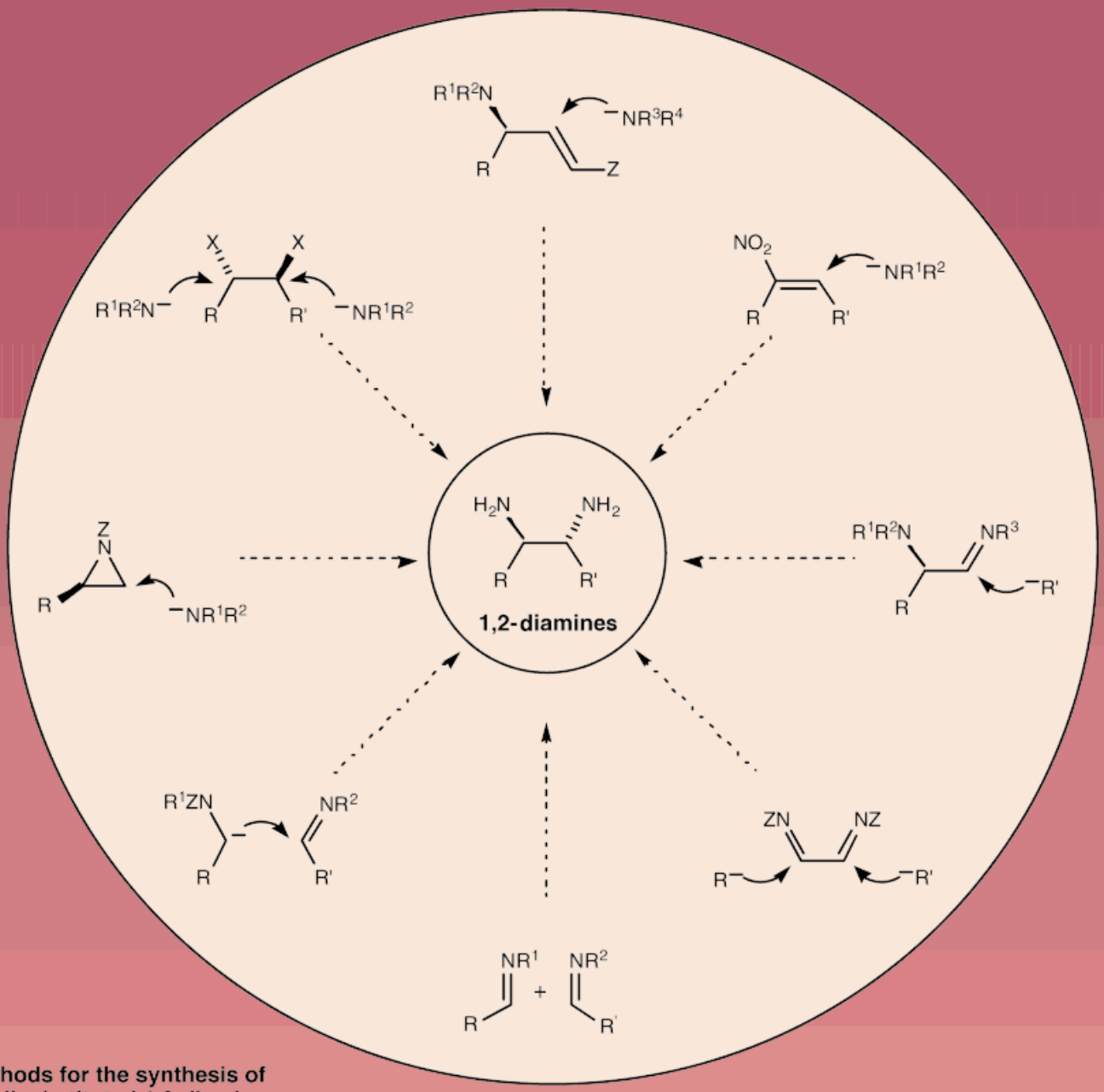
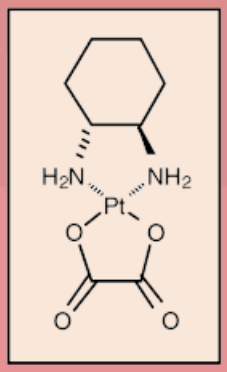


methods for the synthesis of 1,2-disubstituted 1,2-diamines

applications in stereoselective organic synthesis



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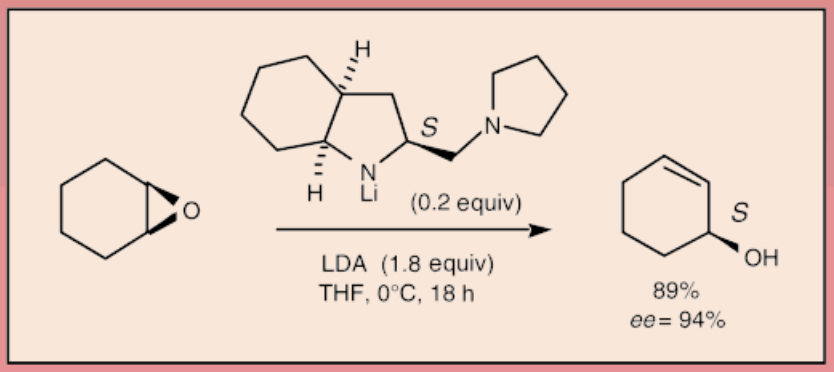

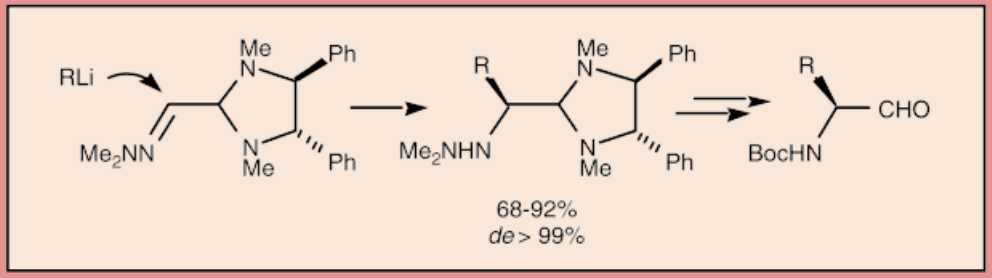

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The Chemistry of Vicinal Diamines

Denis Lucet, Thierry Le Gall,* and Charles Mioskowski*

Compounds incorporating the 1,2-diamine functionality are currently the topic of studies conducted in several fields. For instance, in chemotherapy, various platinum 1,2-diamino complexes are evaluated as antitumor agents that could be employed as substitutes for cisplatin to reduce toxicity and to circumvent drug resistance. Chiral, enantiomerically pure 1,2-diamines (or vicinal diamines) and their derivatives are also used increasingly in stereoselective organic synthesis, for example as chiral auxiliaries, or as metal ligands in catalytic asymmetric synthesis. These utilizations brought about the development of synthetic methods for the preparation of aliphatic 1,2-diamines in diastereomerically and enantiomerically pure form. The problem of stereochemical control encountered in their synthesis depends on the number of substituents on the carbon chain. Thus, it is necessary to control two stereogenic centers when the target compound is disubstituted at the C1 and C2 positions. Numerous strategies have been developed to meet this need. Among relevant methods that have been applied, the diastereoselective introduction of a nitrogen atom in an enantiomerically pure molecule containing another nitrogen atom, and the diastereo- and enantioselective coupling of bisimines, are particularly effective. In the first sections of this account, the occurrence of 1,2-diamines in biologically active compounds—including natural products—and in the field of organic synthesis will be highlighted. In the next section an overview of the methods for preparation of vicinal diamines will be presented.

Keywords: chiral auxiliaries · diamines · N ligands · synthetic methods

1. Introduction

Many natural products that have valuable biological properties contain a 1,2-diamino moiety. In recent years several synthetic diamine derivatives have also been employed as medicinal agents, in particular in chemotherapy. Their use in organic synthesis has also increased considerably recently, especially in the field of catalytic asymmetric synthesis. Hence, interest in these compounds brought about numerous studies aimed at the design of efficient diastereo- and enantioselective routes to 1,2-diamines. This review article firstly presents, briefly, the occurrence of products containing the 1,2-diamine functionality, as well as their biological and therapeutic properties, then the applications of vicinal diamines and their derivatives as tools in organic synthesis, and lastly the methods of preparation of these compounds, essentially covering the literature until October 1997. The review deals only with aliphatic 1,2-diamines, not with aromatic ones.

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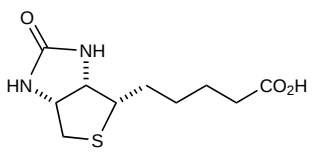
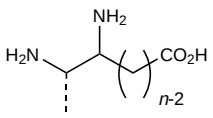
2. Biological Properties and Medicinal Interest of Vicinal Diamines

2.1. Vicinal Diamines in Natural Products

Biotin (or vitamin H, **1**), which is an essential cofactor to carboxylase-catalyzed reactions, is one of the compounds found in nature that contain the 1,2-diamino moiety in their skeleton, in this case included in an imidazolidinone ring.[1] A large number of natural products, especially peptides, contain a *n*,*n*+1-diamino carboxylic acid substructure such as **2**. 2,3-Diaminopropanoic acid is a constituent of several peptidic



biotin **1**



n,*n*+1-diaminocarboxylic acid **2**

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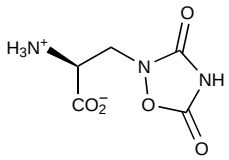
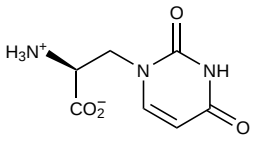
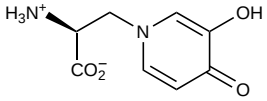
antibiotics such as edeines[2a] and tuberactomycin[2b] derivatives. The bleomycins, first isolated in 1966,[2c] are a family of glycopeptides containing the 2,3-diaminopropanamide moiety; they are chemotherapeutic agents used for the clinical treatment of malignant lymphomas and squamous cell carcinomas.[2d–f] β-(Methylamino)-L-alanine is a neurotoxin that has been linked to the so-called Guam disease.[2g] Neuroexcitatory quisqualic acid (**3**)[2h] and the nonproteinic amino acids willardiine (**4**),[2i] mimosine (or leucenol, **5**)[2j–l] and the isoxazolinone alanine derivative **6**[2m] also all include the 2,3-diaminopropanoic residue. Amphomycin,[3a,b] aspartocin,[3c] lavendomycin,[3d] glumamycin,[3e] antrimycin,[3f] and cirratiomycin,[3g] are potent antibacterial peptides incorporating the 2,3-diaminobutanoic acid residue. Compounds belonging to the emeriamine and emericedines families (**7**, and **8**, respectively) inhibit the oxidation of long-chain fatty acids.[3h]



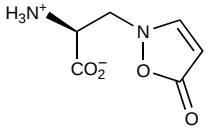
L-quisqualic acid **3**



willardiine **4**



mimosine **5**



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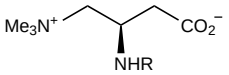


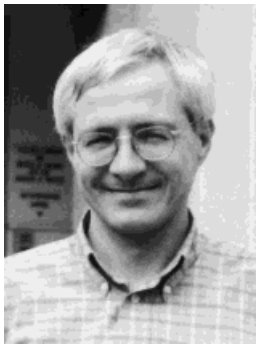
R=H: emeriamines **7**
R=acyl: emericedines **8**

The well known antibiotics penicillins (**9**) and cephalosporins (**10**) also contain a 2,3-diamino carboxylic acid unit, incorporated into the penam and cephem structures, respectively. Nocardicines (**11**) are also 3-amino-β-lactam antibiotics. In several other natural products, one of the two nitrogen atoms is included in an heterocycle. Two significant examples are the indolizidine alkaloid slaframine (**12**),[4a] and the recently isolated balanol (**13**), a potent inhibitor of protein kinase C.[4b]

2.2. Applications in Medicinal Chemistry

The 1,2-diamine functionality can be found in various compounds displaying a broad spectrum of biological activity. In 1989 Michalson and Szmuszkovicz reviewed medicinal agents incorporating the 1,2-diamine unit.[5] Among them we can cite, for instance, antiarrhythmics,[6] antidepressant agents,[7] antihypertensives, antipsychotics, analgesics, anti-

D. Lucet



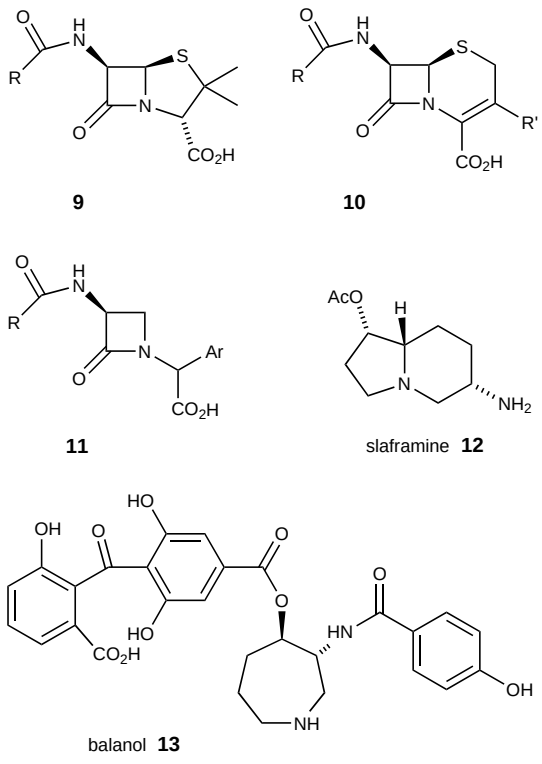
T. Le Gall

C. Mioskowski

Denis Lucet was born in 1968 near Paris. In 1992 he graduated from the École Supérieure de Physique et de Chimie Industrielles (ESPCI) in Paris. After having spent a one year undergraduate research time at the École Polytechnique with Professor J.-Y. Lallemand, he recently completed his doctoral thesis under the supervision of Drs. C. Mioskowski and T. Le Gall at the Commissariat à l'Énergie Atomique (CEA) in Saclay. He spent a two-month post-doctoral time in the group of Professor P. Vogel at the University of Lausanne, and is now working as a development chemist in the Synthetic Chemistry Department of Kodak, in Chalon-sur-Saône (France).

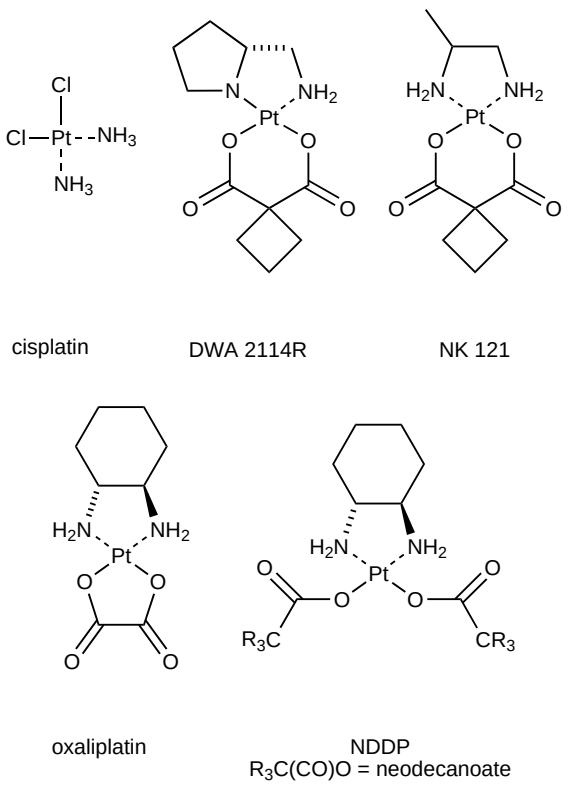
Thierry Le Gall was born in 1959 in Cléden-Poher, Brittany. He studied at the Université de Bretagne Occidentale in Brest, then at the École Nationale Supérieure de Chimie de Rennes (ENSCR). He got a Ph. D. in 1986 on the synthesis of analogues of arachidonic acid metabolites, under the direction of Dr. R. Grée, at the Université de Rennes 1. He spent one year as a post-doctoral researcher under the direction of Professor R. H. Schlessinger at the University of Rochester, NY. He has been working since 1988 in the Service des Molécules Marquées (CEA, Saclay). In recent years, he has been involved in the stereoselective synthesis of myo-inositol analogues and α-amino acids.

Charles Mioskowski was born in 1946 in Falck, Lorraine. He studied at the École Nationale Supérieure de Chimie de Strasbourg (ENSCS). He received a Ph. D. at the Université Louis Pasteur de Strasbourg in 1978 on asymmetric synthesis with chiral sulfoxides. He then joined the group of E. J. Corey at Harvard University as a post-doctoral fellow (1978–1979). He has been Director of Research at the CNRS since 1984, in the Laboratoire de Synthèse Bioorganique at the Faculté de Pharmacie de Strasbourg, and since 1991 he is head of the Service des Molécules Marquées at the CEA, in Saclay. His research interests are organic and bioorganic chemistry.



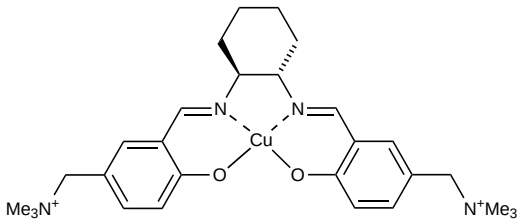
anxiety agents, anticancer drugs, and antiparasitic agents. Some important and illustrative examples will be described in this section.

Antitumoral properties of cisplatin (*cis*-diamminedichloroplatinum(II)) were serendipitously discovered by Rosenberg in the mid 1960s.[8a] Its success in antitumor chemotherapy brought about the synthesis of many diamine–platinum complexes in a search for drugs having greater activity, less toxicity, and to circumvent drug resistance that may develop in certain tumors.[8b] Among the 1,2-diaminoplatinum complexes described, several possess higher antitumoral activity than cisplatin.[8c–h] Some 1,2-diaminoplatinum compounds, either used clinically or at an advanced stage of testing, are depicted in Scheme 1.[8i]



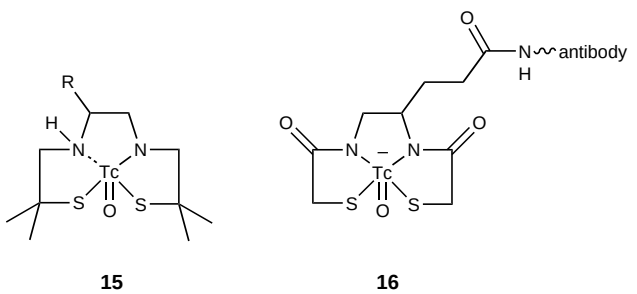
Scheme 1. Cisplatin and some 1,2-diaminoplatinum compounds currently used or evaluated as anticancer drugs.

In recent years, metal complexes of salen Schiff bases such as **14**, were reported to bind selectively with DNA.[9] In the presence of a cooxidant or under aerobic conditions a cleavage of the DNA was observed in several cases. These studies could lead to the development of artificial restriction enzymes or antitumor drugs.

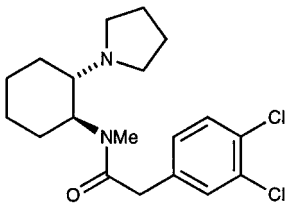


Several compounds that incorporate the 1,2-diamine moiety, such as EDTA (see the Appendix for a list of abbreviations), can strongly chelate metal ions, to form stable complexes. This property has been employed in particular in the field of nuclear medicine, since the complexes of metallic radioactive isotopes can be used as imaging agents.

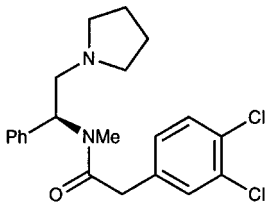
Bleomycin–A_2DM is known to accumulate in the cells of some cancer tumors; the coupling of the Co^{III} complex of this antibiotic with an EDTA-containing derivative led to a compound that could then be labeled by a radioactive metal ion. The ^{111}In-radiolabeled adduct proved to be a useful diagnostic tool for determining both the size and the location of malignancies in cancer patients.[10a] Complexes of technetium-99m (^{99m}Tc) with diamide dithiolate ligand systems have also been used as radiopharmaceuticals for the detection and the evaluation of renal diseases,[10b] or as brain perfusion imaging agents (for example **15**).[10c] When labeled with ^{99m}Tc complexes, antibodies such as **16** can become useful agents for the targeted delivery of radioactivity for diagnostic imaging, as well as for the delivery of therapeutic radionucleides to tumors.[10d,e]



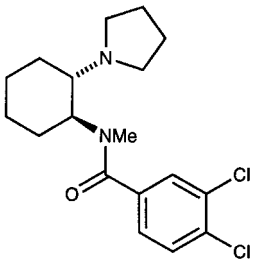
Pharmaceutical studies have disclosed the existence of three major opioid receptor types, namely, μ, δ, and κ.[11a, b] Since the discovery of the opioid properties of the 1,2-diaminocyclohexane derivative U-50,488 (**17**) as a highly selective κ agonist,[11c] many structural analogues (cyclic and acyclic ones) of improved affinity and selectivity for the κ receptor have been reported (for example ICI-199,441 (**18**)).[11d] Highly selective κ-opioid agonists may provide useful analgesics, free from the potential for abuse and the adverse side effects of μ agonists like morphine.[11e, f] Interestingly, benzamide derivatives such as **19** are morphine-like analgesics with affinity for the μ-opioid receptor.[11g] 1,2-Diaminocyclohexane derivatives have again received increasing attention because of the discovery of the selective action of their diastereomers at κ or σ receptor sites. Indeed, compound **20**, which is the *cis* stereoisomer of U-50,488, has practically no affinity for κ receptors, whereas its affinity for non-opioid σ receptors is high.[11h–l]



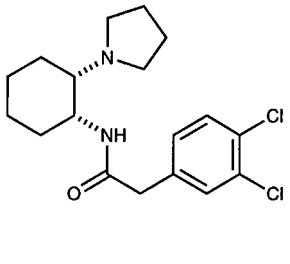
U-50,488 **17**
κ agonist



ICI-199,441 **18**
κ agonist



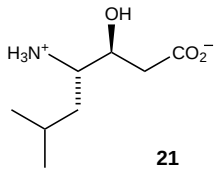
19
μ agonist



20
σ agonist

Analogues of acyclic derivatives such as ICI-199,441 have been modified into affinity labels that are useful pharmacological or biochemical tools to investigate κ opioid receptors.[11l]

Ethylenediamine and *cis*-1,2-diaminocyclohexane are potent irreversible inhibitors of lysyl oxidase, an enzyme involved in the formation of covalent cross-linkage in elastin and collagen. The central role of lysyl oxidase in connective tissue fiber formation has suggested that potent inhibitors of this enzyme may have chemotherapeutic potential as antifibrotic agents.[12a] Peptides that contain amino analogues of statine (**21**), such as **22**, may be potent renine inhibitors and could provide agents for control of cases of renin-associated hypertension.[12b,c]



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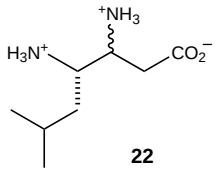

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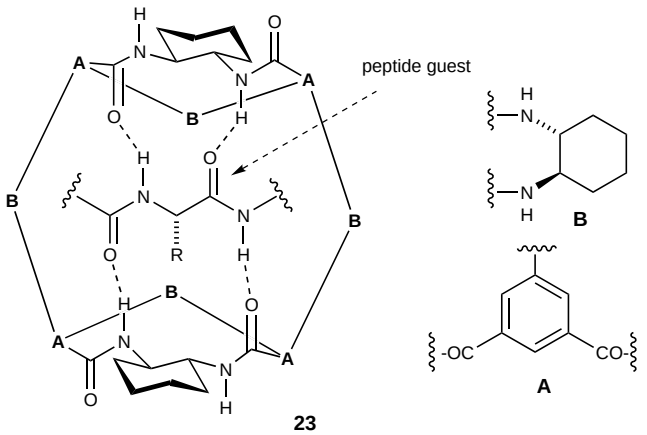
3. Vicinal Diamines in Organic Synthesis

The next sections will highlight the importance of 1,2-diamines in organic synthesis, and of compounds that are easily prepared from 1,2-diamines, such as 1,2-bisimines and 1,2-diamides.

1,2-Diamino compounds are valuable synthetic intermediates for the preparation of heterocycles.[13a] Diamines such as TMEDA are widely used as additives to stabilize and activate organometallic reagents and inorganic salts.[13b]

Vicinal diamines have also found application in cryptand chemistry.[14] Indeed, they are interesting building blocks for the construction of nitrogen-containing macrocycles, for instance diazacrown ether analogues, which could find use in asymmetric synthesis as chiral ligands.

In the field of supramolecular and host–guest chemistry, the synthetic macrocycle **23**, built up from (*R*,*R*)-1,2-diaminocyclohexane, was shown by Still et al. to bind to amino acid residues in peptide chains with very high selectivities for chirality and side-chain identity.[15a] "Two-armed" synthetic receptors that bind peptides in water were more recently described; they are also derived from C_2-symmetric 1,2-diamines (Scheme 2).[15b]



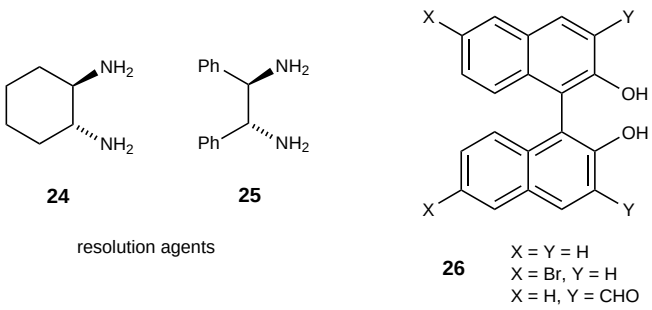
23

Scheme 2. Schematic representation of **23**, a synthetic receptor for peptides.

Chiral non-racemic vicinal diamines have received increasing attention during the last decades. Indeed, enantiomerically pure 1,2-diamines and their derivatives are particularly useful as chiral auxiliaries or ligands, and they have found tremendous application in stereoselective synthesis. In this field, chiral, C_2-symmetric 1,2-diamines[16] and their various derivatives offer especially great promise as new reagents for enantioselective synthesis.

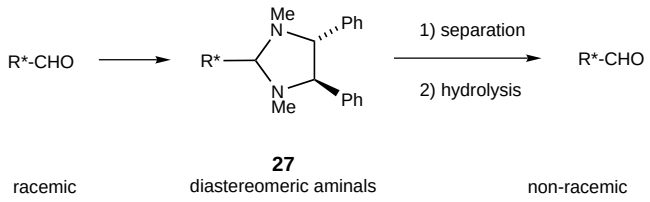
3.1. Resolution of Racemates and Determination of Enantiomeric Excess

Symmetrical vicinal diamines have been used for racemate resolution. For example, (*R*,*R*)-1,2-diaminocyclohexane (**24**) and (*R*,*R*)-1,2-diphenylethylenediamine (**25**, also called stilbenediamine, or stien) were used to resolve atropisomeric binaphthols **26** (Scheme 3).[17]



Scheme 3. 1,2-Diamines used to resolve binaphthol atropisomers.

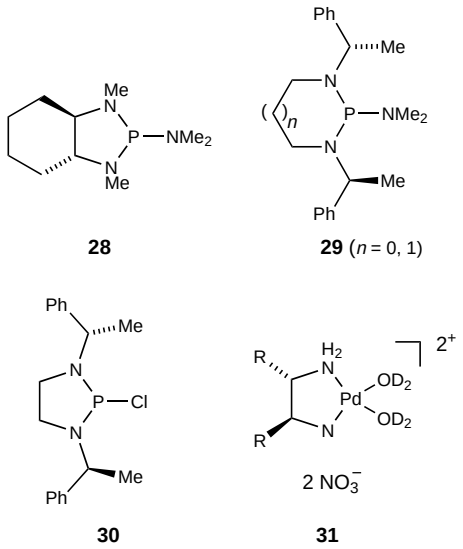
Mangeney and Alexakis et al. showed that symmetrical vicinal diamines are interesting compounds as resolving agents for chiral aldehydes.[18] Thus, the reaction of a racemic aldehyde with an enantiopure symmetrical 1,2-diamine affords diastereoisomeric imidazolidines (aminals) **27** that can be separated into each enantiomer of the aldehyde after acidic hydrolysis (Scheme 4).



Scheme 4. Resolution of aldehydes with a chiral vicinal diamine.

Diastereomeric aminals also allow the determination of the enantiomeric composition of chiral aldehydes and substituted cycloalkanones, either by NMR spectroscopy or by a chromatographic technique (HPLC or GC).[19a, b] Alexakis et al. then introduced phosphorus derivatives such as **28**, which were obtained from C_2-symmetric diamines, for the determination of the enantiomeric composition of chiral alcohols, thiols, and amines by ^{31}P, ^{1}H, ^{13}C and ^{19}F NMR spectroscopy (Scheme 5).[19c,d] Phosphorus compounds **29**[19e] and **30**[19f] were also employed for such a purpose by other authors.

(*R*,*R*)-1,2-Diphenylethylenediamine has been used as a chiral solvating agent for the determination of the enantiomeric purity of chiral carboxylic acids by NMR spectroscopy.[20a] Recently, the enantiomeric ratio of unprotected amino acids was analyzed with the help of palladium complexes **31**.[20b]



Scheme 5. 1,2-Diamine derivatives employed to determine the enantiomeric composition of chiral compounds.

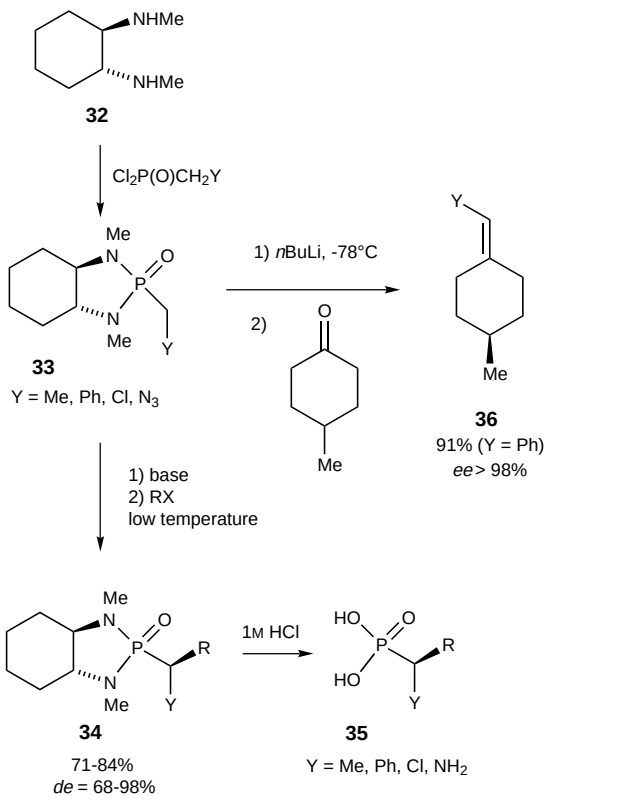
3.2. Vicinal Diamines and Their Derivatives as Chiral Auxiliaries in Diastereoselective Synthesis

Several chiral auxiliaries derived from 1,2-diamines have been employed in highly stereoselective reactions. They often have C_2 symmetry, although early examples described by Mukaiyama involve unsymmetrical auxiliaries.[21] In this section, we will deal successively with bicyclic phosphonamides, imidazolidin-2-ones, diazaborolidines, and aminals as chiral auxiliaries in diastereoselective synthesis.

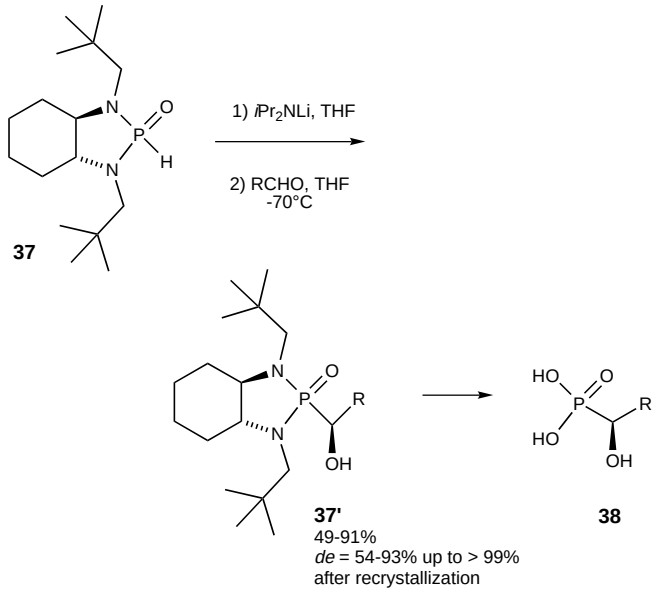
Hanessian[22a–e] and others[22f] have demonstrated the usefulness of chiral bicyclic phosphonamides **33** as chiral auxiliaries in organic synthesis. Reactions of such systems proceed in good yields and with high diastereoselectivities (Scheme 6). Anions derived from **33** can be trapped by an alkyl halide[22a–d] and after hydrolysis of the adducts **34** optically active α-substituted α-alkyl phosphonic acids **35** can be obtained, which are important surrogates for carboxylic acids. Asymmetric olefination through the Wittig reaction on phosphoramides **33** is also possible; alkylidenecyclohexanes **36** were obtained from substituted 2-methylcyclohexanone with very good enantiomeric excesses.[22e]

Spilling et al. have recently described the stereoselective synthesis of α-hydroxyphosphonic acids **38** from the chiral bicyclic phosphinamide **37** (Scheme 7).[22f] The rigidity of these bicyclic systems is probably important in dictating the levels of asymmetric induction observed.

Imidazolidin-2-ones derived from (*S*)- or (*R*)-ephedrine have been employed as chiral auxiliaries in highly diastereoselective reactions[23] (Scheme 8). Helmchen et al.[23a] described the homoaldol addition of the titanium compound obtained from *N*-alkylurea **39** with aldehydes or ketones. This reaction afforded alcohols **39′** ($de = 88-96\,\%$, $de > 98\,\%$ after recrystallization), which were then converted to γ-lactones **40**. Cardillo et al.[23b–g] studied various diastereoselective processes by utilizing 3-acyl-imidazolin-2-ones derived from



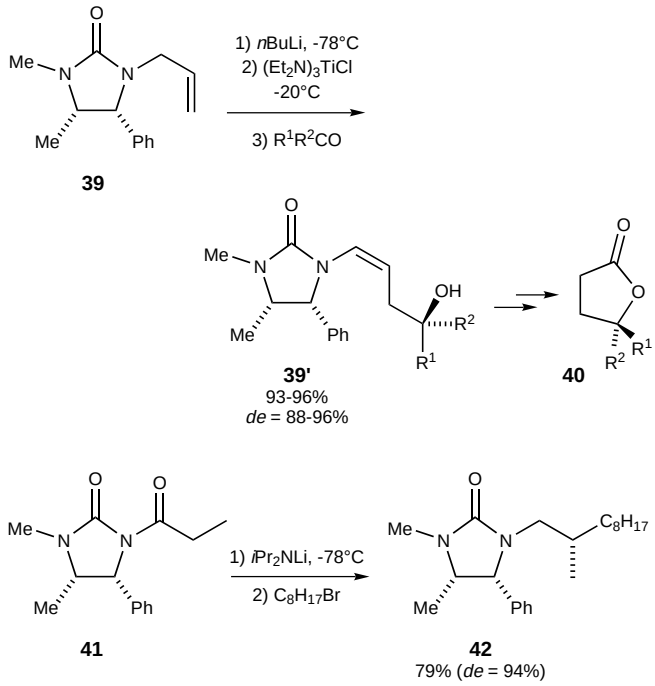
Scheme 6. Chiral bicyclic phosphonamides, derived from a 1,2-diamine, as chiral auxiliaries.



Scheme 7. Use of a chiral bicyclic phosphonamide in the synthesis of α-hydroxyphosphonic acids.

ephedrine, such as the alkylation of compound **41**.[23b] The alkylation of 3-acyl-imidazolin-2-ones derived from several α-amino acids was also reported recently.[24]

Davies et al.[25] utilized imidazolidin-2-ones derived from C_2-symmetric 1,2-diamines as chiral auxiliaries. Dibutylboron enolates of 1,3-diacylimidazolin-2-ones **42** react with aldehydes in a *syn*-stereoselective aldol reaction[25a] (Scheme 9), while the corresponding potassium enolates react stereoselectively with alkyl halides.[25b] After cleavage of the chiral auxiliary and reduction, enantiomerically enriched diols **45** and alcohols **47** are then obtained, respectively.

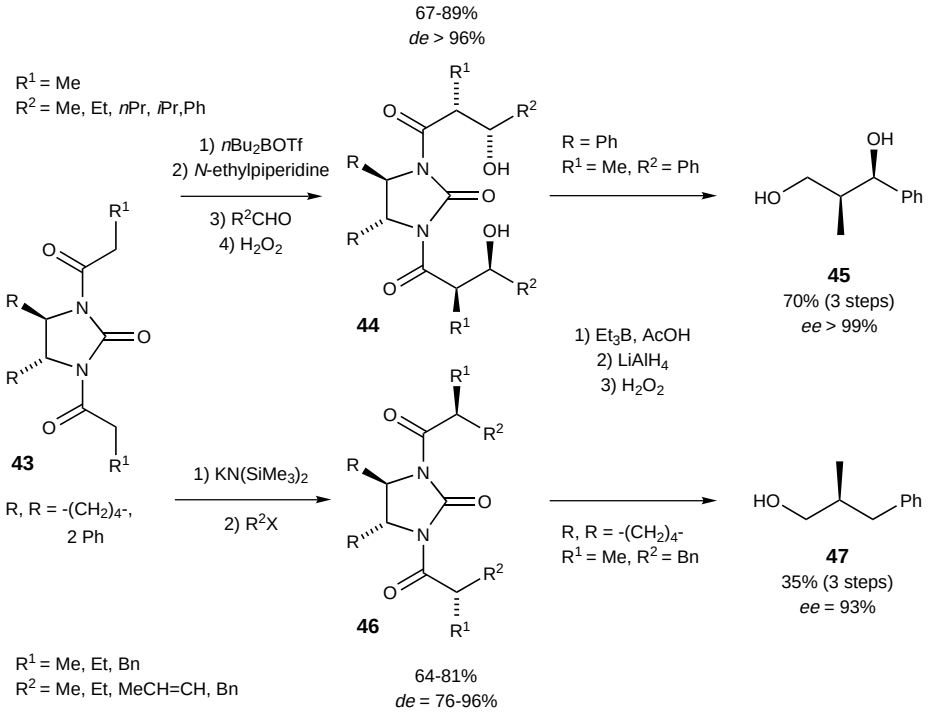


Scheme 8. Diastereoselective syntheses with imidazolidin-2-ones derived from ephedrine.

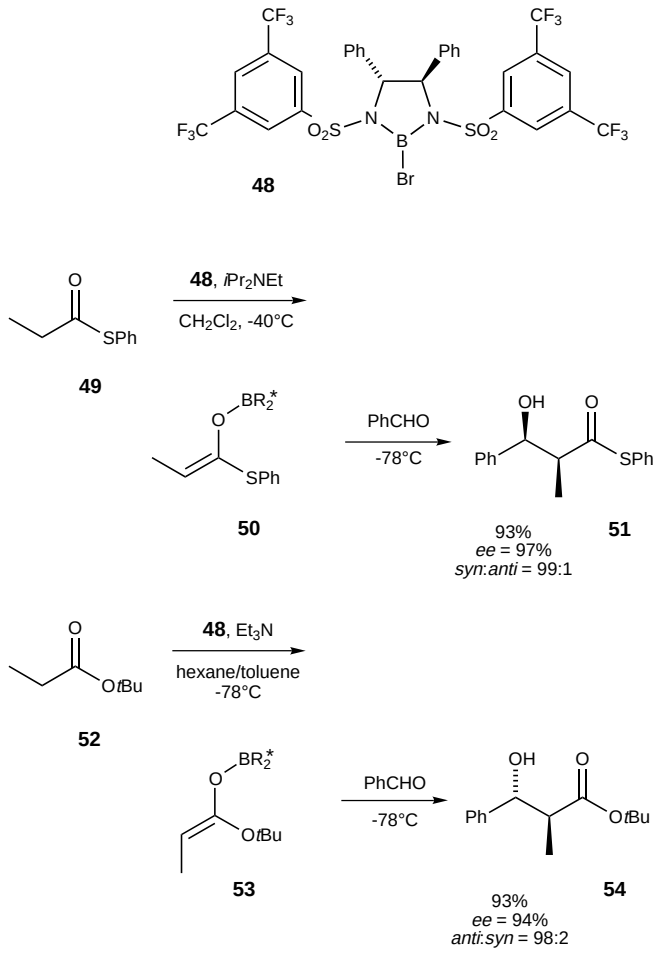
Corey et al. have developed enantioselective processes that make use of chiral, boron-containing chiral auxiliaries derived from 1,2-diphenylethylenediamine.[26] For example, the enantioselective synthesis of either *syn*- or *anti*-aldol products by using the diazaborolidine **48** was described (Scheme 10). Thus, in aldol reactions of benzaldehyde mediated by **48**, *S*-phenyl thiopropionate (**49**) was converted into the *syn*-aldol product **51** ($ee = 97\,\%$, *syn*:*anti* = 99:1, yield = 93 %), while *tert*-butyl propionate (**52**) afforded the *anti*-aldol product **54** ($ee = 94\,\%$, *anti*:*syn* = 98:2, yield = 93 %).[27] The divergence in stereochemistry was attributed to the intermediacy of boron enolates of either *E* or *Z* configuration, depending of the ester structure.

The same diazaborolidine **48** was used to promote other diastereo- and enantioselective processes, such as the reaction of a thiopropionate ester with aldimines, to afford *anti*-β-amino thioesters,[28] a Darzens reaction that led mainly to *anti*-α-bromo β-hydroxy esters,[29] and an Ireland–Claisen rearrangement of achiral allylic esters.[30] In the latter process, either *erythro* or *threo* adducts could be obtained selectively, depending on the conditions used for the enolate formation. As shown in Scheme 11, *syn*-aldol products (**57**) were also obtained with high diastereomeric and enantiomeric excesses from diethyl ketone (**55**), in reactions mediated by the boron reagent **56**.[31]

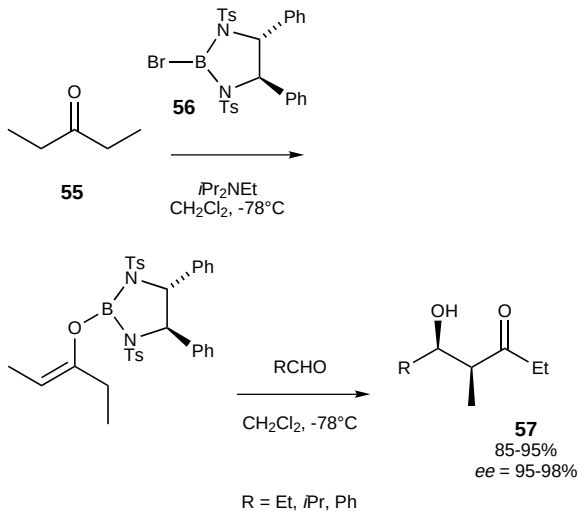
The allylborane derivative **58** (Scheme 12) was shown to be an excellent reagent for the enantioselective allylation of aldehydes ($ee = 95-98\,\%$). The adducts **59** are useful pre-



Scheme 9. C_2-symmetric imidazolidin-2-ones as chiral auxiliaries.



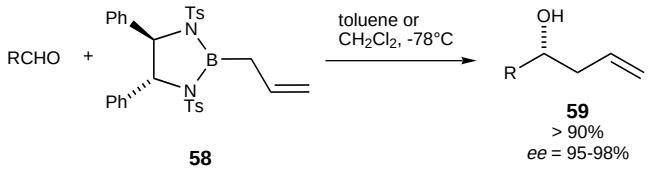
Scheme 10. Diastereo- and enantioselective aldolization reactions of boron enolates derived from a C_2-symmetric diazaborolidine (**48** = R_2^*BBr).



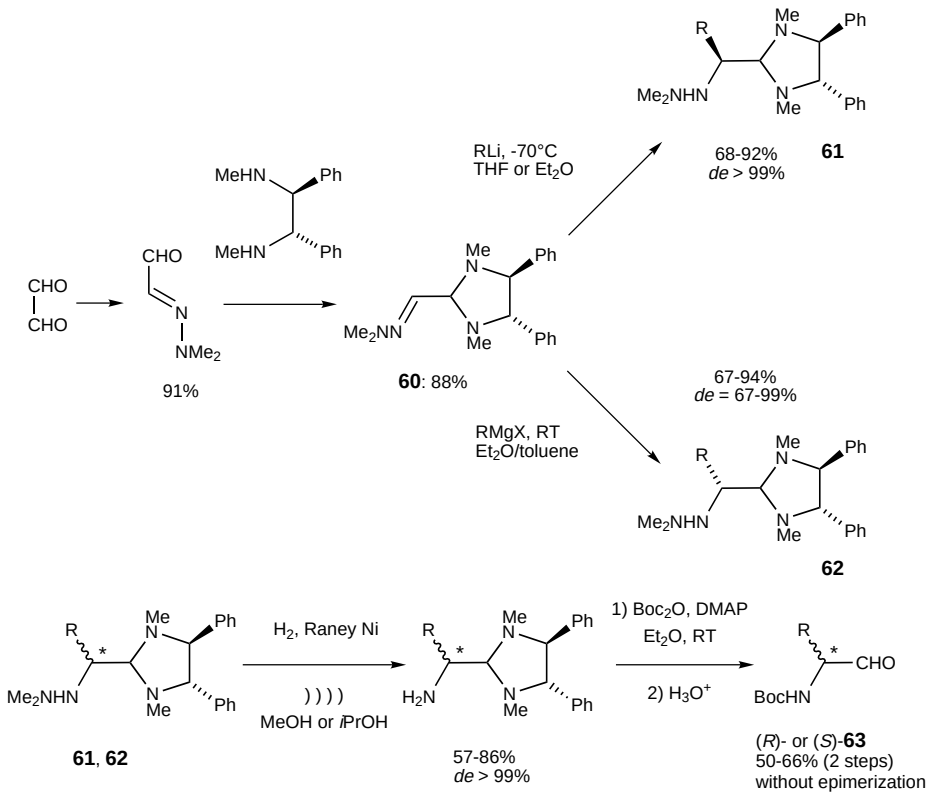
Scheme 11. Use of a C_2-symmetric diazaborolidine in aldolization reactions of diethyl ketone.

cursors of β-hydroxy- and γ-hydroxycarboxylic acid derivatives.[32]

Alexakis and Mangeney et al. utilized chiral aminals obtained from aldehydes and C_2-symmetric 1,2-diamines as chiral auxiliaries,[18c, 33a] and showed that these compounds can



Scheme 12. Enantioselective allylation of an aldehyde with a chiral 1,2-diamine-based allylborane reagent.



Scheme 13. Chiral aminal template in the diastereoselective synthesis of α-amino aldehydes.

exert impressive stereocontrol (Scheme 13). Glyoxal monohydrazone-derived chiron (**60**) gave a single diastereomer upon reaction with an organolithium reagent in THF, through steric control.[33b,c] By contrast, **60** underwent a stereoreverse, chelation-controlled reaction with a Grignard reagent in toluene (to afford the adduct of opposite configuration after removal of the chiral auxiliary). N–N bond cleavage, followed by protection of the amino group, and acidic aminal hydrolysis afforded the corresponding Boc-protected α-amino aldehydes **63** without epimerization.

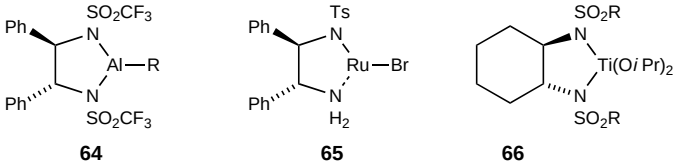
Such chiral C_2-symmetric aminals have also been used as chiral controllers in various reactions,[34, 35] such as the enantioselective *ortho*-lithiation of a tricarbonylchromium complex,[34a] and the 1,3-dipolar cycloaddition of azomethine ylides to α,β-unsaturated carbonyl compounds.[35]

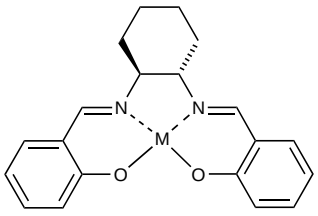
3.3. Vicinal Diamines and Their Derivatives as Chiral Ligands in Asymmetric Synthesis

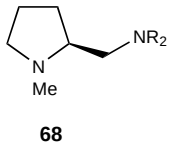
In this section most significant or recent examples of the use of chiral 1,2-diamine ligands (or reagents noncovalently bound to the substrate) in the field of asymmetric synthesis will be presented.[36, 37] In some types of reactions these external ligands are to be used in stoichiometric amount, but in many cases a catalytic amount is sufficient to obtain very good results.

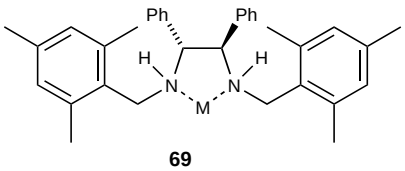
The most widely used ligands incorporating a vicinal diamine moiety are derivatives of 1,2-diphenylethylenediamine and of 1,2-diaminocyclohexane. These chiral derivatives may be mainly divided into three families:

- Lewis acid derivatives, and more generally 1,2-diamines substituted by electron-withdrawing groups (for example the ligands in **64**–**66**);
- ligands obtained from aromatic aldehydes and 1,2-diamines, such as the salen-type ligand (**67**);
- other more simple 1,2-diamine derivatives such as **68** and **69**.







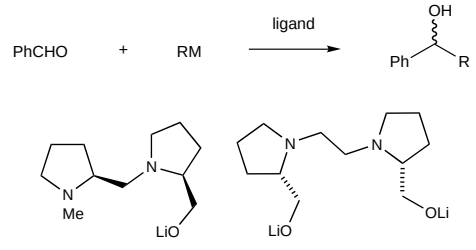


All these chiral compounds are used increasingly in various reactions. Such applications are presented in the following paragraphs.

3.3.1. Alkylation of Aldehydes

Enantioface differentiating addition of organometallic reagents to carbonyl compounds is an important reaction to establish a C–C bond with concomitant control of a stereogenic center. Numerous enantioselective reactions have been performed with the help of external, chiral 1,2-diamine ligands. The approaches listed in Table 1 require very low temperatures and the use of a stoichiometric amount or more of the chiral ligand.

Table 1. Enantioselective addition of organometallic reagents to benzaldehyde in the presence of a 1,2-diamine ligand.



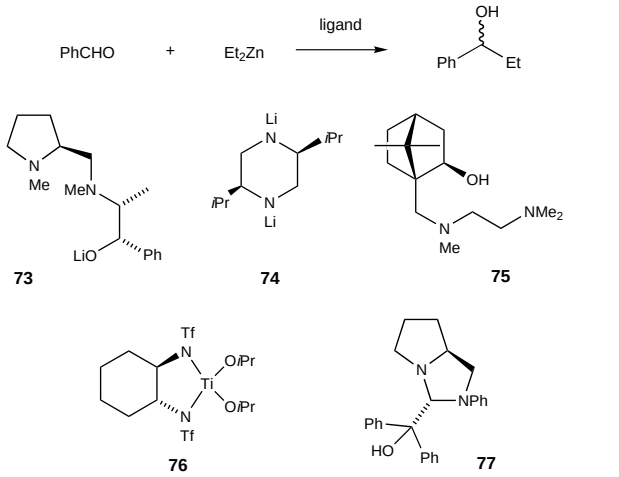
Entry	RM	*T* [°C]	Ligand	*ee* [%]	*R*,*S*	Ref.
1	BuLi	– 123	**70**	95	*S*	[38a]
2	BuLi	– 85	**71**	30	*R*	[38b]
3	1-naphthylMgBr	– 100	**72**	75	*S*	[38c]

The enantioselective nucleophilic addition of dialkyzinc reagents to aldehydes in the presence of a catalytic amount (0.01 to 10 mol %) of a chiral ligand has been studied extensively by several groups.[38] Results obtained in the addition of diethylzinc to benzaldehyde in the presence of 1,2-diamine ligands are depicted in Table 2. In recent years Knochel et al. have extended the scope of this reaction by using aliphatic aldehydes and zinc organometallic reagents.[39] The asymmetric trimethylsilylcyanation of aldehydes catalyzed by chiral (salen)titanium(IV) complexes has also been described.[40]

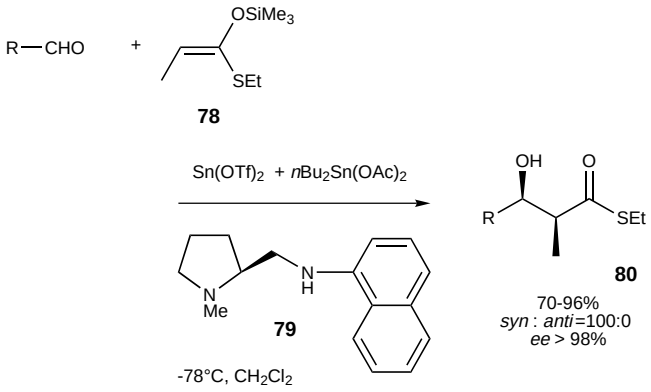
3.3.2. Aldol Reactions

Kobayashi and Mukaiyama et al. have shown that asymmetric aldol reactions of achiral silylenol ethers can be performed with excellent stereochemical control by the combined use of tin(II) triflate, dibutyltin diacetate, and a chiral 1,2-diamine (Scheme 14).[41a] Thus, when vicinal diamine **79** was used in a stoichiometric fashion in the reaction-

Table 2. Enantioselective alkylation of benzaldehyde by diethylzinc in the presence of various 1,2-diamine-based complexes.

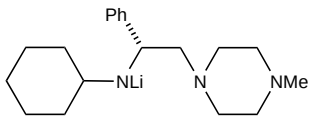


Entry	Ligand	*ee* [%]	*R*,*S*	Ref.
1	**73**	95	*S*	[38d]
2	**74**	90	*R*	[38e]
3	**75**	87	*S*	[38f]
4	**76**	98 – 99	*S*	[38g – i]
5	**77**	96	*S*	[38j]



Scheme 14. Enantioselective Mukaiyama aldolizations in the presence of a chiral vicinal diamine.

of the silylenol ether **78** with various aldehydes the *syn*-aldol products **80** were formed exclusively (*ee* > 98 %). Excellent results were also obtained with tin(II) oxide instead of dibutyltin diacetate.[41b] Very good enantioselectivity (*ee* up to 86 %) was also obtained in aldol reactions that utilized lithium amide **81** as the base.[41c]



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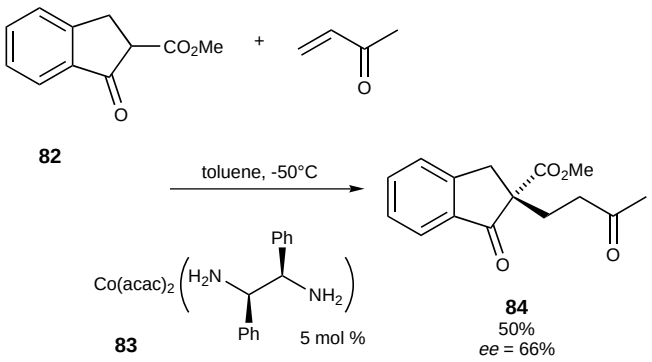
3.3.3. Conjugate Addition of Organometallic Reagents to α,β-Unsaturated Carbonyl Compounds

Asymmetric conjugate addition to α,β-unsaturated carbonyl compounds in the presence of a chiral additive has received

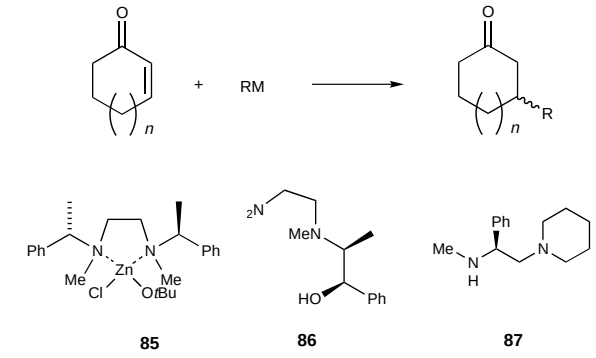
much attention in the last few decades. One of the first studies, carried out by Brunner et al., was a cobalt-catalyzed 1,4-addition:[42] enantiomeric excesses of up to 66% were obtained by using stien as the chiral ligand in complex **83** (Scheme 15).



Scheme 15. Enantioselective conjugate addition in the presence of a 1,2-diaminocobalt complex.

The conjugate addition of Grignard reagents to α,β-unsaturated ketones catalyzed by diaminezinc(II) complexes has been reported.[43a] The reaction of isopropylmagnesium bromide with 2-cyclohexenone in the presence of catalyst **85** proceeded with 8% enantiomeric excess. Much better enantioselectivities were obtained on the addition of chirally modified heterocuprates to cycloalkenones (Table 3).[43b–d]

Table 3. Enantioselective conjugate addition of chirally modified heterocuprates to cycloalkenones.



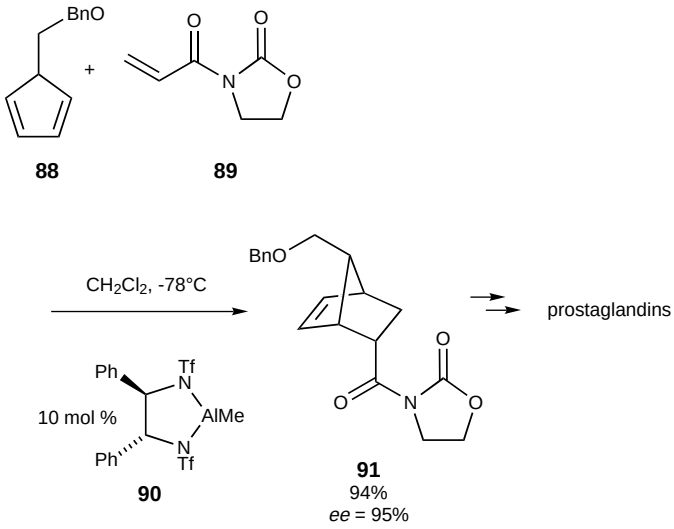
Entry	RM	*n*	Ligand (L*H)	*ee* [%]	Adduct config.	Ref.
1	EtL*CuLi	1	**86**	92	*R*	[43b]
2	MeL*CuLi	0	**87**	32	*R*	[43c]
3	*n*BuL*CuLi	0	**87**	45	*S*	[43c]
4	MeL*CuLi	1	**87**	58	*S*	[43c]
5	*n*BuL*CuLi	1	**87**	83	*S*	[43c]
6	MeL*CuLi	2	**87**	75	*S*	[43c]
7	*n*BuL*CuLi	2	**87**	96	–[a]	[43c]
8	MeL*CuLi	3	**87**	67	–[a]	[43c]
9	*n*BuL*CuLi	3	**87**	86	–[a]	[43c]

[a] The configuration of the adduct was not determined.

Mukaiyama et al.also showed that a chiral diamine derived from hydroxyproline is a good catalyst for the high enantioselective 1,4-addition of thiols to cyclohexen-2-one.[21, 44]

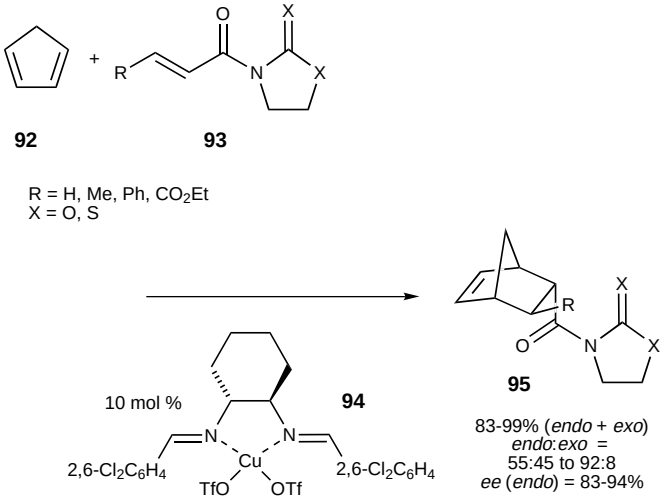
3.3.4. Diels–Alder Reactions

Corey et al. have demonstrated that diazaaluminolidine **90** is an effective Lewis acidic catalyst for the cycloaddition ;of cyclopentadiene derivatives to activated dienophiles (Scheme 16).[31, 45a, b] The cycloadduct **91** is a valuable intermediate for prostaglandins synthesis.[26]



Scheme 16. Use of a 1,2-diaminoaluminum additive in an enantioselctive Diels–Alder addition.

More recently, Evans et al. reported that bisiminecopper(II) complexes of type **94** are also effective chiral catalysts for Diels–Alder reactions and afford cycloadducts **95** with 83–94% enantiomeric excess (Scheme 17).[45c] The use of more

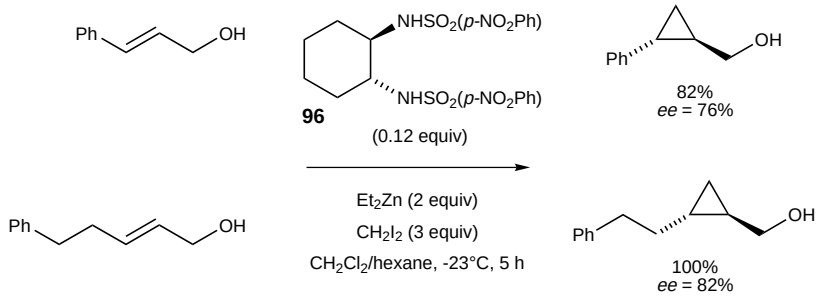


Scheme 17. Enantioselective Diels–Alder addition in the presence of a [Cu^{II}(salen)] complex.

reactive sulfur-containing dienophiles enhanced the *endo*/*exo* diastereoselectivity of the reactions.

3.3.5. Cyclopropanation

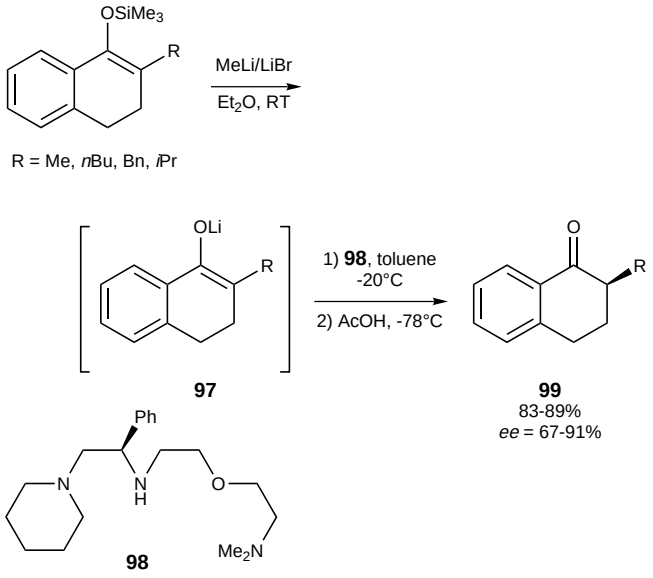
Kobayashi et al. developed a catalytic, enantioselective Simmons–Smith cyclopropanation of allylic alcohols by the $Et_2Zn-CH_2I_2$ system in the presence of a catalytic amount of a chiral sulfonamide, with **96** being the most efficient one (Scheme 18).[46] Other catalysts derived from 1,2-diamines have also been studied.[47]



Scheme 18. Enantioselective cyclopropanation reactions in the presence of the bissulfonamide **96**.

3.3.6. Enantioselective Protonation of Enolates

There are several examples of the use of 1,2-diamino compounds in the enantioselective protonation of enolates. For instance, Yasukata and Koga[48] reported the very efficient protonation with AcOH of complexes formed between cyclic achiral lithium enolates **97**, the chiral vicinal diamine **98**, and LiBr (Scheme 19). The asymmetric induction was much better in toluene than in polar solvents.



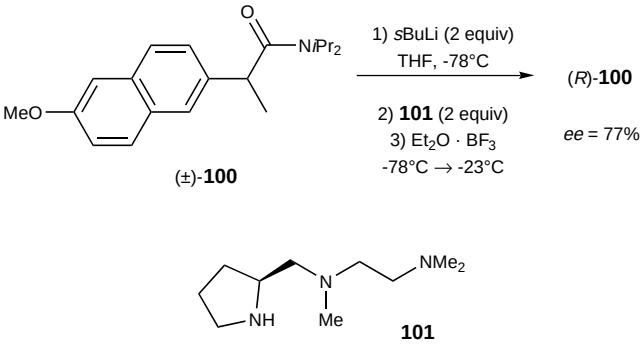
Scheme 19. Enantioselective protonation of cyclic enolates with a chiral 1,2-diamine.

Vedejs et al. have also investigated the use of 1,2-diamines in the enantioselective protonation of amide enolates.[49] As an example, treatment of racemic naproxen amide (**100**) with *s*BuLi, then with triamine **101**, followed by boron trifluoride-diethyl etherate afforded (*R*)-**100** with 77% *ee* (Scheme 20). Slightly lower enantiomeric excesses were obtained with diamines, while monoamines were much less efficient.

3.3.7. Deprotonation With Chiral Lithium Amides

In recent years enantioselective deprotonation of ketones or epoxides with chiral lithium amide bases, often derived from 1,2-diamines, has received much attention and several reviews on the subject have been published.[50]

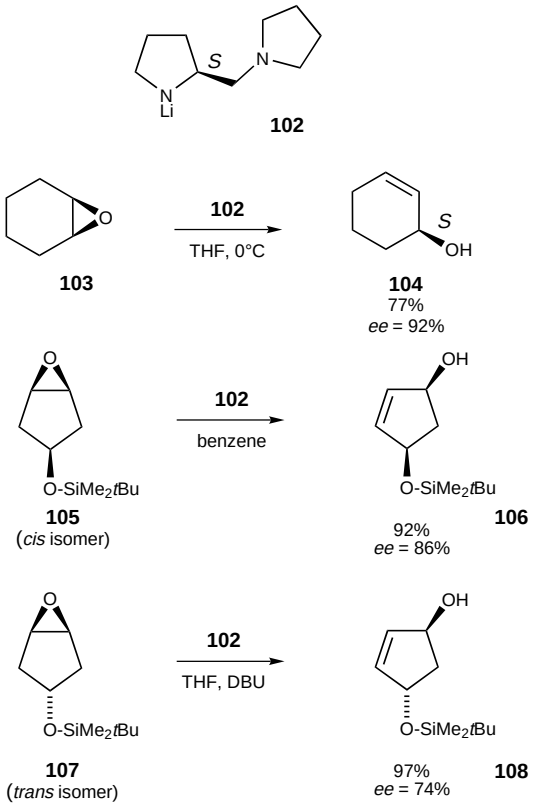
Asami showed that the enantioselective-opening of cyclohexene oxide (**103**) with lithium pyrrolidide (**102**) led to (*S*)-2-cyclohexen-1-ol (**104**) in 92% enantiomeric excess (Scheme 21).[51a–c] Similar results were obtained in the preparation of chiral monoprotected cyclopent-2-en-1,4-diols **106** and **108**, which are useful chiral building blocks.[51d] Other chiral bases derived from 1,2-diamines have been used by Singh et al.[52]



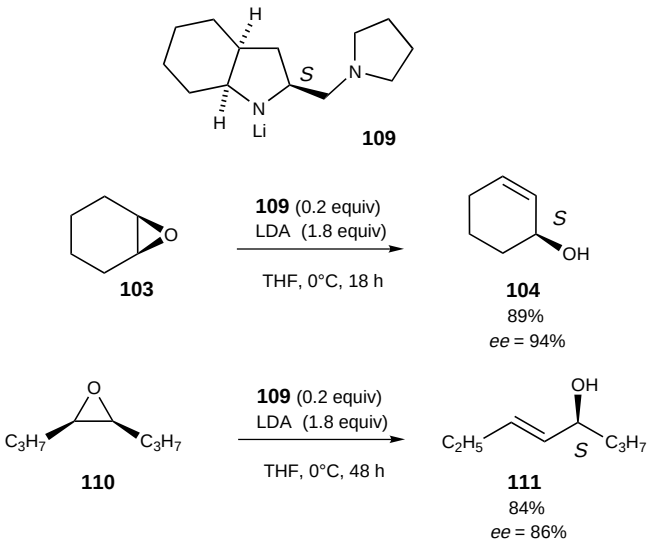
Scheme 20. Enantioselective protonation of an amide enolate with a chiral 1,2-diamine.

Catalytic enantioselective deprotonation of *meso*-epoxides and ketones, which use only a catalytic amount of the chiral lithium base plus a stoichiometric amount of a non-chiral base has also been reported by the groups of Asami,[53a, b] Koga,[53c] and Alexakis.[53d] In a recent example,[53b] (*S*)-2-cyclohexen-1-ol (**104**) was obtained from **103** in 94% *ee* with 20 mol% of the bulky chiral lithium amide **109**, in the presence of 180 mol% of LDA (Scheme 22). A high enantioselectivity was also shown to occur in the reaction of the epoxide **110** derived from an acyclic olefin.

Recently, Simpkins et al.[54] described the enantioselective conversion of episulfoxides that contain prostereogenic centers, such as **112**, into alkenyl sulfoxides by treatment with chiral lithium amides (Scheme 23). The C_2-symmetric bislithium amide **113** was found to effect the rearrangement with up to 88% *ee*.



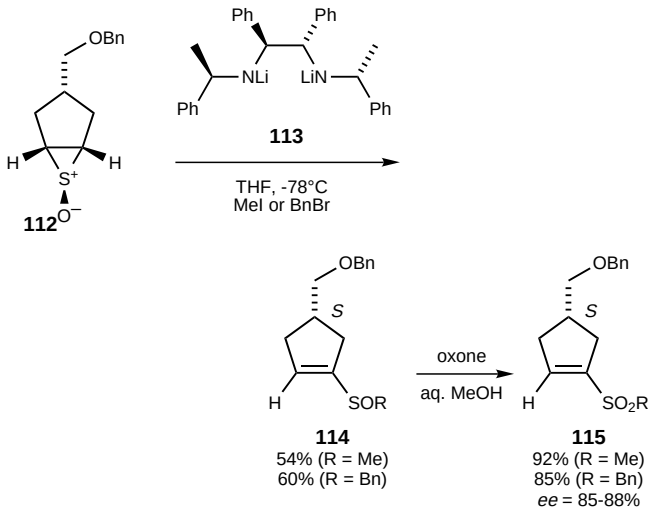
Scheme 21. Enantioselective deprotonation of *meso*-epoxides with the chiral lithium amide **102**.



Scheme 22. Catalytic enantioselective deprotonation of *meso*-epoxides with the chiral lithium amide **109**.

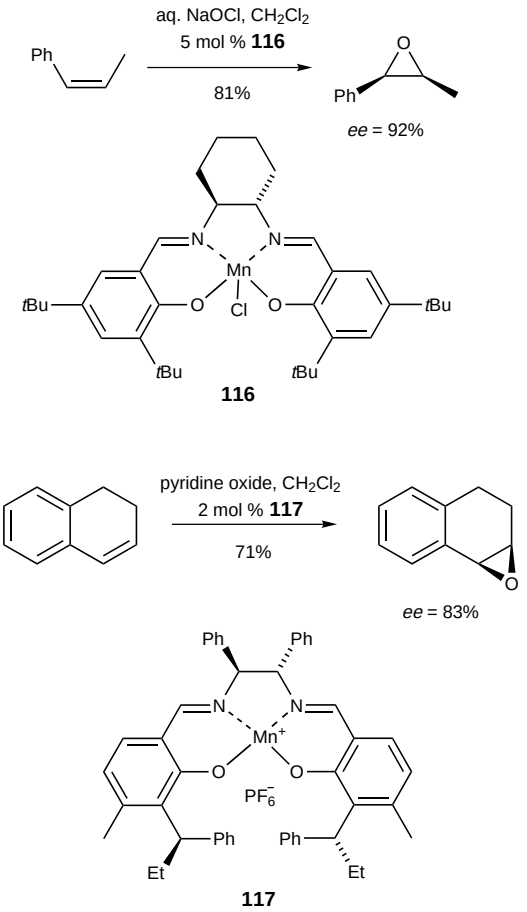
3.3.8. Epoxidation, Dihydroxylation, and Aziridination

Kochi et al. have demonstrated that achiral metal complexes containing salen-type ligands are active catalysts for the epoxidation of nonfunctionalized olefins, with the cationic manganese(III) complexes being the most efficient.[55] Jacobsen et al.[56a–c] and, independently, Katsuki et al.[56d–h] then prepared chiral derivatives of [Mn(salen)] complexes such as **116** and **117** and, by using oxidants such as PhIO or



Scheme 23. Enantioselective conversion of episulfoxides into alkenyl sulfoxides with a bislithium amide.

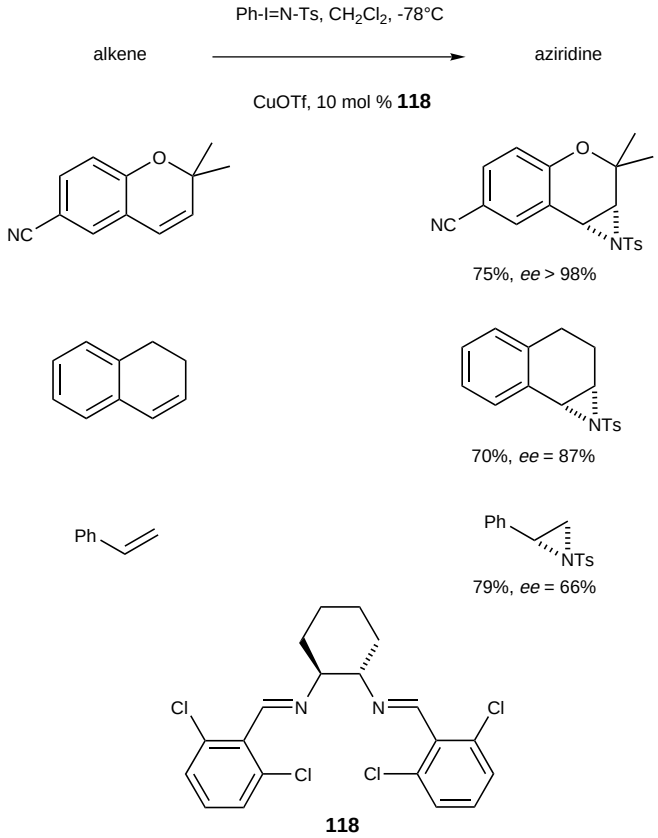
commercial bleach (aqueous solution of NaOCl), achieved the catalytic epoxidation of simple olefins under phase-transfer conditions, with enantiomeric excesses exceeding 90%. The efficient enantioselective epoxidation of dienyl sulfones was also described recently.[56i] Some illustrative examples are shown in Scheme 24. The epoxidation of several



Scheme 24. Enantioselective epoxidation reaction with [Mn(salen)] complexes.

olefins with the Jacobsen catalyst occluded in a polydimethylsiloxane membrane was reported recently by Vankelecom et al. to proceed with enantioselectivities similar to those obtained with the homogeneous catalyst. The catalytic membrane is regenerable by a simple washing procedure.[57]

A reaction closely related to epoxidation is aziridination. Jacobsen et al. have reported that the chiral ligand **118** is quite efficient in the enantioselective Cu^{I}-catalyzed aziridination of unfunctionalized alkenes (Scheme 25).[58]

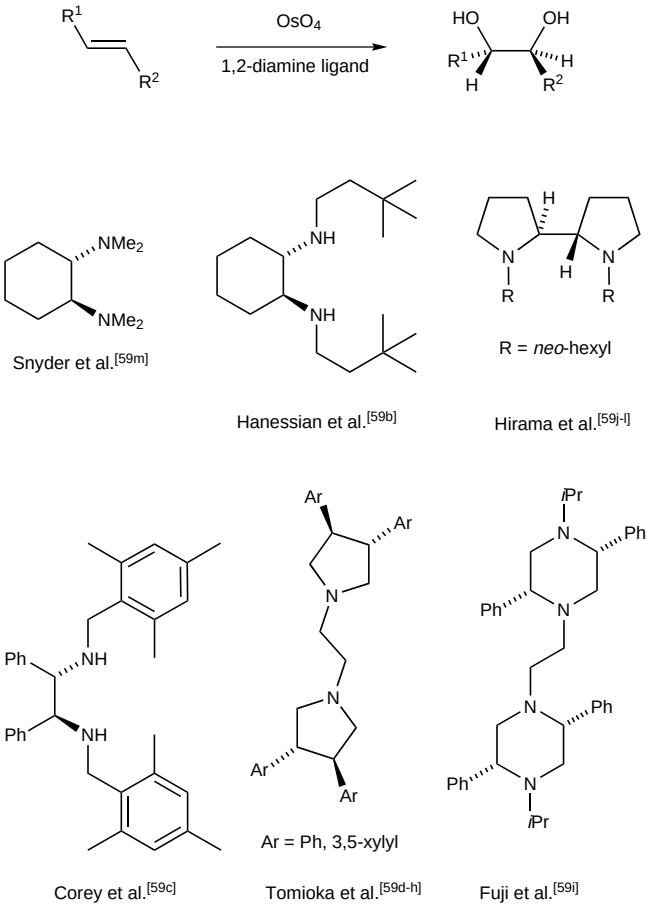


Scheme 25. Enantioselective aziridination reactions in the presence of a salen ligand **118**.

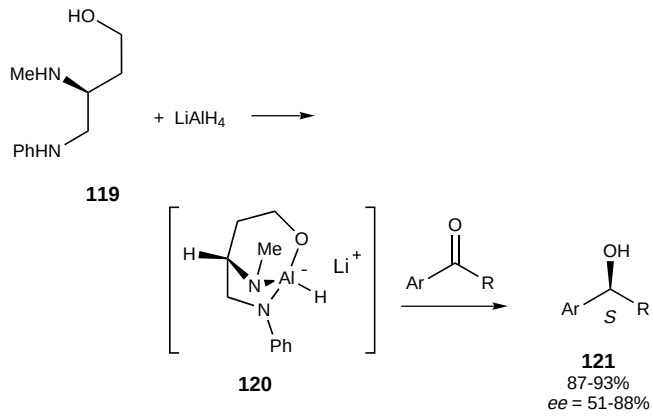
Apart from the outstandingly successful development of OsO_4-catalyzed dihydroxylation of olefins according to the Sharpless procedure, a number of recent methods employ chiral 1,2-diamines as ligands in this reaction (Scheme 26).[38c, 26, 59] Despite the good to excellent enantioselectivities that can be obtained, the reactions are stoichiometric in both OsO_4 and the chiral ligand: in situ recycling is prevented by the formation of very stable chelate complexes between the ligand and osmium(VI) glycolate intermediates.

3.3.9. Reduction of Prochiral Carbonyl Compounds

In 1982 Fujisawa et al.[60] described the enantioselective reduction of alkyl phenyl ketones by using the chiral hydride reagent **120**, prepared from lithium aluminium hydride and (*S*)-4-anilino-3-methylamino-1-butanol (**119**, Scheme 27). The corresponding *S*-configured alcohols **121** were obtained in 51 – 88 % *ee*.



Scheme 26. Chiral 1,2-diamino ligands for asymmetric dihydroxylation under stoichiometric conditions.

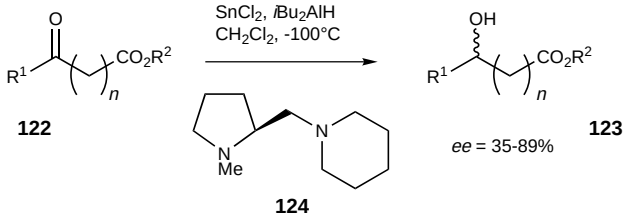


Scheme 27. Enantioselective reduction of alkyl phenyl ketones with a 1,2-diamine-derived chiral hydride reagent.

The asymmetric reduction of prochiral keto esters **122** by a chiral complex derived from **124**, tin(II) chloride, and diisobutylaluminium hydride has been realized by Mukaiyama et al. (Scheme 28).[61]

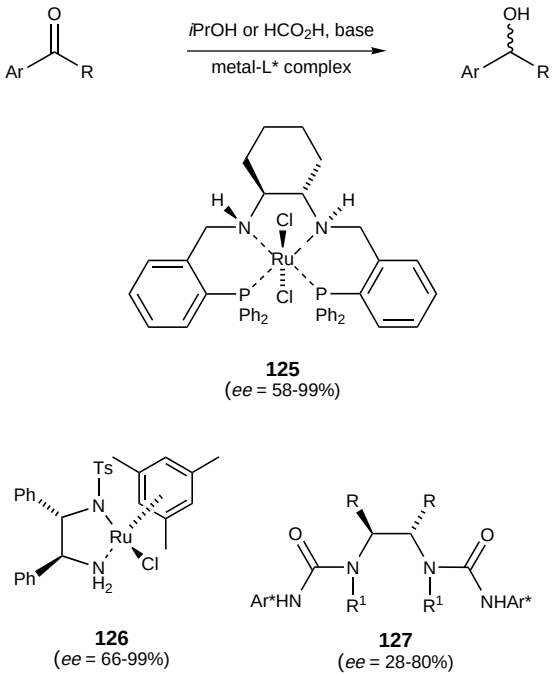
More recently Mukaiyama et al. reported the enantioselective reduction of aromatic, cyclic ketones and imines with sodium borohydride, catalyzed by [Co^{II}(salen)] complexes.[62] Very good enantiomeric excesses (up to 97 %) were obtained.

The reduction of aromatic ketones was also carried out successfully by asymmetric hydrogen transfer (with *i*PrOH or



Scheme 28. Enantioselective reduction of a prochiral ketone in the presence of a chiral 1,2-diamine-based ligand.

HCO_2H used as a hydrogen donor)[63] with ruthenium complexes such as **125**[64a] and **126** (Scheme 29).[64b, c, d] Several recent studies make use of other metal complexes, by using various diamine-derived ligands such as diureas **127**.[64b, e, f, g]



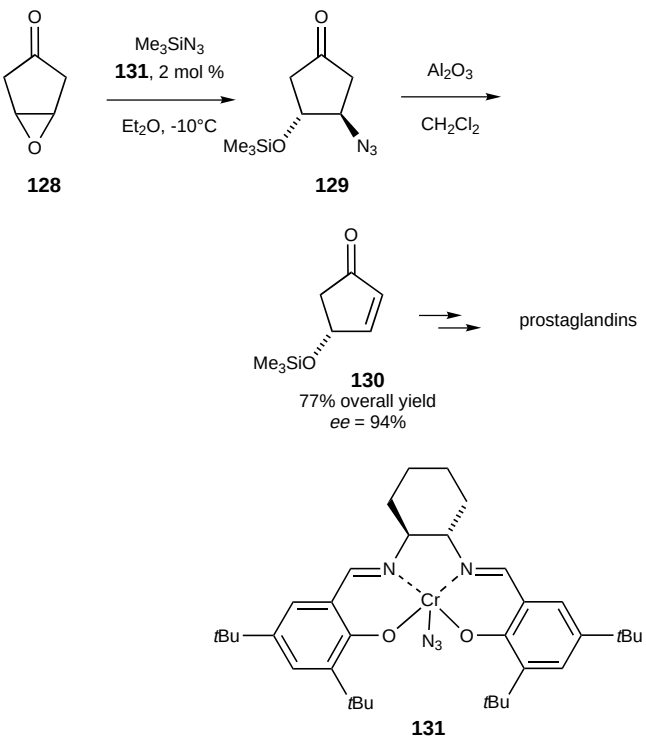
Scheme 29. 1,2-Diamino ligands and metal complexes used in prochiral ketone enantioselective reductions. The enantiomeric excesses obtained are given in parentheses.

Efficient asymmetric-transfer hydrogenation of α,β-acetylenic ketones mediated by **126** and other Ru^{II} catalysts was also reported recently by Noyori et al.[64h]

3.3.10. Miscellaneous Applications

Other recent synthetic applications include the enantioselective *ortho*-lithiation of substituted ferrocenes mediated by (*R*,*R*)-1,2-bis(dimethylamino)cyclohexane.[65] Trost et al. have developed palladium-catalyzed enantioselective allylic alkylations with either carbon or nitrogen nucleophiles that make use of chiral amide ligands derived from 1,2-diamines.[66a–f] Chiral thioarylimidazolines[67a] and diazaphospholidines[67b] derived from C_2-symmetric vicinal diamines were also employed recently as ligands for enantioselective palladium-catalyzed asymmetric allylation.

Jacobsen et al. reported the enantioselective nucleophilic ring opening of epoxides catalyzed by [Cr^{III}(salen)] complexes such as **131** (Scheme 30).[68] By using trimethylsilyl azide as the nucleophile, epoxide **128** was selectively converted into compound **129**; after basic alumina-promoted azide elimination enone **130**, a useful precursor in prostaglandins synthesis, was obtained (*ee* = 94%).



Scheme 30. Enantioselective opening of an epoxide in the presence of a [Cr^{III}(salen)] complex.

Metal complexes containing salen-type ligands were also employed as catalysts in the enantioselective oxidation of sulfides.[69]

Recently Noyori et al. reported that efficient kinetic resolution of racemic alcohols could be achieved by hydrogen transfer catalyzed by a diamine–Ru^{II} complex,[70] and Jacobsen et al. described the kinetic resolution of racemic, terminal epoxides by means of a hydrolysis catalyzed by chiral (salen)–cobalt complexes, which afforded both the unreacted substrates and the products (1,2-diols) in high enantiomeric excess.[71]

3.4. Conclusion

This section has highlighted the growing utility of enantiomerically pure vicinal diamines and their derivatives as chiral auxiliaries and ligands in asymmetric synthesis. Optically active pyrrolidine-containing molecules, 1,2-diphenylethylenediamine, and 1,2-diaminocyclohexane derivatives, more readily available than other ones, are mainly the most widely used. However, the ubiquitous character of the 1,2-diamino moiety and the increasing interest in vicinal diamines brought about the search for new methods for their preparation, especially stereoselective ones. The next section will present the major ways of preparation of such compounds.

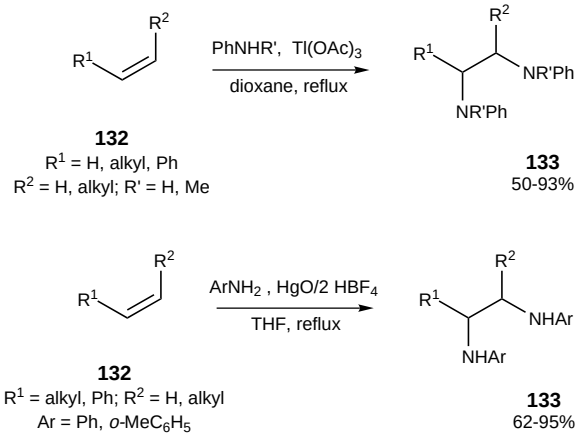
4. Vicinal Diamines: Methods of Preparation

Conceptually, the simplest procedure for the generation of the 1,2-diamino unit is the ammonolysis of the corresponding vicinal dihalide. However, this method, which was applied at the beginning of this century for the preparation of ethylenediamine, mainly yields elimination products in more complex systems.[72a] Although enantiopure 1,2-disubstituted 1,2-diamines have frequently been obtained through resolution[72b–g] diastereo- and enantioselective methods are employed increasingly in their synthesis. In the following paragraphs we will give an overview of the many reported syntheses of 1,2-diamines, with emphasis on the stereoselective ones. The methods will be arranged in the following manner: we will discuss first the ones in which the two nitrogen atoms are introduced concomitantly on the carbon skeleton, then the methods that utilize a compound already containing one of the two final nitrogen atoms of the target 1,2-diamine as the substrate, then the preparation of 1,2-diamines from compounds that already contain both nitrogen atoms, and lastly the syntheses starting from two nitrogen-containing substrates and involves the formation of the C1 – C2 bond.

4.1. Vicinal Diamines from Alkenes by Direct Introduction of Two Nitrogen Atoms

Although several methods are known for the oxidative transformation of alkenes into 1,2-diols (for instance, the dihydroxylation with $KMnO_4$ or OsO_4), the analogous strategy for vicinal diamines has been less developed.[73] Nevertheless, there are some methods that allow such olefin "diamination", which mainly use organometallic reagents.

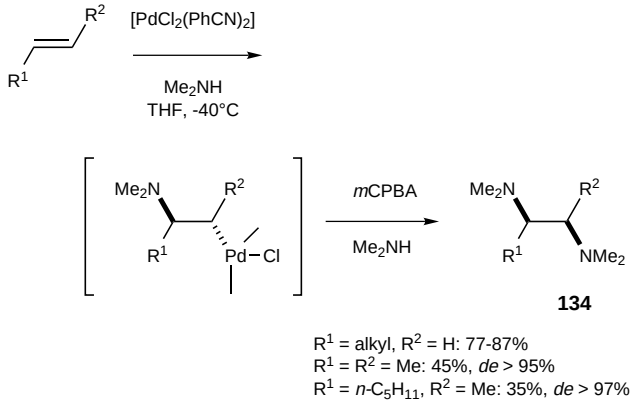
Barluenga et al. have reported a convenient preparation of aromatic vicinal diamines **133** from olefins in the presence of thallium[74] or mercury salts (Scheme 31).[75] The yields are



Scheme 31. Direct diamination of alkenes with thallium or mercury salts.

generally good, but the addition of aliphatic primary amines does not occur in the presence of thallium acetate and has not been reported for the mercury method. This procedure is thus limited to aromatic vicinal diamines.

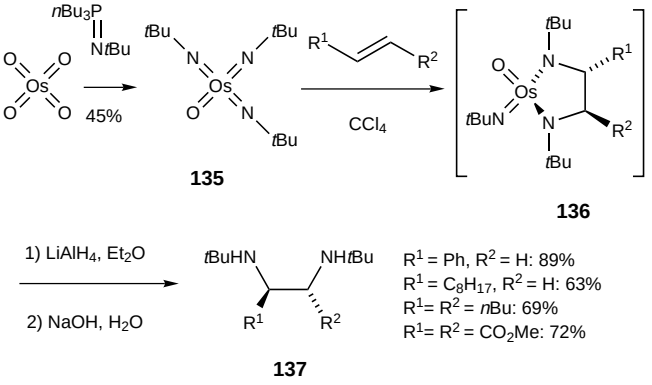
At the same time, Bäckvall showed that the aminopalladation of *E* alkenes, followed by oxidation in the presence of an excess of amine afforded the corresponding vicinal diamines **134** (Scheme 32).[76] Terminal olefins were diaminated in good



Scheme 32. Direct diamination of alkenes via an aminopalladatio compound.

yields (77 – 87 %) and the diamination was overall *cis* stereospecific. No results were reported for *Z* olefins, and only dimethylamine was used. Thus, the procedure has been applied only to the preparation of tertiary (*N,N,N′,N′*-tetramethyl)-*syn*-1,2-diamines.

In 1977 Sharpless et al.[77] showed that the triimidoosmium complex **135** reacted with monosubstituted and disubstituted *E*-olefins through a stereospecific *cis* addition to give vicinal diamines **137** (Scheme 33). However, this method has several

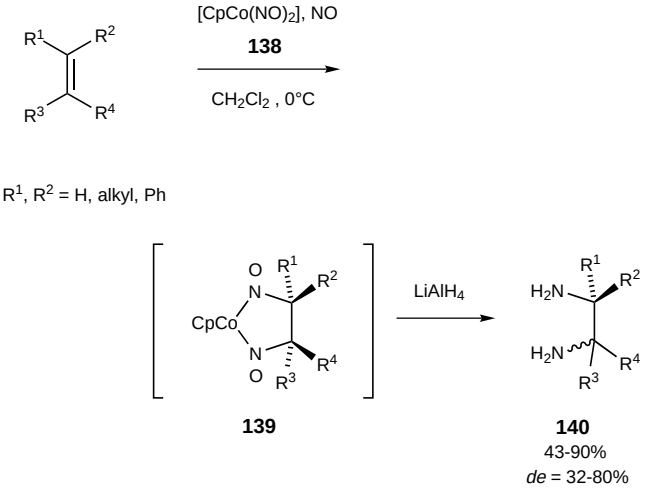


Scheme 33. Direct diamination of alkenes with a diimidoosmium complex.

drawbacks. The complex **135** must be prepared beforehand from OsO_4, which is a costly reagent, and must be used in stoichiometric amounts. Moreover, this complex is unreactive toward disubstituted *Z* olefins, thus the method only allows the preparation of secondary *N*-*tert*-butyl-substituted *syn*-1,2-diamines.

In 1980 Bergman et al. reported a more general 1,2-diamination of alkenes with nitric oxide and a cobalt complex.[78] Indeed, this procedure works satisfactorily for terminal, *E* and *Z*, di-, tri-, and at least some tetra-substituted alkenes and leads to various aliphatic primary 1,2-diamines. It

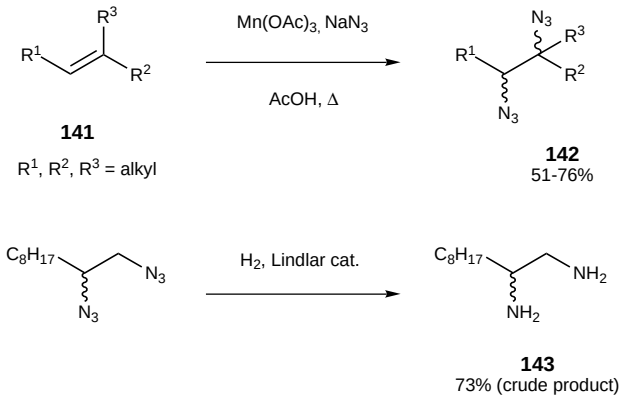
utilizes the cobalt-based reagent **138** and nitric oxide (Scheme 34). Primary vicinal diamines are obtained in moderate to excellent yield. Despite the complete stereospecificity (*cis* addition) of the first step (some 1,2-dinitrosoalkane – Co complexes **139** were isolated), the production of



Scheme 34. Diamination of alkenes with a nitrosylcobalt complex.

diastereomeric diamines arises from epimerization during the $LiAlH_4$ reduction. No examples are given of non-racemic series.

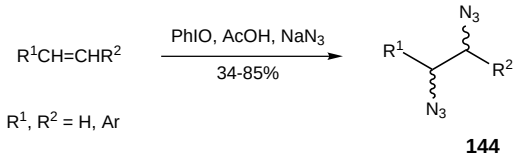
In 1985 Fristad et al. reported a Mn^{III}-catalyzed direct conversion of alkenes **141** into 1,2-diazides **142** (Scheme 35).[79] $Mn^{III}-N_3$ species formed in situ are capable of oxidatively transferring a $N_3^{\bullet}$ radical to alkenes. Yields were moderate to



Scheme 35. Preparation of 1,2-diamines through diazidation of alkenes with a diazide-manganese complex.

good and stereoselectivity was fair (4:1 to 6:1) in cyclic series. The diazidation, coupled with the reduction of the 1,2-diazides, constitutes a simple two-step route to 1,2-diamines such as **143**. Such a reduction step can be performed by hydrogenation over Lindlar's catalyst. However, care should be exercised with azides and oxidizing agents: a case of explosion was reported by the authors!

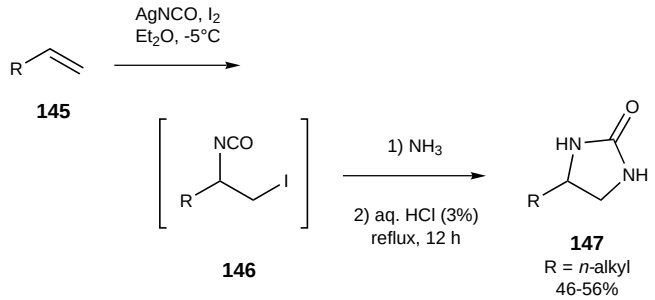
The conversion of alkenes into 1,2-diamines has also been realized from direct diamination procedures not involving organometallic species. For instance, a method for the preparation of vicinal diazides **144** has also been described by Moriarty et al. (Scheme 36).[80] This strategy no longer uses



Scheme 36. Synthesis of vicinal diazides by using hypervalent iodine.

metal complexes as did Fristad's method, but a hypervalent iodine oxidation in the presence of sodium azide. Although this method is direct and quite simple, it lacks stereoselectivity and its scope has been explored mainly with aryl-substituted alkenes.

Substituted imidazolidin-2-ones can be considered as a protected form of 1,2-diamines. In 1983 Ghomi and Orr published a simple preparation of 4-substituted imidazolidin-2-ones **147** (Scheme 37).[81] The first step is analogous to the



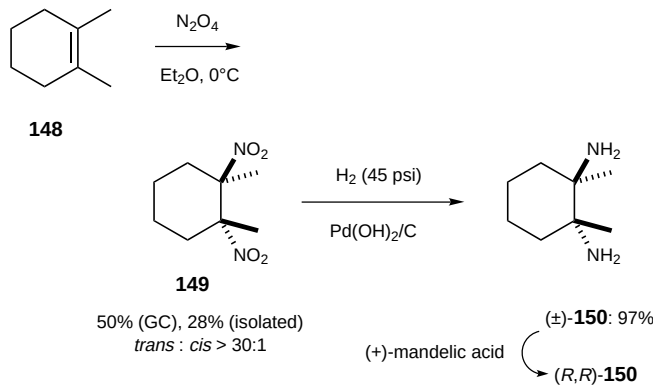
Scheme 37. Preparation of 4-substituted imidazolidin-2-ones from alkenes.

methodology of Swift and Swern (Section 4.5; Scheme 57). Freshly prepared silver isocyanate and iodine are added to a terminal alkene **145** to afford a β-iodoalkyl isocyanate **146**. After treatment with ammonia and dilution with HCl, the corresponding 4-alkylimidazolidin-2-one **147** was obtained (overall yield: 46 – 56 %). No examples concerning polysubstituted alkenes were given.

In the course of the investigation of C_2-symmetric 1,2-diamines as chiral ligands in asymmetric catalysis, Jacobsen and Zhang reported the preparation of *trans*-1,2-diamino-1,2-dimethylcyclohexane (**150**) by the highly diastereoselective oxidation of olefin **148** by dinitrogen tetroxide (Scheme 38).[82] This methodology is mainly suited for the synthesis of vicinal diamines adjacent to tertiary centers because primary and secondary dinitro intermediates would be prone to epimerization.

4.2. Vicinal Diamines from Dienes and Heterodiimides

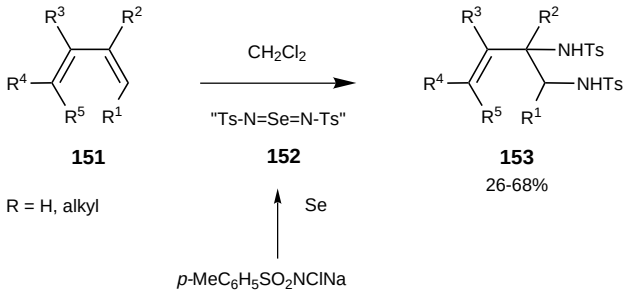
Indirect diamination of double bond containing compounds can also be used to prepare vicinal diamines. Thus, the Diels – Alder adducts of 1,3-dienes and selenium- or sulfur-contain-



Scheme 38. Preparation of cyclic 1,2-diamine by N_2O_4 addition to a cycloalkene.

ing dimides have been shown to undergo rearrangements that lead to unsaturated 1,2-diamines.

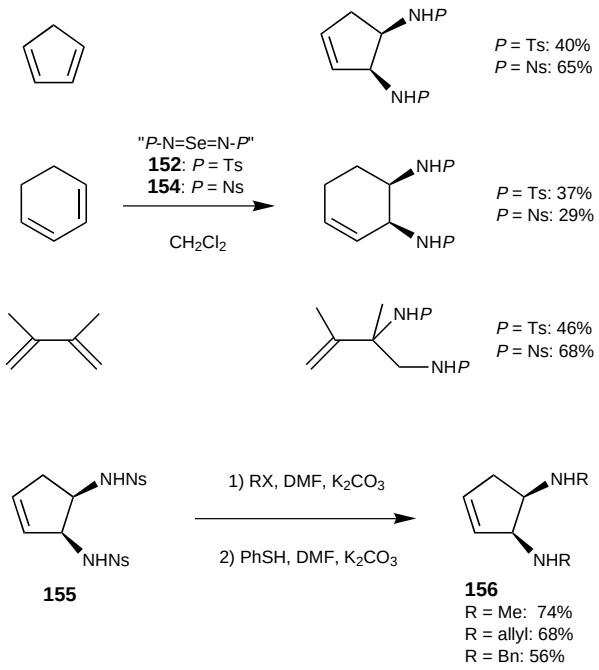
In 1976 Sharpless and Singer reported that the reaction of 1,3-dienes **151** with the diimidoselenium compound **152** afforded 1,2-disulfonamidoalkenes **153**, by a Diels–Alder reaction followed by a [2,3]-sigmatropic rearrangement (Scheme 39).[83a]



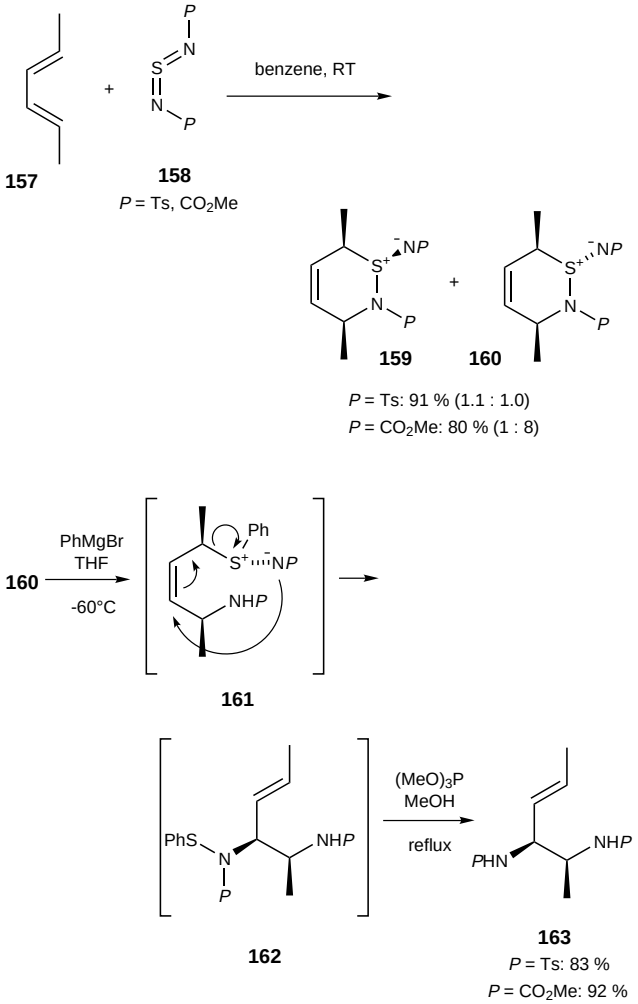
Scheme 39. Diamination of 1,3-dienes with a diimidoselenium species.

The yields were poor to fair (26–68%) and the removal of the *para*-toluenesulfonyl groups required harsh conditions that are incompatible with many other functional groups. More recently, following the publication of a simple method for the deprotection of nitro-substituted benzenesulfonamides,[83b] Sharpless et al. reinvestigated their method by using a modified diimidoselenium reagent **154** that has *ortho*-nitrobenzenesulfonyl residues (Scheme 40).[83c] The yields of the allylic aminations were not improved, but the deprotection of the amine functions were much easier. Dimethyl-, diallyl-, and dibenzyldiamines **156** were thus prepared in good yields.

Weinreb et al. designed a related stereocontrolled synthesis of unsaturated vicinal diamines from the Diels–Alder adducts of sulfur dioxide diimides **158** and 1,3-dienes (Scheme 41).[84] Treatment of adduct **160**, obtained from 2,4-hexadiene (**157**) with phenylmagnesium bromide, and then with trimethylphosphite yielded the *syn*-diamine derivative **163**. The first step is a ring opening mediated by the Grignard reagent, which leads to an allylic sulfinimine **161** that undergoes a [2,3]sigmatropic rearrangement to a sulfenamide **162**. Desulfurization of the sulfenamide with trimethylphosphite afforded the *syn*-diamine derivative. From *E*,*E*- and *E*,*Z*-



Scheme 40. Diamination of 1,3-dienes with a modified diimidoselenium species.

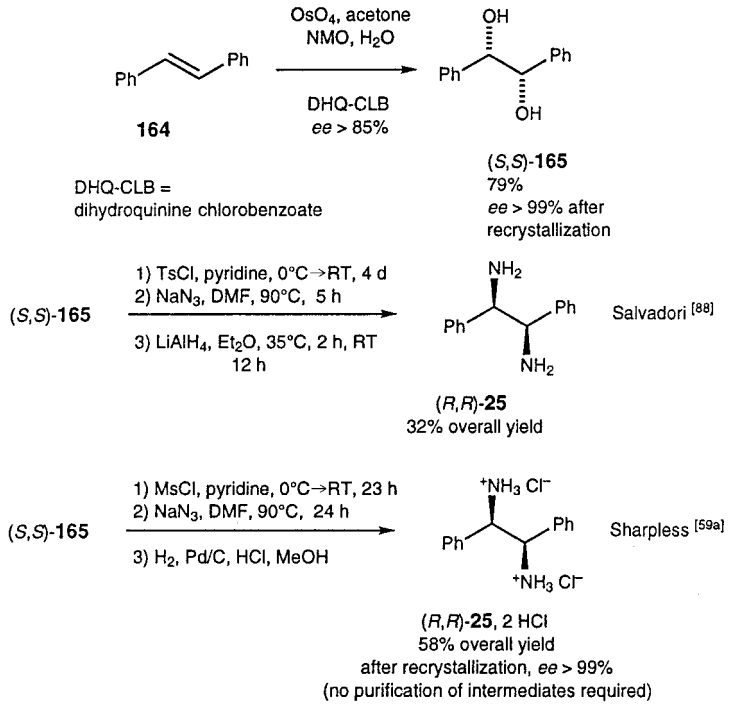


Scheme 41. Stereocontrolled synthesis of unsaturated 1,2-diamine derivatives from Diels–Alder adducts of sulfur dioxide diimides and 1,3-dienes.

1,3-dienes, *syn* and *anti* adducts were obtained, respectively. These adducts contain a double bond that may be used for further functionalization.

4.3. Vicinal Diamines from 1,2-Diols or 1,2-Dihalides

Taking into account the recent developments of catalytic asymmetric epoxidation,[85] of catalytic asymmetric dihydroxylation,[59a, 86] and of catalytic asymmetric aminohydroxylation,[87] a "catalytic asymmetic diamination" may appear in the near future. However, the efficiency and scope of osmium-catalyzed asymmetric dihydroxylation allows access to various enantiomerically pure 1,2-diols that can be converted by several methods into enantiopure vicinal diamines, for instance through double displacement by nitrogen nucleophiles. Such a procedure is illustrated by the syntheses of (*R*,*R*)-stilbenediamine **25** reported by Salvadori et al.[88] and Sharpless et al.[59a] (Scheme 42). This method may be adapted for the preparation of other enantiomerically pure diamines, provided the corresponding alkenes contain no functional groups that are incompatible with osmium tetroxide.



Scheme 42. Syntheses of (*R*,*R*)-stilbenediamine from the 1,2-diol (*R*,*R*)-**165** (≡ (*S*,*S*)-**165**), prepared by catalytic asymmetric dihydroxylation of stilbene.

Since the catalytic asymmetric dihydroxylation developed by Sharpless provides a convenient access to optically active diols **166**, and since cyclic derivatives such as sulfites **167**[89a] or sulfates **168**[89b, c] show a good electrophilic behavior toward various nitrogen nucleophiles, the coupling of these two efficient procedures can be used for the synthesis of optically active vicinal diamines (Scheme 43). 1,2-Dihalides were used as substrates in the synthesis of racemic *n*,*n*+1-diamino carboxylic acid derivatives.[10b] Enantiomerically pure C_2-symmetric 1,2-diamines were also prepared from tartaric acid, either by a twofold Mitsunobu reaction of a diol intermediate with hydrazoic acid[90a] or by displacement of a bismesylate with sodium azide.[90b] The preparation of (2*S*,3*S*)-diaminobutane from the corresponding racemic bismesylate involved a resolution.[90c]

4.4. Vicinal Diamines from β-Amino Alcohols or β-Halogenoalkylamines

There are several methods for the preparation of 1,2-diamines that actually consist of the introduction of a second amino group into compounds already containing a nitrogen functionality. Amines substituted at the β position by an hydroxyl group or by an halide are widely used as such starting materials.

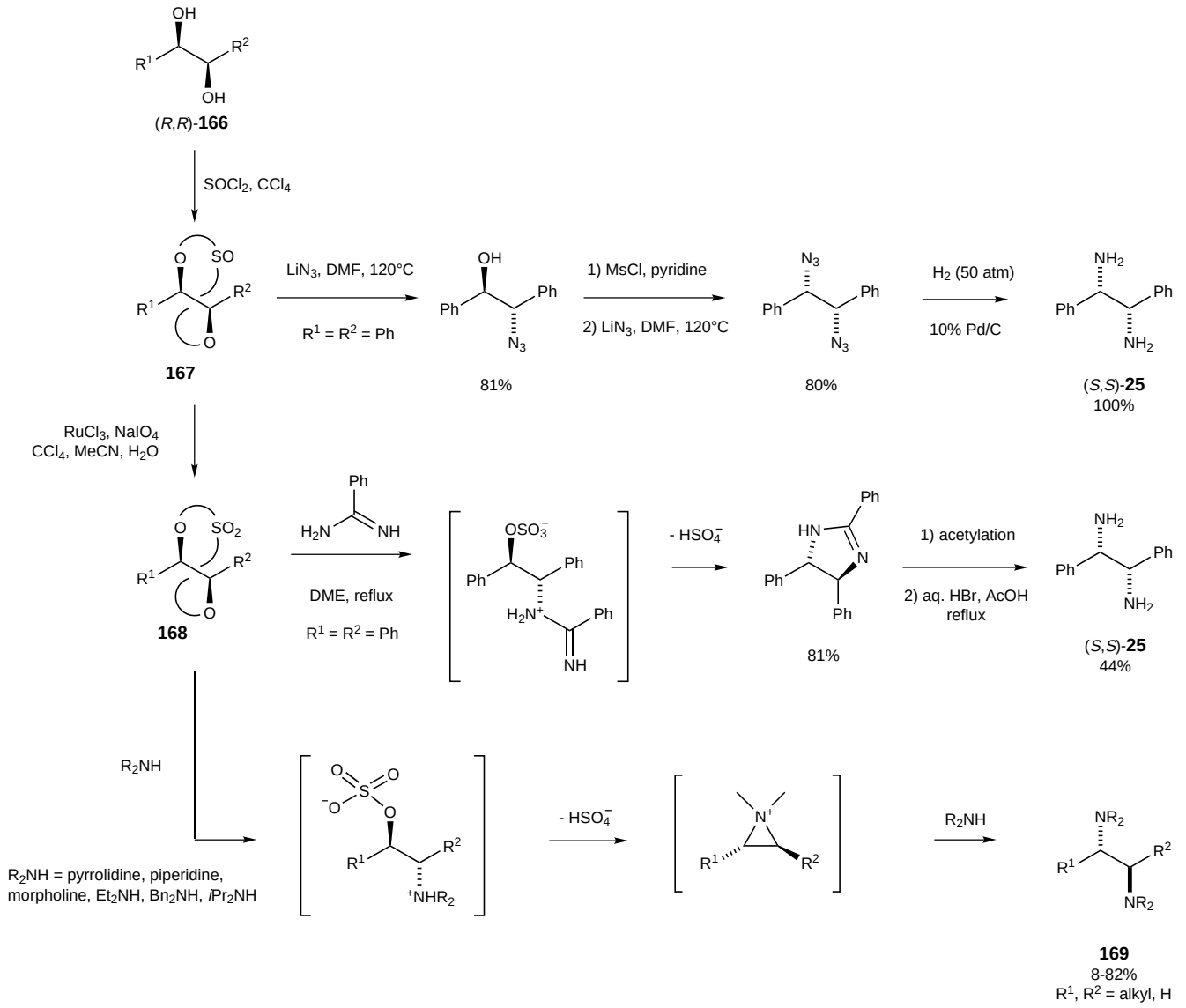
4.4.1. Vicinal Diamines from β-Amino Alcohols

After transformation of the hydroxyl group of a β-amino alcohol into a leaving group, substitution by a nitrogen nucleophile then affords a diamine precursor. Several optically active β-amino alcohols can be found in nature, they can also be prepared, for example, from α-amino acids through alkylation or reduction.

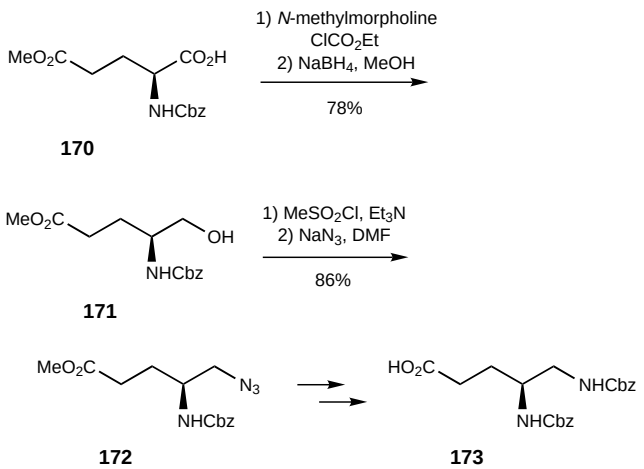
A Mitsunobu reaction may be used to introduce the nitrogen nucleophile (an azide[91a–d] or a phthalimide.[91e–g]) A synthesis of statine analogues involved an intramolecular Mitsunobu reaction.[12c] Nucleophilic displacements of tosylates or mesylates are also frequently employed, as in the synthesis of (−)-slaframine,[92] in the synthesis of (*R*)- and (*S*)-2,3-diaminopropanol from L- and D-serine,[93] or in the synthesis of (3*R*,4*R*)- and (3*R*,4*S*)-β,γ-diamino acids from D-phenylalanine.[94] Several protected, chiral triamines and diamines were synthesized by Kokotos et al.[95] For example, the Cbz-protected 4,5-diaminopentanoic acid **173** was prepared from the glutamic acid derivative **170** through a sequence involving the nucleophilic displacement of a mesyl group by sodium azide (Scheme 44).

A Walden inversion does not always occur during such displacements; for example, Rossi et al. observed a retention of configuration in the reaction of potassium phthalimide with the mesylate **174** as a consequence of the participation of the oxazolidinone nitrogen atom in the displacement mechanism (Scheme 45).[96] However, this effect was completely suppressed by the treatment of **174** with chlorotrimethylsilane and then with sodium azide. Thus, the two diastereomeric amines **176** and **178** could be prepared from a common precursor. The taxol side chain analogue **179** was then synthesized in a few steps from **178**.

A stereo- and regioselective route to chiral diamines, which were required for use as ligands in organocopper conjugate additions, was developed by Dieter et al. from (−)-ephedrine and (−)-pseudoephedrine.[97] Their strategy (Scheme 46) relied on the transformation of a chiral 1,2-amino alcohol



Scheme 43. Preparation of enantiopure 1,2-diamines from cyclic sulfites and sulfates.

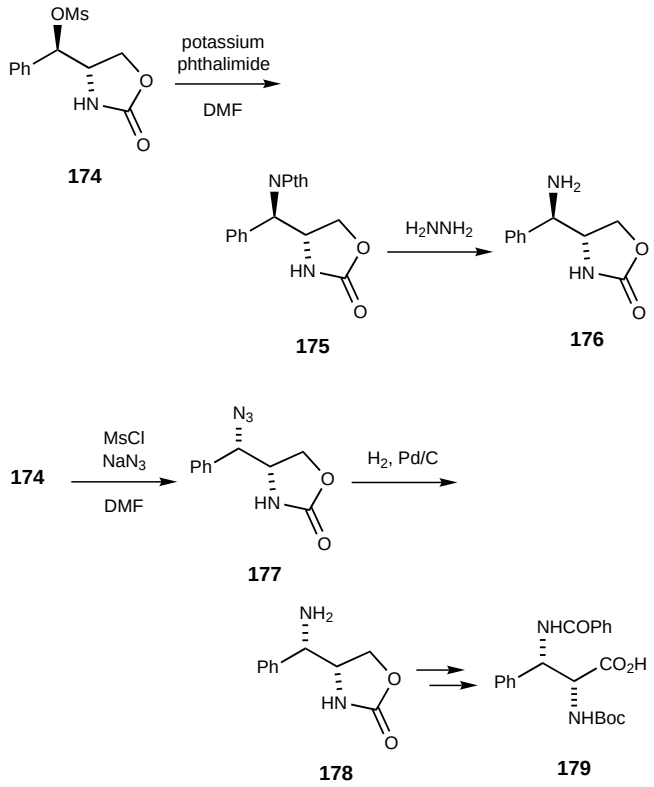


Scheme 44. Synthesis of 4,5-diaminopentanoic acid in the form of its bis(benzyloxycarbamate).

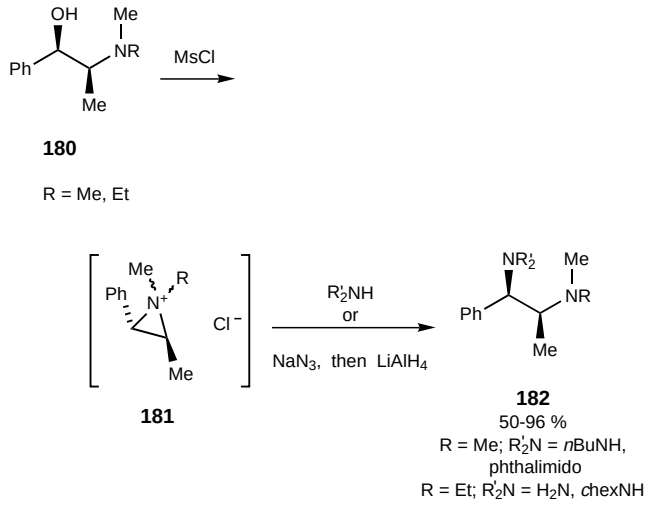
180 into an aziridinium **181** (by intramolecular displacement of a mesylate group), which was then treated with various nitrogen nucleophiles to afford the corresponding diamines or diamine precursors **182**.

Rossiter et al.[98] have described a related method relying on the opening of aziridiniums **187** generated from 1,2-amino alcohols **186** (Scheme 47). These alcohols were prepared from alkenes **183**, by Sharpless asymmetric dihydroxylation, conversion of diols **184** into epoxides **185**, and nucleophilic opening of **185** by piperidine. The reaction of aziridiniums **187** with methylamine afforded single regioisomers **188** (*ee* > 95%). The diamines were employed as ligands for chiral amidocuprates that were used in enantioselective conjugate addition to cyclic enones.

O'Brien et al. then reported a one-pot method to convert (*R*)-styrene oxide (**189**) into 1,2-diamines **191** (Scheme 48).[99a] However, only diamines derived from reactive amines such as



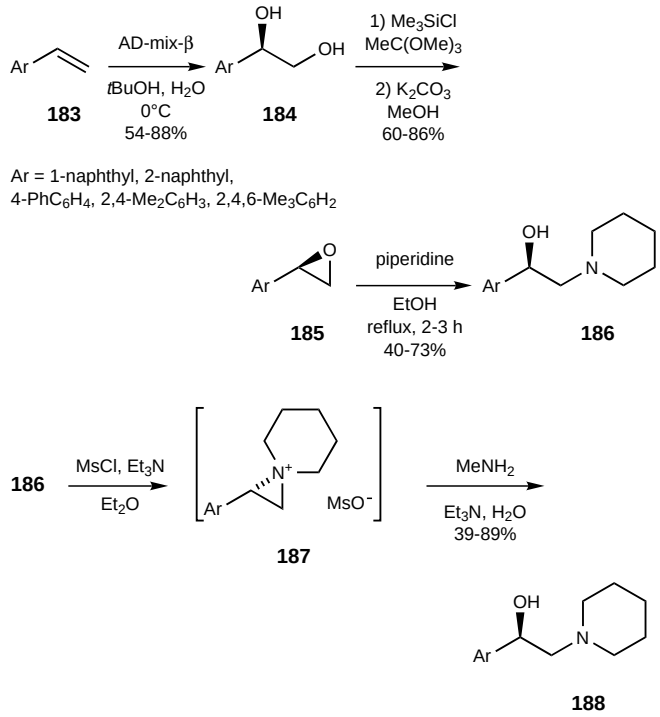
Scheme 45. Synthesis of *syn*- and *anti*-1,2-diamine derivatives from a common mesylate precursor.



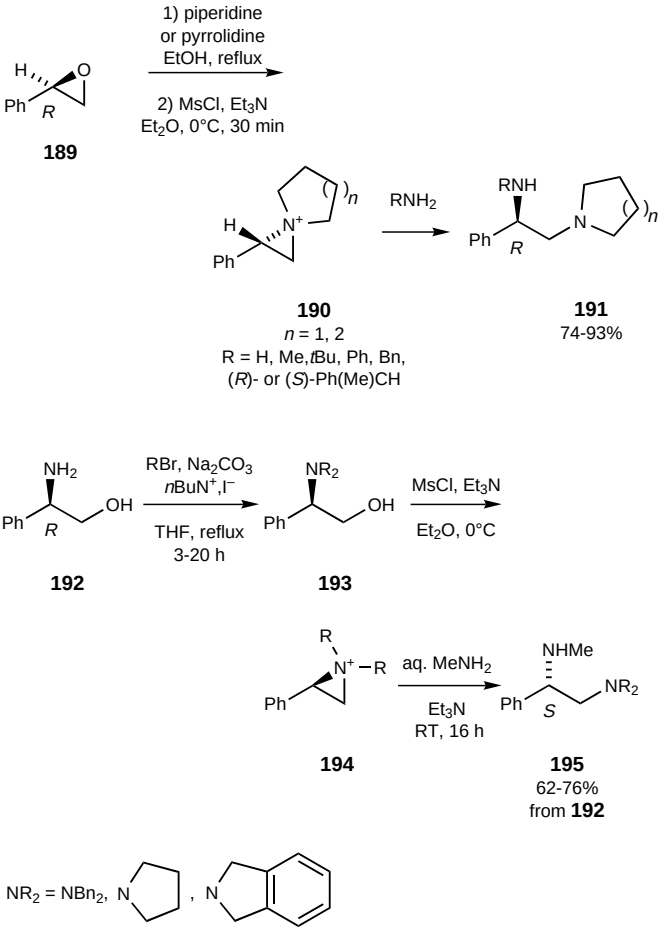
Scheme 46. Synthesis of vicinal diamines from (−)-ephedrine.

piperidine or pyrrolidine were available in this way. In a further improvement they showed that phenylglycinol (**192**), commercially available in both enantiomeric forms, can be used as a precursor to diamines **195** that contain other susbtituents; in this case, a N-dialkylation step is needed prior to the generation of aziridiniums **194**.[99]

Rayner et al. demonstrated recently that 2,3-epoxy amines **196** can also be used as substrates for the generation of aziridinium intermediates **197** (Scheme 49).[100] Addition of nitrogen nucleophiles onto these species proceeded regioselectively, to give 1,2-diamines **198**. Homochiral epoxides **196**

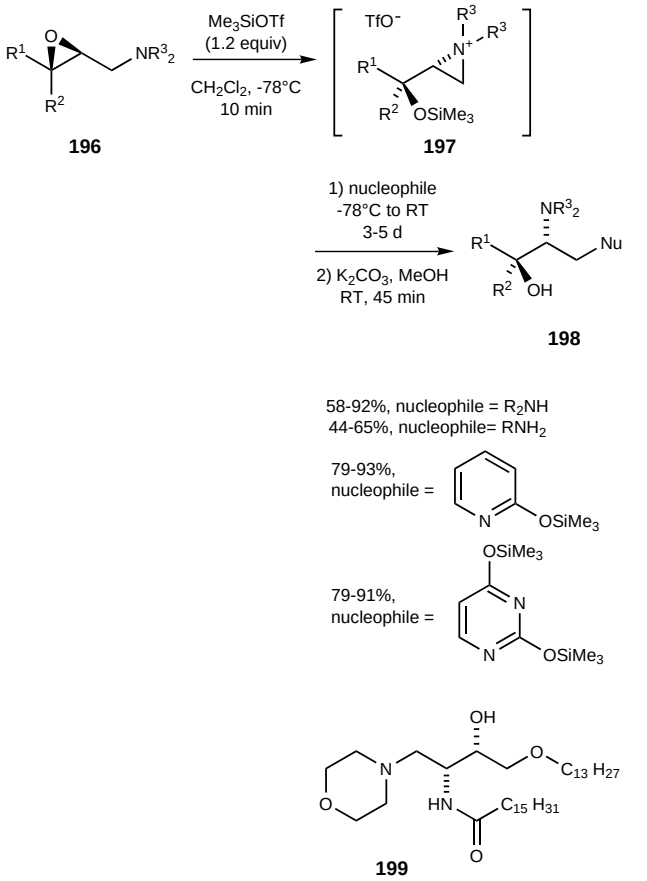


Scheme 47. Synthesis of vicinal diamines from enantiomerically pure aryl epoxides.



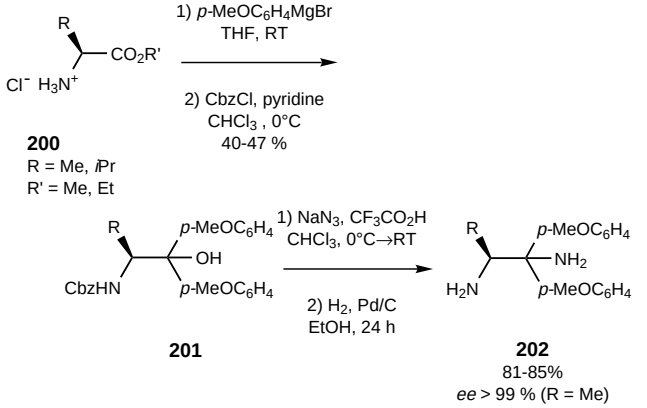
Scheme 48. Synthesis of vicinal diamines from (*R*)-styrene oxide or (*R*)-phenylglycinol.

can be obtained from the corresponding epoxy alcohols prepared by Sharpless asymmetric epoxidation. This methodology was used to synthesize compound **199**, a potential inhibitor of glucosylceramide synthase.



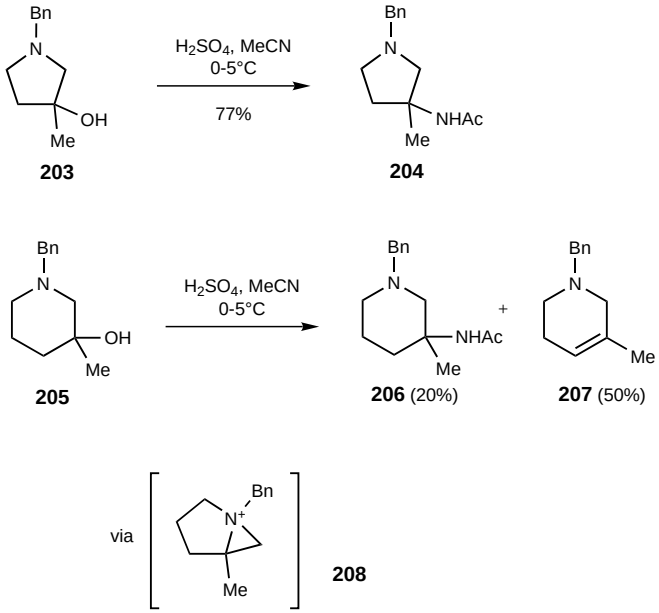
Scheme 49. Synthesis of vicinal diamines from 2,3-epoxy amines via aziridinium salts.

In their reported synthetic route to trisubstituted diamines, Burrows et al. made use of the bisalkylation of α-amino esters **200** (Scheme 50).[101] After substitution of the hydroxyl group with azide under acidic conditions and hydrogenolysis, diamines **202** having the same substituent twice on a carbon atom were obtained. Their incorporation in salen–nickel complexes was then studied.



Scheme 50. Synthesis of vicinal diamines by the bisalkylation of α-amino esters.

The Ritter reaction of several cyclic hydroxyamines was recently studied by Taylor et al. (Scheme 51).[102] While the treatment of the pyrrolidine **203** with acetonitrile and sulfuric acid afforded the expected acetamide **204** in 77% yield, under the same conditions, **205** gave only 20% of acetamide **206**, along with alkene **207**. In the latter case it was suggested that a stable aziridinium compound **208** formed, which would not react easily with acetonitrile because of steric congestion.



Scheme 51. The Ritter reaction of several cyclic β-hydroxyamines.

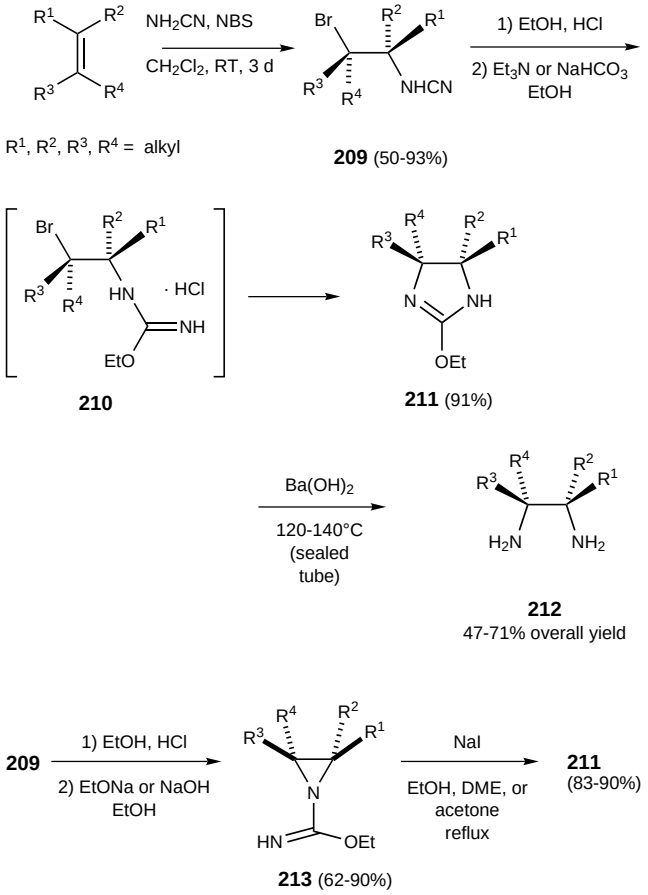
The opening of 2-oxazolines[103] or of serine-derived β-lactones[104] by amines has also been used to prepare 1,2-diamine derivatives.

4.4.2. Vicinal Diamines from β-Halogenoalkylamines

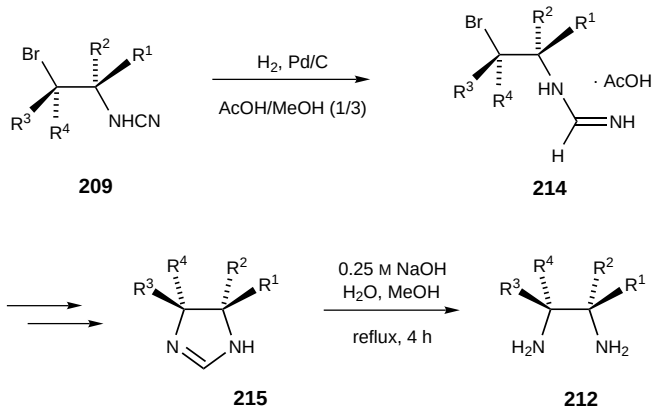
Several conditions can be employed to obtain β-halogenoalkylamines from alkenes; substitution of the halide by a nitrogen nucleophile then affords 1,2-diamine derivatives.

In 1983, Kohn and Jung described a method for the stereospecific preparation of nitrogen-unsubstituted vicinal diamines **212** as outlined in Scheme 52.[105] The first step was the addition of *N*-bromosuccinimide and cyanamide to an unactivated alkene to give a β-bromoalkyl cyanamide **209**. This adduct gave in situ the corresponding isourea **210** in an acidic ethanolic medium. Treatment of this compound with a mild base produced the 2-ethoxyimidazoline **211** directly. Basic hydrolysis in the last step then yielded the vicinal diamine **212** (overall yield: 47% to 71%). More basic conditions must be used to obtain compounds **211** from *Z* alkenes; in this case, aziridine **213** was isolated, and then rearranged to **211** in the presence of sodium iodide.

Less stringent conditions for both the cyclization and the final ring-cleavage steps were also developed by the use of formamidine **214** instead of isourea **210** (Scheme 53).[105] Amidine **214** was obtained without hydrogenolysis of the C–Br bond by catalytic hydrogenation of cyanamide **209**



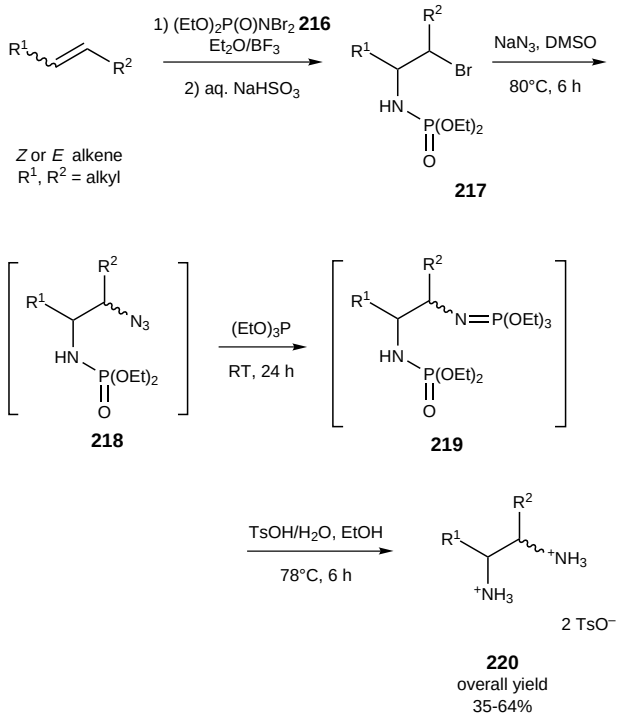
Scheme 52. Synthesis of vicinal diamines from alkenes and cyanamide.



Scheme 53. Modified procedure for the preparation of vicinal diamines from alkenes and cyanamide.

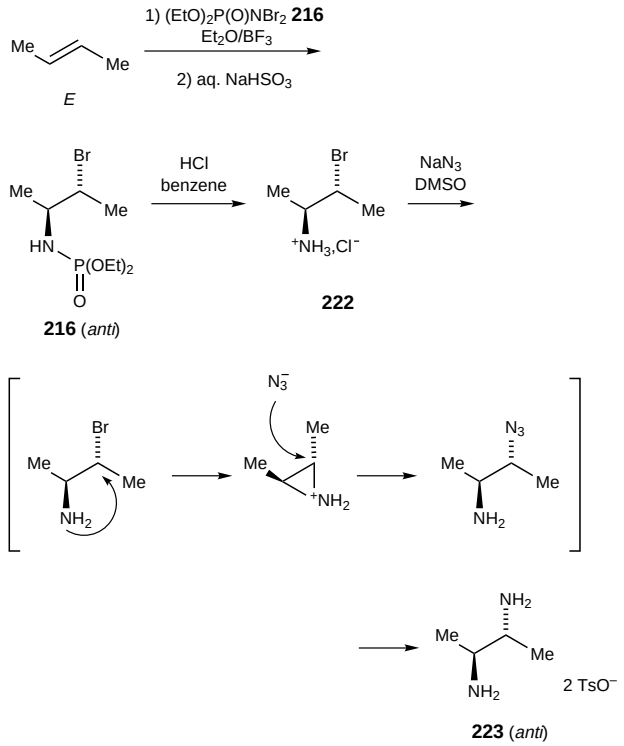
under acidic conditions with palladium on charcoal. Ring cleavage of the imidazoline **215** was then accomplished with diluted NaOH.

More recently, Zwierzak et al. reported an expedient synthesis of vicinal diamines from the bromophosphoramidates **217**, obtained by the reaction of alkenes and diethyl *N*,*N*-dibromophosphoramidate (**216**, Scheme 54).[106] Compounds **217** were converted to vicinal diamines by a one-pot procedure that involved the displacement of the bromide ion by sodium azide and the reduction of the azide in a Staudinger reaction.



Scheme 54. Synthesis of vicinal diamines from alkenes and a dibromophosphoramidate.

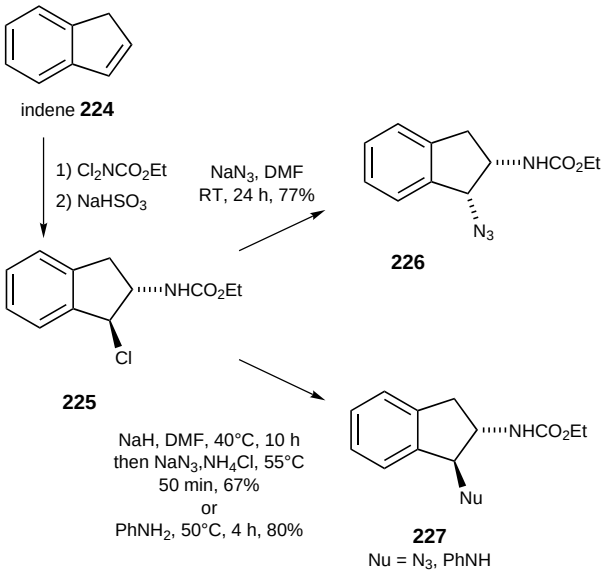
Diamination proceeded stereospecifically only with cyclic alkenes, to give *cis*-1,2-diamines. In the case of acyclic olefins, epimerization occurred, presumably in the azidation step with participation of the amidophosphoryl group. A modification consisting of the cleavage of the N–P bond prior to the azidation, as depicted in Scheme 55,[106] then led to a new



Scheme 55. Stereospecific synthesis of an acyclic *anti*-1,2-diamine from an *E* alkene

stereospecific diamination of open-chain olefins, with *syn*- and *anti*-1,2-diamines being obtained from *Z* and *E* alkenes, respectively. However, this strategy cannot be used in the case of sterically congested alkenes, which cannot undergo aminobromination.

Orlek reported an approach to the preparation of either *cis*- or *trans*-1,2-diamino derivatives of benzobicyclic compounds.[107] An example is described in the Scheme 56. The



Scheme 56. Diastereoselective synthesis of cyclic diamine derivatives.

trans-chloro carbamate **225** was obtained by the reaction of indene (**224**) with ethyl *N*,*N*-dichlorocarbamate, followed by cleavage of the N – Cl bond. The reaction of **225** with nitrogen nucleophiles then led to either *cis* adducts **226** or *trans* adducts **227**, depending on the conditions used.

Other selective syntheses of 1,2-diamines from β-halogenoamine derivatives have been described.[108]

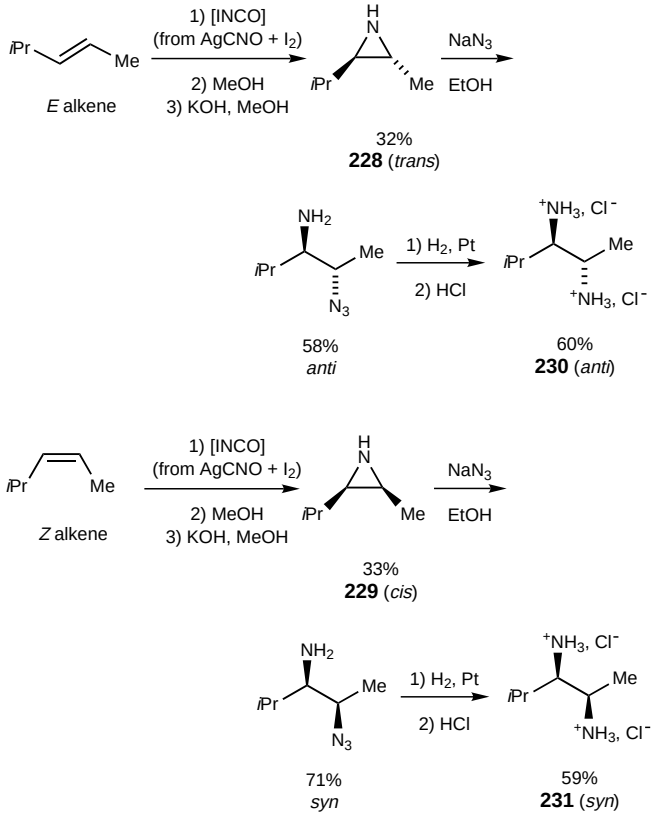
4.5. Vicinal Diamines from the Opening of Aziridines by Nitrogen Nucleophiles

Numerous methods have been reported for the preparation of aziridines.[109] Therefore, it is not surprising that many studies describe the stereoselective synthesis of vicinal diamines by the opening of aziridines by nitrogen nucleophiles. Some features must be kept in mind regarding this method:

1) N-unprotected aziridines can themselves act as nucleophiles and thus lead to the formation of oligomers or polymers.[110] Hence, it is necessary to protect them first, and two types of protected aziridines may be distinguished:
   - "nonactivated" aziridines, the nitrogen atom of which retains basic properties; their opening usually proceeds only after protonation, or quaternarization, or activation by a Lewis acid.
   - "activated" aziridines, in which the nitrogen atom is substituted by an electron-withdrawing group that can stabilize a negative charge, thus facilitating a nucleophilic opening.
2) The regioselectivity observed in the opening of a disubstituted aziridine may not be good, especially when the substituents are structurally close.

It must also be pointed out that although ways to obtain chiral, non-racemic aziridines have been described[109b, c] (from chiral epoxides,[111a, b] from chiral diols,[111c] or by using catalytic asymmetric aziridination of alkenes[58, 112]), none as yet are very general. Of the numerous examples described in the literature, only some significant ones will be detailed here.

In 1967, Swift and Swern[113] disclosed a strategy that provides access to either *syn*- or *anti*-1,2-diamines, and involves the aziridines, obtained from olefins, being opened by the azide ion (Scheme 57). Iodine isocyanate, generated in

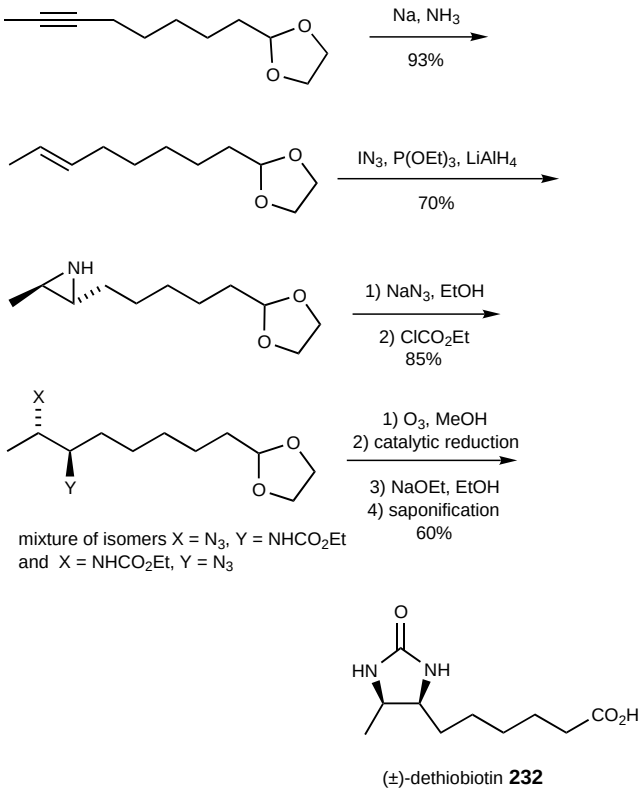


Scheme 57. Stereoselective synthesis of either *syn*- or *anti*-1,2-diamines from *Z* or *E* alkenes through aziridine opening.

situ from silver isocyanate and iodine, added stereospecifically to *Z*- or *E*-4-methyl-2-pentene, to yield *cis*-aziridine **228** and *trans*-aziridine **229**, respectively, after basic treatment. These were then converted into the corresponding diamine hydrochloride salts **230** and **231** by ring opening with the azide ion, followed by catalytic hydrogenation. Although the sequence is stereospecific, the overall yields are quite low: a ketone by-product may be formed during the reaction with iodine isocyanate by an elimination – hydrolysis mechanism.[114] Loss of product can also occur because of the volatility of aziridines and their solubility in water. A related method was applied successfully by Parry et al. to the

synthesis of racemic dethiobiotin **232**, the biological precursor of the vitamin biotin[115] (Scheme 58).

Several other nitrogen nucleophiles have been used instead of sodium azide (Scheme 59).[116] Thus, the opening of *N*-phthalimido-aziridines **233** by aniline,[117] and the ytterbium



Scheme 58. Diastereoselective synthesis of racemic dethiobiotin.

triflate catalyzed opening of N-protected aziridines **236** by amines[118] have been reported. Imidazole was recently shown to add to *N*-acylaziridines **238** under pressure, but modest yields of recovered products were obtained.[119] Aziridine-2-carboxylic esters **240** reacted regioselectively with azidotrimethylsilane, and also with acetonitrile, in the presence of BF_3;[120] in this case, imidazolines **242** were obtained as intermediates, and were then readily hydrolyzed. The reaction of azidotrimethylsilane with *N*-tosylaziridines **244**, catalyzed by an imidochromium species, has also been reported.[121]

The synthesis of a new chiral auxiliary, (1*R*,2*R*,3*R*,6*R*)-3,6-dimethylcyclohexane-1,2-diamine, involved the opening of a *N*-tosylaziridine with sodium azide.[122] Duréault et al.[123] had previously studied the reaction of the diaziridine **249** derived from D-mannitol with four equivalents of sodium azide (Scheme 60). In the absence of BF_3 the nucleophilic opening of one aziridine ring was followed by the intramolecular opening of the second ring, to yield the piperidine **248**. On the other hand, two intermolecular openings by sodium azide occurred in the presence of BF_3, probably because the negative charge of the intermediate amide that results from the first nucleophilic attack is partially masked. The bisazide **250** thus obtained was considered a precursor of *Nα*,*Nβ*-chemodifferentiated *α*,*β*-L-diaminopropionic acids such as **251**.

In 1990 Tanner et al.[124] performed the opening of the non-racemic aziridine **252**, derived from tartaric acid, with various nucleophiles, including sodium azide (Scheme 61). In the latter case, a direct precursor of vicinal diamines was thus obtained as a single adduct **253**, as a consequence of the C_2 symmetry of the substrate. As expected, the two ester groups and the tosyl moiety activate the aziridine.

The optically active aziridine **254** obtained by enzymatic transesterification was used by Fuji et al.[125] as the starting material in their study of both the intramolecular and the intermolecular opening of aziridines (Scheme 62). Treatment of the benzylcarbamate **255** by potassium *tert*-butylate led regioselectively to the corresponding 5-membered cyclic carbamate **256**. However, both regioisomers were formed from intermolecular opening of **257** by using various nucleophiles (Table 4). Lithium anilide gave the best regioselectivity although the chemical yield was not satisfactory in that case.

Table 4. Regioselective outcome in the opening of aziridine **257** with various nucleophiles.

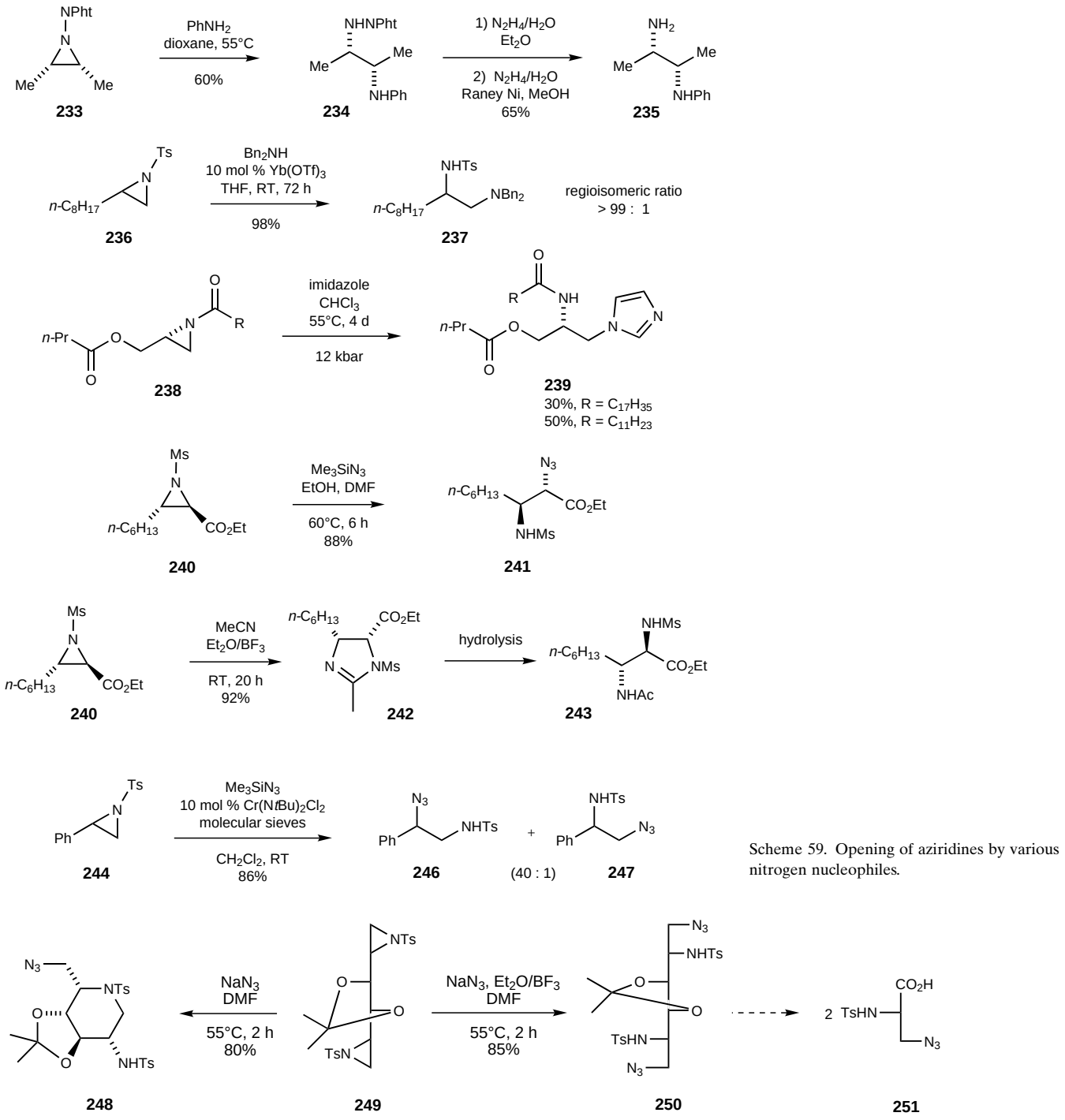
Entry	Nucleophile	Conditions			Yield (**258**) [%]	Yield (**259**) [%]
		solvent	*T*	*t*		
1	$PhNH_2$	–	rt	4 d	54	23
2	PhNHLi	THF	rt	12 h	43	7
3	NaN_3	DMF	50 °C	2 h	60	27
4	Me_3SiN_3	EtOH, DMF	80 °C	6 h	45	22

N-Nosylaziridines such as **260** were recently introduced as activated aziridine electrophiles by Maligres et al.[126] (Scheme 63). They were shown to be 50–60 times more reactive than *N*-tosylaziridines. The reaction of primary and secondary amines with a 2-phenyl-substituted aziridine was not regioselective, while only one regioisomer was obtained from 2-methyl-substituted aziridine **260**. Moreover, the deprotection of the *N*-nosyl group of adducts **261** was performed under mild conditions.

4.6. Vicinal Diamines from Electrophilic Amination

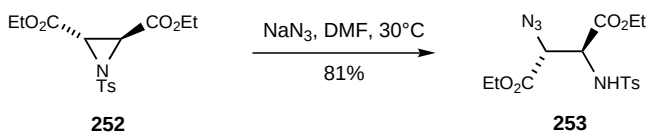
Electrophilic amination of *β*-amino enolates has been used for the preparation of several vicinal diamines. For instance, the C_2-symmetric (*R*,*R*)-2,3-diaminotetraline (**268**) was prepared by Gmeiner and Hummel[127] by the amination of a chiral *β*-amino ketone **265** with dibenzyl azodicarboxylate, which afforded the *trans* adduct **267** exclusively after reduction (Scheme 64). This compound was then transformed in a few steps into the target diamine. It remains to be seen if such selectivity can also be obtained when a similar reaction is performed with acyclic substrates.

Recently, Davies et al. described the preparation of (2*S*,3*S*)-2,3-diaminobutanoic acid by using the diastereoselective conjugate addition of lithium (*α*-methylbenzyl)benzylamide (**270**) to *tert*-butyl crotonate (**269**) as the first step (Scheme 65).[128] The direct trapping of the intermediate enolate by an electrophilic nitrogen source was not possible, so it was carried out in two steps. Thus, the enolate generated from **271** was treated with trisyl azide, to afford **273** as a single diastereomer, although with a low yield (32%). Reduction of



Scheme 59. Opening of aziridines by various nitrogen nucleophiles.

Scheme 60. Influence of $BF_3 \cdot OEt_2$ on the outcome of the opening of a bisaziridine derived from D-mannitol by sodium azide.



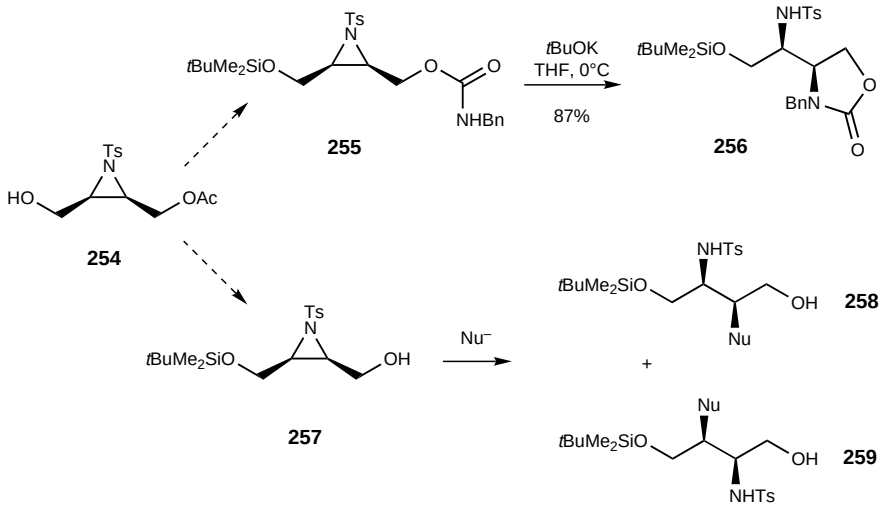
Scheme 61. Opening of an aziridine derived from tartaric acid by sodium azide.

the azide functional group, followed by several deprotections, led to (2*S*,3*S*)-**275**.

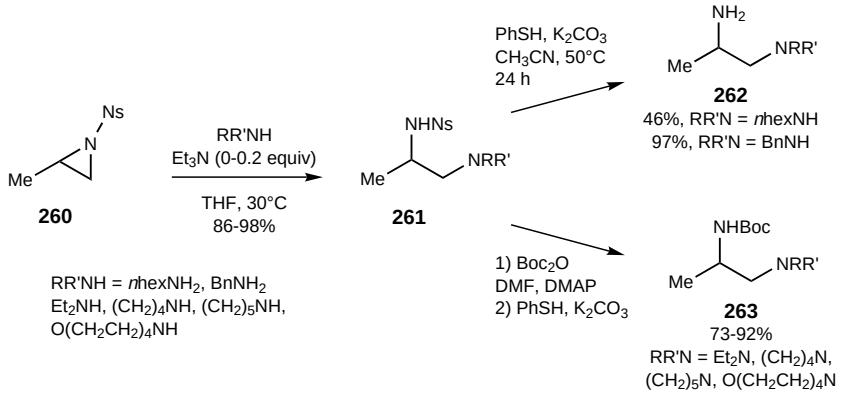
The reaction of *N*-(9-phenylfluoren-9-yl)aspartate enolates with electrophilic aminating agents was studied by Sardina et al.[129] This reaction allowed access to both *syn*- and *anti*-2,3-diaminosuccinic acid derivatives. It was not possible to prepare selectively the *syn* adducts, but highly *anti*-selective conditions were obtained by using either di-*tert*-butyl or dibenzyl azodicarboxylate as the electrophile.

4.7. Vicinal Diamines from Carbon – Carbon Bond Cleavage

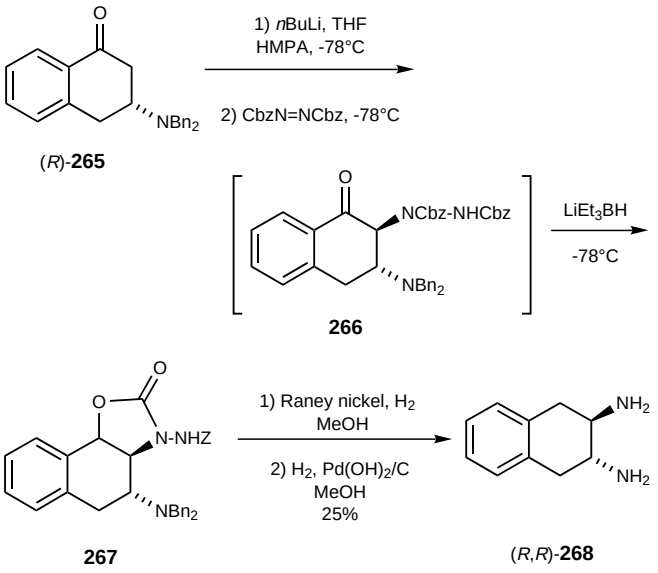
Several degradative rearrangements involve the breaking of a carbon – carbon bond and the formation of a carbon – nitrogen bond; when applied to compounds already having



Scheme 62. Intramolecular versus intermolecular opening of chiral aziridines: influence on the regioselectivity of the opening.



Scheme 63. Synthesis of 1,2-diamines from an *N*-nosylaziridine.



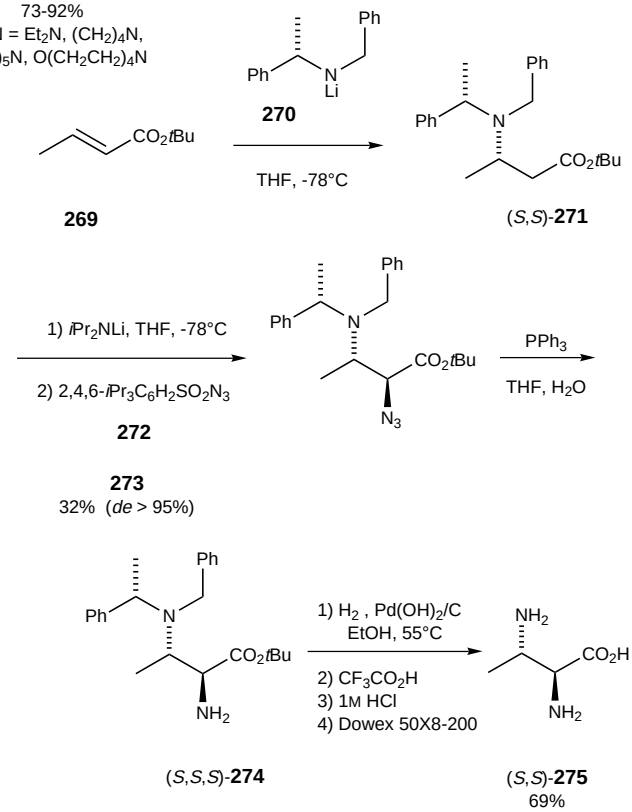
Scheme 64. Synthesis of (*R*,*R*)-2,3-diaminotetraline by the electrophilic amination of a chiral β-amino ketone.

a nitrogen function they lead to 1,2-diamine derivatives. Indeed, such products have been prepared by the Curtius,[130] Hofmann,[104, 131a] Schmidt,[131a, b] and Beckmann[131c–e] rearrangements (Scheme 66). Shioiri et al.[130g] synthesized L-diaminopropanoic acid derivative **277** by using a modified Curtius reaction of acid **276** with diphenyl phosphorazidate, followed by deprotection and protection steps. The compound **277** was then utilized in a synthesis of cyclotheonamide B, a macrocyclic thrombin inhibitor. Stetter et al.[131a] synthesized 1,2-adamantanediamine (**279**) by a Hofmann rearrangement and 1,2-noradamantanediamine (**281**) by a Schmidt rearrangement.

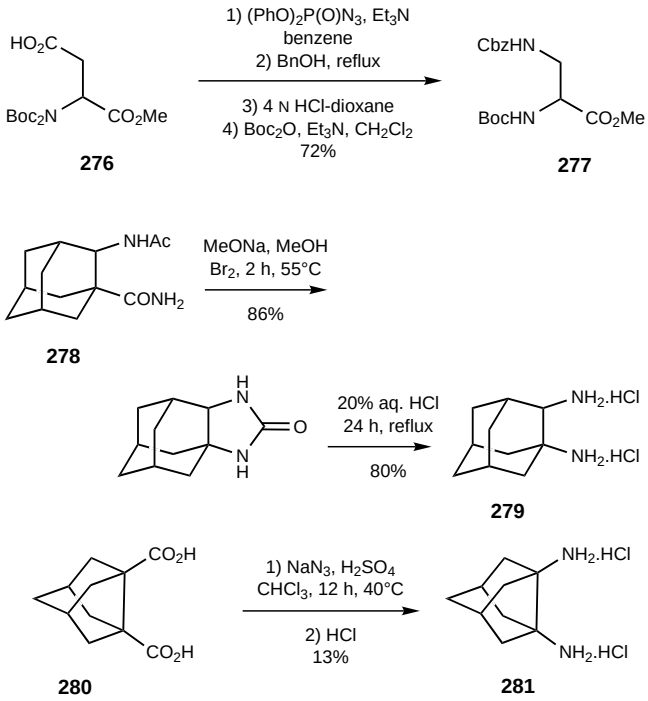
4.8. Vicinal Diamines from Activated β,γ-Unsaturated Amines

The double bond of β,γ-unsaturated amines may be activated by palladium or iodine to undergo the nucleophile additon of a nitrogen group.

For instance, Cardillo et al.[132] described the preparation of monosub-

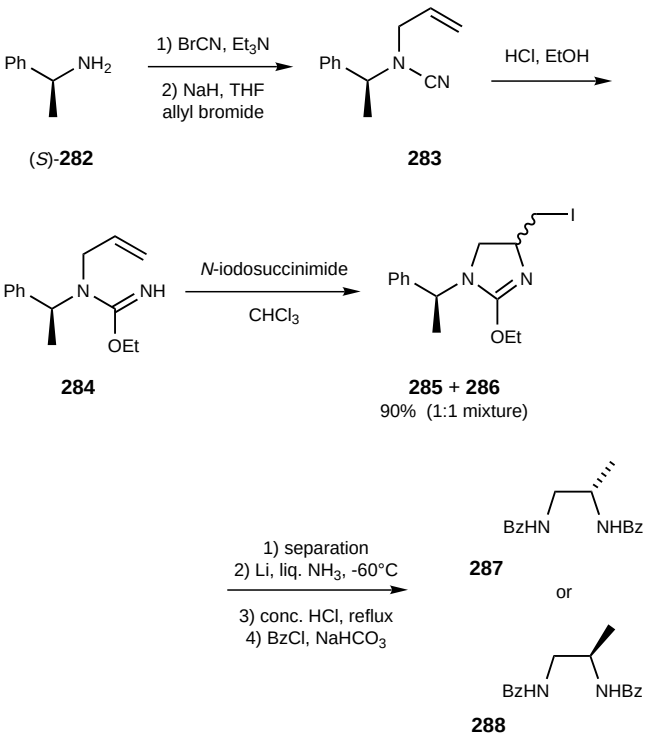


Scheme 65. Preparation of a 2,3-diaminocarboxylic acid through a diastereoselective conjugate addition.



Scheme 66. Examples of rearrangements used in the synthesis of 1,2-diamines.

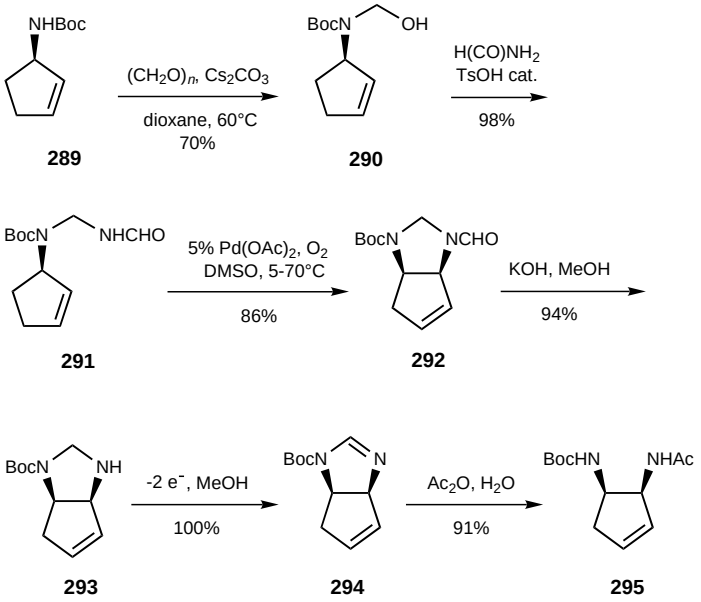
stituted, chiral 1,2-diamines that used the iodofunctionalization of isourea **284** derived from (*S*)-1-phenylethylamine (**282**) as the key step (Scheme 67). The cyclization was not stereoselective, but the two imidazolines **285** and **286** obtained were then separated easily by chromatography. After reduction of the chiral auxiliary with metallic lithium and hydrolysis



Scheme 67. Imidazolines as intermediates in the synthesis of monosubstituted vicinal diamines.

of the imidazolines, the corresponding enantiomeric diamines were obtained, which were isolated as benzamides **287** and **288**.

The palladium(II) catalyzed oxidative cyclization of various allylic aminals to imidazolidines was also reported recently by Hiemstra, Speckamp et al.[133] It was shown that aminals derived from formamide were the most successful nucleophiles. In acyclic compounds, a moderate stereoselectivity was observed, while only *cis*-substituted heterocycles were obtained from cyclopentenylamine-derived aminals such as **291** (Scheme 68). The conversion of the imidazolidine **292** into the



Scheme 68. Synthesis of a cyclic vicinal diamine from an imidazolidine obtained by oxidative cyclization of an allylic aminal.

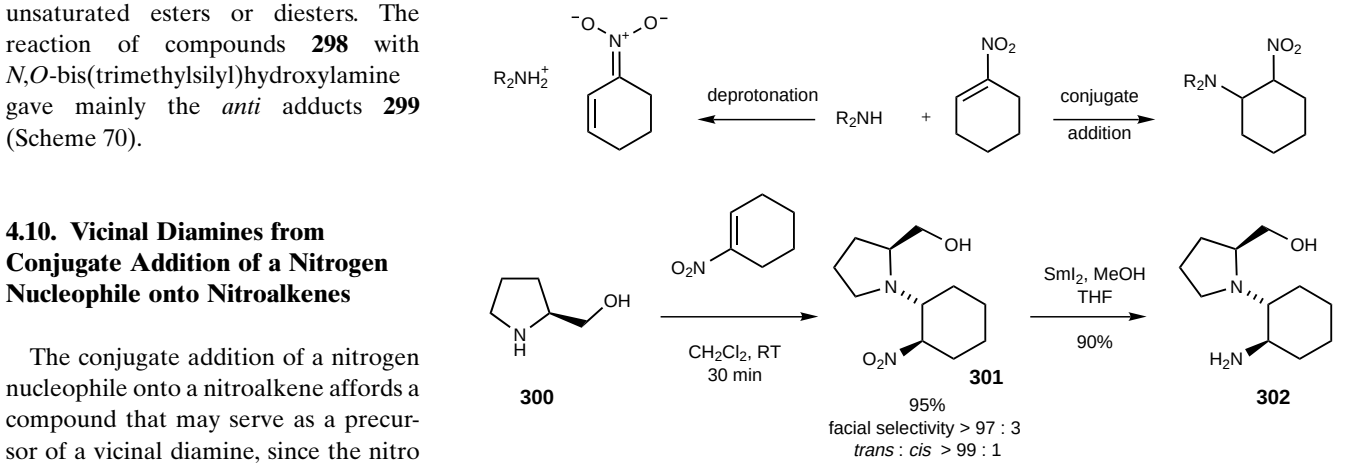
protected vicinal diamine **295**, which included the deformylation of **292**, the electrochemical oxidation of the obtained imidazolidine **293** to imidazoline **294**, and the hydrolytic cleavage of the latter, was described.

In 1993 Ernst and Bellus et al.[134a] reported an elegant way to prepare 1,2-diamines, based on the [3,3]sigmatropic rearrangement of allylic trichloroacetamidates **296** derived from α-amino acids. Under palladium(II)-catalyzed conditions, the aza–Claisen type rearrangement proceeded with a complete chirality transfer, to afford only the corresponding *anti* diastereomer (Scheme 69). Although the yields of adducts **297** were only moderate (43–62%), the excellent diastereoselectivity observed makes this method very attractive and was applied to the synthesis of (2*S*,3*S*)-diaminobutanoic acid. A similar rearrangement was described in the same year by Doherty et al.[134b]

4.9. Vicinal Diamines from β,γ-Unsaturated Amines Activated by an Electron-Withdrawing Group

Aminodeoxystatine was prepared by the nonstereoselective conjugate addition of ammonia to an α,β-unsaturated ester that is γ-substituted by a protected amino group.[12b] More recently, it has been shown by Reetz et al.[135] that nitrogen nucleophiles with a N–O bond add stereoselectively to α,β-

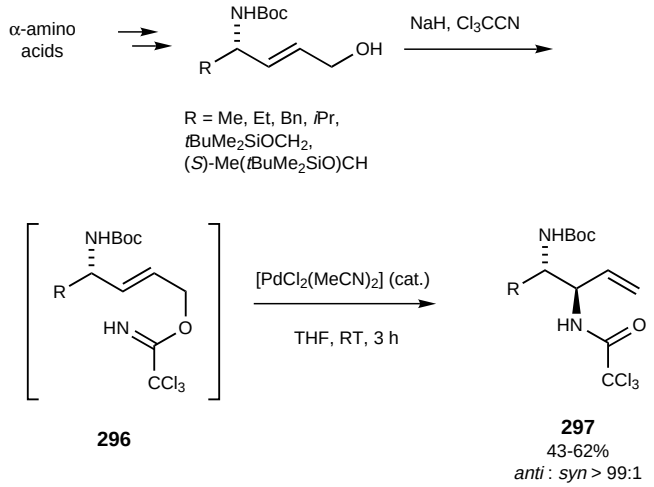
unsaturated esters or diesters. The reaction of compounds **298** with *N,O*-bis(trimethylsilyl)hydroxylamine gave mainly the *anti* adducts **299** (Scheme 70).



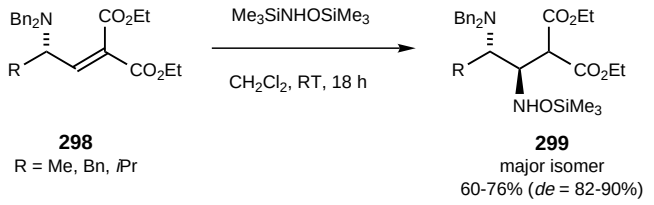
Scheme 71. Diastereoselective addition of (*S*)-2-pyrrolidinemethanol to 1-nitrocyclohexene.

4.10. Vicinal Diamines from Conjugate Addition of a Nitrogen Nucleophile onto Nitroalkenes

The conjugate addition of a nitrogen nucleophile onto a nitroalkene affords a compound that may serve as a precursor of a vicinal diamine, since the nitro group can be reduced to an amine by a variety of reagents. The stereochemical outcome of the addition of amines to (2-nitropropenyl)benzene was studied by Southwick and Anderson,[136] who reported that the *syn* adducts were formed predominantly under thermodynamic conditions. In recent years, several groups used chiral nitrogen nucleophiles, with the aim to design a synthetic route to diastereo- and enantiomerically pure vicinal diamines.



Scheme 69. *Anti*-selective [3,3]sigmatropic rearrangement of allylic trichloroacetamidates derived from α-amino acids.

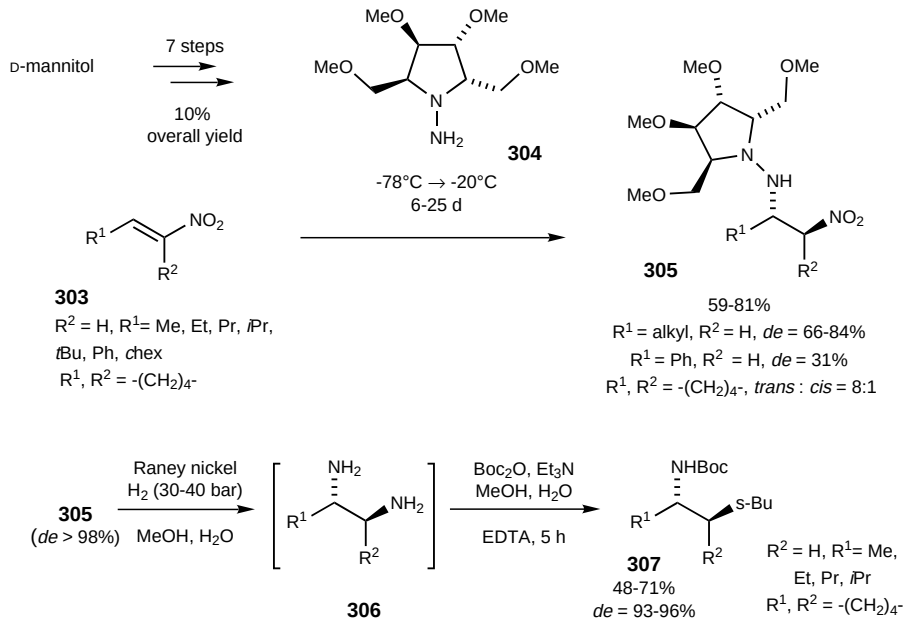


Scheme 70. Diastereoselective conjugate addition of *N,O*-bis-(trimethylsilyl)hydroxylamine on α,β-unsaturated diesters derived from α-amino acids.

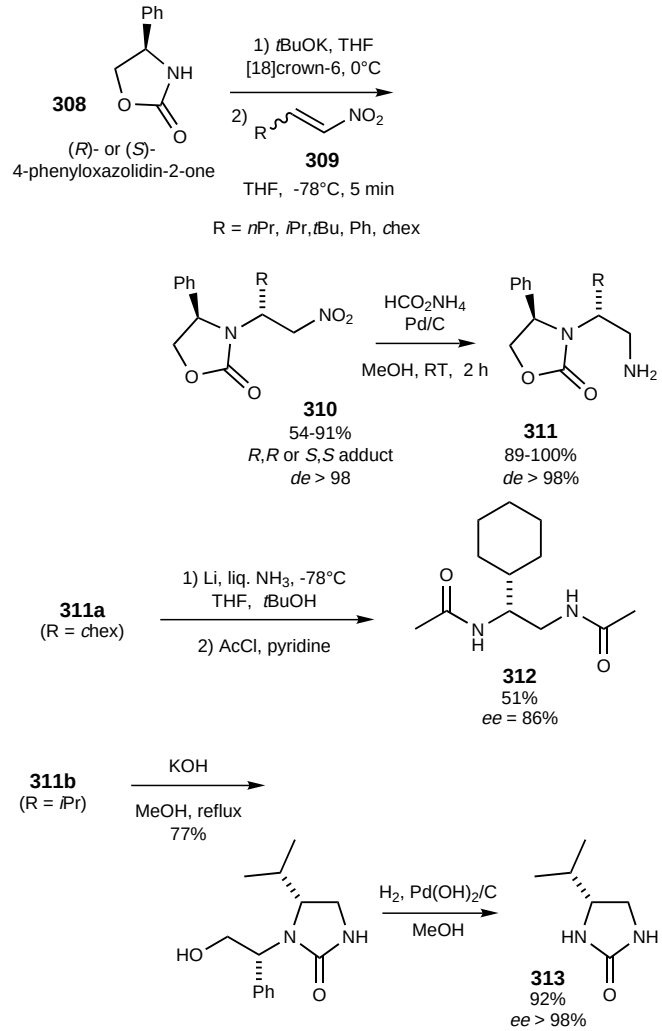
The reaction of various chiral amines with nitroalkenes was evaluated by Sturgess et al., who showed that β-amino alcohols reacted faster than monofunctional amines.[137a] Depending on the nucleophile used, either conjugate addition or deprotonation was observed (Scheme 71). The addition products were often found to be unstable, since they slowly underwent retroaddition at room temperature. However, the reaction of (*S*)-2-pyrrolidinylmethanol (**300**) with 1-nitrocyclohexene afforded a single adduct **301** in both excellent stereoselectivity and yield; its nitro group was then reduced with samarium diiodide in methanol, under conditions that prevent epimerization.[137b]

A related approach was recently published by Enders et al. (Scheme 72).[138] The chiral, C_2-symmetric *N*-aminopyrrolidine **304** derived from D-mannitol was used as the nitrogen nucleophile. It reacted slowly with nitroalkenes at $-20\,^{\circ}C$ in diethyl ether to afford the corresponding adducts **305** with good stereoselectivity ($de = 66-84\,\%$), except in the case of β-nitrostyrene ($de = 31\,\%$). The *trans* adduct was obtained preponderantly from 1-nitrocyclohexene. In most cases, the major isomers were isolated by column chromatography, which had to be performed on deactivated silica gel in order to avoid a degradation of the products by a retro-Michael addition. The adducts **305** were then transformed into the corresponding vicinal diamines **306** in a single step by treatment with hydrogen in the presence of Raney nickel, which reduced the nitro group and cleaved the N–N bond. The Boc-protected diamines **307** were eventually obtained with enantiomeric excesses ranging from 93 to 96 % and with good overall yields (48–71 %). Thus, diastereo- as well as enantioselective access to vicinal diamines is made possible by this method. It still suffers from several drawbacks: the chiral auxiliary is available only as one optical form and its synthesis is lengthy (seven steps from D-mannitol); also, 6 to 25 days are necessary to get the addition to completion.

We recently reported a study on the conjugate addition of the potassium salt of 4-phenyl-2-oxazolidinone (**308**) to monosubstituted nitroalkenes (Scheme 73).[139] This nucleophile was chosen for the following reasons: it is commercially available in both enantiomeric forms, or can be synthesized easily; the adducts were expected to be less prone to β-elimination than β-aminonitroalkanes, since the nitrogen atom would not be basic; the heterocycle could be cleaved easily to generate the amino group; furthermore, we thought that it could give high levels of asymmetric induction. We found that the potassium salt of (*R*)- or (*S*)-**308** added very rapidly to nitroalkenes at $-78\,^{\circ}C$. In all cases, the adducts **311**



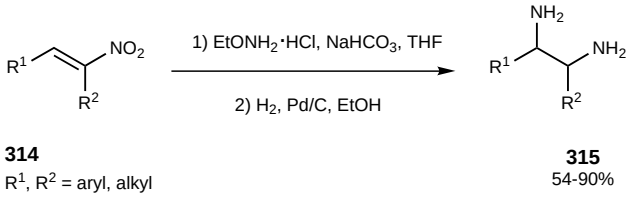
Scheme 72. Diastereoselective conjugate addition of a chiral aminopyrrolidine derived from D-mannitol to various nitroalkenes; enantioselective synthesis of vicinal diamines.



Scheme 73. Diastereoselective addition of (*R*)- or (*S*)-4-phenyl-2-oxazolidinone to monosubstituted nitroalkenes; enantioselective syntheses of protected vicinal diamines.

were obtained with excellent diastereoselectivity, only one isomer being observed in the ^{1}H and ^{13}C NMR spectra. The first examples were carried out in the presence of [18]crown-6; we have recently shown that, while the crown ether accelerates the reaction, it has no effect on the stereochemical outcome. Two of these stable adducts were converted into amines **311**, which are protected forms of vicinal diamines, by using a catalytic hydrogen-transfer reduction of the nitro group. The oxazolidinone moiety of **311a** was cleaved by reduction with lithium in liquid ammonia, to form an acyclic diamine which was isolated as the bisacetamide **312** (*ee* = 86%). In an other example, the basic treatment of **311b** followed by hydrogenolysis afforded the optically pure imidazolidinone **313**.

A one-pot preparation of racemic 1,2-diamines from nitroalkenes recently reported by Mukaiyama et al.[140] is also worthy of note. The adducts obtained from the addition of *O*-ethylhydroxylamine to nitroolefins **314** were reduced directly under hydrogen in the presence of palladium on carbon (Scheme 74). The yields of the diamines **315** ranged from 54 to 90%; *cis-trans* mixtures were obtained from cyclic substrates.



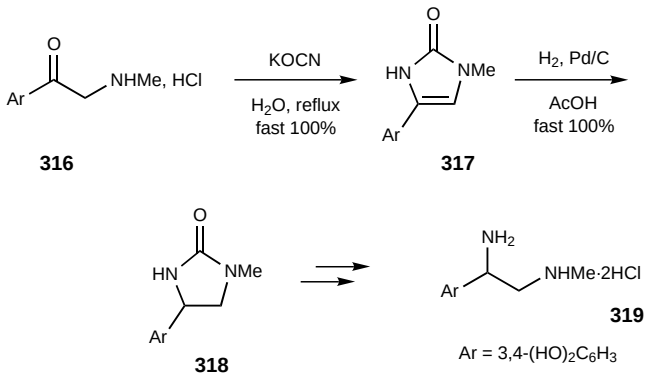
Scheme 74. One-pot preparation of 1,2-diamines from nitroalkenes.

4.11. Vicinal Diamines from α-Amino Ketones or α-Amino Aldehydes

Two widely used methods, the reductive amination and the Strecker condensation, allow the amine groups to be obtained from aldehydes or ketones. When applying these methods to α-amino ketones, products having a 1,2-diamine moiety are thus obtained.

4.11.1. Reductive Amination

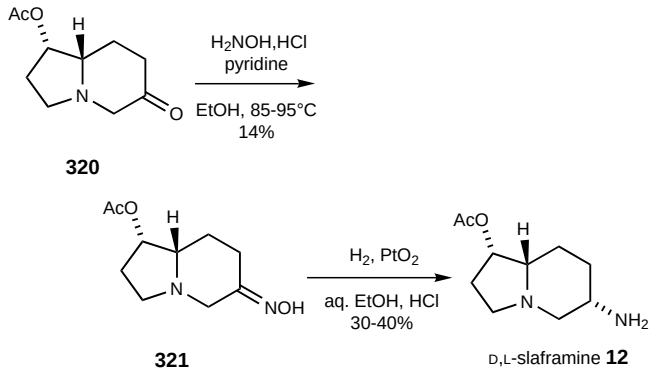
In 1947 Duschinsky et al.[141] described the synthesis of amino analogues of adrenaline, arterenol, and ephedrine from α-amino ketones (Scheme 75). For example, the reaction of potassium cyanate with adrenalone hydrochloride (**316**) in water afforded the imidazolinone **317**, which was then reduced



Scheme 75. Synthesis of an amino analogue of adrenaline.

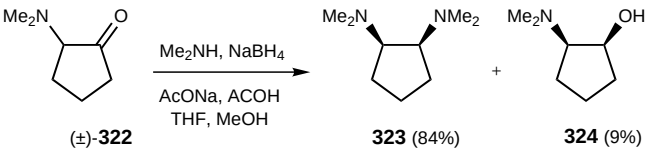
to the corresponding imidazolidinone **318**. The later was then transformed in a few steps into the vicinal diamine **319**.

In the last step of their synthesis of the alkaloid D,L-slaframine, Gensler and Hu[142] utilized the hydrogenation of the oxime **321**, derived from the corresponding ketone **320**, to introduce the amino group stereoselectively, although in low yield (Scheme 76).



Scheme 76. Synthesis of D,L-slaframine by the catalytic hydrogenation of an oxime.

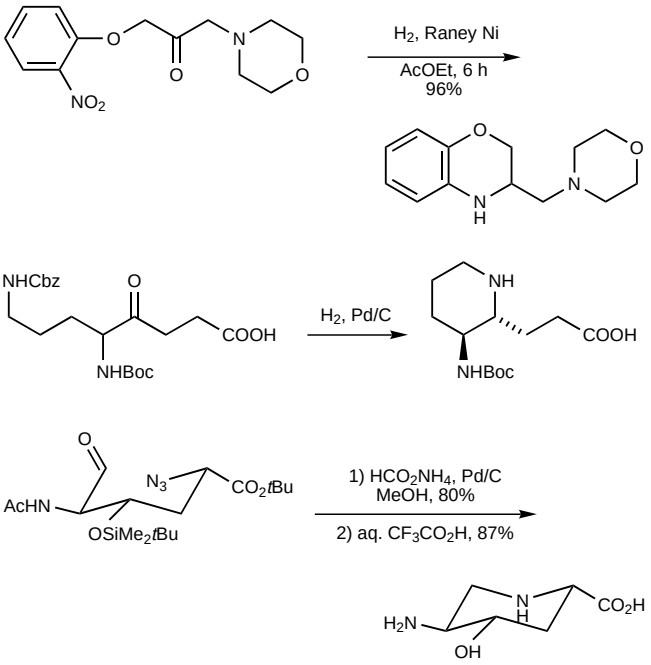
The reductive amination of 2-(dimethylamino)cyclopentanone (**322**) with dimethylamine and sodium borohydride was shown by Fraenkel and Pramanik[143] to give the *cis*-1,2-diamine **323** selectively (Scheme 77). Some amino alcohol



Scheme 77. Stereoselective synthesis of 1,2-bis(dimethylamino)-cyclopentane by reductive amination.

324, which results from the reduction of the ketone, was also obtained in this reaction. The amount of this by-product was lowered by employing a slow addition of the reducing agent.

Several intramolecular reductive aminations that lead to various nitrogen-containing heterocycles have also been reported. In these methods, the amino group that condenses with the carbonyl function may be generated by reduction of a nitro group[144] by reductive cleavage of a protecting group,[145] or by reduction of an azido group[146] (Scheme 78); the other



Scheme 78. Synthesis of 1,2-diamines by intramolecular reductive amination.

amino function must be either substituted or masked by a protecting group stable under these conditions.

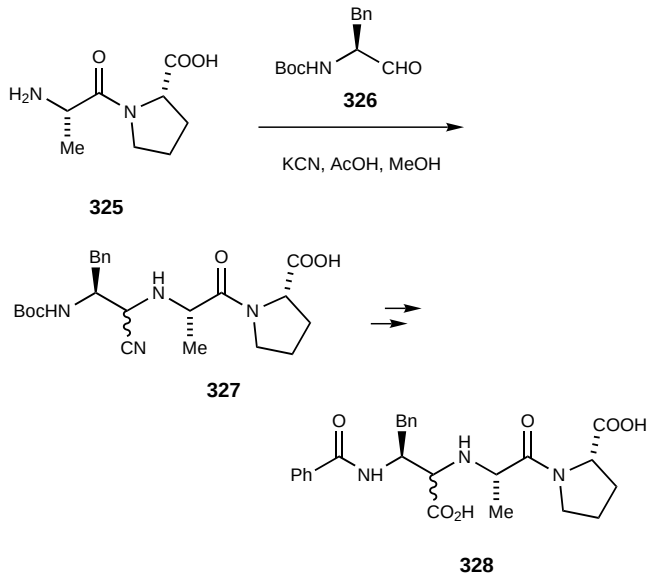
An enantioselective access to 1,2-diaminocyclohexanes was also reported by Schlichter and Frahm,[11k] who used (*S*)-α-methylbenzylamine in the reductive amination step.

4.11.2. Strecker Condensations

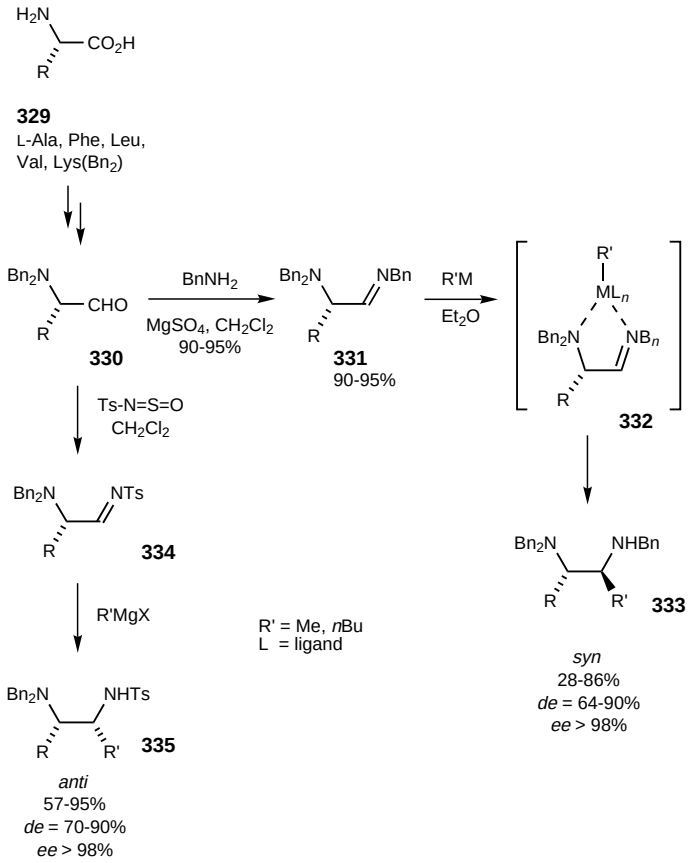
To introduce a carbon atom and a nitrogen atom simultaneously from a carbonyl compound, one can use the Strecker condensation or the related Bucherer–Berg reaction; in the latter case an hydantoin is formed. Both reactions have been applied to the synthesis of products containing nitrogen functionalities on vicinal carbon atoms of α-amino ketones.[147] Greenlee et al.[148] prepared several analogues of the angiotensin-converting enzyme inhibitor enalapril, such as **328**, by a Strecker reaction. The condensation of dipeptide **325** with the porotected α-amino aldehyde **326** afforded compound **327** as a mixture of two epimers (Scheme 79).

4.12. Vicinal Diamines from α-Amino Imines, α-Amino Oximes, or α-Amino Hydrazones

Reetz et al.[149] have developed an approach to the synthesis of vicinal diamines based on the stereoselective alkylation of imines derived from *N*,*N*-dibenzylamino aldehydes **330**, which were obtained from α-amino acids **329** (Scheme 80). A survey of the addition of various organometallic reagents to *N*-benzylimines **331** in diethyl ether showed that the combinations

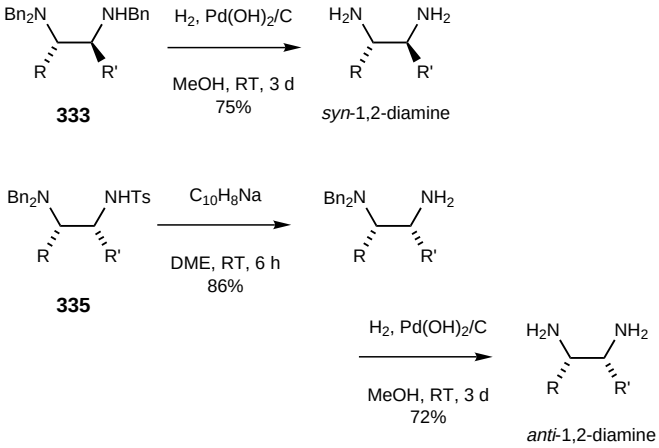


Scheme 79. Synthesis of a 1,2-diamino compound through a Strecker condensation.



Scheme 80. Synthesis of either *syn*- or *anti*-1,2-diamines by alkylation of chiral imines derived from α-amino acids.

*n*BuLi/$CeCl_3$ and 3 MeLi/$CeCl_3$ were the most effective, in terms of both yield and selectivity. Moreover, the addition proceeded without any racemization. To explain the observed *syn* selectivity, the authors postulated the intermediacy of chelates **332**, which would be attacked preferentially from the less hindered face, to give the *syn* adducts **333**. With the aim to reverse the diastereoselectivity, other substrates such as **334** that have a tosyl group instead of the benzyl group were alkylated with Grignard reagents. The electron-withdrawing substituent was expected to reduce the donor strength of the aldimine nitrogen atom and prevent chelation from occurring. Indeed, *anti* adducts **335** were then obtained selectively. The pure diamines were then recovered under conditions that prevented any racemization from occurring (Scheme 81). This

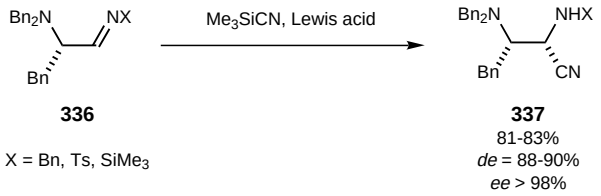


Scheme 81. Preparation of unprotected *syn*- or *anti*-1,2-diamines; cleavage of protecting groups.

method allows the preparation of either (*S*,*R*)- or (*S*,*S*)-diamines from a (*S*)-α-amino acid. While the diastereoselectivity of the alkylations is not complete (> 90 %), this strategy is still very efficient when the target diamine can derive from a natural α-amino acid.

Alkylation of imines derived from α-amino acids has been performed by Laschat et al. by using an hetero–ene reaction.[150]

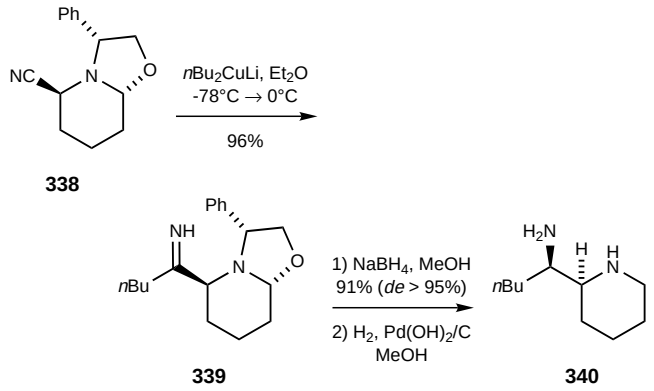
The Lewis acid promoted addition of trimethylsilylcyanide to *N*-benzyl, *N*-tosyl, and *N*-silyl aldimines **336** was also studied by Reetz et al. (Scheme 82).[151] Conditions were



Scheme 82. Addition of trimethylsilylcyanide to chiral imines derived from an α-amino acid.

found that yield selectively the nonchelation-controlled adducts **337**, but an optimization had to be carried out for each substrate.

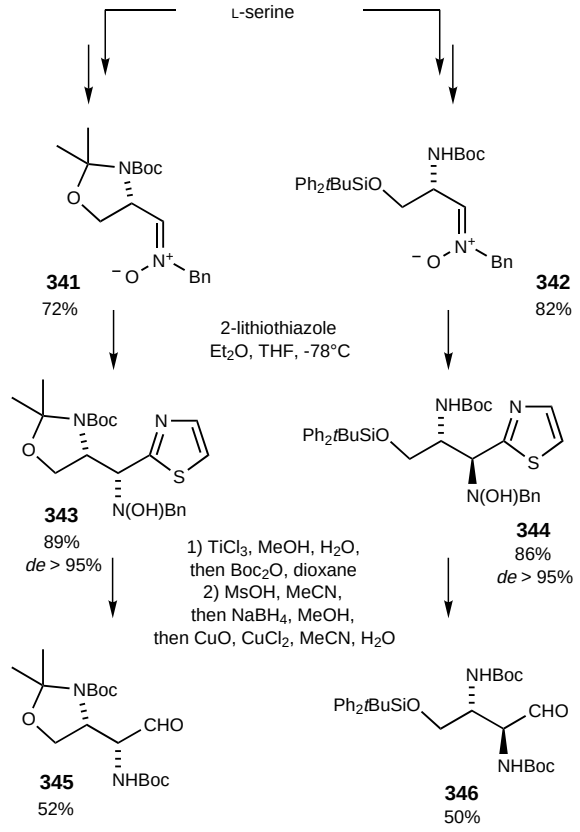
The reduction of imines, which are formed from the alkylation of α-amino nitriles, can be employed to prepare 1,2-diamines. An example of such process has been reported by Husson et al. (Scheme 83).[152a] Imine **339**, obtained from the versatile synthon **338**,[152b] was reduced with high stereoselectivity by sodium borohydride. After cleavage of the



Scheme 83. Preparation of a 1,2-diamine by reduction of an α-amino imine.

chiral auxiliary the 1,2-diamine **340** was obtained. The diamine was then used to prepare an analogue of the alkaloid tetraponerine.

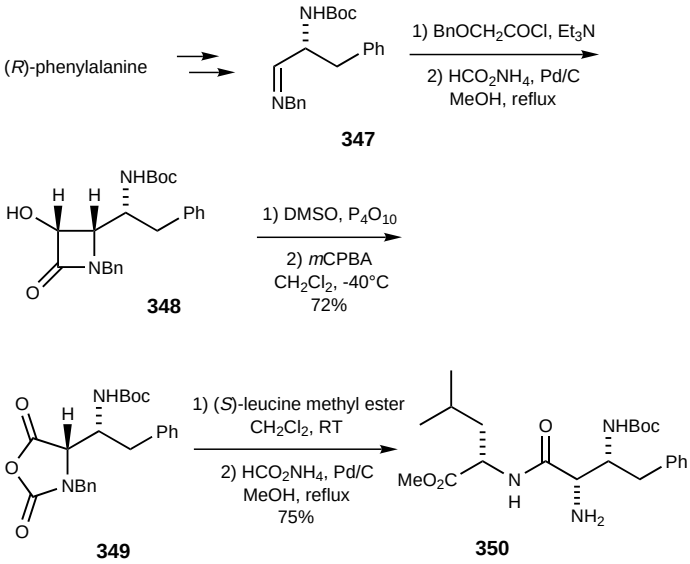
Nitrones derived from α-amino acids can also be used as diamine precursors, as demonstrated by Dondoni, Merino et al.,[153a] who designed a route to both C2 diastereomers of 2,3-diamino-4-hydroxybutanals. Their strategy was based on the addition of 2-lithiothiazole, a nucleophilic aldehyde synthetic equivalent, on differently protected L-serine-derived nitrones **341** and **342** (Scheme 84). While an *anti* selectivity was observed in the addition to the straight chain substrate, to give **343**, the opposite selectivity resulted from the addition to the cyclic substrate **342**. The difference in selectivity was explained by different reactive conformations of the nitrones in the postulated modified Felkin–Anh transition state model. Conversion of the adducts into either protected *syn*- or *anti*-diamino aldehydes **345** and **346**, which are useful synthetic chirons, included $TiCl_3$-mediated hydroxylamine cleavage and a standard sequence to generate the aldehyde function from the thiazolyl group.



Scheme 84. Synthesis of either *syn*- or *anti*-1,2-diamines from L-serine through the addition of 2-lithiothiazole to differently protected nitrones.

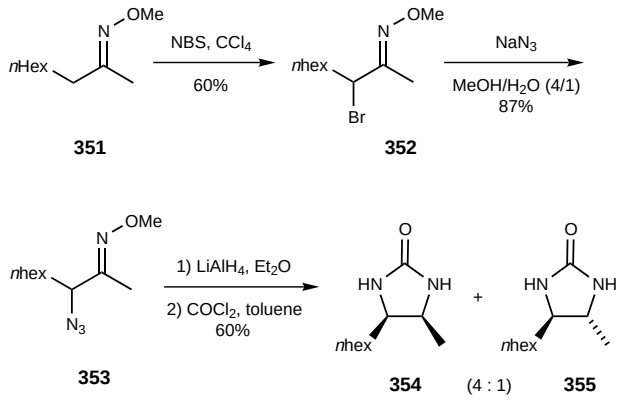
Other nucleophiles, such as Grignard reagents[153b–d] or lithium acetylides,[153e] have been added to α-amino nitrones. Merino et al. described the synthesis of (2*S*,3*R*)- and (2*S*,3*S*)-2,3-diaminobutanoic acids from nitrones **341** and **342**, respectively,[153b] and the synthesis of several vicinal diamines, with *syn* selectivity, with nitrones derived from L-alanine, L-valine, and L-phenylalanine.[153d]

Another use of imines derived from α-amino acids in the synthesis of diamines (Scheme 85) was reported by Palomo et al.[154] The cycloaddition of the imine **347**, obtained from (*R*)-phenylalanine methyl ester, with the ketene, generated from benzyloxyacetyl chloride, proceeded with complete stereoselectivity. After cleavage of the C2–C3 bond of the β-lactam **348**, achieved through an efficient oxidative sequence, the treatment of the obtained *N*-carboxyanhydride **349** with (*S*)-leucine methyl ester, followed by removal of the *N*-benzyl group, afforded **350**, a protected form of amino-deoxybestatine.



Scheme 85. Stereoselective synthesis of a 1,2-diamine derivative from an imine by stereoselective β-lactam formation.

Shatzmiller and Bercovici[155] used the displacement of α-bromo oxime ethers **352** by sodium azide, followed by exhaustive reduction of the adducts **353** by lithium aluminium hydride to selectively prepare *anti* diamines, which were then separated as their imidazolidinones **354** (Scheme 86). The intermediacy of a 5-membered complex formed at first between aluminum and the amino oxime was proposed to account for the *anti* selectivity of the reduction. A similar approach has recently been described by De Kimpe and D'Hondt.[156]

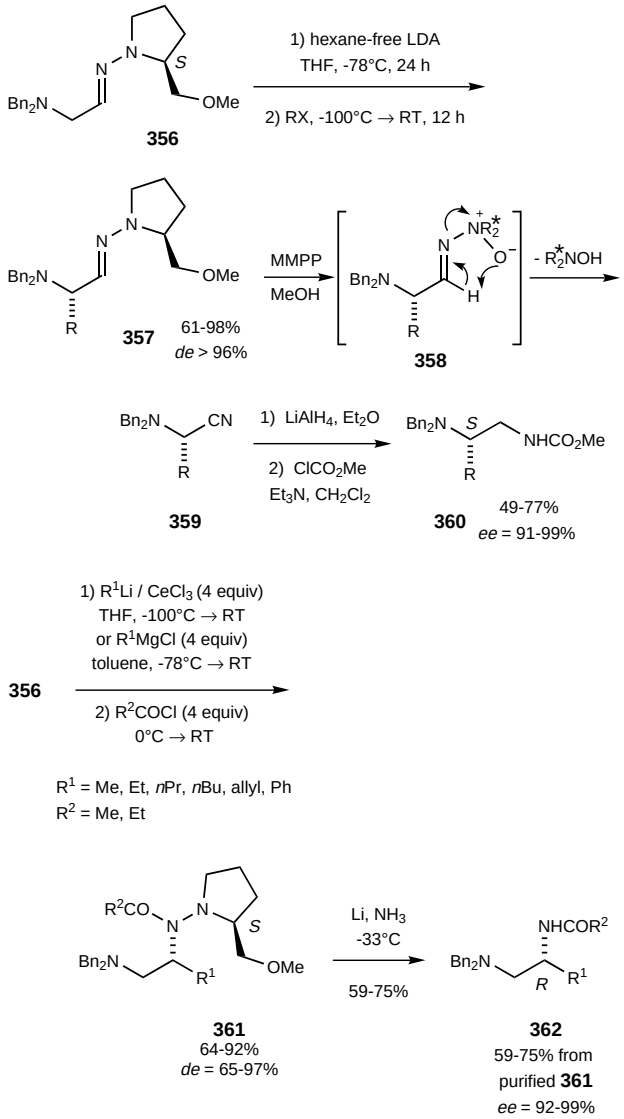


Scheme 86. Synthesis of *cis*- and *trans*-imidazolidin-2-ones, precursors of 1,2-diamines, from an oxime ether.

Two methods for the enantioselective synthesis of monosubstituted vicinal diamines that make use of dibenzylaminoacetaldehyde SAMP-hydrazone (**356**) were recently reported by Enders et al.[157] (Scheme 87). Thus, in the first method,[157a] the anion generated from the chiral hydrazone was treated with various alkyl, allyl, or benzyl halides to afford the corresponding adducts **357**, essentially as one diastereomer ($de > 96\,\%$). To get complete deprotonation of the hydrazone, hexane-free LDA must be used, and the reaction mixture must be kept at $-78\,^{\circ}C$ for 24 hours. Also, purification of the adducts must be performed on a deactivated silica gel to avoid epimerization. After a short reaction sequence, that involved the conversion of the hydrazone into a nitrile **359** by an aza–Cope elimination, differently protected diamines **360** were then obtained ($ee = 91-99\,\%$).

The second method[157b] is based on the 1,2-addition of alkyl cerium compounds or Grignard reagents to the hydrazone **356**, which led selectively, after reaction with an acyl chloride, to the N-protected hydrazines **361** ($de = 65-97\,\%$). It is presumed that one equivalent of the organometallic reagent coordinates both the methoxy group and the nitrogen atom of the auxiliary, and that excess reagent then adds to the *re* face. Reductive cleavage of the N–N bond of the purified major isomers afforded, without much racemization, the differently protected vicinal diamines **362** ($ee = 92-99\,\%$).

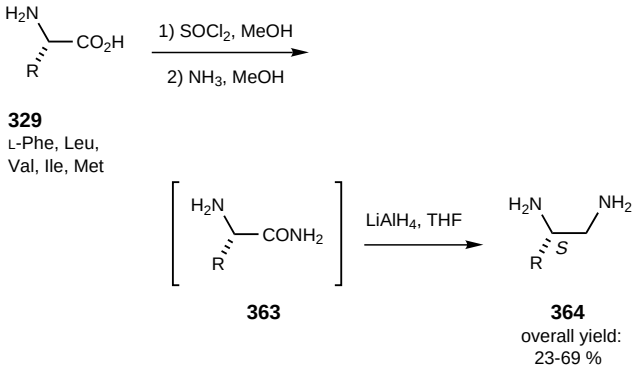
The combination of these two methods could result in the design of a quite general stereoselective access to 1,2-disubstituted 1,2-diamines.



Scheme 87. Enantioselective synthesis of monosubstituted 1,2-diamines from a chiral amino hydrazone.

4.13. Vicinal Diamines by Reduction of α-Amino Amides or α-Amino Nitriles

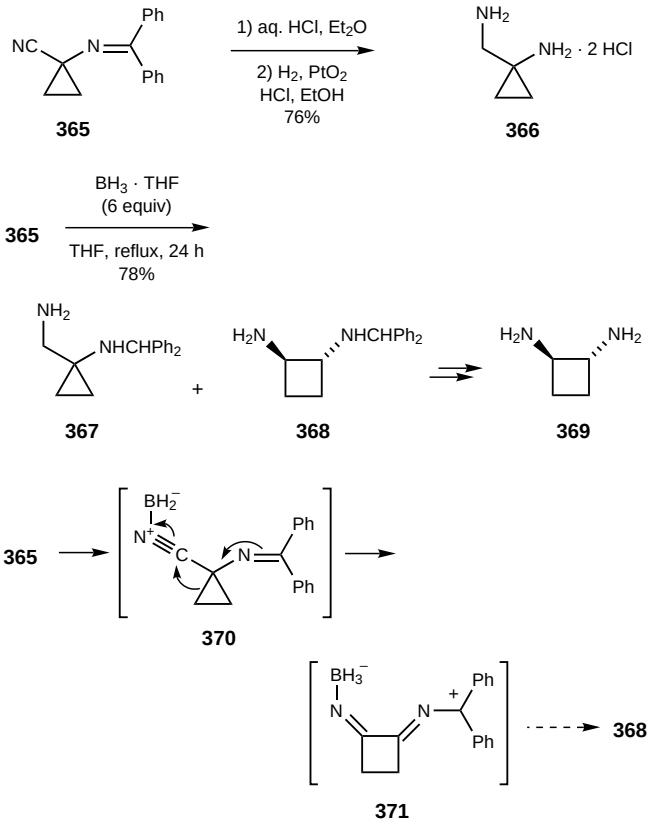
The reduction of amides derived from natural α-amino acids is a convenient way to obtain monosubstituted, vicinal diamines.[158, 43d] For example, Brunner et al. synthesized diamines **364** in this manner with high enantiomeric purity (Scheme 88).[158b] They were then used as ligands in platinum complexes that caused inhibition of DNA synthesis in tumor cells.



Scheme 88. Preparation of monosubstituted vicinal diamines from α-amino acids.

A recently reported synthesis of ^{15}N-labeled ethylenediamine and diethylenediamine made use of the reduction of [^{15}N]tritylglycinamide.[159]

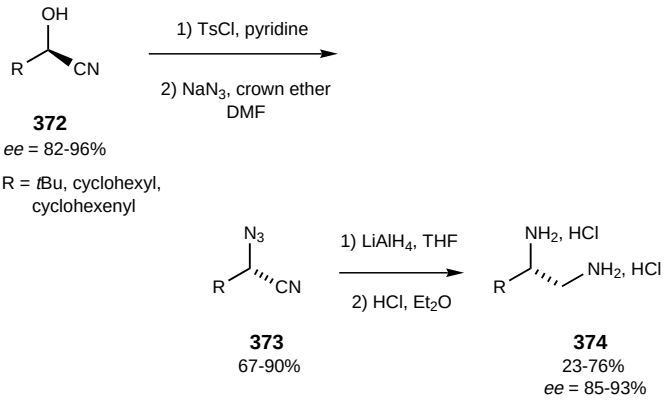
Husson et al. prepared 1-amino-1-(aminomethyl)cyclopropane (**366**) by hydrolysis of imine **365** followed by reduction of the nitrile functionality (Scheme 89).[160] The direct reduc-



Scheme 89. Synthesis of 1-amino-1-(aminomethyl)cyclopropane and *trans*-1,2-diaminocyclobutane.

tion of **365** by a borane – THF complex produced a mixture of diamines **367** and **368**, the latter arising from a ring-expansion reaction of **365**. Compound **368** was then converted into *trans*-1,2-diaminocyclobutane (**369**).

Effenberger et al.[161] took advantage of the ready access to optically active cyanohydrines **372** in their synthesis of monosubstituted 1,2-diamines **374**, which also made use of a nucleophilic substitution by sodium azide (Scheme 90).



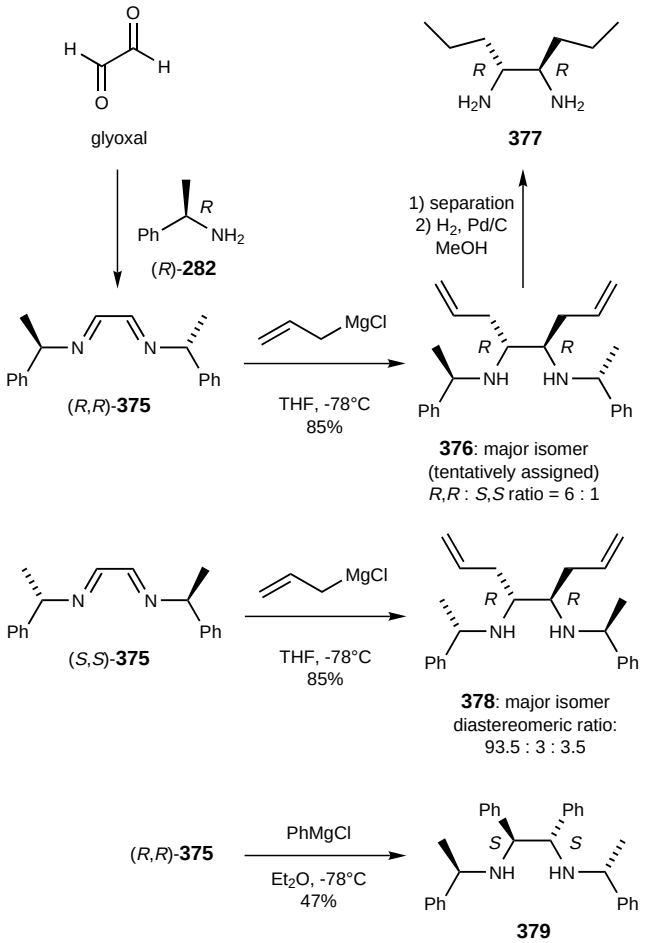
Scheme 90. Synthesis of monosubstituted 1,2-diamines from chiral, non-racemic cyanohydrines.

1,2-Diamines have also been prepared by reduction of optically active α-amino nitriles obtained from asymmetric Strecker reaction.[162]

4.14. Vicinal Diamines by Alkylation of Glyoxal Bisimines

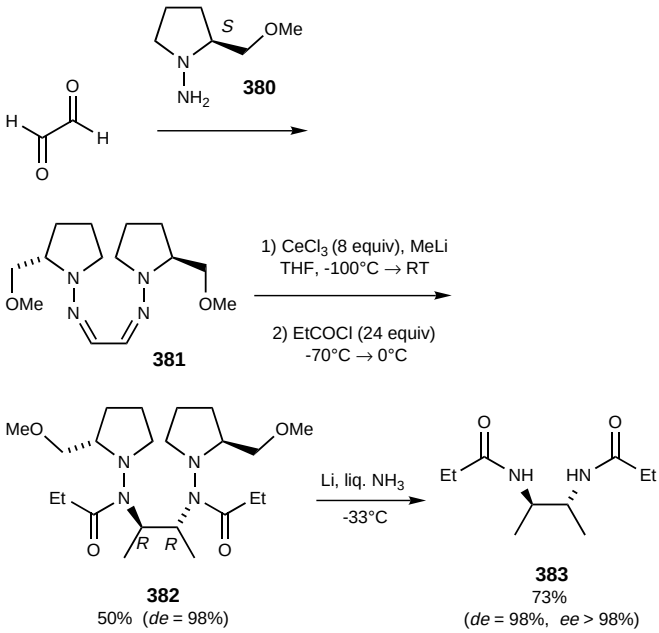
In 1991 Neumann et al. showed that the nucleophilic addition in THF of allylmagnesium chloride to bisimines derived from glyoxal afforded essentially the corresponding *syn*-1,2-diamines. The high *syn* stereoselectivity was presumed to arise from a Cram chelation control. By employing the bisimine (*R*,*R*)-**375**, prepared from commercially available (*R*)-α-methylbenzylamine (**282**), a 6:1 ratio of the two *syn* diastereomers was obtained, the major isomer being tentatively assigned as **376**, which was then converted into enantiomerically pure C_2-symmetric diamine **377** (Scheme 91).[163] Reactions of the same bisimine (or its enantiomer) with other organometallic reagents have since been reported; they also proceed with *syn* selectivity, but with opposite stereochemical outcomes. Savoia et al.[164] obtained the diamine **378** as the major isomer from the reaction of (*S*,*S*)-**375** with allylzinc bromide in THF, and adduct **379** was mainly obtained by Simpkins et al.[165] from the reaction of (*R*,*R*)-**375** with phenylmagnesium chloride in diethyl ether (Scheme 91). In both cases, the configuration of the major isomer was established by X-ray structure analysis.

Enders et al. described the diastereo- and enantioselective synthesis of various C_2-symmetric, protected 1,*n*-diamines from dialdehydes by the alkylation, with organocerium



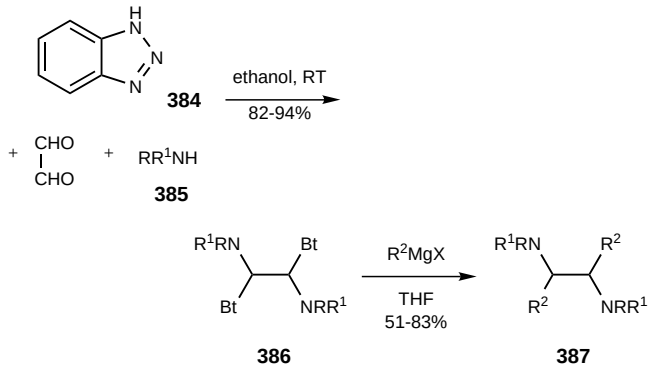
Scheme 91. Addition of Grignard reagents to the bisimine derived from glyoxal and either (*S*)- or (*R*)-α-methylbenzylamine.

compounds, of the bishydrazones derived from the chiral hydrazines SAMP or RAMP.[166] In one example, bishydrazone **381** derived from glyoxal was used as the substrate; while the yield of the addition was moderate, the enantiomeric excess of the final protected C_2-symmetric vicinal diamine **383**, recovered after N–N cleavage, was excellent (Scheme 92).



Scheme 92. Diastereo- and enantioselective bisaddition of an organocerium reagent to a SAMP-derived bishydrazone.

In 1990 Katritzky et al.[167] also employed glyoxal as the starting material in a synthetic route to tertiary and secondary, symmetrical, racemic, vicinal diamines (Scheme 93). Double condensations between benzotriazole (**384**), glyoxal, and either aromatic or secondary aliphatic amines afforded stable adducts **386**; aliphatic primary amines led to oligomers or polymers. Displacement of the benzotriazolyl moieties were then realized by treatment with Grignard reagents, to give the diamines **387** as *syn*–*anti* mixtures.



RR^{1}NH = piperidine, morpholine, nBu$_2$NH, Bn$_2$NH, PhNH$_2$, p-MeC$_6$H$_5$NH$_2$, m-MeC$_6$H$_5$NH$_2$

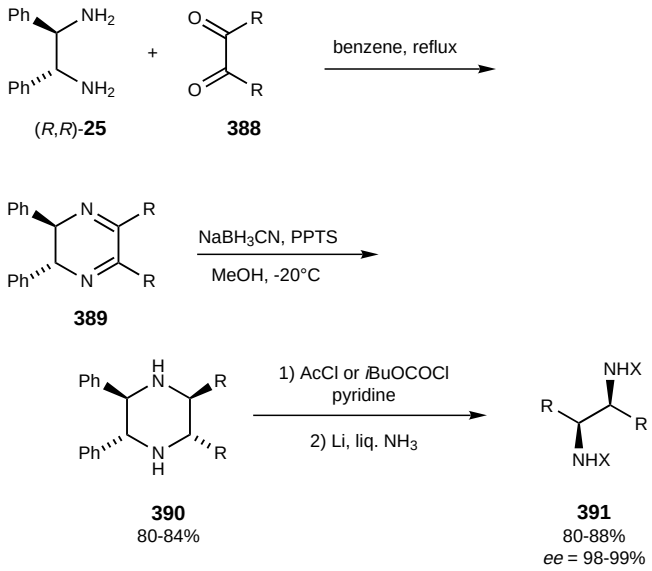
Bt = benzotriazol-1-yl, benzotriazol-2-yl

R^2 = Me, nBu, Bn, Ph

Scheme 93. Synthesis of symmetrical, racemic, vicinal diamines by alkylation of the products of double condensation between benzotriazole, glyoxal, and amines.

4.15. Vicinal Diamines by Reduction of Diketone Bisimines or Bisoximes

An elegant, efficient route to enantiomerically pure C_2-symmetric vicinal diamines that used another such diamine, (*R*,*R*)-1,2-diphenylethylenediamine, as the source of chirality was devised by Nantz et al.[168] (Scheme 94). The reduction of



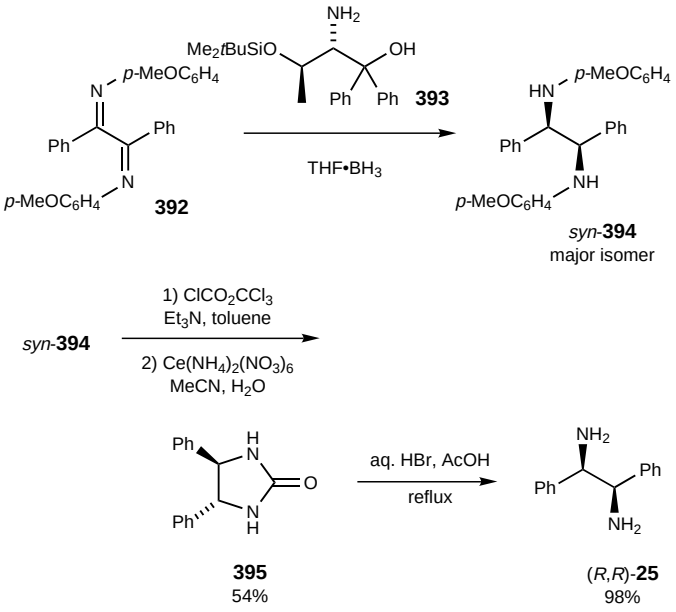
R = alkyl
X = *t*Boc, Ac

Scheme 94. Enantioselective synthesis of C_2-symmetric vicinal diamines by reduction of a chiral dihydropyrazine.

the dihydropyrazine **389** (R = Me), formed from this diamine and 2,3-butanedione, to piperazine **390** (R = Me) by several reagents was studied. Acid-catalyzed sodium cyanoborohydride reduction at $-20\,^{\circ}C$ was found to be the most selective. Various diketones **389** were then reduced under similar conditions. After separation of the minor isomer by chromatography, a short sequence that involved a dissolving metal C–N cleavage provided the protected diamines efficiently **391**. Both enantiomers of stilbenediamine have been prepared by a related strategy involving the reduction of a 2,2-disubstituted 4,5-diphenyl-2*H*-imidazole and a resolution step.[72d]

The catalytic asymmetric reduction of 1,2-bis(*para*-methoxyphenylimino)-1,2-diphenylethane (**392**) was recently reported by Fujisawa et al.[169] (Scheme 95). An oxazaborolidine, obtained from L-threonine derivative **393**, served as the catalyst in a process that afforded selectively the *syn*-diamine **394** in excellent yield. The enantiomeric purity of **394** was excellent (99% *ee*), even when a small amount of catalyst was used (Table 5). No *meso* isomer formed when one equivalent of the ligand was used. Complete deprotection of the amine groups was then carried out, to give the enantiomerically pure (*R*,*R*)-diamine **25**.

1,2-Diamines have also been prepared by reduction of 1,2-bisoximes[131a, 170] or 1,2-bisoxime ethers.[171]



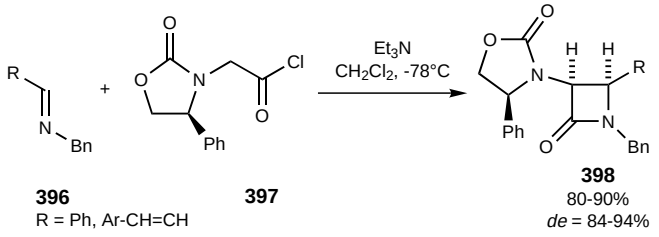
Scheme 95. Enantioselective reduction of a bisimine by using an oxazaborolidine obtained from L-threonine derivative **393**.

Table 5. Diastereo- and enantioselectivity in the reduction of bisimine **392** in the presence of various amounts of **393**.

Entry	Ligand **393** [mol%]	Yield (**394**) (*syn* + *anti*) [%]	*syn*:*anti*	*syn ee* [%]
1	0.5	90	95:5	99
2	50	96	96:4	99
3	100	90	>99:1	99

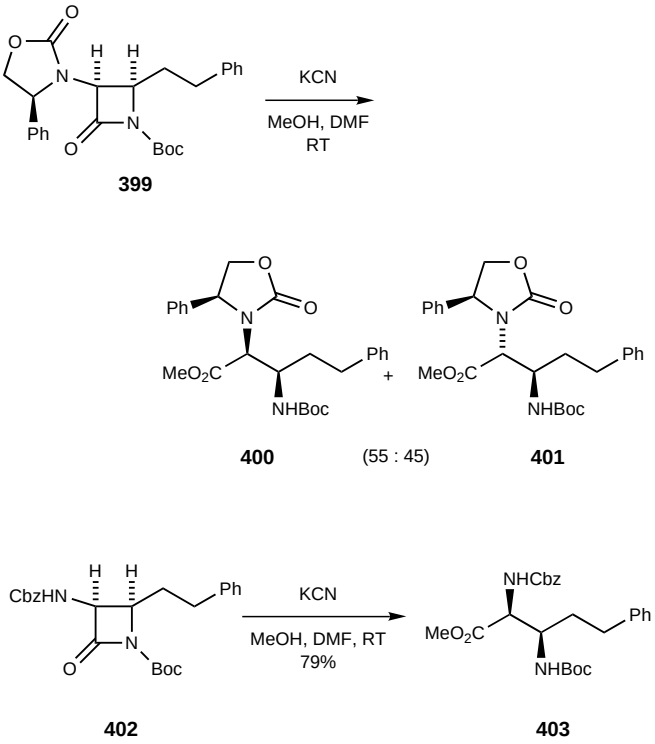
4.16. Vicinal Diamines from 3-Amino-β-lactams

Several approaches to the synthesis of β-lactams with a nitrogen function on the C3 position have been described.[172, 173] A significant example has been reported by Evans and Sjogren (Scheme 96):[174] the Staudinger reaction of



Scheme 96. Diastereoselective synthesis of an 3-oxazolidyl-β-lactam by a Staudinger reaction.

the ketene derived from a chiral, enantiomerically pure oxazolidylacetyl chloride **397** with imines **396** led with very good diastereoselection to the corresponding *cis*-β-lactams **398**. The oxazolidinone ring can then be cleaved to generate an amino group. The diamines can in principle be obtained through opening of the ring of these β-lactams. Such a process has recently been performed by Palomo et al.[175] (Scheme 97). While the methanolysis of β-lactam **399**, substituted with an

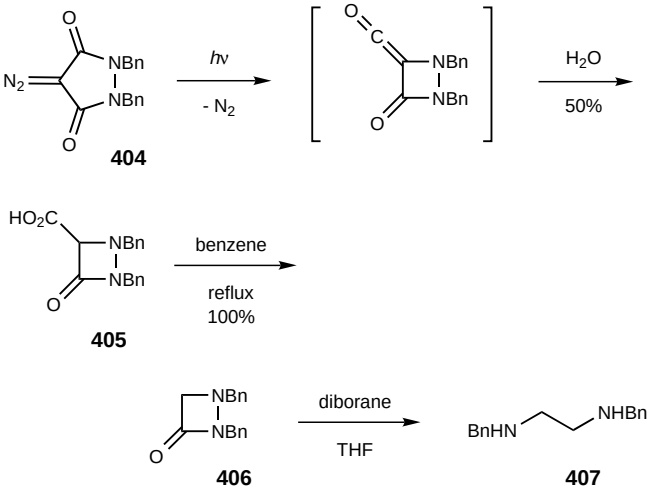


Scheme 97. Ring opening of 3-amino-β-lactams.

oxazolidyl group, afforded a mixture of the *syn* adduct **400** and *anti* adduct **401**, a single protected diamine **403** was obtained from **402** under similar conditions.

4.17. Vicinal Diamines from 1,2-Diazetidinones

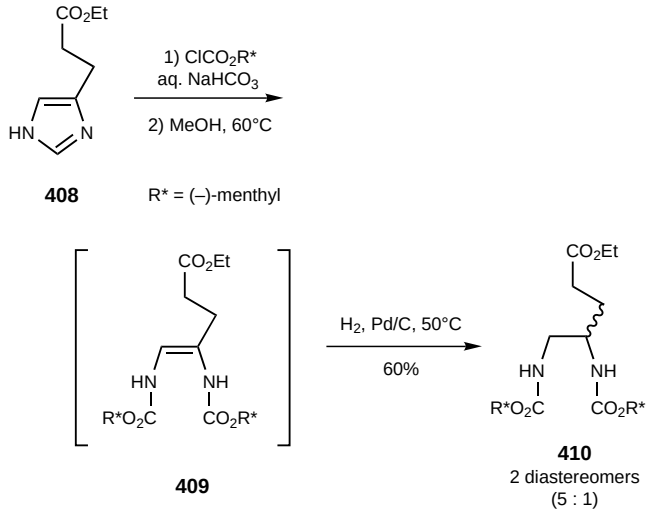
The cleavage of the N–N bond of a 1,2-diazetidine should lead to the corresponding 1,2-diamine. However, since there are no general synthesis of such heterocyclic compounds, this method has not been greatly employed. In one example Moody et al. obtained 1,2-di(benzylamino)ethane (**407**) from the reduction of diazetidinone **406** with diborane in THF (Scheme 98).[176] The diazetidinone itself had been prepared from the photochemical ring contraction of 4-diazopyrazolidine-3,5-dione **404**.



Scheme 98. Synthesis of 1,2-(dibenzylamino)ethane from a diazetidinone.

4.18. Vicinal Diamines from Imidazoles

The Bamberger ring cleavage of imidazoles with an acylating agent leads to ene–diacylamines, which may be reduced to diacylamines. This approach was applied by Altman et al.[177] for the synthesis of enantiomerically enriched diacylamines (Scheme 99). They employed (−)-menthyl chloroformate as the acylating agent; after ring cleavage of

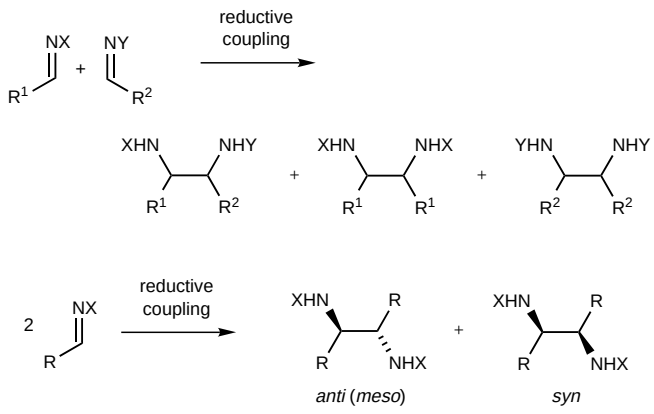


Scheme 99. Diastereoselective reduction of a chiral ene–diacylamine obtained from the Bamberger ring cleavage of an imidazole by using (−)-menthyl chloroformate as the acylating agent.

the imidazole **408**, the catalytic hydrogenation of ene-diacylamine **409** with palladium on carbon afforded a 5/1 mixture of the corresponding diastereomeric vicinal biscarbamates **410**.

4.19. Vicinal Diamines by Reductive Coupling of Imines

In principle, the reductive coupling of imines (with the help of a metal or of a metallic complex) seems a simple way to prepare vicinal diamines; in fact, it is usually applied only to the synthesis of symmetrical diamines, since one can expect to obtain a mixture of products from the coupling of two different imines (Scheme 100).



Scheme 100. Reductive coupling of imines.

Various conditions have been utilized to couple imines, which lead to variable proportions of *anti*- (*meso*-) and *syn*-diamines; some examples follow.

Reductive coupling of aryl *N*-alkylimines can be performed in good yields by photoreduction[178a] or by electrolysis.[178b] Low-valent titanium reagents were employed by Seebach et al.[179a, b] in the reductive coupling of aryl *N*-alkylimines. Similar species, generated from titanium tetrachloride and magnesium amalgam, allowed Mangeney et al.[179c] to obtain symmetrical vicinal diamines with good *anti* selectivity, along with the amine from imine reduction. Periasamy et al. showed that 2-methylimidazolidines are obtained when *N*-alkylimines are coupled with the $TiCl_4/Mg/BrCH_2CH_2Br$ combination in THF.[179d]

The reductive dimerization of *N*-benzylidene aniline with alkali metals was performed by Smith et al., who found conditions that allowed the stereoselective formation of the *syn* or *anti* adducts.[180a] Roskamp and Petersen[180c] prepared unsubstituted vicinal diamines, with moderate to good *anti* selectivity, by coupling *N*-trimethylsilylimines with the d^1 niobium reagent, $[NbCl_4(THF)_2]$. They also developed a method of using nitriles as substrates in conjunction with tributyltin hydride.

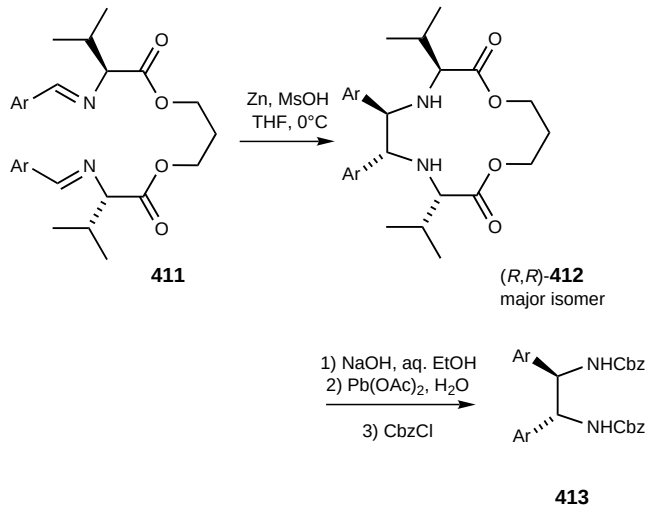
More recently, reductive couplings that used samarium diiodide,[180d, e, i] indium,[180f] and ytterbium[180j] were reported and Pansare et al. described the intramolecular coupling of unsymmetrical dibenzylidene sulfamides mediated either by zinc activated by chlorotrimethylsilane or by samarium diiodide; the cyclic sulfamides obtained were easily converted into the corresponding unsymmetrical 1,2-diaryl-1,2-diamines.[180k] Aluminum, an inexpensive, stable, easy to handle, nontoxic material was used in conjunction with potassium hydroxide.[180b, g] A lead/aluminium bimetallic redox system gave good yields of the adducts, but with poor selectivity.[180h]

Imwinkelried and Seebach also showed that it was possible to prepare 1,2-bis(dialkylamino)-1,2-diaryl ethylene directly from aromatic aldehydes by using an aminative reductive coupling mediated by tris(dialkylamino)methylvanadium (IV).[181]

It is worthy of note that none of these methods allows the direct preparation of enantiomerically pure compounds, which are usually only obtained after an optical resolution.[72] However, reports on the coupling of chiral, non-racemic imines have recently appeared:

Shono et al.[182a] described a stereoselective synthesis of (*R*,*R*)-1,2-diarylethylenediamines **413** by the reductive, intramolecular coupling of chiral, aromatic bisimines **411,** derived from (*S*)-valine methyl ester in the presence of zinc (Scheme 101). A three-carbon chain linkage between the two valine moieties afforded the best selectivity. The selectivity also improved for substrates having a *para*-electron-donating substituent on the aryl group (Table 6). Other macrocycles containing a vicinal diamine moiety have been prepared accordingly, the intramolecular coupling being performed with either electroreduction or zinc powder.[182b]

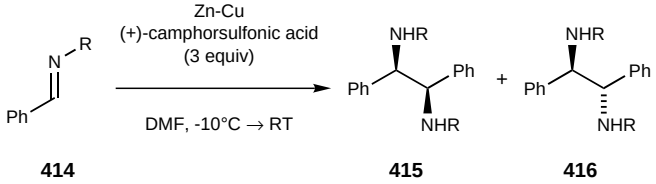
In 1995 Fujisawa et al.[183] reported the enantioselective pinacol coupling of benzaldimine **414**, promoted by the use of a zinc–copper couple, in the presence of three equivalents of (+)-camphorsulfonic acid (Scheme 102). The best results were obtained starting from *N*-*para*-methoxyphenylbenzaldimine, with the *R*,*R* adduct **415** formed with good diaste-



Scheme 101. Intramolecular reductive coupling of chiral, non-racemic bisimines.

Table 6. Diastereoselectivity in the intramolecular reductive coupling of chiral, non-racemic bisimines.

Entry	Ar	Yield (**412**) [%]	*R*,*R*:*R*,*S* (**412**)	Yield (**413**) (two diastereomers)
1	C_6H_5	68	91:9	72
2	*p*-$MeOC_6H_4$	68	97:3	71
3	*p*-ClC_6H_4	63	89:11	73
4	*p*-NCC_6H_4	59	72:28	57



Scheme 102. Enantioselective coupling of imines mediated by a zinc–copper couple in the presence of (+)-camphorsulfonic acid.

reoselectivity and an excellent enantiomeric excess (Table 7). It is presumed that the reaction involves the reductive coupling of a chiral iminium salt formed from the imine and (+)-camphorsulfonic acid.

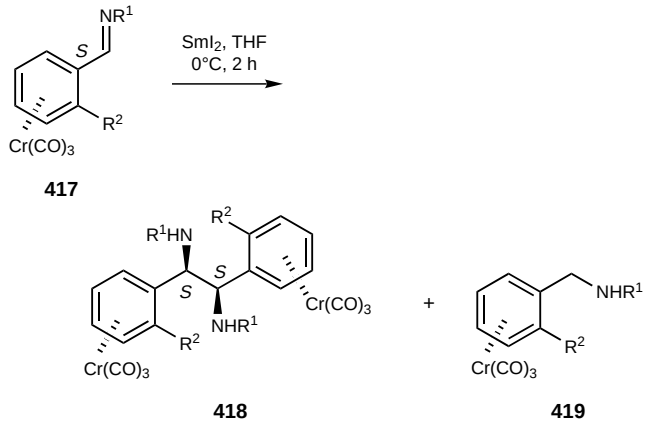
Table 7. Diastereo- and enantioselectivity in the reductive coupling of benzaldimines **414** mediated by a zinc–copper couple in the presence of (+)-camphorsulfonic acid.

Entry	R	Yield (**415**+**416**) [%]	*syn*:*anti*	*ee* (**415**) [%]
1	*p*-$MeOC_6H_4$	88	70:30	97
2	C_6H_5	64	50:50	52
3	$C_6H_5CH_2$	54	53:47	34
4	$(p\text{-}MeOC_6H_4)_2CH$	64	50:50	0

Very recently, Uemura et al.[184] demonstrated that no *anti*, only *syn*-diamines **418** were formed during the samarium diiodide-mediated coupling of enantiomerically pure tricarbonyl(benzaldimine)chromium complexes **417**, along with variable amounts of amines **419** (Scheme 103; Table 8).

Table 8. Reductive coupling of differently substituted chiral tricarbonyl-(benzaldimine)chromium complexes **417** with samarium diiodide.

Entry	R^1	R^2	Yield [**418**] [%]	Yield [**419**] [%]
1	Me	Me	65	25
2	Me	OMe	67	10
3	Me	Br	45	41
4	Me	Cl	48	46
5	$PhCH_2$	Me	54	38
6	$PhCH_2$	*i*Pr	51	29

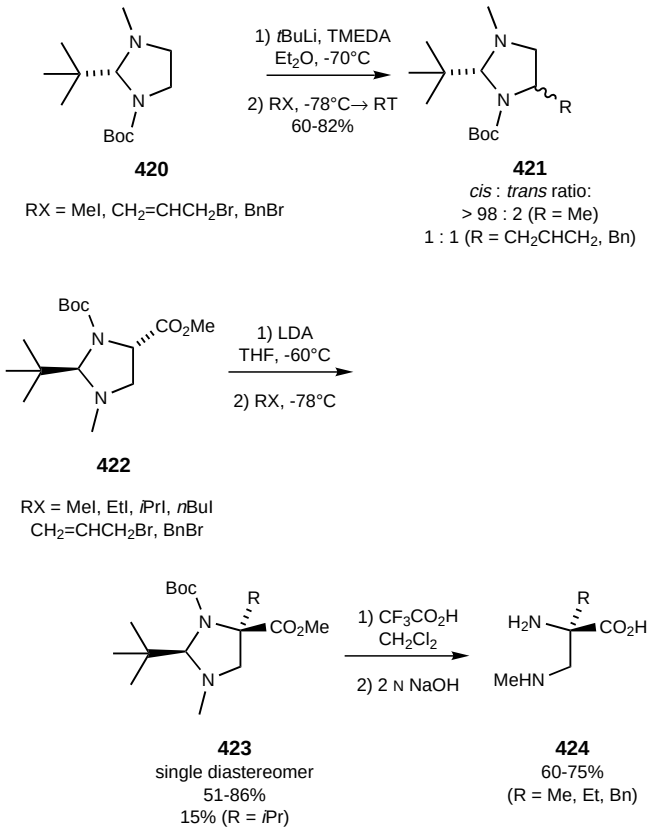


Scheme 103. SmI_2-mediated reductive coupling of chiral tricarbonyl-(benzaldimine)chromium complexes.

4.20. Vicinal Diamines from Other Compounds Containing a 1,2-Diamino Moiety

As seen throughout the preceding sections, the last step of a vicinal diamine synthesis often includes the transformation of a compound already containing a masked 1,2-diamine moiety. For example, the hydrolysis of an imidazolidinone is used in many syntheses. In this section, we will not describe other such transformations in detail. However, the utilization of imidazolines as chiral templates for the preparation of enantiomerically enriched vicinal diamines is worthy of note.

Pfammatter and Seebach[185] reported the reaction of the anion generated from the enantiopure *N*-Boc-imidazolidine **420** with various electrophiles (Scheme 104). While *trans* adducts were usually obtained, as in the reaction with methyl iodide, a 1/1 mixture of diastereomers was obtained with either allyl or benzyl bromide. The cleavage of the heterocycles **421** was not described. The ester **422** was prepared selectively from **420**, and was then used as a precursor to various 2,3-diaminoalkanoic acids. Treatment of **422** with LDA, followed by an alkyl halide, yielded the corresponding α-alkylated ester **423** as a single diastereomer. Even 2-iodopropane could be used as the electrophile, although in this case, a low yield of adduct was obtained. Several adducts **423** were then hydrolyzed to give the free α,β-diamino acids **424**. The conditions used in this two-step procedure cannot be applied conveniently to unbranched substrates (which have an exchangeable proton in the position α to the ester function), since racemization occurs in these cases.

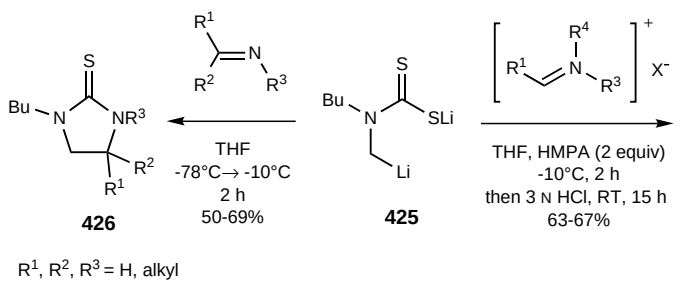


Scheme 104. Stereoselective synthesis of 1,2-diamine derivatives from enantiopure, chiral imidazolidines.

Fraenkel et al.[186] prepared diastereomerically pure *meso*-2,3-bis(methylamino)butane and *cis*-1,2-bis(methylamino)cycloalkanes by the hydrogenation of 1,3-dimethylimidazolin-2-one derivatives. The opening of 2-(aminomethyl)aziridine derivatives by carbon nucleophiles was also used to synthesize vicinal diamines.[187]

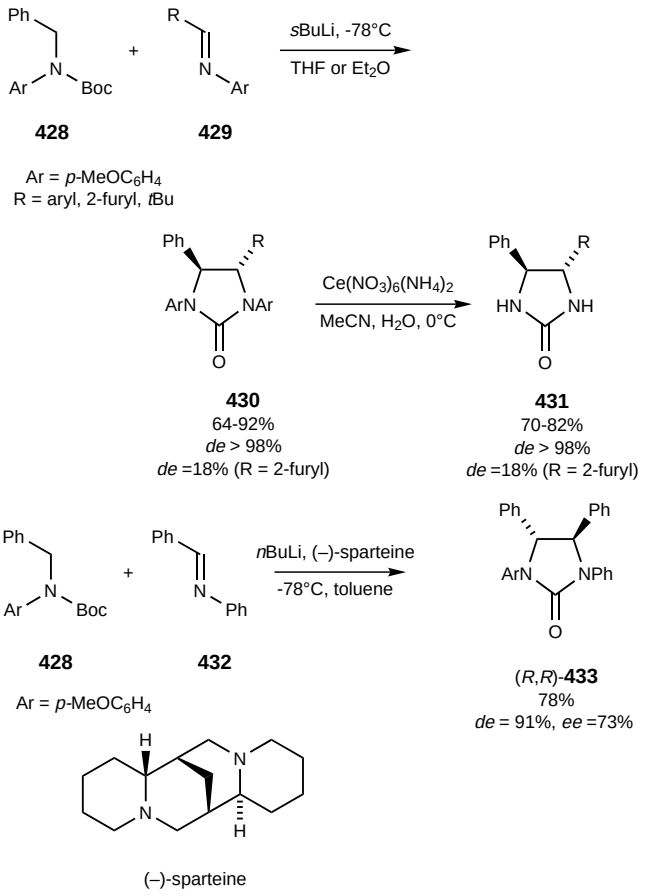
4.21. Vicinal Diamines from Addition of an α-Nitrogen Anion onto Imines or Iminiums

Several authors have recognized that the reaction of an α-nitrogen anion with an imine could yield a 1,2-diamine precursor. For example, Ahlbrecht and Schmitt[188] described a) the reaction of lithium *N*-butyl-*N*-lithiomethyldithiocarbamate (**425**) with imines to give imidazolidine-2-thiones **426**, and b) the reaction with iminium salts to give diamines **427** (Scheme 105).



Scheme 105. Preparation of 1,2-diamine derivatives by reaction of an α-nitrogen anion with imines or iminium salts.

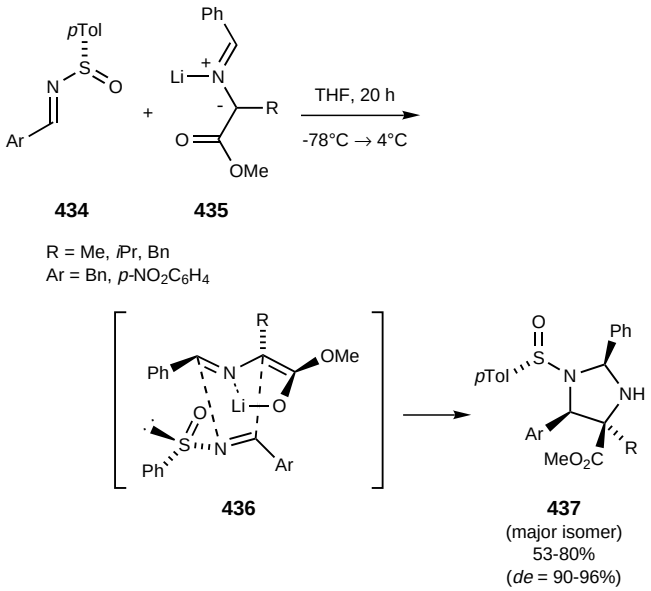
In 1996 Kise, Yoshida et al. reported the stereoselective synthesis of *trans*-imidazolidin-2-ones by the reaction of the carbanion of *N*-benzyl-*N*-Boc-*para*-anisidine (**428**) with imines **429**, which are derived from *para*-anisidine and do not have an exchangeable proton (Scheme 106).[189] Very good stereoselectivities were obtained, either in diethyl ether or in THF, depending on the substrate. Treatment of the adducts **430** with ceric ammonium nitrate afforded in good yields the unprotected *trans*-imidazolidinones **431**, which are precursors of 1,2-diamines. The method was limited to the preparation of adducts substituted only by aryl or *tert*-butyl groups, and also only in racemic form. However, an enantioselective version of this process was soon reported by Beak et al. (Scheme 106).[190] They showed that the reaction of **428** with *n*-butyllithium in toluene, in the presence of (−)-sparteine, followed by addition to *N*-benzylideneaniline (**432**) yielded *trans*-imidazolidinone (*R*,*R*)-**433** as the major adduct with a 73% enantiomeric excess.



Scheme 106. Stereoselective synthesis of *trans*-imidazolidin-2-ones, precursors of 1,2-diamines, by reaction of an α-nitrogen anion with imines.

4.22. Vicinal Diamines by 1,3-Dipolar Cycloaddition of Azomethine Ylides with Imines

1,3-Dipolar cycloaddition of an azomethine ylide with an imine results in the formation of an imidazolidine, which can then be converted into a 1,2-diamine. Only few reports on this reaction have been made, but it was recently applied by Viso, Fernández de la Pradilla et al.[191] to the synthesis of enantiopure *N*-sulfinyl imidazolidines (Scheme 107). The reaction of

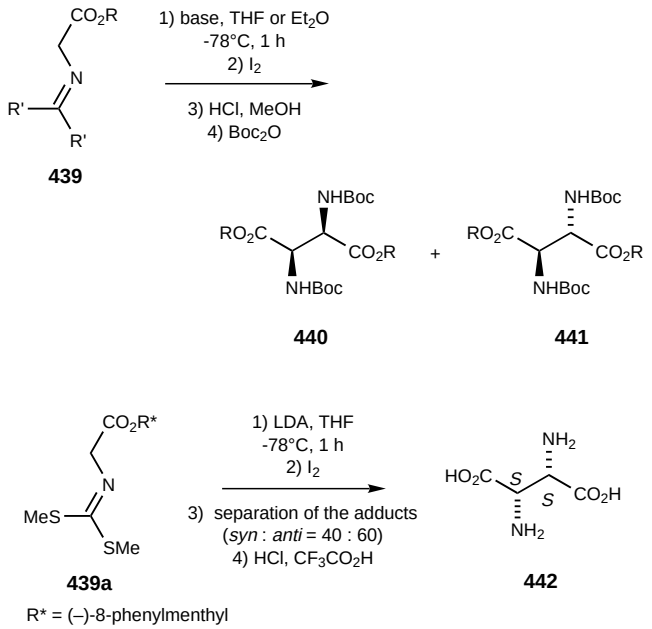


Scheme 107. 1,3-Dipolar cycloaddition of azomethine ylides with enantiopure sulfinimines.

ylides **435,** derived from *N*-benzylidene α-amino esters, with enantiopure sulfinimines **434** afforded the cycloadducts **437** with high diastereoselectivity. A predominant *endo* approach of the ylide to the less hindered β face of the sulfinimine (**436**) was suggested. Diamine **438** was then prepared in two steps from one of these adducts.

4.23. Vicinal Diamines from Oxidative Dimerization of Glycinates

Alvarez-Ibarra et al.[192] recently reported the oxidative dimerization of enolates derived from glycine derivatives **439** in the presence of iodine (Scheme 108). The products were converted into 3-aminoaspartates **440** and **441**. The stereochemical outcome of the reaction depends strongly under the conditions used for the generation of the enolates, which suggests that it is a function of the *E* or *Z* geometry of the



Scheme 108. Synthesis of 3-aminoaspartates by the oxidative dimerization of enolates of glycine esters.

enolates. Excellent *syn* selectivity was obtained when lithium bases were used (Table 9). The dimerization of 8-phenylmenthyl glycinate **439a** proceeded with low diastereoselectivity, but allowed the preparation of C_2-symmetric (2*S*,3*S*)-3-aminoaspartic acid (**442**).

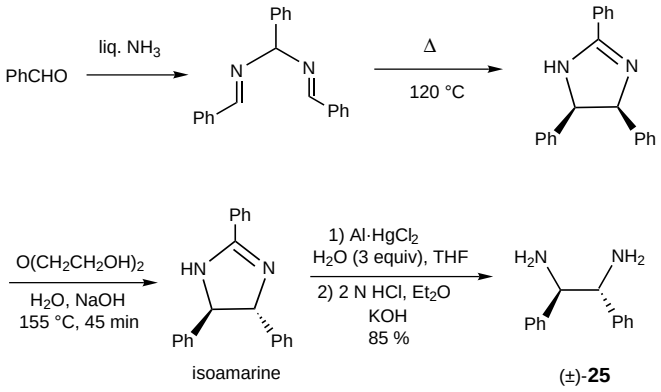
Table 9. Diastereoselectivity in the oxidative dimerization of glycinates.

Entry	R	R′	Base	Solvent	**440**:**441**	Yield [%]
1	Et	SMe	*t*BuLi	THF	55:45	80
2	Et	SMe	*t*BuLi	Et_2O	45:55	60
3	*t*Bu	SMe	*t*BuLi	THF	98:02[a]	80
4	*t*Bu	SMe	LDA	THF	98:02[a]	80
5	*t*Bu	SMe	KO*t*Bu	THF	50:50	80
6	Et	Ph	*t*BuLi	THF	98:02[a]	80
7	Et	Ph	LDA	THF	90:10	90
8	Et	Ph	*t*BuLi	Et_2O	98:02[a]	95
9	Et	Ph	LDA	Et_2O	95:05	85
10	Et	Ph	KO*t*Bu	Et_2O	50:50	60

[a] Only one diastereomer was observed in the 300-MHz ^{1}H NMR spectrum of the crude product.

4.24. Recent Preparations of Vicinal Diamines

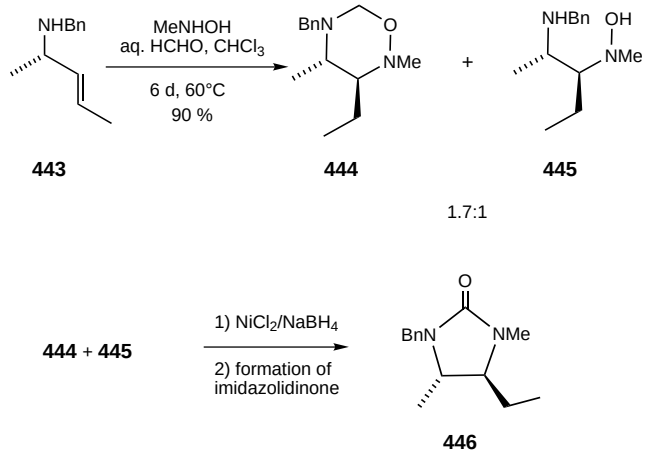
Several recent new relevant syntheses of diamines have appeared since the completion of this review. Saravanan and Singh synthesized various chiral, non-racemic diamines from (*S*)-*O*-acetylmandelic acid, a cheap starting material.[193] A route to the four enantiomers of 2,3-diaminobutanoic acid from *tert*-butyl crotonate, which makes use of the asymmetric aminohydroxylation of Sharpless, was reported by Han et al.[194] An improvement in a previously reported preparation of (±)-1,2-diphenylethylenediamine **25** from isoamarine, which is available from benzaldehyde and ammonia, was described by Corey and Kühnle[195] (Scheme 109).



Scheme 109. Preparation of (±)-1,2-diphenylethylenediamine from benzaldehyde and ammonia.

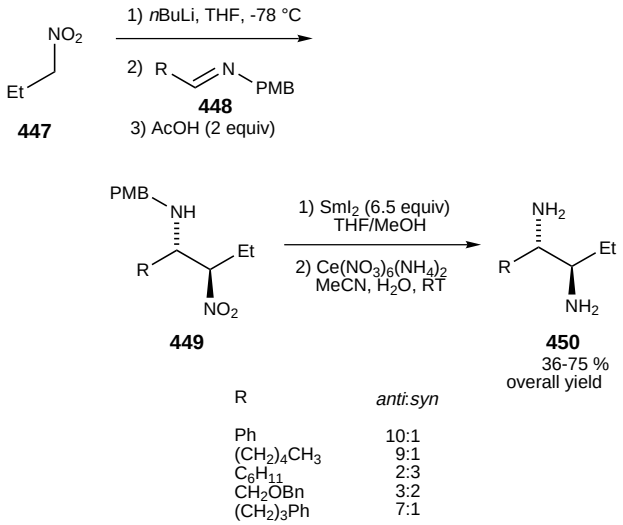
The combined use of samarium diiodide and ytterbium triflate in the reductive coupling of *N*-benzylbenzaldimine under mild conditions was reported by Annunziata et al.[196a] A very good *syn*:*anti* ratio (>98:2) was obtained at room temperature. Lower levels of stereocontrol were observed in the coupling of homochiral imines. A similar coupling was also recently described by Benenji et al.[196b]

Knight et al.[197a] reported the formation of 1,2,5-oxadiazinanes from allylamines and nitrones through a reverse-Cope elimination and a Meisenheimer rearrangement. The conversion of such a compound **444** (obtained from **443** together with amino hydroxylamine **445**) into the corresponding diamine, characterized as the *trans*-imidazolidinone **446** (single diastereomer), was recently published[197b] (Scheme 110).



Scheme 110. Preparation of a *trans*-imidazolidinone from an allylamine and a nitrone.

The nitro–Mannich reaction was employed as the key step in a stereoselective route to 1,2-diamines by Anderson et al.[198] (Scheme 111). Deprotonation of the nitro compound **447** at −78 °C, followed by addition of imine **448** and then of acetic acid, led to *β*-nitro amine **449**. This compound was converted in two steps to the corresponding diamine **450**. Both the nitro compound and the imine tolerate either alkyl or phenyl substituents. *Anti* selectivity was observed in most cases, but the *syn* adduct was obtained from phenylnitromethane and benzaldimine (*anti*:*syn* = 1:15). Treatment of

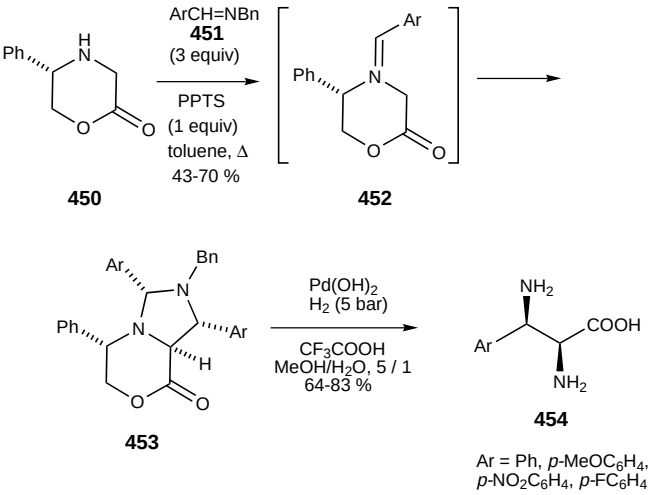


R	*anti*:*syn*
Ph	10:1
$(CH_2)_4CH_3$	9:1
C_6H_{11}	2:3
CH_2OBn	3:2
$(CH_2)_3Ph$	7:1

Scheme 111. Stereoselective synthesis of 1,2-diamines with the ;nitro–Mannich reaction.

propyl nitronate with (*S*)-PhCH(Me)N=CHPh led essentially to one *anti*-*β*-nitro amine; access to homochiral 1,2-diamines by using this method may thus be envisioned.

The cycloaddition of aromatic imines **451** to enantiomerically pure azomethine ylides derived from (5*S*)-phenylmorpholin-2-one **450**, as described by Harwood et al.,[199] was completely diastereoselective (Scheme 112). Hydroge-



Scheme 112. Two-step synthesis of *syn*-(2*S*,3*R*)-3-aryl-2,3-diamino acids by cycloaddition of chiral azomethine ylides with aromatic imines.

nolysis of the cycloadducts **453** under acidic conditions afforded the corresponding *syn*-(2*S*,3*R*)-3-aryl-2,3-diamino acids **454**, which were thus prepared in a straightforward two-step sequence.

Bennani and Hanessian[200] published a review dealing with the use of *trans*-1,2-diaminocyclohexane derivatives as chiral reagents. A review by O'Brien detailed the recent uses of chiral lithium amide bases, including those derived from 1,2-diamines, in asymmetric synthesis.[201] Other recent papers reporting utilizations of vicinal diamines or their derivatives in organic synthesis are noted in the references.[202–212]

5. Summary and Outlook

In this review article, we saw that various compounds incorporating the 1,2-diamino functionality have important biological properties. These compounds may be natural products or synthetic compounds and some of them are useful medicinal agents. Vicinal diamine derivatives also find increasing utilization in organic synthesis, either as chiral auxiliaries or as metallic ligands, especially in the field of catalytic asymmetric synthesis. The importance of the vicinal diamine moiety has brought about numerous methods of preparation. However, few of them are of broad scope. Most of them are only well suited for the preparation of specific classes of 1,2-diamines such as primary, secondary, or tertiary diamines, or only *syn* or *anti* compounds. Other ones only allow the formation of symmetrical 1,2-diamines.

A more general way to prepare vicinal diamines selectively is thus still sought after. Considering the topical development of catalytic enantioselective synthesis, one can envision that asymmetric diamination of alkenes might be a convenient response to this problem. Other solutions will probably then be designed, since, as can be seen from the many examples of syntheses summarized in this review, one thing organic chemists certainly do not lack is imagination.

Appendix: Abbreviations

acac	acetylacetonate
aq.	aqueous
Boc	*tert*-butyloxycarbonyl
Bt	benzotriazolyl
Cbz	benzyloxycarbonyl
Cp	cyclopentadienyl
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
EDTA	ethylenediaminetetraacetic acid
hex	hexyl
*c*hex	cyclohexyl
HMPA	hexamethylphosphorotriamide
L	ligand
LDA	lithium diisopropylamide
liq.	liquid
*m*CPBA	*meta*-chloroperbenzoic acid
MMPP	magnesium monoperoxyphthalate
Ms	methanesulfonyl
Mt	mesityl
NBS	*N*-bromosuccinimide
NMO	*N*-methylmorpholine
Ns	4-nitrobenzenesulfonyl
PPTS	pyridinium *para*-toluenesulfonate
RAMP	(*R*)-1-amino-2-(methoxymethyl)pyrrolidine
salen	*N,N′*-bis(salicylidene)ethylenediamine
SAMP	(*S*)-1-amino-2-(methoxymethyl)pyrrolidine
stien	stilbenediamine
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TMEDA	*N,N,N′,N′*-tetramethylethylenediamine
tosyl	*para*-toluenesulfonyl
trisyl	2,4,6-triisopropylbenzenesulfonyl
trityl	triphenylmethyl
Ts	*para*-toluenesulfonyl

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