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Recent applications of α-phenylethylamine (α-PEA) in the preparation of enantiopure compounds. Part 3: α-PEA as chiral auxiliary. Part 4: α-PEA as chiral reagent in the stereodifferentiation of prochiral substrates[1]

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Contents

1. α-PEA as chiral auxiliary

Most organic natural products are chiral and nature usually produces them in a single enantiomeric form. In contrast, chemists seeking to synthesize enantiopure substances depend on the availability of chiral starting materials, reagents, auxiliaries, or catalysts. In this regard, the general importance of chiral amines is well-recognized and α-phenylethylamine (α-PEA) is well known as a simple, yet powerful, chiral adjuvant. Furthermore, both enantiomers of α-PEA are readily produced[1] and accessible at a low price, so that their recovery may not be critical even after use on a large scale. Indeed, one advantage of α-PEA as an auxiliary is its convenient reductive removal.

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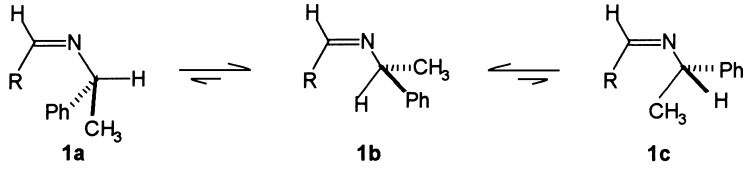
In a previous report,[1] we highlighted recent applications of α-PEA and some of its derivatives as chiral adjuvants in the resolution of racemates and as ligands in asymmetric catalysis. The present report covers the use of α-PEA as chiral auxiliary and as a chiral base in asymmetric synthesis, with special attention given to applications appearing in the 1989–1998 period.

1.1. Chiral imines (1,3-stereoinduction)

Condensation of aldehydes with (*R*)- or (*S*)-α-PEA affords the corresponding chiral imines, where the substantial difference in size between the substituents at the stereogenic center (H vs CH_3 vs C_6H_5) can be anticipated to effectively differentiate the diastereotopic faces at the prochiral C=N group, provided that one particular conformation of the reactive species predominates at the transition state for reaction (e.g. towards hydrogenation, nucleophilic addition, etc.).

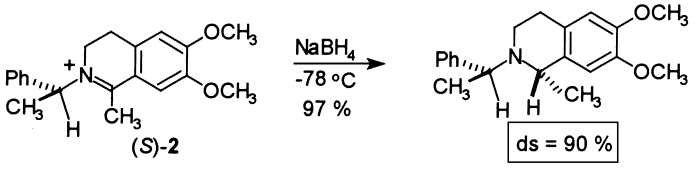
1.1.1. Conformational aspects: $A^{1,3}$ strain

The concept of allylic 1,3-strain ($A^{1,3}$ strain)[2] dictates that for reactions at the double C=N bond in *Z*-imines such as **1**, one needs to consider mainly the conformation **1b**, because conformations **1a** and **1c** are substantially destabilized by allylic 1,3-strain. Indeed, the conformational analysis of **1** carried out by Broeker et al.[3] led to the conclusion that this chiral imine is effectively locked in the ground state **1b** (C–H bond eclipsing the double bond). Thus, the methyl and phenyl groups efficiently differentiate the diastereotopic faces of the C=N bond in the transition states for reaction, since factors that influence reactant conformational energies will also influence transition state conformational energies (Scheme 1).



Scheme 1.

Hoffmann[2b] has pointed out that a clear-cut example in which the product formation is dictated by allylic $A^{1,3}$ strain is **2**. The phenyl and the methyl groups at the stereogenic center differentiate the prochiral C=N group, so that addition of hydride from the side of the less bulky methyl group is preferred (Scheme 2).[4]

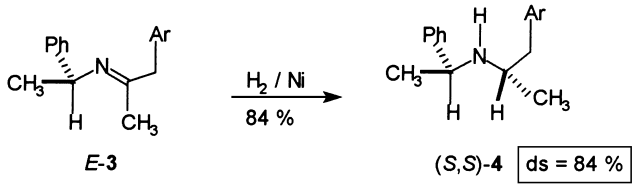


Scheme 2.

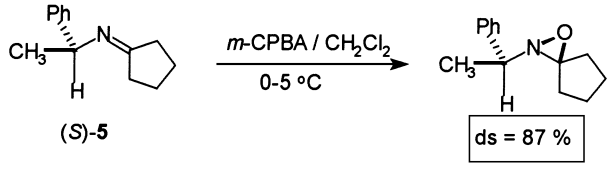
Similarly, *E*-configured imine **3** is hydrogenated with good diastereoselectivity,[5] apparently as a result of allylic $A^{1,3}$ strain control, to produce (*S*)-**4** (Scheme 3).

Furthermore, allylic $A^{1,3}$ strain is also responsible for the asymmetric induction recorded for the oxaziridination of imine (*S*)-**5** (Scheme 4).[6]

Interestingly, crystal-structure and NMR-spectroscopic studies revealed that conformer **A** in phenylethylrhodamines **6**–**8** highly predominates in the conformational equilibria depicted in Scheme 5.[7] That is, the methine proton points towards the thiocarbonyl sulfur atom, probably to minimize steric repulsion

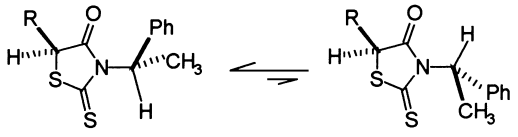


Scheme 3.



Scheme 4.

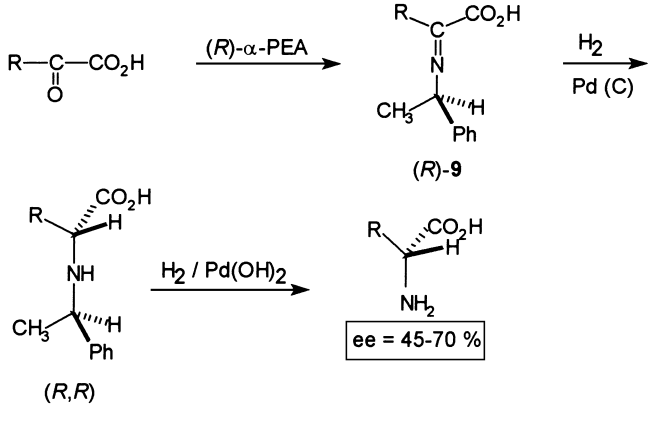
with the phenyl and methyl groups. This information can be of practical importance in the prediction of relative reactivities for diastereotopic faces in related compounds.



Scheme 5.

1.1.2. Pioneering applications in asymmetric synthesis

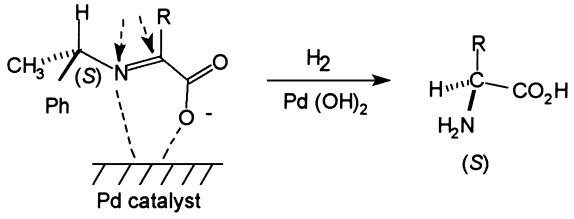
An early application of (*R*)- and (*S*)-α-PEA in the stereoselective synthesis of α-amino acids (Scheme 6) was reported by Hiskey and Northrop in 1961,[8] who carried out the diastereoselective hydrogenation of chiral imines **9**.



Scheme 6.

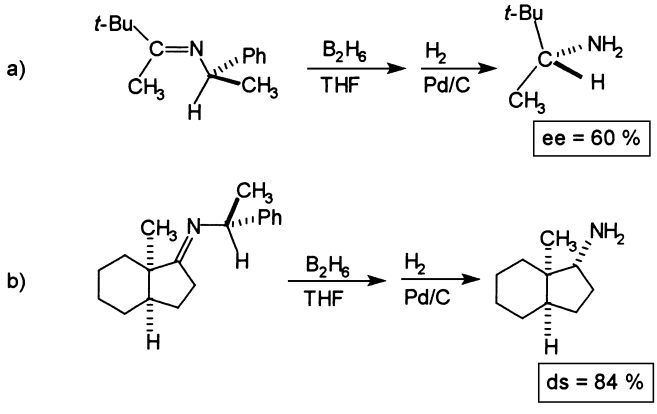
Hiskey and Northrop[8] pointed out that the configuration of the α-amino acid produced was the same as that of the α-PEA from which it was derived; however, no model was advanced to explain this

observation. A rationalization of the stereochemical results was proposed by Kanai and Mitsui,[9] but this was contradicted by the observations of Harada and co-workers,[10,11] who advanced the model presented in Scheme 7, where Pd catalyst-bonded hydrogen approaches the unsaturated substrate from the less hindered side. It will be appreciated that the Harada mechanism uses a substrate conformation where the methine bond is eclipsed to the C=N double bond, as predicted from A[1,3] strain considerations (see Section 1.1.1).



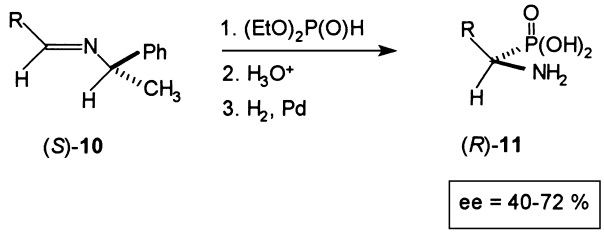
Scheme 7.

During the late sixties and early seventies, Solladie and co-workers[12] developed a useful procedure for the enantioselective synthesis of chiral amines based on the diastereoselective reduction of chiral imines derived from (*R*)- and (*S*)-α-PEA (Scheme 8).



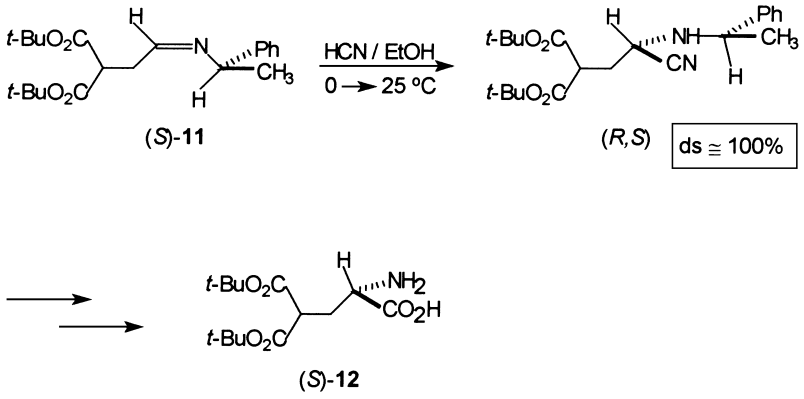
Scheme 8.

One of the first procedures for the enantioselective synthesis of chiral aminophosphonic acids was described by Gilmore and McBride,[13,14] who treated imines **10** with diethyl phosphite. The resulting diastereoisomeric products were hydrolyzed and hydrogenolyzed to give the desired enantioenriched aminophosphonic acids, (*R*)-**11** (Scheme 9).



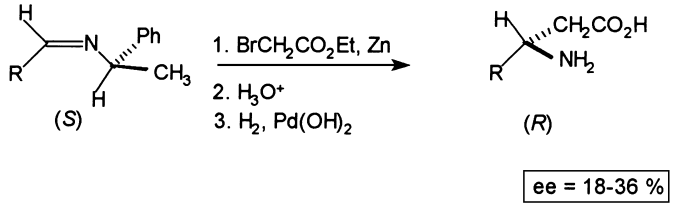
Scheme 9.

In the late seventies, Schwyzer and collaborators[15] modified the Strecker method in order to obtain enantiopure α-amino acids. A typical example of their modification is the preparation of the *t*-butyl ester derivative of (*S*)-ɣ-carboxyglutamic acid, (*S*)-**12**, from (*S*)-**11** (Scheme 10).



Scheme 10.

In 1978, Furukawa and co-workers[16] described a pioneering procedure for the asymmetric synthesis of β-amino acids[17] based on the reaction of α-PEA derived imines with Reformatsky reagents (Scheme 11). Nevertheless, the enantiomeric purities of the final products were low.



Scheme 11.

In this context, in 1980, Ojima and Inaba[18] reported the asymmetric synthesis of β-lactams using the reaction of ketene silyl acetals with chiral imines (*S*)-**13** in the presence of titanium tetrachloride. Some of their results are summarized in Table 1 (assignment of the configuration at C(4) in β-lactams **14** was achieved by chemical correlation with (*S*)-leucine).[18]

1.1.3. Recent applications of N-α*-phenylethylimines in asymmetric synthesis*

In 1990, Bringmann and co-workers[19] described the preparation of enantiopure protected (3*S*,4*S*)-statine **15**. The crucial step in this synthesis was the highly diastereoselective hydrogenation of imine (*S*)-**16**, obtained by condensation of (*S*)-α-PEA and isovalerophenone (Scheme 12).

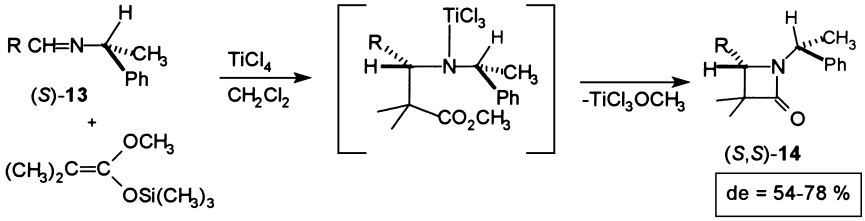
More recently, the Bringmann group[20] reported a convenient procedure for the synthesis of all possible stereoisomers of tetrahydroisoquinoline alkaloids **17** (Scheme 13). The key reaction here was the diastereoselective (ds >90%) reductive amination of 1-aryl-2-propanone **18**.

In a related development, Hattori and co-workers[21] described the enantioselective synthesis of β-andrenoreceptor agonist FR165914 [(*R*,*S*)-**19**]. This asymmetric synthesis employed epoxide (*R*)-**20** and aminobenzocycloheptene (*S*,*S*)-**21**, obtained by the diastereoselective reduction of (*S*)-phenylethylimine (*S*)-**22** (Scheme 14).

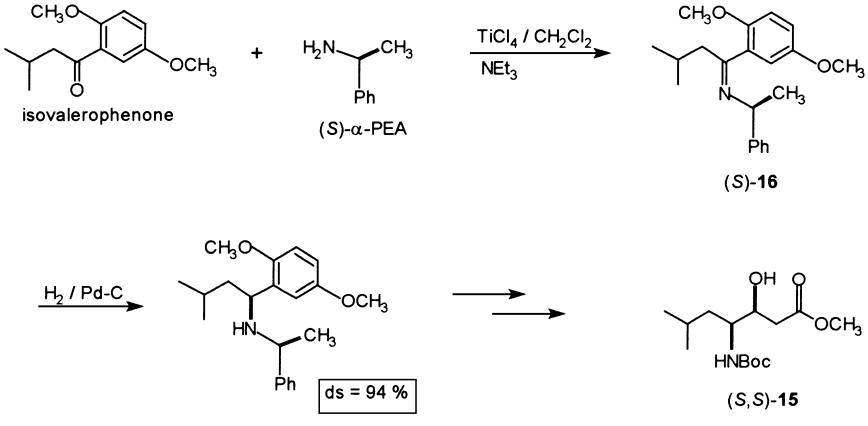
Very recently, Frahm and co-workers[22,23] achieved the diastereo- and enantioselective synthesis of *cis*-2-hydroxycyclohexanamines **23** via the catalytic hydrogenation of imines **24** with Raney-nickel, followed by catalytic hydrogenolysis of the chiral auxiliary (Scheme 15).

Although the hydrogenation step could lead in principle to four diastereomeric amines, ^{13}C NMR spectra correlated with a single product of (1′*S*,1*S*,2*R*) configuration (Scheme 15). This was explained

Table 1
Asymmetric synthesis of β-lactams by reaction of ketene silyl acetals with (*S*)-phenylethylimines[18]



R	Yield (%)	dr [(*S*,*S*) : (*R*,*S*)]	de (%)
Et	66	77 : 23	54
n-Pr	72	83 : 17	66
n-Bu	73	83 : 17	66
i-Bu	71	89 : 11	78



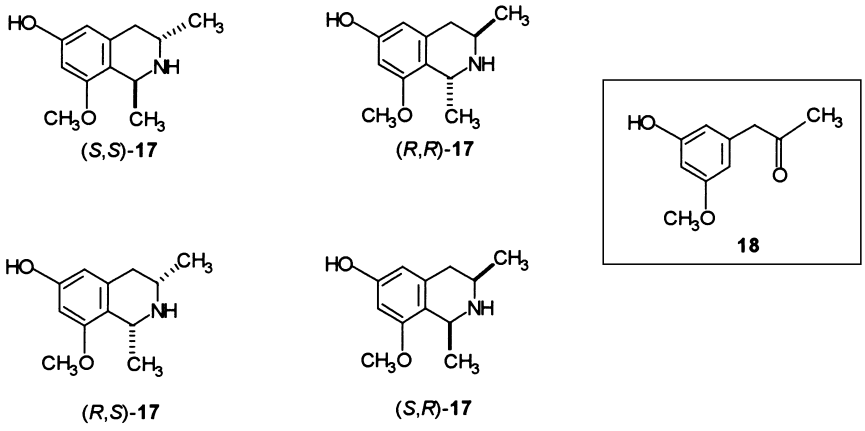
Scheme 12.

by a diastereoselective *cis* hydrogenation of the imines from the sterically less hindered *Si*-face followed by epimerization. (Dynamic kinetic resolution!)

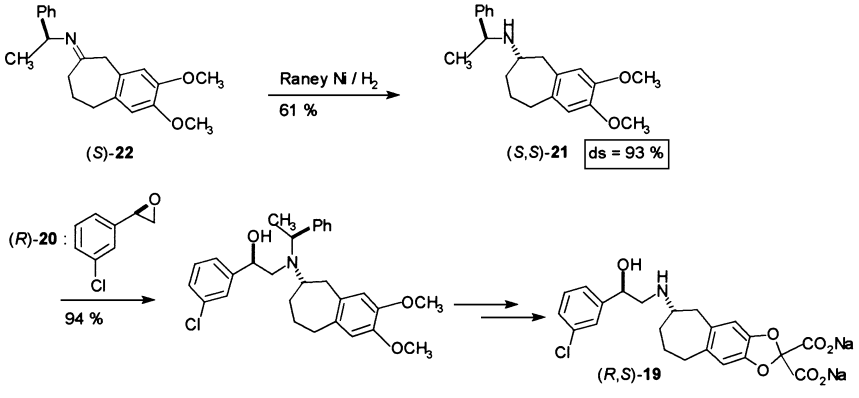
Hydride addition to α-phenylethylimines also takes place with high stereoselectivity. For example, David et al.[24] disclosed in 1990 that the imine formed from 1-acetylferrocene and (*R*)-α-PEA, undergoes a highly diastereoselective reduction with $NaBH_4$ to give diastereomerically pure (*R*,*R*)-**25** after a single recrystallization. This was then converted to (*R*)-1-ferrocenylethyl acetate of high enantiomeric purity (Scheme 16).

In a related development, (*S*)-3-aminoquinuclidine **26**, an important building block for the synthesis of enantiopure 5-HT_3 serotonin receptor antagonists, was prepared from 3-quinuclidinone and (*R*)-α-PEA.[25] The key reaction was the reduction of the chiral imine by $NaBH_4$ (Scheme 17).[26]

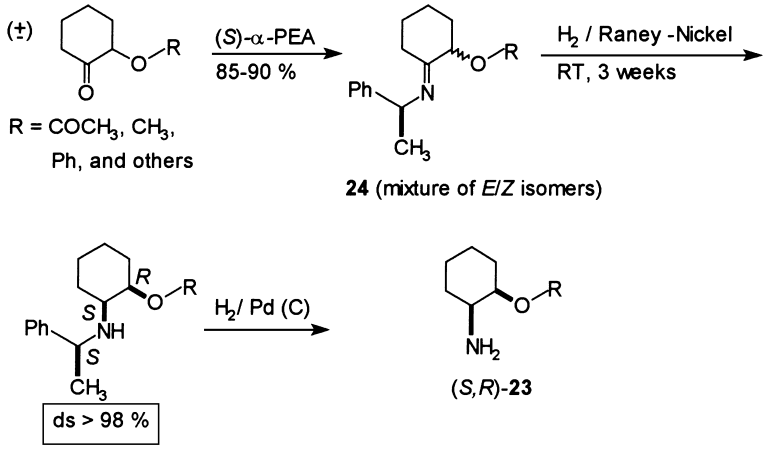
Similarly, enantiopure neopentylamine derivatives (*R*)-**27** were readily prepared from ketones **28** in a sequence involving imine formation with (*R*)-α-PEA followed by a highly diastereoselective reduction with $NaBH_4$ (Scheme 18).[27]



Scheme 13.

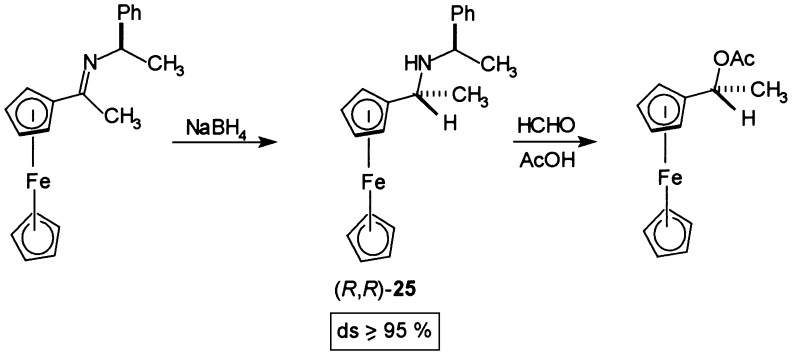


Scheme 14.

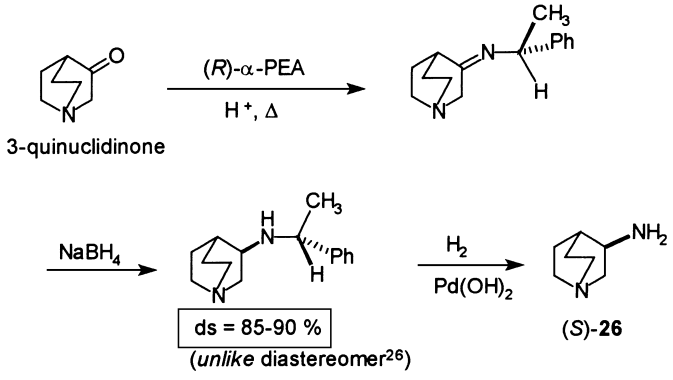


Scheme 15.

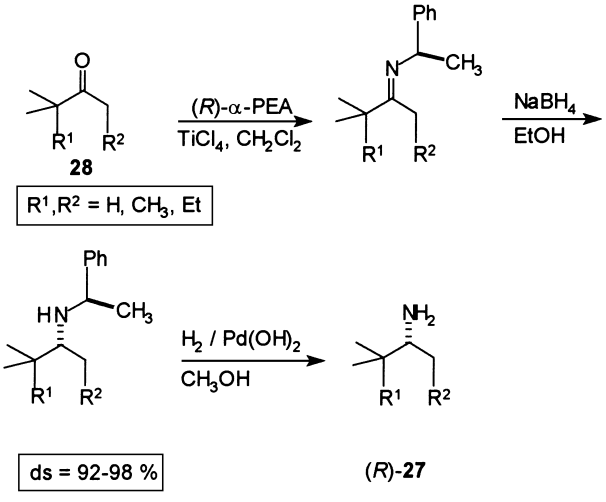
In this context, reduction of isoquinolinium ion (*S*)-**29** with $NaBH_4$ afforded essentially pure (*S*,*S*)-**30**,[28] which was then converted to the structure advanced for dehassiline, an alkaloid isolated from the bark of *Dehassia kurzii*.[29] Nevertheless, the spectral data for the synthetic compound (Scheme 19) differed from those reported for natural dehassiline, which means that the proposed structure must be reexamined.



Scheme 16.

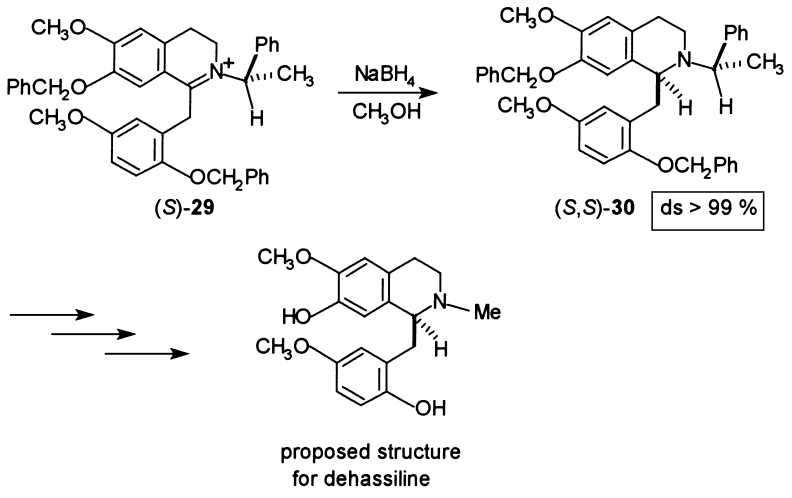


Scheme 17.



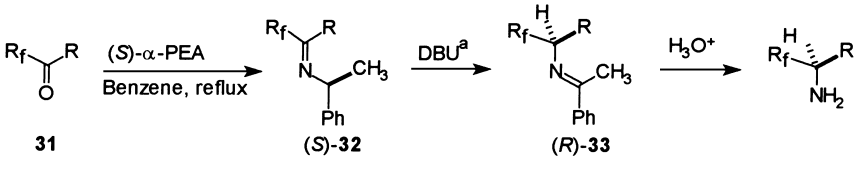
Scheme 18.

An interesting biomimetic reductive amination procedure has recently been developed by Soloshonok and co-workers.[30] In this work, a [1,3]-proton shift reaction is used as an efficient, reducing-agent-free method for the synthesis of various fluorine-containing amines. Direct condensation of ketones **31** and (*S*)-α-PEA afforded *anti* diastereoisomers **32**, which were isomerized under basic conditions to give rearranged derivatives (*R*)-**33** as the main enantiomeric products. Final hydrolysis afforded the desired chiral amines in high enantiomeric purities (Table 2).



Scheme 19.

Table 2
Asymmetric isomerization of (*S*)-**32** to (*R*)-**33**[30]

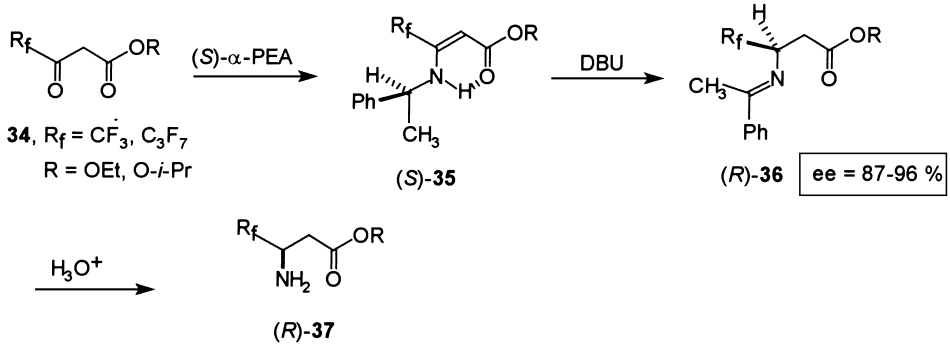


R	R_f	DBU (equiv)	T (°C)	Yield (%)	ee (%)
$PhCH_2$	CF_3	1	50	86	88
$PhCH_2$	CF_3	1	80	82	85
$PhCH_2$	CF_3	2	21	93	88
CH_3	CF_3	1	60	90	93
CH_3	CF_3	1.5	60	94	93
Et	CF_3	1	60	87	87
Et	CF_3	1.5	60	90	87
CH_3	C_3F_7	1.5	60	74	97

[a]DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene.

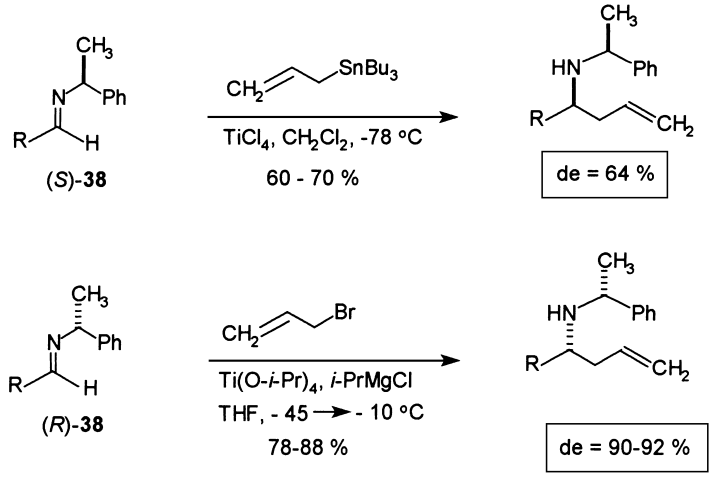
In another application of the stereospecific [1,3]-proton shift reaction, direct condensation between β-keto ester **34** and (*S*)-α-PEA afforded (*Z*)-enamine **35**, stabilized by intramolecular hydrogen bonding. Treatment of **35** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) catalyzed the isomerization to the target

product **36** with high enantiomeric purity. Imines **36** were readily hydrolyzed to β-amino acids (*R*)-**37** (Scheme 20).[31]



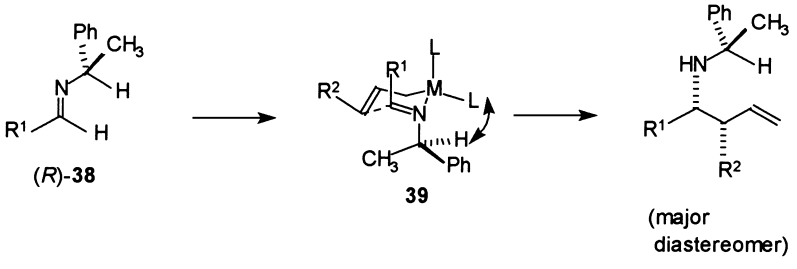
Scheme 20.

The allylation of *N*-phenylethylamines **38** (Scheme 21) was recently reviewed by Enders and Reinhold.[32] Salient results include the Lewis-acid-induced addition of allylstannanes in the presence of $TiCl_4$ (ds=82–91%), reported by Yamamoto et al.[33] and the reaction of the in situ prepared reagents [allylic halides and $Ti(O\text{-}i\text{-}Pr)_4$, *i*-PrMgCl in diethylether] (ds=95–96%) developed by Sato and Gao.[34]



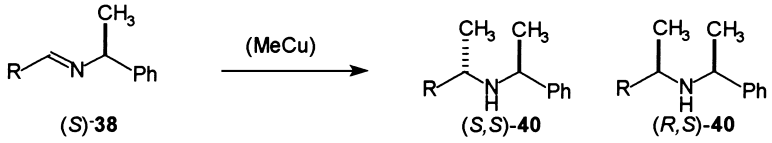
Scheme 21.

A cyclic chair transition state model (**39**, Scheme 22) has been used to explain the observed stereoselectivity in the allylation reaction. Steric interaction between the α-phenylethyl group and the ligand L in **39** may overcome allylic $A^{1,3}$ strain (Section 1.1.1).



Scheme 22.

Table 3
Diastereoselective addition of methylcopper and dimethylcuprate reagents to *N*-(α-phenylethyl)-imines in the presence of BF_3[35]

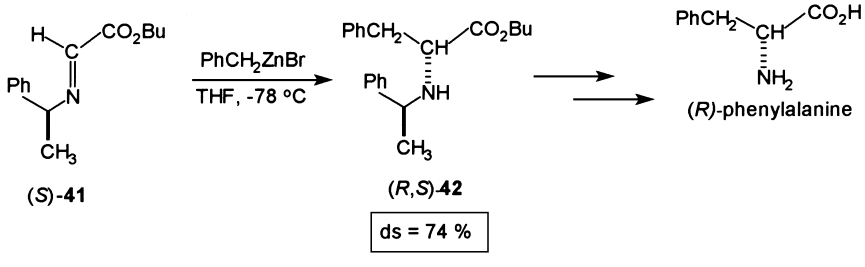


(*S*)-**38** (*S,S*)-**40** (*R,S*)-**40**

R	MeCu (equiv)	yield (%)	Diastereoselectivity (*S,S*) : (*R,S*)
Ph	Me_2CuLi-BF_3-LiI (5)	47	93 : 7
Ph	Me_2Cu-BF_3-LiI (2)	43	94 : 6
Ph	$Me_2CuMgCl$-BF_3-MgICl (2)	70	86 : 14
Ph	MeCu-BF_3-$MgCl_2$ (2)	87	90 : 10
o-C_6H_4-OCH_3	" "	80	73 : 27
o-C_6H_4-OCH_3	$Me_2CuMgCl$-BF_3-MgICl (2)	70	70 : 30
n-C_5H_{11}	" (5)	80	15 : 85
t-Bu	" (2)	0	-

In a series of contributions from the Bologna School,[35–39] various nucleophiles have been added to chiral imines **38** with high diastereoselectivity. For example, in 1990, Boga et al.[35] demonstrated the feasibility of using organocopper compounds in the presence of boron trifluoride (Table 3). Several trends were identified in this work: (1) copper(I) reagents are more reactive and more selective than cuprates; (2) copper reagents prepared from methylmagnesium chloride are more reactive than analogous derivatives prepared from methyllithium; and (3) both the reactivity and diastereoselectivity are influenced by the nature of the R group at the imine (Table 3).

In this context, a pioneering study by Yamamoto and Ito[40] showed that organozinc reagents reacted with chiral α-iminoester **41** at the α-carbon, whereas other organometallic reagents (RM, R=Mg, Al, Cu, Ti, B) reacted at the nitrogen atom. In particular, benzylzinc bromide produced (*R*)-**42** with moderate diastereoselectivity (absolute configuration determined by correlation with phenylalanine) (Scheme 23).

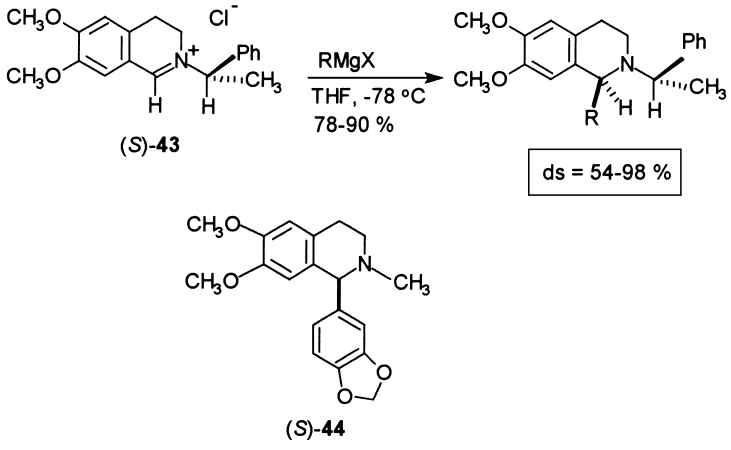


(*S*)-**41** (*R,S*)-**42**

ds = 74 %

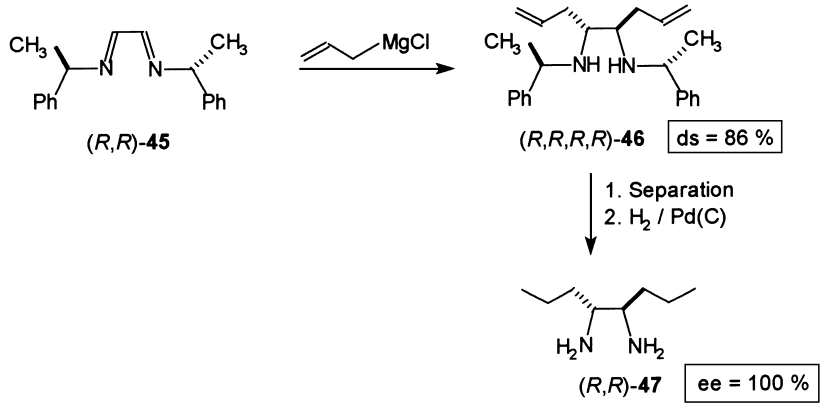
Scheme 23.

In related experiments, iminium ions (*S*)-**43** were found to participate in diastereoselective nucleophilic addition reactions with Grignard reagents (Scheme 24).[41] The stereospecific synthesis of (*S*)-cryptostyline I, (*S*)-**44**, is a nice application of this methodology.



Scheme 24.

In 1991, Neumann and co-workers[42,43] described a diastereoselective synthesis of vicinal diamines, important ligands for metal chelation, via the reaction of allylic Grignard reagents with C_2-symmetric 1,2-bisimine (*R*,*R*)-**45**. Thus, double allylation afforded all-(*R*) diamine **46** as the main diastereomeric product. Separation and hydrogenolysis gave enantiopure diamine (*R*,*R*)-**47** (Scheme 25).

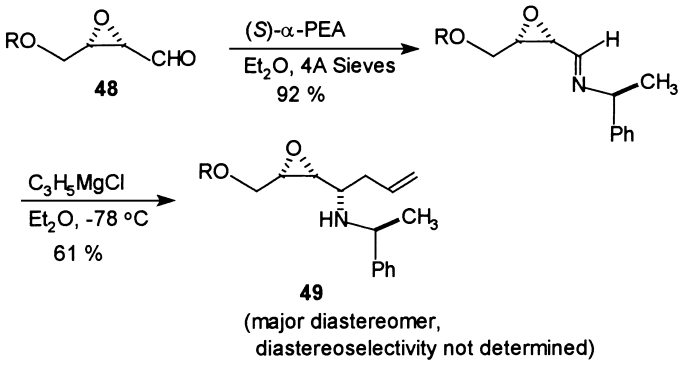


Scheme 25.

In related work, Procter and co-workers[44] reported that α,β-epoxyaldehydes such as **48** (available via Sharpless asymmetric epoxidation) can be used for the stereoselective synthesis of β,γ-epoxiamines **49**, according to the route summarized in Scheme 26.

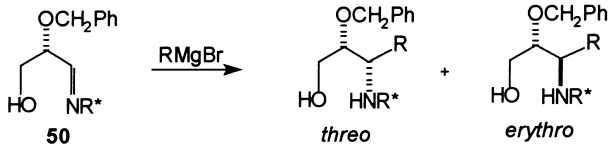
More recently, Hou and co-workers[45] described additional examples of addition of allyl bromide to (*R*)- and (*S*)-**38** under Barbier-type conditions with magnesium foil or zinc dust. The diastereoselectivities found by these researchers were low (ds ≤72%).[45] That allylation of imine (*S*)-**38** can be carried out with allyl bromide and indium powder was reported by Mosset et al.[46] who found moderate diastereoselectivities (ds ~80%).

More attractive are the results of Jager and co-workers,[47] who found that Grignard reagents add to 2-*O*-benzylglyceraldehyde-*N*-(α-phenylethyl)imines **50** in high yield and diastereoselectivity (Table 4).



Scheme 26.

Table 4
Addition of Grignard reagents to *N*-(α-phenylethyl)glyceraldehyde imine **50**[47]



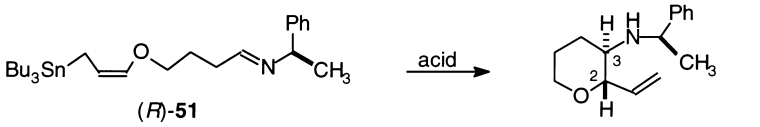
R	R*	yield (%)	*Threo* : *erythro*
CH_3	(*R*)-CH(CH_3)Ph	67	92 : 8
n-Bu	"	86	99 :1
i-Bu	"	98	> 99 :1
Ph	"	90	91 : 1
CH_3	(*S*)-CH(CH_3)Ph	95	6 : 94
n-Bu	"	82	14 : 86
i-Bu	"	81	6 : 94
t-Bu	"	67	< 5: 95

Very recently, Yamamoto and co-workers[48] developed an asymmetric synthesis of β-amino cyclic ethers by means of intramolecular reaction of γ-alkoxyallylstannane (*R*)-**51**, containing an *N*-(*R*)-phenylethyl chiral auxiliary. Products **52** were obtained in high diastereoselectivities as well as good yields (Table 5). The absolute configuration of *trans*-**52** was assigned by comparison with an authentic sample of enantiopure (2*R*,3*S*,1′*S*)-**52**. The model outlined in Scheme 27 may account for the stereochemical observations.[48]

Also in 1998, Barbier and co-workers[49] disclosed that chiral isoquinolinium derivative (*R*)-**53**, when treated with Grignard reagents, gave 1,2-dihydroisoquinolines **54** in excellent yield and moderate to good diastereoselectivity (Scheme 28).

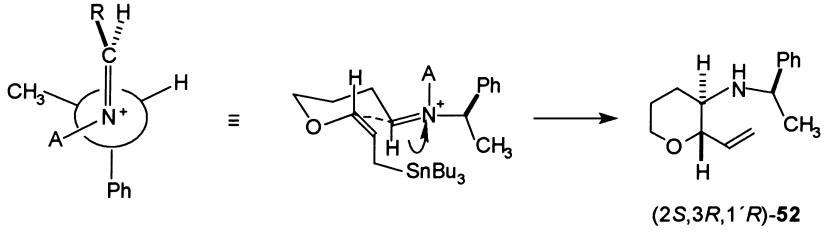
In contrast, moderate diastereoselectivities were observed upon addition of alkyl radicals to glyoxylate imines bearing the (*S*)-α-phenylethyl chiral auxiliary. The addition of primary, secondary, and tertiary

Table 5
Asymmetric synthesis of β-aminotetrahydropyrans[48]



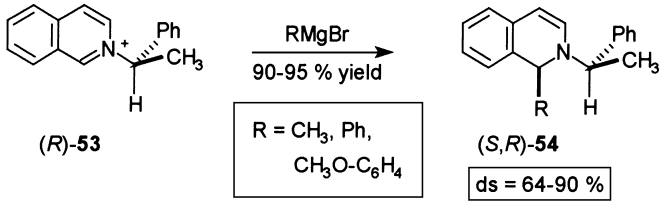
(*R*)-**51** *trans*-(2*S*,3*R*,1′*R*)-**52**

reagent	temp (°C)	yield (%)	de (%)
$TiCl_2(O\text{-}i\text{-}Pr)_2$	-78	63	> 95
Yb $(OTf)_3$	25	70	> 95
$ZrCl_4$	-78	97	91
HCl (aqueous)	0	98	92
$BF_3 \bullet OEt_2$	-78	88	81
CF_3CO_2H	0	97	63
$ZnCl_2$	0	94	68
$AlCl_3$	-78	87	82
$EtAlCl_2$	0	89	72
Et_2AlCl	0	94	74



(2*S*,3*R*,1′*R*)-**52**

Scheme 27.

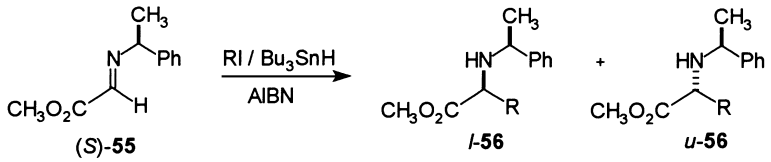


(*R*)-**53** (*S*,*R*)-**54**

ds = 64-90 %

Scheme 28.

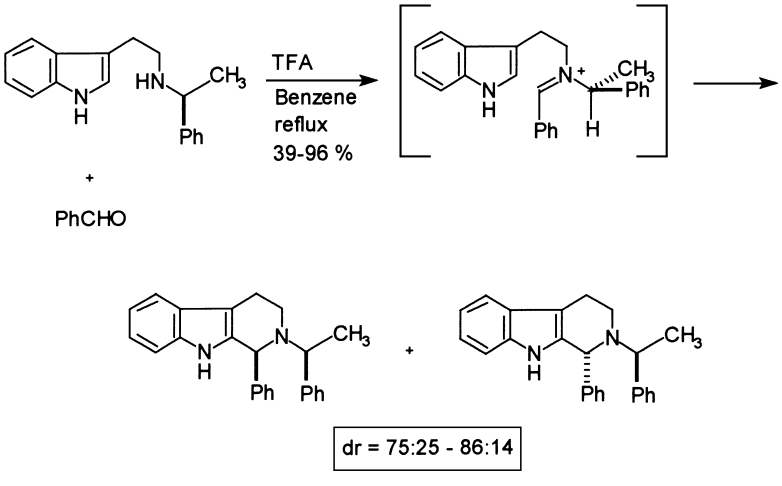
Table 6
Diastereoselectivity of addition of alkyl radicals to chiral imine (*S*)-**55**[50]



R	yield (%)	*l*-**56** : *u*-**56**
Et	67	58 : 42
c-C_6H_{11}	63	61 : 39
t-Bu	40	64 : 36

alkyl radicals, generated from alkyl iodides and Bu_3SnH/AIBN to imine (*S*)-**55**, provided the results summarized in Table 6.[50]

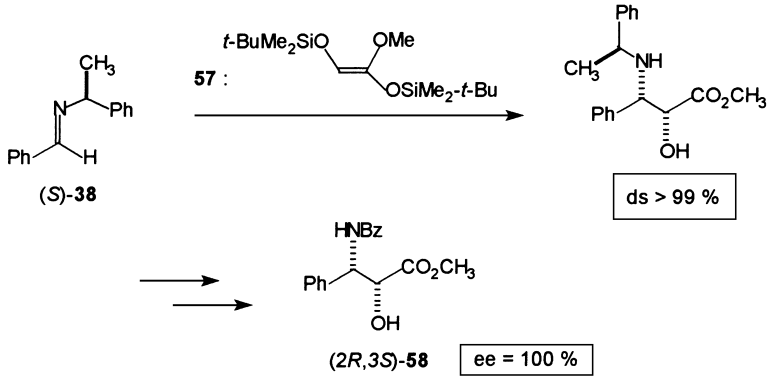
Recently, Nakagawa et al.[51] developed an asymmetric variant of the Pictet–Spengler reaction using (*S*)-α-PEA as chiral auxiliary. The best diastereoselectivities were observed with trifluoroacetic (TFA) as catalyst (Scheme 29).



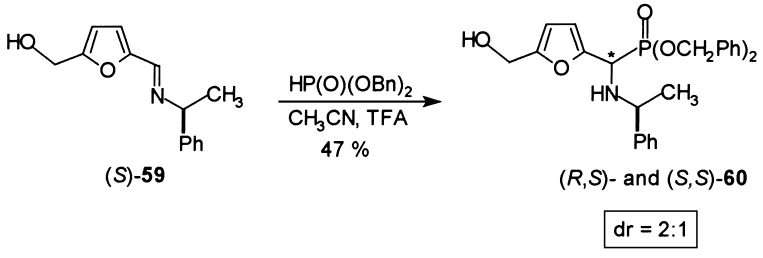
Scheme 29.

Asymmetric modifications of the Strecker synthesis, involving cyanide addition to chiral *N*-α-phenylethylimines, have recently been described by the groups of Ogura[52] and Frahm.[53] In this context, a stereospecific synthesis of the side chain of Taxol, *N*-benzoyl-3-phenylisoserine, **58**, involved the reaction of the (*Z*)-ketene acetal **57** with (*S*)-**38** (Scheme 30).[54]

In contrast, 5-hydroxymethylfurfural was condensed with (*S*)-α-PEA to give chiral imine (*S*)-**59**, which was treated with dibenzylphosphite to afford a 2:1 diastereomeric mixture of aminophosphonates **60**. The configuration of the major product was not assigned (Scheme 31).[55]



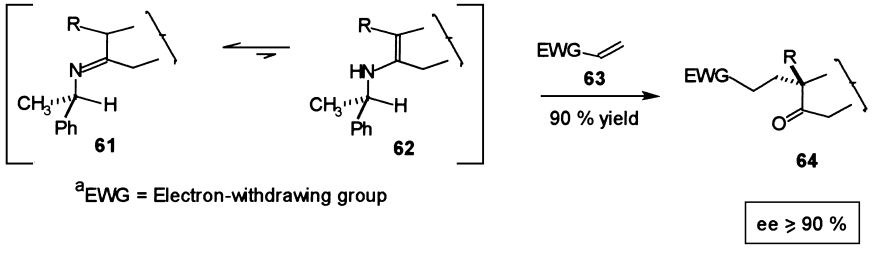
Scheme 30.



Scheme 31.

1.2. Chiral N*-phenylethyl enamines (1,4-stereoinduction)*

In a series of publications,[56] d'Angelo and co-workers disclosed that *N*-phenylethylimines **61**, derived from racemic α-substituted cyclanones and (*R*)- or (*S*)-α-PEA, undergo Michael addition reaction with electron-deficient olefins **63** to produce α,α-disubstituted ketones **64** with excellent enantiomeric excesses after hydrolysis. It was established that the reactive nucleophilic species involved in the process is the chiral enamine **62**, which exists in tautomeric equilibrium with imine **61** (Scheme 32).[56]

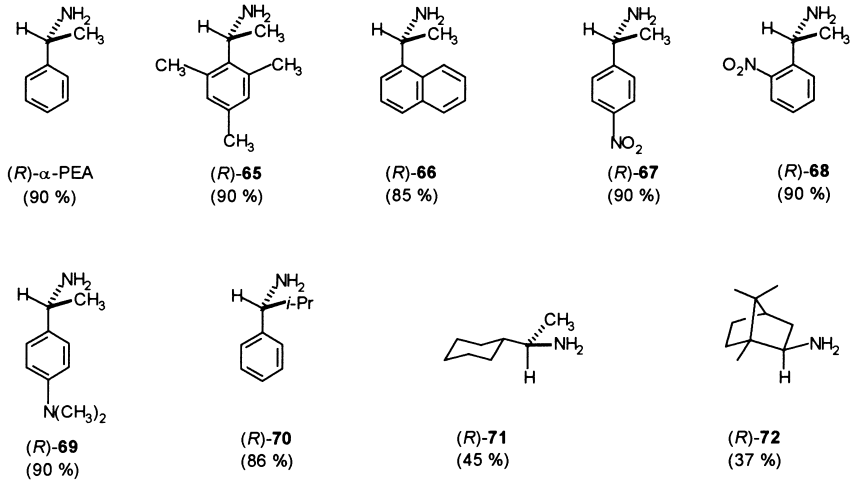


Scheme 32. [a]

Comparison of the stereoselectivity obtained with (*R*)-PEA as chiral auxiliary with selectivities found with chiral amines **65**–**72** (Fig. 1) led d'Angelo to conclude that the presence of an aromatic ring in the α position to the amine group is crucial to ensure a good diastereofacial differentiation during alkylation (cf. Scheme 32).[57]

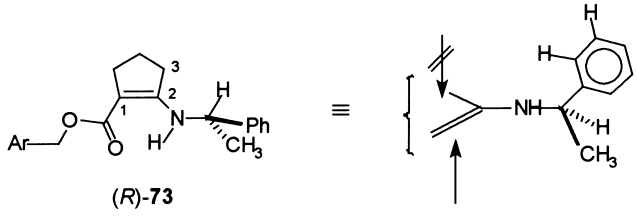
Furthermore, an X-ray crystallographic structure determination for derivative **73** showed that the phenylethyl C–H bond eclipses the C(2)–C(3) bond, so that the enamine olefinic face *syn* to the aromatic ring is sterically hindered for addition (Scheme 33).[57]

The synthetic strategy outlined in Scheme 32 has been exploited by d'Angelo and collaborators in



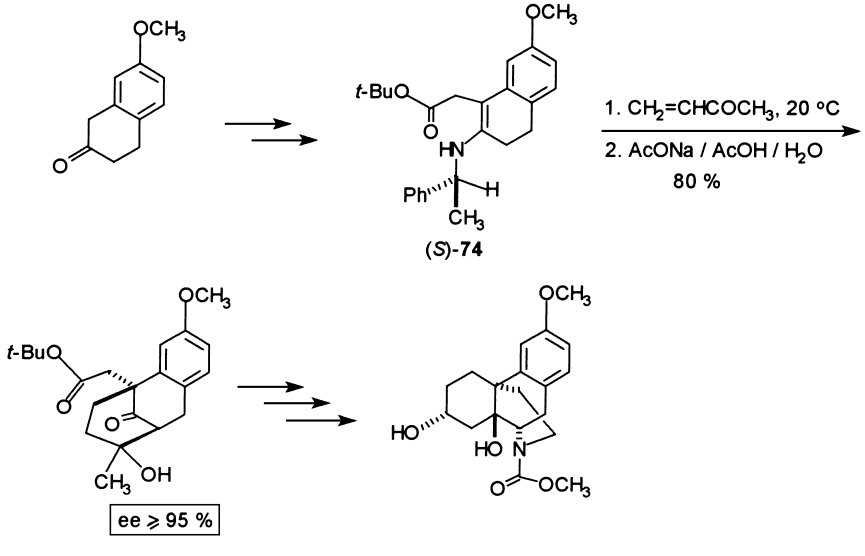
[a]Diastereoselectivities in parentheses (Cf. Scheme 32).

Figure 1.

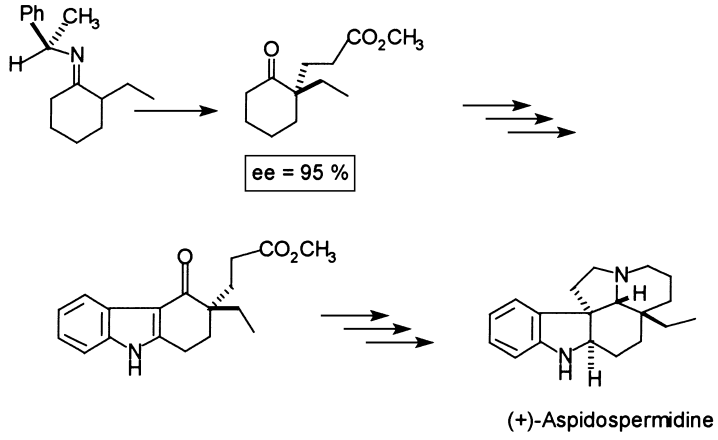


Scheme 33.

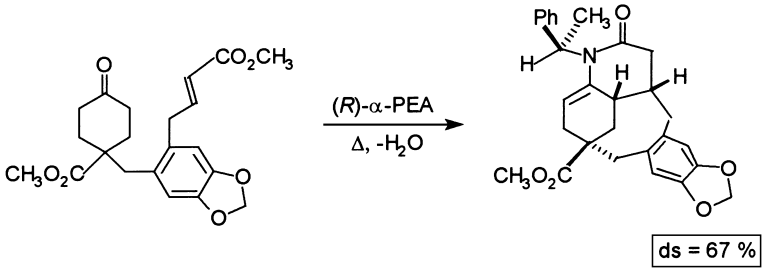
the synthesis of enantiopure morphinans (Scheme 34),[58] aspidosperma alkaloids (Scheme 35),[59] various furanones,[60] as well as polycyclic systems related to the taxane core (Scheme 36).[61,62]



Scheme 34.

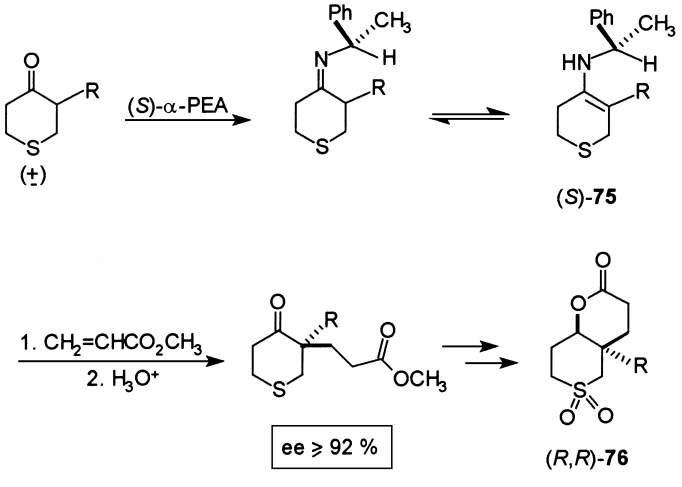


Scheme 35.



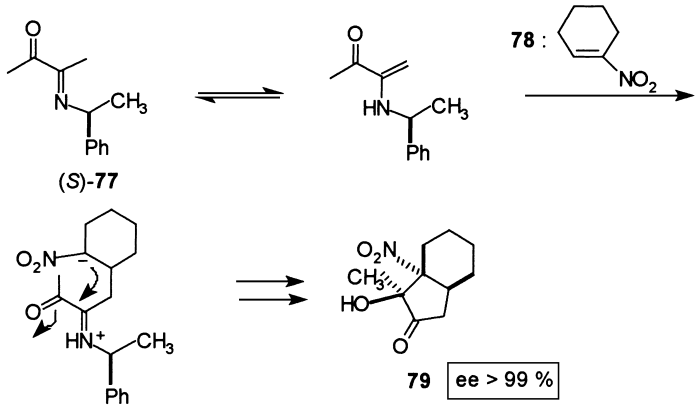
Scheme 36.

In related experiments, Matsuyama et al.[63] have described the enantioselective synthesis of quaternary carbon centers through Michael-type alkylation of *N*-phenylethyl chiral imines. A representative example is the conversion of 3-alkyl-4-thianones (*S*)-**75** to enantioenriched lactones **76** (Scheme 37).[63a]



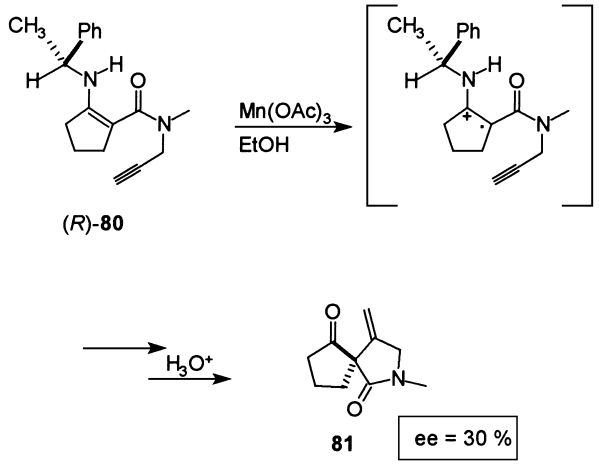
Scheme 37.

In 1992, Pitacco and co-workers[64] reported a highly diastereo- and enantioselective annulation reaction of imine (*S*)-**77** with nitroalkene **78**, following the reaction pathway indicated in Scheme 38. The 2-hydroxy-3-nitrocyclopentanone **79** was obtained as an enantiopure product.



Scheme 38.

In contrast, modest diastereoselectivity was found by Cossy and co-workers[65] in the radical cation cyclization of unsaturated *N*-[(*R*)-α-phenylethyl]enamine (*R*)-**80**, induced by manganese acetate (Scheme 39).



[a]Absolute configuration of spirolactam **81** was not determined

Scheme 39. [a]

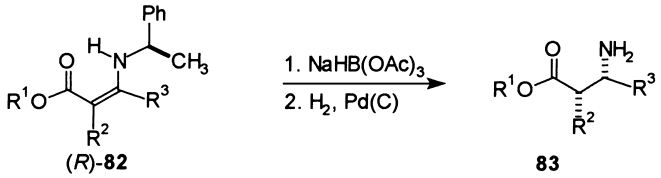
Recently, Cimarelli et al.[66] described a convenient procedure for the diastereo- and enantioselective preparation of β-amino esters, based on the stereoselective hydride reduction of *N*-(α-phenylethyl)-β-enaminoesters (*R*)-**82** (Table 7).

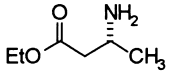
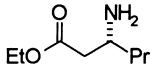
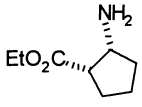
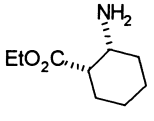
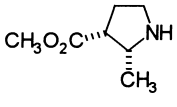
Further application of the diastereoselective Michael reaction of chiral cyclic *N*-(α-phenylethyl) containing enamines has been reported by Pfau and co-workers (Scheme 40).[67]

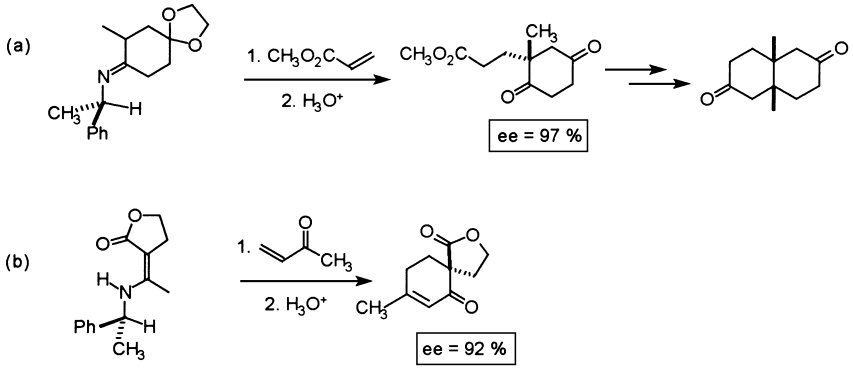
Very recently, Lucero and Houk[68] offered an explanation for the remarkable π-facial stereoselectivity that is generally observed in the reactions of *N*-(α-phenylethyl) enamines with Michael acceptors. Ab initio RHF (restricted Hartree–Fock) calculations with the 6-31G* basis set gave transition-state structures **84** and **85** for the reaction between *N*-(methylamino)cyclohexene and acrylonitrile. Axial attack (**84**) is 2 kcal/mol lower in energy than equatorial attack (**85**), presumably because bond staggering is optimum in the former (Fig. 2).

Lucero and Houk[68] propose that for an achiral aminocyclohexene there exist two enantiomeric

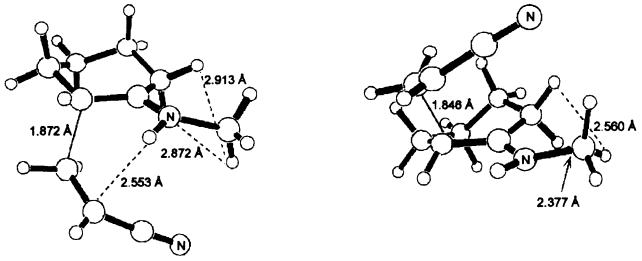
Table 7
Reduction of β-enamino esters **82**[66a]



product, **83**	de, %	yield, %	Configuration
	58	61	(*R*)
	39	56	(*R*)
	85	66	(1*S*,2*R*)
	81	73	(1*S*,2*R*)
	74	72	(2*R*,3*R*)



Scheme 40.



84 **85**

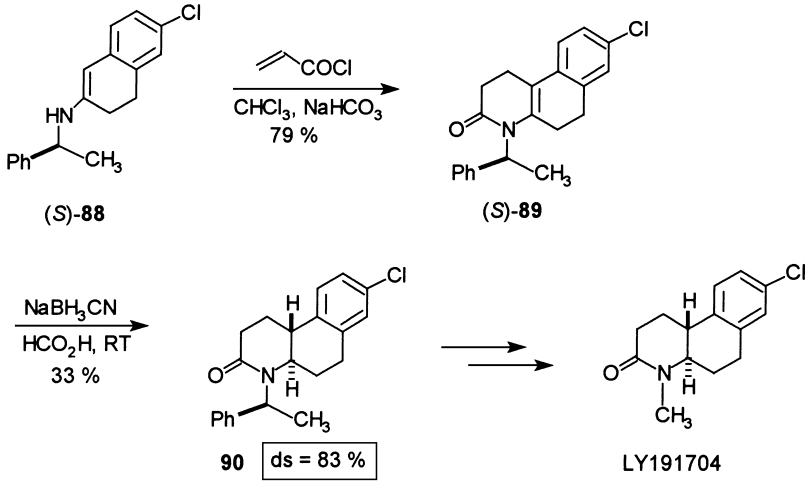
Figure 2.

86 **87**

Figure 3.

transition-state structures leading to axial attack. However, with a chiral *N*-(α-phenylethyl) substituent, the two half chair transition-state structures are diastereomers, and calculation indicates that **86** is the preferred conformation of the (phenylethyl)amine group, being 0.8 kcal/mol more stable than **87** (Fig. 3).[69]

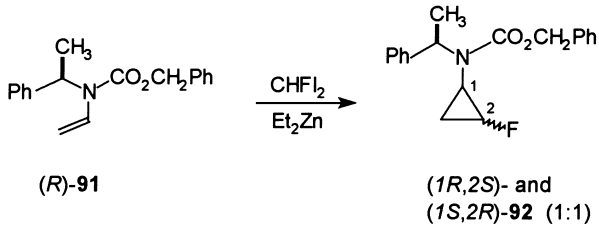
In this context, condensation of (*S*)-α-PEA and 6-chloro-2-tetralone gave enantiopure enamine (*S*)-**88**, which was acylated with acryloyl chloride to afford enantiopure (*S*)-**89**. Treatment of (*S*)-**89** with cyanoborohydride gave (−)-**90** (83% diastereoselectivity), which was converted to Human Type 1 steroid 5-α-reductase inhibitor LY191704 (Scheme 41).[70]



Scheme 41.

In related studies, Lhommet and co-workers[71] developed a short synthesis of (−)-iso-retronecanol, while Sequeira et al.[72] reported an enantioselective synthesis of differently substituted octalones. In contrast, the reaction of benzyl *N*-(α-phenylethyl)-*N*-vinylcarbamate (*R*)-**91** with zinc-monofluorocarbenoid afforded cyclopropyl derivative **92** without diastereofacial selectivity (Scheme 42).[73]

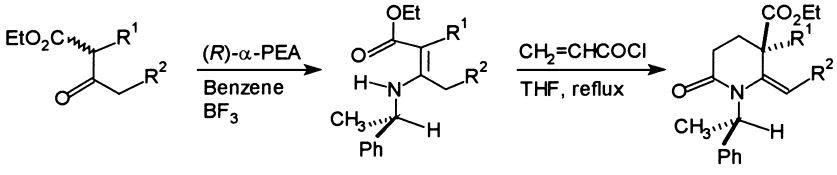
Recently, Barta et al.[74] developed an excellent method for asymmetric aza annulation reactions based



(*R*)-**91** (*1R,2S*)- and (*1S,2R*)-**92** (1:1)

Scheme 42.

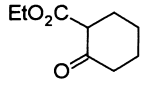
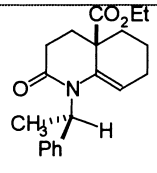
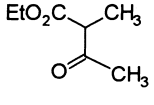
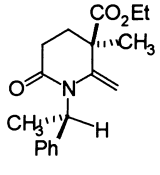
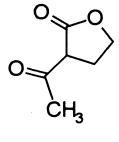
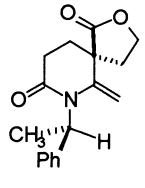
on the general strategy outlined in Scheme 43. The effect of substrate variation on asymmetric induction is presented in Table 8.



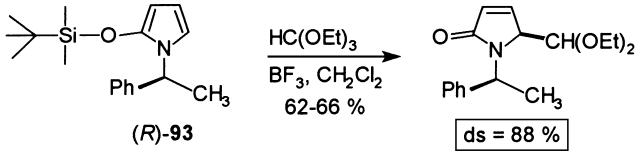
Scheme 43.

More recently, Karchava and co-workers[75] reported the diastereoselective hydride reduction of *N*-(α-phenylethyl)indoles, whereas Belfield and Seo[76] developed enantioselective syntheses of several chiral decalin derivatives via the stereoselective alkylation of *N*-(α-phenylethyl) enamines. In a related

Table 8
Aza-annulation of chiral β-enamines[74]

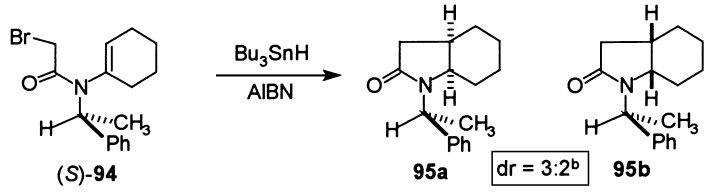
Substrate	product	diastereomer ratio	yield, %
		> 97 : 3	85
		97 : 3	92
		94 : 6	80

development, Poli and co-workers[77] disclosed that *N*-(α-phenylethyl)-2-silyloxypyrrole (*R*)-**93** is a useful 1,5-dihydropyrrol-2-one-5-anion equivalent (Scheme 44).



Scheme 44.

Additional studies of radical cyclization of chiral enamines containing the *N*-(α-phenylethyl) auxiliary have been reported by Ishibashi et al.[78] who exploited Bu_3SnH-mediated radical cyclization of bromoacetamide (*S*)-**94** to give diastereomeric heterocycles **95**, with low diastereoselectivity (Scheme 45).



[a]AIBN = azobis(isobutyronitrile). [b]Absolute configuration was not assigned.

Scheme 45. [a]

1.3. Diastereoselective alkylation of organolithiums containing the α-(phenylethyl)amino chiral group

In pioneering contributions, Schoellkopf and co-workers[79] developed a convenient asymmetric synthesis of α-alkyl-α-amino acids via the diastereoselective alkylation of 4-metalated 1-[(*S*)-(α-phenylethyl)]-2-imidazolidin-5-ones, (*S*)-**96**, followed by hydrolysis to the amino acids (Table 9).

The model outlined in Fig. 4 was advanced by Schoellkopf to explain the experimental findings. In the most stable conformation of (*S*)-**96**-Li, the C–H bond of the chiral adjuvant is oriented towards the oxygen atom, so that the relative size of phenyl and methyl groups determines the preferred direction of electrophile addition.

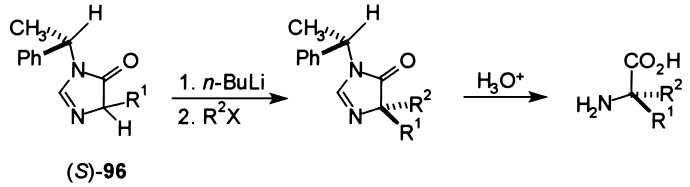
A few years later, Meyers and Fuentes[80] reported the results of a diastereoselective alkylation of formamidine (*R*)-**97**, which led to enantioenriched 1-alkyl tetrahydroisoquinolines **99** in moderate ee (Table 10). In this system, much better results were obtained when (1*S*,2*S*)-1-phenyl-2-amino-1,3-propanediol bis-silylate (BISPAD) was employed as the chiral auxiliary (Table 10).

More recently, Orena et al.[81] reported that treatment of (3*S*)-3-methylpiperazine-2,5-dione (*S*)-**100** with lithium hexamethyldisilazide (LHMDS) followed by alkylation of the corresponding enolate with methyl iodide affords (*S*,*S*)-dimethyl derivative (*S*,*S*)-**101** in 98% de. Cleavage of the heterocyclic ring with 57% HI leads to (*S*)-alanine (Scheme 46).

In this context, Cardillo and co-workers[82] have recently described the conversion of 1,3,5-tris[(*S*)-α-phenylethyl]hexahydrotriazine (*S*)-**102** into enantiopure *N*-substituted imidazolidinones **103** and perhydropyrimidinones **104** (Fig. 5). Subsequent highly diastereoselective alkylation of **104** led to the enantioselective synthesis of α-substituted β-amino acids **105** (Scheme 47).[83]

In related work, Palmieri and co-workers[84] developed a highly diastereoselective synthesis of either (*R*) or (*S*) chiral 1,3-diketones **108** through asymmetric alkylation of chiral β-enamino ketones (*R*)-**106** (Table 11). This methodology was then extended to stereoselective aldol reactions.[85]

Table 9
Stereoselectivity of alkylation of *N*-(α-phenylethyl) substituted enolate (*S*)-**96**-Li



R^1	R^2	Yield, %	ds, %	Config
CH_3	CH_2Ph	86	~ 100	(*S*)
CH_3	(1-naphthyl)methyl	84	> 95	(*S*)
CH_2CH_3	CH_2Ph	85	95	(*S*)
CH_2-CH= CH_2	CH_2Ph	75	90	(*S*)
i-Pr	CH_2Ph	78	95	(*R*)
CH_2Ph	CH_2-CH= CH_2	86	43	(*R*)
CH_2Ph	CH_2-CO_2Et	75	31	(*S*)

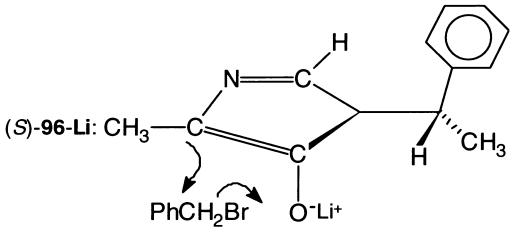


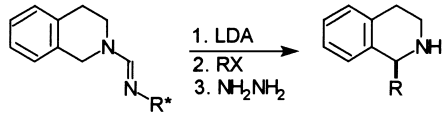
Figure 4.

The synthetic utility of 2-alkyl-substituted 1,3-imidazolidinones for the enantioselective preparation of α-amino acids is well documented in the literature.[86] Recently, Juaristi and co-workers[87] discovered that the incorporation of a *N*-(α-phenylethyl) group in these heterocycles leads to substantial enhancements in the diastereoselectivity of alkylation of the corresponding lithium enolates. Thus, whereas methylation of the C(2)-isopropyl analogue (*S*)-**109** affords a *trans*:*cis*=85:15 product mixture (Scheme 48a),[86] methylation of the N(3)-[(α-phenylethyl)] analogue (*S*,*S*)-**110** proceeds with 95% diastereoselectivity (Scheme 48b).[87] An X-ray crystallographic structure of (*S*,*S*)-**110** shows that steric congestion forces the C(2)-isopropyl into a conformation in which one of its methyl groups points into the imidazolidinone ring; thus, as a consequence of a long-distance relay effect, the effective size of the isopropyl group becomes larger, and so does the observed diastereoselectivity of alkylation.[87]

N-(α-Phenylethyl)-substituted imidazolidinones closely related to (*S*,*S*)-**110** have been applied with much success to the synthesis of enantiopure (*R*)- and (*S*)-2-amino-5-phosphonopentanoic acids (*R*)- and (*S*)-**111**,[88] as well as their higher analogues (*R*)- and (*S*)-**112** (Fig. 6).[89]

Recently, Porzi and Sandri[90] revealed that the alkylation of morpholine-2,5-dione derivatives **113** and

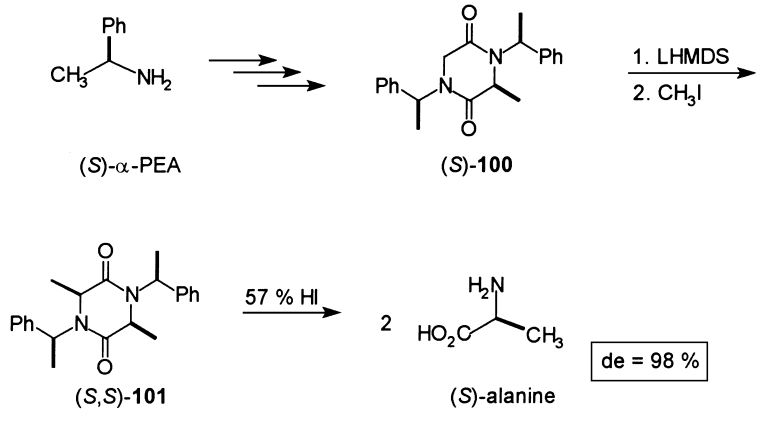
Table 10
Diastereoselective alkylation of chiral 1,2,3,4-tetrahydroisoquinolines (*R*)-**97** and (*S*,*S*)-**98**[80]



(*R*)-**97**, R* = (*R*)-α-PE
(*S*,*S*)-**98**, R* = (*S*,*S*)-BISPAD

99

R*	RX	Yield, %	ee, %	Config
(*R*)-α-PE	CH_3I	85	10	(*R*)
(*R*)-α-PE	*i*-BuBr	84	27	(*R*)
(*R*)-α-PE	*n*-BuBr	93	19	(*R*)
(*R*)-α-PE	$PhCH_2Br$	97	35	(*R*)
(*R*)-α-PE	$PhCH_2CH_2Br$	89	52	(*S*)
(*S*,*S*)-BISPAD	CH_3I	79	> 99	(*S*)
(*S*,*S*)-BISPAD	*n*-BuBr	80	91	(*S*)
(*S*,*S*)-BISPAD	$PhCH_2Br$	70	93	(*S*)
(*S*,*S*)-BISPAD	$PhCH_2CH_2Br$	65	> 99	(*S*)



(*S*)-α-PEA
(*S*)-**100**
(*S*,*S*)-**101**
(*S*)-alanine

Scheme 46.

114 gives, exclusively, the *trans* products **115** and **116**, with >98% diastereoselectivity. Cleavage of these heterocycles leads to enantiopure α-amino acids, (*R*)- and (*S*)-**117** (Scheme 49).

Sandri and co-workers[91] have used synthons **113** and **114** for the enantioselective preparation of 4-hydroxyprolines **118** and bulgecinines (Fig. 7).

Although treatment of (*S*)-*N*-(α-phenylethyl)valerolactam (*S*)-**119** with LDA followed by alkylating

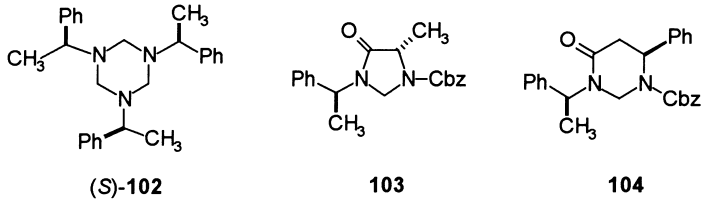
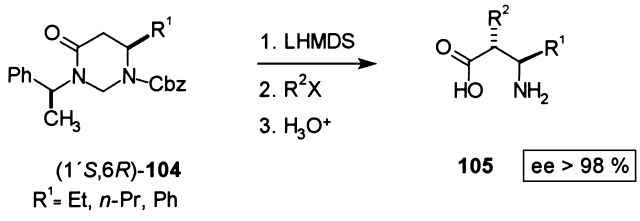
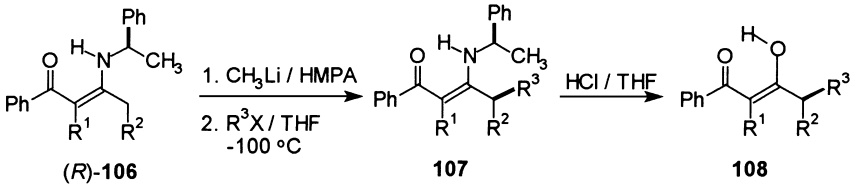


Figure 5.



Scheme 47.

Table 11
Diastereoselective alkylation of enaminones (*R*)-**106**[84]

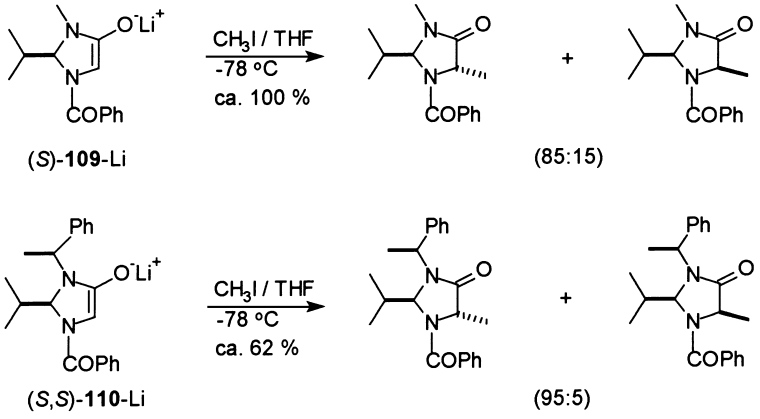


R^1	R^2	R^3X	yield, %	de (**107**)	Config (**108**)
$(CH_2)_2$	$(CH_2)_2$	CH_3I	93	27	(*S*)
$(CH_2)_2$	$(CH_2)_2$	EtI	87	74	(*S*)
$(CH_2)_2$	$(CH_2)_2$	*i*-Pr	75	93	(*R*)
$(CH_2)_3$	$(CH_2)_3$	EtI	82	98	(*S*)
H	CH_3	EtI	95	92	(*R*)
H	CH_3	*i*-PrI	88	98	(*R*)
H	$PhCH_2$	CH_3I	93	85	(*S*)
H	$PhCH_2$	*i*-PrI	91	95	(*R*)
H	*i*-Pr	CH_3I	87	31	(*S*)

agent **120** gave a ~1:1 diastereomeric mixture of **121**, subsequent spirocyclization with KHMDS furnished the desired spirocyclic lactam **122** with 86% diastereoselectivity (1,4-induction) (Scheme 50).[92]

Very recently, Cardillo and co-workers[93] disclosed the diastereoselective halogenation of pyrimidinone (1′*S*,6*R*)-**104** to produce the corresponding 2-carboxylaziridines **123**, which are useful precursors of enantiopure threonines and *allo*-threonines (Scheme 51).

In a very interesting development by Beak et al.[94] the chiral homoenolate (*S*)-**124**-Li reacts with high diastereoselectivity with a variety of electrophiles (Scheme 52a). In a demonstration of this approach, the synthesis of enantiopure coumarin **125** was described (Scheme 52b).[94]



Scheme 48.

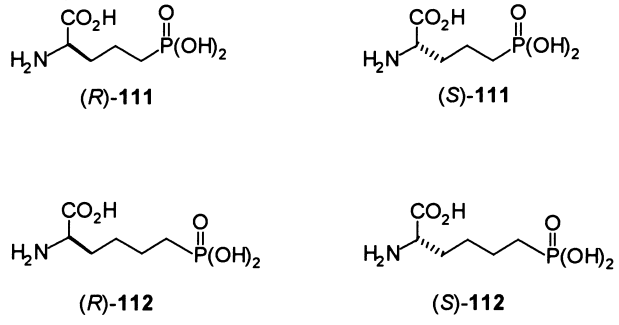
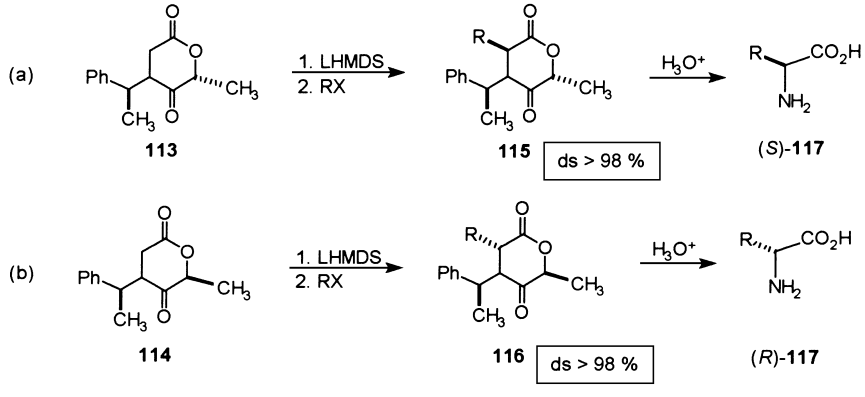


Figure 6.



Scheme 49.

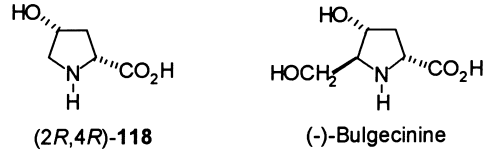
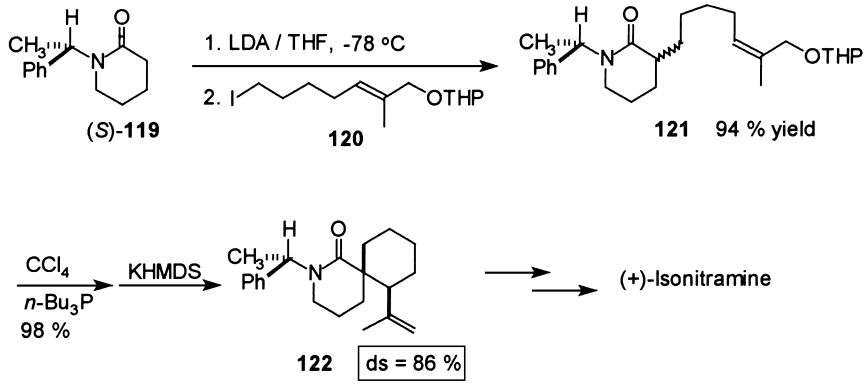
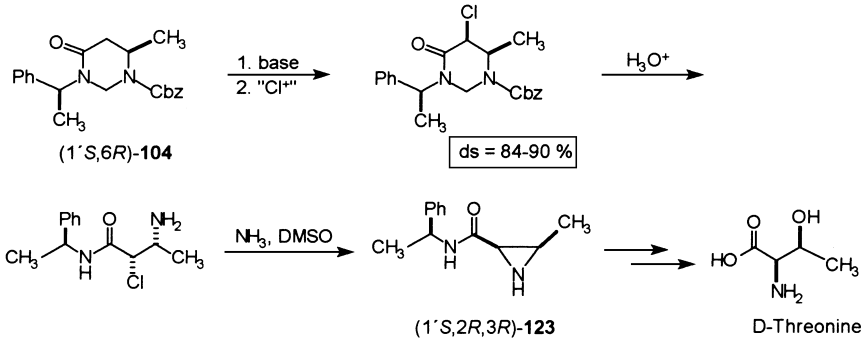


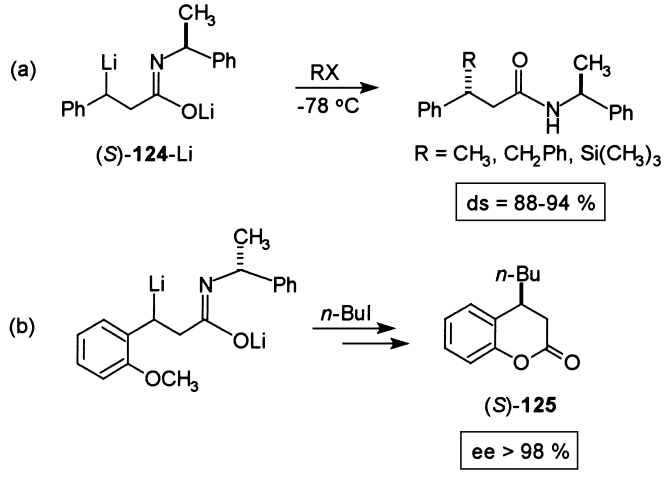
Figure 7.



Scheme 50.



Scheme 51.



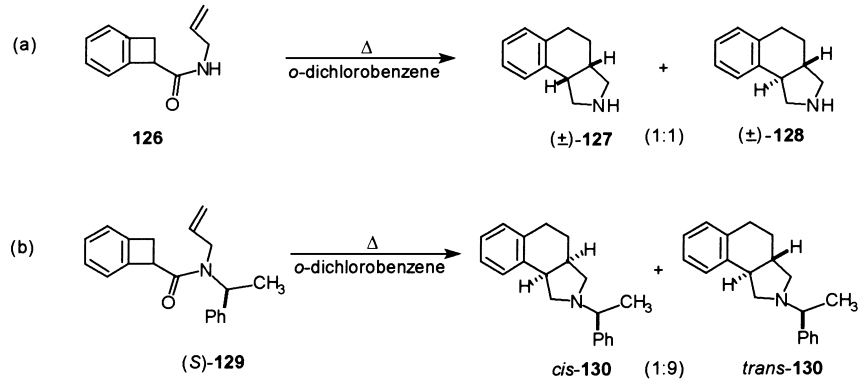
Scheme 52.

Additional interesting examples of diastereoselective alkylation of *N*-(α-phenylethyl)-containing enolates are cited in the literature.[95]

1.4. Use of the N-*(α-phenylethyl) group in asymmetric cycloaddition reactions*

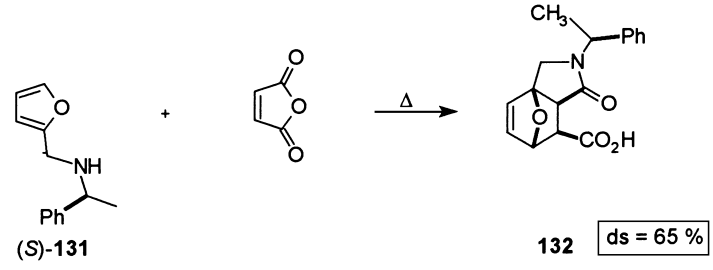
In 1991, Basha and co-workers[96] demonstrated the potential of the *N*-(α-phenylethyl) chiral auxiliary in order to carry out diastereoselective Diels–Alder reactions of *o*-quinodimethanes. Thus, whereas

thermolysis of substrate **126** afforded **127** and **128** as a 1:1 *cis*:*trans* mixture, thermolysis of (*S*)-**129** proceeded with high diastereoselectivity to give *trans*-**130** (Scheme 53).



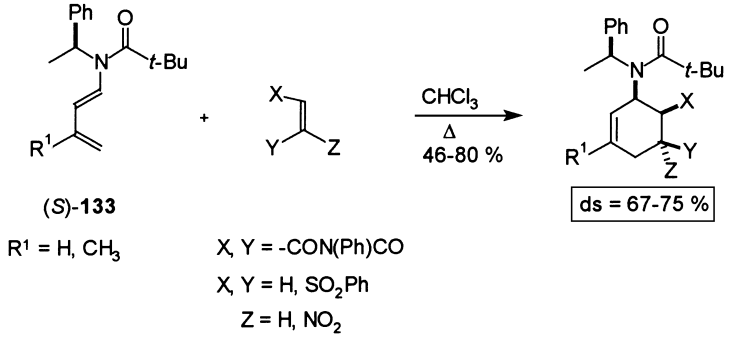
Scheme 53.

More recently, Zylber and co-workers[97] found that *N*-(α-phenylethyl)furfuryl amine (*S*)-**131** underwent intramolecular Diels–Alder reaction with maleic anhydride to give adduct **132** in 65% ds (Scheme 54).



Scheme 54.

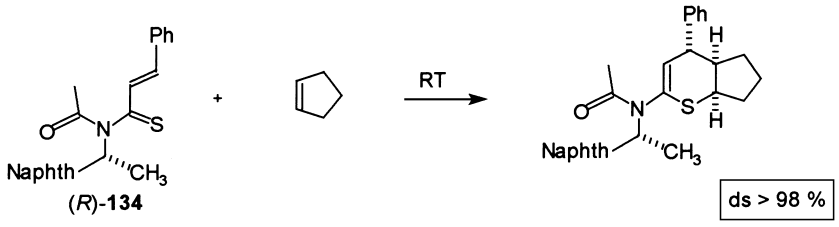
Moderate diastereoselectivities were also reported by Murphy et al.[98] in the intermolecular Diels–Alder reaction between chiral dienamide (*S*)-**133** and *N*-phenyl maleimide (Scheme 55).



Scheme 55.

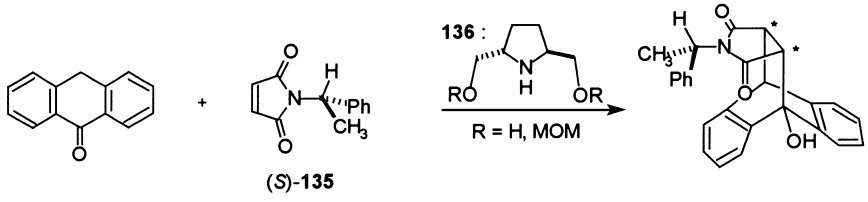
Much better results were obtained by Bell and co-workers[99] in the cycloaddition reaction of (*R*)-*N*-(α-naphthylethyl)diene (*R*)-**134** with cyclopentene as dienophile, as indicated in Scheme 56.

In contrast, Tokioka and co-workers[100] carried out the base-catalyzed asymmetric cycloaddition of anthrone with *N*-(α-phenylethyl) substituted maleimide (*S*)-**135** in the presence of C_2-chiral pyrrolidines



Scheme 56.

Table 12
Double stereodifferentiation in the Diels–Alder cycloaddition of maleimide (*S*)-**135**[100]



pyrrolidine	major product	yield, %	de, %
R = MOM, (*S,S*)-**136**	(*R,R*)	90	70
R = MOM, (*R,R*)-**136**	(*S,S*)	86	12
R = H, (*S,S*)-**136**	(*R,R*)	90	80
R = H, (*R,R*)-**136**	(*S,S*)	87	58

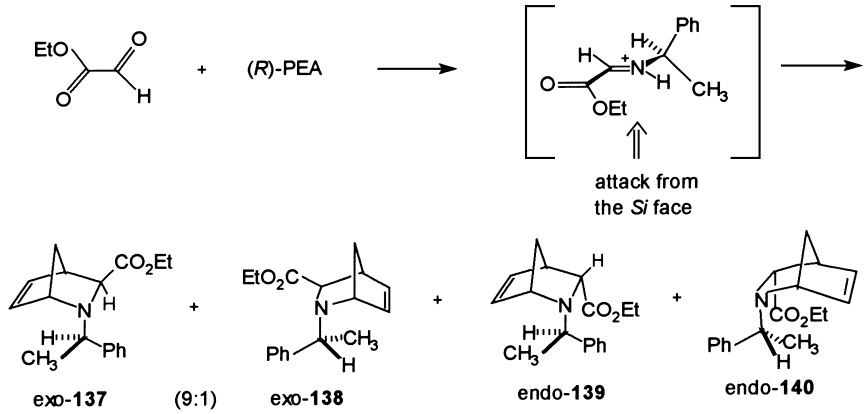
136 as chiral base. Diastereomeric excesses of the adducts up to 80% were observed as a result of double diastereodifferentiation (Table 12).

Several reports on the use of chiral iminium ions in aza-Diels–Alder reactions have recently appeared. For example, with (*R*)-phenylethylamine as chiral auxiliary, bicyclic amino acids **137**–**140** were formed in 52% combined yield (Scheme 56).[101] The *exo*:*endo* ratio was found to be 6:1, and the diastereomeric ratio for the *exo* isomers amounted to 90:10. A model in which the C–H bond at the phenylethyl group eclipses the C=N double bond seems to account for the observed diastereoselectivity (preferred addition on the *Si* face) (Scheme 57).

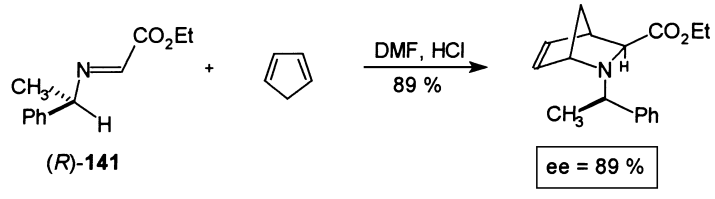
Similarly, Bailey et al.[102] observed high diastereo- and enantioselectivity in the [4+2] aza-Diels–Alder cycloaddition of (*R*)-**141** and cyclopentadiene or 1,3-cyclohexadiene: *exo*:*endo* ratio=32:1; de=89% (Scheme 58).

In contrast, the diastereoselectivity of the aza-Diels–Alder reaction of the (*R*)-*N*-(2,2-difluoroethylidene) (α-phenylethyl)amine (*R*)-**142** with 1-methoxy-3-trimethylsiloxy-1,3-butadiene turned out to be highly sensitive to the Lewis acid catalyst, with BF_3 being the most effective (Table 13).[103]

Early reports on the potential of [2+2] cycloaddition reactions for the synthesis of enantiopure azetidinones originated from the groups of Teutsch,[104] and Rogalska and Belzecki.[105] In 1989, Thomas[106] described the diastereoselective cycloaddition reaction of salt **144** and imine (*R*)-**145**. The ratio of dia-

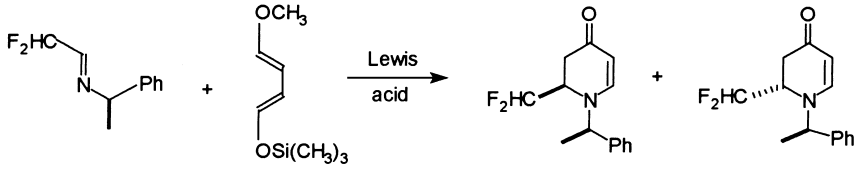


Scheme 57.



Scheme 58.

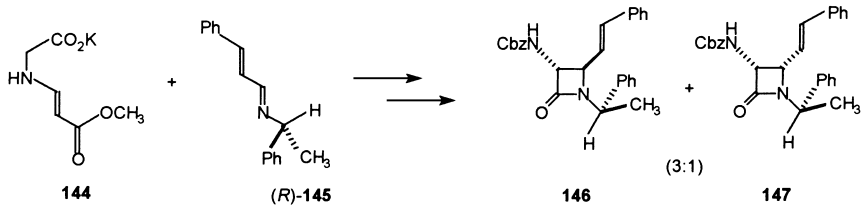
Table 13
Aza-Diels–Alder reaction mediated by Lewis acid[103]



(*R*)-**142** **143a** **143b**

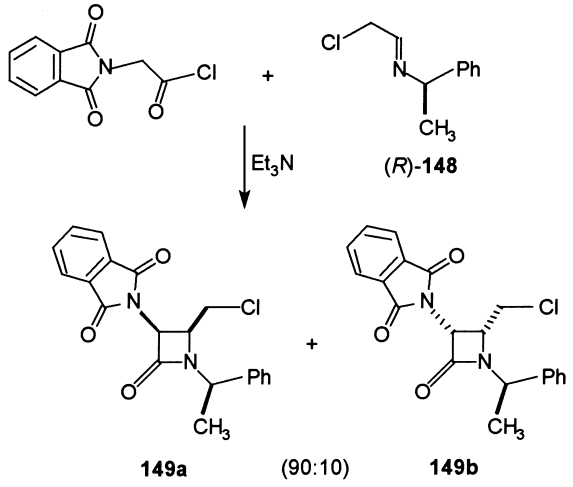
Lewis Acid	solvent	temp, °C	yield, %	**143a** : **143b**
$ZnCl_2$	THF	25	70	48 : 52
$ZnCl_2$	CH_2Cl_2	-78	50	46 : 54
BF_3	CH_2Cl_2	-78	82	19 : 81
$TiCl_4$	CH_2Cl_2	-78	61	41 : 59
$AlCl_3$	CH_2Cl_2	-78	21	35 : 65
$B(OPh)_3$	CH_2Cl_2	-78 → 25	65	25 : 75
$LiClO_4$	Et_2O	25	85	53 : 47

stereomers **146**:**147** was 3:1; nevertheless, a single recrystallization of the crude product gave enantiopure **146** in 46% isolated yield (Scheme 59).



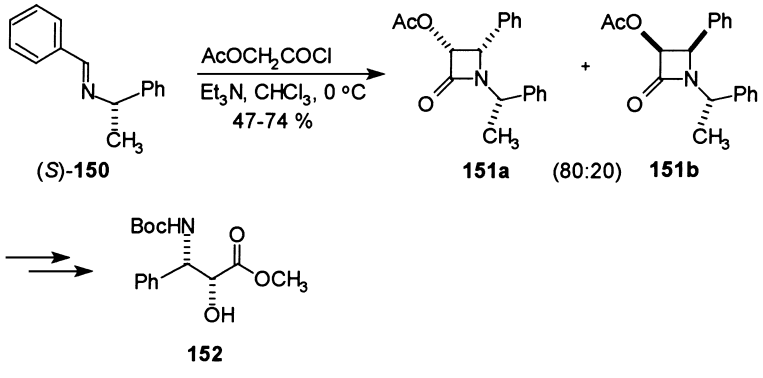
Scheme 59.

In 1990, Aszodi and co-workers[107] reported that β-lactam **149a** with 80% de was obtained by using imine (*R*)-**148** (Scheme 60).



Scheme 60.

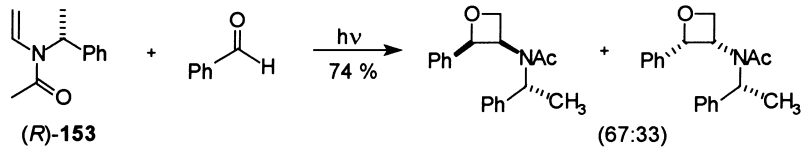
In this context, Bourzat and Commercon[108] condensed imine (*S*)-**150** with acetoxyacetyl chloride to give azetidinones **151a** and **151b** (ratios varying from 75:25 to 80:20), which were modified to yield *N*-protected phenylisoserinates **152**, the side chain of Taxol (Scheme 61).



Scheme 61.

In related developments, Hashimoto et al.[109] and Jayaraman et al.[110] have described systematic studies aimed to design suitable partners of the ketene and *N*-(α-phenylethyl)imine [2+2] cycloaddition, so that product diastereoselectivity can be improved. Furthermore, Bach and co-workers[111] determined the

diastereoselectivity in the photocycloaddition of chiral *N*-acyl enamine (*R*)-**153** to benzaldehyde to give the corresponding oxetanes in good yield but low stereoselectivity (Scheme 62).



Scheme 62.

In a related development, Cinquini and co-workers[112] tested several amines as chiral auxiliaries in the stereoselective synthesis of β-lactams by condensation of the titanium enolates of 2-pyridyl thioesters with chiral imines (Fig. 8). (*R*)- and (*S*)-α-PEA was identified as the chiral auxiliary leading to the best combination of good reactivity and satisfactory levels of stereocontrol (Table 14).

In pursuing the total synthesis of antifungal agent Sch 38516, *N*-benzylhydroxylimine **161a** was heated to 85°C in the presence of vinylene carbonate to afford the [3+2] cycloaddition products **162a** and **163b** as a 3.5:1 mixture of *endo* diastereomers (Scheme 63).[113] In contrast, *N*-hydroxyl-α-phenylethylamine derivative **161b** gave **162b** with 20:1 diastereoselectivity (Scheme 63).[113]

In this context, Keirs and co-workers[114] developed a general asymmetric synthesis of β-amino acids based on the dipolar cycloaddition of nitrones (*R*)-**164** with vinyl acetate **165a**, ketene acetal **165b** or α-chloroacrylonitrile **165c**. Diastereoselectivity ranged between 2:1 and 11:1 (Scheme 64).

Nitrone cycloaddition reactions have also been used by Takano et al.[115] and Broggini et al.[116] in the synthesis of enantiopure polyhydroxylated pyrrolidines and 3-hydroxymethylchromanes, respectively. Nevertheless, these processes proceeded with low diastereoselectivity (Scheme 65).

In contrast, cycloaddition of nitrone (*R*)-**166** to α-chloroacrylonitrile followed by hydrolysis afforded the isoxazolidinone **167** as a single diastereomer (Scheme 66).[117]

Finally, 1.3-dipolar cycloaddition of sulfones **168a**–**c** with nitrones **169a**–**c** gave the corresponding isoxazolidines with moderate diastereoselectivity (Scheme 67).[118]

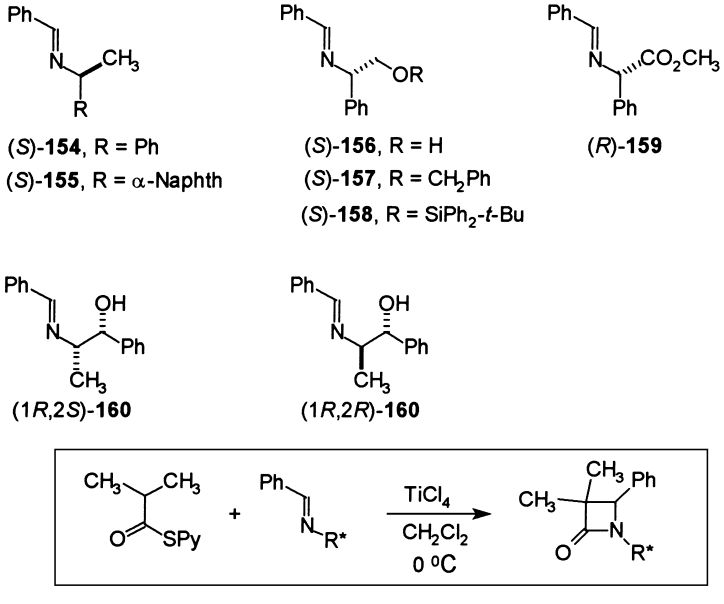
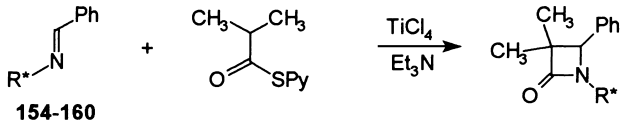


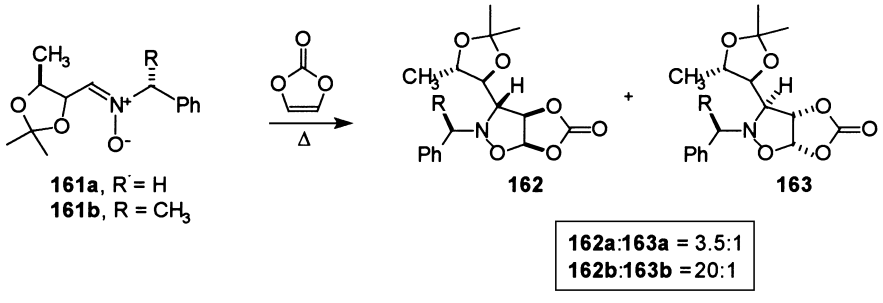
Figure 8.

Table 14
Stereoselective synthesis of β-lactams from thioester and imines **154**–**160**[112]

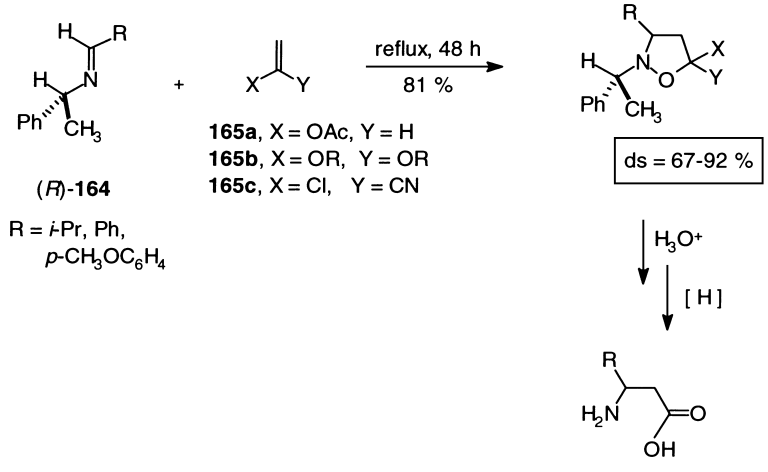


imine	yield, %	dr	config.
(*S*)-**154**	80	96:4	(*S*)
(*S*)-**155**	79	95:5	(*S*)
(*S*)-**156**	50	>98:2	(*R*)
(*S*)-**157**	33	80:20	(*R*)
(*S*)-**158**	13	74:26	(*R*)
(*R*)-**159**	54	75:25	(*S*)
(1*R*,2*S*)-**160**	25	>98:2	n.d.[a]
(1*R*,2*R*)-**160**	75	58:42	n.d.[a]

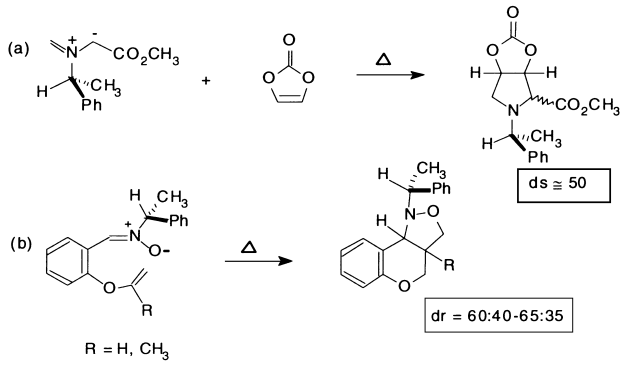
[a]Not determined.



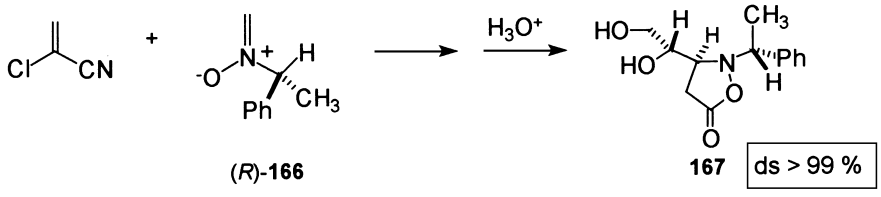
Scheme 63.



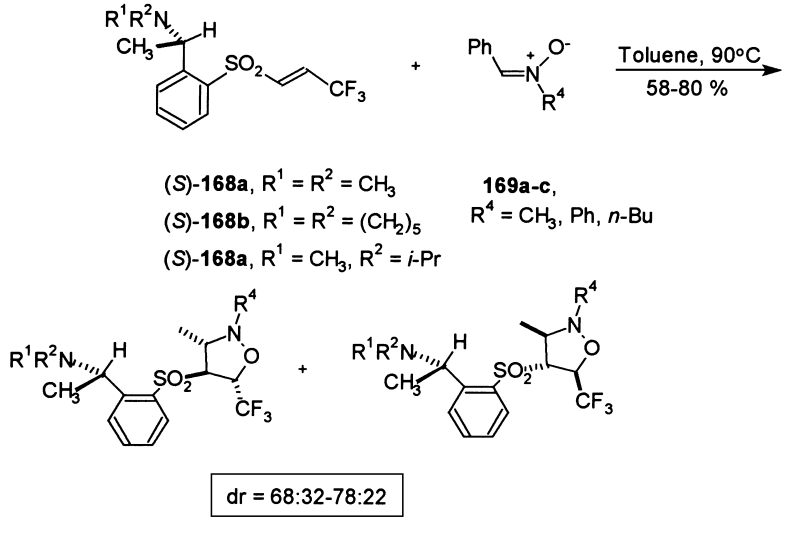
Scheme 64.



Scheme 65.

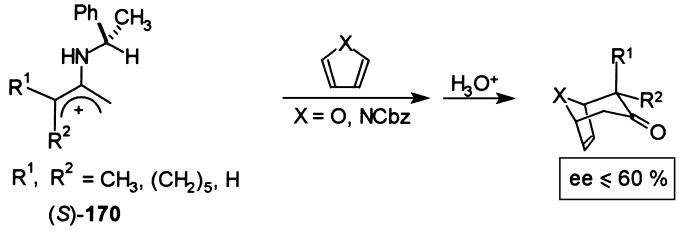


Scheme 66.



Scheme 67.

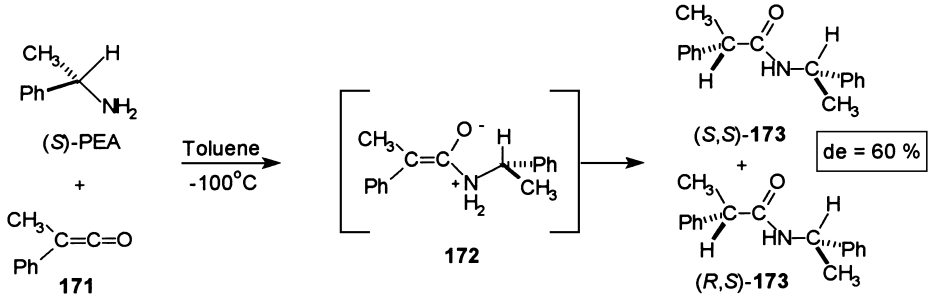
Very recently, Kende and Huang[119] reported the first asymmetric [4+3] cycloadditions of chiral *N*-(α-phenylethyl)aminoallyl cations (*S*)-**170** to furan and pyrrole (Scheme 68).



Scheme 68.

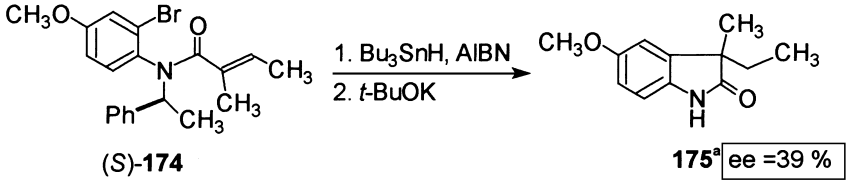
1.5. Miscellaneous diastereoselective modifications of substrates containing α-PEA

Pioneering studies on the use of α-PEA in asymmetric synthesis by Pracejus and Tille[120] are discussed in Morrison and Mosher's classical book.[121] Addition of (*S*)-PEA to phenylmethylketene **171** affords intermediate **172**, where hydrogen transfer to the diastereotopic faces of the enolate determines the configuration of the generated amides (*S*,*S*)-**173** and (*R*,*S*)-**174** (Scheme 69).



Scheme 69.

In 1989, Jones and McCarthy[122] reported that *ortho*-haloacryloylamides (*S*)-**174** carrying the (*S*)-α-phenylethyl chiral auxiliary on nitrogen undergo radical cyclization to give oxoindoles **175** in low ee (Scheme 70).



[a]The configuration of **175** was not assigned.

Scheme 70.

In contrast, Fox and Gallagher[123] observed that Ag(I)-mediated cyclization of allenic amines **176** affords pyrrolidine products **177** with diastereoselectivities as high as de=81% (Table 15).

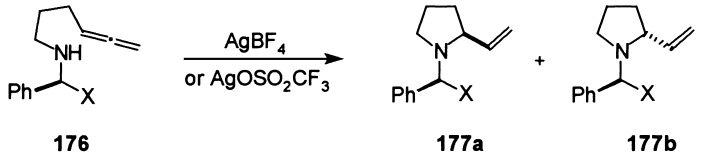
In this context, Cardillo and co-workers[124] reported the synthesis of enantiopure imidazolidin-2-ones **179** by means of nondiastereoselective iodocyclization of allylic tosylureas (*S*)-**178**. This procedure allows the preparation of both (*R*)- and (*S*)-2,3-diaminopropanoic acid (Scheme 71).

In a different approach to asymmetric cyclization, Kawabata et al.[125] developed the synthesis of β-lactams through an intramolecular oxidative coupling of dianions generated from acyclic tertiary amides containing the *N*-(α-phenylethyl) chiral auxiliary. The choice of oxidant is crucial for the control of stereochemistry, as it can be appreciated in Table 16.

In the search for synthetic routes to endopeptidase inhibitors of the glutaramide series, Barnish and co-workers[126] necessitated efficient syntheses of β-amino acid derivatives (*S*)-**184**. Accordingly, an interesting strategy based upon diastereoselective addition of lithium enolates to C_2-symmetric (*S*,*S*)-**182**, affording 1,4-adducts **183** with excellent results (up to 98% de, Scheme 72), was developed.[126]

In a series of recent papers, Orena and co-workers[127] studied the diastereoselective intramolecular conjugate addition of *N*-(α-phenylethyl)-containing amides (*S*)-**185** and (*S*)-**186**. One application of this cyclization reaction is the conversion of either **187** or **188** to (*S*)-3-pyrrolidineacetic acid, (*S*)-**189** (Scheme 73).[127a]

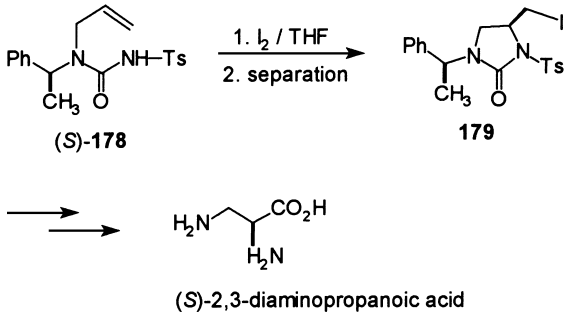
Table 15
Diastereoselectivity of Ag(I)-mediated cyclization of allenic amine **176**[123]



176 **177a** **177b**

X	Mol % Ag(I)	solvent	**177a** : **177b**	yield, %
CH_3	46	CH_2Cl_2	2 : 1	87
CO_2CH_3	62	CH_2Cl_2	4 : 1	71
CO_2CH_3	42	DMSO	4.7 : 1	n.d.[a]
CH_2OH	15	CH_2Cl_2	4 : 1	90
CH_2NHCH_3	50	CH_2Cl_2	9.3 : 1	90
CH_2NHCH_3	38	CH_2Cl_2	6.3 : 1	89
CH_2NHCH_3	45	CH_2Cl_2	8 : 1	63
CH_2NHCH_3	54	DMSO	4 : 1	90

[a]Not determined.



(*S*)-**178** **179**

(*S*)-2,3-diaminopropanoic acid

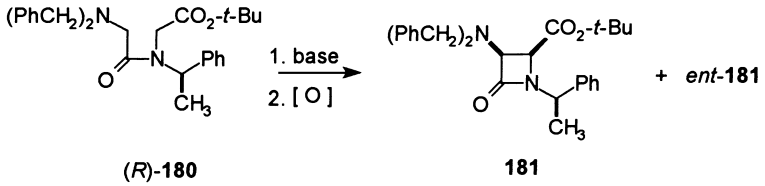
Scheme 71.

Very recently, Petasis and Zavialov[128] described a highly efficient procedure for the synthesis of α-amino acids, involving the condensation of an organoboronic acid **190** with (*R*)-2-phenylglycinol, (*R*)-**191**, and glyoxylic acid (Scheme 74a). With (*S*)-α-PEA as the chiral amine, the observed diastereoselectivity was lower, but still remarkable (Scheme 74b).[128]

In another interesting observation, Magnus and Magnus[129] found that treatment of the acyclic sulfone (*R*)-**192** with *n*-BuLi at −100°C followed by PhCHO gave only two diastereomeric carbinols **193**, out of four possible stereoisomeric products (Scheme 75). This result is surprising considering that the chiral inducing entity is nine bonds away from the prochiral methylene group. Bicyclic intermediate **194** was advanced to explain the unexpected stereoinduction.

Pioneering studies of Wakabayashi and Saito[130] and Munegumi and Harada[131] have demonstrated the potential of *N*-(α-phenylethyl)-containing carbonylic compounds for diastereoselective reduction and hydrogenation. In a recent development, Nakayama and Schultz[132] reported the use of antibodies to carry out catalytic, stereoselective reductions of α-ketoamide (*S*)-**195**. (The (*S*)-α-PEA group was incorporated into the substrate to facilitate analysis of reaction stereoselectivity.) The uncatalyzed reaction afforded α-

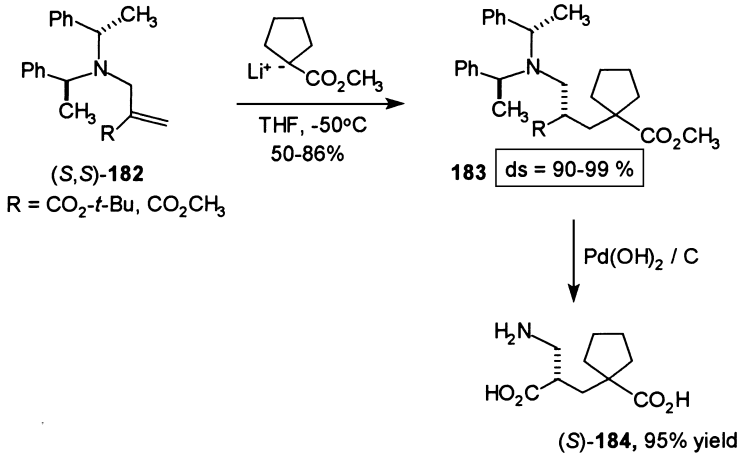
Table 16
Synthesis of β-lactams by oxidative coupling of dianions derived from (*R*)-**180**[125]



(*R*)-**180** **181**

base	oxidant	yield, %	**181** : *ent*-**181**
t-BuLi	NIS[a]	30	3.5 : 1
n-BuLi	NIS	22	> 8 : 1
n-BuLi/TMEDA	NIS	58	18 : 1
n-BuLi	$Cu(OAc)_2$	63	2 : 1

[a]NIS, *N*-iodosuccinimide.

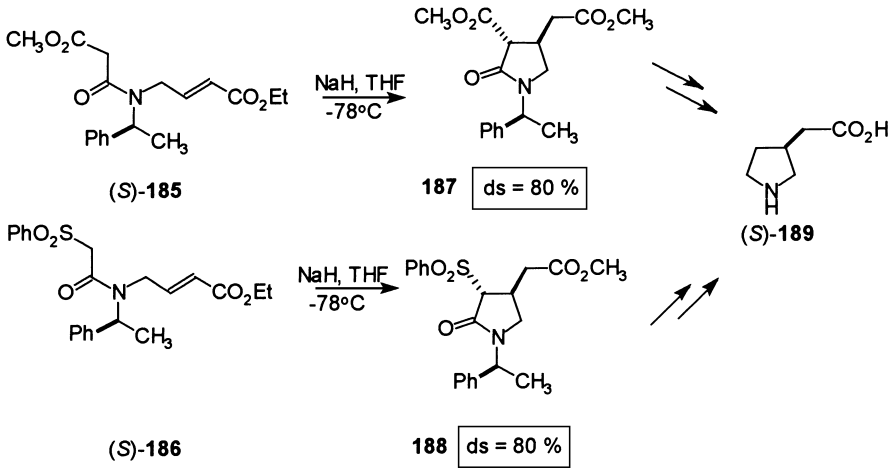


Scheme 72.

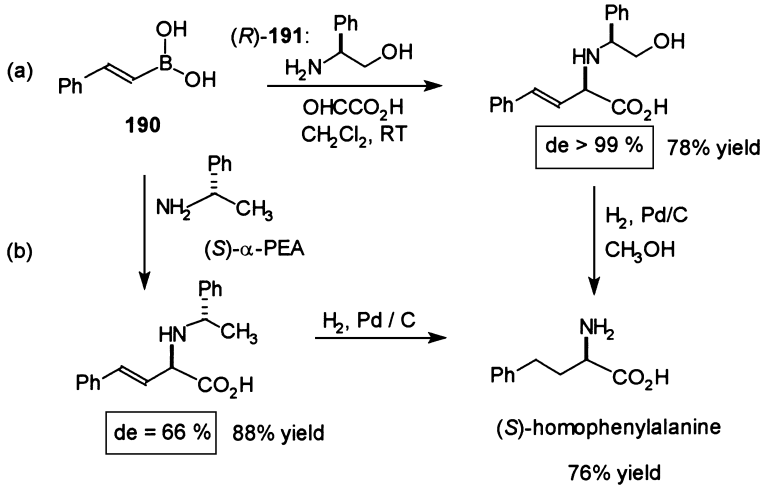
hydroxy amide (*R*)-**196** with a diastereomeric excess of 56%. In contrast, the antibody-catalyzed reaction afforded (*S*)-**196** with de >99% (Scheme 76).

In another stereoselective biotransformation, Hudlicky et al.[133] extended the resolution potential of baker's yeast reduction of *rac*-β-keto amide (±)-**197** (Scheme 77).

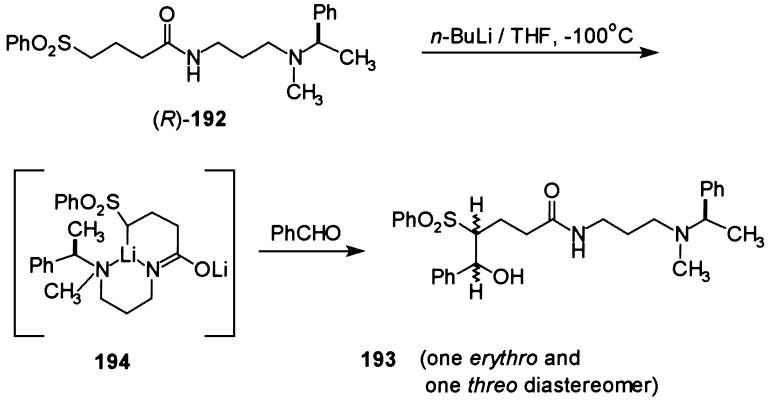
Very recently, Paquette and co-workers[134] disclosed results regarding the diastereoselective reaction of *N*-(α-phenylethyl)-2,3-azetidinediones with allylmetals.



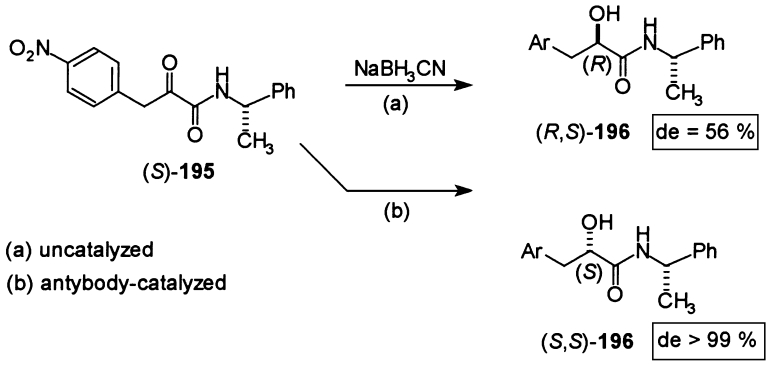
Scheme 73.



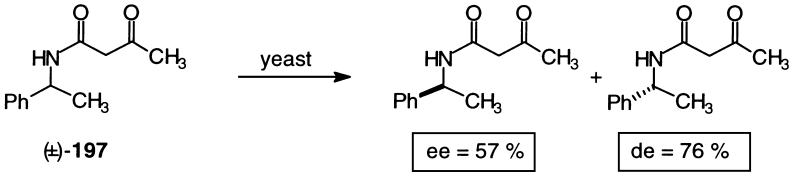
Scheme 74.



Scheme 75.



Scheme 76.

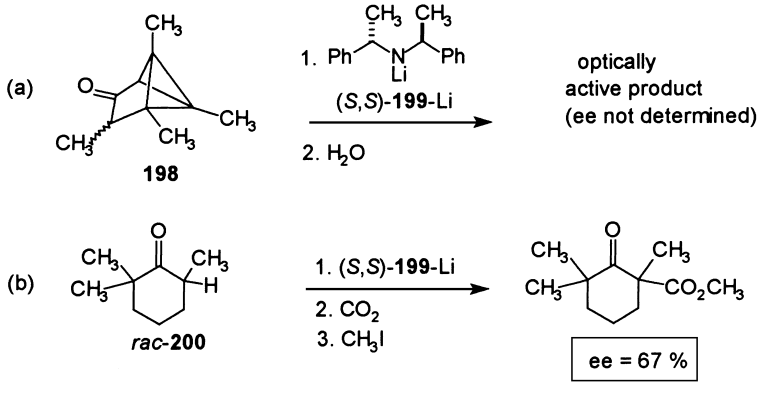


Scheme 77.

2. α-PEA as chiral reagent in the stereodifferentiation of prochiral substrates

2.1. Asymmetric deprotonation of prochiral ketones

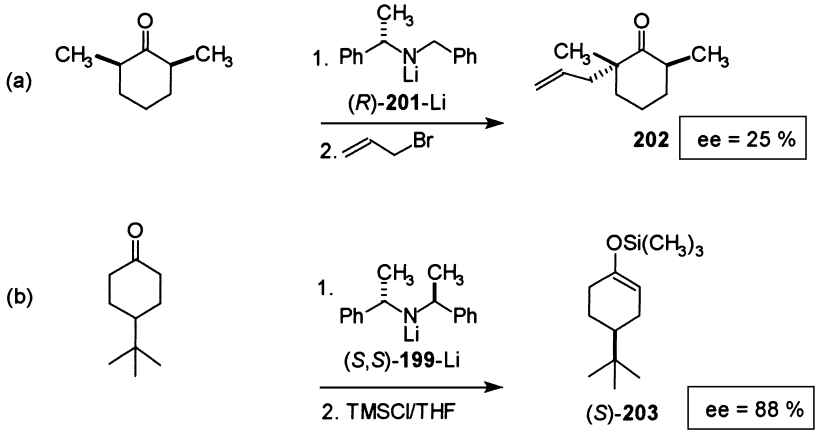
The pioneering applications of *N*-(α-phenylethyl)lithium amide bases in reactions in which a symmetrically substituted prochiral ketone is modified enantioselectively via removal of one enantiotopic proton have been reviewed by Cox and Simpkins.[135] In particular, Hogeveen and Zwart[136] reported the enantioselective deprotonation/protonation reaction of ketone **198**, using (*S*,*S*)-**199**-Li, followed by quenching with water to afford optically active **198** (Scheme 78a). Furthermore, *rac*-2,2,6-trimethylcyclohexanone **200** was deprotonated with (*S*,*S*)-**199**-Li and shown to undergo enantioselective carboxylation with CO_2 (Scheme 78b).[136b]



Scheme 78.

In related experiments, *cis*-2,6-dimethylcyclohexanone was treated with (*R*)-**201**-Li followed by allyl bromide to give alkylated product **202** with 25% ee (Scheme 79a),[137a] and 4-*t*-butylcyclohexanone was

deprotonated with (*S*,*S*)-**199**-Li and then quenched with trimethylsilylchloride to afford (*S*)-**203** in 88% ee (Scheme 79b).[137b]



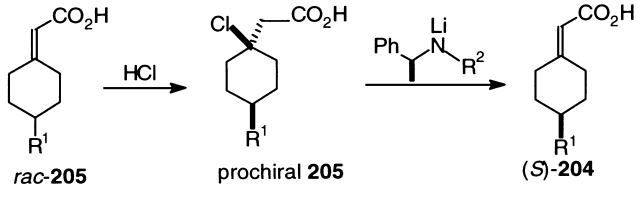
Scheme 79.

Duhamel and co-workers[138] have described the deracemization of unsaturated carboxylic acid **204** by enantioselective dehydrohalogenation of prochiral species **205** with chiral lithium amides (Table 17).

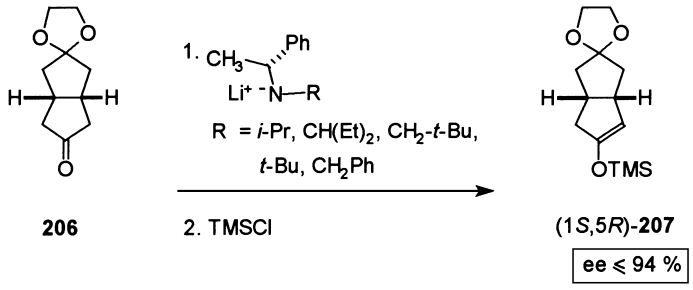
In 1989, Izawa et al.[139] reported that kinetic deprotonation of ketone **206** by chiral lithium amides in the presence of excess TMSCl afforded the corresponding silyl enol ethers **207** in up to 94% ee (Scheme 80). Furthermore, Koga and co-workers[140] noticed that the enantioselectivity of deprotonation reaction of 4-*t*-butylcyclohexanone by (*R*,*R*)-**199**-Li in THF is strongly influenced by the presence of lithium halides (Table 18).

Very recently, Aoki and Koga[141] discovered that α-phenylethylamine-derived lithium amide (*R*)-**208**-Li, possessing a fluoroethyl group can induce high enantioselectivity in the kinetic deprotonation of 4-*t*-butylcyclohexanone in the presence of excess trimethylsilyl chloride to give the corresponding silyl enol ether (*S*)-**209** in up to 92% ee (Table 19).

Table 17
Enantioselective dehydrochlorination[138]

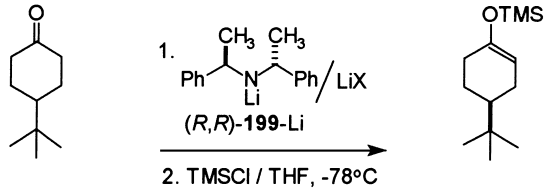


R^1	R^2	ee, %	Yield, %
t-Bu	*t*-Bu	54	88
t-Bu	1-adamantyl	82	84
CH_3	*t*-Bu	52	73
CH_3	1-adamantyl	80	75



Scheme 80.

Table 18
Salt effects in the enantioselective deprotonation of 4-*t*-butylcyclohexanone[140]



LiX (equiv.)	ee (%)	Yield (%)
——	44	84
LiCl (0.6)	87	86
LiCl (1.2)	88	87
LiCl (3.6)	88	73
LiBr (1.2)	63	89
LiBr (3.6)	86	82
LiI (1.2)	44	85
LiI (3.6)	43	79

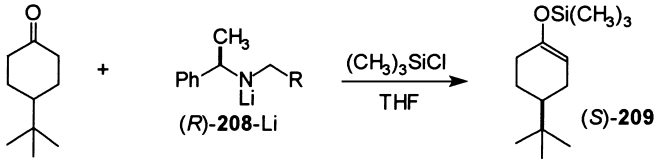
In a series of relevant papers, Simpkins and co-workers[142] reported the use of α-PEA-derived lithium amide bases for the enantioselective deprotonation of 4-*t*-butylcyclohexanone, achieving high enantioselectivities in several cases (ee ≤88%). Furthermore, remarkable effects of LiCl[143a] and $ZnCl_2$[143b] on enantioselectivity were observed, and an application involving the total synthesis of the alkaloid anatoxin-A was described.[143c]

More recently, Ewin et al.[144] have demonstrated that tricarbonyl(η^6-arene)chromium complexes can be desymmetrized, in up to 99% ee, via enantioselective deprotonation at the benzylic position using α-PEA-derived lithium amide bases. For an example, see Scheme 81.

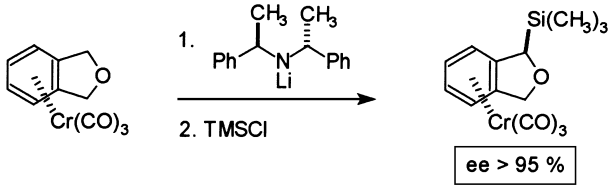
Finally, Blake et al.[145] found that reaction of sulfoxide **210** with bis-lithium amide **211**-Li_2 gave the rearranged product **212** as a mixture of diastereomers (epimeric at sulfur), each of which was formed in 82% ee (Scheme 82).

Relevant contributions to the field of enantioselective lithium enolate formation by means of α-PEA-derived lithium amide bases have also been advanced by Majewski and co-workers,[146] MaGee et al.,[147] and Honda et al.[148] Very recently, Kropf and Weinreb[149] reported the first examples of a most interesting

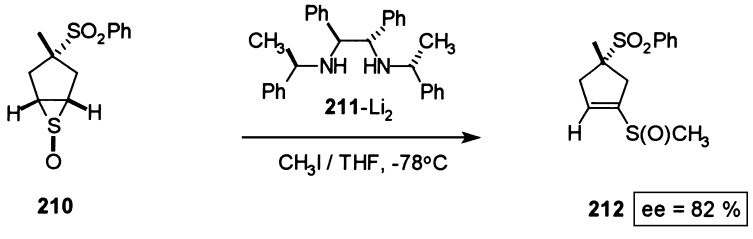
Table 19
Enantioselective deprotonation with (*R*)-**208**-Li



R	temp. (°C)	yield, %	ee, %
CH_2F	-78	61	43
CHF_2	-78	66	59
CF_3	-78	98	89
CF_3	-100	86	92



Scheme 81.



Scheme 82.

intramolecular cyclization of prochiral cyclohexanone **213** with α-PEA-derived chiral lithium amide bases in good enantiomeric excesses (Table 20).

2.2. Enantioselective transformation of prochiral epoxides

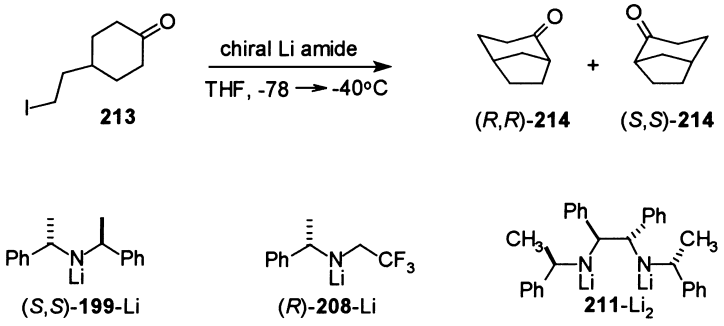
In an early application, C_2-symmetric[150] chiral lithium amide (*S*,*S*)-**199**-Li was used for enantioselective deprotonation in the rearrangement of *meso* epoxide **215** to chiral allylic alcohol (*R*)-**216** (Scheme 83).[151]

In 1990, Leonard and co-workers[152] reported that the *meso* epoxide **217** was cleaved via enantioselective deprotonation by means of chiral lithium amide bases derived from α-PEA, to provide carbinol **218** (absolute configuration was not assigned) with up to 76% ee (Scheme 84).

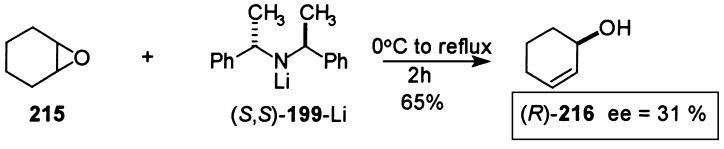
In a related study, Hodgson and Wisedale[153] achieved the enantioselective (ee=49%) α-deprotonation-rearrangement of *exo*-norbornene oxide **219** to (−)-nortricyclanol **220** using (*S*,*S*)-**199**-Li (Scheme 85).

Very recently, Fukuzawa et al.[154] prepared chromium tricarbonyl derivative (*R*,*S*)-**221**, which reacted

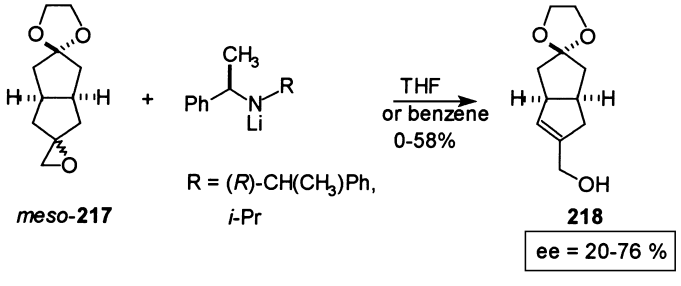
Table 20
Enantioselective intramolecular cyclization of prochiral cyclohexanones with chiral Li amides[149]



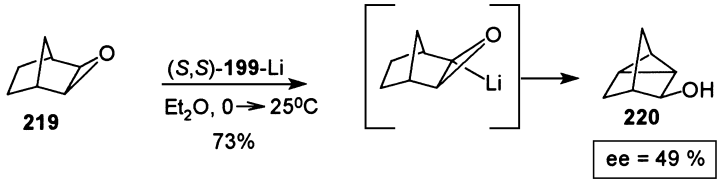
Li amide	additive	temp, °C	Product	ee
(*S*,*S*)-**199**-Li	LiCl	-60 → -20	(*R*,*R*)	58
(*S*,*S*)-**199**-Li	LiCl	-80 → -40	(*R*,*R*)	80
(*R*)-**208**-Li	LiCl	-60 → -20	(*S*,*S*)	60
(*R*)-**208**-Li	LiCl	-80 → -40	(*S*,*S*)	78
211-Li_2	LiCl	-80 → -40	(*R*,*R*)	46



Scheme 83.

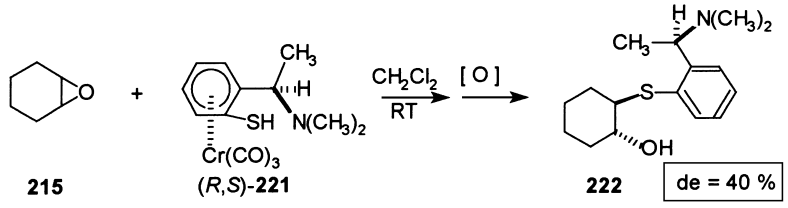


Scheme 84.



Scheme 85.

with cyclohexene oxide to give, after removal of the chromium moiety, *trans*-β-hydroxy aryl sulfide **222** with moderate diastereoselectivity (Scheme 86).

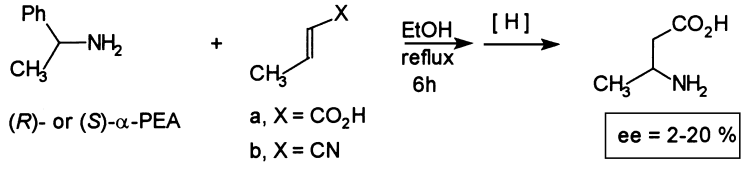


215 (*R*,*S*)-**221** **222**

Scheme 86.

2.3. Diastereoselective Michael additions

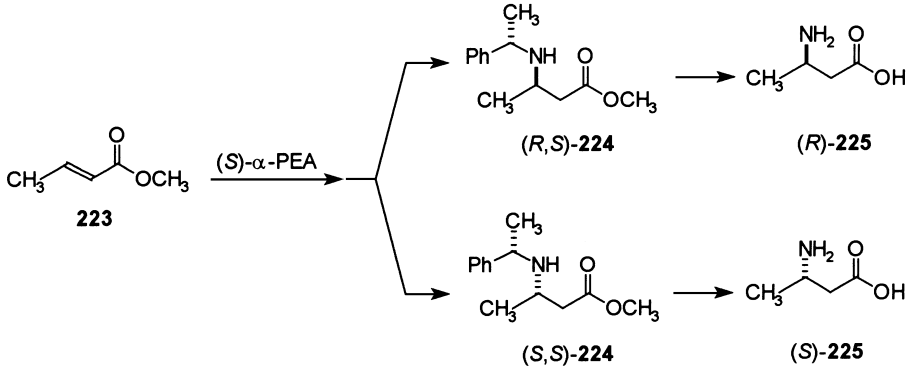
In 1965, Terentev and co-workers[155] reported the first example of an enantioselective addition of (*R*)- and (*S*)-α-PEA to crotonic acid; nevertheless, the enantioselectivities obtained were quite poor (Scheme 87a). Similarly disappointing were the studies of Furukawa et al.[156] on the corresponding conjugated nitriles (Scheme 87b).



(*R*)- or (*S*)-α-PEA a, X = CO_2H b, X = CN

Scheme 87.

Michael additions of (*S*)-α-PEA to methyl crotonate **223** afford a 3:2 mixture of the (3*R*,1′*S*) and (3*S*,1′*S*) diastereoisomers **224**, which can be separated by preparative HPLC[157] or by flash chromatography.[158] Hydrogenolytic removal of the phenylethyl group with concomitant ester hydrolysis gives enantiopure 3-aminobutanoic acids (*R*)- and (*S*)-**225** (Scheme 88).



223 (*R*,*S*)-**224** (*R*)-**225** (*S*,*S*)-**224** (*S*)-**225**

Scheme 88.

The synthetic usefulness of secondary amines **226**, **227**, and **228** (Fig. 9) as "chiral ammonia equivalents in Michael additions" has been most masterly demonstrated by Davies and co-workers.[159,160]

For example, Michael addition of **226**-Li to benzyl (*E*)-crotonate was highly stereoselective (dr=97.5:2.5), giving, after debenzylation with Pearlman's catalyst, enantiopure (*R*)-**225** (Scheme 89a).[159] Similarly, addition to methyl (*E*)-(*p*-benzyloxy)cinnamate was completely stereoselective, leading to enantiomerically pure (*S*)-β-tyrosine, (*S*)-**229** (Scheme 89b).[159]

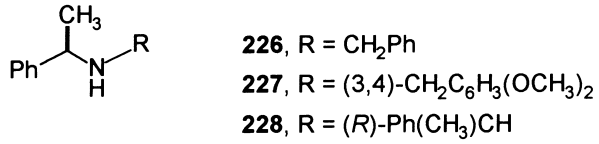
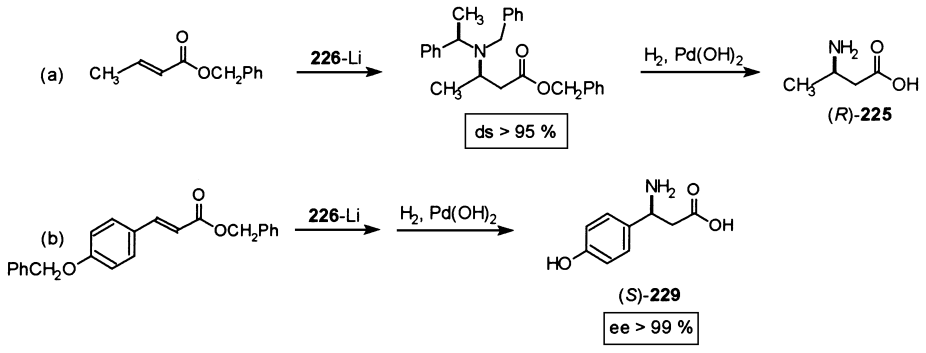
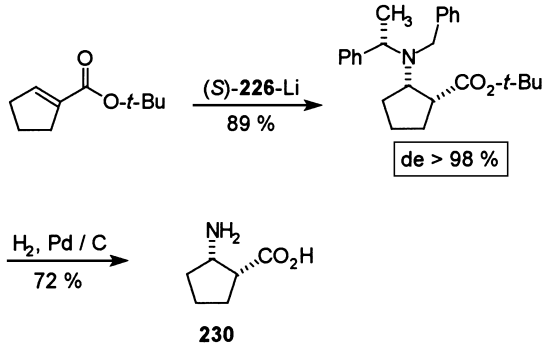


Figure 9.



Scheme 89.

In a further elegant application, the antifungal antibiotic (1*R*,2*S*)-2-aminocyclopentane-1-carboxylic acid (cispentacin, **230**) was prepared via the highly stereoselective Michael addition of (*S*)-**226**-Li to *t*-butyl 1-cyclopentene-1-carboxylate (Scheme 90).[161]



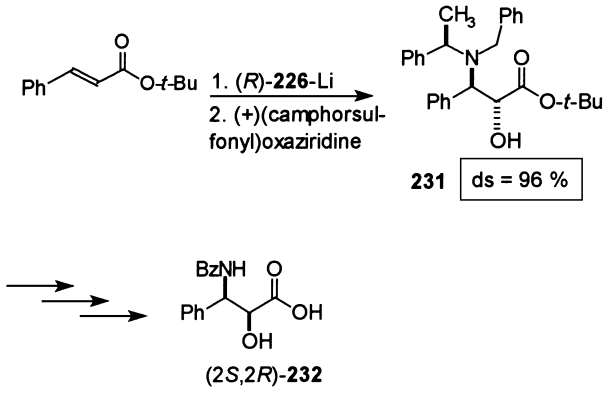
Scheme 90.

Another important achievement was the enantioselective preparation of various derivatives of 3-phenylisoserine, **232**, the side chain in Taxol. Conjugate addition of (*R*)-**226**-Li to *t*-butyl cinnamate was followed by hydroxylation of the intermediate enolate to give amino ester **231** in 96% diastereoselectivity (Scheme 91).[162] This synthetic approach was applied in the enantioselective preparation of (2*S*,3*R*)-**233** and (2*S*,3*S*)-**234** (Fig. 10).[163]

Additional contributions in this area by the Davies group are listed in the literature.[164]

In 1990, Carroll and co-workers[165] reported the preparation of (−)-6-methyl-6-azabicyclo[3.2.1]octan-3-one, (−)-**238**, from racemic lactone (±)-**235**, according to the reaction sequence shown in Scheme 92. In this procedure, (*R*)-α-PEA enables the resolution of (±)-**235**. The cyclization step (**236** → **237**) proceeds with complete diastereoselectivity, as a consequence of the relative configuration of the starting material.

More recently, Bovy and co-workers[166] described a highly stereoselective Michael addition of (*R*)-**240** to ethyl *trans*-3-pyridineacrylate **239** as the crucial step in the synthesis of novel β-amino acid (*S*)-**241** (Scheme 93).



Scheme 91.

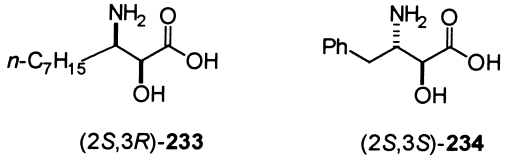
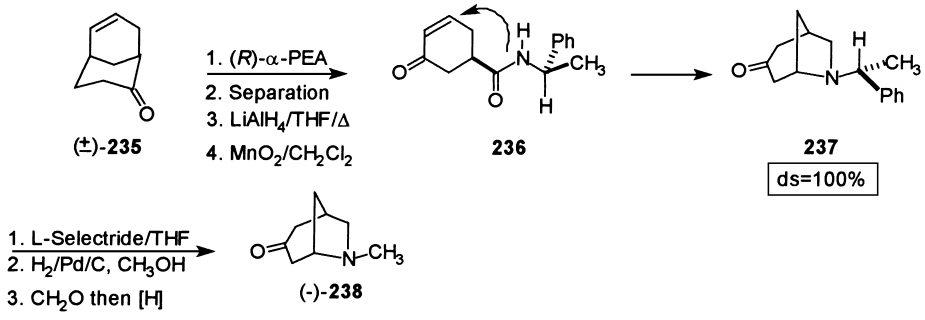
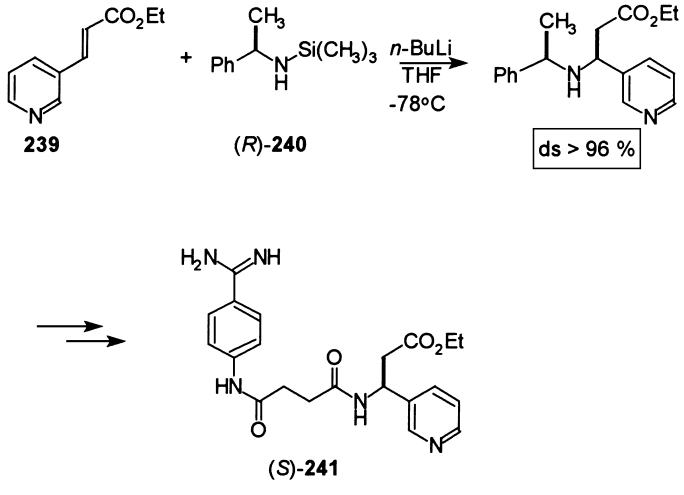


Figure 10.

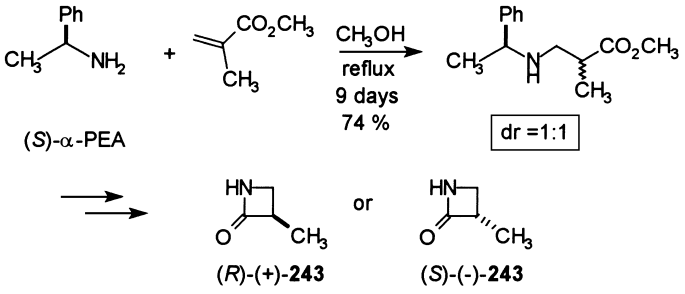


Scheme 92.



Scheme 93.

In contrast, addition of (*S*)-α-PEA to methyl methacrylate afforded amino ester **242** as a ca. 1:1 diastereomeric mixture. Nevertheless, fractional crystallization of the corresponding hydrochloride salts allowed the preparation of (+)- and (−)-**243**, as shown in Scheme 94.[167]



Scheme 94.

Very recently, Ma and Zhang[168] reported the highly diastereoselective (~100% ds) conjugate addition of (*S*)-**226**-Li to α,β-unsaturated ester **244**. Yamada et al.[169] described the highly diastereoselective addition of (*S*)-α-PEA to acrylic acid **245** (de=85–98%). Finally, Ishikawa and co-workers[170] found 80% de in the Michael addition of (*S*)-*N*-(α-phenylethyl)hydroxylamine to chiral ester **246** (double stereodifferentiation). In a related study, Nagaoka and Tomioka[171] carried out the conjugate addition of (*R*)-**226**-Li to alkenylphosphonate **247** (Fig. 11) with 72% de.

2.4. Stereoselective additions to prochiral carbonyl substrates

In 1995, Yus and collaborators[172] reported that the successive reaction of chiral allyl amine (*R*)-**248** with *n*-BuLi and then with *t*-BuLi led to the corresponding intermediate (*R*)-**249**-Li_2, which by treatment with prochiral ketones such as pivalaldehyde afforded a ca. 1:1 diastereomeric mixture of the corresponding aminoalcohols (*R*,*R*)-**250** and (*R*,*S*)-**250** (Scheme 95).

In contrast, pure diastereomers, obtained directly by reaction of hypophosphorus acid salts of (*R*)- or (*S*)-α-PEA with prochiral aldehydes, provide a convenient synthesis of α-aminophosphonic acids in high enantiomeric purity (Table 21).[173]

More recently, Cavé et al.[174] reported that when imine (*S*)-**251** was added to maleic anhydride, adduct **252** was obtained as a single diastereoisomer (Scheme 96a). In contrast, addition of imine (*S*)-**253** to citraconic anhydride furnished a 4:1 mixture of diastereomeric adducts **254** and **255** (Scheme 96b).

Very recently, Iseki and co-workers[175] reported that (*S*,*S*)-*N*,*N*-bis(α-phenylethyl)formamide, (*S*,*S*)-**256**, functions as Lewis base catalyst for allylation of aliphatic aldehydes, with high enantioselectivity (up to 98% ee) (Table 22).

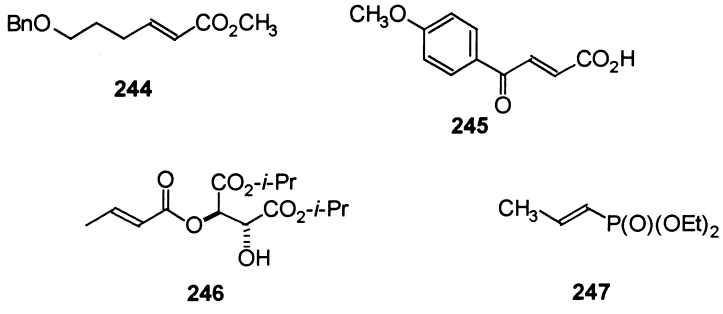
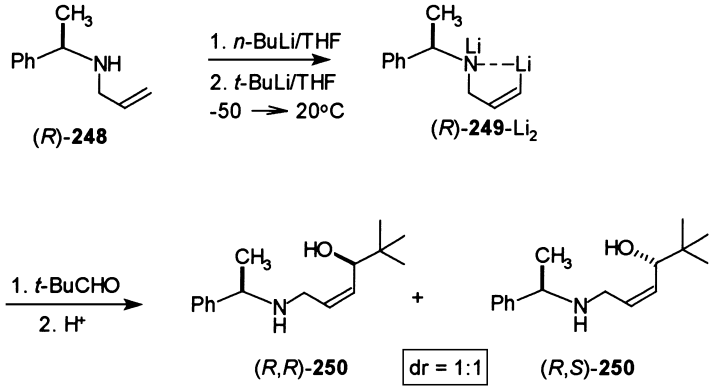
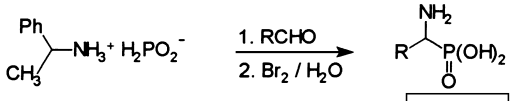


Figure 11.



Scheme 95.

Table 21
Enantioselective synthesis of α-aminophosphonic acids[173]



config. α-PEA	R	yield, %	config. product
(*S*)	$(CH_3)_2CH$	88	(*R*)
(*S*)	$(CH_3)_2CHCH_2$	67	(*R*)
(*S*)	*c*-C_6H_{11}	65	N.d.[a]
(*S*)	Ph	77	(*R*)
(*S*)	$PhCH_2$	87	(*R*)
(*R*)	$(CH_3)_2CH$	87	(*S*)
(*R*)	$(CH_3)_2CHCH_2$	82	(*S*)
(*R*)	*c*-C_6H_{11}	83	N.d.[a]
(*R*)	Ph	82	(*S*)
(*R*)	$PhCH_2$	92	(*S*)

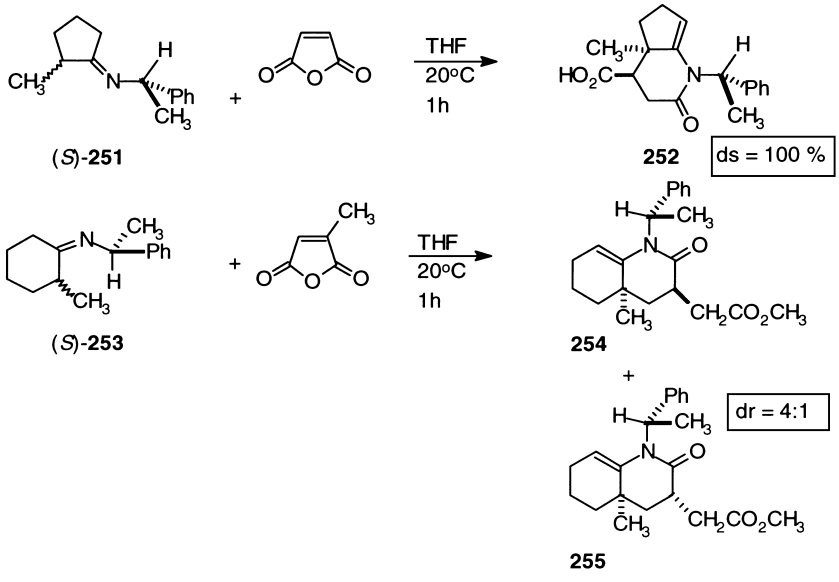
[a]Not determined.

3. Concluding remarks

The low price of both enantiomers of α-PEA make this chiral amine attractive for the preparation of enantiomerically pure compounds. The present summary of the application of α-PEA as chiral reagent may motivate further interest by chemists in academia and also in industry to take advantage of this simple but powerful chiral adjuvant.

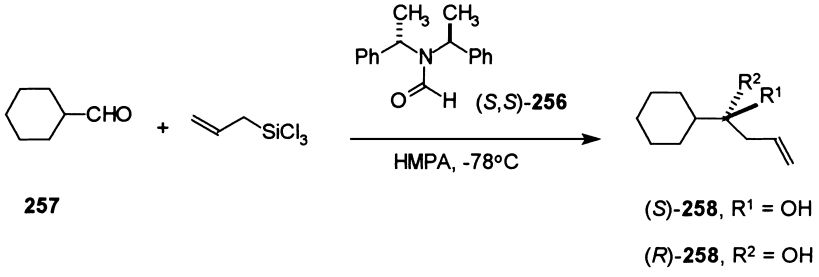
Acknowledgements

We are indebted to the Editor (Professor D. P. Curran) and the reviewers, for many useful recommendations.



Scheme 96.

Table 22
Enantioselective allylation of aldehyde **257** with allyltrichlorosilane, catalyzed by (*S*,*S*)-**256**[175]



mol % (*S*,*S*)-**256**	mol % HMPA	yield	(*S*)-**258** / (*R*)-**258**
100	0	81	16/84
25	0	20	65/35
100	100	89	2/98
20	100	80	1/99

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