbon–carbon bond (Scheme 20). The group of Jackson has developed a new route to enantiopure *anti*- α,β -diamino acids based on the stepwise condensation of (*p*-tolylthio)nitromethane, **185**, and α -amino aldehydes **184a**–**c**. The resulting nitroalkenes, **186a**–**c**, were submitted to nucleophilic epoxidation using lithium *tert*-butyl hydroperoxide and diastereoselective epoxide cleavage using NH_3 to render α,β -diamino thioesters **187a**–**c**. Only for **184a**, small amounts of oxazoline **187d**

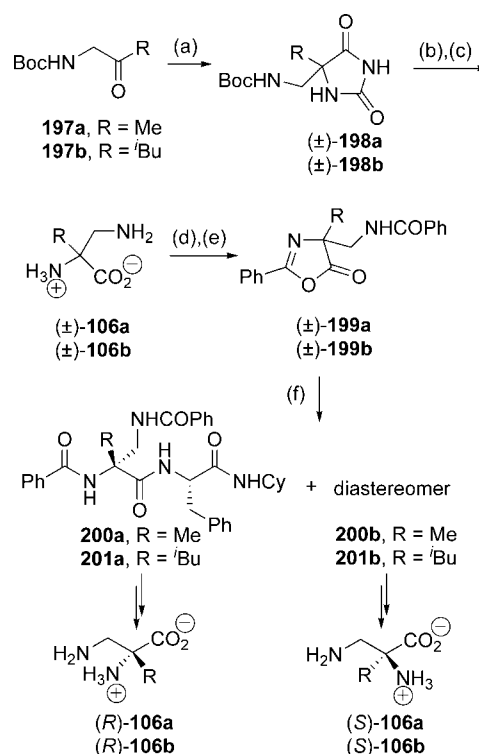
Scheme 21^a

^a Reagents and conditions: (a) LiC≡TMS, THF, −80 °C, 68–97%; (b) Bu₄NF, THF, rt, 70–80%; (c) Ac₂O, pyr, 1 h, rt; (d) RuCl₃–NaIO₄, MeCN, rt; (e) CH₂N₂, Et₂O, 72–76% (3 steps).

(10%) were isolated as a result of a secondary carbamate cyclization process. Finally, **187a–c** were transformed in two steps into differentially protected *anti*- α,β -diamino acids **188a–c**.¹³¹ On the other hand, diamino sulfone **189**, readily prepared from L-proline in a few steps, can act as an *N*-acyliminium synthetic equivalent in the addition of nitromethane anion giving nitro diamine **190** in a 90:10 diastereomeric ratio. The major anti isomer was submitted to Nef reaction followed by esterification to give a 72% yield of α,β -diamino ester **191** that can be transformed into bicyclic piperazine **192** by a reported procedure.¹³²

The use of terminal alkynes as synthetic equivalents of the carboxylic acid moiety is well documented in organic synthesis and has been applied to the synthesis of α,β -diamino acids (Scheme 21). The group of Merino has demonstrated that addition of lithium trimethylsilylacetylide to nitronitrone **193a**, readily available from L-serine, takes place with a high degree of diastereoselectivity (>95:5) to give propargylhydroxylamine **(3*S*,4*R*)-194a**. In contrast, changing protecting groups in the starting nitronitrone (**193b**) allows for an inversion of the diastereoselectivity giving **(3*R*,4*R*)-194b** as a major isomer (85:15). Subsequently, **(3*S*,4*R*)-194a** and **(3*R*,4*R*)-194b** were transformed into *syn*-**195** and *anti*-**196** α,β -diamino esters, respectively, by removal of the trimethylsilyl group, *O*-acylation, alkyne oxidation with RuCl₃–NaIO₄, and esterification. These authors also reported that a parallel strategy can be carried out using 2-lithiofuran instead of lithium trimethylsilylacetylide in the addition to the nitronitrone.¹³³

The group of Obrecht has examined the Bücherer–Bergs reaction of α -amido ketones **197a,b** and potassium cyanide in the presence of ammonium carbonate to produce racemic hydantoin **198a,b** in good yields that, after cleavage of the protecting carbamate and saponification, rendered α -alkyl α,β -diamino acids **106a** and **106b** as racemic materials. Further *N*-benzoylation and cyclization to oxazolones **199a** and **199b** followed by condensation with L-phenylalanine cyclohexylamide furnished diastereomeric peptides **200a,b** and **201a,b** that were readily separated and submitted to X-ray analysis. Finally, peptide cleavage and removal of benzamide protecting groups rendered independently both enantiomers of 2-aminomethyl alanine **106a** and 2-aminomethyl leucine **106b** (Scheme 22).^{134a} Recently, this approach

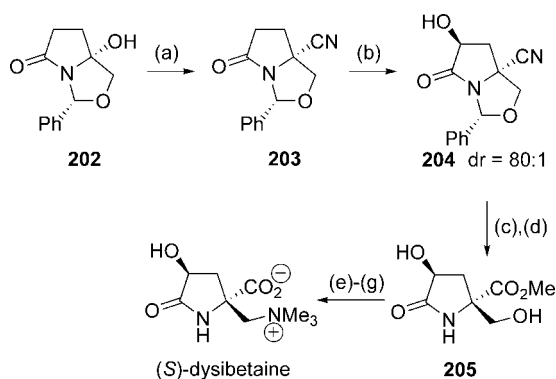
Scheme 22^a

^a Reagents and conditions: (a) (NH₄)₂CO₃, KCN, EtOH–H₂O; (b) TFA, CH₂Cl₂; (c) Ba(OH)₂·H₂O, Δ; (d) TMSCl, ^tPr₂EtN, CH₂Cl₂, PhCOCl; (e) DCC, CH₂Cl₂; (f) (S)-NH₂(Bn)CHCONHCy, NMP, 80 °C.

has been used for the synthesis of α,β -diamino acids derived from proline^{134b} and pipercolic acid^{134c} that have served as monomers for assembling, by solid-phase synthesis, larger molecular entities with a well-defined secondary structure in solution. The Bücherer–Bergs reaction is also the key step in the synthesis of α,β -diamino acid (–)-cucurbitine from 4-hydroxy proline.^{134d}

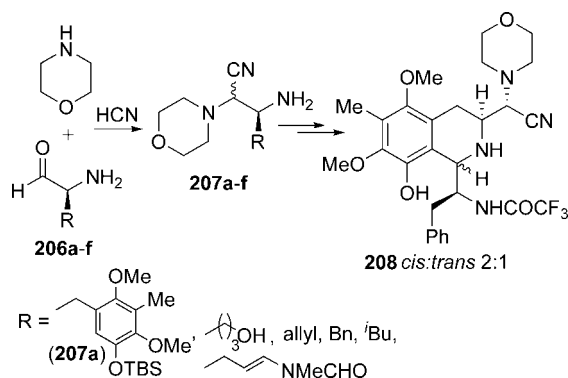
On the other hand, the Strecker reaction, involving addition of cyanide to α -amino imines, provides an efficient access to α,β -diamino nitriles that in some cases have been transformed into different α,β -diamino acid derivatives. This strategy was employed to synthesize peptidic enalapril analogues containing an α,β -diamino acid residue, as inhibitors of the angiotensin-converting enzyme,^{66a} as well as for the synthesis of octapeptide angiotensin II analogues containing an α,β -diamino acid unit.^{64b} Very recently, the Strecker methodology has been used in the total synthesis of enantiopure dysibetaine and related compounds (Scheme 23).¹³⁵ In fact, enantiopure bicyclic δ -lactam **202** was used as precursor of an *N*-acyliminium ion for the diastereoselective addition of trimethylsilyl cyanide to render **203**. After a highly diastereoselective hydroxylation at C-4 to give **204** (dr = 80:1), hydrogenolysis followed by acidic hydrolysis and esterification rendered hydroxymethyl lactam **205**. Substitution of the side-chain hydroxyl group was effected by means of azide displacement onto a mesylate derivative, and then suitable manipulation of the functional groups afforded natural (2*S*,4*S*)-dysibetaine. In the same paper, the synthesis of a racemic analogue is described through direct C-4 alkylation of methyl pyroglutamate using Eschenmoser's salt.

The Strecker protocol has been applied to the preparation of α,β -diamino nitriles useful as C-protected α -amino

Scheme 23^a

^a Reagents and conditions: (a) TMSCN, SnCl₄, 65%; (b) KHMDS, MoOPH, toluene, THF, 81%; (c) 6 N HCl; (d) CH₂N₂, Et₂O, 59% over 2 steps; (e) (i) MsCl-Pyr, (ii) NaN₃, DMF, 28% over 2 steps; (f) H₂, Pd-C, MeOH; (g) (i) MeI, Pr₂EtN, THF, (ii) Dowex 550A, 61%.

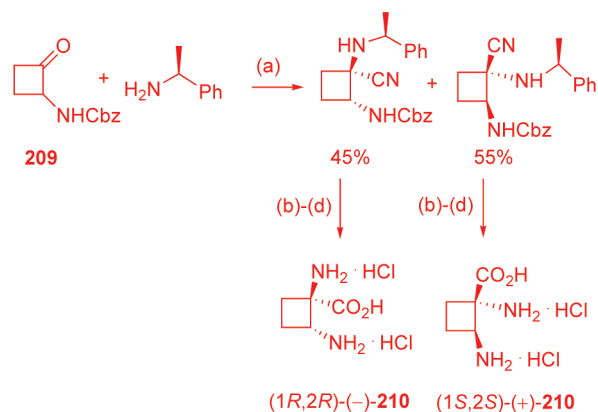
Scheme 24



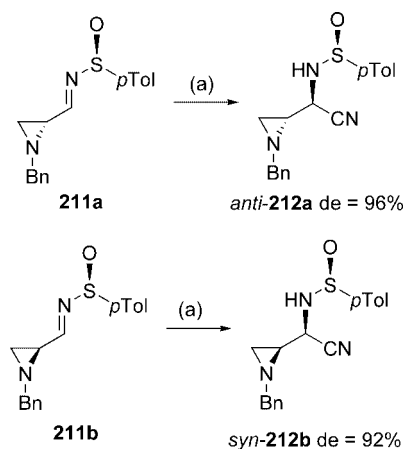
aldehydes (Scheme 24). The group of Myers has reported the transformation of optically pure α -amino aldehydes **206a–f** into α,β -diamino nitriles **207a–f** as a mixture of diastereomers at C-1 but with complete retention of the configuration at C-2. The lability of the amino nitrile can be modulated depending on the nature of the amine, with morpholino derivatives being more stable. The stability of diamino nitrile **207a** toward epimerization under different reaction conditions has also been proven carrying out the synthesis of tetrahydroisoquinoline **208** related to saframycin.¹³⁶

Asymmetric Strecker reactions have been carried out using chiral imines generated from enantiopure (*R*)- α -phenylethylamine with moderate diastereoselectivity.^{137a} This methodology has been recently applied to the synthesis of enantiopure 1,2-cyclobutane carboxylic acids **210** from racemic 2-aminocyclobutanone **209** (Scheme 24a).^{137b} In contrast, enantiopure 2-aziridinesulfonimines^{138a} and glucopyranose derived aldimines^{138b} provide, with high diastereocontrol, amino nitriles that have been used in the synthesis of α,β -diamino acids. Thus, 2-aziridinesulfonimines **211a** and **211b** have been treated with trimethylsilylcyanide with high diastereocontrol by the sulfinyl moiety to give, after crystallization, enantiopure aziridine amino nitriles **212a** and **212b** (Scheme 25).

Recently, the modular synthesis of *syn*- α,β -diamino ester **217** has been reported via sequential addition of cyanocuprate and cyanide to a dimethoxyimidazolidinone. The key intermediate enantiopure dimethoxyimidazolidinone, **214**, generated in five steps from **213**, underwent nucleophilic addition of *iso*-butylcyanocuprate to an in situ-generated acyliminium ion followed by introduction of a tosyl group and removal

Scheme 24a^a

^a Reagents and conditions: (a) HOAc, NaCN, 50 °C, 90%; (b) H₂O₂, K₂CO₃, rt, 85–90%; (c) H₂, Pd(OH)₂/C, (Boc)₂O, EtOH, 90%; (d) 6 M HCl, reflux, quant.

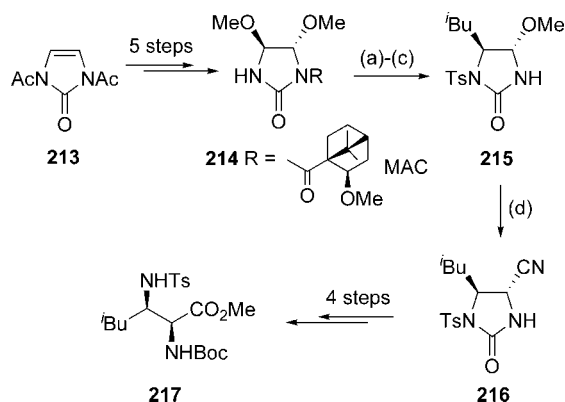
Scheme 25^a

^a Reagents and conditions: (a) TMSCN, CsF, THF, -50 °C, 98%.

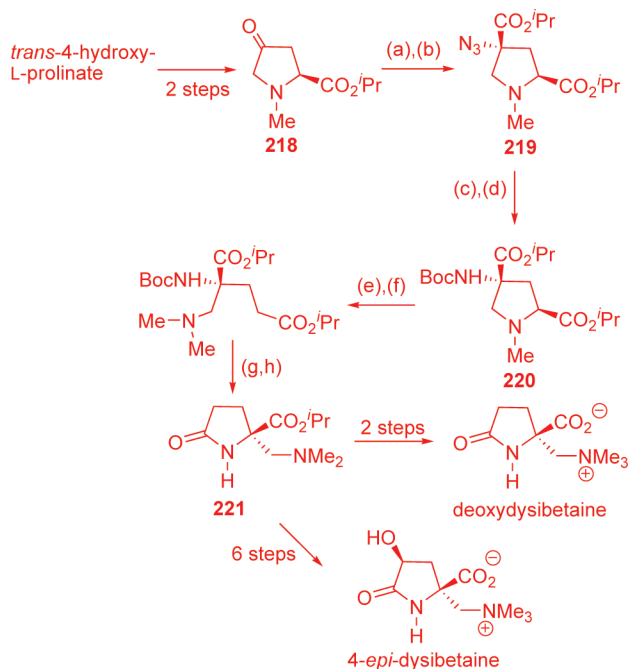
of the chiral auxiliary (MAC) to afford *N*-tosyl methoxyimidazolidinone **215** that was submitted to diastereoselective Lewis acid-mediated addition of TMSCN to give **216**. Finally, four steps comprising acidic hydrolysis of the cyanide group and imidazolidinone cleavage rendered enantiopure *syn*- α,β -diamino ester **217** in good yield (Scheme 26).^{139a}

Alternatively, the enantioselective syntheses of (*R*)-deoxydysibetaine and (–)-4-*epi*-dysibetaine have been accomplished from 4-hydroxy prolinic acid in 11 and 15 steps, respectively. The construction of the α,β -diamino ester motif in **219** is carried out through a two-step stereoselective procedure that entailed treatment of ketone **218** with LiHMDS/CHCl₃ and then DBU/NaN₃/18-crown-6 in *i*-PrOH. After azide reduction and subsequent protection, **220** was submitted to reductive C–N cleavage with SmI₂ and *N*-methylation. Further deprotection (Boc) and cyclization rendered **221** that contains the pyrrolidinone core of the target compounds (Scheme 26a).^{139b}

Finally, the multicomponent Ugi condensation has been used as the key step for the assembly of piperazine-2-carboxamides (Scheme 27). This one-pot procedure consists of reaction between a mono-*N*-alkylethylenediamine, **222**, α -chloroacetaldehyde, **223a**, an isocyanide, **224**, and a carboxylic acid, **225**, to give racemic piperazine carboxamides **226** in a very efficient manner. Furthermore, access to enantiopure piperazines is also possible using α,α -dichlo-

Scheme 26^a

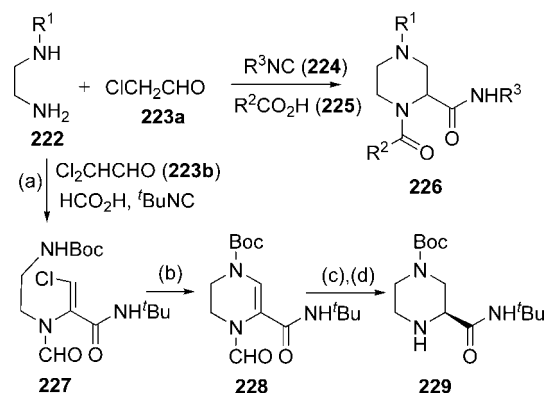
^a Reagents and conditions: (a) *t*BuCuCNMgBr, LiCl, BF₃·Et₂O, THF; (b) TsCl, BuLi, THF; (c) BnSH, BuLi, THF; (d) TMSCN, BF₃·Et₂O, CH₂Cl₂.

Scheme 26a^a

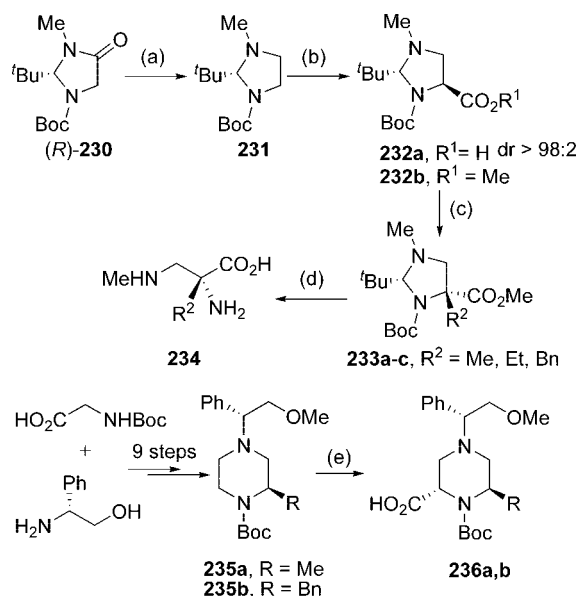
^a Reagents and conditions: (a) LiHMDS, CHCl₃, THF, −78 °C; (b) DBU, NaN₃, 18-cr-6, ⁱPrOH; (c) 10% Pd-C, H₂, EtOAc; (d) (Boc)₂O, TEA, rt, CH₂Cl₂; (e) Sml₂, DMEA, THF, 0 °C; (f) 37% HCHO, 10% Pd-C, H₂, MeOH; (g) ZnBr₂, CH₂Cl₂, rt; (h) toluene, reflux.

roacetaldehyde, **223b**, through a stepwise sequence. Indeed, isolation of open-chain intermediate, **227**, followed by sequential treatment with Et₃N and KO^tBu, led to tetrahydropyrazine **228**. Asymmetric hydrogenation of **228** in the presence of Rh-BINAP catalyst allowed for the synthesis of enantiopure piperazine **229** a fragment of HIV-protease inhibitor indinavir. **Recently, the Ugi condensation has been successfully used as a key step in the total synthesis of (−)-dysibetaine.**^{140c,d}

3.1.2.2. Electrophilic Synthetic Equivalents of CO₂R and Other Approaches. In contrast to the approaches above, the introduction of the carboxylic group as an electrophile has been scarcely explored. An example developed by the group of Seebach starts from glycine-derived imidazolidinone (*R*)-**230** (Boc-BMI) (Scheme 28). Deoxygenation of **230** using lithium triethylborohydride in combination with lithium borohydride rendered acylimidazolidine **231**, which upon

Scheme 27^a

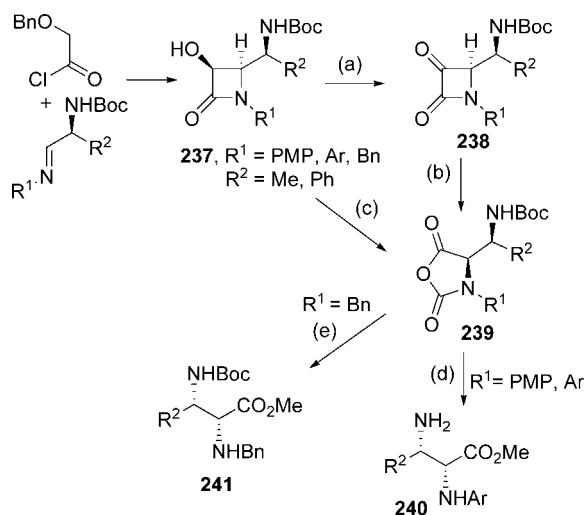
^a Reagents and conditions: (a) **222**, toluene, 50 °C, then **224**, **225**, MeOH, 2 days, rt, then Et₃N, 3 h, rt, (~100%); (b) KO^tBu, THF, 3 h, 60%; (c) MeOH, [(*R*)-BINAP(COD)Rh]OTf, H₂, 100 atm; (d) aqueous NH₂NH₂, 100 °C, 91%.

Scheme 28^a

^a Reagents and conditions: (a) LiBH₄ cat., LiBHEt₃, THF, reflux, 90 min, 90%; (b) TMEDA, ^tBuLi, Et₂O, −70 °C, 30 min then CO₂, 3 h, (84% for **232a**) or CO₂, 3 h then CH₂N₂ (84% for **232b**); (c) ⁱPr₂NH, THF, ^tBuLi, −60 °C to rt, 20 min, R^{2X}, 12 h, 60–86%; (d) (i) TFA, CH₂Cl₂, 14 h, (ii) Two N NaOH, rt, 1 h, (iii) Dowex 50 × 8, 60–75%; (e) ^tBuLi, TMEDA, CO₂, THF, 50% for **236a** and 71% for **236b**.

directed-metalation by treatment with ^tBuLi followed by trapping with CO₂ diastereoselectively afforded carboxyimidazolidines **232a,b** (dr > 98:2). Subsequent diastereocontrolled alkylation of **232b** using alkyl halides and then acidic hydrolysis allowed for the isolation of a number of enantiopure free α,β-diamino acids **234a–c**. In addition, since (*S*)-**230** is equally accessible, the enantiomeric α,β-diamino acids are also available. A parallel approach has been used in the synthesis of 2-carboxypiperazines by the group of Quirion. In fact, piperazines **235a,b**, available in nine steps from (*R*)-(*−*)-phenylglycinol and *N*-Boc-glycine, were transformed into 2-carboxypiperazine **236a,b** by diastereoselective metalation of C-6 and quenching with CO₂, furnishing the 2,6-trans isomers as single products.¹⁴¹

On the other hand, [2 + 2] ketene–imine cycloadditions have been applied to form the α–β carbon–carbon bond of α,β-diamino acids with the oxidative treatment of β-lactams

Scheme 29^a

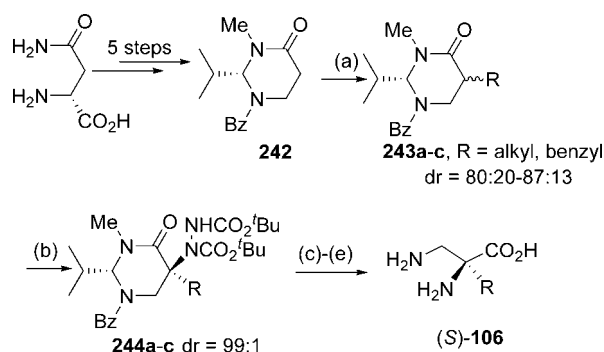
^a Reagents and conditions: (a) DMSO, P_2O_5 , 16 h, rt, 78–83%; (b) *m*-CPBA, CH_2Cl_2 , -40°C , 1 h, 90–98%; (c) NaOCl, TEMPO cat., NaHCO_3 , KH_2PO_4 – K_2HPO_4 , KBr, CH_2Cl_2 , 0°C , 92%; (d) MeOH, TMSCl, rt, 24 h, 80%, (e) MeOH, reflux, 72–90%.

as key step of this strategy (Scheme 29). Indeed, in 1994, the group of Palomo reported that enantiopure 3-hydroxy-4-(aminoalkyl) β -lactams **237**, readily available from the corresponding acid chloride and optically pure α -amino imines, were efficiently oxidized to α -keto β -lactams **238** under Collin's conditions (DMSO , P_2O_5) and then to *N*-carboxy anhydrides (NCAs) **239** under Baeyer–Villiger conditions (*m*-CPBA). In addition, a couple of years later, the authors found an improved one-step oxidative cycloexpansion protocol using TEMPO that allows for direct transformation of 4-hydroxy β -lactams **237** into NCAs **239**. No epimerization was detected in any of the above oxidative processes. Ensuing esterification of NCAs **239** upon reaction with MeOH and trimethylsilyl chloride rendered enantiopure, differentially protected *syn*- α,β -diamino esters **240** and **241**.¹⁴²

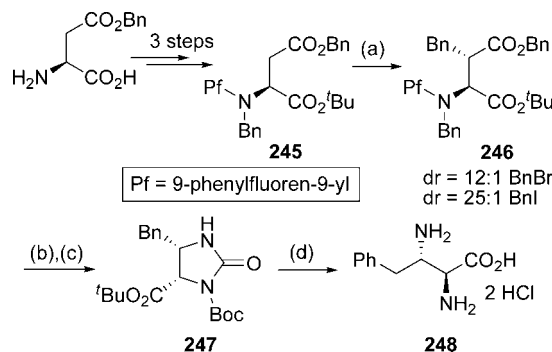
3.1.3. Methods in Which the *b*–*b'* or *c*–*c'* Bonds Are Formed

The number of routes to introduce carbon substituents on the diamino acid skeleton is considerably smaller than the number of approaches found for the above disconnections. One of these methods, developed by the group of Juaristi, relies on optically pure pyrimidinone **242** available in five steps from (*R*)-asparagine (Scheme 30). This cyclic intermediate, **242**, is submitted to enolate alkylation using LDA and alkyl halides with low diastereoselectivity to produce **243a–c**, which undergo a highly diastereoselective electrophilic amination of the enolate with di-(*tert*-butyl) azodicarboxylate (DBAD) affording **244a–c**. After three more steps to remove the cyclic iminal and protecting groups, free α -alkyl- α,β -diamino acids (*S*)-**106** ($R = \text{alkyl, benzyl}$) are obtained. A parallel route from (*S*)-asparagine provided the enantiomeric diamino acids.¹⁴³

Another remarkable example reported by Rapoport in 1990 relied on an *N*-protected aspartic acid derivative as starting material **245**, in which the two carboxyl groups are differentially protected (Scheme 31). Selective alkylation at carbon 3 with KHMDS and benzyl halides took place, affording **246** with a high degree of diastereocontrol essentially exerted by the specific substitution at nitrogen and influenced by the

Scheme 30^a

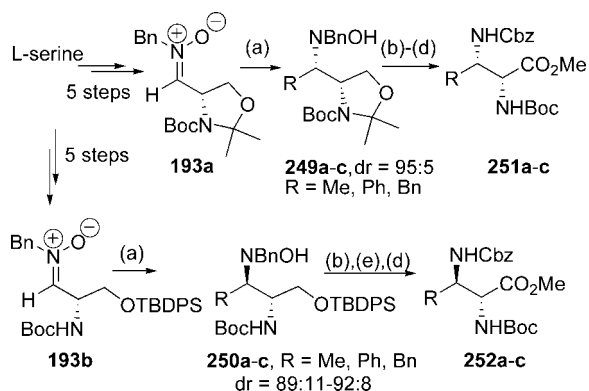
^a Reagents and conditions: (a) LDA, RX, THF, 80–85%; (b) LDA, DBAD, 45–73%; (c) TFA, CH_2Cl_2 , rt; (d) Raney Ni, MeOH, 69 bar, rt; (e) 6 N HCl, 90°C , 27–89% (3 steps).

Scheme 31^a

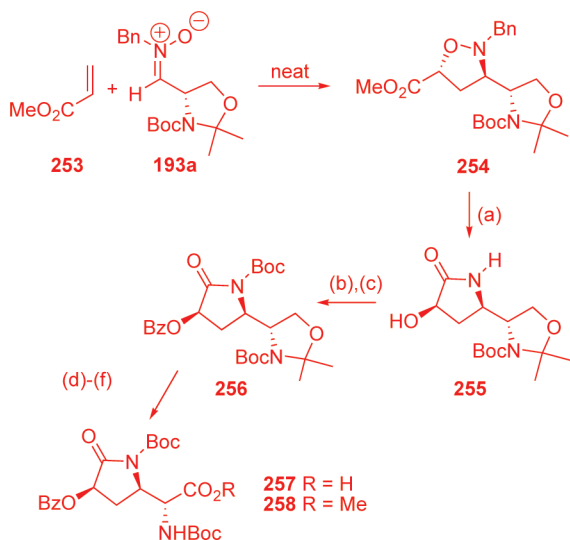
^a Reagents and conditions: (a) KHMDS, BnX, 75%; (b) H_2 , Pd-C, $(\text{Boc})_2\text{O}$, 60 psi, 86%; (c) DPPA, Et_3N , MeCN, 91%; (d) 2 N HCl.

nature of the benzyl halide (I vs Br). After selective reduction of the benzyl ester and exchange of protecting group at nitrogen, Curtius reaction with diphenyl phosphorazidate (DPPA) gave Boc-imidazolidinone **247**, which upon acidic hydrolysis finally rendered enantiopure *syn*- α,β -diamino acid **248**.¹⁴⁴

Within this family of methods, the group of Merino has reported an effective route for the diastereoselective synthesis of *syn*- or *anti*- α,β -diamino esters. Indeed, nucleophilic additions of Grignard reagents to nitrones **193a** and **193b**, both prepared from L-serine in five linear steps, take place with opposite diastereoselectivity by attack to the *Si* and *Re* faces, respectively (Scheme 32). The different behavior found for **193a** and **193b** is attributed to the influence that the protecting groups exert on the reactive conformation of the nitrones. The resulting *N*-benzylhydroxylamines **249a–c** and **250a–c** were submitted to hydrogenation, exchange of the protecting groups, oxidation of the hydroxymethyl moiety, and esterification to render optically pure α,β -diamino esters **251a–c** (*syn*) and **252a–c** (*anti*).^{145a,b} The same group has reported the synthesis of conformationally constrained *syn*- and *anti*- α,β -diamino acids also using nitron chemistry (Scheme 32a). Stereoselective 1,3-dipolar cycloaddition between L-serine derived nitron **193a** and methyl acrylate **253** produced a mixture of four diastereomers (35:7:7:1) with **254** as the major isomer. Catalytic hydrogenation of **254**, followed by protection of the hydroxy group, gave pyrrolidinone **256**, which then yielded *anti*- α,β -diamino ester **258** upon treatment with *p*-toluenesulfonic acid, oxidation, and methylation of the free carboxylic acid.^{133b}

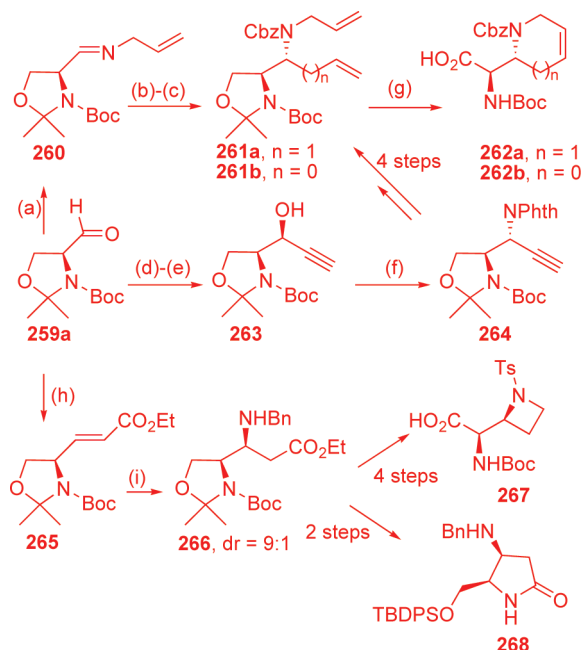
Scheme 32^a

^a Reagents and conditions: (a) RMgX (3 equiv), THF, -50°C ; (b) H_2 , $\text{Pd}(\text{OH})_2\text{-C}$, 70 psi, rt then CbzCl , aqueous NaHCO_3 , THF, rt; (c) $p\text{TsOH}$, MeOH, reflux; (d) RuCl_3 , NaIO_4 , CCl_4 , H_2O , rt then CH_2N_2 , Et_2O , 0°C ; (e) Bu_4NF , THF, rt.

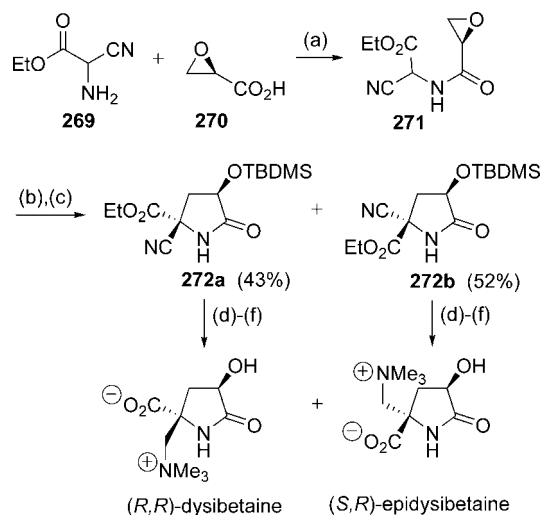
Scheme 32a^a

^a Reagents and conditions: (a) H_2 , 100 atm, $\text{Pd}(\text{OH})_2$, rt, 95%; (b) PhCOCl , Py, CH_2Cl_2 , 0°C ; (c) Boc_2O , Et_3N , DMAP, CH_2Cl_2 , 80% 2 steps; (d) $p\text{-TsOH}$, MeOH, 45°C , 6 h, 80%; (e) TEMPO, [bis(acetoxy)iodo]benzene, $\text{CH}_3\text{CN-H}_2\text{O}$; (f) CH_2N_2 , Et_2O , rt, 50% 2 steps.

Recently, the group of Chattopadhyay has developed different strategies for the synthesis of conformationally restricted diamino acids **262a**, **262b**, **267**, and **268** starting from Garner's aldehyde **259a** (Scheme 32b). Alkylation of imine **260** with allylmagnesium bromide followed by protection of the resulting amine afforded anti product **261a**.^{145c} Using chelating allylation conditions (allylzinc bromide) the syn product (not shown) was obtained with moderate yield and diastereoselectivity (anti:syn = 18:82). Alternatively, addition of lithium ethynyltrimethylsilane and zinc bromide to Garner's aldehyde and subsequent deprotection of the alkyne afforded syn amino alcohol **263**.^{145d} In the absence of zinc bromide, the corresponding anti product was obtained with good diastereoselectivity (anti:syn = 19:1). Next, syn-**263** was submitted to a Mitsunobu amination, providing anti diamine **264**, which was transformed into bisallylic amine **261b** in four steps. Ring closing metathesis of **261a** and **261b** allowed for the synthesis of 2-piperidinylglycine and 2-pyrrolidinylglycine derivatives, respectively. Finally, the authors have also described the addition of benzyl amine to Garner's aldehyde-derived unsaturated ester **265**.^{145e} Syn product **266**

Scheme 32b^a

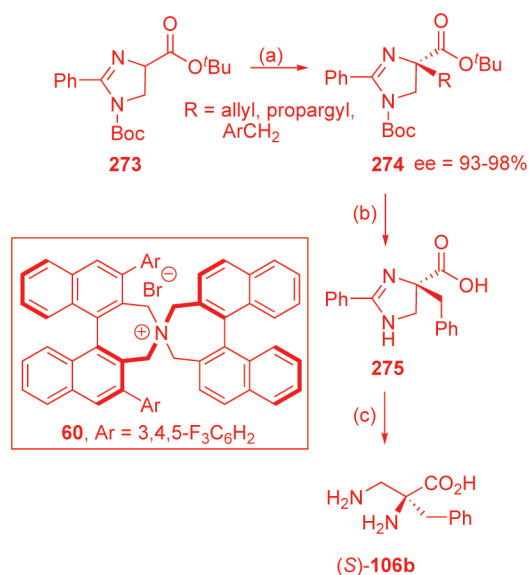
^a Reagents and conditions: (a) AllylNH_2 , 4 Å MS, CH_2Cl_2 , 0°C , 95%; (b) AllylMgBr , $\text{Et}_2\text{O:THF}$ (9:1), -30°C , 12 h, 67%, dr = 99:1; (c) CbzCl , NaHCO_3 , $\text{H}_2\text{O-EtOAc}$, rt, 85%; (d) Ethynyltrimethylsilane, $n\text{-BuLi}$, ZnBr_2 , Et_2O , -78°C to rt, 81%; (e) NH_4F , $n\text{-Bu}_4\text{N}^+\text{HSO}_4^-$, CH_2Cl_2 , rt, 86%; (f) phthalimide, Ph_3P , DIAD, toluene, 0°C to rt, 47%; (g) Grubbs' first generation cat., CH_2Cl_2 , rt, **262a** (86%), **262b** (87%); (h) triethyl phosphonoacetate, aqueous K_2CO_3 , $\text{Bu}_4\text{N}^+\text{I}^-$, 86%; (i) BnNH_2 , borax, $\text{EtOH-H}_2\text{O}$ (1:1), 82%.

Scheme 33^a

^a Reagents and conditions: (a) DCC, EtOAc , 85%; (b) NaOEt , THF; (c) TBSOTf, 2,6-lutidine, CH_2Cl_2 ; (d) PtO_2 , H_2 , EtOH , HCl, 100%; (e) (i) H_2CO , Pd-C , H_2 , (ii) NaHCO_3 , MeI, THF, 100%; (f) Dowex 550A, MeOH, 55°C , 97%.

was obtained with good diastereoselectivity which was dependent on the amine. Compound **266** was transformed into 2-azetidinyglycine and aminopyrrolidone derivatives.

Also, in a recent report from the group of Snider, the total synthesis of (–)- and (+)-dysibetaine has been addressed using as a key step the intramolecular cleavage of an oxirane ring to construct the pyrrolidinone ring (Scheme 33). Initial *N*-acylation of ethyl amino(cyano)acetate **269** with (*R*)-glycidic acid **270** gave glycinamide **271** that underwent intramolecular alkylation upon treatment with NaOEt to give

Scheme 33a^a

^a Reagents and conditions: (a) **60** (cat.), RBr, KOH, toluene, 0 °C, 87–98%; (b) EtOH–H₂O (1:1), reflux, 24 h, 100%; (c) i) Ac₂O, reflux, (ii) 6 M HCl, reflux, 24 h, 54%.

a 45:55 mixture of diastereomeric hydroxy pyrrolidinones that was readily separated after silylation to **272a,b**. Subsequent hydrogenation of the cyano group followed by permethylation and saponification of **272a** and **272b** rendered (*R,R*)-dysibetaine and (*S,R*)-epidysibetaine, respectively.^{146a}

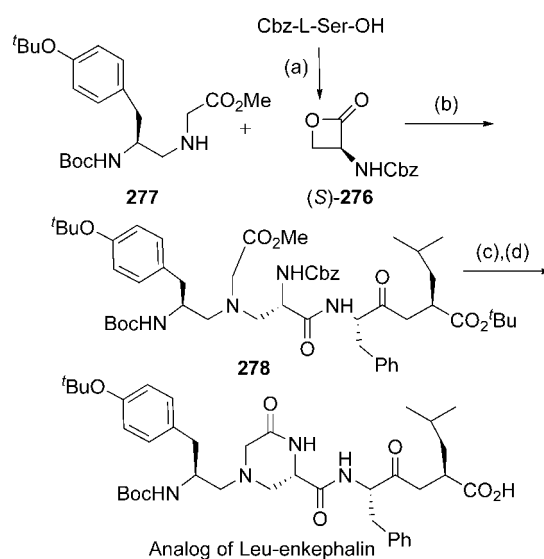
Recently, the group of Park and Jew has reported a very effective enantioselective alkylation of imidazolidinones **273** in the presence of a chiral quaternary ammonium catalyst **60** (Scheme 33a). High enantioselectivities were obtained for allylic, propargylic and benzylic halides (**274**). Removal of the *N*-Boc and the *tert*-butyl ester (R = benzyl) in refluxing EtOH–H₂O afforded **275**, which, upon acetylation and acid hydrolysis, gave α -alkyl- α,β -diaminopropionic acid (*S*)-**106b**. The authors observed that acetylation of the nitrogen in **275** was necessary prior to hydrolysis because the protonated form of **275** was quite stable under acidic conditions.^{146b}

3.2. Introduction of the Nitrogen Atoms in the Carbon Backbone

3.2.1. From Readily Available α -Amino Acids

Among the compounds available from nature, α -amino acids bearing suitable functional groups attached to the side chain represent one of the key starting materials for the synthesis of α,β -diamino acids. Indeed, a plethora of synthetic approaches can be found through the literature consisting of the manipulation of functional groups that already exist in commercially available α -amino acids with the additional advantage of using enantiopure starting materials.

3.2.1.1. From Serine and Related Amino Acids. Within this context, α -amino acids containing a β -hydroxy group, such as serine, threonine, and allo-threonine, have been frequently employed for the synthesis of α,β -diamino acids through conversion of the alcohol into an amine,¹⁴⁷ and by far, the most studied approach is the Mitsunobu reaction. This protocol has been successfully applied in a number of examples;¹⁴⁸ however, a suitable combination of protecting

Scheme 34^a

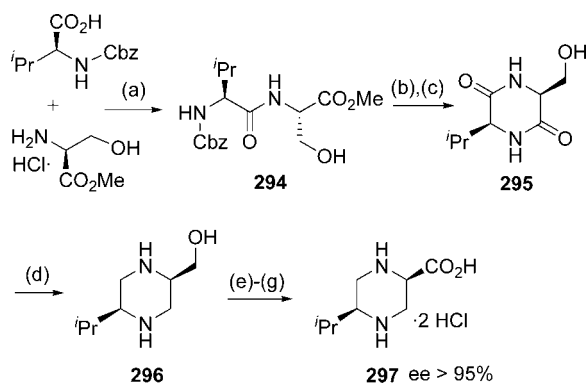
^a Reagents and conditions: (a) PPh₃, DMAD, THF, –78 °C to rt, 72%; (b) MeCN, 65 °C, then H-Phe-Leu-O^tBu, EDC, NHS, DMF, 23 °C, 24 h, 55%; (c) H₂, 1 atm, Pd–C (10% mol), EtOH, 23 °C; (d) 1:1 TFA–CH₂Cl₂, 23 °C, 6 h, quantitative.

groups at the acid, the α -nitrogen, and the newly introduced β -nitrogen should be chosen to prevent undesired side reactions such as β -elimination, aziridine formation, etc. and to ensure a reasonable yield of α,β -diamino acid derivative.^{38b,149a–f,g}

On the other hand, the group of Vederas has found that, when Mitsunobu conditions are applied to *N*-protected L-serine in the absence of an external nucleophile, (*S*)-3-[(*tert*-butoxycarbonyl)amino]oxetan-2-one **276** is readily formed without epimerization.¹⁵⁰ This enantiopure intermediate has been useful in the synthesis of natural β -amino alanines such as β -pyrazol-1-yl-L-alanine,^{151a} β -*N*-methylamino-L-alanine derivatives^{151b} and analogues of willardine,^{9b} and in the synthesis of enantiopure 2-carboxypiperazine derivatives,¹⁵² such as a constrained Leu-enkephalin analogue.⁸⁰ A key step in this synthesis was the one-pot opening of β -lactone **276** with secondary amine **277** followed by coupling of the resulting free acid with a dipeptide. The linear tripeptide, **278**, generated underwent cyclization upon hydrogenolysis of the Cbz group to form the piperazinone ring. Deprotection using 1:1 TFA/CH₂Cl₂ yielded the target compound, an analogue of Leu-enkephalin (Scheme 34).

In contrast, the direct nucleophilic substitution on suitable protected β -tosyl serine and threonine derivatives or even on β -chloroalanine is scarcely documented.^{73a,153} One of the strategies to circumvent secondary reactions is the temporary reduction of the carboxylic group of L-serine or L-threonine to a protected hydroxymethyl derivative, which then, after azide nucleophilic substitution at β -carbon, is reoxidized to the α,β -diamino acid.^{39b,154}

The group of Baldwin has used *N*-Boc-L-serine carboxamide for internal delivery of the amide nitrogen onto the β -carbon atom of serine to provide *N*-hydroxy β -lactam **279**¹⁵⁵ that was cleanly isomerized to isoxazolidin-4-one **280** in the presence of 3% LiSEt in THF. From this cyclic intermediate, suitable manipulation of the nitrogen (*N*-2) followed by hydrogenolysis of the N–O bond furnished enantiopure β -amino alanine derivatives such as L-quisqualic acid (Scheme 35).¹⁵⁶ A more efficient route to isoxazolidin-4-ones **280** was reported by the same group; in this route isoxazolidin-4-ones **280b,c** were obtained in good yields

Scheme 37^a

^a Reagents and conditions: (a) EtOCOCl, EtOAc, 4-methylmorpholine, -10 to 25 °C, 16 h, 66%; (b) Pd-C (10% mol), cyclohexane-MeOH, 70 °C, 5 h; (c) MeOH, 70 °C, 110 h, 86%; (d) LAH, THF, 65%; (e) (Boc)₂O, MeCN, rt, 20 °C, 87%; (f) NaIO₄, acetone-H₂O, RuO₂·H₂O, 25 °C, 3 h, 85%; (g) 3 M HCl, EtOAc, rt, 30 min, 63%.

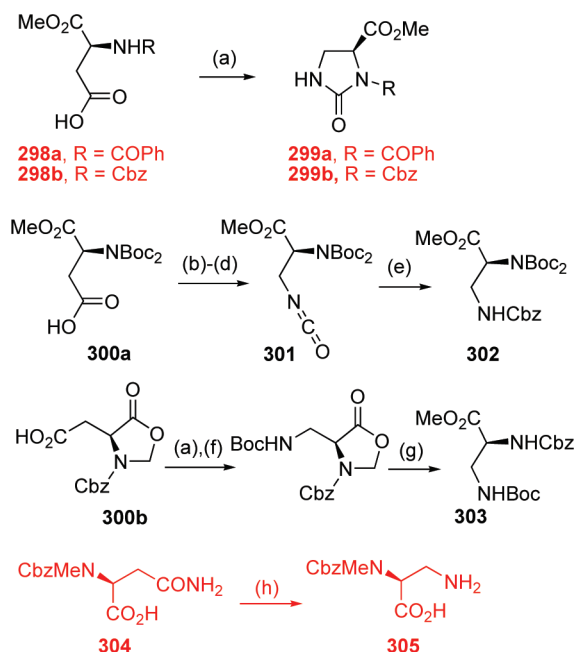
dioxopiperazine **295** with an excess of lithium aluminum hydride gave 2-hydroxymethylpiperazine, **296**. Subsequent Boc protection, ruthenium-catalyzed oxidation with sodium periodate, and complete deprotection under acidic conditions afforded enantiopure 5-*iso*-propyl-2-carboxypiperazine as hydrochloride **297** (ee > 95%). The same group reported an efficient stereocontrolled synthesis of (*R*)-2-carboxy-4-(3-phosphonopropyl)piperazine [(*R*)-CPP] derivatives, a selective antagonist of the NMDA receptor, by this strategy. The enantiomerically pure 2-substituted ring was prepared through cyclo-Gly-Ser from commercial products.^{81a,165}

3.2.1.2. From Aspartic Acid and Related Amino Acids.

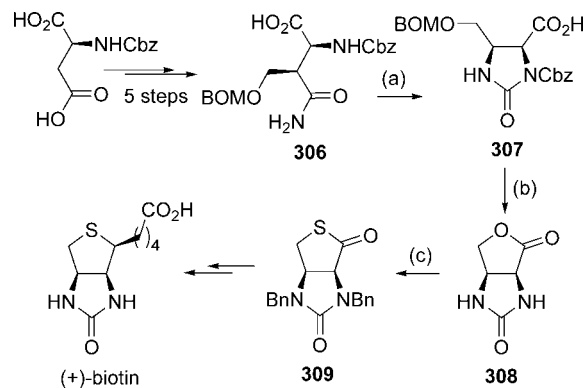
Aside from using β -hydroxy amino acids, a common approach to L-Dpr involves either a Curtius rearrangement of free L-aspartic acid^{166a,b} or a Hofmann reaction of an L-asparagine derivative.^{148c} The main side process in these reactions is formation of imidazolidinones through intramolecular trapping of the isocyanate intermediate by the vicinal nitrogen atom. In fact, an *N*-acetamido L-asparagine derivative in the presence of Br₂ and NaOH or L-aspartic acid derivatives **298a** and **298b** with diphenylphosphoryl azide (DPPA) or iodosobenzene diacetate respectively provide exclusively imidazolidinones **299a–b** (Scheme 38).^{167a–b,c}

However, a suitable combination of *N*-protecting groups and reagents efficiently converts asparagine and aspartic acid derivatives into α,β -diamino acid derivatives.^{163b,168} Furthermore, it has been illustrated by different groups that a clever use of the reagents can provide orthogonally protected L-Dpr derivatives **302** and **303** by reacting isocyanate intermediates such as **301**, from the Curtius rearrangement of **300a,b**, with benzyl alcohol or *tert*-butyl alcohol, respectively (Scheme 38).^{169a–c,d} Similarly, a Hofmann rearrangement of asparagine **304** afforded L-Dpr derivative **305**, which was an intermediate in the synthesis of the antibiotic TAN-1057A.

Within the same context, L-aspartic acid has been used as starting material for the synthesis of **309**, a key intermediate for the synthesis of (+)-biotin.¹⁷⁰ Indeed, enantiopure β -hydroxymethyl asparagine derivative **306**, prepared from *N*-Cbz L-aspartic acid in five steps, was submitted to Hofmann rearrangement to afford cyclic urea **307** with no epimerization. Removal of the protecting group (BOM) by hydrogenation led to bicyclic γ -lactone **308** that was converted into **309** by *N*-benzylation and thiolactone formation (Scheme 39).

Scheme 38^a

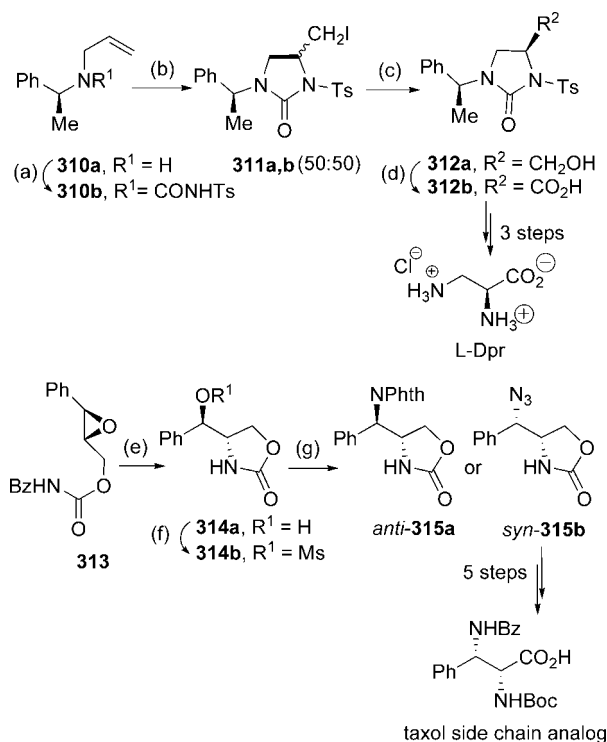
^a Reagents and conditions: (a) DPPA, Et₃N, 80 °C for **298a** or PhI(OAc)₂, DBU, THF/H₂O, 0 °C-rt for **298b**; (b) EtOCOCl, Et₃N; (c) aqueous NaN₃; (d) toluene, reflux, 87% over 3 steps; (e) BnOH, CuCl, 95%; (f) ^tBuOH, SnCl₄, 70 °C; (g) (i) 1 N NaOH, acetone, 0 °C, (ii) 6 N HCl; (h) PhI(OCOCF₃)₂, DMF/H₂O, pyridine, 20 °C, 75%.

Scheme 39^a

^a Reagents and conditions: (a) NaOCl, NaOH, H₂O, 70%; (b) H₂, Pd(OH)₂-C, MeOH, 80%; (c) (i) BnBr, NaH, DMF, 84%, (ii) KSAc, DMF, 92%.

3.2.2. From Allylic Alcohols and Amines

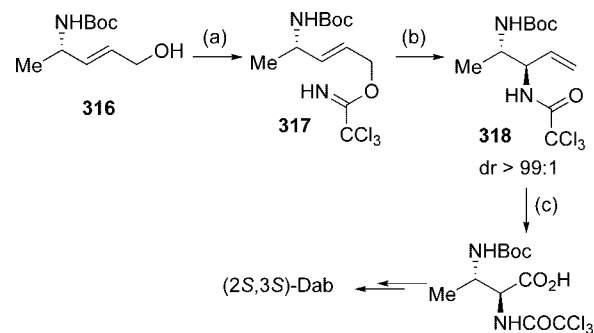
Optically pure allylic alcohols and amines are valuable precursors to α,β -diamino acids. The key step in these approaches is an internal delivery of a nitrogen atom from the group attached to the hydroxy or amino group to the unsaturated carbon–carbon bond. Consequently, the degree of diastereoselectivity in the intramolecular transfer is crucial for efficient access to the target molecules. A few examples of these approaches are gathered below. In the first, developed by the group of Cardillo (Scheme 40), enantiopure allylic amine **310a**, prepared from (*S*)- α -phenylethylamine, was readily converted into *N*-tosyl urea **310b**. Iodine-mediated cyclization was nonselective, affording a 50:50 mixture of iodo imidazolidinones **311a,b**. Subsequent chromatographic separation of **311a** followed by transformation into hydroxymethyl imidazolidinone **312a** and oxidation rendered acid **312b**, which after three steps gave L-Dpr.¹⁷¹

Scheme 40^a

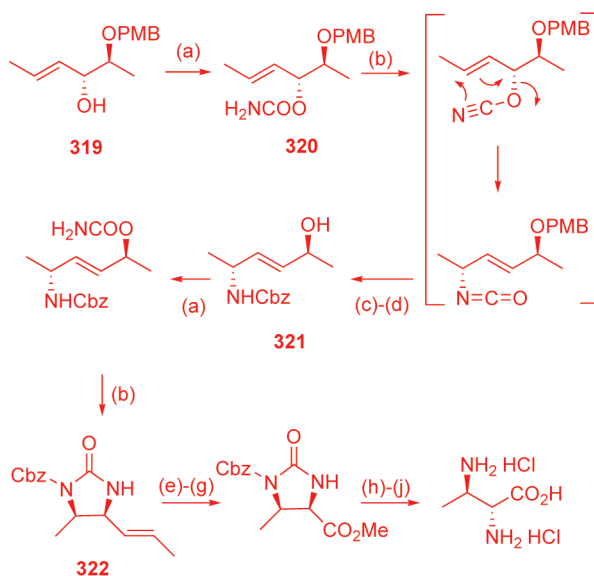
^a Reagents and conditions: (a) $\text{TsN}=\text{C}=\text{O}$, rt, >99%; (b) I_2 , THF, NaHCO_3 , 92%; (c) (i) chromatography SiO_2 , (ii) AgOAc , HOAc , reflux, (iii) K_2CO_3 , EtOH , 80%; (d) CrO_3 , H_2SO_4 , H_2O , acetone, 60%; (e) (i) NaH , THF, reflux, 88%, (ii) LiOH , H_2O , THF, rt, 85%; (f) MsCl , NEt_3 , 89%; (g) KPhthalimide , DMF , 79% for **315a** and NaN_3 , TMSCl , DMF , 64% for **315b**.

In a related route reported by the group of Rossi in an approach to a taxol side-chain analogue, enantiopure epoxy carbamate **313**, prepared from cinnamyl alcohol via Sharpless asymmetric epoxidation, was treated with sodium hydride to produce oxazolidinone **314a** with complete inversion of stereochemistry at the epoxide carbon. Activation of the hydroxyl group as a methanesulfonate ester, **314b**, and further displacement using potassium phthalimide with undesired retention of configuration, gave *anti*-**315a**, which after treatment with hydrazine was submitted to an X-ray analysis. In contrast, when mesylate **314b** was treated with sodium azide and TMSCl , *syn*-**315b** was produced exclusively. Intermediate **315b** was transformed into the target α,β -diamino acid derivative by suitable manipulation of the protecting groups and oxidation in five steps (Scheme 40).¹⁷²

In a different example, reported by the group of Ernst and Bellus (Scheme 41), allylic alcohol **316** was transformed into trichloroacetimidate **317** and further palladium-catalyzed aza-Claisen rearrangement led exclusively to anti vicinal diamine **318** (dr > 99:1). Oxidative cleavage of the double bond and removal of the protecting groups gave (2*S*,3*S*)-diaminobutanoic acid.^{173a} In this context, the group of Ichikawa has reported the synthesis of *syn*- and *anti*-2,3-diaminobutanoic acids from allylic 1,2-diols (Scheme 41a). Treatment of anti diol **319** with trichloroacetyl isocyanate followed by hydrolysis afforded allylcarbamate **320**. Dehydration provided an allyl cyanate which underwent [3,3]-sigmatropic rearrangement, and the resultant isocyanate was trapped with benzyl alcohol. Removal of the *p*-methoxybenzyl group provided an allylic alcohol **321** susceptible to a second [3,3]-sigmatropic rearrangement. In this case, the resultant isocyanate was trapped intramolecularly to afford imidazolidinone **322**.

Scheme 41^a

^a Reagents and conditions: (a) Cl_3CCN , NaH , Et_2O , rt, 1 h, 96%; (b) $\text{PdCl}_2(\text{MeCN})_2$ (6% mol), rt, 3 h, 48%; (c) $\text{RuCl}_3 \cdot \text{H}_2\text{O}$ (cat.), NaIO_4 , H_2O - MeCN-CCl_4 , rt, 81%.

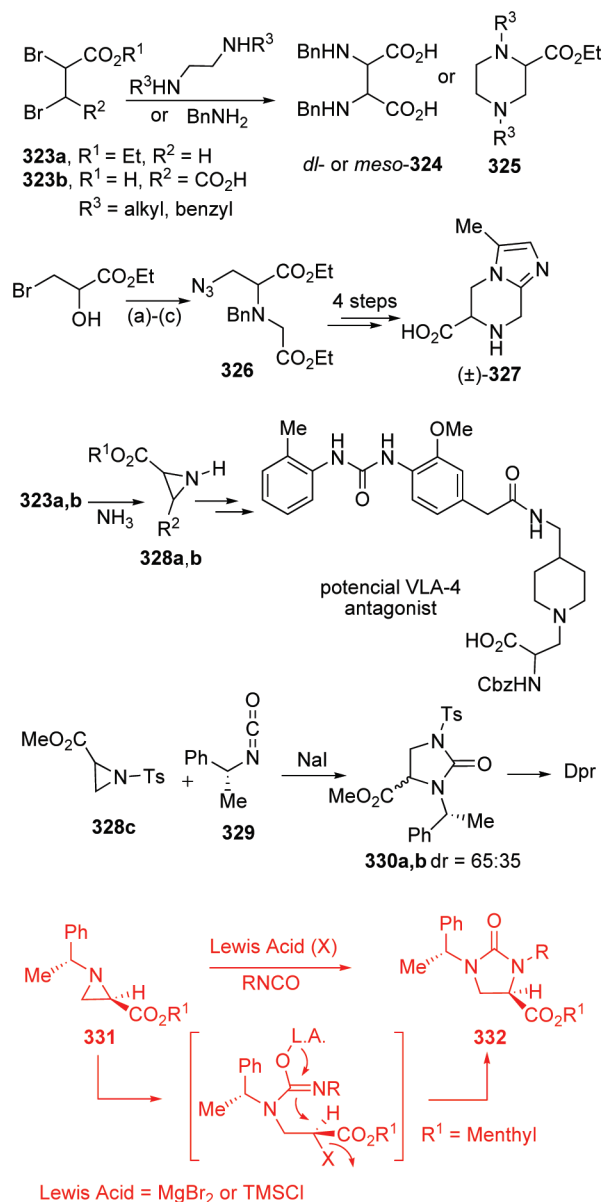
Scheme 41a^a

^a Reagents and conditions: (a) CCl_3CONCO , CH_2Cl_2 , then K_2CO_3 , MeOH ; (b) PPh_3 , CBr_4 , Et_3N , CH_2Cl_2 ; (c) BnOH , $\text{Bu}_3\text{SnOCH}_2\text{Ph}$, 93%, 2 steps; (d) DDQ , $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$, 94%; (e) Ac_2O , DMAP , Et_3N , CH_3CN , 85%; (f) RuCl_3 , H_3IO_6 , $\text{CCl}_4/\text{CH}_3\text{CN}/\text{H}_2\text{O}$; (g) CH_2N_2 , MeOH , 72%, 2 steps; (h) 2 N HCl , 90 °C; (i) Dowex 50W-X8 ; (j) 1 N HCl , 89%, 3 steps.

322. Finally, oxidation of the double bond and several protecting group manipulations provided the enantiopure, *anti*-2,3-diaminobutanoic acid. Starting from a *syn* diol, the authors also synthesized the corresponding *syn*-2,3-diaminobutanoic acid following the same sequence.^{173b}

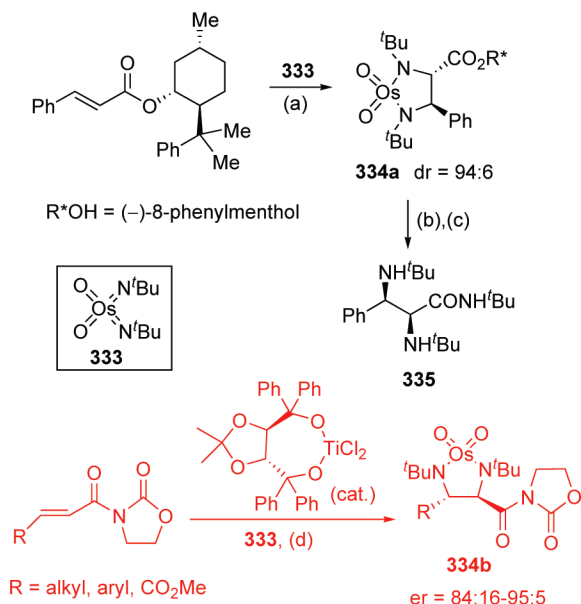
3.2.3. From α,β -Unsaturated Alkenoates and Functionalized Alkanoates

3.2.3.1. From Haloalkanoates. One of the most efficient routes found among the earlier endeavors to synthesize these compounds consists of treating α,β -dibromo propionates **323a** or succinates **323b**, either commercially available or prepared by addition of bromine to α,β -unsaturated precursors, with nitrogen nucleophiles (Scheme 42). Following this approach, *meso*- and *DL*-2,3-diaminosuccinic acid derivatives **324** have been independently synthesized upon reaction with 2 equiv of benzylamine,¹⁷⁴ and 2-carboxypiperazines **325** can be readily obtained when 1,2-ethylenediamine derivatives are used.¹⁷⁵ Furthermore, sequential introduction of the nitrogen nucleophiles has also been reported in the context of the synthesis of piperazines fused to azole rings using ethyl- β -

Scheme 42^a

^a Reagents and conditions: (a) NaN_3 , $\text{EtOH-H}_2\text{O}$, 75 °C, 17 h; (b) $(\text{F}_3\text{CSO}_2)_2\text{O}$, lutidine, CH_2Cl_2 , 0 °C, 15 min; (c) $\text{BnNHCH}_2\text{CO}_2\text{Et}$, CH_2Cl_2 , 0 °C to rt, 90 min.

bromo- α -hydroxy propanoate as starting material. Bromide displacement with sodium azide followed by triflate formation and substitution with ethyl-*N*-benzyl glycinate gave azido amino ester **326**, which was finally manipulated furnishing piperazine carboxylic acids **327** (Scheme 42).¹⁷⁶ However, when ammonia is used as the nucleophile, racemic methoxycarbonyl aziridines **328a,b**, readily resolved by enzymatic means, were obtained.¹⁷⁷ This protocol has been recently used for the synthesis of enantiopure Dpr¹⁷⁸ and of VLA-4 antagonists containing an α,β -diamino acid residue by submitting the aziridine intermediates to nucleophilic ring-opening with ammonia or sodium azide.⁶⁷ Alternatively, in a recent report from the group of Nadir, a facile route for the synthesis of α,β -diamino acids is disclosed by reaction of 2-methoxycarbonyl aziridine, **328c**, generated from an α,β -unsaturated ester, with chiral isocyanate **329** in the presence of sodium iodide to produce a mixture of imidazolidinones **330a,b** with low diastereoselectivity (65:35) by means of initial iodide-mediated aziridine opening. After

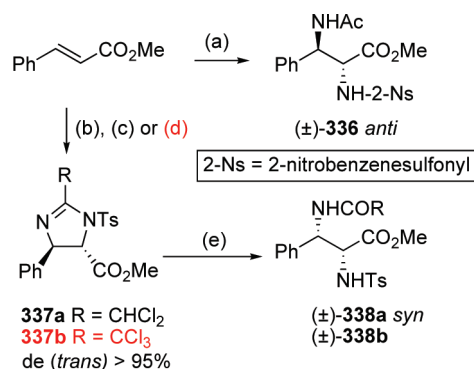
Scheme 43^a

^a Reagents and conditions: (a) THF, -15 °C; (b) $t\text{-BuNH}_2$, ZnCl_2 ; (c) NaBH_4 , EtOH , rt, 95%; (d) 4 Å MS, toluene, 5 °C.

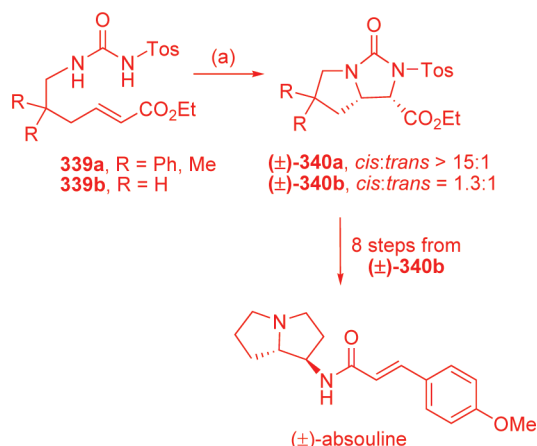
separation and acidic cleavage, both enantiomers of Dpr are available. Similarly, an additional alkyl substituent can be placed α to the ester moiety of the starting aziridine allowing for the synthesis of α -alkyl- α,β -diamino acids.^{179a} Enantiomerically pure imidazolidinones **332** have also been synthesized by the group of Lee and Ha.^{179b} The Lewis acid-catalyzed ring expansion of commercially available chiral aziridine **331** and isocyanates proceeded regio- and stereospecifically with retention of configuration at C-2 of the aziridine via a double inversion process.

3.2.3.2. From Alkenoates. Aside from the above examples, it could be easily envisioned that enantioselective diamination of α,β -unsaturated acids is the shorter route to α,β -diamino acids; however, the direct asymmetric diamination of olefins is a reaction comparatively less studied than the related dihydroxylation process. In fact, the stoichiometric osmium-mediated diamination of fumarates and cinnamates with bis(*tert*-butylimido) complex **333** is a stepwise process and in the presence of $(\text{DHQD})_2\text{PHAL}$ or $(\text{DQD})_2\text{PHAL}$ leads essentially to racemic products. However, incorporation of a (-)-8-phenylmenthyloxy auxiliary to the cinnamate provides complex **334a** in excellent diastereomeric ratio (94:6). Further reaction with *tert*-butylamine and ZnCl_2 provides an amide that was submitted to osmium removal with sodium borohydride furnishing α,β -diamino amide **335** in good yield (Scheme 43).^{180a,b} More recently, the first enantioselective catalytic diamination of α,β -unsaturated oxazolidinones with bis(*tert*-butylimido) complex **333** has been described.^{180c} In this process, the use of an enantiopure Ti-TADDOL catalyst accelerates the catalyzed pathway and allows for the formation of complexes **334b** with a good enantiomeric ratio. Additionally, osmium-diamine chelates related to **334a,b** have been recently used in the aminohydroxylation of symmetrical and unsymmetrical olefins.^{180d}

The group of Li has reported the first direct electrophilic diamination of α,β -unsaturated esters using *N,N*-dichloro-2-nitrobenzenesulfonamide (2-NsNCl_2) in acetonitrile (Scheme 44).¹⁸¹ The process takes place with complete anti diastereoselectivity, and the use of acetonitrile is crucial since a

Scheme 44^a

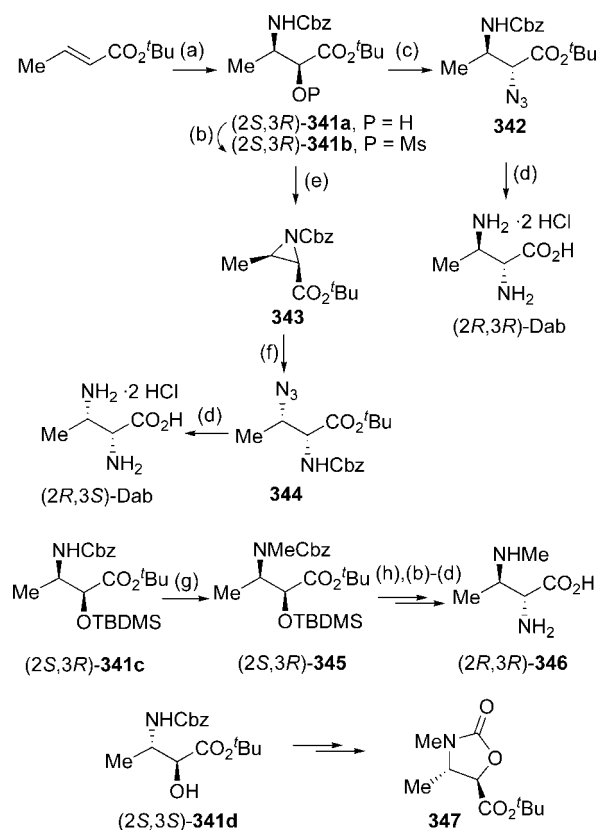
^a Reagents and conditions: (a) (i) 2-NsNCl₂, MeCN, (ii) aqueous Na₂SO₃, 74%; (b) TsNCl₂, MeCN, [(C₃F₇CO₂)₂Rh]₂·PPh₃ (cat.), 4 Å MS, 51%; (c) TsNCl₂, MeCN, FeCl₃·PPh₃ (cat.), 63%; (d) TsNCl₂, MeCN, MnO₂ (cat.), 50 °C, 56%. (e) 6 N HCl, 70 °C, 92%.

Scheme 44a^a

^a Reagents and conditions: (a) Pd(OAc)₂ (cat.), Na₃PO₄, CuBr₂, DMF, 40 °C.

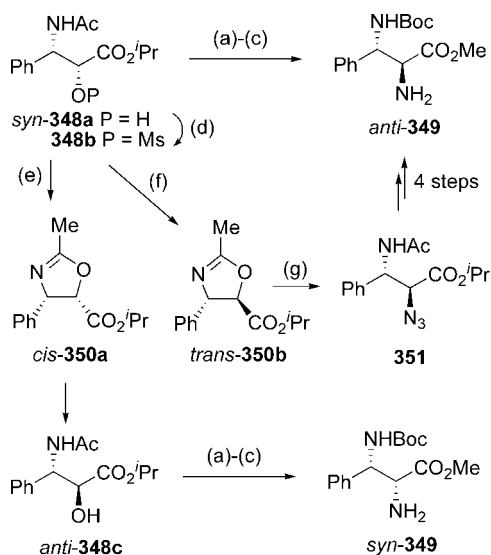
molecule of solvent is apparently responsible for delivering the second nitrogen atom to the final racemic *anti*-α,β-diamino ester **(±)-336**. Further studies by this group have revealed that the use of *N,N*-dichloro-*p*-toluenesulfonamide in the presence of Rh(II)- or Fe(III)-containing metal catalysts using acetonitrile again provides efficient access to racemic trans imidazolines **337a** that can be readily transformed into *syn*-α,β-diamino esters **(±)-338a** upon acidic hydrolysis.^{182a–d} Additionally, the same authors found that less expensive manganese(IV) oxide can replace Rh(II) and Fe(III) catalysts in the diamination process.^{182e} When the reaction is carried out at 50 °C, the CHCl₂ group (R) on the imidazoline can be transformed into CCl₃ (**337b**). The *N*^β-trichloroacetyl group resulting from hydrolysis can be also removed under mild conditions.

Recently, the group of Muñiz has reported a new palladium-catalyzed diamination reaction of acrylic esters **339**. Using a Pd(II) catalyst and copper(II) bromide as oxidant, α,β-diamino esters **340** were obtained (Scheme 44a). The diastereoselectivity of the reaction depended on the size of the ester group and the backbone substitution. Diastereoselectivities were high for methyl and ethyl esters while only moderate for benzyl and *t*-butyl derivatives. Additionally, the diastereoselectivity diminished significantly for substrates with no substituents on the tether (R = H). Diamino ester **340b** was further transformed into natural alkaloid absoulone.^{182f}

Scheme 45^a

^a Reagents and conditions: (a) (DHQD)₂PHAL (5%), K₂OsO₂(OH)₄ (4%), CbzNHCl, MeCN-H₂O, 0 °C; (b) MsCl, Et₃N, CH₂Cl₂; (c) NaN₃, DMF; (d) (i) H₂, Pd-C, MeOH, (ii) TFA, CH₂Cl₂ then 1 N HCl; (e) KO^tBu, THF; (f) TMSN₃, MeOH; (g) NaH, Me₂SO₄, THF; (h) 5% HF, MeCN.

Different groups have envisioned that α,β-diamino acid derivatives could be prepared efficiently by Sharpless asymmetric aminohydroxylation of α,β-unsaturated esters followed by adequate manipulations of the resulting amino alcohols. The group of Janda (Scheme 45)¹⁸³ has described that the regio- and enantioselective aminohydroxylation of *tert*-butyl crotonate using (DHQD)₂PHAL gave (2*S*,3*R*)-**341a**, and then mesylation of the alcohol, afforded *syn*-amino mesylate **341b**. Nucleophilic substitution of the mesylate with sodium azide to give **342** followed by hydrogenation and deprotection under acidic conditions rendered enantiopure *anti*-α,β-diamino acid (2*R*,3*R*)-Dab. In contrast, treatment of mesylate **341b** with KO^tBu rendered *cis*-aziridine **343**, which was cleaved with trimethylsilyl azide to give **344**. Subsequent hydrogenation and deprotection produced enantiopure *syn* diamino acid (2*R*,3*S*)-Dab. Williams followed a parallel approach (Scheme 45) to independently synthesize both enantiomers of *anti*-2-amino-3-methylaminobutanoic acid **346**.¹⁸⁴ In fact, silyl ether **341c**, prepared from (2*S*,3*R*)-**341a**, was *N*-methylated with sodium hydride and dimethyl sulfate to render **345**, which after five steps, comprising mesylate formation and displacement with azide, was transformed into (2*R*,3*R*)-**346**. The above approach allowed for the synthesis of (2*S*,3*S*)-**346** by simply using (DHQ)₂PHAL as a ligand in the aminohydroxylation step; however, the synthesis of the *syn* isomers was unsuccessful, since all attempts to process (2*S*,3*S*)-**341d**, prepared by Mitsunobu reaction of (2*R*,3*S*)-β-amino alcohol, following the same series of transformations, yielded oxazolidinone **347** as major product.

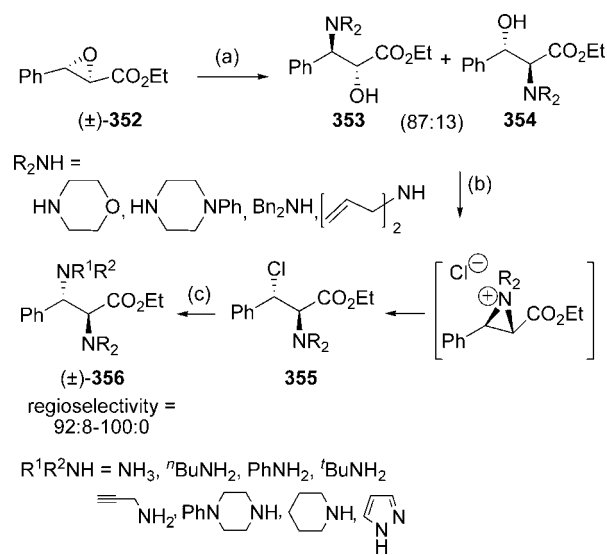
Scheme 46^a

^a Reagents and conditions: (a) (i) HCl, MeOH, reflux, (ii) Boc₂O, Et₃N, 0 °C to rt, 87%; (b) PPh₃, HN₃, DEAD, 90%; (c) H₂, Pd-C, EtOAc, 99%; (d) MsCl, Et₃N, CH₂Cl₂, 93%; (e) KHCO₃, acetone, H₂O, 70 °C, 62%; (f) DBU, CHCl₃, reflux, 76%; (g) TMSN₃, MeOH, 70 °C, 90%.

In a very similar sequence recently reported by the group of Lee, *syn*-**348a**, prepared by Sharpless aminohydroxylation of isopropyl cinnamate, was used for the synthesis of the corresponding enantiopure α,β -diamino ester *anti*-**349** using a Mitsunobu reaction with hydrazoic acid to invert the hydroxyl group attached at the α -carbon (Scheme 46). In addition, *syn*-**348a** was converted to *anti*-**348c** through mesylation and in situ formation of an oxazoline intermediate, **350a**, promoted by the presence of the acetamido group at the β -carbon. Finally, *anti*-**348c** was transformed into enantiopure α,β -diamino ester *syn*-**349** following the same synthetic sequence. Furthermore, treatment of mesylate **348b** with DBU results in a clean epimerization and cyclization to trans oxazoline **350b**. Attempts of nucleophilic ring cleavage in both epimers, **350a** and **350b**, revealed huge differences in reactivity that can be predicted by ab initio molecular calculations. In particular, trans oxazoline **350b** reacted with trimethylsilyl azide affording anti azide **351**, while cis **350a** was cleanly recovered under identical reaction conditions. After hydrogenation, azide **351** was finally transformed into enantiopure *anti*- α,β -diamino ester **349**.¹⁸⁵

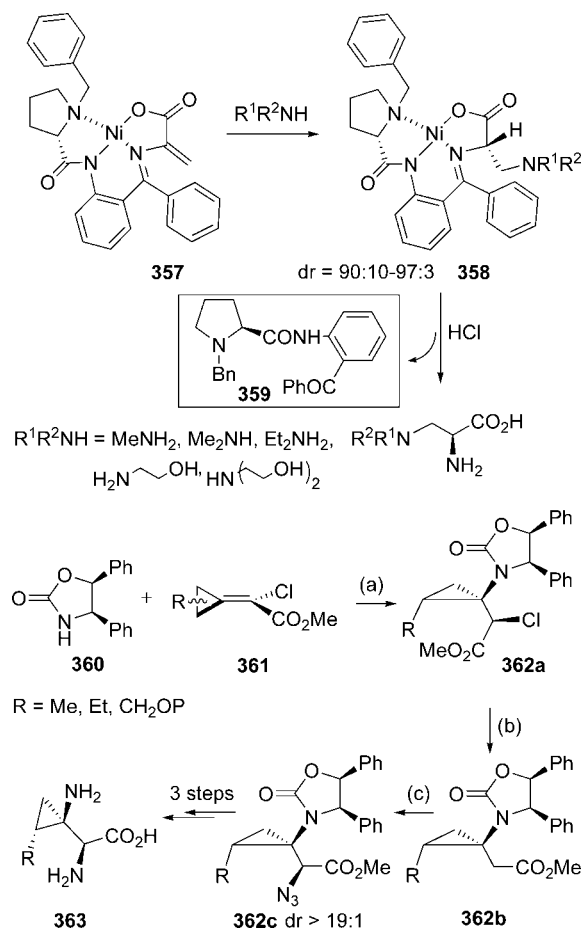
Within the same context, the group of Sharpless has outlined a short and highly versatile route to a series of α,β -diamino esters from the mixture of regioisomeric anti aminohydroxy propanoates, **353** and **354**, prepared from trans glycidic ester **352** and a secondary amine (Scheme 47). Subsequent mesylation of the mixture provided exclusively β -chloroamino ester **355** in quantitative yield via in situ chloride attack to an aziridinium ion. Regeneration of the aziridinium ion from isolated **355**, followed by in situ reaction with a wide range of nitrogen nucleophiles, took place with excellent yields and regioselectivities, furnishing racemic *anti*- α,β -diamino esters **356** as major products. Furthermore, the mixture of **353** and **354** underwent a one-pot procedure, mesylation, and nucleophilic attack of the amine, to give **356** through the aziridinium ion in an extremely efficient manner.¹⁸⁶

A different approach takes advantage of the Michael-acceptor character of α,β -unsaturated acid derivatives to nitrogen nucleophiles. Within this context, α,β -dehydroala-

Scheme 47^a

^a Reagents and conditions: (a) R₂NH, EtOH, reflux, 94–99%; (b) MsCl, Et₃N, CH₂Cl₂, 0 °C, 94–99%; (c) R¹R²NH, K₂CO₃, MeCN, 72–99%.

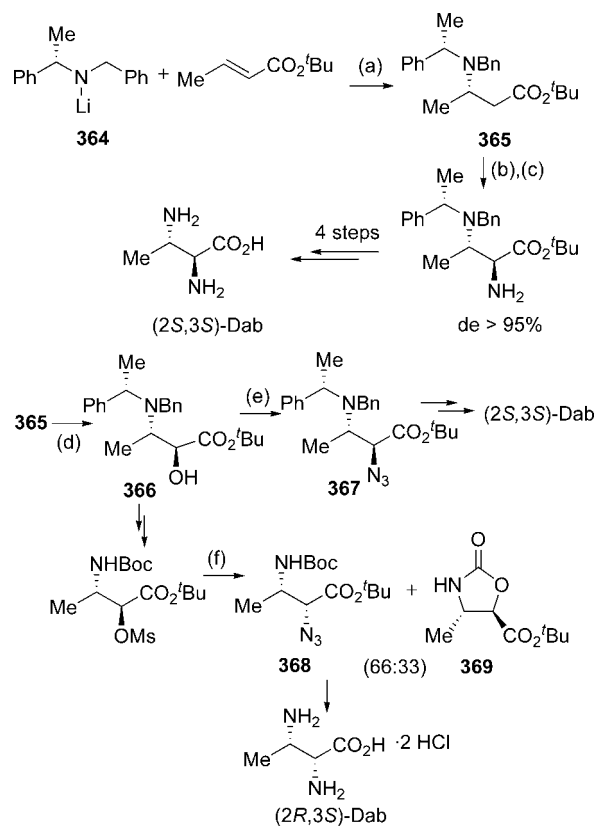
nine derivatives have been extremely useful starting materials containing the α -nitrogen for the Michael addition of amines.^{11a,187} In an interesting example of the above methodology (Scheme 48) from the group of Belokon, the asymmetric synthesis of α,β -diamino acids is performed via a chiral complex of Ni(II) with a dehydroalanine derivative, **357**. The presence of chiral ligand **359** in the complex provides a high facial discrimination for the attack of an amine, affording the *Re* adduct **358** in diastereomeric ratios ranging from 90:10 to 97:3 depending on the nature of the reacting amine. After crystallization of the mixtures, treatment under acidic conditions allowed for the synthesis of the enantiopure (*S*)- α,β -diamino acids and the recovery of the chiral ligand **359**.¹⁸⁸ In another asymmetric example, optically active oxazolidinone **360** was used as Michael donor in the addition to 2-chloro-2-cyclopropylideneacetates **361**, affording Michael adducts **362a** with excellent trans selectivity (Scheme 48). After separation and reductive dehalogenation, two diastereomeric cyclopropyl acetic acid derivatives **362b** were obtained. Either diastereomer can be used as precursor to new cyclopropyl α,β -diamino acids, introducing the amino group by electrophilic azide transfer. In fact, once the lithium enolate is formed, quenching with trisyl azide led to azide **362c** with high diastereoselectivity, which after deprotections afforded conformationally restrained enantiopure *anti*- α,β -diamino acids **363**.¹⁸⁹ More recently, a related strategy starting with 2-chloro-2-cyclopropylideneacetate **361** (R = H) has been employed for the synthesis of cyclopropylmethoxycarbonyl piperazine derivatives.^{190a} The addition of nitrogen nucleophiles to α -nitroalkenoates followed by reduction of the nitro group has recently been used for the synthesis of racemic α,β -diamino esters but with low diastereoselectivity.^{190b} On the other hand, the regioselectivity of the Michael addition can be reversed by the presence of a nitro group attached to the β -carbon of the α,β -unsaturated ester. However, this approach, employed in a study for the synthesis and evaluation of angiotensin II analogues, provided a nondiastereoselective mixture of *syn*- and *anti*- α,β -diamino acids as racemic materials.^{64b} Following a similar strategy, the group of Ballini has observed that nucleophilic addition of secondary amines to β -nitroacrylates provides β -nitro α -amino esters with good

Scheme 48^a

^a Reagents and conditions: (a) DB-18-cr-6, THF, KH and separation, 48–79%; (b) Zn–Cu, THF–H₂O, 61–92%; (c) (i) LiHMDS, trisylazide, –78 °C, (ii) HOAc, rt, 65–85%.

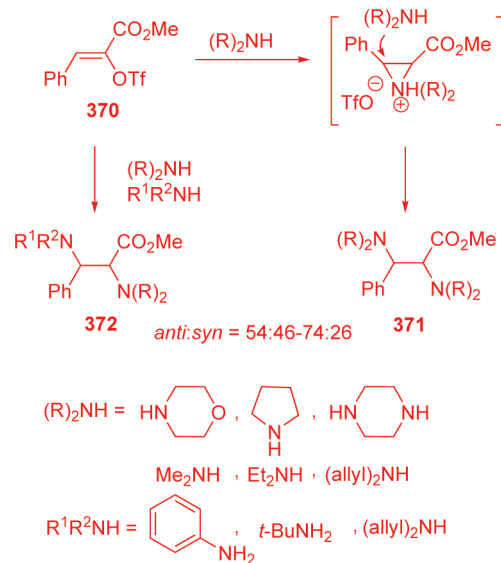
diastereoselectivity (75:25–95:5).^{190c} The relative stereochemistry of the products was not determined.

In this context, when the starting α,β -unsaturated ester does not have a pre-existing nitrogen atom in the molecule, the synthesis of the α,β -diamino acid requires two steps, Michael addition of an amine to introduce the β -nitrogen and subsequent amination of an enolate to introduce the α -nitrogen. The groups of Seebach and Davies have independently examined the above methodology (Scheme 49).^{191,192a,b} In particular, Davies showed that addition of chiral secondary lithium amide **364** was crucial to obtain β -amino ester **365** with complete diastereocontrol. Further diastereoselective trapping of the enolate with trisyl azide (anti, de > 95%) followed by Staudinger reaction and hydrolysis of the iminophosphorane intermediate led, after four more steps, to enantiopure anti- α,β -diamino acid, (2*S*,3*S*)-Dab. Furthermore, after anti α -hydroxylation of the enolate using chiral (–)-(camphorsulfonyl)oxaziridine, these authors envisioned that amino alcohol **366** could undergo a double inversion of the α -hydroxyl group by submission to Mitsunobu conditions through the in situ formation of an aziridinium ion. In fact, the efficiency of the double-inversion process was proven using either diphenylphosphoryl azide, hydrazoic acid, or phthalimide, affording **367** with retention of the configuration. After suitable manipulation, **367** was transformed into anti- α,β -diamino acid (2*S*,3*S*)-Dab. In contrast, displacement of the mesylate derived from **366** with sodium azide gave a 66:33 mixture of syn azide **368** and

Scheme 49^a

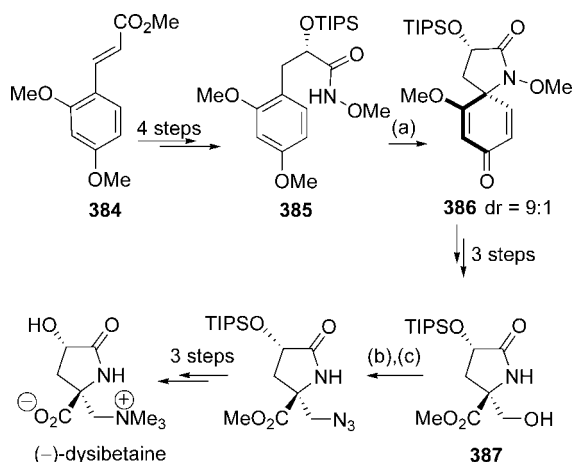
^a Reagents and conditions: (a) THF, –78 °C; (b) (i) LDA, THF, –78 °C, (ii) trisylazide, THF, –78 °C, (iii) HOAc, THF, –78 °C to rt, 32%; (c) PPh₃, THF, H₂O, rt, 91%; (d) (i) LDA, THF, –78 °C, (ii) (–)-(camphorsulfonyl)oxaziridine; (e) PPh₃, DEAD, HN₃ or (PhO)₂PON₃ or phthalimide; (f) NaN₃, DMF, 55%.

Scheme 49a

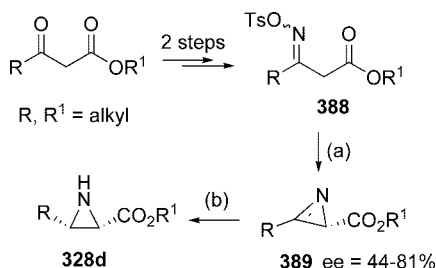


oxazolidinone **369**. After separation, hydrogenation, and acidic deprotection, enantiopure syn- α,β -diamino acid (2*R*,3*S*)-Dab was also available.

The reaction of secondary amines and vinyl triflates of α -keto esters represents another means of introducing the two nitrogen atoms in a single transformation (Scheme 49a).^{192c} One equivalent of amine adds to the α -keto ester **370**, forming an aziridinium ion that can be trapped by a

Scheme 52^a

^a Reagents and conditions: (a) PIFA, CH₂Cl₂, MeOH, -78 to -30 °C, 99%; (b) MsCl, Et₃N, CH₂Cl₂, 0 °C, 87%; (c) NaN₃, DMF, 80 °C, 63%.

Scheme 53^a

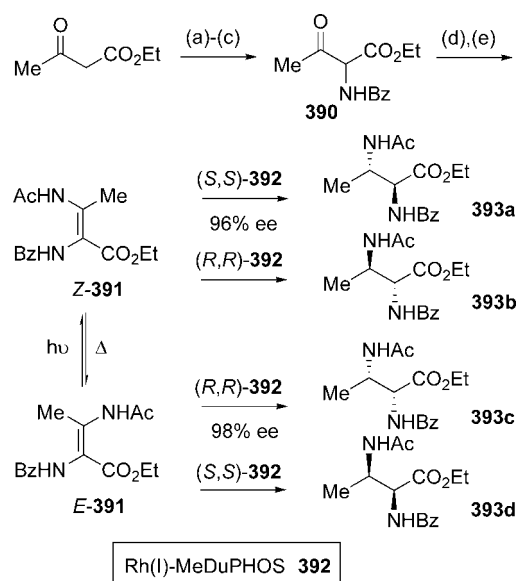
^a Reagents and conditions: (a) quinidine (10% mol or stoichiometric), K₂CO₃, toluene; (b) NaBH₄.

phenyliodine(III) bis(trifluoroacetate) (PIFA) promoted spirocyclization to afford spirodienone **386** as an inseparable 9:1 mixture of C-5 epimers. After ozonolysis, formyl group reduction, and N–O reductive cleavage, **386** was converted into **387**. Azide displacement onto a mesylate generated from **387** followed by removal of the silyl group, hydrogenation of the azide, permethylation, and ester hydrolysis, finally furnished (–)-dysibetaine.¹⁹⁸

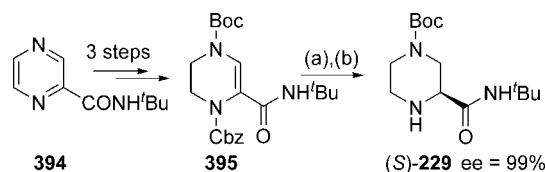
3.2.3.4. From β -Keto Esters and Related Compounds.

The use of β -keto esters as precursors to α,β -diamino acid derivatives is also documented in the literature. For instance, enantioenriched alkoxy carbonyl aziridines **328d** were prepared by an asymmetric Neber reaction (Scheme 53), consisting of treatment of sulfonic esters of ketoximes **388** with a catalytic amount (10%) of quinidine and 10 equiv of K₂CO₃. Disubstituted azirines **389** thus generated in moderate ee's (80%) suffered subsequent reduction with sodium borohydride to give exclusively *cis*-alkoxy carbonyl aziridines **328d** in good yields.¹⁹⁹

In another recent report by the group of Robinson, ethyl acetoacetate was used as a starting material for an α -nitro-sation, followed by reduction and benzylation to furnish α -amino- β -ketoester **390** (Scheme 54). Subsequent treatment of **390** with ammonium acetate and acetylation led to α,β -unsaturated α,β -diamino esters **391** as a separable 4:1 mixture of *E/Z* isomers that can be interconverted by thermal or photochemical isomerization. Nevertheless, the key process in this report is the highly enantioselective hydrogenation of α,β -unsaturated α,β -diamino esters *E*-**391** or *Z*-**391** using (*R,R*)- or (*S,S*)-MeDuPHOS-Rh(I) triflate **392** as chiral catalyst that provides all four isomers of α,β -diaminobutanoic

Scheme 54^a

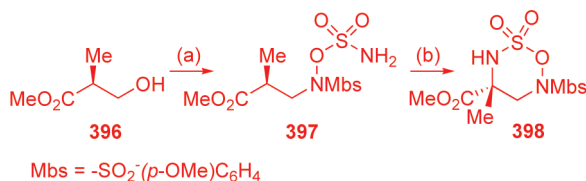
^a Reagents and conditions: (a) NaNO₂, aqueous HOAc, 0 °C, 81%; (b) Al(Hg), THF; (c) BzCl, 63% (3 steps); (d) NH₄OAc, MeOH, 81%; (e) AcCl, pyr, CH₂Cl₂-Et₂O.

Scheme 55^a

^a Reagents and conditions: (a) H₂, [(*R*)-BINAP(COD)Rh]OTf, MeOH, 70 bar, 96%; (b) Pd-C, H₂, MeOH.

acid derivatives **393a–d** in ee > 95%.²⁰⁰ Similarly, a bisferrocenyl phosphine has been used as chiral ligand in the asymmetric hydrogenation of α,β -dehydro- α,β -diamino esters catalyzed by a rhodium(I) complex.²⁰¹ Furthermore, the recent availability of routes to α,β -unsaturated α,β -diamino ester derivatives²⁰² could increase the versatility of this approach.

Within this context, asymmetric hydrogenation of pyrazine derivatives is one of the more efficient routes to enantiopure 2-carboxypiperazine derivatives. Classically, routes to enantiomerically pure piperazine-2-carboxylic acid were based on fractional crystallization of diastereomeric ammonium salts from chiral acids [i.e., (*S*)-CSA]^{83c,203} or diastereomeric menthyl esters²⁰⁴ and enzymatic kinetic resolution.²⁰⁵ Indeed, very recently, a novel amidase acting on (±)-piperazine-2-*tert*-butylcarboxamide has been identified from *Pseudomonas* sp. MCI3434. The enzyme acts on the *R*-isomer to yield (*R*)-piperazine-2-carboxylic acid.²⁰⁶ However, recent reports of asymmetric hydrogenation have provided a convenient route to these cyclic α,β -diamino acid derivatives (Scheme 55).^{207,208} In fact, pyrazine **394** was submitted to partial hydrogenation and then to sequential introduction of *N*-protecting groups to afford a tetrahydropyrazine. The catalytic enantioselective hydrogenation of tetrahydropyrazine **395** using [(*R*)-BINAP-(COD)Rh]TfO afforded the orthogonally protected piperazine in 96% yield and 99% ee; subsequent hydrogenolytic removal of the Cbz group gave enantiopure (*S*)-**229**, a valuable intermediate in the synthesis of indinavir.

Scheme 55a^a

^a Reagents and conditions: (a) MbsNHOSO₂NH₂, DEAD, PPh₃, THF, 57%; (b) Rh₂(Oct)₄ (cat.), MgO, PhI(OAc)₂, C₆H₆, 82%.

3.2.3.5. From β -Hydroxy Esters. The group of Du Bois has reported the Rhodium-catalyzed C–H amination of sulfamate **397**, which was easily synthesized under Mitsunobu conditions from Roche ester **396** (Scheme 55a).²⁰⁹ Treatment of **397** with Rh₂(Oct)₄ in the presence of magnesium oxide and iodosobenzene diacetate gave the oxidative cyclization product **398**. The authors pointed out the advantage of using a *p*-methoxybenzenesulfonyl (Mbs) derivative, which facilitates the cyclization by reducing the sp² character of the nitrogen center relative to the Boc and formyl derivatives. Reduction of the N–O bond using Zn(Cu) followed by treatment with methanolic HCl would then provide the monoprotected diamine.

4. Conclusions

The remarkable ubiquity of these nonproteinogenic amino acids along with the widespread presence of this structural motif in a number of molecules with diverse therapeutic applications have been brought to light in this overview of the chemistry of α,β -diamino acids. Furthermore, this article shows that α,β -diamino acids are becoming useful tools for the study of the nature of peptidic entities seeking to control and to modify the behavior of peptidic molecules with a relevant role in living organisms. Therefore, the development of short, general, and efficient synthetic routes to α,β -diamino acids is important. Despite the number of approaches to these diamino acids, there are still many challenges in the area, in particular, focused in structurally diverse and enantiopure materials, with the catalytic enantioselective carbon–carbon bond formation and the enantioselective hydrogenation of α,β -unsaturated α,β -diamino acids being among the more promising approaches to fulfill the above requirements.

This article clearly demonstrates that the rich chemistry of α,β -diamino acids has suffered a great advance in the past decades; new applications and synthetic routes for these products have been developed; however, future endeavors in this area will provide new routes and applications of these fascinating molecules.

5. Acknowledgments

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