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Stereoselective Synthesis of Quaternary Proline Analogues

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This review describes available methods for the diastereoselective and asymmetric synthesis of quaternary prolines. The focus is on the preparation of α-functionalized prolines in which the pyrrolidine moiety is not embedded in a polycyclic frame. The diverse synthetic approaches are classified according to the bond that is formed to complete the quaternary skeleton.

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1. Introduction

Biologically active peptides and proteins regulate most vital physiological processes and are therefore targets for potential medical applications across the full spectrum of human disease.[1] However, the pharmacological applicability of native peptides is greatly limited by profound factors such as lack of selectivity for a specific receptor, enzymatic instability, or low bioavailability.[2] The diverse functionalities of peptides are based on the physical and chemical properties of specific amino acid side chains and on

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Carlos Cativiela is Full Professor of Organic Chemistry at the University of Zaragoza since 1996. His scientific activity started in the field of asymmetric synthesis oriented towards the preparation of amino acids. He has developed different methodologies for the synthesis of a wide variety of non-natural constrained amino acids in enantiomerically pure form either by enantio- or diastereoselective syntheses or by chromatographic resolution procedures. Current research interests also involve the incorporation of such non-natural amino acids into peptides of structural or biological interest. He is author of more than 320 papers and 10 reviews.

their three-dimensional structures, the folding. The modification of native peptides through the incorporation of rigid amino acid surrogates into their structures constitutes a powerful means to overcome their shortcomings since a limited conformational freedom often protects from proteolytic degradation and sometimes leads to improved selectivity and potency.[3]

In this context, proline analogues[4] are of special interest given the key role of proline in nucleating the secondary structures, and hence the biological behavior, of peptides.[5] Such significance is due to the exceptional conformational rigidity conferred on proline by its cyclic structure and the hinge-like behavior displayed at peptide bonds involving the pyrrolidine nitrogen. In particular, quaternary proline analogues are of ongoing interest as modulators of proline conformational constraint for peptide engineering purposes.

Although little has been explored with regard to their conformational preferences,[6,7] α-substituted prolines are also attractive templates in structure–function relationship studies directed towards elucidation of biologically active conformations, just like proline chimeras.[8] The large number of papers and patents dealing with the incorporation of α-methylated[7,9,10] analogues of proline into bioactive peptides and other biologically relevant systems reveal the enormous potential of this type of proline analogues. Their increasing interest is also linked to potential uses in regulation of protein–protein interactions mediated through proline-rich binding domains[11] and to peptidomimetic design based on mimicry of protein recognition motifs such as β-turns.[12] Moreover, their utility expands further into the design of new organic catalysts and auxiliaries for asymmetric synthesis.[13]

Despite the growing interest in them, the exploitation of α-substituted proline derivatives relies on ready accessibility to their enantiomerically pure forms. For this reason, we wish to illustrate the progress in the enantio- and diastereoselective synthetic methods utilized for their construction. Although the stereoselective synthesis of α,α-disubstituted amino acids has been broadly collated both by ourselves[4b,14] and by others,[15] only a few reports have particularly covered the preparation of α-substituted proline analogues.[4a,4b]

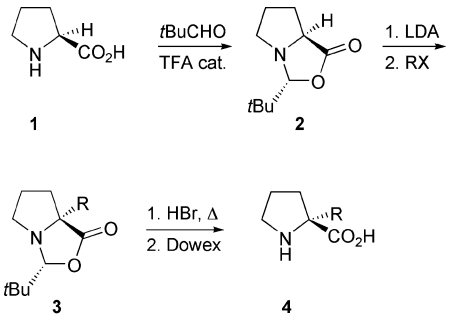
In this review, the synthetic approaches have been classified according to the bond that is formed to complete the quaternary proline skeleton. Well established strategies such as the alkylation of enolate derivatives of existing α-amino acids or 1,3-dipolar cycloadditions have been collected, as well as more recent asymmetric catalytic approaches. Because of the abundant literature in the field, reactions leading to polycyclic proline-type compounds have not been included.

2. Syntheses from Proline Derivatives

A number of strategies devised for the synthesis of α-substituted proline derivatives involve the α-functionalization of L-proline itself. Most often, the assembly of the fully substituted stereocenter is accomplished by electrophilic alkylation of L-proline enolate equivalents. Some of these approaches have been the subject of recent reviews.[4a,4b]

2.1 Self-Reproduction of Chirality

In 1983, Seebach et al. reported a methodology that formally allows the direct α-alkylation of L-proline without loss of the optical purity and with retention of configuration,[16–18] thus constituting a showcase of their concept of *self-reproduction of chirality*.[19] L-Proline was condensed with pivalaldehyde to give a single stereoisomer of 2-*tert*-butyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one (**2**), which upon deprotonation with LDA gave a chiral nonracemic enolate that combined with alkyl halides to afford the corresponding α-alkylated compounds in moderate to high yields and with essentially complete diastereoselection (Scheme 1).[17,20,21] In addition, the intermediate **2** was also phenylated with (benzene)(tricarbonyl)chromium and thiolated with diphenyl disulfide.[17] The hydrolytic cleavage of the products **3**, which can be difficult under acidic conditions, could be performed under mild conditions by using a suspension of silica gel in methanol/water[22] or, alternatively, carboxamide derivatives could be obtained after treatment with lithium amides.[17]



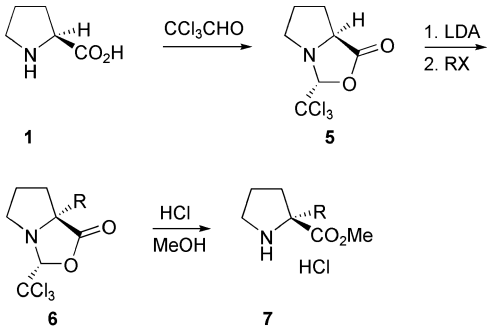
RX	Yield **3** (%)	Ref.
MeI	93[a]	[17]
CH_2=$CHCH_2Br$	87[a]	[17]
BnBr	91[a]	[17]
Me_2N^+=CH_2 Cl^-	56[a]	[17]
MeO_2CCH_2Br	40[a]	[17]
$Me_2N(O)CCH_2Cl$	70[a]	[17]
$BnOCH_2Cl$	62[b,c]	[20]
$MeCH$=$CHCH_2Br$	64[b]	[21]

[a] *dr* > 95:5
[b] Single diastereoisomer
[c] Yield from L-proline

Scheme 1.

A related strategy pursued by Germanas et al. involved the use of 2-(trichloromethyl)oxazolidin-5-one **5** as the precursor to enantiomerically pure α-substituted prolines (Scheme 2).[23–26] In terms of the stereochemical course of the reaction, their results were similar to those reported by Seebach, but the use of a trichloromethyloxazolidinone is preferable because of its greater stability and lower cost of

production. The cleavage of the chloral auxiliary often required hydrochloric acid/methanol at reflux to produce the desired methyl ester hydrochloride salt. Interestingly, Williams et al. reported that treatment of the lactone **6** (R = allyl) with Na in methanol, followed by the addition of acetyl chloride to the solution and heating to reflux, readily removes the trichloroacetaldehyde auxiliary.[27] In this manner, (*R*)-allylproline methyl ester hydrochloride salt was prepared on a 20 g scale and was used as a building block for the total synthesis of the fungal metabolites (–)-stephacidin A, (+)-stephacidin B, and (+)-notoamide B. Besides this, the (trichloromethyl)oxazolidinones could also be readily transformed into amides by nucleophilic ring-opening with amines.[28]



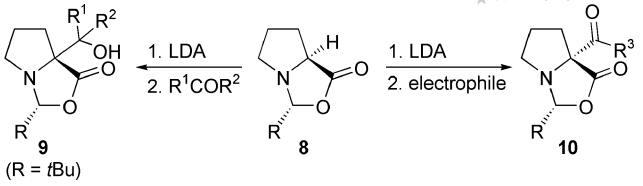
RX	Yield **6** (%)	Ref.
MeI	58[a]	[23]
EtI	46[a]	[24]
CH_2=$CHCH_2Br$	69[a]	[23]
BnBr	51[a]	[23]
EtO_2CCH_2I	30[a]	[23]
$BrCH_2CH$=$CHCH_2Br$	55[b]	[25]
HC≡CCH_2Br	24[b]	[26]
TMSC≡CCH_2Br	42[b,c]	[26]

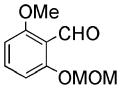
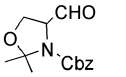
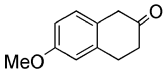
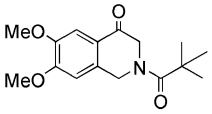
[a] *dr* > 95:5
[b] Single diastereoisomer
[c] Based on converted oxazolidinone (87% conv.)

Scheme 2.

Both versions of this methodology have been profusely applied in the synthesis of enantiomerically pure α-alkylproline derivatives for use as intermediates in the synthesis of more complex structures. In particular, enantiomerically pure α-allylproline has shown plentiful applications in the synthesis of type II[29] and type VI[30] β-turn[31] mimetics, spirolactams[25,32] as conformationally restricted pseudopeptides, biologically active natural products,[21,27,33] and peptidomimetics.[24,34]

As well as alkylation reactions, additions to carbonyl groups of aldehydes[17,35] and ketones,[17] Michael additions,[17] and acylation reactions[17,32b] have also been reported (Scheme 3). The additions to aldehydes and ketones afforded isomers epimeric at the carbinol center, Michael additions gave rise to the formation of constitutional isomers, and the acylation reactions generated quite unstable compounds.[17]



R^1COR^2	Yield **9** (%)[a]	Ref.
MeCHO	88	[17]
PhCHO	72	[17]
*t*BuCHO	85	[17]
	72	[35b]
	51	[35a]
MeCOMe	93	[17]
$MeCOCH_2CO_2Me$	67	[17]
3,4-$(MeO)_2$-$C_6H_3COCH_2NO_2$	79	[17]
	70	[17]
	67	[17]
	91	[17]

R	R^3	Yield **10** (%)	Ref.
*t*Bu	Me	80	[17]
*t*Bu	C_6H_5	80	[17]
*t*Bu	OMe	85	[17]
CCl_3	H	65	[32b]

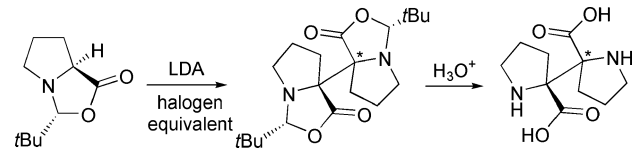
[a] *dr* ranging from 67:33 to 95:5 at the carbinol center

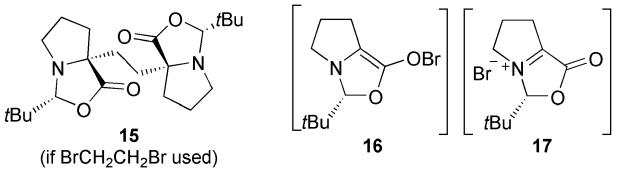
Scheme 3.

More recently, Johnson et al. reported the synthesis of the (*R*,*R*)-α,α′-biproline **13** and the *meso*-α,α′-biproline **14** through a temperature-dependent diastereoselective dimerization of Seebach's oxazolidinone (Scheme 4).[36] Alkylation of the lithium enolate of **2** with vicinal dihalides at –78 °C primarily afforded not the C2-linked bisoxazolidinone **15**, but the dimer **11**, while at –20 °C the dimer **12** was obtained as the major diastereoisomer. The *vic*-dihalides essentially function as halogen equivalents in this oxidative process. To account for the temperature-dependent reversal in diastereoselectivity the authors suggest the involvement of two different intermediates in the reaction. Thus, the organohypobromite **16** and the iminium halide **17** are proposed to serve as intermediates for the enolate of **2** to give **13** and **14**, respectively, after hydrolysis.

The *self-reproduction of chirality* principle has also been applied to the synthesis of 2-alkyl-4-hydroxyprolines starting from (2*S*,4*R*)-*O*-acetyl-4-hydroxyproline (Scheme 5).[37] The reactions between the dienolate generated by treatment of compound **19** with LDA and different electrophiles occur with retention of configuration. In this way, 2-methyl- and 2-allyl-4-hydroxyprolines have been prepared. When carbonyl compounds were used as electrophiles, mixtures of diastereoisomers at the carbinol center were obtained.

In 2002, Trauner and Hughes reported a remarkable exception to the *cis* rule governing *self-reproduction of chiral-*

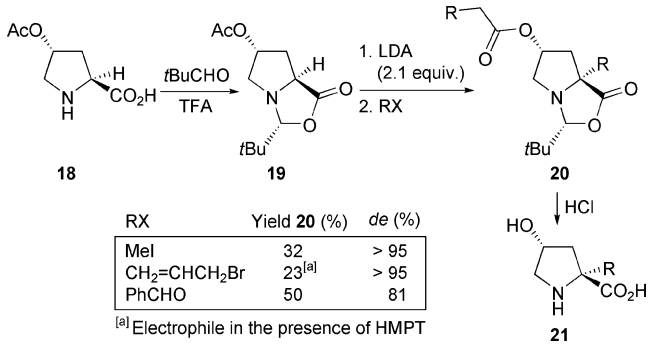




Halogen equivalent	T (°C)	Ratio **11** / **12**	Yield (%)
$BrCH_2CH_2Br$	–78	13 : 1	63[a]
$BrCH_2CH(C_6H_5)Br$	–78	15 : 1	43
$BrCH_2CH(C_6H_5)Br$	–20	<1 : 20	56[a]
$BrCH_2CH(C_6H_5)Br$	–20	1 : 9	46

[a] 3 equiv. HMPA

Scheme 4.

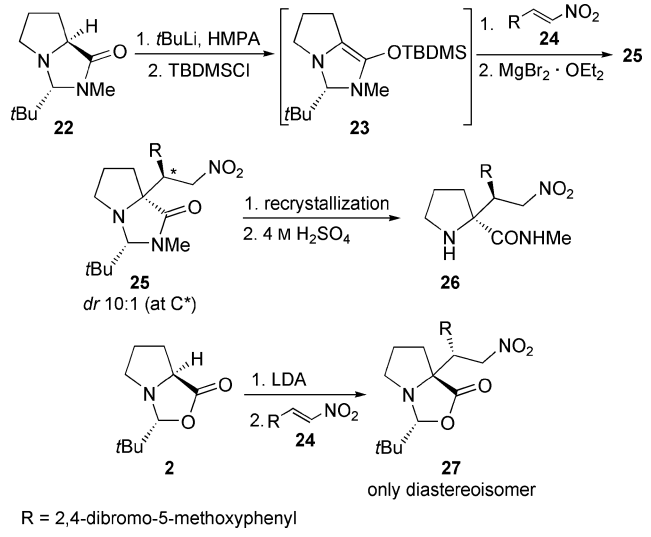


RX	Yield **20** (%)	*de* (%)
MeI	32	> 95
CH_2=$CHCH_2Br$	23[a]	> 95
PhCHO	50	81

[a] Electrophile in the presence of HMPT

Scheme 5.

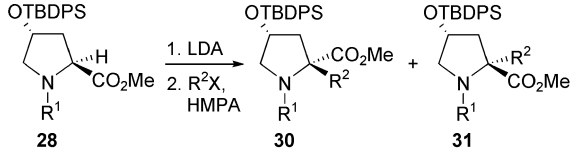
ity chemistry in a project directed towards the total synthesis of the marine alkaloid (–)-amathaspiramide F (Scheme 6).[38] The *N*,*N*-acetal **22** cleanly afforded the enolate **23** on treatment with *t*BuLi in the presence of HMPA. Conjugate addition to the nitro olefin **24** was possible when the enolate **23** was generated in situ and treated further in the presence of $MgBr_2$·OEt_2. A 10:1 mixture of diastereoisomers **25**, both *S*-configured at the newly formed quaternary center, was obtained. According to the authors, the bulky *tert*-butyldimethylsilyl group crowds the diastereoface of the double bond at the convex side of the diazabicyclo[3.3.0]octene framework, thus preventing nucleophilic attack on that side. In contrast, the *N*,*O*-acetal **2** afforded the expected (*R*)-*cis* product **27** as the only diastereoisomer.



Scheme 6.

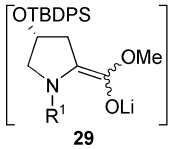
2.2 Diastereoselective Alkylations

Over the last few years, a variety of stereoselective alkylations of substituted L-proline esters have been reported, and much effort has been dedicated to explaining the factors controlling the diastereoselectivity of the process. In this context, the stereochemical outcomes of alkylation of enolates **29** derived from (2*S*,4*R*)-*N*-Boc- and -*N*-benzoyl-4-*tert*-butyldiphenylsilyloxyproline methyl esters have been particularly studied.[39,40] Kawahara et al. found that the diastereoselectivity of the alkylation reaction is dependent on the alkylating reagent and the *N*-protecting group.[40] Whereas retention of configuration was observed upon alkylation of the *N*-Boc derivative with allylic and homoallylic halides, the use of benzylic halides led preferentially to products with inversion of configuration. In the case of the *N*-benzoyl derivatives the alkylation occurred with inversion of configuration when benzylic or allylic halides were used, and in the case of benzylic halides high diastereoselectivities were observed (Scheme 7).



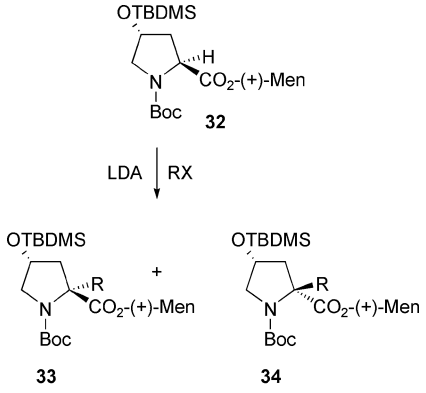
R^2X	R^1	Yield (%)	Ratio **30** / **31**
CH_2=$CHCH_2Br$	2-Br-C_6H_4CO	96	46 : 54[a]
BnCl	Boc	74	71 : 29
BnBr	Boc	95	70 : 30
BnBr	C_6H_5CO	66	>95 : 5
4-MeO-$C_6H_4CH_2Cl$	Boc	83	66 : 34
4-MeO-$C_6H_4CH_2Cl$	C_6H_5CO	56	>95 : 5
CH_2=$CHCH_2Br$	Boc	78	40 : 60
CH_2=$CHCH_2Br$	C_6H_5CO	69	77 : 23
MeI	Boc	77	23 : 77
CH_2=$CHCH_2CH_2I$	Boc	74	27 : 73
CH_2=$CHCH_2CH_2I$	C_6H_5CO	14	37 : 63

[a] TBDMS as hydroxy protecting group; LHMDS as base



Scheme 7.

Afterwards, in 2001, Sato et al. showed that the diastereoselectivities during alkylations of *N*-Boc-4-(*tert*-butyldimethylsilyloxy)proline esters can be improved when menthyl ester derivatives are engaged (Scheme 8).[41] The reactions proceeded with improved diastereoselectivities, relative to the case of a methyl ester, either with (+)- or (–)-menthyl esters when electrophiles bearing no π-electron system were employed. According to the authors, the steric bulkiness of the ester group rather than the absolute configuration of the chiral auxiliary plays a crucial role in enhancing the selectivity.



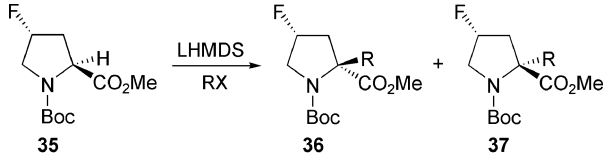
RX	Yield (%)	Ratio[a] **33** / **34**
CH_2=$CHCH_2Br$	98	89 : 11
MeI	96	94 : 6
*n*PrI	94	93 : 7
BnBr	93	53 : 47[b]
EtO_2CCH_2Br	96	69 : 31

[a] Determined at the corresponding alcohols after $LiAlH_4$ reduction
[b] Stereochemistry not determined

Scheme 8.

Diastereoselective alkylations of 4-hydroxy-substituted prolines have found application in the preparation of novel β-peptide oligomers[42] and the asymmetric synthesis of biologically active natural products such as the alkaloids (–)-velbanamine, (–)-aphanorphine,[43] and (–)-TAN1251A.[44]

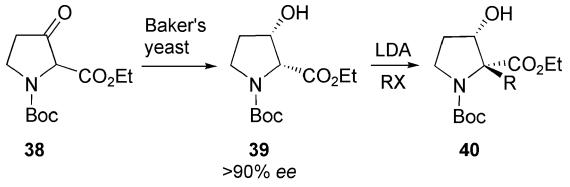
In 2006, Filosa et al. found that alkylations of (4*S*)- and (4*R*)-4-fluoro-*N*-Boc-L-proline methyl esters also proceed with high yields and diastereoselectivities (Scheme 9).[45] According to the authors, the stereochemical outcomes of the experiments indicate different behavior of enolates produced from 4-fluoroprolines from that seen with *O*-protected 4-hydroxyprolines.



RX	Yield (%)	Ratio **36** / **37**
BnBr	97	2 : 98
CH_2=$CHCH_2Br$	93	97 : 3
MeI	72	47 : 53

Scheme 9.

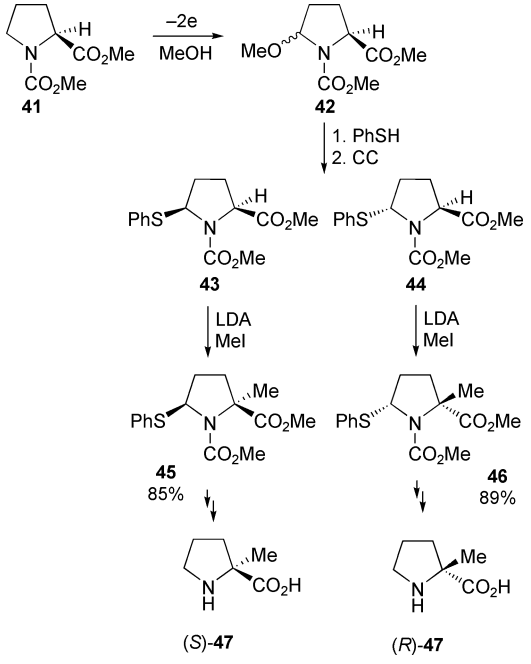
(2*R*,3*S*)-*N*-Boc-3-hydroxyproline ethyl ester, which is readily available from racemic 3-ketoproline **38** by baker's yeast reduction, has been alkylated with different electrophiles with retention of configuration and with moderate to good yields and excellent diastereoselectivity (Scheme 10).[46] This represents a useful procedure for the synthesis of α-alkyl-β-hydroxyproline derivatives **40**; in fact, the β-functionalized α-prenylated proline derivative synthesized in this manner has been used as an intermediate in the total synthesis of paraherquamide A.[47]



RX	Yield **40** (%)
$(TBDMSOCH_2)(Me)C$=$CHCH_2I$	70
Me_2C=$CHCH_2I$	73
BnBr	53
MeI	57
$Br(CH_2)_4Br$	49

Scheme 10.

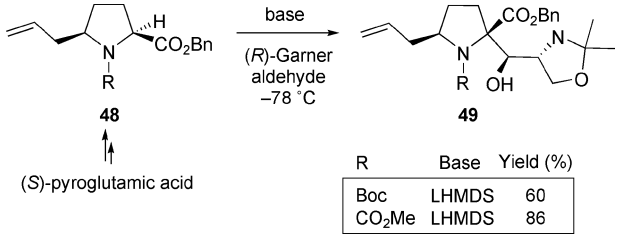
With regard to stereoselective alkylations of proline derivatives substituted at position C5, Matsumura et al. described a synthetic strategy for the preparation of both enantiomers of α-methylproline.[48] The electrochemical methoxylation of *N*-methoxycarbonyl-L-proline methyl ester (**41**), followed by the replacement of the methoxy group with a phenylthio group, afforded an almost equimolecular mixture of diastereoisomers that were easily separated by



Scheme 11.

column chromatography. Subsequent α-methylation and reductive removal of the phenylthio group led to both enantiomers of α-methylproline (Scheme 11).

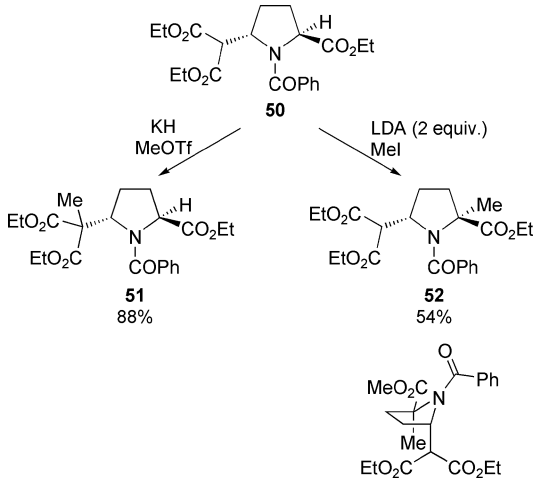
In 2001, Ma et al. reported a highly diastereoselective aldol reaction between an L-proline benzyl ester bearing an allyl substituent at its 5-position and (*R*)-Garner aldehyde,[49] with the objective being to assemble the right-hand part of kaitocephalin, which is the first naturally occurring AMPA/KA antagonist without cytotoxic effects. The allyl substituent did not seem to influence the diastereoselectivity of the aldol reaction, with treatment of **48** with LDA providing four isomers in almost equal amounts. In contrast, a single compound was obtained when LHMDS was used as a base (Scheme 12).



R	Base	Yield (%)
Boc	LHMDS	60
CO_2Me	LHMDS	86

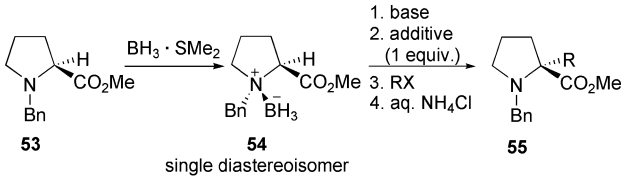
Scheme 12.

An alternative route to 2,5-disubstituted pyrrolidines, based on the reduction of enamines derived from pyroglutamic acid, was reported by Moloney et al.[50] They showed that the regioselective manipulation of position C2 or in the malonate substituent in (2*S*,5*S*)-**50** (Scheme 13) are possible, providing access to substituted pyrrolidines in a very limited number of cases. In particular, the double deprotonation of *trans*-**50** with an excess of LDA and alkylation provided the monomethyl adduct **52** as the result of alkylation at the more reactive enolate position and in an anti-sense to the benzoyl group with a kinetic pseudoaxial preference.



Scheme 13.

Mioskowski et al. reported the asymmetric synthesis of α-alkylproline derivatives by a method that involved successive chirality transfers via the chiral borane-amine adduct **54**, which was in turn prepared as a single isomer from L-proline (Scheme 14).[51] Optimal results were obtained by generation of the enolate through treatment with LDA followed by quenching in the presence of HMPA or, alternatively, by treatment with KHMDS and 18-crown-6 as an additive. In general, the quantity of additive had a great impact on the level of enantioselectivity. Interestingly, the absence of the crown ether caused a reversal of diastereoface selection during the alkylation of the potassium enolate (when RX = BnI), presumably for steric reasons.



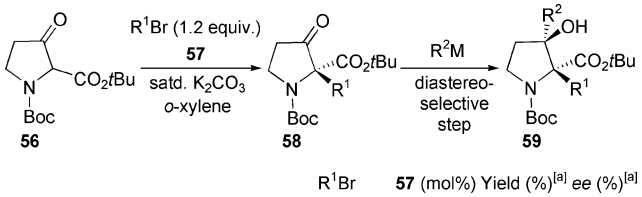
RX	Base	Additive	*ee* **55** (%)
BnI	LDA	HMPA[a]	88
BnI	KHMDS	18-crown-6	80
MeOTf[b]	KHMDS	18-crown-6	88[c,d]
$CH_3(CH_2)_4OTf$	KHMDS	18-crown-6	92[d]
2,5-$(MeO)_2$-$C_6H_3CH_2$I	KHMDS	18-crown-6	91[d]

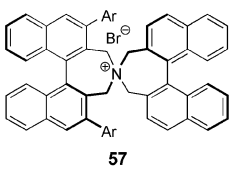
[a] 3 equiv.
[b] 44% *ee* if MeI is used
[c] Precision ±5%
[d] Absolute configuration not determined

Scheme 14.

2.3 Alkylations under Phase-Transfer Catalysis Conditions

In 2005, Maruoka et al. reported an approach for the preparation of various optically active quaternary 3-oxoprolines based on the highly enantioselective, phase-transfer-catalyzed alkylation of the racemic α-amino β-keto ester **56** (Scheme 15).[52] The assembly of the quaternary stereocenter was achieved by applying the C_2-symmetric chiral quaternary ammonium salt **57** as the catalyst, together with *o*-xylene as the solvent since it provided a substantial en-





R^1Br	**57** (mol%)	Yield (%)[a]	*ee* (%)[a]
4-F-3-Br-C_6H_3	1	94	95
4-MeO-3-Br-C_6H_3	1	99	94
2-Br-naphthyl	1	94	93
4-Ph(C=O)-3-Br-C_6H_3	1	85	95
CH_2=CHCH$_2$Br	2	84	90
PhCH=CHCH$_2$Br	1	92	89

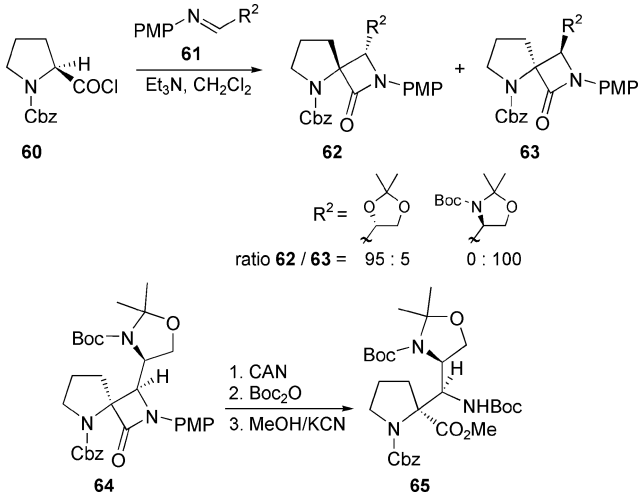
[a] Yield and *ee* for compound **58**

Scheme 15.

hancement of the reaction rate. Carrying out the reaction with allylic and benzylic bromides provided diverse chimeras of 3-oxoproline and phenylalanine in 89–95% *ee*s. Moreover, selective alkylations with various Grignard reagents at the 3-keto carbonyl group proceeded smoothly and allowed the construction of α-substituted prolines with two adjacent stereochemically defined quaternary centers.

2.4 [2+2] Cycloadditions of Cyclic Ketenes with Imines

The nucleophilic ring-opening of spiro β-lactams of type **62** has been described as a new methodology for the asymmetric synthesis of modified prolines. The β-lactams **62** and **63** were prepared by [2+2] cycloadditions between a cyclic ketene generated in situ and optically active imines (Scheme 16).[53] The [2+2] cycloaddition reactions took place with complete stereoselectivity, thus giving the expected spiro β-lactams with *cis* relative dispositions of the substituents at the iminic carbon atoms and the proline nitrogen and with excellent asymmetric induction. In particular, the use of **64** as starting material provided access to the orthogonally protected enantiomerically pure α-(1-aminoalkyl)proline **65**.



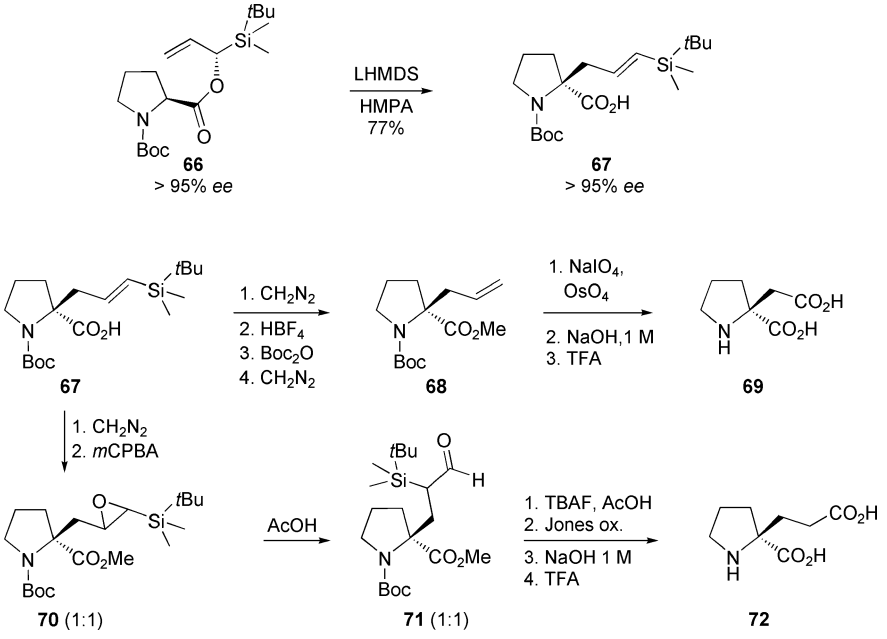
Scheme 16.

2.5 Ester-Enolate Claisen Rearrangements of α-Vinyl-α-acyloxysilanes

The ester-enolate Claisen rearrangement is a powerful method for enantio- and diastereoselective C–C bond formation from an original chiral ester. This method is characterized by the complete transfer of the masked chirality of the carbon attached to the acyloxy and silyl groups to the newly formed carbon center. Very recently it has been applied to an α-acyloxy-α-vinylsilane possessing a proline as the acyloxy group (Scheme 17).[54] The enolate generated from **66**[55] underwent the Claisen rearrangement, through a chair-like transition state with a *Z*-enolate in the presence of HMPA, to give the α-substituted proline derivative **67** with transfer of the original chirality of the ester counterpart. The rearranged product provided access to proline chimeras **69** and **72** after suitable transformations at the α-alkyl chain.

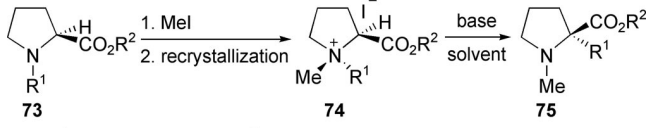
2.6 Chirality Transfer via Cyclic Ammonium Ylides

(*S*)-*N*-Benzylic proline-derived ammonium salts **74** have proven to undergo [1,2]-Stevens rearrangements[56] with remarkably high levels of N-to-C chirality transmission when



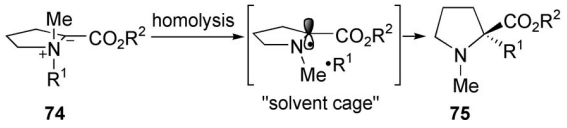
Scheme 17.

carried out under solid–liquid biphasic conditions, to afford α-benzylic proline derivatives **75** in high enantiopurities (Scheme 18).



R^1	R^2	Base	Solvent	Yield **75** (%)	*ee* (%)
Bn	Me	*t*BuOK[a]	THF	73	54
Bn	*t*Bu	*t*BuOK[a]	THF	80	72
Bn	*t*Bu	CsOH[b]	$Cl(CH_2)_2Cl$	73	92
4-Me-$C_6H_4CH_2$	*t*Bu	CsOH[b]	$Cl(CH_2)_2Cl$	77	84
4-MeO-$C_6H_4CH_2$	*t*Bu	CsOH[b]	$Cl(CH_2)_2Cl$	56	86
4-F-$C_6H_4CH_2$	*t*Bu	CsOH[b]	$Cl(CH_2)_2Cl$	69	90
4-(*t*BuO$_2$C)-$C_6H_4CH_2$	*t*Bu	CsOH[b]	$Cl(CH_2)_2Cl$	42[c]	>99

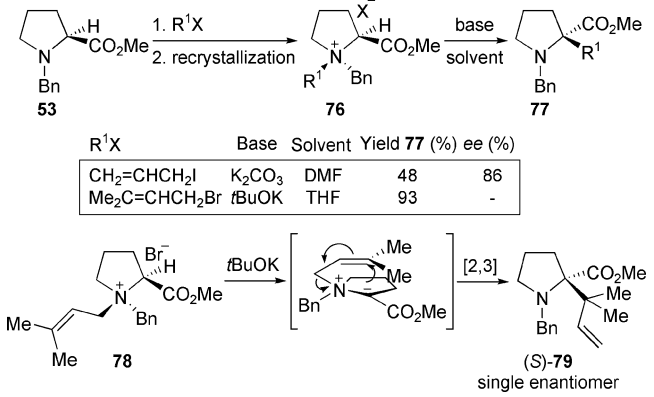
[a] 1.5 equiv. was used
[b] 5 equiv. was used
[c] *tert*-Butyl *p*-toluate was isolated in 55% yield



Scheme 18.

This rearrangement is assumed to proceed by a radical cleavage-recombination mechanism. Tayama et al. suggested that the stability of the benzylic radicals involved and the solid–liquid biphasic reaction conditions employed determine the stereochemical course of the reaction. The recombination of the radical pair initially formed from the *N*-ylide **74** occurs more rapidly in a solvent cage and hence more preferentially in a retentive fashion.

Exclusive [2,3]-shifts of an allyl and a prenyl group for substrate **76** had previously been reported by West[57] and by Coldham,[58] respectively (Scheme 19). In this case, the rearrangements are stereospecific because the [2,3]-migrations are restricted to the same face, and the stereoselectivity arises from the previous *N*-alkylation step.



R^1X	Base	Solvent	Yield **77** (%)	*ee* (%)
CH_2=$CHCH_2I$	K_2CO_3	DMF	48	86
Me_2C=$CHCH_2Br$	*t*BuOK	THF	93	-

Scheme 19.

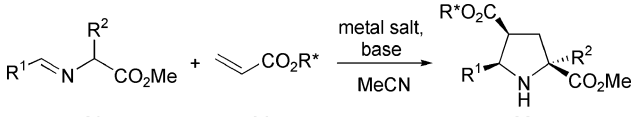
3. Syntheses with Formation of the Pyrrolidine Ring

3.1 1,3-Dipolar Cycloadditions: Azomethine Ylides

1,3-Dipolar cycloaddition reactions of azomethine ylides and alkenes are a powerful method for the stereocontrolled synthesis of polysubstituted pyrrolidines and have been the subject of comprehensive accounts.[59] Below we review the application of this methodology to the asymmetric synthesis of quaternary polysubstituted prolines, the preparation of which has often been perfunctorily studied. Stereocontrol has been achieved either by a chiral auxiliary approach, based on the presence of a chiral moiety at the azomethine ylide or the dipolarophile, or alternatively by employing chiral catalysts with achiral substrates. For this reason the reviewed approaches have been classified according to the nature of the dipolarophiles and ylides involved.

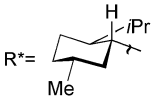
3.1.1 Chiral dipolarophiles

Grigg et al. reported complete regioselective and *endo*-selective cycloadditions of several Ag^I- and Li^I-metallated ylides onto (–)-menthyl acrylate (Scheme 20). The high diastereofacial selectivity achieved in the formation of adducts **82** was explained by assuming a transition state model in which the isopropyl group of the menthyl moiety induces a facial shielding effect on the dipole.[60]



R^1	R^2	Salt	Base	Yield (%)
2-Nph	Me	AgOAc	*t*BuTMG	75
Ph	Me	AgOAc	*t*BuTMG	71
Cy	Me	AgOAc	*t*BuTMG	83[a]
3-Py	Bn	AgOAc	*t*BuTMG	78
2-Nph	Ph	LiBr	DBU	86
Ph	Ph	LiBr	DBU	84
p-MeO-C_6H_4	Ph	LiBr	DBU	71
PhCH=CH	Ph	LiBr	DBU	64
3-Py	Ph	LiBr	Et_3N	56

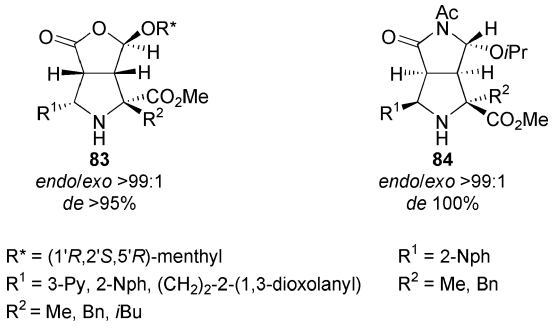
[a] Toluene was used as solvent



Scheme 20.

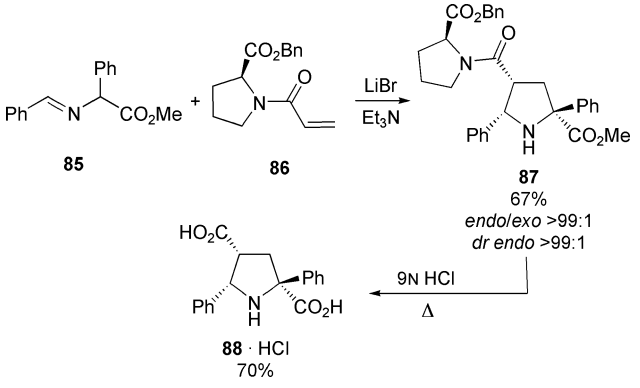
The racemic version of this type of procedure has recently found application for the synthesis of *N*-acyl polysubstituted proline inhibitors of the hepatitis virus RNA-dependent RNA polymerase, both in solution and solid phase. The resolution of the racemic quaternary proline derivatives was achieved by crystallization of diastereomeric salts or by chromatographic techniques.[61]

In addition, Grigg et al. treated similar Ag^I-metallated ylides, generated either from aromatic or aliphatic imines of α-amino acids, with chiral cyclic alkenes such as (5*R*)-(1′*R*,2′*S*,5′*R*-menthyloxy)-2(5*H*)-furanone or (5*R*)-*N*-acetyl-5-isopropoxy-2(5*H*)-pyrrolone. The resulting cycloadducts **83** and **84** were formed with complete regioselectivity and *endo* selectivity, and with very high facial diastereoselectivities (Scheme 21).[62]



Scheme 21.

Another contribution to this type of transformation used *N*-acryloyl-(*S*)-proline esters as chiral dipolarophiles.[63] Metallated azomethine ylides, derived from aliphatic or aromatic aldehydes and aliphatic or aromatic α-amino acids, underwent highly *endo*-diastereoselective cycloadditions with the acrylamide of proline benzyl ester (**86**). An illustrative example is depicted in Scheme 22.

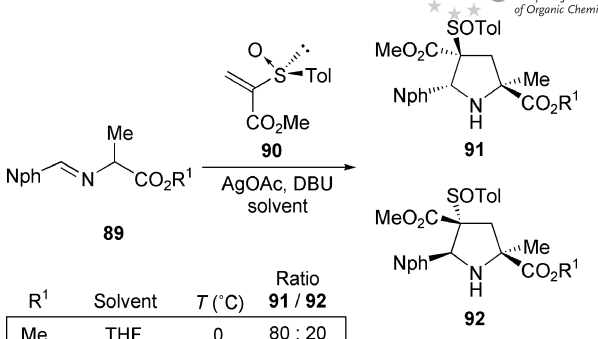


Scheme 22.

Similarly, the cycloadditions of azomethine ylides and the chiral vinyl sulfoxide **90** have been reported to proceed with complete regioselectivity and high *endo*-selectivity to produce **91** and **92**, which are separable by column chromatography. Interestingly, the facial diastereoselectivity is, in some cases, strongly influenced by the nature of the solvent, thus providing an opportunity to access prolines with *trans* or *cis* arrangements of substituents at the C2 and C5 positions (Scheme 23).[64]

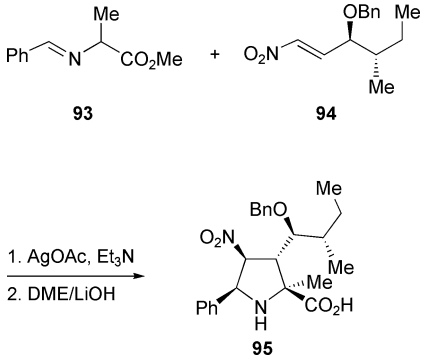
Also, the [3+2] cycloaddition between the chiral *E*-nitroalkene **94** and the imine **93** provided **95** with complete stereocontrol (Scheme 24).[65] This polysubstituted proline belongs to a new family of inhibitors of α4β1-integrin-mediated hepatic melanoma metastasis.

More recently, Nájera et al. reported the use of methyl (*S*)-lactate acrylate **97** as dipolarophile in 1,3-dipolar cycloaddition reactions with silver azomethine ylides derived from benzaldimines of alanine, leucine, and phenylalanine.[66] Enantiomerically enriched quaternary prolines resulting from the *endo* approach were obtained in moderate to good yields and with *de*s of 86–92% (Scheme 25).

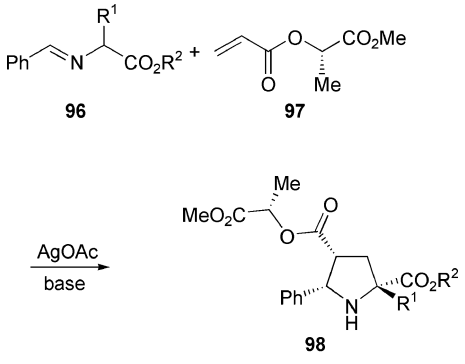


R1	Solvent	T (°C)	Ratio 91 / 92
Me	THF	0	80 : 20
Me	THF	r.t.	90 : 10
Me	THF	reflux	78 : 22
Et	THF	0	83 : 17
Et	CH_3CN	0	25 : 75
Et	CH_3CN	r.t.	20 : 80
Et	CH_3CN	reflux	94 : 6

Scheme 23.



Scheme 24.



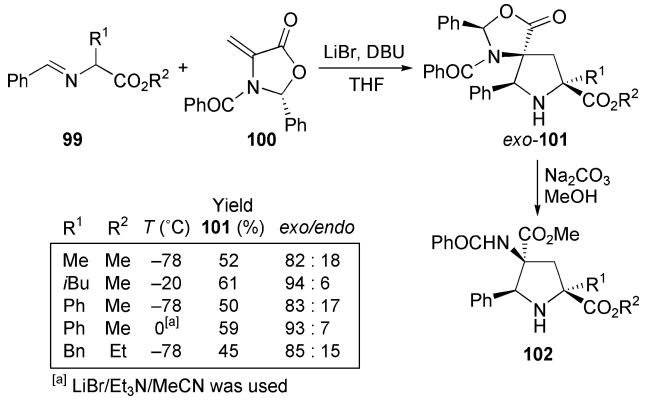
R1	R2	Base	Yield[a] (%)	de (%)
Me	Me	KOH	65	88–90
Me	Me	Et_3N	64	88–90
Me	*t*Bu	KOH	70	92
*i*Bu	Me	KOH	32	90
Bn	Me	KOH	67	86

[a] Yield after flash chromatography

Scheme 25.

In contrast, chiral oxazolidinone **100** has been reported to undergo regioselective but *exo*-diastereoselective cycloaddition reactions with azomethine ylides derived from *N*-benzylidene α-amino acid esters **99** (Scheme 26).[67] The

best diastereoselectivities were achieved when working at low temperatures with LiBr/DBU/THF for the ylide generation. Some of the cycloaddition products were conveniently converted into polyfunctional prolines in high enantiomeric purity. The preference for *exo* adducts was interpreted by assuming chelation between the lithium cation, the *N*-benzoyl carbonyl group, and the ylide.

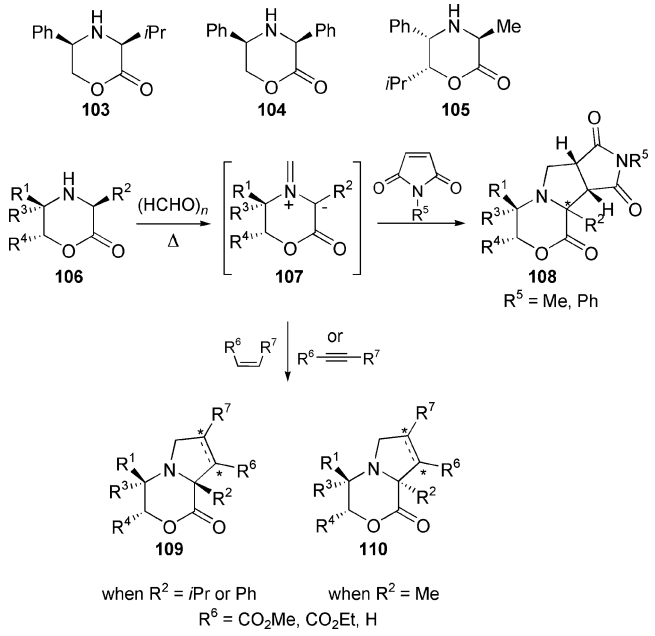


R^1	R^2	*T* (°C)	Yield **101** (%)	*exo*/*endo*
Me	Me	–78	52	82 : 18
*i*Bu	Me	–20	61	94 : 6
Ph	Me	–78	50	83 : 17
Ph	Me	0[a]	59	93 : 7
Bn	Et	–78	45	85 : 15

[a] $LiBr/Et_3N/MeCN$ was used

Scheme 26.

amino acid is "memorized" through a sequence involving chirality transfer to the cyclic template, followed by azomethine ylide generation and enantiospecific cycloaddition to regenerate the center lost during the ylide formation.



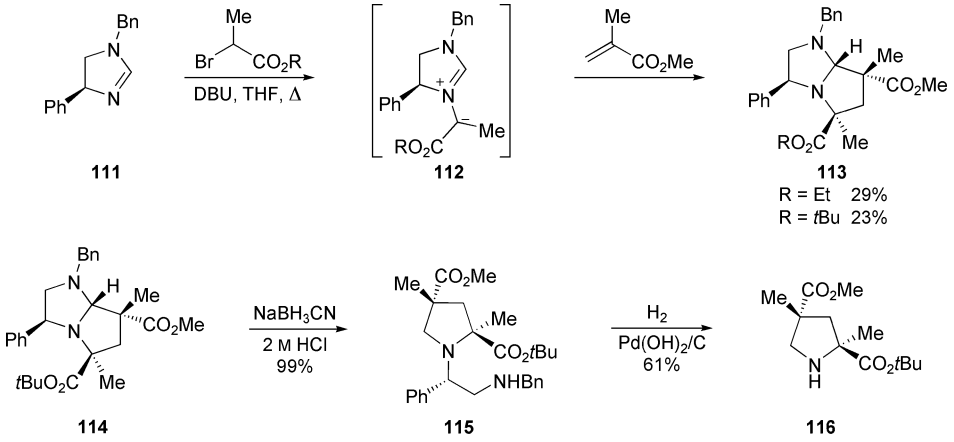
Scheme 27.

3.1.2 Chiral Azomethine Ylides

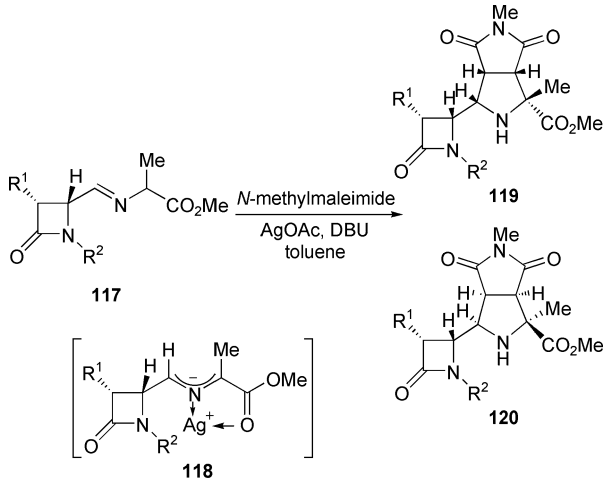
The saturated oxazin-2-ones **103**,[68] **104**,[69] and **105**[70] proved to be useful systems for the generation of chiral carboxy-stabilized azomethine ylides of type **107** under thermal conditions (Scheme 27). These species reacted with dipolarophiles bearing electron-withdrawing groups mainly with *endo* selectivity (high *endo*/*exo* ratios for compounds of type **109** and **110**, but lower ratios for adducts of type **108**). The removal of the morpholin-2-one templates has on various occasions led to α-alkyl or α-phenylproline derivatives. Formally, it is suggested that the α-chirality of the

Similarly, homochiral (4*R*)-phenylimidazolinium ylides **112**, in which the auxiliary is conformationally restrained by virtue of a heterocyclic ring, underwent *endo*-selective cycloadditions to various dipolarophiles (Scheme 28).[71]

Grigg et al. described the use of *N*-metallated azomethine ylides containing a β-lactam ring as the chiral auxiliary[72] in cycloaddition reactions to *N*-methylmaleimide (Scheme 29). The ratios of the cycloadducts **119** and **120** were determined by the nature of the substituents on the *cis*-β-lactam ring. The formation of only two diastereoisomers was attributed to *endo*-specific cycloadditions on both faces of the *E*,*E*-(*syn*)-dipole **118**.



Scheme 28.

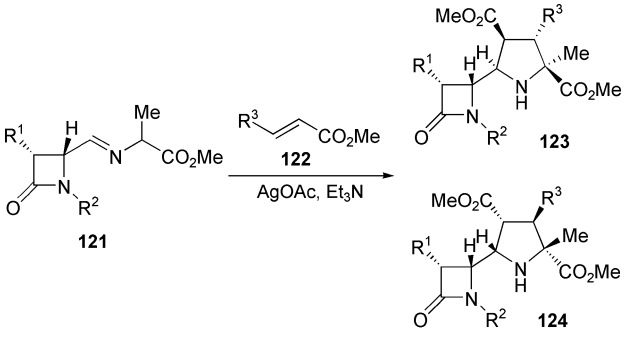


R^1	R^2	Yield (%)	**119** / **120**
Et	4-MeO-C_6H_4	92	2 : 1
BnO	4-MeO-C_6H_4	57	1 : 3
Phth	4-MeO-C_6H_4	88	> 30 : 1
*t*Bu	4-MeO-C_6H_4	57[a]	9 : 1
BnO	allyl	83[b]	1.5 : 1
BnO	$(MeO)_2CHCH_2$	71[b]	2 : 1

[a] Cyclohexane was used as solvent, 9 : 1 mixture of **119** and a Michael adduct
[b] Et_3N was used as base

Scheme 29.

In addition, closely related ylides derived from **121**[73] gave similar results in their reactions with α,β-unsaturated esters, and have found straightforward applications in the syntheses of enantiopure pyrrolizidine, indolizidinone, diazatriquinane, and fused tricyclic azetidin-2-one systems (Scheme 30).

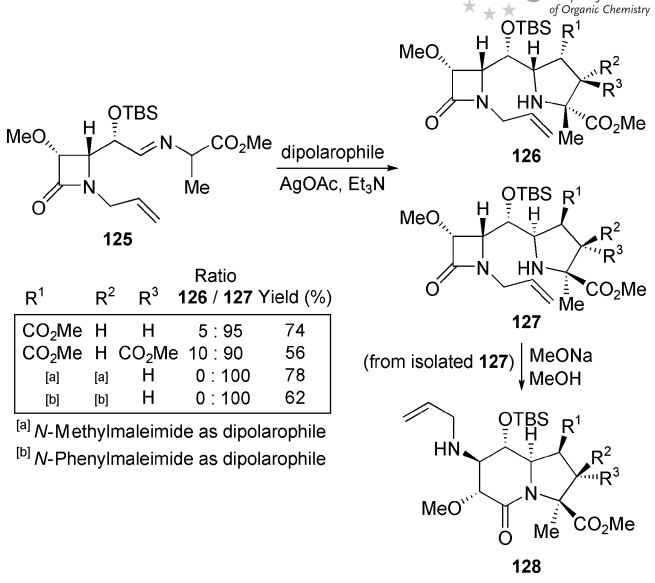


R^1	R^2	R^3	Ratio **123** / **124**	Yield (%)[a] **123**, **124**
H	4-MeO-C_6H_4	H	100 : 0	48, 0
MeO	4-MeO-C_6H_4	H	65 : 35	39, 21
MeO	4-MeO-C_6H_4	CO_2Me	58 : 42	45, 33
MeO	2-propenyl	H	66 : 34	49, 25
MeO	2-propenyl	CO_2Me	60 : 40	45, 30
MeO	4-pentenyl	H	59 : 41	47, 33
2-propenyl	4-MeO-C_6H_4	H	75 : 25	43, 14

[a] Isolated yields

Scheme 30.

Alternatively, intermolecular 1,3-dipolar cycloaddition reactions involving chiral ylides derived from **125**[74] provided access to indolizidinone aminoesters (Scheme 31).

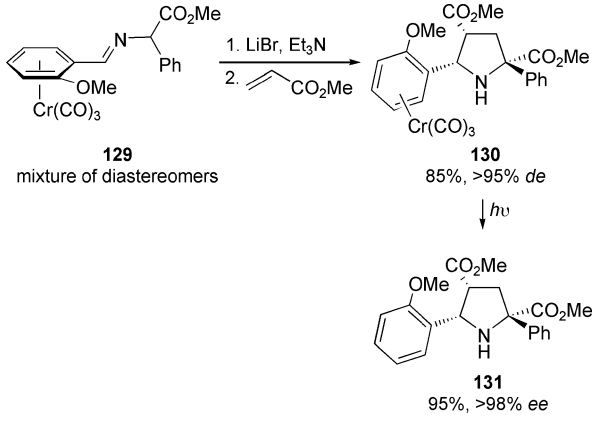


R^1	R^2	R^3	Ratio **126** / **127**	Yield (%)
CO_2Me	H	H	5 : 95	74
CO_2Me	H	CO_2Me	10 : 90	56
[a]	[a]	H	0 : 100	78
[b]	[b]	H	0 : 100	62

[a] *N*-Methylmaleimide as dipolarophile
[b] *N*-Phenylmaleimide as dipolarophile

Scheme 31.

Another contribution to this type of stereocontrol used the *N*-lithiated azomethine ylide derived from **129**, linked to a planar chiral arene $Cr(CO)_3$ complex. Its cycloaddition reaction with methyl acrylate proceeded in a high diastereoselective fashion.[75] The authors explained the exclusive *syn* and *endo* selectivity by assuming chelation between the lithium, the imine nitrogen, and the carbonyl oxygen, thus making the face opposite to the chromium tricarbonyl fragment of the azomethine ylide the one that approached the dipolarophile (Scheme 32).

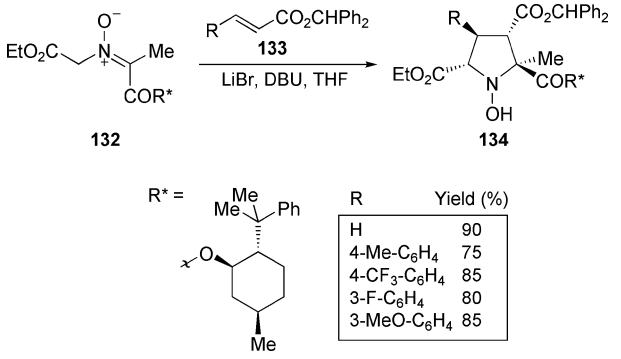


Scheme 32.

3.2 1,3-Dipolar Cycloadditions: Nitrone Enolate Ylides

Stereoselective cycloadditions of chiral nonracemic nitrone enolate-ylides derived from glycinate esters with electron-deficient alkenes afford *N*-hydroxypyrrolidines, which upon reduction provide polysubstituted prolines (Scheme 33). Hanessian et al. reported that, in particular, cycloadditions of 8-phenylmenthyl ester nitrones **132** and benzhydryl cinnamates are completely stereoselective and provide *N*-hydroxypyrrolidines **134** as single isomers.[76] The

bulky esters on the dipole and dipolarophile appear to have a cooperative effect that ensures the high diastereoselectivity of the reaction. They also pointed out that, unlike cyclizations of azomethine ylides, the reaction of nitrones **132** requires the presence of LiBr as an additive, and no reaction takes place when AgOAc, $MgBr_2$, or $CoCl_2$ are employed.

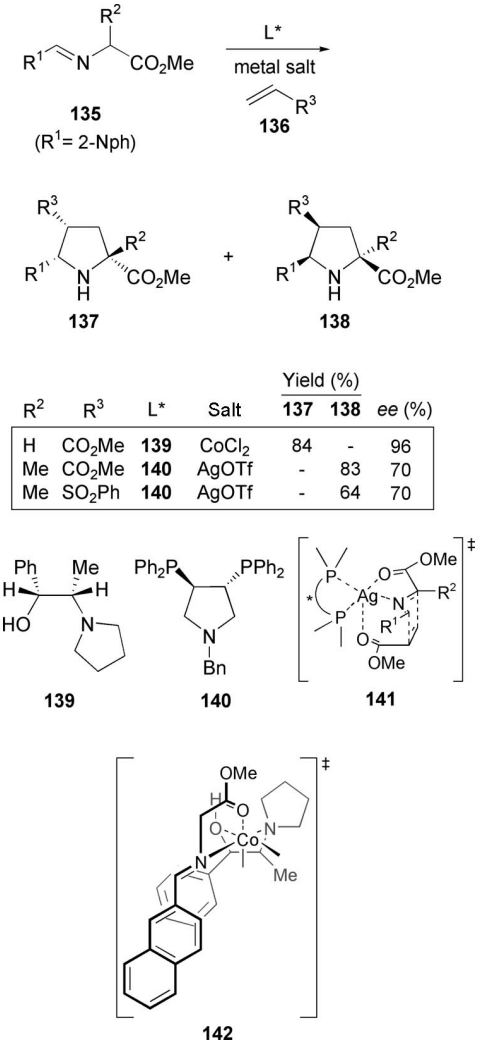


R	Yield (%)
H	90
4-Me-C_6H_4	75
4-CF_3-C_6H_4	85
3-F-C_6H_4	80
3-MeO-C_6H_4	85

Scheme 33.

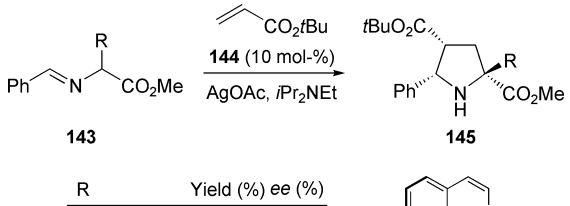
3.3 Asymmetric 1,3-Dipolar Cycloadditions in the Presence of a Chiral Catalyst

In recent years, extensive research has been devoted to achieve catalytic asymmetric versions of 1,3-dipolar cycloaddition reactions of *N*-metallated azomethine ylides.[59] In 1995, Grigg et al. reported that the presence of a stoichiometric amount of the catalytic system **139**/$CoCl_2$ in reactions between the dipole generated from **135** and activated alkenes **136** gives excellent *ee*s of **137** or **138** (Scheme 34).[77] The total *endo* selectivity displayed was explained by the transition state model **142**, which shows effective shielding of one face of the putative *N*-metallated dipole. In comparison, the stoichiometric catalyst formed from bisphosphane **140**/AgOTf admitted a wider range of dipolarophiles to afford the other enantiomer *endo*-**138**, albeit with lower enantioselection.[78] The still high enantiomeric excesses of the resulting 2-substituted prolines could be explained by the compact transition state **141**.



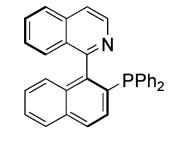
Scheme 34.

The first asymmetric catalytic 1,3-dipolar cycloaddition reactions involving substoichiometric amounts of a chiral metallic complex were described by Zhang et al. in 2002 and involved Ag^I complexes with a variety of chiral diphosphane ligands.[79] Afterwards, Schreiber et al. performed studies on the Ag^I-catalyzed enantioselective cycloadditions using substituted imine precursors other than glycinates,[80] applying AgOAc/(*S*)-QUINAP as catalytic system. Interestingly, the enantioselectivity (77–81% *ee*) was not significantly influenced by varying the α-substituent while the yields were highly dependent on this moiety (Scheme 35).



R	Yield (%)	*ee* (%)
H	84	91
Me	98	80
*i*Bu	77[a]	80
Bn	93	77
3-indolylmethyl	47[b]	81

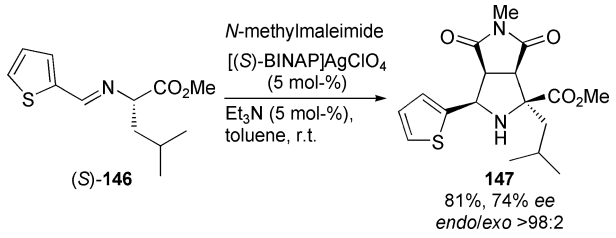
[a] Conversion of 85%
[b] Conversion of 50%



(*S*)-QUINAP (**144**)

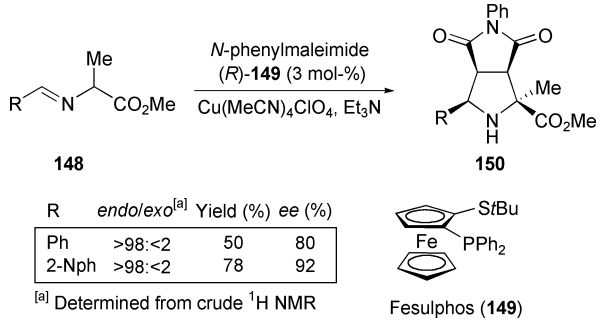
Scheme 35.

Very recently, the first enantioselective 1,3-dipolar cycloaddition reactions of amino acid-derived azomethine ylides and maleimides catalyzed by stable and recyclable chiral (*R*)- or (*S*)-BINAP/$AgClO_4$ complexes have been reported by Nájera et al.[81] The methodology, in which the catalyst is recovered by simple filtration, was applied to the preparation of a few quaternary polysubstituted prolines, which were obtained with high *endo* diastereoselectivities and good enantioselectivities (Scheme 36).



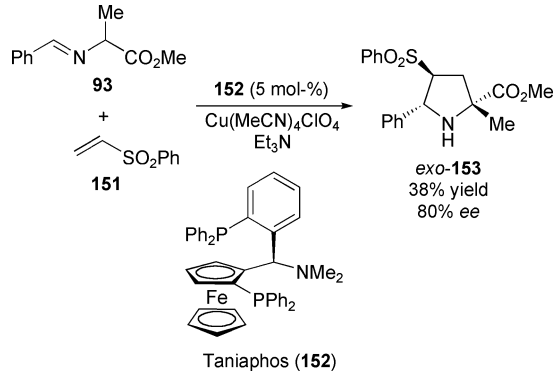
Scheme 36.

Carretero et al. reported a copper-mediated catalytic system that displayed good performances in enantioselective 1,3-dipolar cycloadditions between azomethine ylides derived from **148** and *N*-phenylmaleimide.[82] The high reactivity of the combination of $CuClO_4$ with the planar chiral P,S-ligand Fesulphos allowed a significant reduction in catalyst loading and afforded the quaternary *endo* adduct as the sole reaction product (Scheme 37). This is atypical behavior, since it had been reported for this transformation that the use of Cu^{II}/P,P-ligands affords high *exo* selectivities and enantioselectivities.



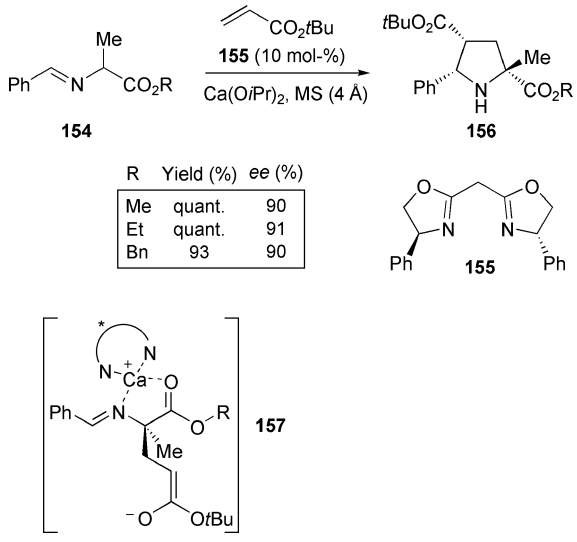
Scheme 37.

A similar copper-mediated cycloaddition employing a vinylic sulfone as dipolarophile was later reported by the same group. In this case, a Cu^{I}-Taniaphos combination was optimal for achieving total *exo* selectivity and good enantiocontrol (Scheme 38).[83] However, the low chemical yield reflected the sensitivity of the process to steric effects introduced by the α-substituent at the ylide.



Scheme 38.

Recently, Kobayashi et al. reported the use of chiral calcium complexes as novel Brønsted base catalysts that effectively promoted two types of asymmetric additions of α-amino acid derivatives with α,β-unsaturated carbonyl compounds: 1,4-additions and [2+3] cycloaddition reactions (Scheme 39).[84] In particular, DL-alanine derivatives **154** reacted with several α,β-unsaturated carbonyl compounds to afford the corresponding proline derivatives with excellent yields and stereoselectivities. The authors proposed a plausible catalytic cycle involving a monomeric Ca-Box complex that removes the α-proton of the derivative **154** to give a chiral calcium enolate, which reacts with the α,β-unsaturated carbonyl compound to afford an initial Michael adduct **157**. When the reactivity of the enolate in this adduct is high, an intramolecular cyclization occurs to afford a proline derivative exclusively.



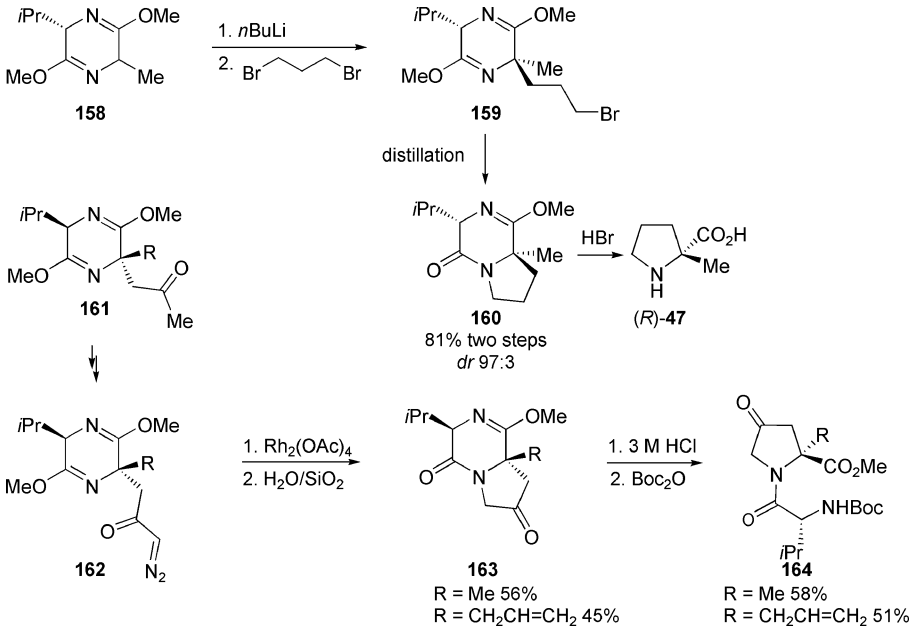
Scheme 39.

3.4 Intramolecular Cyclizations of Chiral Amino Acid Derivatives

3.4.1 Cyclization through C–N Bond Formation

Some of the methodologies developed for the asymmetric synthesis of α-alkylprolines are based on the construction of the pyrrolidine ring by intramolecular cyclization of a geminally disubstituted glycine equivalent with an appropriate leaving group on the side chain. In the last 20 years several types of reagents for electrophilic alkylations have been developed. Among them, bis-lactim ethers, oxazolidines, morpholinones, and oxazinones have been advantageously applied.

In 1987, Schöllkopf's methodology, initially developed for the synthesis of acyclic quaternary amino acids, was applied to the synthesis of α-alkylproline derivatives by use of suitable dielectrophiles. Thus, the commercially available bis-lactim ether of *cyclo*-(L-Val-Ala) (**158**) was alkylated with 1,3-dibromopropane to provide the corresponding di-



Scheme 40.

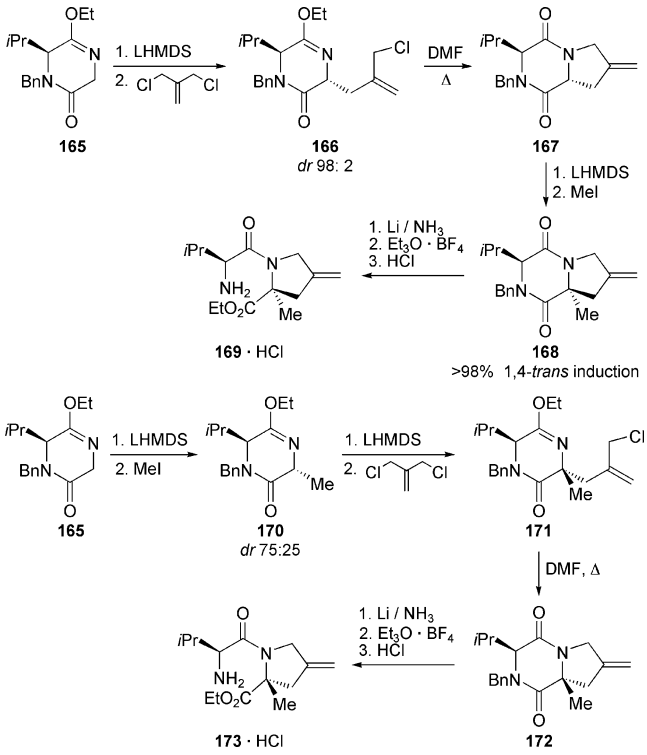
alkylated bis-lactim ether **159**, which upon cyclization by heating afforded the (*R*)-2-methylproline precursor **160** (Scheme 40).[85] Later, Undheim et al. demonstrated an alternative annulation procedure involving rhodium(II)-catalyzed carbenoid insertions into diazoketone substrates **162**.[86] The insertion reactions occurred with complete chemoselectivity at the adjacent annular nitrogen in preference to C–C double bond additions or C–H insertions, and no racemization was observed either in the carbenoid reaction or in the subsequent hydrolysis.

More recently, Porzi and Sandri described the use of the mono-lactim ether **165**, derived from L-valine, as the chiral synthon for stereoselective alkylations.[87] The approach allowed the preparation of pseudo-peptides **169** and **173**, which differ only in the configuration of one stereogenic center. This was accomplished on the basis of *trans*-induction in the alkylation reaction of the chiral synthon **165**, and changing the sequence of the electrophiles employed (Scheme 41).

Viallefont et al. described the synthesis of (*S*)-α-methylproline methyl ester (**176**) by a similar strategy that involves the highly diastereoselective alkylation of a Schiff base derived from alanine and enantiomerically pure (2*R*,3*R*,5*R*)-2-hydroxypinan-3-one.[88] The treatment of **174** with 1-chloro-3-iodopropane, followed by hydrolytic cleavage of the auxiliary and cyclization, afforded **176** in 95% *ee* (Scheme 42).

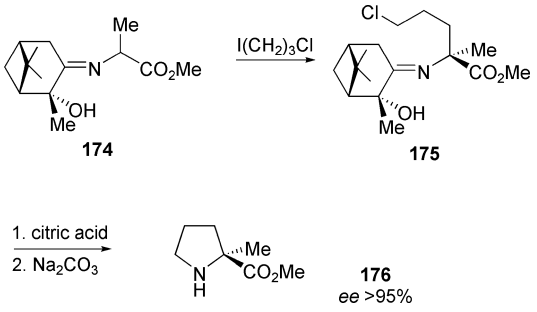
Alternatively, Seebach et al. reported the use of an imidazolidinone as the enantiomerically pure glycine derivative. The alkylation of *tert*-butyl (*R*)-2-*tert*-butyl-3-methyl-4-oxo-imidazolidinecarboxylate **177**, first with methyl iodide and then with 1-bromo-3-chloropropane, afforded the intermediate **178**, which after cyclization and hydrolysis provided (*R*)-2-methylproline (Scheme 43).[89]

(*R*)-Phenylglycinol-based morpholinones and oxazolidines have also served as chiral heterocyclic precursors for

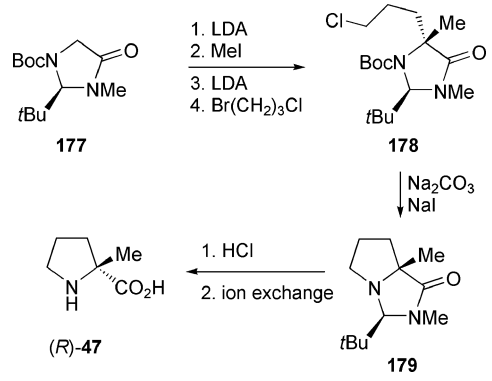


Scheme 41.

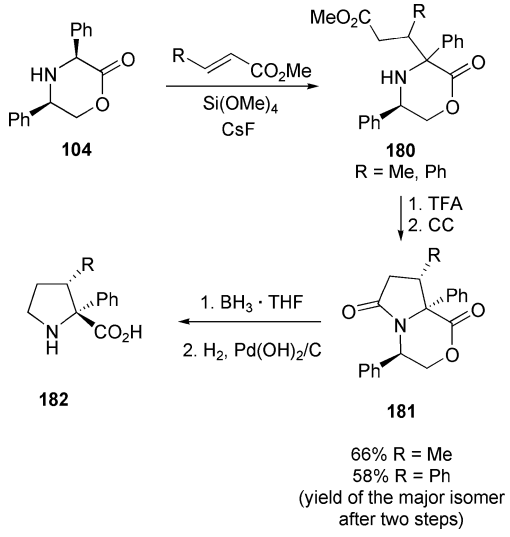
the construction of pyrrolidine rings in a similar manner.[90,91] Harwood et al. reported that (3*S*,5*R*)-3,5-diphenylmorpholin-2-one (**104**) undergoes 1,4-addition reactions with acrylates to give mixtures of products from which the major compounds can be isolated after lactamization.[90] Chemoselective reduction of the lactam rings and hydrogenolysis of the chiral auxiliaries afforded enantiomerically pure 3-substituted 2-phenylprolines **182** (Scheme 44).



Scheme 42.

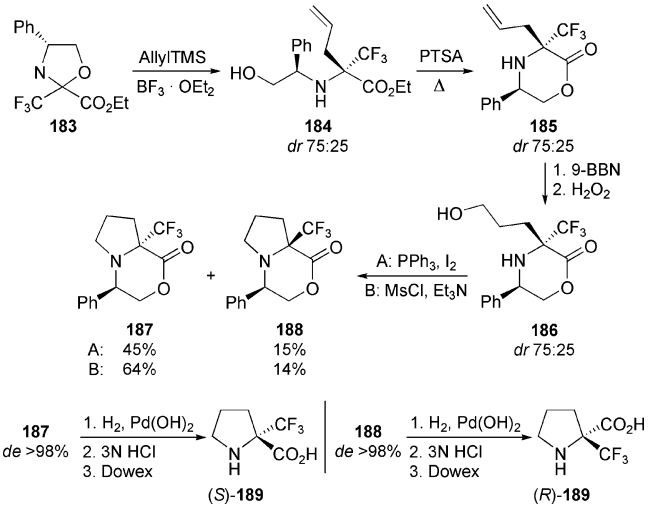


Scheme 43.



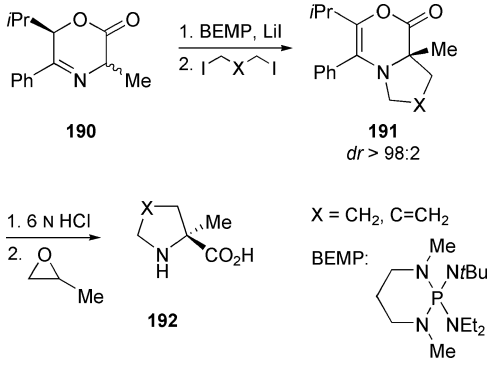
Scheme 44.

Brigaud et al. described the use of the (*R*)-phenylglycinol-based oxazolidine **183** as a chiral intermediate for the introduction of a fluorinated group at the α-position of proline (Scheme 45).[91] The strategy involved allylation of the oxazolidine **183**, initially obtained as a 75:25 diastereomeric mixture from ethyl trifluoropyruvate and (*R*)-phenylglycinol with PPTS catalysis. The resulting diastereoisomeric allylic amino esters **184** were converted into the morpholinones **185**, which were subjected to hydroboration and cyclization by means of iodine substitution or mesylate activation of the hydroxyl group. The two bicyclic diastereomers, which can be separated by column chromatography, furnished the corresponding enantiopure α-trifluoromethylprolines upon removal of the chiral auxiliaries by hydrogenolysis.



Scheme 45.

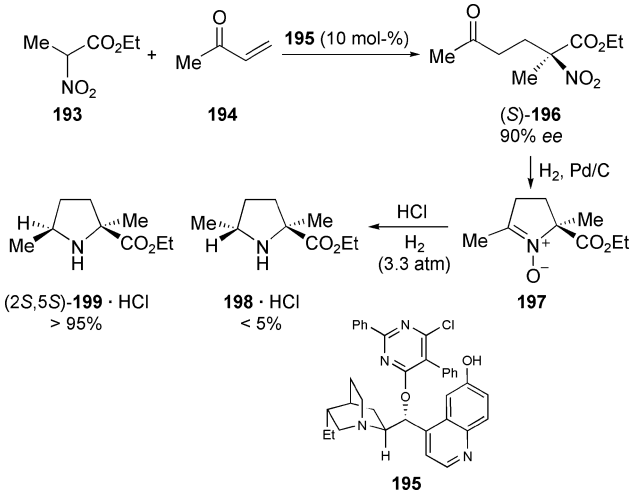
Nájera et al. proposed the use of oxazinone **190**, an easily enolizable chiral alanine template with cyclic structure, for alkylation with dielectrophiles (Scheme 46).[92] The chiral 3,6-dihydro-2*H*-1,4-oxazin-2-one **190** was diastereoselectively dialkylated with 1,3-diiodopropanes in the presence of 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,2,3-diazaphosphorine (BEMP) as a base, together with lithium iodide. Subsequent acid hydrolysis and treatment with propylene oxide to release the free amino acid afforded (*S*)-α-methylproline derivatives in 99% *ee*.



Scheme 46.

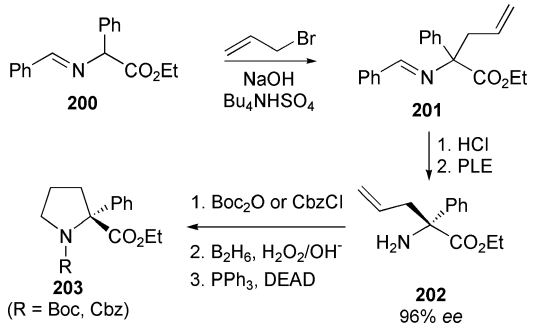
In 2006, Snider et al. reported the synthesis of (–)-*cis*-2,5-dimethylproline ethyl ester (**199**) as a key intermediate in the total synthesis of (+)-NP25302, a cell–cell adhesion inhibitor structurally related to the antitumoral jenamidines A_1/A_2 (Scheme 47). The efficient and stereospecific preparation[93] of **199** started with the enantioselective Michael reaction of ethyl 2-nitropropionate (**193**) and methyl vinyl ketone (**194**) in the presence of the modified hydroquinone **195** as catalyst. The construction of the pyrrolidine ring was achieved by reductive cyclization of the

chiral nitro ketone followed by hydrogenation of **197** in a one-pot procedure. Hydrogenation of **196** (1 atm.) over Pd/C (10%) in the presence of Na_2SO_4 in EtOH gave the nitrone **197**, which afforded the quaternary proline **199** (*dr* >20:1), when the hydrogenation was carried over at 3.3 atm., after addition of HCl.



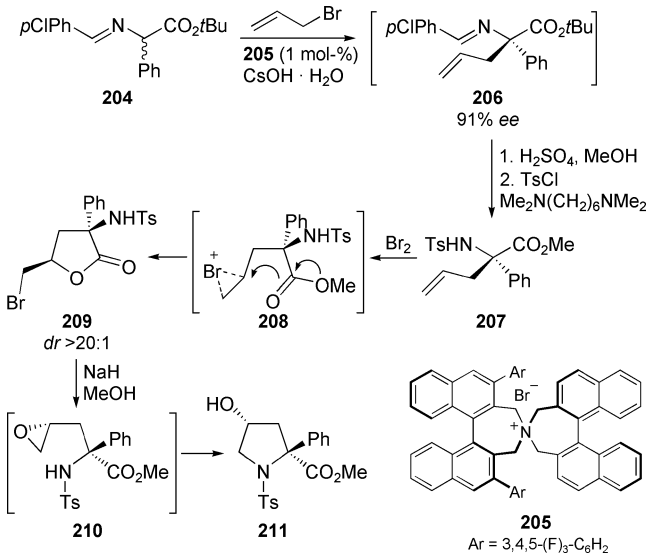
Scheme 47.

A convenient synthesis of protected (*R*)-α-phenylproline derivatives, based on the construction of the pyrrolidine ring through a Mitsunobu reaction, was developed[94] by Tourwé et al. *N*-Benzylidene phenylglycine ethyl ester (**200**) was allylated under phase-transfer catalysis conditions, and the resulting product was enzymatically resolved by use of pig liver esterase (Scheme 48). Protection, hydroboration, oxidation, and subsequent ring-closure by the Mitsunobu protocol gave enantiomerically pure (*R*)-α-phenylproline.



Scheme 48.

A highly stereoselective synthesis of (2*S*,4*R*)-*N*-tosyl-4-hydroxy-2-phenylproline methyl ester was achieved by developing a chiral synthesis of the 2-allyl-2-phenylglycine derivative **207** followed by a stereoselective bromine-mediated cyclization (Scheme 49).[95] Maeda et al. reported the generation of (*S*)-α-allyl phenylglycine methyl ester derivative **207** by catalytic asymmetric alkylation of **204** in the presence of (*S*,*S*)-**205** and subsequent hydrolysis, transesterification, and tosylation of the aldimine intermediate. The bromolactonization of **207** afforded the γ-lactone **209** with high diastereoselectivity. A NaOMe-mediated opening of the γ-lactone ring, followed by an intramolecular attack of the tosylamide nitrogen on the epoxide terminus of **210**, furnished the desired 4-hydroxy-2-phenylproline derivative.



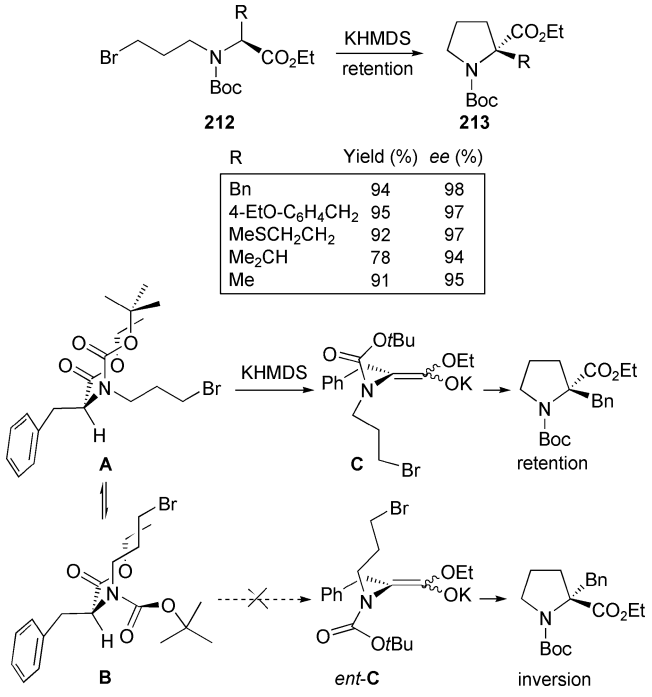
Scheme 49.

3.4.2 Cyclization through C–C Bond Formation: Memory of Chirality

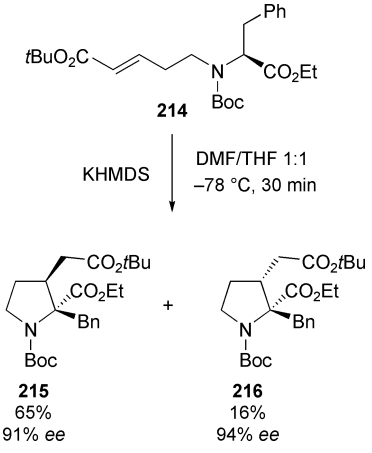
Kawabata et al. reported an efficient protocol that affords α-quaternary prolines in high enantiomeric purities by application of a *memory of chirality* strategy,[96] which relies on a retentive deprotonation/alkylation procedure at the α-carbon of an appropriate chiral amino ester (Scheme 50).[97] *N*-Boc-*N*-ω-bromoalkyl-α-amino acid derivatives were designed as substrates for these asymmetric intramolecular cyclizations. Their treatment with KHMDS in DMF at –60 °C gave diverse α-quaternary proline derivatives **213** of high enantiomeric purity. The key insights of this method are the preservation of the chirality of the starting amino ester in the form of transient conformational chirality of the reactive enolate intermediate and the high stereospecificity during the subsequent cyclization. The choice of the protecting group on the nitrogen has proven to be critical for the generation of the chiral nonracemic enolate intermediate.

The asymmetric construction of α-quaternary prolines with contiguous tertiary stereocenters[98] was achieved by the intramolecular conjugate addition of an enolate with a chiral C–N axis according to the strategy illustrated in Scheme 51. The intramolecular cyclization, in the presence of KHMDS, took place with retention of configuration at the α carbon and a relative *trans* stereochemistry between the two ester groups.

More recently, conditions for the enantiodivergent intramolecular cyclization of *N*-Boc-*N*-ω-bromoalkyl-α-amino acid derivatives **212** have been reported (Scheme 52).[99] Their treatment with lithium amide bases in poorly coordinative solvents, such as THF or toluene, enforces chelation of the carbonyl groups with the lithium cation prior to de-



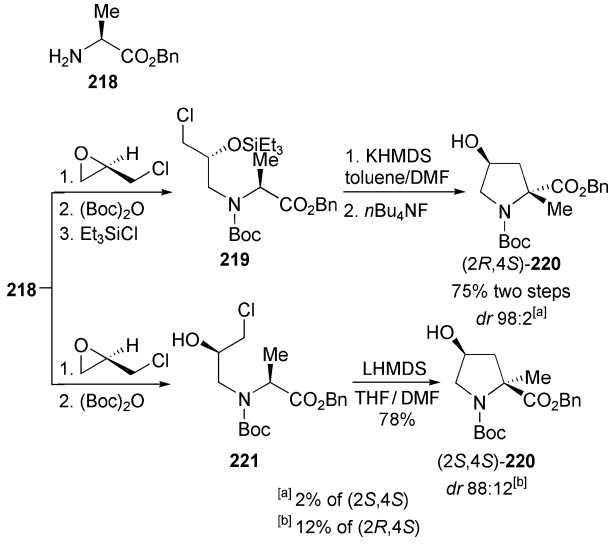
Scheme 50.



Scheme 51.

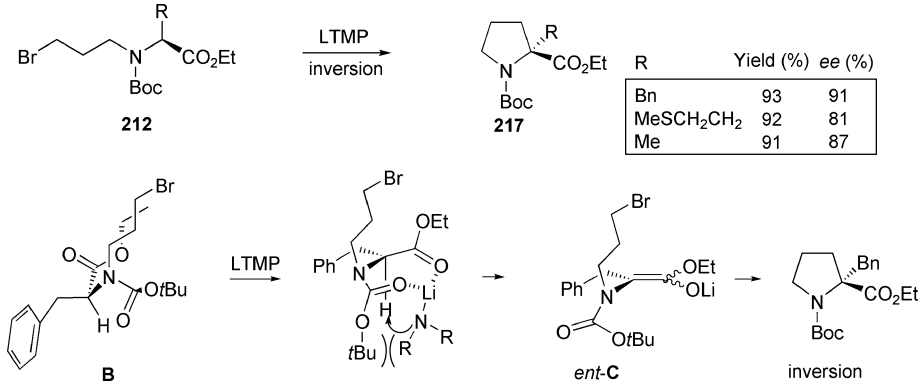
protonation. The transient conformational chirality of the resulting reactive enolate results, upon cyclization, in α-quaternary prolines with inversion of configuration.

Kolaczkowski et al. applied this methodology to the stereoselective synthesis of 4-hydroxy-α-methylprolines.[100] Their approach builds on the observation that epichlorohydrin reacts stereospecifically with carboxy-protected alanines to give the corresponding chiral chlorohydrins. Installation of protecting groups in the (2*S*,4*R*)-chlorohydrin and cyclization by the standard *memory of chirality* methodology (KHMDS, DMF, –60 °C) led to the selective formation of the *trans*-4-hydroxy-α-methylproline (Scheme 53). Interestingly, the omission of the hydroxyl protecting group in the (2*S*,4*R*)-chlorohydrin led to the *cis* diastereoisomer upon deprotonation with LHMDS.



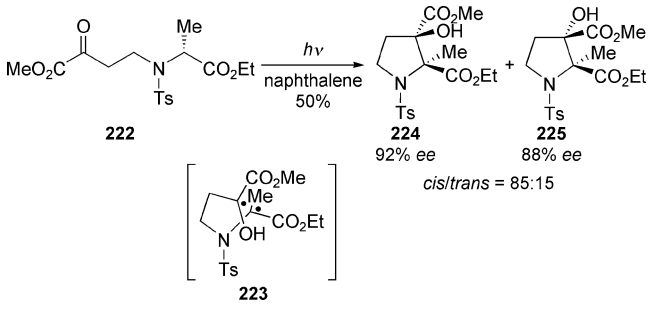
Scheme 53.

In 1999, a remarkable example of a photochemical *chiral-memory effect* furnishing α-methylproline derivatives was described by Giese et al.[101] The stereospecific singlet Norrish–Yang photocyclization of the L-alanine derivative **222** in the presence of the triplet quencher naphthalene yielded isomer **224** with the *cis* configuration as the major product (92% *ee*). The attacked sp^3-hybridized chiral center in **222** was transferred into the product **224** with retention, although it had been converted into a prochiral sp^2-hybridized radical center in the diradical intermediate **223** (Scheme 54). Ab initio calculations suggest that the confor-



Scheme 52.

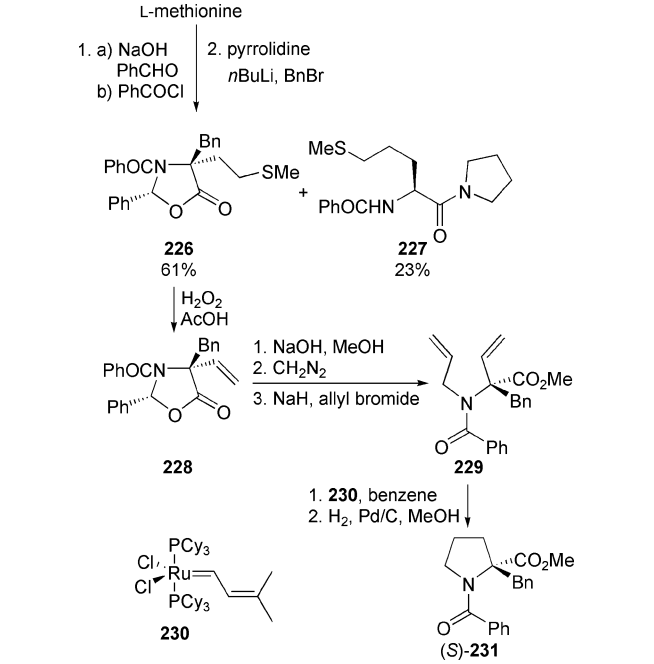
mational freedom of the diradical intermediate is restrained with a specific hydrogen bond network involving three centers.[102]



Scheme 54.

3.4.3 Cyclization through C–C Bond Formation: Ring-Closing Metathesis

The synthesis of a phenylalanine mimic constrained in a proline-like conformation by ring-closing metathesis was described by Abell et al. in 2000 (Scheme 55).[103] They envisaged the synthesis of α-benzylproline **231** through a metathesis reaction of diene **229**, itself prepared by α-benzylation of an L-methionine-derived oxazolidinone, followed by elimination, ring hydrolysis, and *N*-allylation. Besides the Grubbs RCM chemistry, the synthetic sequence utilizes Seebach's oxazolidinone chemistry to introduce the α-benzyl group with control of the absolute configuration and a methionine side chain to provide a masked vinyl group.



Scheme 55.

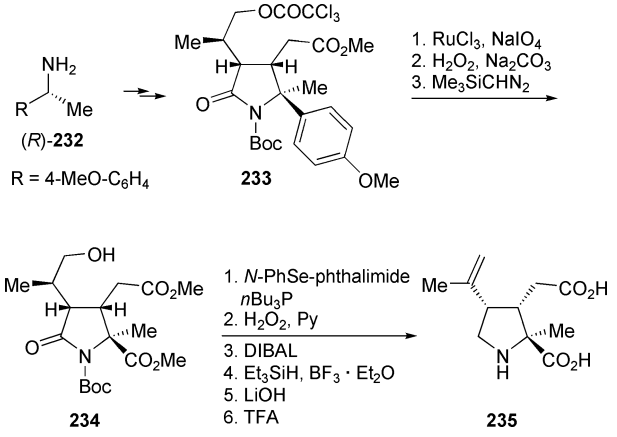
4. Resolution Procedures

In 1977, Overberger and Jon reported the resolution of 2-methylproline.[104] The L enantiomer was obtained from the fractional crystallization of the quinine salt of (–)-*N*-carbobenzoxy-2-methylproline, and the D enantiomer from the collected filtrates. The indirect and direct analytical separation of enantiomers of α-substituted proline analogues has been studied by high-performance liquid chromatography. In this field, the chiral derivatizating agent (*S*)-*N*-(4-nitrophenoxycarbonyl)phenylalanine methoxyethyl ester has been successfully applied for indirect analytical HPLC resolution of enantiomers of α-alkyl-, α-allyl-, and α-benzylproline analogues.[105] Direct HPLC methods that rely on the use of a D-penicillamine-based chiral ligand exchange column,[106] or a quinine-derived chiral anion-exchanger stationary phase[107] have also been reported by Péter et al. More recently, Zhao and Pritts have developed a direct HPLC method using a commercially available polysaccharide type of chiral stationary phase (Chiralpak AD-H) and have conducted the analytical separation of Boc-2-methylproline, Boc-2-methylproline benzyl ester, and Boc-4-hydroxy-2-methylproline benzyl ester with baseline or near baseline resolution under optimized conditions.[108]

5. Miscellaneous

5.1 Ruthenium-Catalyzed Oxidation

Clayden et al. described the asymmetric synthesis of the α-methyl analogue of (–)-kainic acid (**235**) by a procedure that involves the oxidative degradation of **233** as the way to introduce the carboxyl substituent at the α carbon of **234** (Scheme 56).[109] Despite the susceptibility of the *p*-methoxyphenyl group to oxidation with Ru^{VIII}, this stage of the synthesis stopped short of completion and required further hydrogen peroxide treatment to oxidize any α-keto acid to the carboxylic acid.

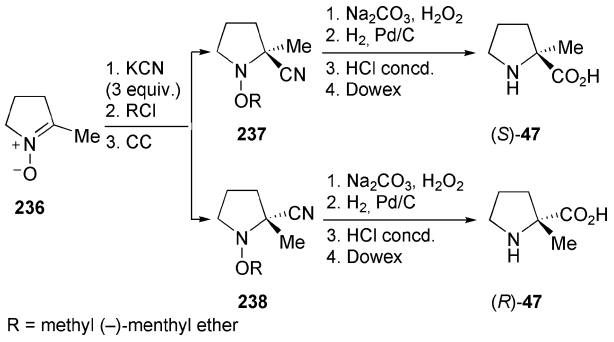


Scheme 56.

5.2 Nucleophilic Addition to a Cyclic Nitrone

Shatzmiller et al. reported the preparation of optically pure chloromethyl (–)-menthyl ether and its application to the asymmetric synthesis of α-methylproline (Scheme 57).[110] Treatment of 5-methyl-3,4-dihydro-2*H*-

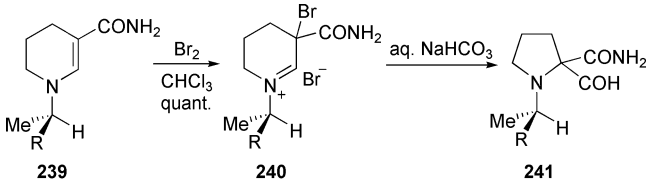
pyrrole-1-oxide (**236**) with KCN, followed by addition of chloromethyl (–)-menthyl ether, afforded a mixture of diastereomeric amino nitriles **237** and **238**, which were separable by column chromatography. The hydrolysis of the chiral nitriles, followed by cleavage of the N–O bonds and hydrolysis of the resulting amides into carboxylic acids, provided access to both enantiomers of α-methylproline.



Scheme 57.

5.3 Duhamel Ring-Contraction

An approach to various proline chimeras containing quaternary α-stereogenic centers by Duhamel ring-contraction of enamines was described by Plaquevent et al.[111] A "removable chiral auxiliary" strategy to induce diastereoselectivity during the ring-contraction process was employed (Scheme 58). The chiral enamines **239** were prepared by hydrogenation of the corresponding pyridinium salts, and were converted into iminiun bromides **240**. The best diastereoselectivities were achieved at 0 °C with crowding of the enamine (R = 1-naphthyl). According to the authors, the inversion of diastereoselectivity in the two-step procedure with respect to the one-pot method, when R = Ph, suggests the competition of two mechanisms.



Procedure	R	Yield (%)	*dr*
one pot	Ph	62	40 : 60
	1-Nph	74	70 : 30
two-step (r.t.)	Ph	70	55 : 45
	1-Nph	75	78 : 22
two-step (0 °C)	1-Nph	76	85 : 15

Scheme 58.

6. Conclusions

In this review we have collected available methods for the stereoselective and asymmetric synthesis of α-substituted prolines. Although a number of strategies have been applied widely and effectively, many other approaches for the construction of fully substituted stereocentres in proline analogues have also been established. In this context, some methods are appropriate for the synthesis of proline derivatives incorporating α-alkyl, α-phenyl, or α-benzyl substituents, whereas others are more suited for the preparation of polysubstituted quaternary prolines. The recent emergence of asymmetric catalytic approaches for the construction of quaternary α,α-disubstituted amino acids has also delivered noteworthy contributions in the area of proline analogues. The selected methods described in this microreview should encourage further investigations focusing on the refinement of efficient methods and the development of straightforward catalytic processes attractive for scalable purposes.

7. Acronyms

Acronyms used in this article are summerized in Table 1.

Table 1. Acronyms.

Ac	acetyl
9-BBN	9-borabicyclo[3.3.1]nonane
BEMP	2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,2,3-diazaphosphorine
BINAP	2,20-bis(diphenylphosphanyl)-1,10-binaphthyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
CAN	cerium ammonium nitrate
Cbz	benzyloxycarbonyl
CC	column chromatography
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DEAD	diethyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
HMPA	hexamethylphosphorous triamide
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
LTMP	lithium 2,2,6,6-tetramethylpiperidide
m-CPBA	*m*-chloroperoxybenzoic acid
Men	menthyl
Mes	methylsulfonyl
MS	molecular sieves
Nph	naphthyl
Pht	phthaloyl
PLE	pig liver esterase
PMP	*p*-methoxyphenyl
PPTS	pyridinium *p*-toluenesulfonate
PTSA	*p*-toluenesulfonic acid
Py	pyridyl
QUINAP	1-(2-diphenylphosphanyl-1-naphthyl)isoquinoline
TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
*t*BuTMG	2-*tert*-butyl-1,1,3,3-tetramethylguanidine
TFA	trifluoroacetic acid
Tf	trifluoromethylsulfonyl
TMS	trimethylsilyl
Tol	*p*-tolyl
Ts	*p*-tolylsulfonyl

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