Asymmetric Electrophilic α-Amination of Carbonyl Groups

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The electrophilic amination constitutes an unconventional C–N bond-forming reaction. Asymmetric versions have been developed using chiral reagents or catalysts and starting from optically pure substrates. The aminated products can be obtained with high stereoselectivities. These methodologies are flexible routes for the synthesis of α-amino acids and nitrogen heterocycles.

1. Introduction

The electrophilic amination of organometallic species allows a wide range of aminated compounds to be prepared using the "umpolung" methodology for the formation of C−N bonds. Amines are important building blocks in organic chemistry and provide fundamental functionalities in natural products. Several detailed reviews describe the chemistry of nitrogen reagents as "NH_2^+" equivalents.[1] Recently, new electrophilic aminating reagents have been developed for the introduction of free or protected amino moieties. These reagents include ceric ammonium nitrate/sodium azide,[2] iminomalonate,[3] oxime *O*-sulfonates,[4] *N*-protected oxaziridines,[5] *N*,*O*-disubstituted hydroxylamines [lithium *tert*-butyl-*N*-tosyloxycarbamate[6] and *N*,*O*-bis(trimethylsilyl)hydroxylamine[7]], and alkyl arylaminocarbonyl diazenecarboxylates.[8]

Asymmetric versions of electrophilic amination reactions have been investigated using chiral aminating reagents, chi-

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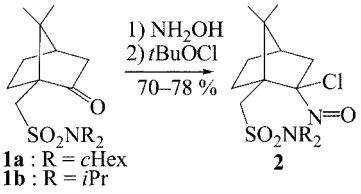
Christine Thomassigny passed her PhD in 1997 under the guidance of Professor Jacques Gelas in Clermont-Ferrand. After one postdoctoral stay in Oeiras, Portugal, at the Instituto Tecnico de Química e Bioquímica with Professor C. D. Maycock, she moved to Monte da Caparica, Portugal, for a second postdoctoral position under the direction of Professor M. T. Barros. In 2002, she has joined the team of Professor Christine Greck as Maître de Conférences at the University of Versailles Saint-Quentin-en-Yvelines. Her research program is asymmetric organic synthesis.

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

ral catalysts, or chiral carbanions.[9,10] This microreview discusses recent advances in the area of asymmetric electrophilic amination of enolates and their synthetic applications.

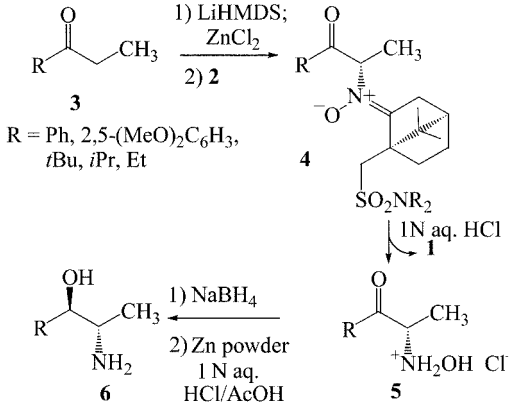
2. Chiral Reagents

The first example of an asymmetric electrophilic amination using a chiral reagent was reported in 1992 by Oppolzer and co-workers[11] who developed chiral α-chloro-α-nitroso reagents capable of aminating prochiral ketone enolates with high enantiofacial differentiation. The α-chloro-α-nitroso compounds **2** were obtained by oximation of the corresponding chiral sulfonamides **1**, followed by chlorination, and they are readily accessible in both antipodal forms (Scheme 1).



Scheme 1

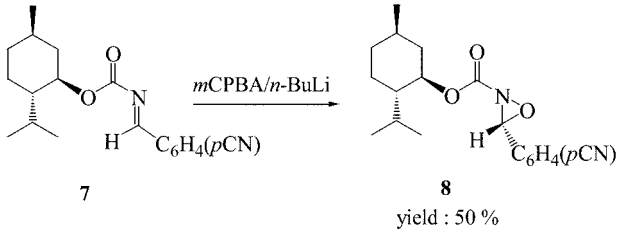
Zinc enolates of ketones reacted with these α-chloro-α-nitroso reagents **2** to give nitrones with high diastereoisomeric excesses. For example, the electrophilic amination of the propiophenone **3** (R = Ph) with **2a** gave exclusively the aminated ketone **4** with the (*S*)-absolute configuration at the C_α center (Scheme 2). Hydrolysis of the adduct, followed by *erythro*-selective reduction of the carbonyl group and *N*,*O*-hydrogenolysis, afforded the (−)-norephedrine **6** (R = Ph) with excellent diastereoisomeric and enantiomeric excesses (*de* = 90%; *ee* = 96%) and 68% overall yield. The starting sulfonamide **1a** was recovered after the hydrolysis step by extraction of the acidic medium.



Scheme 2

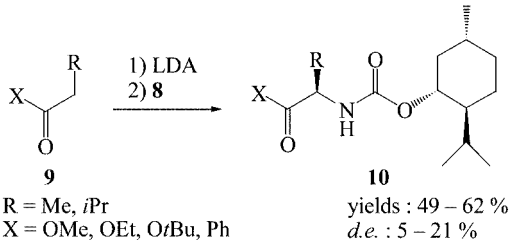
The authors postulated that the observed C_α *si*-face topicity of the C−N bond formation process is consistent with a cyclic "chair" transition state involving the zinc (*Z*)-enolate and the nitroso group bearing the bulky sulfonamide functionality.

The first enantiomerically pure *N*-acyloxaziridine was described in 1992.[12] A new chiral 3-aryl-*N*-(alkyloxycarbonyl)-oxaziridine, derived from menthol, was reported in 2001 and tested as a reagent for asymmetric electrophilic amination of enolates.[13] The aminated products were obtained in low stereoselectivities of up to 21%. The chiral oxaziridine **8** was prepared by oxidation of the imine **7** derived from *p*-cyanobenzaldehyde and (−)-menthylcarbonyliminophosphorane (Scheme 3). This oxidation proceeds highly diastereoselectively, giving (*E*) and (*Z*) isomers having identical absolute configurations at the carbon ring and interrelated by inversion at the nitrogen atom.



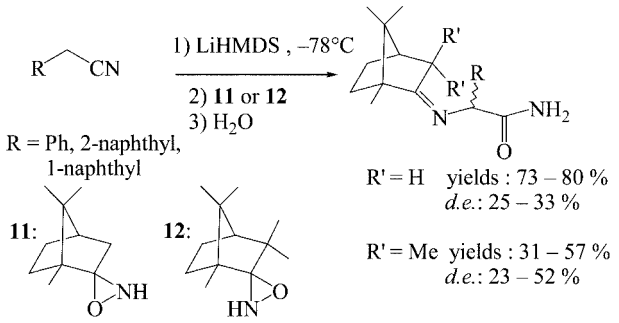
Scheme 3

Achiral ketone and ester enolates have been aminated with the non-racemic *N*-(alkyloxycarbonyl)oxaziridine **8** (Scheme 4). The best result was obtained using ethyl isovalerate as the substrate: the addition of $Ti(OiPr)_4$ to the lithium enolate afforded a small increase in the amination's diastereoselectivity, giving the corresponding adduct **10** in 51% yield and 21% *de*.



Scheme 4

The preparation of the first stable, enantiomerically pure, chiral N−H oxaziridines has recently been accomplished.[14] The N−H oxaziridines **11** and **12**, derived from (1*R*)-(+)-camphor and (1*R*)-(−)-fenchone, respectively, were prepared by oxidation of the corresponding imines. They were tested as asymmetric sources of nitrogen atoms in the amination of various carbon nucleophiles, such as esters and nitriles (Scheme 5). Yields were moderate to good, especially when **11** was used with nitriles. The observed diastereoselectivities were improved when **12** was employed as the chiral aminating reagent. Its lower reactivity is a consequence of the steric hindrance generated by

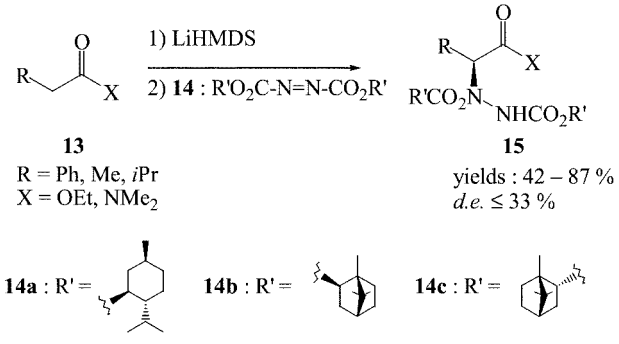


Scheme 5

the *endo*-methyl group, but the diastereoisomeric ratios are promising.

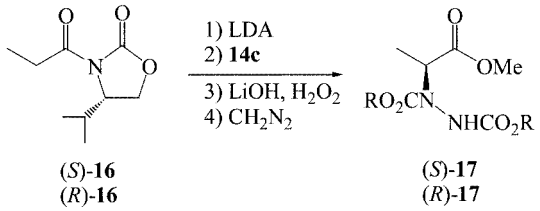
The mechanism involved in the reaction at the oxaziridine unit has been proposed to be a stepwise process. The first step may be nucleophilic attack of the anion at the nitrogen atom of the oxaziridine ring to cause N−O bond cleavage and give a hemiaminal oxy anion as the intermediate. The second step may be the attack of this anion on the nitrile moiety to form a heterocyclic intermediate that, in turn, breaks down to generate a species containing an imine unit. Simple protonation during workup occurs to give the primary amide.

Azodicarboxylates have been used extensively as aminating reagents that lead to hydrazine derivatives. These compounds are direct precursors of amines by removal of the carbamate moieties and hydrogenolysis of the N−N bond of the resulting hydrazine. Chiral azodicarboxylates[15] and dicarboxamides[16] have been synthesized and reacted with achiral enolates. In 1995, Vederas and coworkers prepared a series of chiral dialkyl diazodicarboxylates,[15a] menthyl (**14a**), bornyl (**14b**), and isobornyl (**14c**), by conversion of the corresponding alcohols into chloroformates, condensation with hydrazine, and oxidation. Macrocyclic azodicarboxylates containing a steroid skeleton were also obtained using a similar route.[15b] Ester and amide enolates were aminated using the chiral azodicarboxylates **14** (Scheme 6). The reaction displayed no stereoselectivity, except when ethyl phenylacetate **13** (R = Ph; X = OEt) was reacted with di-(−)-menthyl azodicarboxylate (**14a**). In this case, a diastereoisomeric ratio of 2:1 was observed in favor of the α-hydrazino ester **15**, which presents an (*S*) absolute configuration at the C2 center. The menthyl moiety, however, proved to be very stable and difficult to remove.



Scheme 6

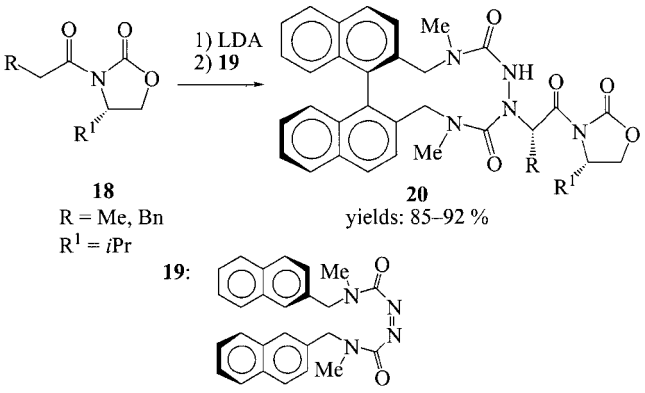
Double diastereoselection was tested using chiral enolates: enantiomerically pure *N*-acyloxazolidinone (*S*)-**16** and its antipode, (*R*)-**16**, were aminated by **14c** (Scheme 7). In both cases, only one stereoisomer of the adduct could be detected. Cleavage of the oxazolidinone auxiliary and esterification generated the α-hydrazino methyl esters **17**, which have the opposite absolute configuration at the C2 center.



Scheme 7

Amination of either (*S*)- or (*R*)-**16** with the achiral dibenzyl azodicarboxylate (DBAD) gave a 9:1 ratio of diastereoisomers having the same relative stereochemistry. The diastereoselectivity is completely controlled by the geometry of the Evans enolate and the bulky isobornyl moiety solely increased the diastereoisomeric ratio.

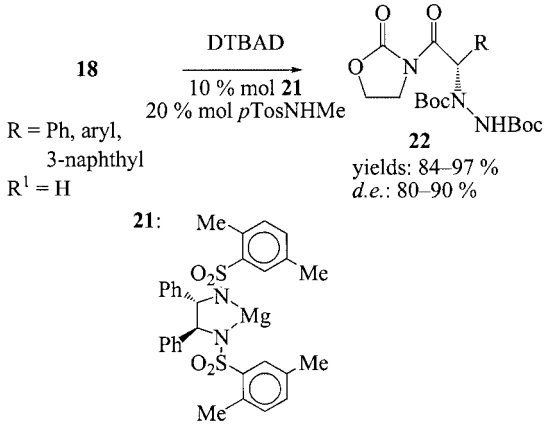
A synthesis of a chiral carboxamide containing a bridging binaphthyl moiety was described by the same authors.[16] Achiral enolates were aminated with excellent diastereoselectivity: only one diastereoisomer of the adduct **20** was observed with an (*S*) absolute configuration at the newly created stereogenic center (Scheme 8). Attempts to cleave the cyclic carboxamide have been unsuccessful.



Scheme 8

3. α-Amination in the Presence of Chiral Catalysts

A first enantioselective amination of *N*-acyloxazolidinones in the presence of a chiral catalyst was reported by Evans and coworkers in 1997.[17] The magnesium bis(sulfonamide) complex **21** derived from the chiral *threo*-diphenylethanamine catalyzed the electrophilic amination of aryl-

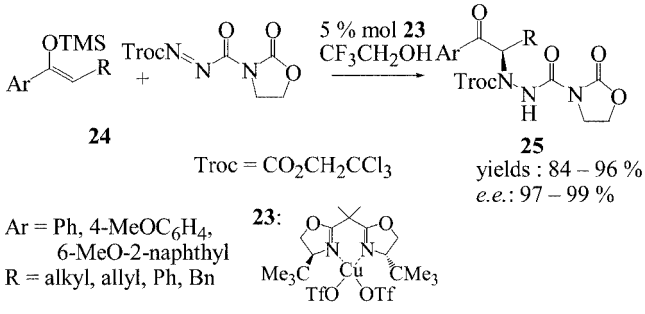


Scheme 9

acetylimides **18** by di-*tert*-butyl azodicarboxylate (DTBAD; Scheme 9). High yields and enantiomeric excesses were observed for the α-hydrazinoimides **22**.

The role of *N*-methyl-*p*-toluenesulfonamide in the catalytic process has not been completely elucidated. This addend, however, clearly accelerates the reaction: the first-order dependence of the reaction rate on this addend has been determined.

The catalytic enantioselective amination of enolsilanes using C_2-symmetric copper(II) complexes as chiral Lewis acids was reported by the same authors in 1999.[18a] The chiral bis(oxazoline)copper(II) complex [Cu·(*S*,*S*)-*tert*-butyl-Box](OTf)$_2$ (**23**) catalyzed the electrophilic amination of the isomerically pure enolsilanes of aryl ketones **24** with azodicarboxylates derivatives (Scheme 10). The (*R*)-hydrazino adducts **25** were obtained in excellent yields and the enantiomeric excesses were higher than 97%. The reaction was completely regioselective on the azo reagent.



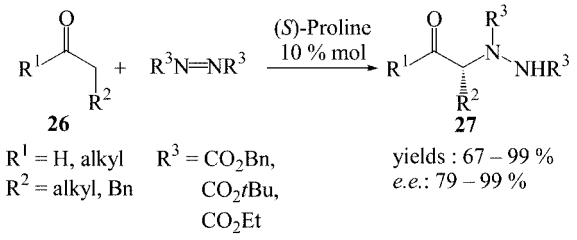
Scheme 10

This methodology was extended to thioester silylketene acetals and acylpyrrole enolsilanes. The ketohydrazides **25** have been transformed into synthetically useful building blocks, such as orthogonally protected hydrazines, *anti*-hydrazino alcohols, and *N*-aminooxazolidinones.

A simple synthetic approach to optically active *syn*-β-amino-α-hydroxy esters has been reported more recently by asymmetric direct α-amination reactions of 2-keto esters using bis(oxazoline)copper(II) complexes as catalysts.[18b]

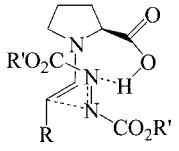
Silver-catalyzed amination of silyl enol ethers has also been investigated.[19] Silver triflate (AgOTf) was found to be the most efficient among the catalysts tested in the reactions. The $AgClO_4$/BINAP asymmetric system showed high enantioselectivity: silyl enol ethers reacted with DBAD smoothly to afford the corresponding amination adducts in excellent yields and up to 86% *ee*.

Proline has been found to catalyze direct asymmetric α-amination of carbonyl compounds with azodicarboxylates.[20] This reaction is a highly efficient and enantioselective process. Proline-catalyzed α-amination reactions of aldehydes and ketones with azodicarboxylates produced the α-hydrazino adducts in excellent yields and enantioselectivities (Scheme 11).[20a–20c]



Scheme 11

The observed stereochemistry has been explained by considering a transition state involving a proline enamine (Scheme 12). This reaction is the first direct α-amination of carbonyl compounds that requires a relatively low amount of an inexpensive and non-toxic catalyst that is available in both enantiomeric forms.

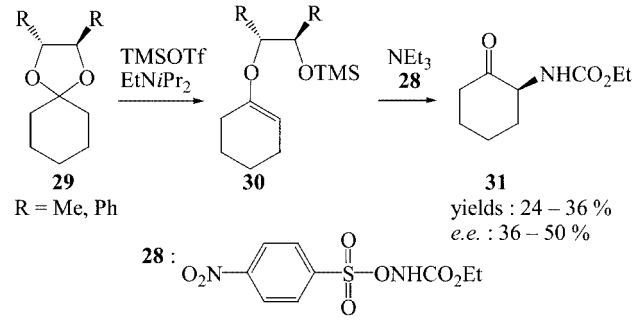


Scheme 12

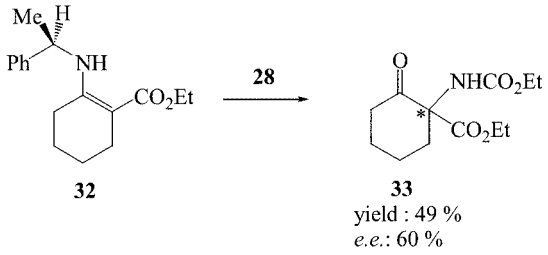
4. Electrophilic α-Amination of Aldehydes and Ketones

Since 1965, ethyl *N*-[(*p*-nitrobenzenesulfonyl)oxy]carbamate (**28**) has been known as a precursor of nitrene.[21] This reagent has been used in the synthesis of *N*-protected α-amino ketones from enamines. Asymmetric induction has been described using proline-derived optically active enamines of cyclohexanone to give the aminated product in low yields.[22] The yield and stereoselectivity of this reaction were significantly enhanced when using chiral enol ethers generated from C_2-symmetric acetals of cyclohexanone **29** (Scheme 13).[23] The best result (36% yield and 50% *ee*) was obtained for acetal **29** (R = Ph) with the use of a fivefold excess of reagent **28** and an equimolar amount of triethylamine.

More recently, a route to α-amino β-keto esters from chiral β-enamino esters was reported by the same authors (Scheme 14).[24] The amination reaction was performed using the sulfonyloxycarbamate **28** in the absence of base.



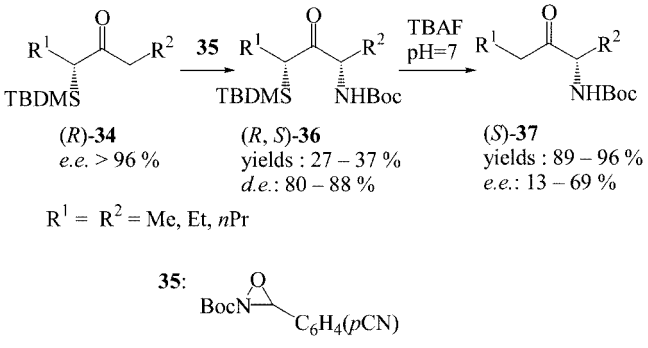
Scheme 13



Scheme 14

The β-enamino ester **32** derived from (*R*)-1-phenylethylamine was aminated under these conditions and the product **33** was isolated with 60% *ee*, but the absolute configuration of the new stereocenter has not been determined. Other chiral β-enamino esters derived from C_2-symmetric pyrrolidines have been tested. In all cases, an intermediate has been detected − possibly the aziridine − whose spontaneous hydrolysis during the reaction gave the α-amino-β-keto ester adducts.

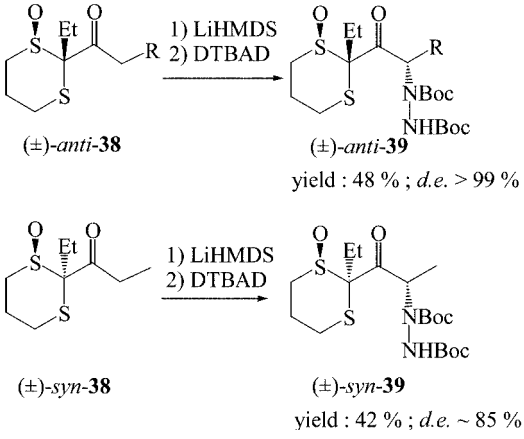
Enantioselective syntheses of α-amino ketones have been described starting from α-silyl ketones through the electrophilic transfer of an NHBoc group of an oxaziridine (Scheme 15).[25] The regioselective deprotonation of enantiomerically pure α-silyl ketones **34** afforded reactive chiral enolate nucleophiles that were trapped by the oxaziridine **35**. The α-aminated α'-silyl ketones **36** were isolated in moderate yields and good diastereoselectivities. Finally, the silyl controlling group was cleaved and the *N*-Boc-protected α-amino ketones were obtained.



Scheme 15

Lower diastereoisomeric excess (41%) was observed when the R^2 substituent of the α-silyl ketone was a benzyl group. The use of tetrabutylammonium fluoride (TBAF) for the cleavage of the silyl group led to the complete racemization of the α-amino ketone. The best conditions were obtained when the reaction was performed at low temperature and using TBAF in a buffer solution. The adducts were obtained almost quantitatively in moderate enantiomeric excesses, which indicates that partial racemization occured.

Diastereoselective electrophilic amination of ketone enolates mediated by the DITOX (1,3-dithiane 1-oxide) asymmetric building block was as first proposed in 1994 and reported in full in 2000.[26] The lithium enolates of (±)-*anti*- or (±)-*syn*-2-ethyl-2-propanoyl-1,3-dithiane 1-oxides **38** were diastereoselectively aminated using DTBAD as the nitrogen electrophile (Scheme 16).



Scheme 16

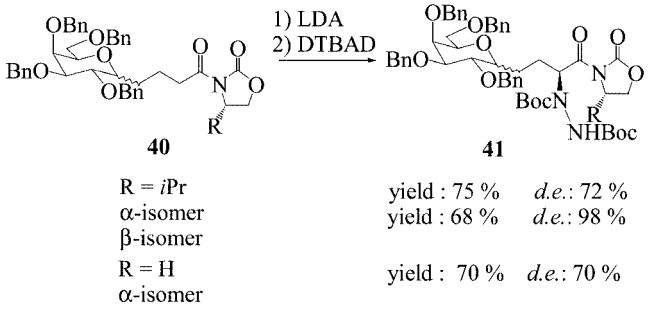
The sense of the induced stereochemistry was rationalized on the basis of a simple chelation-control model. The absolute configuration of the newly created stereocenter was proven by conversion of two other non-racemic examples into known α-hydrazino acids. The non-racemic (+)-*anti*-acyldithiane oxides **38** (R = Bn, *i*Pr) were investigated and the (*S*) absolute configuration of the aminated stereocenter was confirmed after analysis of the optical rotations of the α-hydrazino benzyl esters. These compounds were derived from the corresponding α-hydrazino ketones (+)-*anti*-**39** by removal of the sulfoxide moiety, oxidative cleavage of the resulting diketones, and esterification.

5. Electrophilic α-Amination of Carboxylic Acid Derivatives

The electrophilic amination of diethylmalonate with azodicarboxylates was reported as far back as 1924.[27] In 1986, Oppolzer[28] and Gennari[29] independently reported the asymmetric amination of chiral silylketene acetals with DTBAD. In the same year, Evans[30] and Vederas[31] both published enantioselective synthetic routes to α-amino acids using chiral *N*-acyloxazolidinone enolates and DTBAD. These methods presented the advantages of high to excel-

lent diastereoisomeric excesses and good chemical yields for the electrophilic amination step, easy prediction of the absolute configuration of the reaction products, the potential to obtain both enantiomers of the α-amino acids, and the ability to recycle the chiral auxiliaries.

These chiral approaches to α-amino acids have been developed extensively. Recently, the syntheses of C-linked α-galactoserine and homoserine derivatives have been described from the reaction of oxazolidinone enolates derived from galactosyl compounds with DTBAD (Scheme 17).[32] The chiral oxazolidinones enolates **40** that bear α- and β-perbenzylated galactosyl moieties were aminated to give the corresponding α-hydrazino products **41** in 72 and 98% diastereoisomeric excesses, respectively.

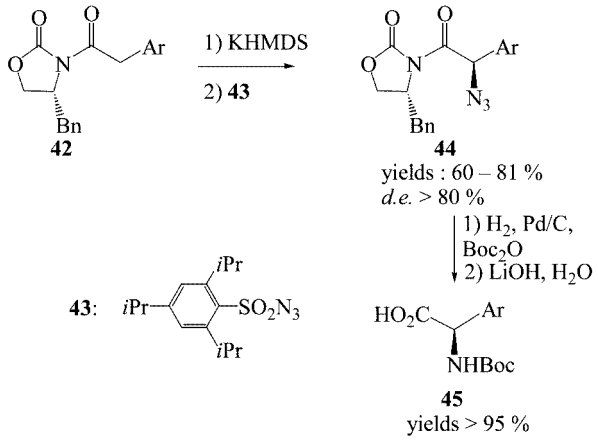


Scheme 17

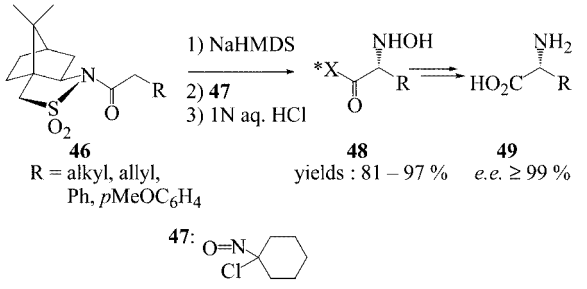
It has been proposed that the benzyl protecting group at the C2 position of the α-galactosyl moiety hinders the approach of the electrophile. A higher diastereoselectivity (92%) was observed for the reaction of DTBAD with the less-hindered permethylated α-galactosyl derivative. The role of the perbenzylated α-galactosyl moiety in inducing 1,4-remote asymmetric induction during the electrophilic amination step has been examined by removing the chirality of the oxazolidinone (R = H); the expected product was obtained with a diastereoisomeric excess of 70%. The absolute configuration, however, of the new aminated stereocenter has not been determined.

The azido transfer in the reaction with enolates was investigated by Evans and coworkers, as was the partitioning of the reaction between the azido- and diazo-transfer pathways.[33] Azidation reactions with the trisylazide **43** enjoy considerable scope, while displaying high yields and high levels of stereoselectivity. The amino derivatives were obtained by subsequent fragmentations of the triazene intermediates, followed by reduction. Several syntheses of vancomycin-related arylglycine **45** have been performed using enolate electrophilic azidation (Scheme 18).[34]

Chiral amide enolates have also been used as substrates in electrophilic amination reactions for the asymmetric syntheses of α-amino acids. In 1990, Oppolzer and coworkers proposed approaches to α-amino and α-*N*-hydroxyamino acids using enolates of *N*-acylbornylsultams **46** and 1-chloro-1-nitrosocyclohexane (**47**) (Scheme 19).[35] The bornane[10,2]sultam auxiliary and its antipode are readily available on kilogram scales and have proved to be extremely effective as stereodirecting groups.



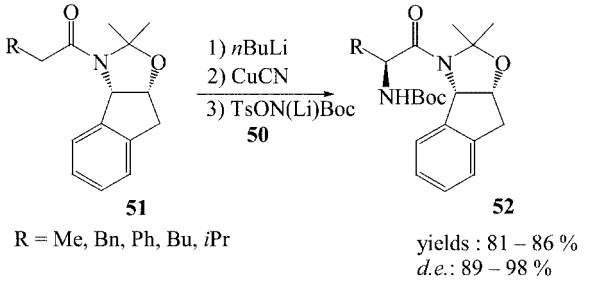
Scheme 18



Scheme 19

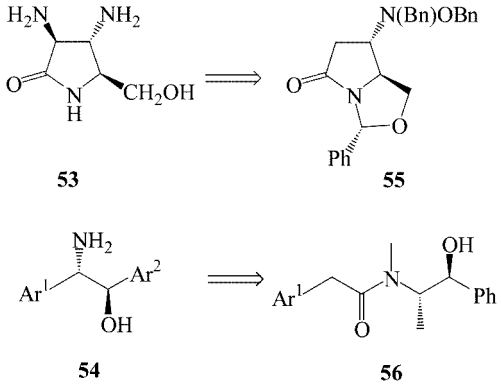
The observed reaction topicity is consistent with the kinetically controlled formation of chelated (*Z*)-enolates and attack by the nitroso electrophile from the face opposite the lone pair of electrons of the nitrogen atom.

Later, the Merck group applied the electrophilic amination using lithium *tert*-butyl *N*-tosyloxycarbamate (**50**) to the chiral amide derived from the *cis*-aminoindanol **51** (Scheme 20).[36] The sense of the asymmetric induction was consistent with the preferential approach of the aminating reagent from the least-hindered face of the amide cuprate.



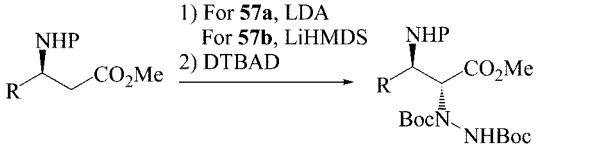
Scheme 20

More recently, electrophilic aminations using chiral amide enolates and DTBAD have been employed as key steps for the syntheses of azasugar analogues[37] **53** and 1,2-diaryl-2-aminoethanols[38] **54** (Scheme 21); the amide substrates were a chiral γ-lactam **55** derived from (*S*)-pyroglutamic acid and (*S*,*S*)-(+)-pseudoephedrine arylacetamides **56**, respectively.



Scheme 21

The use of azodicarboxylates is particularly valuable in the *anti*-diastereoselective amination of 3-functionalized esters by the corresponding metal enolates. 2,3-Diamino acids and 2-amino-3-hydroxy acids have been synthesized diastereoselectively by electrophilic amination of 3-amino and 3-hydroxy esters, respectively. In 1988, Seebach and coworkers described the electrophilic amination of the *N*-protected 3-aminobutanoic methyl ester **57a** using DTBAD (Scheme 22).[39] The *anti* product was obtained in 96% yield and excellent diastereoselectivity (> 99%). In 1994, Sardina and coworkers applied this method to *N*-protected dimethyl aspartate derivatives.[40] The best result was observed for the *N*-Pf-dimethyl aspartate derivative **57b** (Pf = 9-phenylfluorenyl) when using LiHMDS in the presence of HMPA as the base and DTBAD as the electrophilic aminating reagent. The *anti* aminated adduct **58** was isolated in 80% yield and 93% diastereoisomeric excess.

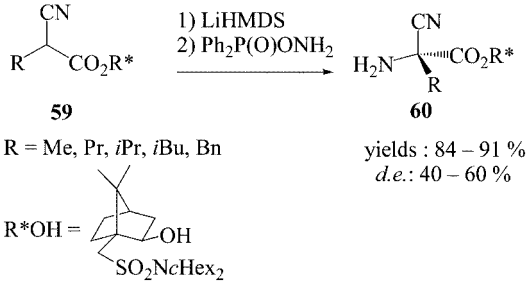


57a R = Me ; P = Bz
57b R = CO_2Me ; P = Pf

58a yield : 96 % ; *d.e.* > 99 %
58b yield : 80 % ; *d.e.* = 93 %

Scheme 22

Another route to 2,3-diamino acids was developed through the electrophilic amination of chiral 2-cyano esters derived from (1*S*,2*R*,4*R*)-10-(dicyclohexylsulfamoyl)isobornanol.[41] These compounds were aminated using *O*-(diphenylphosphanyl)hydroxylamine (Scheme 23). The corresponding 2-amino-2-cyano esters **60** were obtained in high yields and with moderate to acceptable diastereoselectivities.



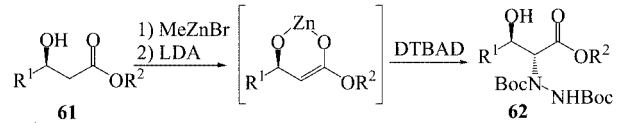
Scheme 23

Compounds **60** were reduced and hydrolyzed to form the 2-alkyl-2,3-diaminopropanoic acids, which are (*R*)-2-aminomethyl analogues of natural α-amino acids.

Chiral 3-hydroxy esters and 1,3-dioxa-4-ones are well-known substrates for the diastereoselective α-alkylation reactions developed by Frater[42] and Seebach[43]. These chiral compounds are available in both enantiomeric forms and have been aminated at the α-carbon center with high to excellent stereoselectivity: 60−80% for 3-hydroxy esters and > 95% for 1,3-dioxa-4-ones. Two reports describing similar results appeared simultaneously in 1988.[44] The 3-hydroxy ester lithium enolates reacted rapidly at −78 °C with DTBAD to give a readily separable mixture of *syn* and *anti* adducts, of which the *anti*-2-hydrazino-3-hydroxy ester was the major product. These compounds are very useful intermediates for the synthesis of *anti*-2-amino-3-hydroxy acids. D-Allothreonine[43] and (*S*)-trifluorothreonine methyl ester[45] have been synthesized diastereoselectively from the corresponding 3-hydroxybutanoic and 4,4,4-trifluoro-3-hydroxybutanoic acids protected as 1,3-dioxa-4-ones.

A number of different synthetic applications have been developed starting from (*S*)-ethyl 3-hydroxybutanoate and (*S*)-dimethyl malate, such as synthetic equivalents of 2,4-deoxy-2-amino-L-threose and L-erythrose,[46a] 4-acetylamino-2,4,6-trideoxy-L-ribohexose,[46b] *N*-acetyl-L-tolyposamine,[46c] *cis*-monobactams,[46d] and tetraacetyl-D-ribosphingosine.[46e]

Another alternative for obtaining excellent diastereoselectivity in the electrophilic amination of 3-hydroxy ester enolates is chelation of the dianion by higher organometallic species; the zinc enolates appear to be particularly suitable for this process (Scheme 24).[47] Generating the enolate by using LDA as base, in the presence of MeZnBr, gave the *anti* product **62** with diastereoisomeric excesses > 98%. Functionalized 3-hydroxy esters **61** were aminated under these conditions.

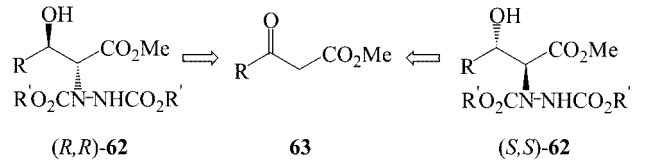


61
R^1 = alkyl, aryl, alkenyl, $(MeO)_2CH(CH_2)_n$
R^2 = Me, Et

62
yields: 53 – 70 %
de > 98 %

Scheme 24

Both antipodes of enantiomerically pure 3-hydroxy esters have been obtained almost quantitatively by hydrogenation of 3-keto esters in the presence of chiral ruthenium catalysts.[48] A general and practical method for the preparation of both enantiomers of *anti*-2-hydrazino-3-hydroxy esters (*R*,*R*)-**62** and (*S*,*S*)-**62** from the 3-keto esters **63** has been proposed by coupling two sequential reactions, namely catalytic hydrogenation and electrophilic amination (Scheme 25).



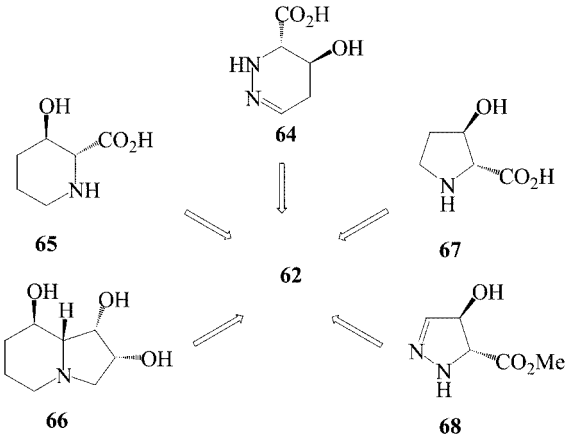
(*R,R*)-**62** **63** (*S,S*)-**62**

Scheme 25

Syntheses of β-hydroxytyrosines have been developed starting from 3-keto esters. (2*R*,3*R*)-3-(3-chloro-4-hydroxyphenyl)-3-hydroxyalanine was obtained from **63** (R = *m*-Cl-*p*-$BnOC_6H_3$) and was included in a dipeptide that constitutes the eastern part of vancomycin.[49a] The synthesis of (2*S*,3*S*)-3-(3-hydroxy-4-methoxyphenyl)-3-hydroxyalanine from **63** (R = *m*-BnO-*p*-$MeOC_6H_3$) has been described in the first approach to the cycloisodityrosine unit of RA IV.[49b]

Recently, a short total synthesis of sulfobacin A was proposed starting from **63** (R = $Me_2CH(CH_2)_{11}$].[50]

anti-2-Hydrazino-3-hydroxy esters **62** are also chiral building blocks for the synthesis of functionalized nitrogen heterocycles (Scheme 26).[51] (*S,S*)-**62** (R = EtCH=CH) was the key intermediate in the synthesis of the (3*S*,4*S*)-4-hydroxy-2,3,4,5-tetrahydropyridazine-3-carboxylic acid (**64**) component of luzopeptine A.[52a] (2*R*,3*R*)-3-Hydroxypipecolic acid[52b] (**65**) and (−)-swainsonine[52c] (**66**) were obtained via (*R,R*)-**62** (R = $Me_2C=CHCH_2$). *trans*-3-Hydroxy-D-proline[52d] (**67**) and (4*S*,5*R*)-4-hydroxy-5-methoxycarbonyl-Δ^2-pyrazoline[52e] (**68**) were synthesized respectively from (*R,R*)-**62** [R = $(MeO)_2CHCH_2$] and (*R,S*)-**62** [R = $(MeO)_2CH$].

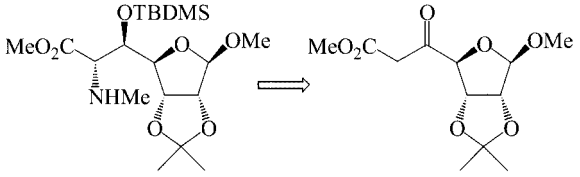


64 **65** **62** **67** **66** **68**

Scheme 26

An asymmetric route to the ribosyl-derived 2-amino-3-hydroxy ester, a component of the ribosyl-diazepanone core of the liposidomycins, was reported very recently.[53] The *anti*-*N*-methylated-*O*-silylated 2-amino-3-hydroxy ester **69** was obtained from the D-ribosyl-derived 3-keto ester **70** (Scheme 27).

Catalytic hydrogenation of the optically pure 3-keto ester **70** has been conducted under classical conditions at atmospheric pressure in the presence of chiral ruthenium complexes.[48d] The diastereoselectivity was completely controlled by the chirality of the diphosphane ligand in the catalyst. The diastereoselective amination step was carried out with DBAD because the conditions of deprotection of the benzylcarbamate are compatible with the presence of an acetal group on the ribosyl moiety. The relative and absolute configurations of the C2 and C3 stereocenters were confirmed by crystallographic analysis.



69 **70**

Scheme 27

6. Conclusion

In this microreview, we have presented several promising new asymmetric methods to generate C−N bonds by electrophilic amination. Amination at the α-position of carbonyl groups provides one of the most efficient methods for the synthesis of α-amino acids and their derivatives.

Synthetic applications have been described by which highly functionalized target compounds and nitrogen heterocycles can be obtained.

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