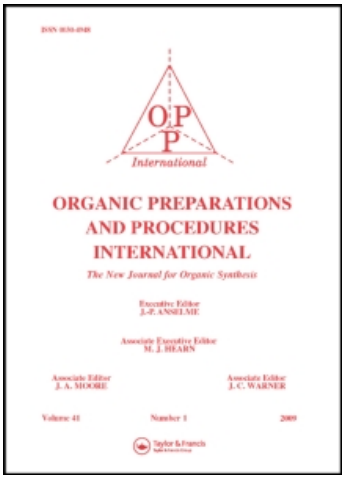

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INTRODUCTION

Whereas the formation of carbon-carbon bonds by nucleophilic addition to aldehydes and ketones has always been a cornerstone of synthetic organic chemistry, the corresponding reactions with their aza analogs are much less explored,[1] despite the widespread occurrence of the resulting amines in natural products and bioactive compounds. This is due to the low electrophilicity of the imine carbon and the propensity to enolization when α-hydrogen atoms are present.[2] Only in the last two decades have methods for the stereoselective addition to aldimine derivatives emerged, and such additions to ketimine derivatives were virtually unknown until just two or three years ago. To show this exciting progress, we herein discuss nucleophilic additions to ketone-derived C=N compounds. In reviewing amine synthesis *via* C–C bond formation by nucleophilic addition to ketimine derivatives, we do not include pericyclic additions to imine derivatives (such as Diels-Alder, Staudinger and ene reaction), radical additions, the Strecker reaction, Pictet-Spengler and related reactions.[3] Additions to 1,3-oxazolidines (and -oxazines) are included, because secondary 1,3-oxazolidines generally exist in equilibrium[4] with the corresponding open-chain hydroxyimines,[5] and tertiary oxazolidines often react *via* an iminium ion. We cover the literature from 1997, that has not been mentioned in previous reviews, and older references have been included when appropriate. For previous literature coverage the reader is referred to the reviews in ref [1].

To achieve stereoselective additions to imine derivatives, the stereochemical information can be incorporated into the imine substrate, the nucleophile (such as metalated sulfoxides or chiral organoboron reagents), or by means of chiral additives or catalysts. In the most common approaches, stereogenic centers adjacent to the imine carbon or nitrogen control the configuration at the newly formed stereocenter. When a stereogenic center adjacent to the imine carbon bears a potential coordination site, the reaction can occur through chelated intermediates, with or without internal delivery of the nucleophile, and open-chain transition states that might lead to different diastereomers (*Fig. 1*).

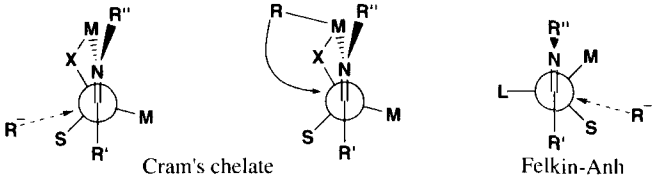
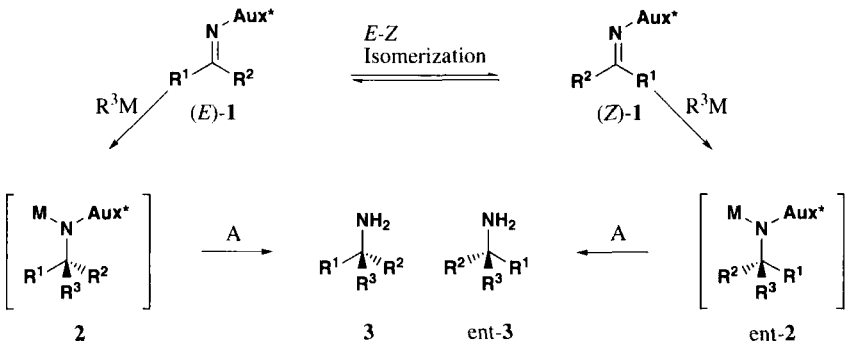


Fig. 1

Often the proper choice of nucleophiles (*e. g.* organocerium reagents, which are capable of chelation, *vs.* cuprates) or solvents (*e. g.* THF *vs.* toluene) makes both stereoisomers accessible.

When a stereogenic center adjacent to the imine nitrogen controls the face of attack on the carbon-nitrogen double bond, controlling the C=N bond geometry is a prerequisite for obtaining high selectivity because the (*E*) and (*Z*) isomers would lead to the opposite configuration in the product **3** (*Scheme 1*).



Scheme 1

An imine carbon is typically less electrophilic compared to that of an aldehyde or a ketone. This difference in electrophilicity allows for the selective addition of nucleophiles to ketones or aldehydes in the presence of imines. However, a Lewis acid that coordinates to and preferentially activates the imine can reverse the selectivity. The groups of Kobayashi,[6] Akiyama,[7] and Yamamoto[8] demonstrated that a variety of carbon nucleophiles could be added selectively to aromatic and aliphatic aldimines in the presence of the corresponding aldehydes by using $Yb(OTf)_3$, $Sc(OTf)_3$ or π-allylpalladium chloride dimer, respectively. Catalytic amounts of HBF_4 or $BF_3{\cdot}OEt_2$ in aqueous media led to aldimine-selective addition of silyl enol ethers.[9] These methods, however, have not yet been applied to the synthetically more relevant substrates having an aldimine and an aldehyde in the same molecule and to ketimines.[10]

I. ADDITION TO KETIMINES

1. General

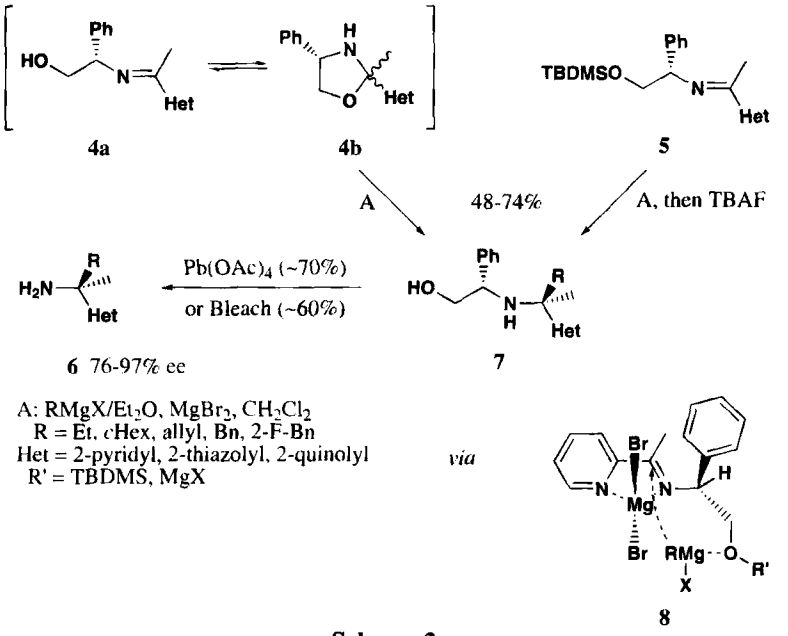
Ketimines usually exist as mixtures of (*E*/*Z*) isomers. Due to facile isomerization ($\Delta G^{\neq} \approx 15$, 20 and 25 kcal·mol^{-1} for *N*-sulfinyl, -aryl and -alkyl ketimines, resp.)[11,12] and hydrolysis during chromatography the separation of the isomers is in most cases impossible. Trifluoromethyl-substituted imines, however, are reported to be stable to chromatography on deactivated silica gel.

Allylic organometallic reagents have a higher reactivity towards addition to imines than alkyl or aryl organometallics and react successfully in a number of cases where other reagents fail.

2. *Addition to Open-chain Ketimines*

a) With *N*-Alkyl or *N*-Aryl Substituents

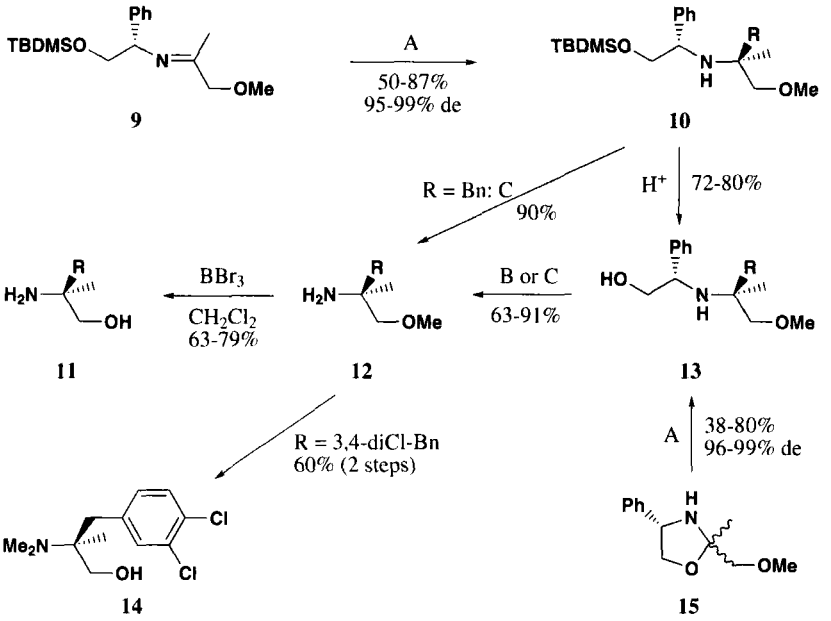
Spero and Kapadia reported one of the first methods for the addition of a variety of Grignard reagents to this class of ketimines containing a 2-heteroaryl substituent, using phenylglycinol or its *O*-TBDMS derivative as chiral auxiliaries (*Scheme 2*).[13] Crucial for high yields and selectivities were the use of CH_2Cl_2 as reaction solvent, $MgBr_2$ as Lewis acid and Et_2O as solvent for the Grignard reagents. The auxiliary could be removed with $Pb(OAc)_4$ or, very conveniently and preferably from an environmental standpoint, by refluxing with bleach in EtOH to give the desired amines **6**.



Scheme 2

The observed 1,3-asymmetric induction can be explained by the transition state **8**. Chelation of the pyridine and imine nitrogens with $MgBr_2$ "locks" the imine into the (*E*) configuration. $A^{1,3}$ strain favors the conformation shown, in which the phenyl ring blocks the *re* face, and the delivery of the nucleophile, which might be oxygen-assisted, occurs then from the less hindered *si* face.

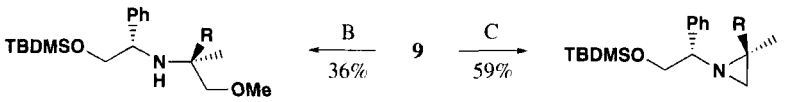
Steinig and Spero extended this method towards the synthesis of 2,2-disubstituted 1,2-aminoalcohols **11** (*Scheme 3*).[14] Excellent diastereoselectivities and generally good yields in the addition were achieved, despite the different coordination ability of the methoxy oxygen compared to the pyridine nitrogen and the fact that these substrates have two potential sites for enolization. $MgBr_2$ proved again to be the most effective Lewis acid, and the Grignard bromides gave better yields and selectivities than the corresponding chlorides.[15] The sense of 1,3-asymmetric induction in additions to **9** and **15** was the same as with the 2-heteroaryl substrates **4** and **5**. This method was applied to the first asymmetric synthesis of the selective serotonin reuptake inhibitor Cericlamine (**14**).



A: $RMgBr/Et_2O$, $MgBr_2$, CH_2Cl_2; B: $Pb(OAc)_4$; C: NH_4HCO_2, Pd/C
R = Bn, 3,4-diCl-Bn, Ph, allyl, allenyl/propargyl

Scheme 3

Alkyl groups could be introduced using trialkylaluminum reagents (*Scheme 4*).[16] Depending on the quantity of aluminum compound, amines **10** or aziridines **16** were obtained, each with high diastereoselectivity.

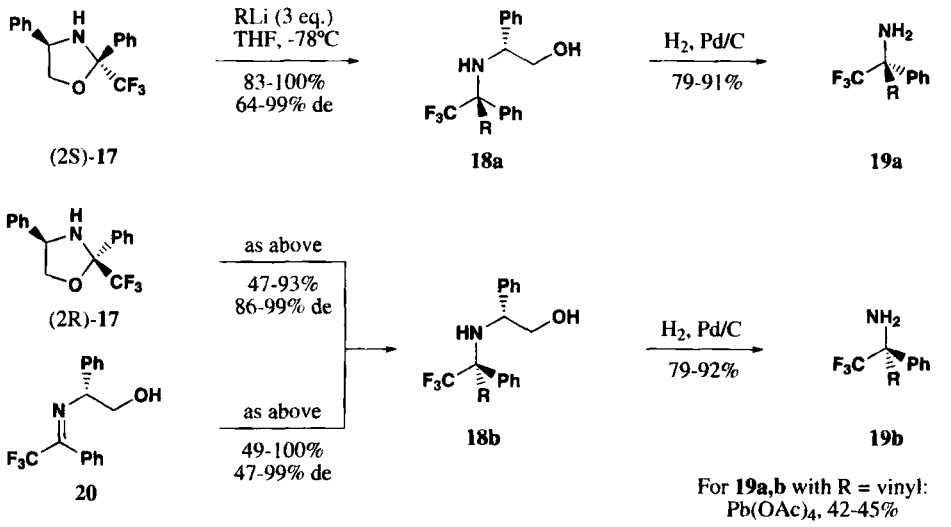


10 >95% de **16** >95% de

R = *n*-alkyl
B: AlR_3 (2 eq.), CH_2Cl_2, r.t.; C: AlR_3 (4 eq.), CH_2Cl_2, r.t.

Scheme 4

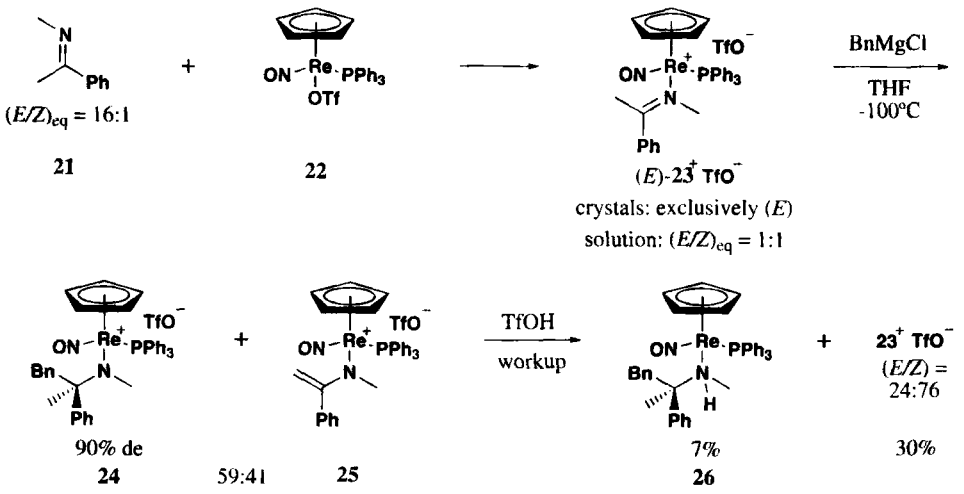
Higashiyama, Mikami *et al.* reported the addition of organolithium reagents to the phenylglycinol-derived 1,3-oxazolidines **17** and imine **20** of 2,2,2-trifluoroacetophenone (*Scheme 5*).[17] In contrast to the 2,2-disubstituted 1,3-oxazolidines **4** and **15** where the diastereomeric ratio did not influence the selectivity of the addition,[4] the diastereomers of the 2-trifluoromethyl-substituted oxazolidines **17** led to different diastereomers of **18**. In addition, yields and selectivity were slightly different from those observed in the addition to the imine **20**. These results suggest that **17** undergoes direct reaction with RLi with retention of configuration at C-2 instead of reacting through an *O*-deprotonated hydroxyimine. Hydrogenolysis of **18** cleaved regioselectively the benzylic carbon-nitrogen bond of the auxiliary, yielding the α-trifluoromethyl-substituted amines **19** in 79–92% yield. In order to obtain **19** with R = vinyl, the auxiliary had to be cleaved by $Pb(OAc)_4$ instead.



R = Me, *n*Bu, *i*Pr, vinyl (Et after hydrogenation), *p*Tolyl

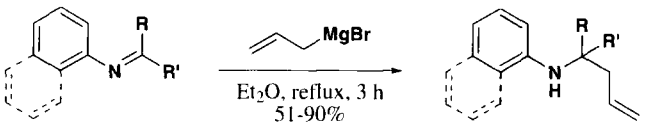
Scheme 5

Gladysz and Stark prepared the complex **23** of imine **21** with the rhenium Lewis acid $[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)]^+$ (*Scheme 6*).[18] It is interesting to note that the imine geometry changed on coordination with the rhenium complex.[19] In the addition of BnMgCl to **23**, ^{31}P NMR showed that 59% of the adduct **24** (with 90% de) was formed along with 41% of enolization product **25**. On workup, however, the yield of isolated complex **26** was only 7%.



Scheme 6

Zvolinski *et al.* reported the addition of allylmagnesium bromide to *N*-aryl ketimines **27** (*Scheme 7*).[20] Even the ketimine with R' = Bn, which is very prone to enolize, underwent addition giving **28**, albeit only in 51% yield.

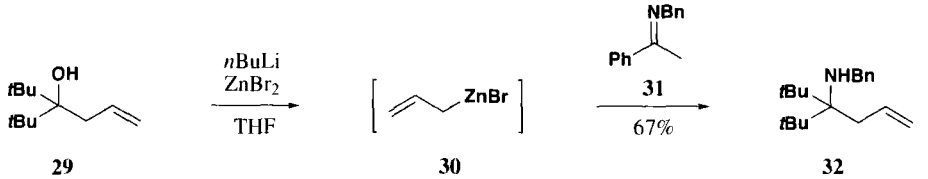


27 28

R = Me, Ph
R' = Ph, 4-MeO-Ph, Bn, 4-[2.2]paracyclophanyl

Scheme 7

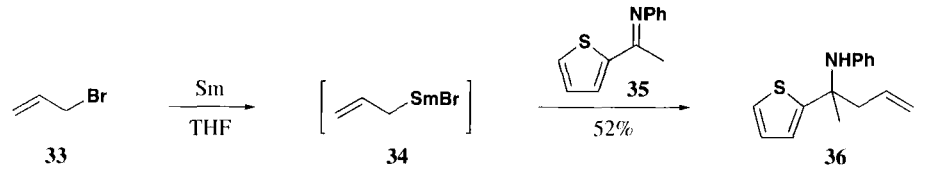
Knochel and Jones generated allylzinc bromide (**30**) using the *in situ* fragmentation of the zinc alkoxide of the sterically hindered alcohol **29**.[21] The zinc reagent added to the ketimine **31** in 67% yield (*Scheme 8*). Additions of **30** to enolizable aldimines occurred in 63–90% yield. This reaction is an example for the higher reactivity of allylic organometal reagents towards addition to imines, because Et_2Zn could not be added to *N*-phosphorylketimines[22] or to our substrates **4**, **5**, **9**, and **15**.



29 30 32

Scheme 8

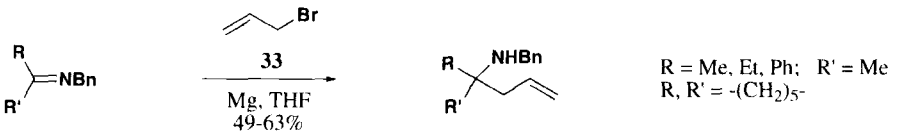
Zhang *et al.* generated *in situ* allylsamarium bromide (**34**) which added to the 2-acetylthiophene-derived ketimine **35** in 52% yield (*Scheme 9*).[23] Additions of **34** to aromatic aldimines occurred in 66–80% yield.



33 34 36

Scheme 9

Paulmier *et al.* obtained the homoallylamines **38** in a Barbier-type reaction from the ketimines **37**, allyl bromide (**33**) and magnesium in THF in 49–63% yield (*Scheme 10*).[24]



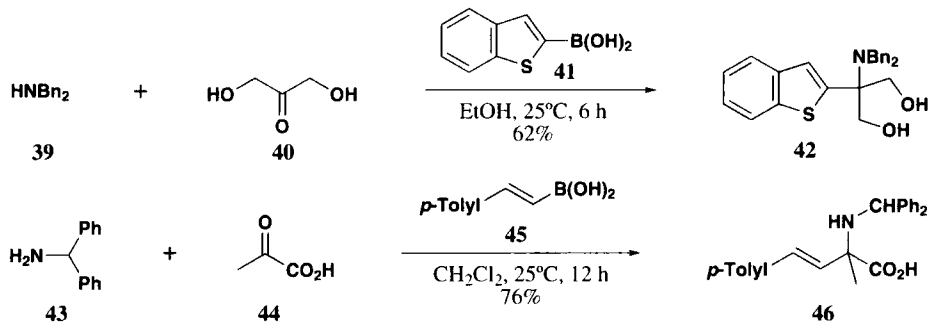
37 38

R = Me, Et, Ph; R' = Me
R, R' = -$(CH_2)_5$-

Scheme 10

Petasis *et al* described a one-pot three-component synthesis of α-aminoacids and 1,2-aminoalcohols.[25] Imines are formed *in situ* from primary or secondary amines and a carbonyl compound. Alkenyl- or arylboronic acids or boronates then add to these imines or iminium ions. The

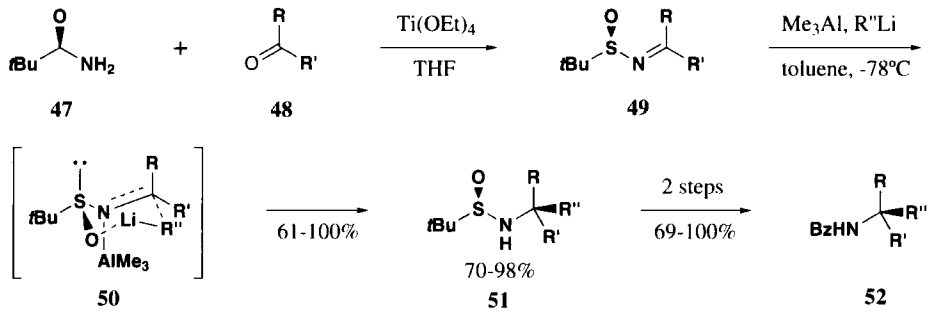
two examples with ketones as carbonyl component involve dihydroxyacetone (**40**) and pyruvic acid (**44**) (*Scheme 11*). The unprotected hydroxy groups and the free acid did not interfere with the reaction. An asymmetric version of this process using phenylglycinol as amine component was reported to give very high selectivity when aldehydes were used, but no examples were given for ketones.



Scheme 11

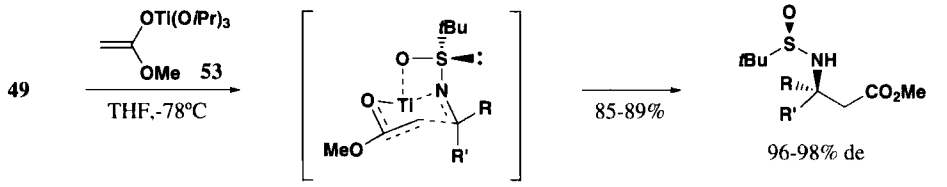
b) With Electron-withdrawing Group on Imino Nitrogen

On the basis of Hua's successful addition of allylic Grignard reagents to toluenesulfinimines,[26] Ellman *et al.* reported the addition of alkyl- and phenyllithium to optically pure *tert*-butylsulfinimines **49**, precomplexed with Me_3Al, in toluene (*Scheme 12*).[27] The adducts **51** were isolated in 61–100% yield with 70–98% de and could readily be deprotected and benzoylated. The use of coordinating solvents resulted in drastically reduced yields and selectivities. The authors explained the observed selectivities by the six-membered transition state **50** in which the bulky *tert*-butyl group and the larger imine substituent occupy equatorial positions. It is interesting to note that these conditions (RLi, Me_3Al, toluene) were not effective for sulfinylaldimines and that the optimized conditions for nucleophilic additions to sulfinylaldimines (RMgBr/Et_2O, CH_2Cl_2) gave – except for allylmagnesium bromide – only poor results with the corresponding ketimines.



Scheme 12

Two examples for additions of the titanium enolate **53** of methyl acetate to **49**, giving β-amino acid derivatives **55**, were also reported (*Scheme 13*).[28] For the acetophenone-derived sulfinimine, selectivity and yield were almost identical to the corresponding toluenesulfinyl imines reported earlier by Davis *et al.*[29]

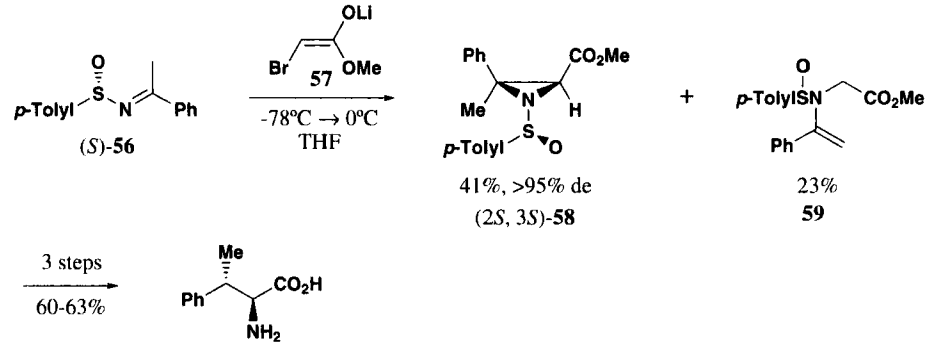


54 55

R = Me; R' = *i*Pr, Ph

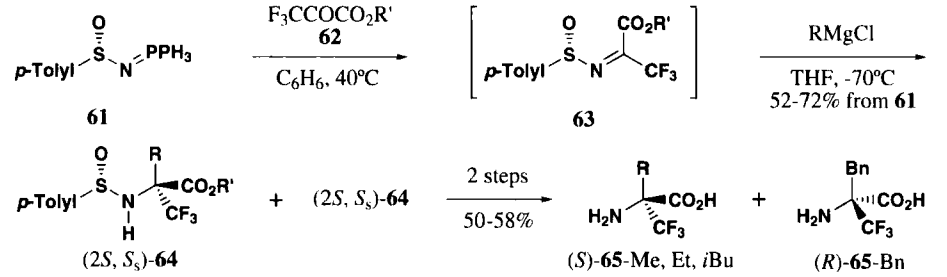
Scheme 13

Davis and co-workers described the asymmetric aza-Darzens reaction of the acetophenone-derived sulfinimine **56** and the lithium enolate **57** of methyl bromoacetate (*Scheme 14*).[30] The 3,3-disubstituted aziridine (2*S*,3*S*)-**58** was isolated with greater than 95% de in 41% yield, accompanied by the *N*-sulfinyl enamine **59** (23%), which arises from enolization of the ketimine and *N*-alkylation by methyl bromoacetate.[29] The aziridine **58** was then converted to (2*S*,2*S*)-3-methylphenylalanine (**60**). In contrast, addition of MeMgBr to a 2*H*-azirine gave the (2*S*,3*R*) isomer of *N*-unsubstituted **58** (see chapter I.3., *Scheme 24*).



Scheme 14

Bravo, Zanda *et al.* reported the addition of Grignard reagents to chiral *p*-toluene-sulfinimines **63** of trifluoropyruvates **62** (*Scheme 15*).[31] With alkylmagnesium halides, the selectivity

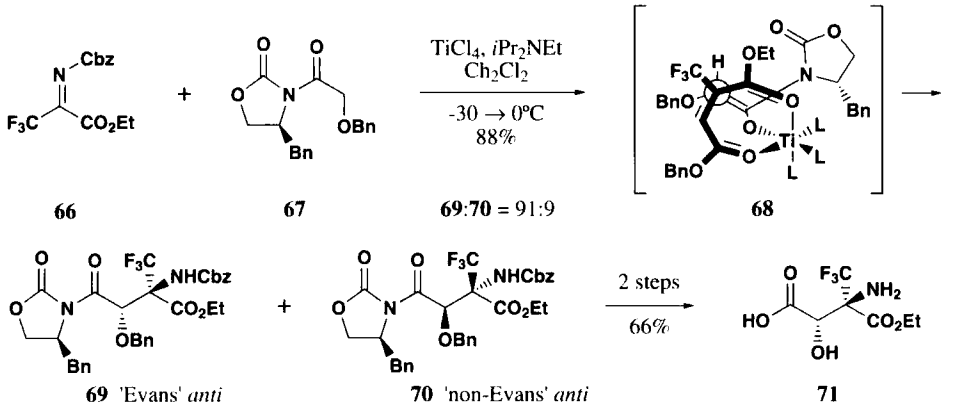


R = alkyl: 10-74% de R = Bn: 40% de
R' = Me, Et

Scheme 15

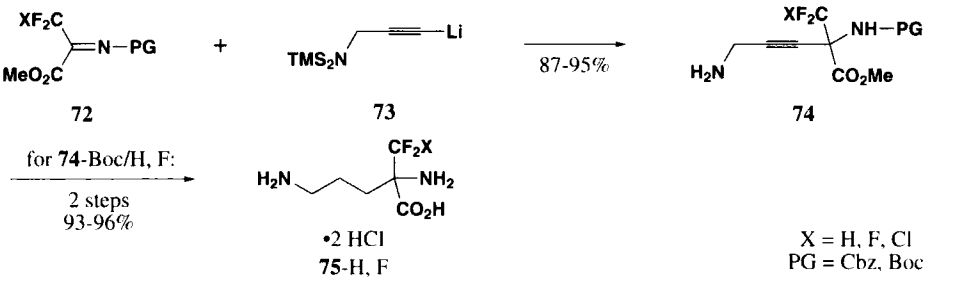
increased with steric bulk (R = Me: 10% de, *i*Bu: 74% de), but also racemization at sulfur (>96% → 88% ee) was observed. Interestingly, with BnMgCl the opposite diastereoisomer dominated (40% de). This was rationalized with the addition occurring *via* a six-membered transition state analogous to **50** in the case of alkylmagnesium halides, but under non-chelation control with BnMgCl, perhaps in a radical process. From the adducts **64** the α-trifluoromethyl aminoacids **65** were obtained in two steps (50–58% yield).

The addition of the enolate generated from the oxazolidinone **67** using $i\text{Pr}_2\text{NEt}$ and $TiCl_4$ to the *N*-Cbz imine **66** of ethyl trifluoropyruvate occurred in 88% yield (*Scheme 16*).[32] The "Evans"- and "non-Evans"-*anti* adducts **69** and **70** were obtained in a 91:9 ratio; the *syn* adducts were not detected. To explain the observed selectivity, the authors proposed the transition state **68** where the carbonyl oxygens of the Cbz group and the ethyl ester form a seven-membered ring with the titanium. The imine nitrogen is not involved in the coordination because of its very poor Lewis basicity. The imine **66** exists as a single geometric isomer by NMR. The (*Z*) isomer of **66** was calculated to be 10 kcal·mol^{-1} less stable than the (*E*) isomer.[32] It should therefore exist only as (*E*) isomer (CF_3 and nitrogen substituent *trans*). Removal of the Evans auxiliary with LiOOH and of the benzyl ethers by hydrogenation gave the α-trifluoromethyl aminoacid **71** (66%).



Scheme 16

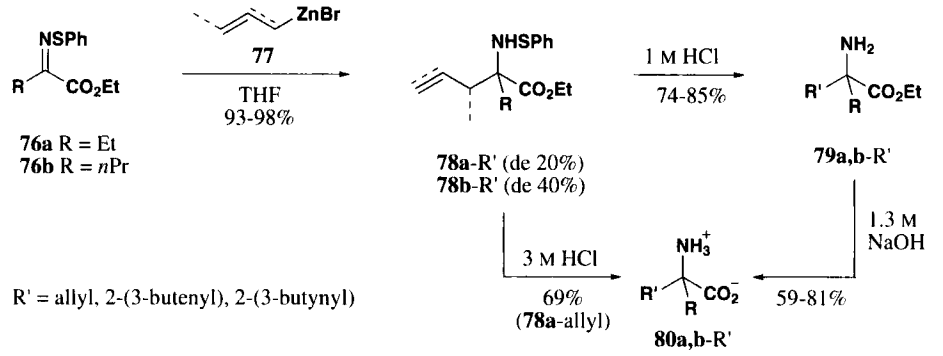
Osipov, Burger *et al.* added lithium *N*,*N*-bis(trimethylsilyl)aminomethyl acetylide **73** to alkoxycarbonyl imines **72** of methyl di- and trihalopyruvates (*Scheme 17*).[33] The adducts **74** could be



Scheme 17

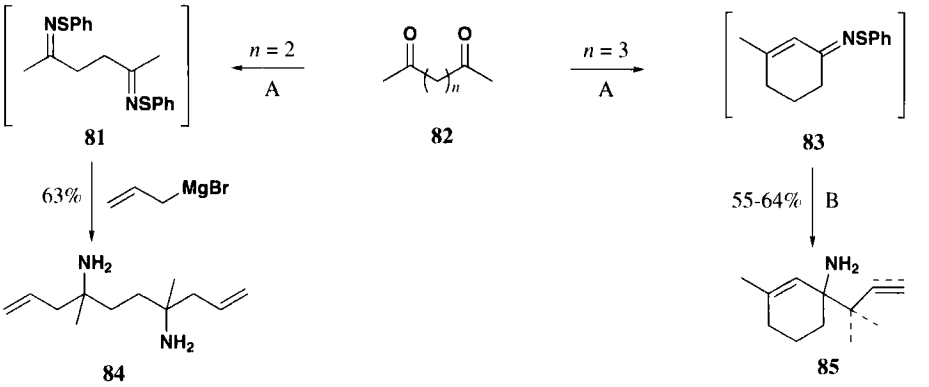
obtained in 87–95% yield. From the Boc-protected di- and trifluoro compounds the corresponding ornithine derivatives **75** were prepared in high yield. **75-H** is used clinically for the treatment of African sleeping disease and of *Pneumocystis carinii* pneumonia.

Miginiac *et al.* reported the addition of allyl-, crotyl-, and 1,2-butadienylzinc reagents **77** to the *N*-phenylsulfeneketimines derived from ethyl alaninate **76a** and norvalinate **76b** (*Scheme 18*).[34] The adducts **78**, obtained in high yields (93–98%) but with low diastereoselectivity, were easily transformed into the aminoesters **79** (1 M HCl) and the free aminoacids **80** (1.3 M NaOH with **79**, 3 M HCl with **78**).



Scheme 18

The same authors also reported the addition of allylic and allenic Grignard reagents to *in situ* generated *N*-phenylsulfeneketimines derived from 2,*n*-diketones **82** (*n* = 5–7) (*Scheme 19*).[35] With 2,6-heptanedione, only cyclohexenic primary amines **85** were obtained because this diketone underwent intramolecular aldol condensation completely under the conditions for forming the sulfenimine. 2,5-Hexanedione gave the expected diamine **84** with allylmagnesium bromide (63%).

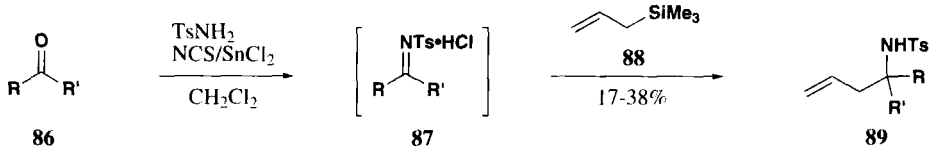


A: $PhSN(TMS)_2$ (2.2 eq.), TBAF (0.01 eq.), THF B: (subst.) allyl/allenylMgBr

Scheme 19

Masuyama *et al.* reported that *N*-tosyliminium species **87**, prepared *in situ* from ketones **86** (cyclopentanone, cyclohexanone, and acetophenone) and $TsNH_2$ with NCS and $SnCl_2$, were allylated

with allyltrimethylsilane **88** in low yields (17–38%) (*Scheme 20*).[36] Under the same conditions, aromatic (except for furfural) and aliphatic aldehydes gave the homoallylic tosylamides corresponding to **89** in 47–96% yield.

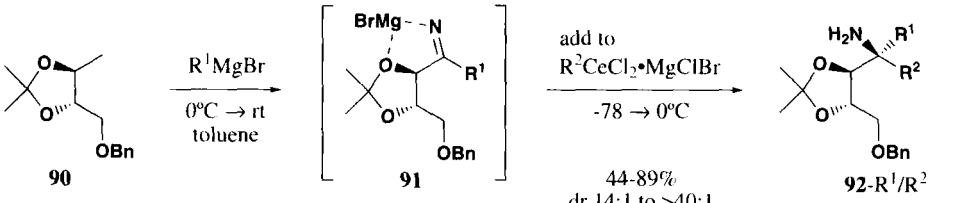


R = Me, R' = Ph; R, R' = $(CH_2)_n$ (n = 4,5)

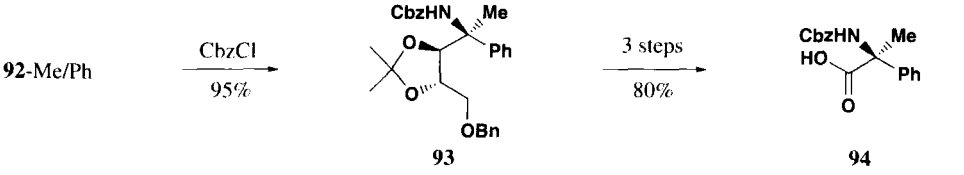
Scheme 20

c) With *N*-Metal Substituent

Charette et al. generated *N*-magnesio ketimines **91** *in situ* by addition of Grignard reagents to the tartrate-derived α-alkoxynitrile **90**.[37] The addition of these ketimines to organocerium reagents, prepared from Grignard reagents and $CeCl_3$ in a 1:1 ratio, furnished the amines **92** with diastereoselectivities ranging from 14:1 to >40:1 and yields from 44–89% (*Scheme 21*). The configuration of the newly formed stereocenter, which is in accord with a chelation-controlled nucleophilic addition from the less hindered face of **91**, was determined simply by the order of addition. Conversion to the amino acid **94** was effected in three steps after protection of the amino group in **92** as Cbz carbamate.

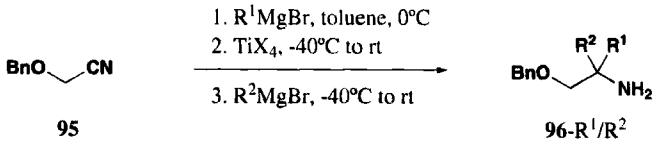


R^1, R^2 = *n*-alkyl, *c*-hex, allyl, Ph, $PhCH_2CH_2$



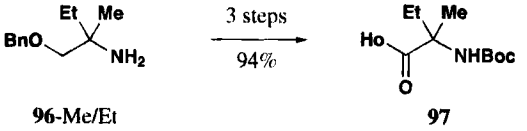
Scheme 21

This methodology was extended to *O*-protected achiral cyanohydrins (*Scheme 22*): The iminate chelate corresponding to **91** was transmetalated to titanium by $Ti(OiPr)_4$ before a second Grignard reagent was added.[38a] Enantiomerically enriched material could be produced by using titanium complexes with enantiopure diols.[38b] Without this transmetallation, only allylmagnesium bromide reacted smoothly as the second nucleophile. The resulting *O*-protected aminoalcohol **96-Me/Et** was easily transformed into the amino acid **97**.



95 96-R^1/R^2

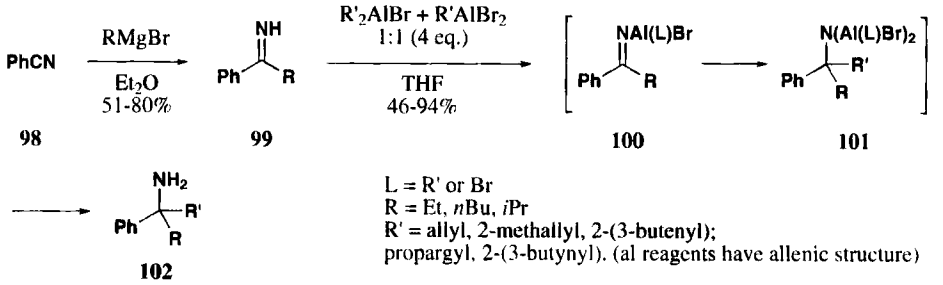
R^1 = Me, Et, *i*Pr, $PhCH_2CH_2$; R^2 = Me, Et, Ph
TiX_4 = $Ti(OiPr)_4$ (yields 15-100%), Ti-BINOL complexes (yields 21-71%, 42-72% ee)



96-Me/Et 97

Scheme 22

A related non-stereoselective, two-step procedure was reported earlier by Miginiac *et al.*[39] *N*-unsubstituted ketimines **99** were synthesized by addition of alkyl Grignard reagents to benzonitrile (**98**) and reacted with the organoaluminum sesquihalides (1:1 mixture of R_2AlX and $RAlX_2$) prepared from allylic and propargylic bromides. The amines **102** were obtained in 46–94% yield (*Scheme 23*). For comparison, the addition of other allyl metal species to ethyl phenyl ketimine was examined, and aluminum reagents were found to be the most effective (94% vs. 61% for allylZnBr/THF and 70% for allylMgBr/Et_2O). It is interesting to note that alkylaluminum chlorides did not add to the ketimine **9** (I.2.a),[16] confirming the higher reactivity of allylic organometallic compounds towards imines.



98 99 100 101 102

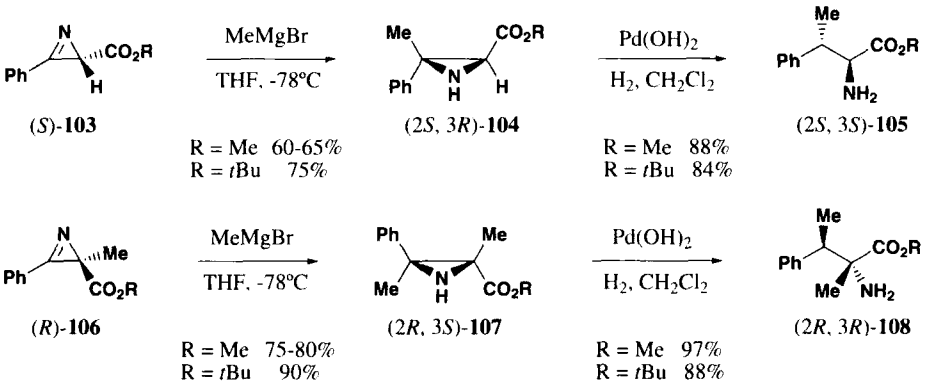
L = R' or Br
R = Et, *n*Bu, *i*Pr
R' = allyl, 2-methallyl, 2-(3-butenyl); propargyl, 2-(3-butynyl). (al reagents have allenic structure)

Scheme 23

3. Addition to Cyclic Ketimines

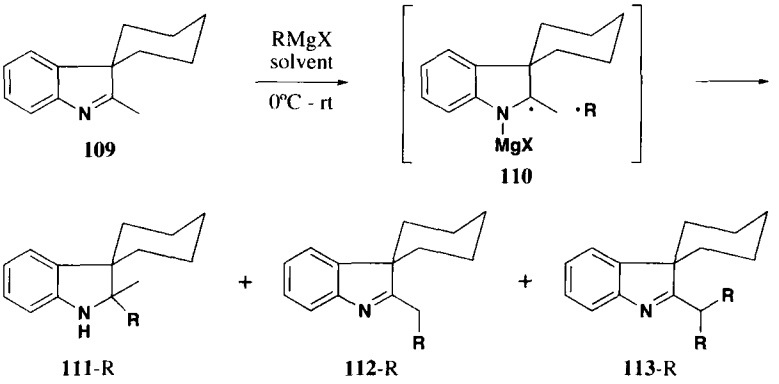
Davis et al. reported the asymmetric synthesis of β-substituted α-amino acids by addition of MeMgBr to enantiopure 2*H*-azirine-2-carboxylates **103** and **106** (*Scheme 24*).[40]

The addition of the Grignard reagent occurred *syn* to the ester moiety, which is the more hindered face of the azirine. This result was explained by chelation of MeMgBr with the carbomethoxy group. MeLi was ineffective for this reaction because it mainly attacked the carbonyl group. Both aziridines **104** and **107** were then hydrogenolyzed to give the β-substituted α-amino acid esters **105** and **108.** The free acid of **105** was also synthesized *via* an asymmetric aza-Darzens reaction of an acetophenone-derived sulfinimine with the lithium enolate of methyl bromoacetate (see chapter I.2.b), *Scheme 14*).[30]



Scheme 24

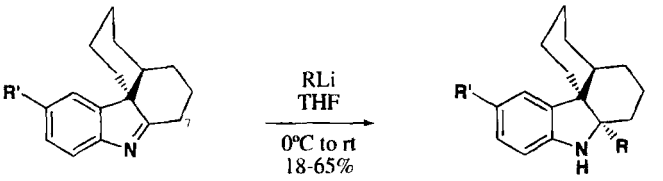
Rodríguez and co-workers examined additions of Grignard reagents to 2'-methylspiro-[cyclohexan-1,3'-3'*H*-indole] derivatives **109** (*Scheme 25*).[41] Allylmagnesium iodide gave the expected addition product **111-allyl**, and benzylmagnesium chloride gave the normal addition product **111-Bn** in toluene and ether as solvents. However, the insertion product **112-Bn** dominated in THF. With methylmagnesium iodide only the single and the double insertion products **112-Me** and **113-Me** were observed. The authors proposed a radical mechanism with **110** as intermediate. Stabilized radicals such as benzyl and allyl would simply combine, giving **111** (alternatively, an ionic mechanism could operate). Methyl radicals, however, would abstract a hydrogen atom from the methyl group at C-2 of the indole to give an exocyclic double bond. Another methyl radical from MeMgI added then to this double bond, giving the insertion product **112-Me**. EPR spectra from the reaction with MeMgI were in accord with a radical on the C-2' atom in **110**.



Grignard	solvent	product	yield(%)
AllylMgI	ether/toluene 1:3	**111**-allyl	91
BnMgCl	toluene	**111**-Bn	75
	THF	**112**-Bn	17
MeMgI	ether/THF 1:5	**112**-Me	79
	ether/toluene 2:1	**113**-Me	47

Scheme 25

Sainsbury *et al.* and a group at Astra Hässle reported additions to the annelated spiro-3*H*-indoles **114** (*Scheme 26*).[42] A variety of organolithium reagents could be employed successfully, but *t*BuLi led only to deprotonation at C-7. In all cases, the nucleophile added selectively from the less hindered bottom face of the imine. The adducts **115** act as antioxidants. Some of these compounds show very selective binding to low density lipoprotein (LDL) particles in human plasma and are thus of interest as potential drugs to control atherosclerosis.

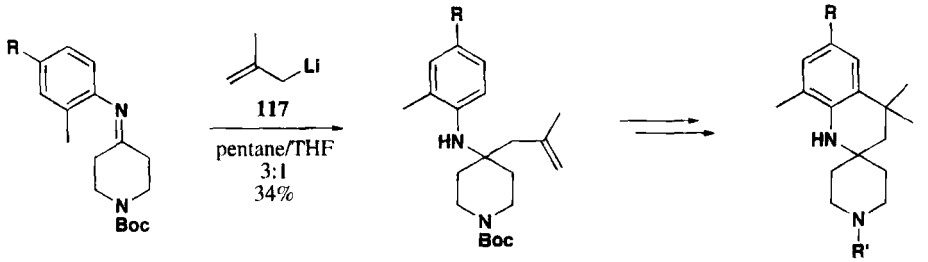


114 **115**

R = Me, *n*Bu, Ph, 4-*t*Bu-Ph, $(CH_2)_4OPh$, $(CH_2)_6OPh$, $(CH_2)_4O(CH_2)_6OPh$, $(CH_2)_6NBn_2$
R' = *i*Pr, *t*Bu

Scheme 26

A related series of compounds **119** was prepared *via* the addition of 2-methylallyllithium (**117**) to ketimine **116** followed by cyclization of the allyl moiety onto the phenyl ring and alkylation of the piperidine nitrogen (*Scheme 27*).

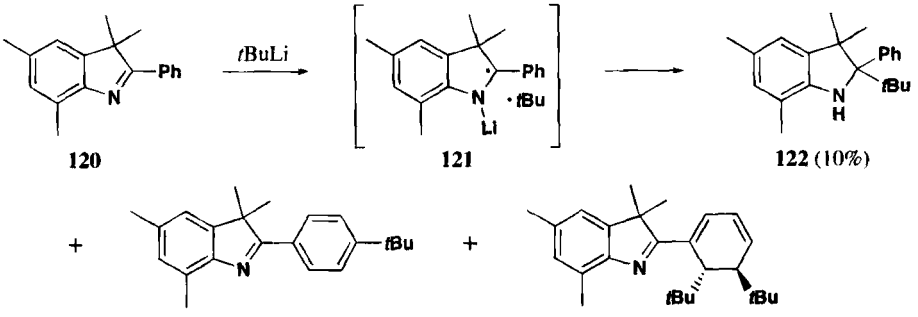


116 **118** **119**

R = Me, OMe
R' = alkyl

Scheme 27

Surprisingly, with *tert*-butyllithium the related 3*H*-indole **120** gave not only the expected addition product **122** but mainly **123** and a trace of **124** (*Scheme 28*).[43] Similar observations were



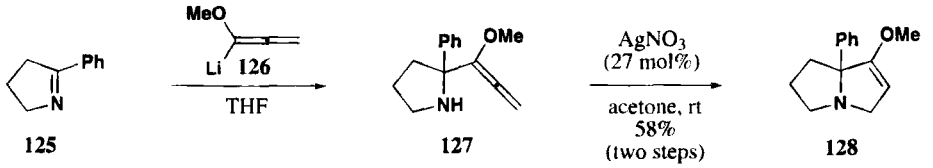
120 **121** **122** (10%)

123 (26%) **124** (0.5%)

Scheme 28

made with 6,7-dimethyl-3-phenyl-2*H*-1,4-benzoxazine. The authors concluded that in these cases radical mechanisms operated with **121** or the corresponding 1,4-benzoxazine as intermediates. In contrast, phenyllithium gave with both substrates only the expected addition products.

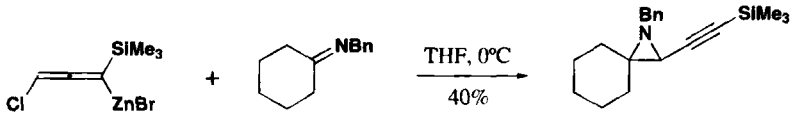
Reissig and co-workers reported the addition of lithiated methoxyallene (**126**) to the pyrrolidine **125** (*Scheme 29*).[44] The primary addition product **127** was cyclized to the 2,3,5,7a-tetrahydro-1*H*-pyrrolizine **128** with substochiometric amounts of silver nitrate.



125 127 128

Scheme 29

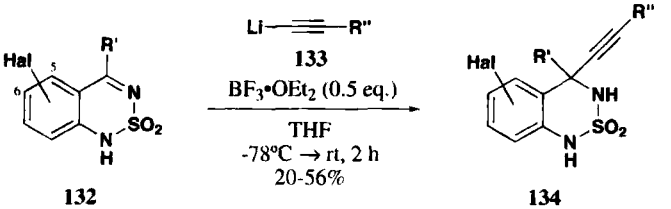
Chemla *et al.* could add 3-chloro-1-trimethylsilyl zincioallene (**129**), generated from TMS-propargyl chloride by deprotonation with LDA and transmetallation with $ZnBr_2$, to the ketimine **130**, giving the propargylic spiroaziridine **131** in 40% yield (*Scheme 30*).[45] Additions to aromatic and aliphatic aldimines proceeded in 13–67% yield with *anti*/*syn* ratios of >98:2.



129 130 131

Scheme 30

Corbett *et al.* reported the additions of lithium acetylides **133** in the presence of boron trifluoride etherate to the 2,2-dioxide-1-*H*-2,1,3-benzothiadiazines **132** yielding 4,4-disubstituted 2,2-dioxide-1,3-*H*-2,1,3-benzothiadiazines **134** in moderate yields (*Scheme 31*).[46] The compounds **134** are non-nucleoside reverse transcriptase inhibitors (NNRTIs), with the most potent compound (Hal = 6-Cl, R' = *c*Pr, R'' = *i*Pr) having an IC_{90} = 180 nM in a whole cell assay.



132 134

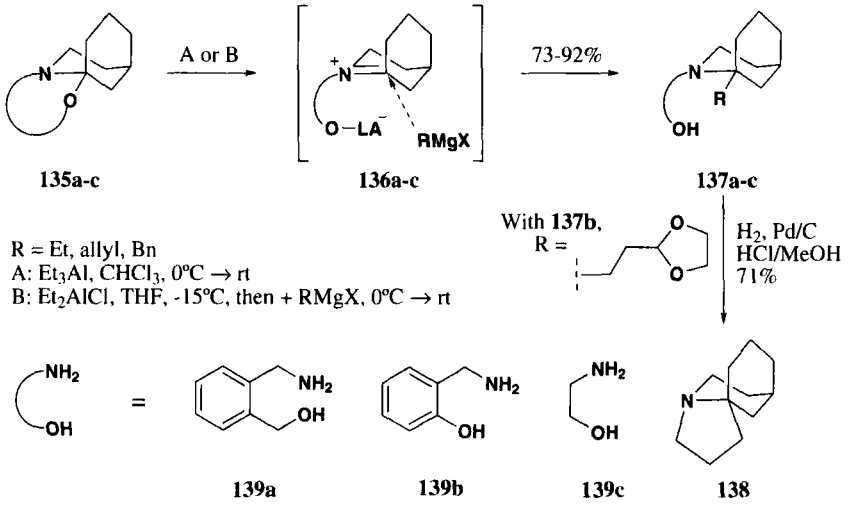
Hal = 6-Cl:
R' = *i*Pr, *c*Pr; R'' = Et, *i*Pr, *c*Pr, Ph, 2-Pyridyl

Hal = 5,6-diF:
R' = CF_3; R'' = *c*Pr

Scheme 31

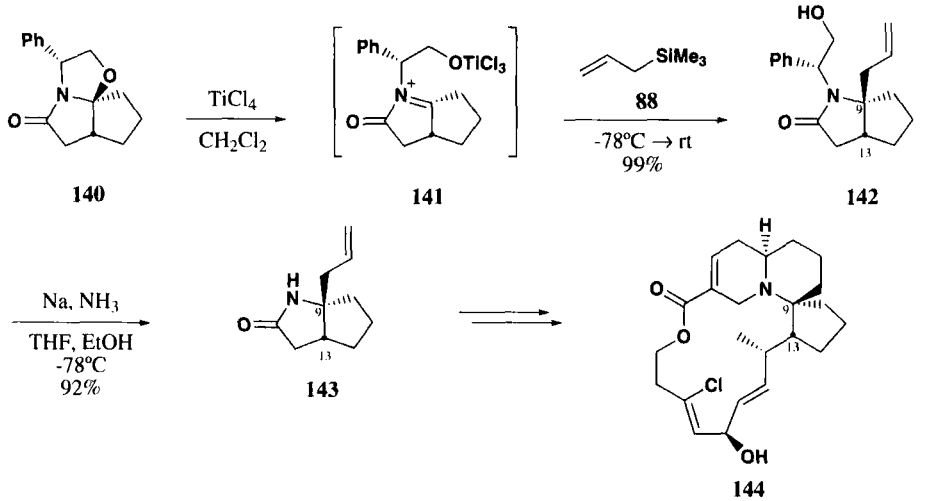
Kibayashi *et al.* reported the nucleophilic alkylation of the bridgehead iminium ions **136** generated *in situ* from tricyclic *N,O*-acetals **135** (*Scheme 32*).[47] Activation of **135** with Et_2AlCl was

required for additions of Grignard reagents, while Et_3Al reacted directly. Hydrogenation using Pd/C cleaved the benzylic C-N bond in **137b**. From the adduct of **137b** with the Grignard reagent from 2-bromoethyl-1,3-dioxolane, the tricycle **138** was thus obtained. **138** constitutes the core structure of the novel immunosuppressant FR901483.



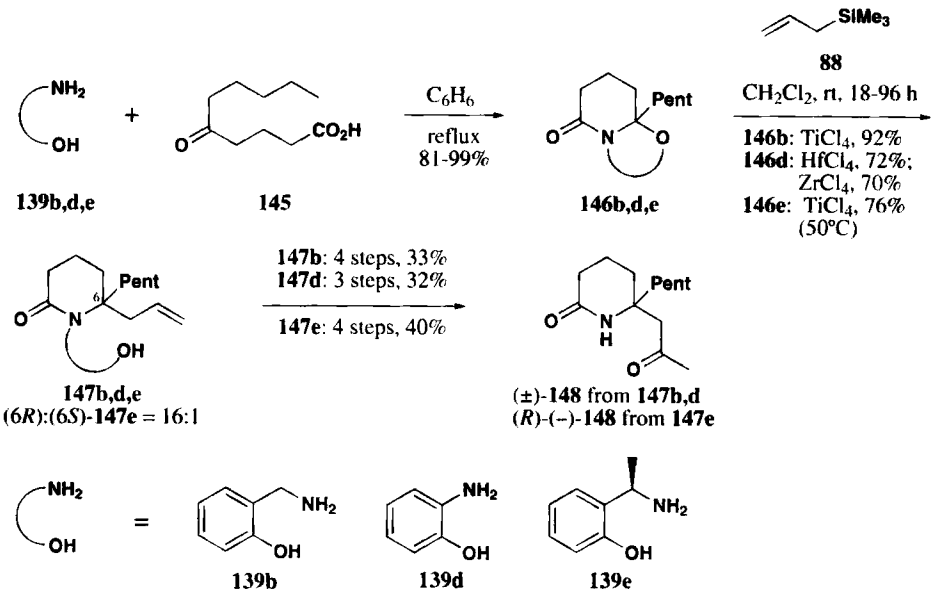
Scheme 32

In the course of their total synthesis of the marine alkaloid halichlorine (**144**), Danishefsky and Trauner used the allylation of the bicyclic lactam **140** with allyltrimethylsilane (**88**) in the presence of titanium tetrachloride to establish the configuration at C-9 (*Scheme 33*).[48] The efficiency of this reaction (99% yield, single isomer) was ascribed to the high reactivity of the strained bicyclic *N*-acyliminium ion intermediate **141**. The auxiliary was removed under reductive conditions, yielding lactam **143**.



Scheme 33

A related reaction was reported by Kibayashi *et al.* (*Scheme 34*).[49] Harsher reaction conditions were required, however, to allylate the lactams **146** with allyltrimethylsilane (**88**) and group IV metal tetrachlorides. The adducts **147** could be transformed into the alkaloid (±)-adalinine (**148**). With the chiral aminophenol **139e**, the allylated product **147e** was obtained with a d.r. of (6*R*/6*S*) = 16:1. The adducts **147** could be transformed into the alkaloid adalinine (**148**). The optical rotation of **148** prepared from **147e** was in agreement with that for the natural product, thus establishing its absolute configuration as (*R*).

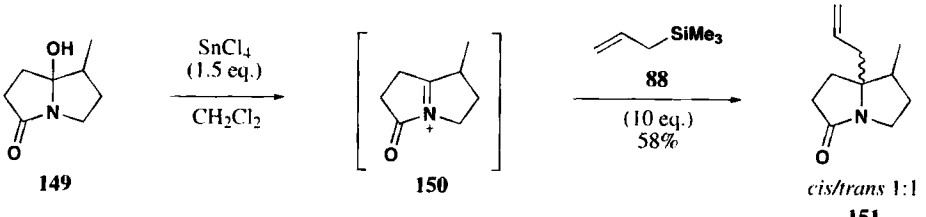


Scheme 34

The dissociation of the oxygen to form an iminium ion analogous to **141** is facilitated by the much higher acidity of phenols compared to alcohols. This might explain why the reaction with the corresponding lactams from 3-aminopropanol and 2-(aminomethyl)benzyl alcohol gave poorer yields.

In the reactions discussed so far the iminium species was generated from 1,3-oxazolidines and -oxazines. This can also be done from acyclic *N,O*-acetals by ionization of a hydroxy group (instead of alkoxy that is part of a ring), as shown in the following examples (*Schemes 35–37*).

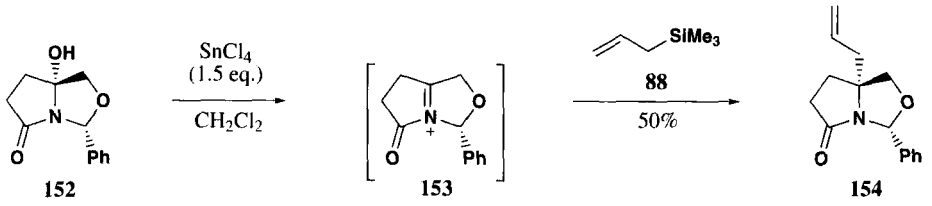
Rutjes, Hiemstra *et al.* could allylate the hydroxypyrrolidinone **149** with allyltrimethylsilane (**88**) in the presence of tin(IV)chloride (*Scheme 35*).[50] The bicycle **151** was obtained in 58% yield as a



Scheme 35

1:1 *cis/trans* mixture. Interestingly, six-membered ring homologs of **149** did not yield any allylation products. Under a variety of conditions only elimination of H_2O to form enamides was observed.

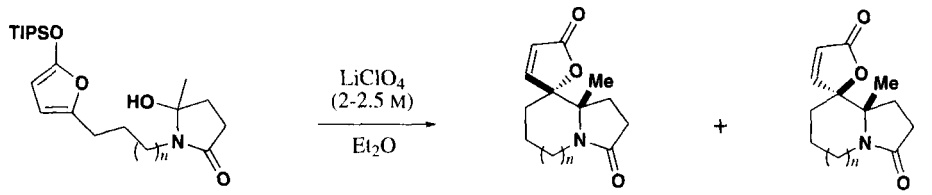
Langlois and Choudhury reported the allylation of the related hydroxypyrrolidinone **152** with the same reagents (*Scheme 36*).[51] The allylated product **154** (which might again serve as precursor for an *N*-acyliminium ion at the aminoacetal center) was isolated as single stereoisomer in 50% yield together with an undisclosed amount of starting material.



152 **153** **154**

Scheme 36

The intramolecular addition to *N*-acyliminium ions generated from the hydroxypyrrolidinones **155a,b** was reported by Martin and Bur (*Scheme 37*).[52] The only Lewis acids that effected ionization and cyclization were solutions of $LiClO_4$ (2–2.5 M) in ether. Under these conditions, **155a** gave a 20:1 mixture of the six-membered **156a** and **157a** in 58% yield, whereas yield and selectivity were lower (2:1, 32%) for the seven-membered **156b/157b**.



155a: $n = 1$ **156a+157a**: 58% **156a** 20:1 **157a**
155b: $n = 2$ **156b+157b**: 32% **156b** 2:1 **157b**

Scheme 37

II. ADDITION TO KETOXIME ETHERS

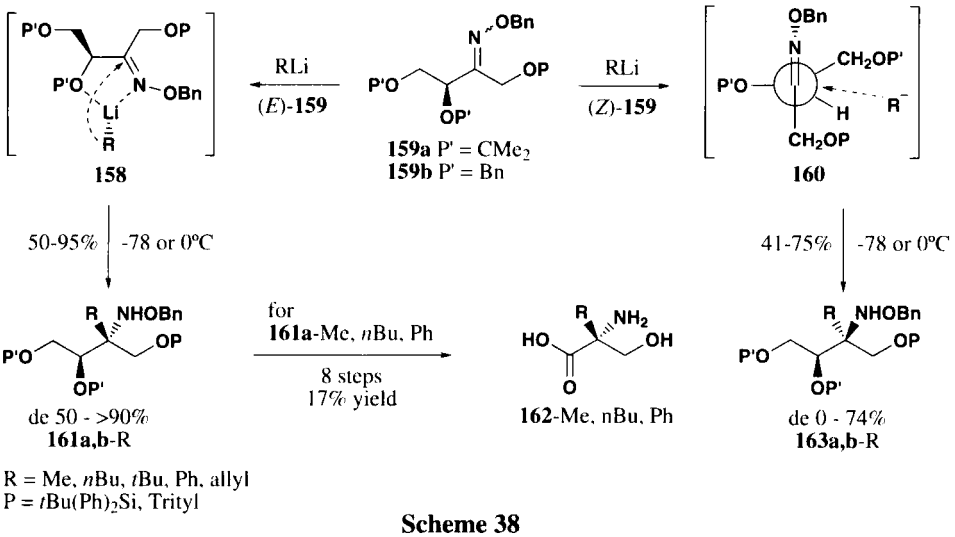
1. General

While ketoxime ethers are usually formed as mixtures of *E/Z* isomers, their separation by column chromatography is possible due to the high barrier to *E-Z* isomerization (>39 kcal·mol^{-1})[11] and their higher stability towards hydrolysis, as opposed to imines. With alkyl/aryl and especially with electron-withdrawing substituents on the oxime oxygen, the Beckmann rearrangement and aziridine formation (*via* a 2*H*-azirine intermediate) can occur as side reactions. The *O*-mesyl and *O*-tosyl derivatives of *sym*-trifluoromethyl-substituted benzophenone oximes, however, neither reacted with Grignard reagents by addition to the C=N bond nor underwent Beckmann rearrangement. Instead, the sulfonate was displaced to give *N*-alkyl/aryl imines, which were then hydrolyzed to yield primary amines.[53]

Radical additions to aldoxime ethers have been used in a number of total syntheses of natural products.[54] Hatem *et al.* reported the tin-mediated radical cyclization of a number of β-allenyl-benzoylketoximes.[55] The addition of alkyl radicals to phenylsulfonyl ketoxime benzyl ethers was reported by Kim and co-workers.[56] The initial addition products, however, lose the phenylsulfonyl group giving ketoxime benzyl ethers and therefore no amines are isolated.

2. Addition to Open-chain Oxime Ethers

Marco, Carda *et al.* reported the addition of organolithium reagents (Me, *n*Bu, *t*Bu, Ph, allyl) to erythrulose-derived oxime benzyl ethers **159** to afford α-substituted serines **162-R** (*Scheme 38*).[57] The oxime ethers were formed as 1:1 (*E*/*Z*) mixtures and then were separated by chromatography. High selectivity was observed with the (*E*) oxime ethers, the (*Z*) isomers gave the opposite stereoisomers (except with PhLi) with much lower selectivity and yield. Only the oxime ether (*E*)-**159a** gave adducts with *t*BuLi.

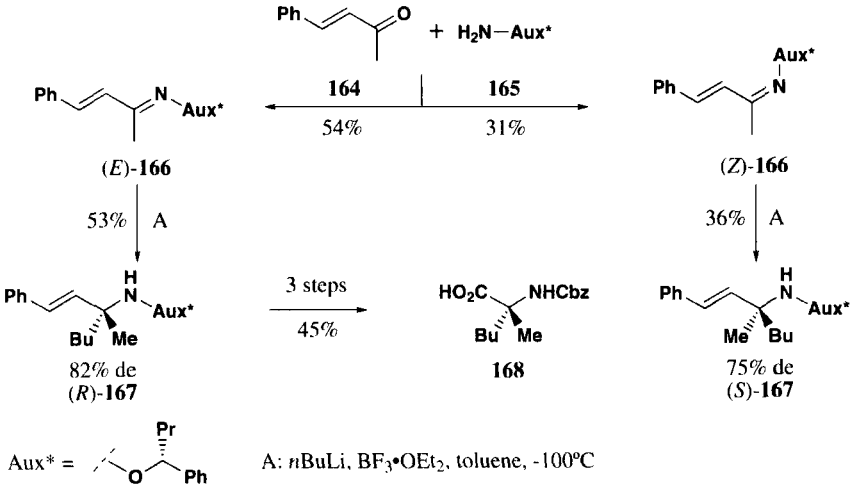


Scheme 38

The authors explained these observations by the formation of a five-membered chelate **158** involving the lithium, nitrogen and the C-3 oxygen in the (*E*) isomers, followed by an internal lithium-to-carbon 1,3-transfer within the chelate. Computational studies supported this mechanism. In the (*Z*) isomers, however, the C-1 oxygen is too hindered for coordination; therefore, they react through a non-cyclic Felkin-Anh transition state **160** that leads predominantly to the other diastereoisomer. The acetonides **161a-R** with R = Me, *n*Bu, Ph were transformed into the α-substituted serines **162-R** in 8 steps (17% yield).

Moody *et al.* reported the reaction of *n*BuLi with the (*R*)-*O*-(1-phenylbutyl)hydroxylamine oximes **166** of benzylidene acetone (*Scheme 39*).[58] The addition to the (*E*) and the (*Z*) isomer at −100° in toluene in the presence of BF_3·OEt_2 gave the diastereomers (*R*)- and (*S*)-**167** in 53 and 36% yield with 82 and 76% de, respectively. (*R*)-**167** was then converted to the amino acid **168** (45% yield over

3 steps). Addition of *n*BuLi and other organolithium reagents, except *t*BuLi, to aldoximes derived from this auxiliary occurred in considerably higher yields (76–95%) and better selectivities (90–93% de).



Scheme 39

3. Addition to Cyclic Oxime Ethers

No examples for additions to this substrate type have been reported (see IV.3.).

III. ADDITION TO KETOHYDRAZONES

1. General

The barrier to *E-Z* isomerization in *N*-alkyl/aryl hydrazones is around $\Delta G^{\neq} \approx 20$ kcal·mol^{-1} (similar to imines)[11] so that in most cases the isomers cannot be separated at ambient temperatures. As expected, the sterically less crowded isomer usually predominates.

Ketone arenesulfonylhydrazones generally afford alkenyllithiums on treatment with two or more equivalents of RLi (Shapiro reaction).[59] Only in a few cases was addition to the C=N double bond observed, also followed by loss of arenesulfinate and dinitrogen.

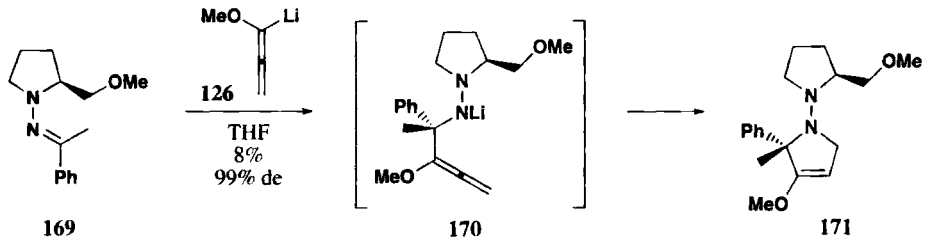
Kim and co-workers reported the addition of alkynylborane reagents to *N*-aziridinyl-ketimines[60] and anionic cyclizations of bis- and trisaziridinylimines triggered by addition of Grignard or organolithium reagents.[61] Because the initial addition products lose styrene and dinitrogen, and therefore no amines are isolated, we will not discuss them further.

2. Addition to Open-chain Hydrazones

a) With *N*-Alkyl or *N*-Aryl Substituents

J. Goré *et al.* reported the addition of lithiated methoxyallene (**126**) to the acetophenone SAMP hydrazone **169** in only 8% isolated yield (*Scheme 40*).[62] The primary addition product **170** was

not isolated; the reaction afforded directly the cyclized **171**, as opposed to Reissig's observation in additions of the same nucleophile to *N*-tosyl, *N*-aryl and *N*-alkyl imines (*Scheme 29*).[44] In comparison, additions to the SAMP hydrazones of aromatic aldehydes gave the pyrrolines corresponding to **171** in 76–88% yield.

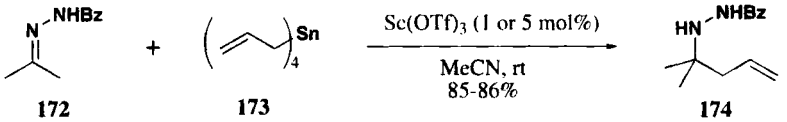


169 **170** **171**

Scheme 40

b) With Electron-withdrawing Group on Imino Nitrogen

The only example of this class is the $Sc(OTf)_3$-catalyzed allylation of acetone benzoylhydrazone **172** with tetraallyltin (**173**) to give **174** in 85–86% yield, reported by Kobayashi *et al.* (*Scheme 41*).[63] The additions to benzoylhydrazones from a variety of aliphatic and aromatic aldehydes under these conditions occurred in 81–98% yield.



172 **173** **174**

Scheme 41

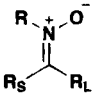
3. Addition to Cyclic Hydrazones

No examples for additions to this substrate type have been reported.

IV. ADDITION TO KETONITRONES

1. General

The isomer in which the nitrone oxygen and the larger substituent on carbon are *cis* to each other usually predominates (*Fig. 2*).[64]



175

R_L and O *cis*:
(*Z*) isomer if priorities are O > R and $R_L > R_S$

Fig. 2

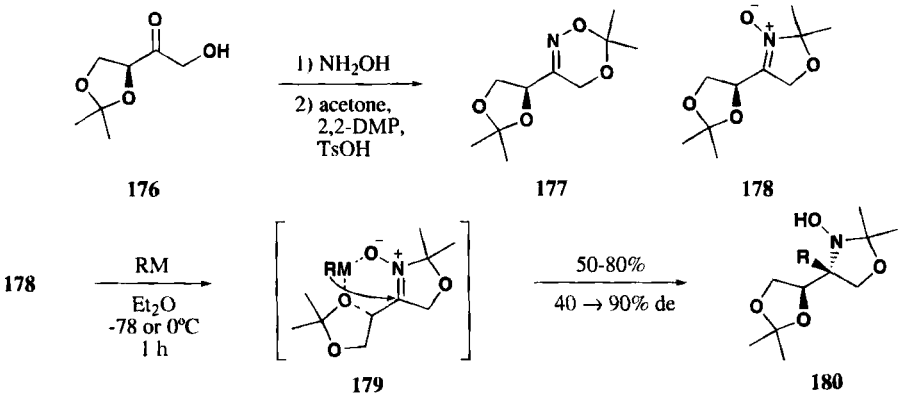
Murahashi *et al.* showed that generating *N*-acyloxyiminium species *in situ* from nitrones and acyl halides could increase the reactivity of nitrones towards soft nucleophiles such as enolates.[65] All of the reported examples, however, involve aldonitrones only.

2. Addition to Open-chain Ketonitrones

No examples for additions to this substrate type have been reported.

3. Addition to Cyclic Ketonitrones

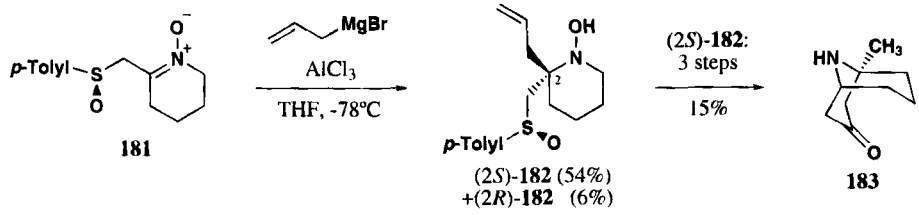
Marco, Carda *et al.* reported the addition of organolithium and Grignard reagents to the nitrone **178** (*Scheme 42*).[66] It was obtained together with the dioxazine **177** from erythrulose acetonide **176** by reaction with hydroxylamine, acetone, and 2,2-dimethoxypropane. Whereas **177** proved unreactive towards a number of organometallic reagents, **178** reacted with a variety of organolithium and Grignard reagents (alkynyl, aryl, alkenyl and alkyl, but not *tert*-butyl) to give the adducts **180** (major isomer shown) in 50–80% yields with 40–>90% de. The observed selectivity can be explained by chelation of the metal with the nitrone oxygen and the proximal oxygen of the acetonide **179**.



M = Li, Mg
R = alkyl, alkenyl, aryl, allyl, alkynyl

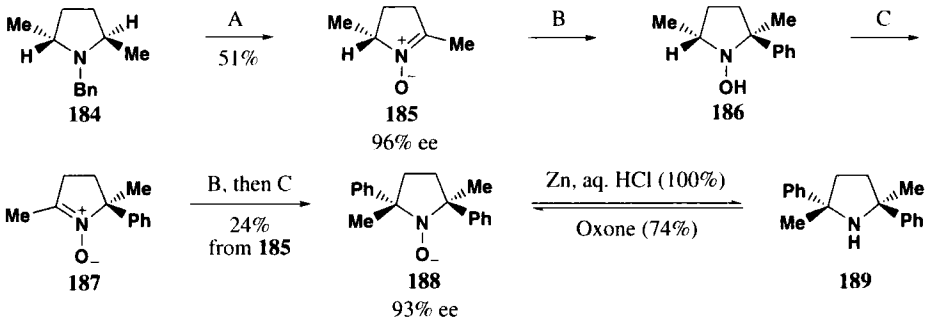
Scheme 42

Murahashi *et al.* reported that the addition of allylmagnesium bromide to the β-sulfinyl ketonitrone **181** in the presence of $AlCl_3$ afforded a mixture of (2*S*)- and (2*R*)-**182** in 54% and 6% yield, respectively (*Scheme 43*).[67] The (2*S*) diastereomer was transformed to the homotropane alkaloid (+)-euphococcinine (**183**).



Scheme 43

Einhorn *et al.* prepared the C_2-symmetric nitroxide **188** and the corresponding amine **189** by two successive oxidation-nucleophilic addition sequences (*Scheme 44*).[68] Each stereocenter of the pyrrolidine **184** was alternately destroyed upon oxidation to a nitrone. The remaining stereocenter then directed the addition of phenylmagnesium bromide to this nitrone to the less hindered face with high selectivity (93% ee for **188** starting from **184** with 96% ee). however, the ee was much lower with other Grignard reagents (4-*t*Bu-PhMgBr, 79% ee; BnMgBr, 7% ee).



A: H_2, $Pd(OH)_2/C$; then CH_3ReO_3, urea•H_2O_2, rt
B: PhMgBr, THF, -78°C to rt
C: $Cu(OAc)_2$, aq. NH_3, O_2, rt

Scheme 44

V. CONCLUSION

The carbon-carbon bond formation by nucleophilic 1,2-addition to ketone-derived imino compounds has emerged in recent years as a viable synthetic route to amines. Impressive progress has been made, and methods are now available to create nitrogen-substituted quaternary carbon stereocenters with high stereoselectivity, using internal chirality of the substrates. No longer are these reactions restricted to non-enolizable imino compounds or allylic nucleophiles. Additions to ketimines seem to be more promising in terms of yield, stereoselectivity and generality, compared to ketoxime ethers, ketohydrazones, and ketonitrones. Applications to the syntheses of natural products and biologically active compounds have begun to appear. Nevertheless, much remains to be done to achieve the same level of sophistication as for additions to ketones. For example, the asymmetric synthesis of nitrogen-substituted quaternary carbon stereocenters using chiral catalysts still remains to be developed.[69]

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