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Intermolecular addition reactions of N-acyliminium ions (Part II)

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Abstract

This review highlights the advances in the literature up to July 2008 on the intermolecular reactions of acyclic and cyclic N-acyliminium ions. This is an update of an earlier review in 2000 oil this topic and does not include intramolecular addition reactions to N-acyliminium ions which was recently reviewed. This review is presented in two parts, with the first part having dealt with acyclic and pyrrolidinone-based N-acyliminium ions. Part II continues with other five-membered heterocyclic derivatives and higher systems.

Keywords

intermolecular, acyliminium, ii, ions, reactions, part, addition, n, CMMB

Disciplines

Life Sciences | Physical Sciences and Mathematics | Social and Behavioral Sciences

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Intermolecular Addition Reactions of *N*-Acyliminium Ions (Part II)[1]

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Abstract: This review highlights the advances in the literature up to July 2008 on the intermolecular reactions of acyclic and cyclic *N*-acyliminium ions. This is an update of an earlier review in 2000 on this topic and does not include intramolecular addition reactions to *N*-acyliminium ions which was recently reviewed. This review is presented in two parts, with the first part having dealt with acyclic and pyrrolidinone-based *N*-acyliminium ions. Part II continues with other five-membered heterocyclic derivatives and higher systems.

Part I

Part II

Key words: *N*-acyliminium ion, nucleophilic addition, cycloaddition, aromatic electrophilic substitution, radical addition, peptides, pyrrolidines, piperidines

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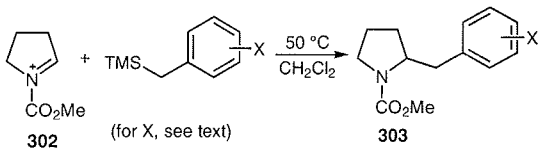
3.2.2 Reactions of *N*-Acylpyrrolidine-Based *N*-Acyliminium Ions with Nucleophiles

3.2.2.1 Silicon-Based Nucleophiles

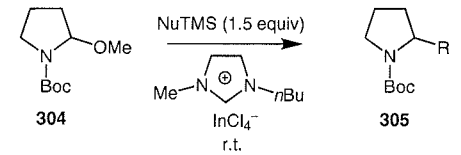
Treatment of the *N*-acyliminium ion **302** with benzyltrimethylsilanes afforded 2-benzylated pyrrolidines **303**. 4-Fluorobenzyl-, benzyl-, and 2-methylbenzyltrimethylsilane did not react with the *N*-acyliminium ion. Reactions of 3,5-dimethylbenzyl-, 4-methylbenzyl-, 2,4,6-trimethylbenzyl-, 4-methoxybenzyl-, and 2,3,4,5,6-pentamethylbenzyltrimethylsilanes gave the corresponding products in 12–88% yields. Use of 4-methylbenzylstannanes (0.1 equiv), as an additive in the reactions of 4-fluorobenzyltrimethylsilane and 4-methylbenzyltrimethylsilane, resulted in 50% and 97% yields of **303**, respectively (Scheme 117).[50]

The reaction of *N*-Boc-2-methoxypyrrolidine (**304**) with silicon nucleophiles in an ionic liquid, BMI·$InCl_4$, led to the formation of 2-substituted pyrrolidines **305** in yields of 76–80% (Scheme 118).[81]

Treatment of pyrrolidinone **304** with similar silicon nucleophiles in the presence of indium(III) chloride under solvent-free conditions afforded the corresponding prod-

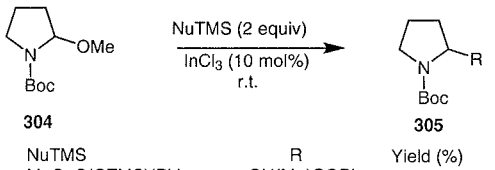


Scheme 117



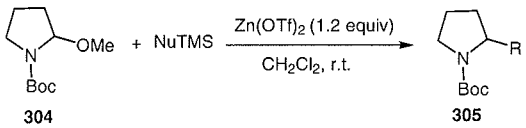
NuTMS	R	Yield (%)
CH_2=$CHCH_2TMS$	-CH_2CH=CH_2	80
CH_2=C(OTMS)(Ph)	-CH_2COPh	77
MeCH=C(OTMS)(Ph)	-CH(Me)COPh	76
Me_2C=C(OTMS)(OMe)	-$C(Me)_2CO_2Me$	77

Scheme 118



NuTMS	R	Yield (%)
MeC=C(OTMS)(Ph)	-CH(Me)COPh	97
$(Me)_2C$=C(OTMS)(OMe)	-$C(Me)_2CO_2Me$	100
BuCH=C(OTMS)(Bu)	-C(Bu)COBu	93
CH_2=C(OTMS)(Ph)	-CH_2COPh	92

Scheme 119



NuTMS	R	Yield (%)
CH_2=$CHCH_2TMS$,	-CH_2CH=CH_2	68
CH_2=C(OTMS)(Ph),	-CH_2COPh	71
MeCH=C(OTMS)(Ph)	-CH(Me)COPh	80 dr = 80:20

Scheme 120

ucts **305** in 92–100% yields (Scheme 119).[82a] The use of indium(IV) chloride in sodium dodecylsulfate and water has also been described for these reactions.[82b]

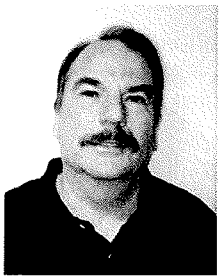
In a similar study, pyrrolidine **304** reacted with silicon nucleophiles under catalysis by zinc triflate to afford the desired adducts **305** in 68–80% yields (Scheme 120).[52]

The reactions of silicon nucleophiles with pyrrolidine **304** in the presence of bis(trifluoromethane)sulfonimide or triisopropylsilyl triflate under solvent-free conditions afforded the corresponding adducts **305** in good to excellent yields (Scheme 121). It was found that 0.3 mol% of bis(trifluoromethane)sulfonimide catalysed the reaction of allyltrimethylsilane, while the silyl enol ether of acetophenone required 1.0 mol% of catalyst. The trimethylsilyl enol ether of cyclohexanone and the triisopropylsilyl ether of methyl isobutyrate and trimethylsiloxyfuran required 5 mol% of bis(trifluoromethane)sulfonimide. The use of 1 mol% of triisopropylsilyl triflate as a Lewis acid in these reactions gave the desired adducts in the same or similar yields.[63]

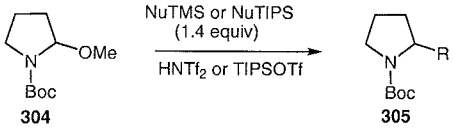
Chiral 2-methoxypyrrolidines **306a,b** underwent addition reactions with 2-*tert*-butyldimethylsilyloxyfuran in the presence of a catalytic amount of titanium(IV) chloride or trimethylsilyl triflate in dichloromethane at –78 °C to form only two out of four possible diastereomeric prod-

Biographical Sketches

Arife Yazici obtained her MSc degree in chemistry at Hacettepe University-Ankara (Turkey) in 2005. She is currently doing her PhD studies with Professor Stephen Pyne at the University of Wollongong. Her area of study is the total synthesis of Stemona alkaloids.



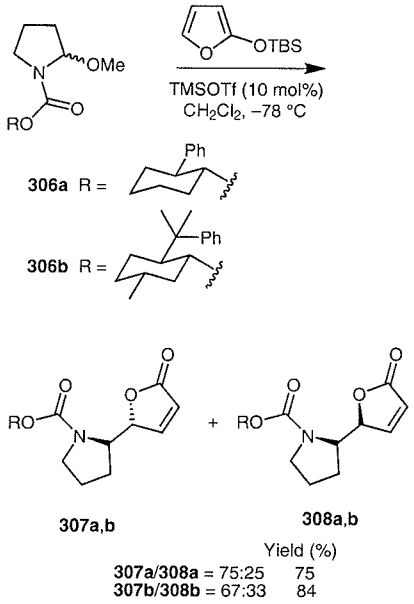
Stephen G. Pyne is a Professor of Chemistry at the University of Wollongong (UOW) and Chair of the Division of Organic Chemistry of the Royal Australian Chemical Institute. He obtained his BSc (Hons) degree at the University of Adelaide with Dr. Ralf Massey-Westrop and his PhD degree with Professor Lew Mander (Australian National University) in 1979. After post-doctoral positions with Professor Phil Fuchs (Purdue) and Professor E. J. Corey (Harvard), he was appointed a lecturer at UOW in 1985. His research interests include the total synthesis of bioactive alkaloids, natural products chemistry, drug design and synthesis, and fullerene chemistry.



NuTMS	R
CH_2=$CHCH_2TMS$	-CH_2CH=CH_2
CH_2=C(Ph)(OTMS)	-CH_2COPh
c-C_6H_9OTMS	-2-cyclohexanonyl
$(Me)_2C$=C(OMe)(OTMS)	-$C(Me)_2CO_2Me$
CH_2=$C(CO_2Me)$(OTIPS)	-$CH_2CO(CO_2Me)$

Scheme 121

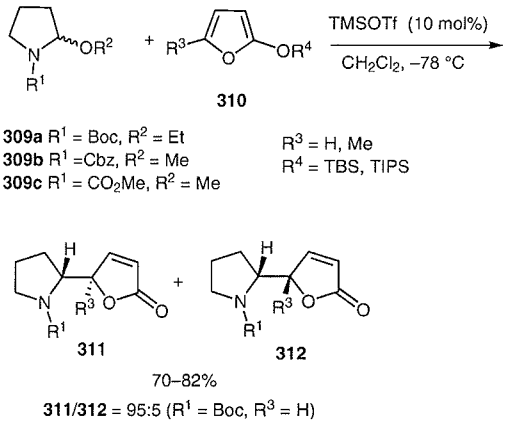
ucts, **307a,b** and **308a,b** (Scheme 122). The reactions of **306a** and **306b** with the silyloxyfuran in the presence of titanium(IV) chloride gave products in 60% and 55% yields, respectively. The use of trimethylsilyl triflate as a catalyst increased the yields to 84% and 75%, respectively. The diastereomeric ratios for **307a/308a** and **307b/308b** were found to be 75:25 and 67:33 after hydrogenation, and the stereochemistry of the major products **307** was determined as 2′*R*,5*R* by X-ray diffraction analysis.[83]



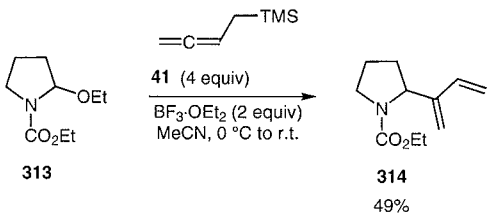
Scheme 122

Silyloxyfurans **310** reacted with 2-alkoxypyrrolidines **309** upon exposure to trimethylsilyl triflate. The *N*-Boc-protected pyrrolidine derivative **309a** gave the best yield of 82% and the highest diastereomeric ratio of 95:5 when R^3 = H (Scheme 123).[84]

The reaction of allenyltrimethylsilane with the 2-ethoxypyrrolidine **313** in the presence of boron trifluoride–diethyl ether complex provided the 2-substituted pyrrolidine **314** in 49% yield (Scheme 124). Treatment of *N*-tosyl-2-hydroxypyrrolidine under the same reaction conditions afforded the *N*-tosyl analogue of piperidine **314** in 74% yield.[30a]

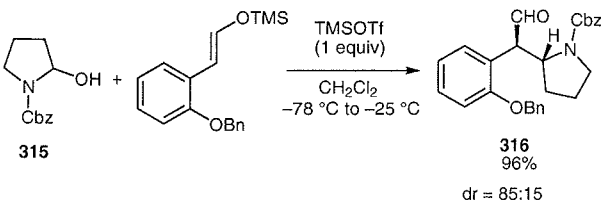


Scheme 123



Scheme 124

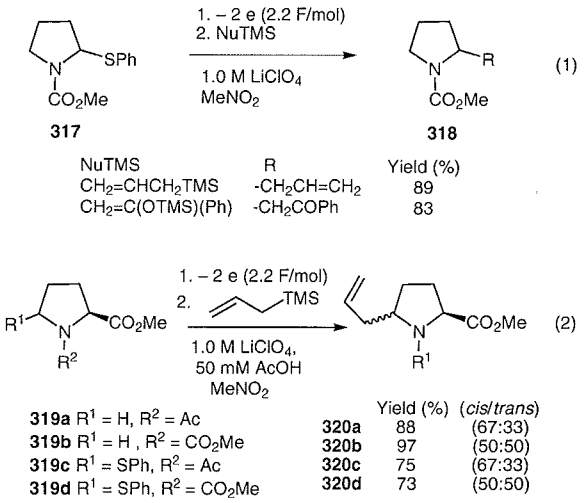
N-Carbobenzyloxy-2-hydroxypyrrolidine (**315**) reacted with a silyl enol ether in the presence of trimethylsilyl triflate (1.0 equiv) in dichloromethane to afford the 2-substituted pyrrolidine **316** in 96% yield (Scheme 125).[85]



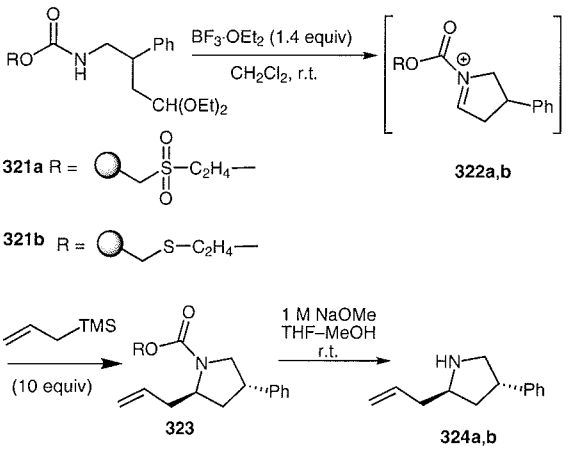
Scheme 125

The *N*-acyliminium ion which was generated by anodic oxidation of **317** was treated with silicon nucleophiles and afforded the corresponding alkylated products **318** (Scheme 126, equation 1). Similarly, the reactions of allyltrimethylsilane with the in situ generated *N*-acyliminium ion of amides and carbamates **319** under the same reaction conditions gave products **320** in 73–97% yields (Scheme 126, equation 2).[49]

Treatment of the immobilised amines **321a,b** with boron trifluoride–diethyl ether complex led to the formation of *N*-acyliminium ions **322a,b** which were trapped with allyltrimethylsilane to give the desired adducts **323** (Scheme 127). Cleavage of the adduct from the resin with 1 M sodium methoxide in tetrahydrofuran–methanol gave the *trans*-2,4-disubstituted pyrrolidines **324a,b** in 81% and 52% yields, respectively.[5]



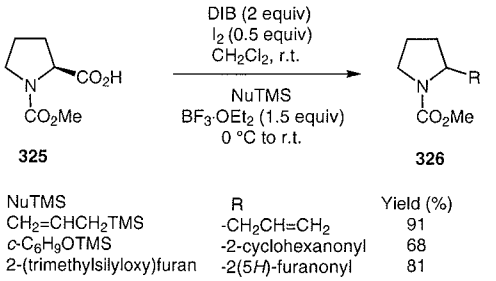
Scheme 126



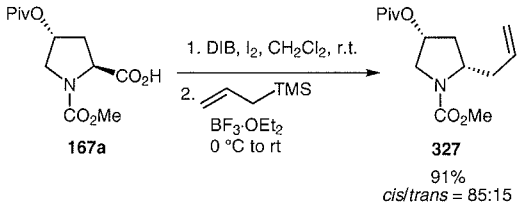
Scheme 127

Decarboxylation and oxidation of the proline derivative **325** with (diacetoxyiodo)benzene and iodine gave the corresponding *N*-acyliminium ion. The reaction of allyltrimethylsilane with the the latter under boron trifluoride–diethyl ether complex catalysis gave the 2-allylated product **326** in 91% yield (Scheme 128). The reaction did not take place in the absence of the Lewis acid: only the corresponding 2-hydroxypyrrolidine was isolated. Treatment of **325** with (trimethylsilyloxy)cyclohexene and trimethylsilyloxyfuran under the same reaction conditions gave addition products in 68% and 81% yields, respectively.[46] In a similar study, treatment of **325** with isopropenyl acetate (5.0 equiv) in the presence of boron trifluoride–diethyl ether complex afforded the expected product in 58% yield.[47]

When the one-pot decarboxylation–oxidation–alkylation methodology was applied to the 4-trimethylacetyloxy-L-proline derivative **167a**, the desired allylated product **327** was isolated in 91% yield with a *cis*/*trans* ratio of 85:15 (Scheme 129).[46,47]

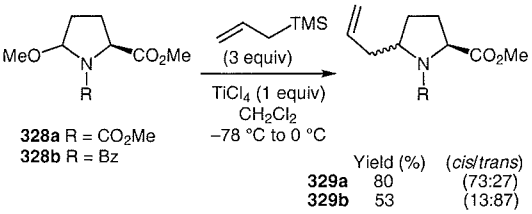


Scheme 128



Scheme 129

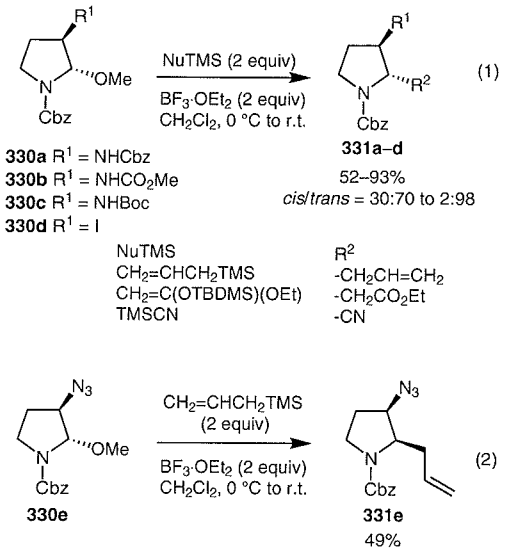
The reaction of the *N*-acylprolines **328a** and **328b** with allyltrimethylsilane in the presence of titanium(IV) chloride yielded the allylated products **329a** and **329b** in 80% and 53% yields, respectively (Scheme 130).[86]



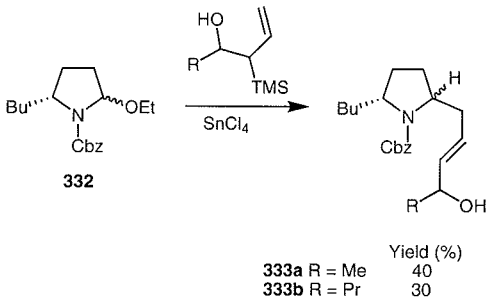
Scheme 130

The 3-substituted *N*-Cbz pyrrolidines **330a–e** reacted with allyltrimethylsilane, cyanotrimethylsilane, and *tert*-butyl[(1-ethoxyvinyl)oxy]dimethylsilane in the presence of boron trifluoride–diethyl ether complex to give products **331a–e**. 3-Carbamoyl-2-methoxypyrrolidines **330a–c** and 3-iodo-2-methoxypyrrolidine **330d** gave the adducts in moderate to excellent yields and with 2,3-*trans* selectivity (Scheme 131, equation 1), while 3-azido-2-methoxypyrrolidine **330e** gave the adduct **331e** in 49% yield and with high 2,3-*cis* selectivity (88:12) (Scheme 131, equation 2). The 2,3-*trans* selectivity in the reactions of **330a–d** was suggested to arise from neighbouring-group participation of the R^1 group (R^1 = $NHCO_2R$ or I).[87,88]

The reaction of 2-ethoxy-4-butylpyrrolidine **332** with allylsilanes afforded the corresponding adducts **333** in 30–40% yields as isomeric mixtures (Scheme 132). The diastereomeric ratios were not determined. However, when R = Me, the mixture was converted into a 80:20 mixture of indolizidines, with the major isomer having arisen from the initial 2,5-*trans* adduct.[89]

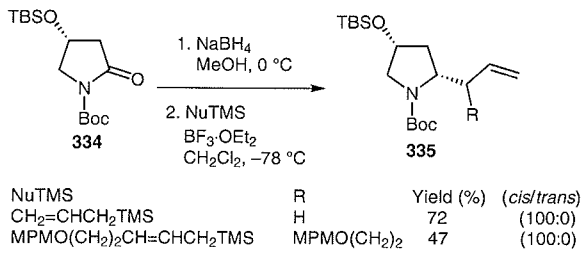


Scheme 131



Scheme 132

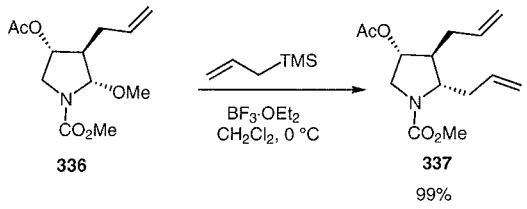
The reaction of pyrrolidine **334** with silicon nucleophiles in the presence of boron trifluoride–diethyl ether complex provided the desired adduct **335** with complete 2,4-*cis* selectivity (Scheme 133).[76]



Scheme 133

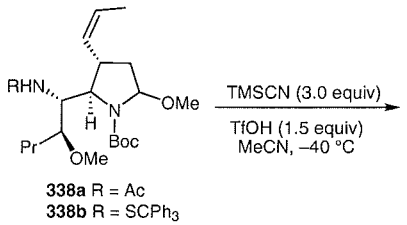
Treatment of pyrrolidine **336** with allyltrimethylsilane in the presence of boron trifluoride–diethyl ether complex provided the 2,3-*trans* product **337** in 99% yield (Scheme 134).[90]

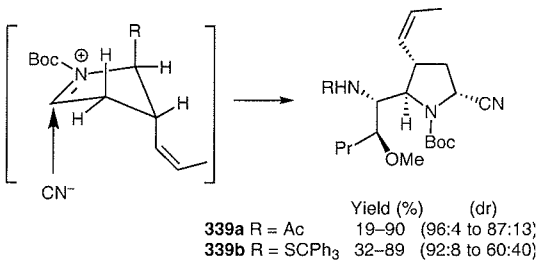
The cyano group was introduced into the *N*-Boc pyrrolidines **338a,b** stereoselectively (Scheme 135). The reaction of **338a** with trimethylsilyl cyanide (3.0 equiv) in the



Scheme 134

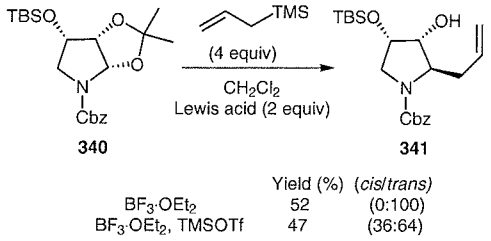
presence of trifluoromethanesulfonic acid (1.5 equiv) in acetonitrile at –40 °C resulted in the best yield (90%) and diastereomeric ratio (96:4). The use of tetrahydrofuran, toluene and dichloromethane as solvents in this reaction gave the product **339a** in poor to good yields (19–60%) with reduced diastereoselectivities (dr = 87:13 to 90:10). Using trimethylsilyl triflate as catalyst gave product **339a** in 67% yield with a diastereomeric ratio of 93:7. The reaction of **338b** with trimethylsilyl cyanide in the presence of boron trifluoride–diethyl ether complex (1.5 equiv) in dichloromethane afforded product **339b** in the highest yield (89%) and diastereomeric ratio of 92:8. The use of tin(IV) chloride and trimethylsilyl triflate as Lewis acids in toluene provided product **339b** in 32% and 68% yields and with diastereomeric ratios of 66:33 and 75:25, respectively. The high diastereoselectivity was suggested to be the result of attack of the nucleophile from the face *anti* to the C-5 substituent. This substituent was proposed to adopt a pseudo-axial orientation to minimise $A^{1,2}$ strain with the *N*-Boc group.[91]





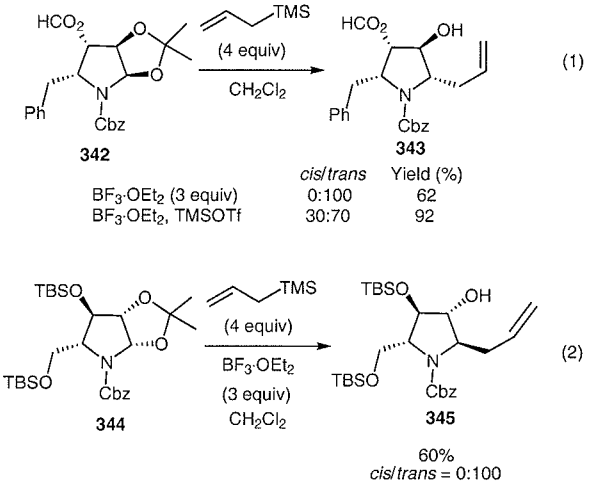
Scheme 135

The 2,3-*O*-isopropylidene-protected pyrrolidine **340** reacted with allyltrimethylsilane in the presence of boron trifluoride–diethyl ether complex to give the 2-allylated pyrrolidine **341** in 52% yield and with complete 2,3-*trans* selectivity (*trans*/*cis* = 100:0) (Scheme 136). Magnesium bromide, tin(IV) chloride, dichlorodiisopropoxytitanium(IV), and ytterbium(III) triflate were found to be ineffective in this reaction.[92]



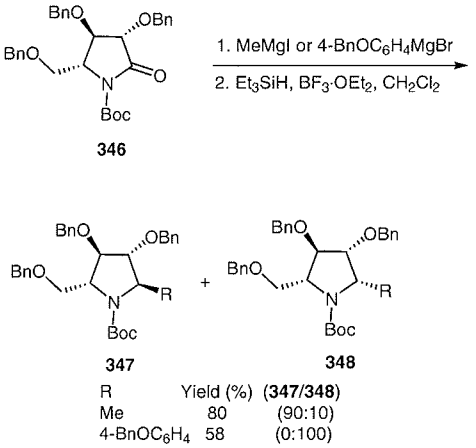
Scheme 136

The 5-substituted 2,3-*O*-isopropylidene-protected pyrrolidines **342** and **344** gave allylated products **343** and **345**, respectively, with exclusive 2,3-*trans* selectivity and good yields, when they were treated with allyltrimethylsilane in the presence of boron trifluoride–diethyl ether complex (Scheme 137). The allyltrimethylsilane attacked from the *exo* face of the bicyclic aminal, independent of the C-4 and C-5 substituents and their configurations. The lower diastereoselectivities observed when the stronger Lewis acid mixture of boron trifluoride–diethyl ether complex and trimethylsilyl triflate was employed was thought to be due to initial cleavage of the bicyclic aminal prior to nucleophilic attack.[92]



Scheme 137

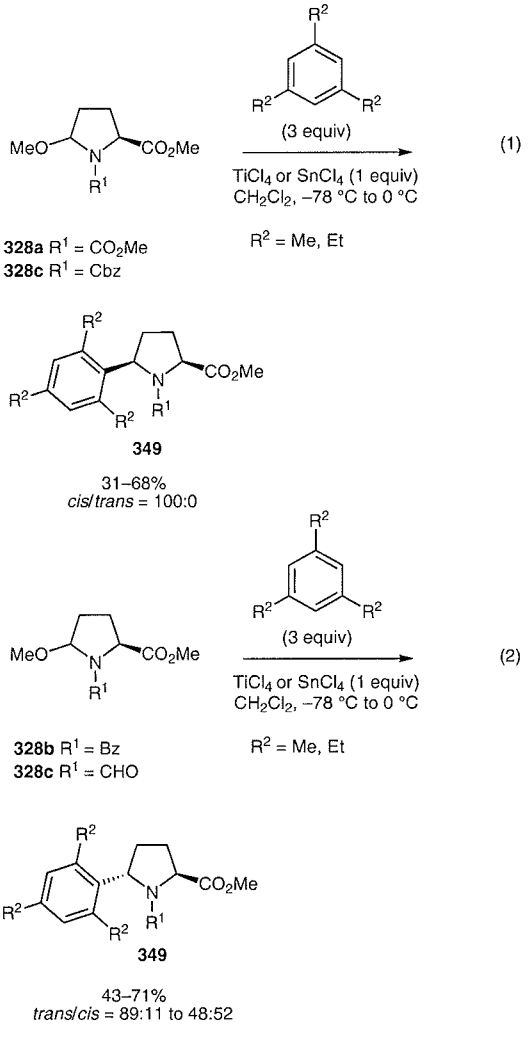
Treatment of pyrrolidinone **346** with Grignard reagents and then triethylsilane in the presence of boron trifluoride–diethyl ether complex afforded adducts **347** and **348**. This reaction sequence using methylmagnesium iodide gave adduct **347** in 80% yield and with high 3,5-*cis* selectivity, while that using of 4-benzyloxyphenylmagnesium bromide provided only the 3,5-*trans* adduct **348** in 58% yield (Scheme 138).[72]



Scheme 138

3.2.2.2 Aromatic Nucleophiles

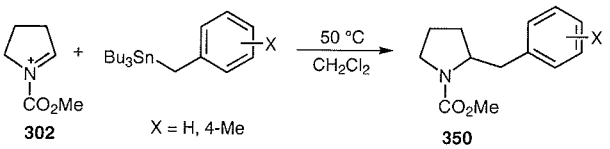
Treatment of benzene derivatives with the proline derivatives **328a–d** in the presence of titanium(IV) chloride or tin(IV) chloride gave the arylated adducts **349** in 31–71% yields. The prolines **328a,c** ($R^1 = CO_2Me$ or Cbz) gave exclusively the 2,5-*cis* products (Scheme 139, equation 1), whereas the prolines **328b,d** (R^1 = CHO or Bz) yielded the arylated adducts **349** as a mixture of isomers favouring the *trans* isomer (Scheme 139, equation 2).[86]



Scheme 139

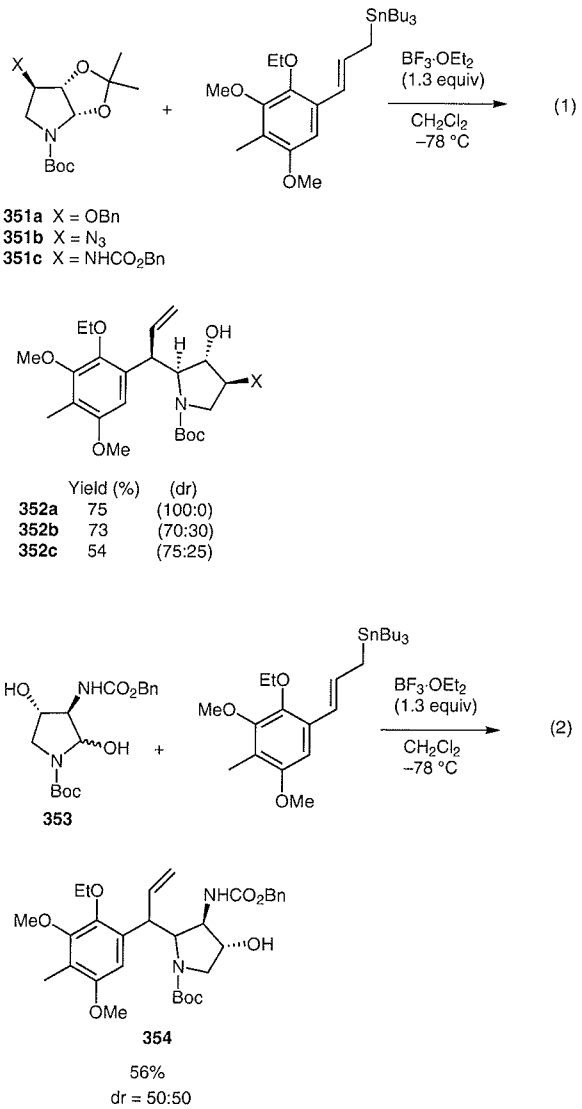
3.2.2.3 Organostannanes

Treatment of benzyltributylstannane and 4-methylbenzyltributylstannane with the *N*-acyliminium ion **302** provided the 2-benzylated pyrrolidines **350** in 51% and 71% yields, respectively (Scheme 140).[50]



Scheme 140

A cinnamylstannane reacted with pyrrolidines **351a–c** in the presence of boron trifluoride–diethyl ether complex to give adducts **352a–c**. While pyrrolidine **351a** gave the product **352a** in 75% yield and as a single diastereomer, **351b** and **351c** gave the products **352b** and **352c** in yields of 73% and 54%, and with a diastereomeric ratio of 70:30 and 75:25, respectively (Scheme 141, equation 1). When pyrrolidine **353** was treated under the same reaction conditions, the addition product **354** was obtained in 56% yield as a 50:50 mixture of diastereomers (Scheme 141, equation 2). In contrast to the reactions reported in Schemes 136 and 137, a ring-opened monocyclic iminium ion intermediate was proposed for the reactions of **351a–c**.[93]



Scheme 141

3.2.2.4 Organometallic Reagents

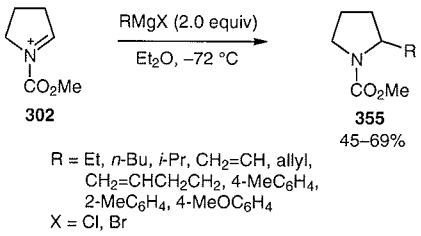
The *N*-acyliminium ion **302** underwent reactions with Grignard reagents to afford 2-substituted pyrrolidines **355** in moderate to good yields. The reaction took place with alkyl-, alkenyl-, alkynyl- and arylmagnesium halides (Scheme 142).[38]

Treatment of organozinc and organoaluminium reagents with the *N*-acyliminium ion **302** provided 2-ethylpyrrolidine **356** in 55–74% yields (Scheme 143). The use of diethylzinc, ethylzinc iodide, triethylaluminium and diethylaluminium chloride gave the ethylated product in 74%, 65%, 72%, and 55% yields, respectively.[38]

The reactions of zinc alkynylides, prepared in situ, with 2-methoxypyrrolidine **304** in the presence of zinc triflate afforded the corresponding 2-substituted products **357** (Scheme 144).[52]

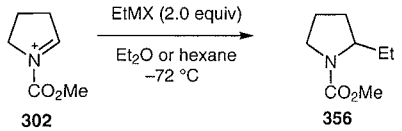
Alkynes reacted with 2-methoxypyrrolidines **309b,c** in the presence of copper(I) bromide in water at 40–50 °C under sonication conditions to afford 2-substituted pyrrolidines **358** (Scheme 145).[94]

As an extension of an earlier study,[95a] the reaction of the racemic 2,3-dihydroxypyrrolidine **359** with an alkenylboronate led to the 2,3-*cis* product **360** in 99% yield and with high 2,3-*cis* selectivity (*cis*/*trans* = 98:2) (Scheme 146).[95b]



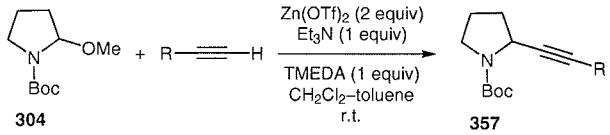
Scheme 142

Organocopper reagents were treated with 3-substituted 2-methoxypyrrolidines **361** in the presence of boron trifluoride–diethyl ether complex to afford adducts **362** in 50–97% yields after Boc deprotection. These reactions showed 2,3-*trans* selectivity (*trans*/*cis* = 60:40 to 91:9) (Scheme 147). The *trans* selectivity increased with the use of bulky organocopper reagents.[96]



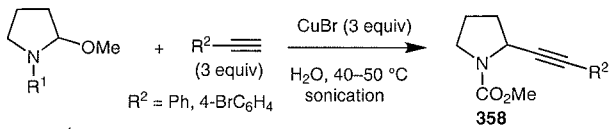
EtMX	Yield (%)
Et_2Zn	74
EtZnI	65
Et_3Al	72
Et_2AlCl	55

Scheme 143



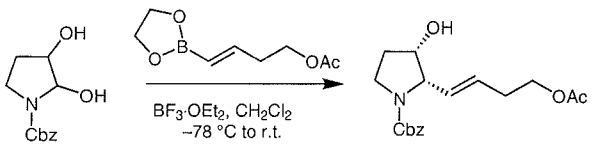
R = Ph 48%
R = TMS 59%

Scheme 144



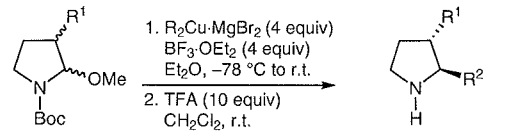
58–81%

Scheme 145



98%
cis/*trans* = 98:2

Scheme 146



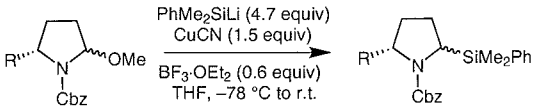
R1 = Me, Ph

R2 = *i*-Bu, Ph, 3-MeC_6H_4, 3-FC_6H_4

50–97%
trans/*cis* = 60:40 to 91:9

Scheme 147

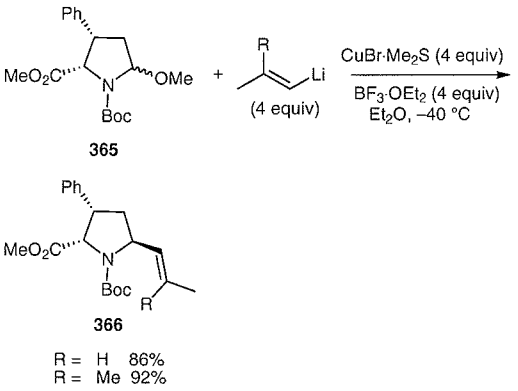
The silylcuprate reagent $PhMe_2SiLi$/CuCN underwent reaction with the 5-substituted 2-methoxypyrrolidine **363a** and 2-phenylsulfonylpyrrolidine **363b** in the presence of boron trifluoride–diethyl ether complex. 2-Methoxypyrrolidine **363a** gave the desired 2,5-disubstituted adduct **364a** in 8% yield, while the 2-phenylsulfonylpyrrolidine **363b** gave adduct **364b** in 71% yield (Scheme 148). The reaction took place between 2-phenylsulfonylpyrrolidine and the silylcuprate reagent even in the absence of the Lewis acid. It was postulated that either the copper behaves as a Lewis acid to generate the *N*-acyliminium ion, or the reaction follows an S_N2 mechanism.[24]



364a 8%
364b 71%
364c 61%

Scheme 148

The 3,5-disubstituted *N*-Boc proline **365** reacted with 2-methylpropenyllithium and *trans*-1-lithiopropene in the presence of copper bromide–dimethylsulfide complex and boron trifluoride–diethyl ether complex to give the 2,5-*trans* products **366** (Scheme 149).[97]



R = H 86%
R = Me 92%

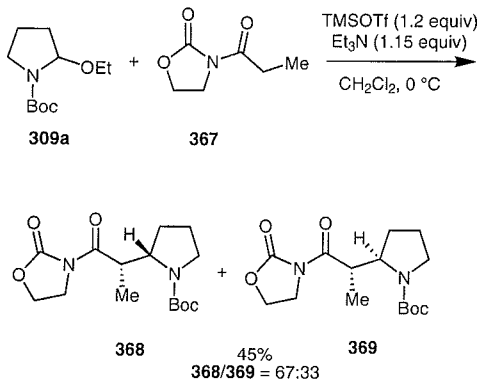
Scheme 149

3.2.2.5 Carbonyl Compounds

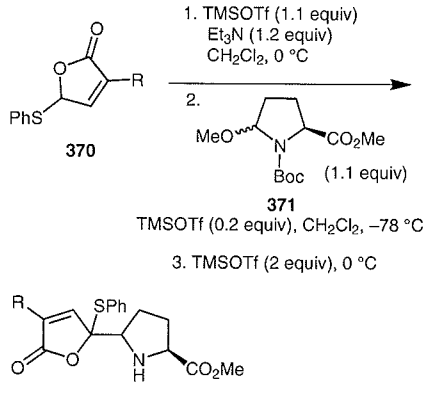
The reaction of *N*-Boc-2-ethoxypyrrolidine **309a** with the *N*,*O*-silylketene acetal, itself prepared in situ by treatment of *N*-propionyloxazolidin-2-one **367** with trimethylsilyl triflate and triethylamine, provided a 67:33 mixture of the 2-substituted pyrrolidines **368** and **369** in 45% yield (Scheme 150).[98]

The 5-methoxyproline derivative **371** reacted with trimethylsilyloxyfuran compounds, themselves generated in situ by treatment of butenolides **370** with trimethylsilyl triflate under basic conditions, in the presence of trimethylsilyl triflate at –78 °C to give a mixture of diastereomeric adducts. Addition of an excess amount of trimethylsilyl triflate to these adducts afforded deprotected pyrrolidines **372** as a mixture of four diastereomers (Scheme 151).[99]

The titanium enolates of *N*-acyloxazolidinones **373a–d** reacted with *N*-*tert*-butyloxycarbonyl-2-ethoxypyrrolidine (**309a**) to afford the corresponding 2-substituted pyrrolidines **374a–d** and **375a–d**. Treatment of pyrrolidine **309a** with **373a** and **373b** in the presence of titanium(IV)

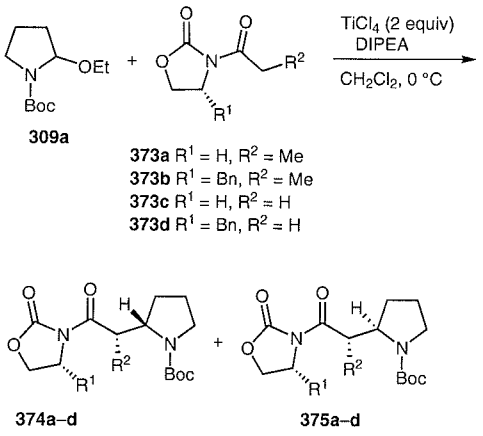


Scheme 150



	Yield (%)	dr
R = -$C_2H_4CO_2Bn$	91	46:43:6:5
R = -$C_2H_4CO_2Me$	73	53:41:4:2

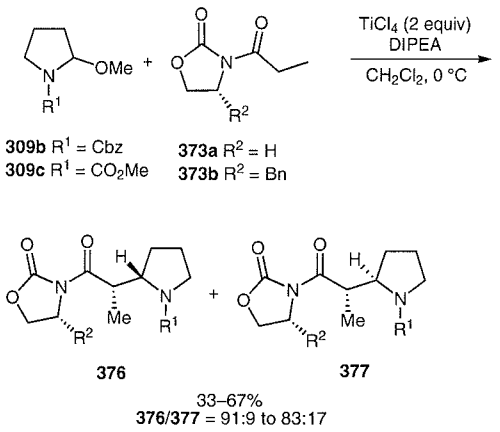
Scheme 151



Scheme 152

chloride gave the desired products with **374/375** ratios of 93:7 and 90:10 and in 72% and 85% yields, respectively; while treatment of **309a** with **373c** afforded only product **374c** in 46% yield. The reaction of pyrrolidine **309a** with **373d** gave the desired product in 70% yield with no selectivity (**374d/375d** = 50:50) (Scheme 152).[98]

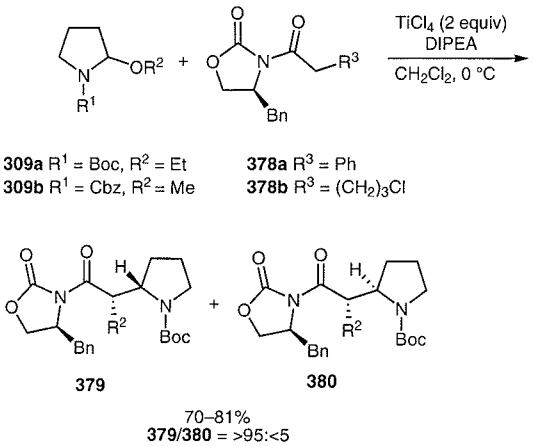
The reaction of 2-alkoxypyrrolidine **309b** with *N*-acyloxazolidinones **373a** and **373b** in the presence of titanium(IV) chloride provided the corresponding products in 67% and 57% yields, and with product ratios (**376/377**) of 91:9 and 83:17, respectively. Treatment of **309c** with **373a** and **373b** under the same reaction conditions resulted in 33% and 50% yields, respectively and with product ratios (**376/377**) of 91:9 and 86:14, respectively (Scheme 153).[98]



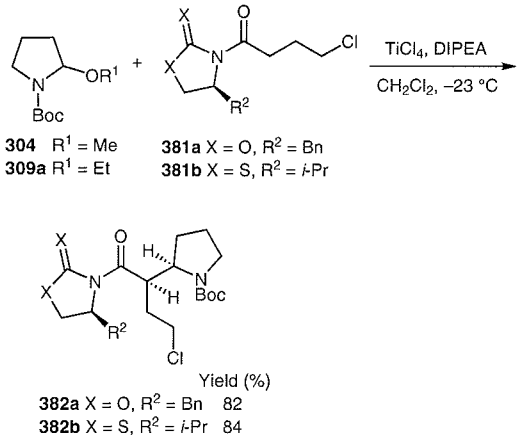
Scheme 153

The titanium enolates of **378a** and **378b** reacted with 2-alkoxypyrrolidines **309a** and **309b** to afford the *N*-Boc- and *N*-Cbz-2-substituted pyrrolidines **379** and **380**. The reactions of **309a** with **378a** and **378b** in the presence of titanium(IV) chloride and diisopropylethylamine gave products **379** and **380** with high selectivity >95:<5 in yields of 70% and 81%, respectively. Treatment of **309b** with **378b** under the same experimental conditions afforded **379** and **380** in 73% yield, with the same selectivity (Scheme 154).[98]

The 2-alkoxypyrrolidines **304** and **309a**, when treated with the titanium enolate of *N*-acyloxazolidinone **381a** (X = O) or its thio analogue **381b** (X = S), respectively,



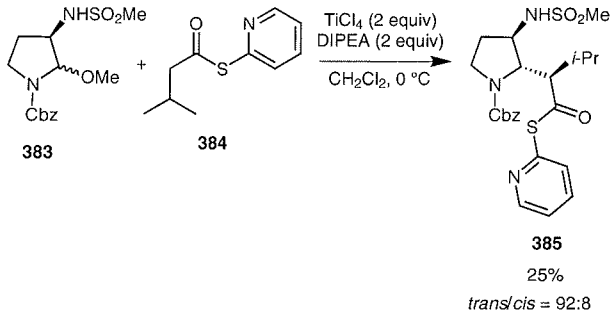
Scheme 154



Scheme 155

gave the addition products **382a,b** as single isomers in 82–84% yields (Scheme 155).[100]

The titanium enolate of 2-pyridylthio ester **384** was treated with 2-methoxypyrrolidine **383** in the presence of titanium(IV) chloride to give the 2,3-*trans* product **385** in 25% yield and with a diastereomeric ratio of 92:8 (Scheme 156).[101]

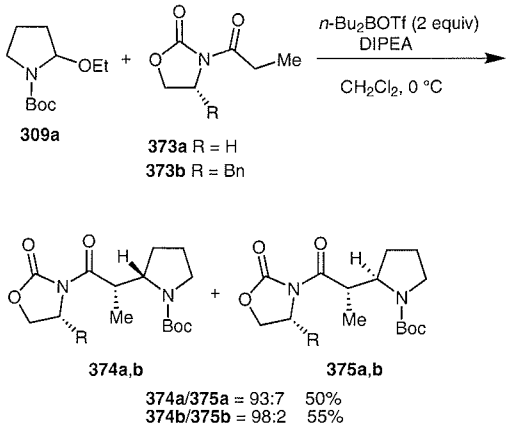


Scheme 156

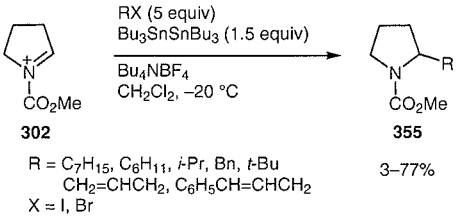
The boron enolates of the oxazolidin-2-ones **373a,b** were treated with *N*-*tert*-butyloxycarbonyl-2-ethoxypyrrolidine (**309a**) in the presence of dibutylboryl triflate (2.0 equiv) to afford the corresponding *N*-Boc-2-substituted pyrrolidines **374a,b** and **375a,b**. The reaction using **373a** gave a mixture of **374a** and **375a** (dr = 93:7) in 50% yield, while the reaction with **373b** under the same reaction conditions provided products **374b/375b** in 55% yield (dr = 98:2) (Scheme 157).[98]

3.2.2.6 Alkyl Radicals

The *N*-acyliminium ion **302** reacted with alkyl halides in the presence of hexabutyldistannane to give the 2-substituted pyrrolidine adducts **355** (Scheme 158).[41,42]



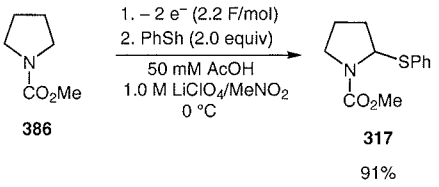
Scheme 157



Scheme 158

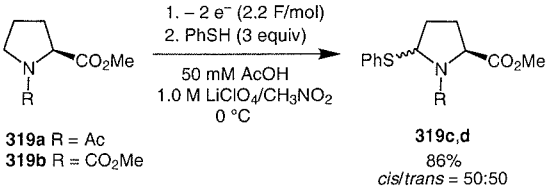
3.2.2.7 Thiols

Anodic oxidation of pyrrolidine **386** in a 1 M lithium perchlorate/nitromethane electrolytic solution in the presence of 50 mM acetic acid gave an intermediate *N*-acyliminium ion, which was trapped with thiophenol to afford the 2-phenylsulfanyl pyrrolidine **317** in 91% yield (Scheme 159).[49]



Scheme 159

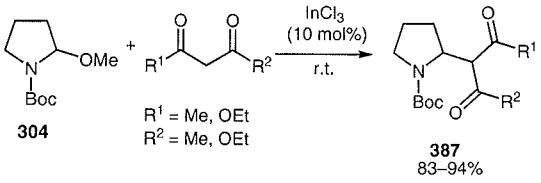
Treatment of amide or carbamate proline derivatives **319a** and **319b** with thiophenol under the same electrolytic oxidative conditions gave adducts **319c,d** in 86% yield as a 50:50 mixture of diastereomers (Scheme 160).[49]



Scheme 160

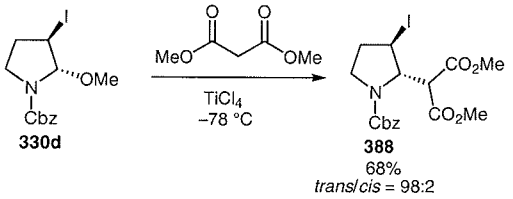
3.2.2.8 Active Methylene Compounds

1,3-Dicarbonyl compounds were treated with α-methoxypyrrolidine **304** in the presence of indium(III) chloride under solvent-free conditions to afford the 2-substituted pyrrolidines **387** (Scheme 161). Use of ethyl acetylacetonate (R^1 = Me, R^2 = OEt), acetylacetonate (R^1 = R^2 = Me) and diethyl malonate (R^1 = R^2 = OEt) gave products in 92%, 94%, and 83% yields, respectively.[82a] The use of indium(IV) chloride in sodium dodecylsulfate and water has also been described for these reactions.[82b]



Scheme 161

The reaction of 3-iodo-2-methoxypyrrolidine **330d** with dimethyl malonate in the presence of titanium(IV) chloride afforded product **388** in 68% yield and high selectivity (*trans*/*cis* = 98:2) (Scheme 162).[87]

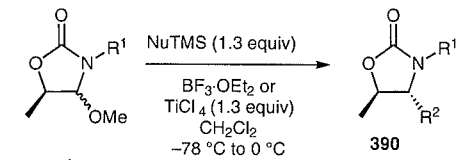


Scheme 162

3.2.3 Reactions of Oxazolidinone-Based *N*-Acyliminium Ions with Nucleophiles

3.2.3.1 Silicon-Based Nucleophiles

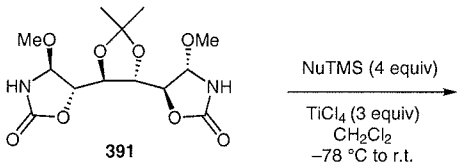
Treatment of the chiral oxazolidinones **389** with allyltrimethylsilane and 2-bromoallyltrimethylsilane in the presence of boron trifluoride–diethyl ether complex or titanium(IV) chloride afforded 4,5-*trans* products **390** with very high selectivity (*trans*/*cis* = 87:13 to 98:2) in 85–92% yields (Scheme 163).[102]



NuTMS	R^2
CH_2=$CHCH_2TMS$	-CH_2CH=CH_2
CH_2=$CBrCH_2TMS$	-CH_2CBr=CH_2

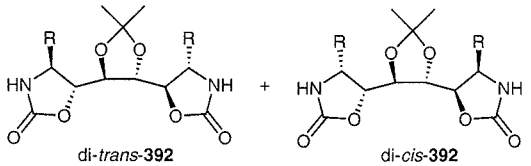
Scheme 163

The reaction of bisoxazolidinone **391** with silicon nucleophiles in the presence of titanium(IV) chloride gave disubstituted products **392** in yields of 17–59%, in favour of the di-*trans* products (Scheme 164).[103]



NuTMS
CH_2=$CHCH_2TMS$
CH_2=$C(CH_2Cl)CH2TMS$
CH_2=$C(Br)CH_2TMS$
CH_2=$C(CH_2OAc)CH_2TMS$

HC≡CCH_2TMS



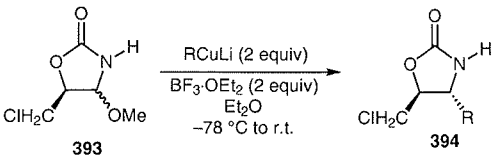
R	Yield (%)	(*trans*/*cis*)
-CH_2CH=CH_2	59	(96:4)
-$CH_2C(CH_2Cl)$=CH_2	58	(91:9)
-$CH_2C(Br)$=CH_2	53	(92:8)
-$CH_2C(CH_2OAc)$=CH_2	38	(93:7)
-CH_2=C=CH_2	17	(94:6)[a]

[a] BF_3·OEt_2 (2.2 equiv) and Ac_2O (2 equiv) were used.

Scheme 164

3.2.3.2 Organometallic Reagents

Treatment of oxazolidinone **393** with organocopper reagents in the presence of boron trifluoride–diethyl ether complex led to the formation of products **394** in 52–62% yields and good 4,5-*trans* diastereoselectivities (Scheme 165).[102]



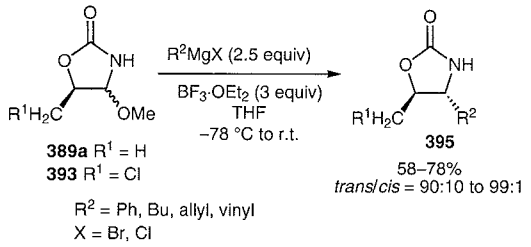
R	Yield (%)	(*trans*/*cis*)
Ph	62	(96:4)
Bu	59	(98:2)
Bu	52	(94:6)[a]

[a] *n*-BuCu/BF_3 was used.

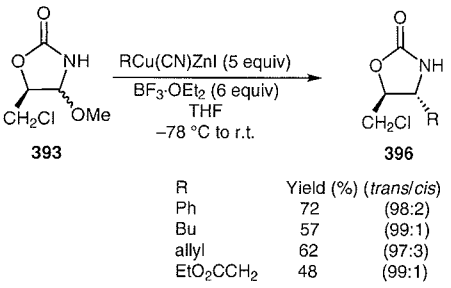
Scheme 165

The boron trifluoride–diethyl ether complex catalysed reaction of oxazolidinones **389a** and **393** with Grignard reagents provided products **395** in 58–78% yields with very high 4,5-*trans* selectivity (Scheme 166).[102]

Oxazolidinone **393** was treated with organocopper–zinc reagents in the presence of boron trifluoride–diethyl ether



Scheme 166



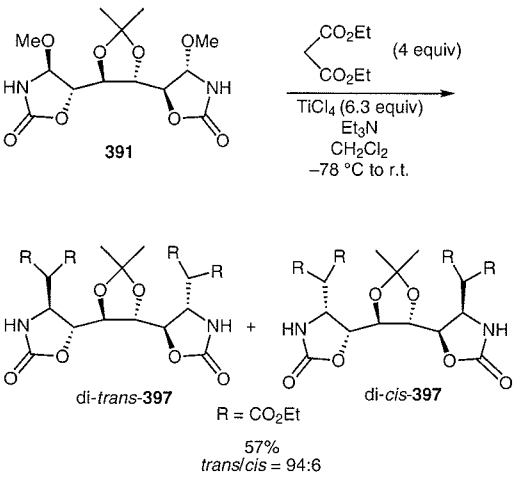
R	Yield (%)	(*trans*/*cis*)
Ph	72	(98:2)
Bu	57	(99:1)
allyl	62	(97:3)
EtO_2CCH_2	48	(99:1)

Scheme 167

complex to give the 4,5-*trans* products **396** in 48–72% yields (Scheme 167).[102]

3.2.3.3 Active Methylene Compounds

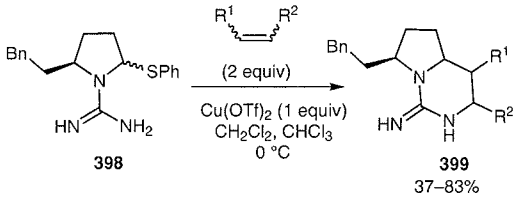
Bisoxazolidinone **391** reacted with a titanium enolate, prepared in situ from the treatment of diethyl malonate with titanium(IV) chloride in the presence of triethylamine, to afford predominantly the di-*trans* product **397** (*trans*/*cis* = 94:6) in 57% yield (Scheme 168).[103]



Scheme 168

3.2.4 Cyclocondensation Reaction of *N*-Aminidinyl Iminium Ions

The cyclocondensation reaction of **398** with alkenes and dienes provided the desired cycloadducts **399** in 37–83% yields (Scheme 169).[104]



alkene/diene
styrene, (*E*)-propenylbenzene, (*Z*)-propenylbenzene, 1*H*-indene, 1,2-dihydronaphthalene, (*E*)-1,3-hexadiene, (*E*)-ethyl-3,5-hexadionate, (*E*)-ethyl-5,7-octadionate, (*Z*)-1,3-pentadiene

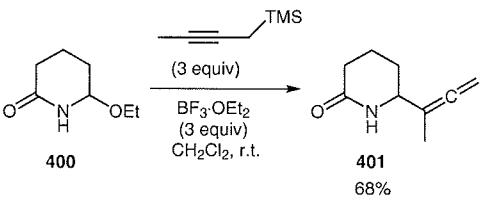
Scheme 169

3.3 Six-Membered-Ring *N*-Acyliminium Ions

3.3.1 Reactions of Piperidinone-Based *N*-Acyliminium Ions with Nucleophiles

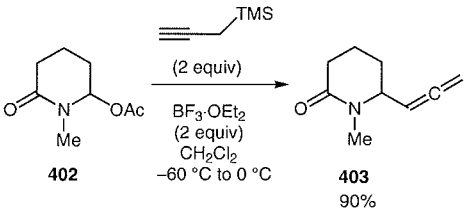
3.3.1.1 Silicon-Based Nucleophiles

The reaction of 6-ethoxypiperidinone (**400**) with but-2-ynyltrimethylsilane under catalysis by boron trifluoride–diethyl ether complex yielded 6-methylallenepiperidinone **401** in 68% yield (Scheme 170).[51]



Scheme 170

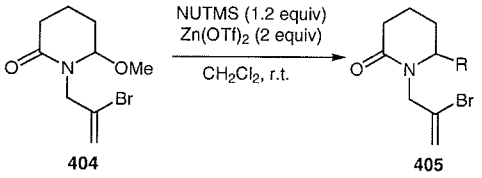
6-Acetoxypiperidinone **402** underwent reaction with propargyltrimethylsilane to provide the allene product **403** in 90% yield (Scheme 171).[105]



Scheme 171

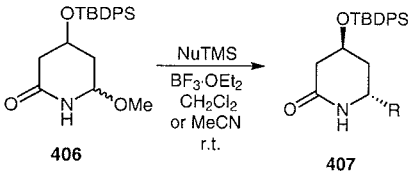
The addition reaction of silicon nucleophiles with 6-methoxypiperidinone **404** in the presence of zinc triflate provided the desired 6-substituted piperidinones **405** in 50–52% yields (Scheme 172).[52]

The reaction of racemic 6-methoxypiperidinone **406** with silicon nucleophiles in the presence of boron trifluoride–diethyl ether complex in dichloromethane or acetonitrile afforded the corresponding racemic products **407** in 42–100% yields, in favour of the 4,6-*trans* isomer (*trans*/*cis* = 57:43 to 89:11) (Scheme 173). In the same study, piperidinone **406** reacted with CH_2=C(OTMS)(Ph) in the



NuTMS	R	Yield (%)
CH_2=$CHCH_2TMS$	-CH_2CH=CH_2	52
CH_2=C(OTMS)(Ph)	-CH_2COPh	50

Scheme 172



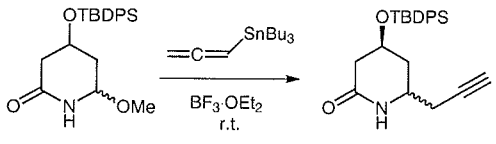
NuTMS	R
CH_2=$CHCH_2TMS$	-CH_2CH=CH_2
TMSCN	-CN
CH_2=C(OTMS)(Ph)	-CH_2COPh

Scheme 173

presence of scandium(III) triflate in acetonitrile to give product **407** in 88% yield and with a *trans/cis* ratio of 78:22.[106]

3.3.1.2 Organostannanes

Treatment of racemic piperidinone **406** with allenyltributylstannane in the presence of boron trifluoride–diethyl ether complex in acetonitrile afforded the racemic product **408** as a mixture of isomers (*trans/cis* = 51:49) in quantitative yield. The use of dichloromethane as a solvent decreased the yield to 85%, but increased the diastereoselectivity slightly (*trans/cis* = 59:41) (Scheme 174).[106]

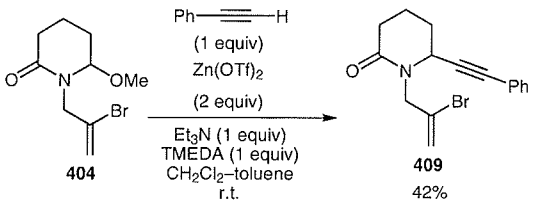


Solvent	Yield (%)	(*trans/cis*)
MeCN	100	(51:49)
CH_2Cl_2	85	(59:41)

Scheme 174

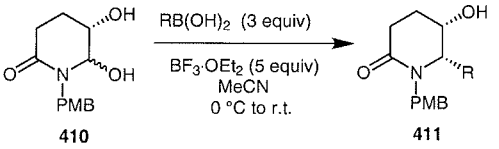
3.3.1.3 Organometallic Reagents

Treatment of piperidinone **404** with an in situ generated zinc alkynylide in the presence of zinc triflate yielded the propargylic adduct **409** in 42% yield (Scheme 175).[52]



Scheme 175

Treatment of the chiral 5,6-dihydroxypiperidinone **410** with boronic acids in the presence of boron trifluoride–diethyl ether complex afforded the products **411** in 49–77% yields, with very good 5,6-*cis* selectivity (80:20 to >98:<2) (Scheme 176). In the same study the 5-methoxy analogue of piperidinone **410** reacted with potassium (*E*)-2-styryltrifluoroborate in the presence of boron trifluoride–diethyl ether complex to give the corresponding methoxy analogue of adduct **411** in 96% yield with a *cis/trans* ratio of 65:35.[64]



R	Yield (%)	(*cis/trans*)
-CH=CHPh	77	(98:2)
-CH=CHPh[a]	72	(92:8)
-2-furyl	49	(80:20)
-2-benzofuranyl	70	(98:2)
-C≡C—TMS[a]	41	(95:5)
-C≡C—TMS[a]	37	(100:0)

[a] The corresponding RBF_3K was used.

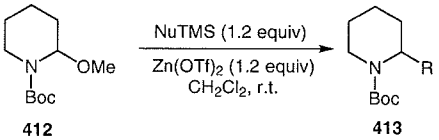
Scheme 176

3.3.2 Reactions of *N*-Acylpiperidine-Based *N*-Acyliminium Ions

3.3.2.1 Reactions with Nucleophiles

3.3.2.1.1 Silicon-Based Nucleophiles

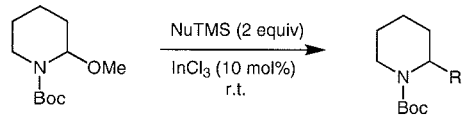
The zinc triflate mediated reaction of *N*-*tert*-butyloxycarbonyl-2-methoxypiperidine (**412**) with silicon nucleophiles afforded the expected 2-substituted piperidines **413** in 52–68% yields (Scheme 177).[52]



NuTMS	R	Yield (%)
CH_2=$CHCH_2TMS$	-CH_2CH=CH_2	52
CH_2=C(OTMS)(Ph)	-CH_2COPh	68
MeCH=C(OTMS)(Ph)	-C(Me)COPh	63 (*threo/erythro* = 91:9)

Scheme 177

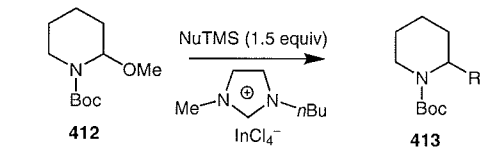
Treatment of piperidine **412** with similar silicon nucleophiles in the presence of indium(III) chloride under solvent-free conditions gave the desired 2-alkylated piperidines **413** in 79–92% yields (Scheme 178).[82a] The use of indium(IV) chloride in sodium dodecylsulfate and water has also been described for these reactions.[82b]



NuTMS	R	Yield (%)
MeC=C(OTMS)(Ph)	-CH(Me)COPh	92
$(Me)_2C$=C(OTMS)(OMe)	$-C(Me)_2CO_2Me$	87
BuCH=C(OTMS)(Bu)	-C(Bu)COBu	87
CH_2=C(OTMS)(Ph)	$-CH_2COPh$	79

Scheme 178

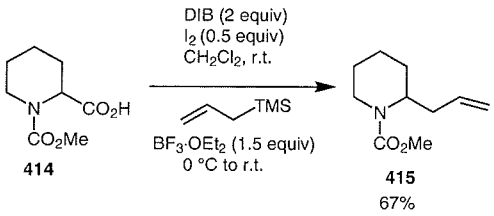
Piperidine **412** also reacted with silicon nucleophiles in an ionic liquid ($BMI{\cdot}InCl_4$) to yield the corresponding 2-substituted piperidines **413** in 65–76% yields (Scheme 179).[81]



NuTMS	R	Yield (%)
CH_2=$CHCH_2TMS$	$-CH_2CH$=CH_2	69
CH_2=C(OTMS)(Ph)	$-CH_2COPh$	65
MeCH=C(OTMS)(Ph)	-CH(Me)COPh	76 (*erythro*/*threo* = 83:17)
$(Me)_2C$=C(OTMS)(OMe)	$-(Me)_2CCO(OMe)$	67

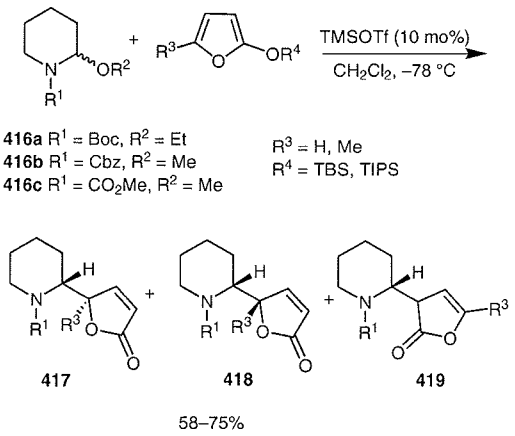
Scheme 179

The one-pot decarboxylation–oxidation–allylation reaction of *N*-methyloxycarbonyl piperidine **414** afforded 2-allylpiperidine **415** in 67% yield (Scheme 180).[47]



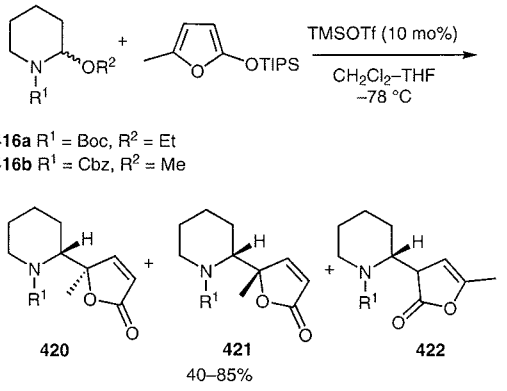
Scheme 180

Treatment of *N*-acylpiperidines **416a–c** with 2-silyloxyfurans under trimethylsilyl triflate catalysis afforded products **417**, **418** and **419** in 58–75% yields (Scheme 181). The reactions of **416a–c** with 2-silyloxyfuran (R^3 = H, R^4 = TBS) gave products **417** and **418** in 58%, 63%, and 74% yields, and with product ratios (**417**/**418**) of 88:12, 67:33, and 75:25, respectively. The reaction of piperidines **416a–c** with another silyloxyfuran (R^3 = Me, R^4 = TIPS) afforded products **417**, **418**, and **419** in 67%, 75%, and 70% yields, with **417**/**418**/**419** product ratios of 3:60:36, 33:67:0, and 16:84:0, respectively. The relative stereochemistry of **419** was not determined.[84]



Scheme 181

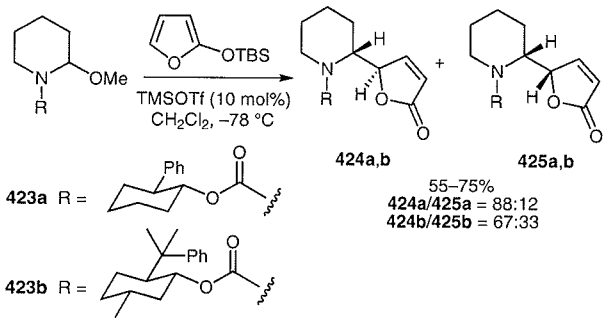
In a very similar study, piperidine **416a** reacted with 2-[(triisopropyl)siloxy]-5-methylfuran in a tetrahydrofuran and dichloromethane solvent mixture in the presence of trimethylsilyl triflate or boron trifluoride–diethyl ether complex to afford products **420**, **421** and **422** in 67% and 40% yields, respectively with product ratios (**420**/**421**/**422**) of 60:4:36 and 58:4:38, respectively. The reaction of piperidine **416b** with silyloxyfuran in the presence of trimethylsilyl triflate, titanium(IV) chloride, and boron trifluoride–diethyl ether complex in dichloromethane, diethyl ether, tetrahydrofuran, and tetrahydrofuran–dichloromethane gave products **420** and **421** in 42–85% yields and with **420**/**421** product ratios of 52:48 to 67:33. The regioisomer **422** was not obtained from the reaction of piperidine **416b** (Scheme 182).[107]



Scheme 182

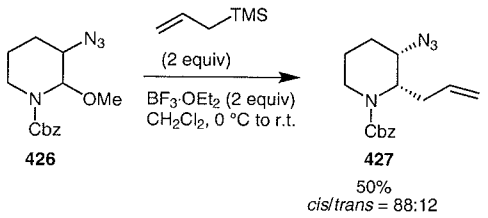
The reaction of chiral 2-methoxypiperidines **423a,b** with 2-*tert*-butyldimethylsilyloxyfuran under titanium(IV) chloride or trimethylsilyl triflate catalysis provided the

adducts **424a,b** and **425a,b** (Scheme 183). Treatment of **423a** with the silyloxyfuran in the presence of titanium(IV) chloride or trimethylsilyl triflate gave products **424a** and **425a** in 55% and 75% yields (**424a/425a** = 88:12). Reaction of **423b** with the silyloxyfuran under trimethylsilyl triflate catalysis gave the adducts **424b** and **425b** in 73% yield, with a diastereomeric ratio of 67:33.[83]



Scheme 183

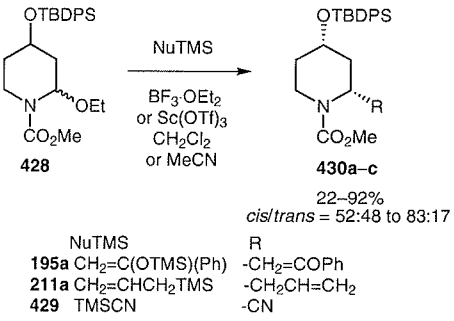
The reaction of racemic 3-azido-2-methoxypiperidine **426** with allyltrimethylsilane in the presence of boron trifluoride–diethyl ether complex provided the racemic 2-allylated piperidine **427** as a mixture of isomers with a *cis*/*trans* ratio of 88:12 in 50% yield (Scheme 184).[87,88]



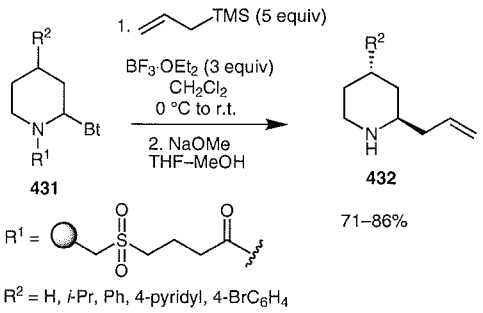
Scheme 184

Treatment of racemic piperidine **428** with silicon nucleophiles **195a**, **211a** and **429** in the presence of scandium(III) triflate in acetonitrile yielded products **430** in 89%, 92%, and 86% yields, respectively, and with *cis*/*trans* ratios of 52:48, 54:46 and 74:26, respectively. When the reaction of piperidine **428** with **211a** and **429** was performed under boron trifluoride–diethyl ether complex catalysis in acetonitrile, products **430** were obtained in yields of 92% and 79%, respectively, in favour of the *cis* isomer (*cis*/*trans* = 72:28 and 61:39, respectively). The use of dichloromethane as a solvent in the reaction of **428** with **195a** and **211a** resulted in 22% (*cis*/*trans* = 75:25) and 65% (*cis*/*trans* = 83:17) yields, respectively (Scheme 185).[106]

The boron trifluoride–diethyl ether complex mediated reaction of allyltrimethylsilane with resin-bound racemic piperidine **431** gave racemic 2,4-*trans* isomers **432** in 71–86% yields after they were cleaved from the resin (Scheme 186). Piperidine **431**, where R^2 = Ph, was treated



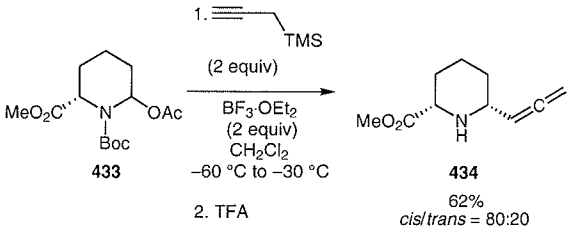
Scheme 185



Scheme 186

with CH_2=C(Me)(CH_2TMS) to afford the corresponding racemic 2,4-*trans* adduct exclusively in 76% yield.[108]

N-*tert*-Butyloxycarbonyl-6-acetoxypiperidine **433** reacted with propargyltrimethylsilane under boron trifluoride–diethyl ether complex catalysis to afford the allene **434** in 62% yield, in favour of the *cis* isomer (*cis*/*trans* = 80:20) (Scheme 187).[105]

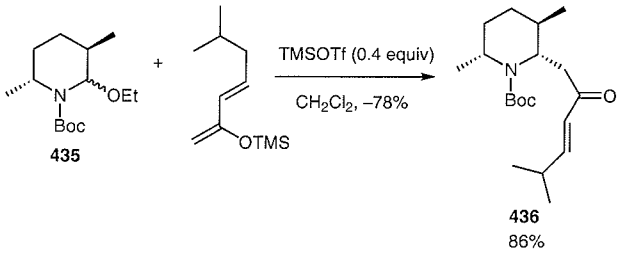


Scheme 187

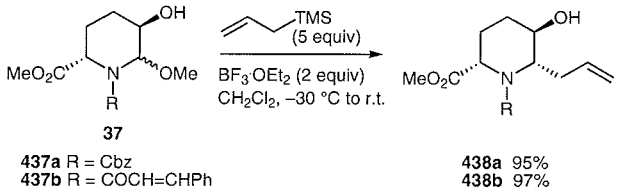
The reaction of b*N*-Boc piperidine **435** with a silyl dienol ether in the presence of trimethylsilyl triflate yielded exclusively the 2,3-*trans* isomer of adduct **436** in 86% yield (Scheme 188).[109]

The *N*-acyl piperidines **437a,b** were treated with allyltrimethylsilane in the presence of boron trifluoride–diethyl ether complex to give exclusively the corresponding 2,3-*trans* adducts **438a** and **438b** in 95% and 97% yields, respectively (Scheme 189).[110]

Treatment of the *N*-Fmoc piperidine **439** with silicon nucleophiles in the presence of boron trifluoride–diethyl ether complex provided the products **440** and **441** in a

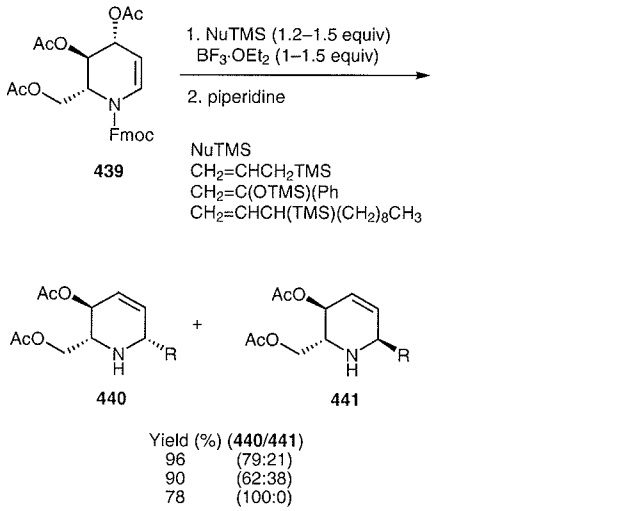


Scheme 188



Scheme 189

range of yields (78–96%), with good 2,6-*cis* selectivity. The reaction of **439** with CH_2=CHCH(TMS)$(CH_2)_8$Me afforded the corresponding 2,6-*cis* adduct exclusively (Scheme 190).[111]



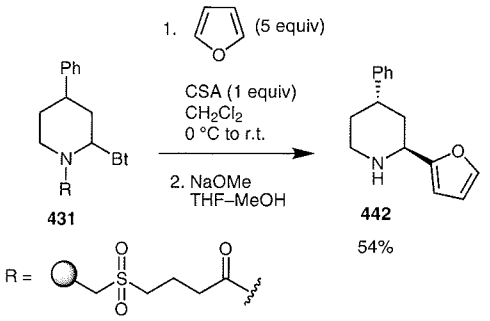
Scheme 190

3.3.2.1.2 Aromatic Nucleophiles

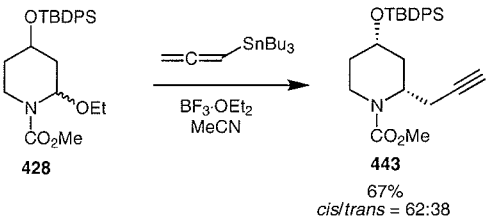
The treatment of polymer-bound racemic piperidine **431** with furan in the presence of camphorsulfonic acid provided the racemic 2-furylpiperidine adduct **442** exclusively in 54% yield (Scheme 191).[108]

3.3.2.1.3 Organostannanes

Treatment of racemic piperidine **428** with allenyltributylstannane in the presence of boron trifluoride–diethyl ether complex afforded product **443** in 67% yield, in favour of the 2,4-*cis* isomer (Scheme 192).[106]

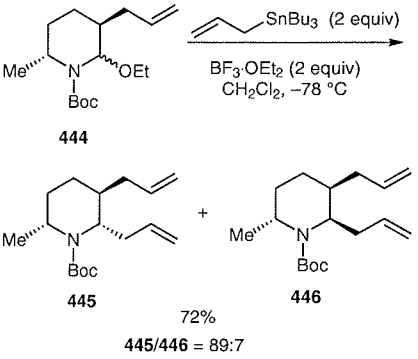


Scheme 191



Scheme 192

The reaction of the *N*-Boc piperidine **444** with allyltributylstannane in the presence of boron trifluoride–diethyl ether complex gave products **445** and **446** and one other isomer in a ratio of 89:7:4, respectively, and in combined yield of 72% (Scheme 193). The third isomer was suggested to be the result of partial epimerisation of the stereocentre in the *N*-acyliminium ion intermediate.[112]



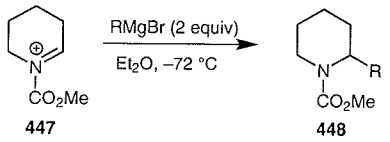
Scheme 193

3.3.2.1.4 Organometallic Reagents

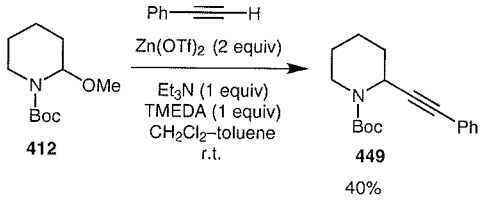
The *N*-acyliminium ion **447**, generated in situ from the corresponding carbamate by electrochemical oxidation, reacted with Grignard reagents in diethyl ether to afford the 2-substituted piperidine products **448** in 50–57% yields (Scheme 194).[38]

Piperidine **412** reacted with an in situ generated zinc alkynylide to give the corresponding propargylic adduct **449** in 40% yield (Scheme 195).[52]

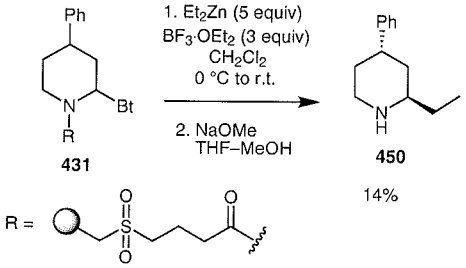
The polymer-bound racemic piperidine **431** was treated with diethylzinc in the presence of boron trifluoride–



Scheme 194



Scheme 195



Scheme 196

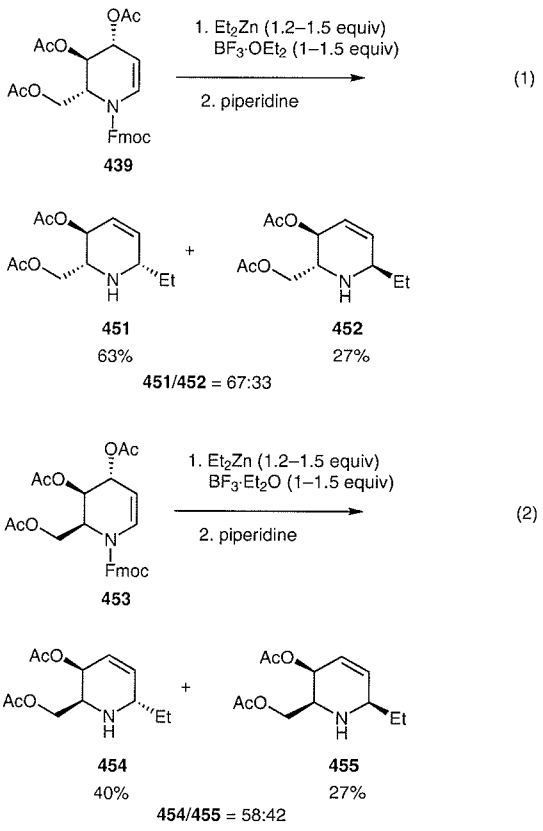
diethyl ether complex to give the racemic 2,4-*trans* isomer **450** exclusively in 14% yield (Scheme 196).[108]

The reaction of piperidines **439** with diethylzinc in the presence of boron trifluoride–diethyl ether complex yielded products **451** and **452** in 63% and 27% yields, respectively (Scheme 197, equation 1). Treatment of **453**, a diastereomer of piperidine **439**, with diethylzinc under the same reaction conditions afforded products **454** and **455** in yields of 40% and 27%, respectively (Scheme 197, equation 2).[111]

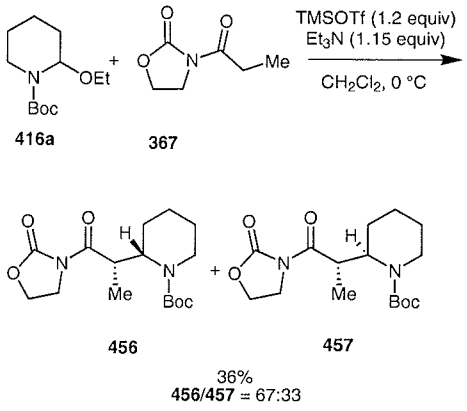
3.3.2.1.5 Carbonyl Compounds

The reaction of *N*-*tert*-butyloxycarbonyl-2-ethoxypiperidine (**416a**) with an *N*,*O*-silylketene acetal, itself prepared in situ by treatment of *N*-propionyloxazolidine-2-one **367** with trimethylsilyl triflate and triethylamine, led to the formation of 2-substituted piperidines **456** and **457** in 36% combined yield (**456/457** = 67:33) (Scheme 198).[98]

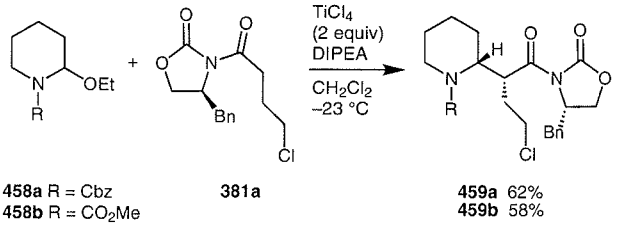
Treatment of the 2-methoxypiperidines **458a,b** with the titanium enolate of **381a** led to the formation of **459a** and **459b** in 62% and 58% yields, respectively (Scheme 199), whereas treatment of the *N*-Boc analogue of piperidine **458** with titanium enolate of **381a** under the same reaction conditions did not give the desired product.[113]



Scheme 197

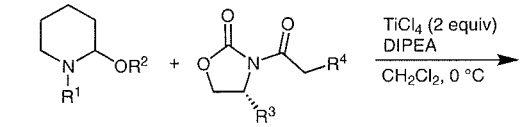


Scheme 198



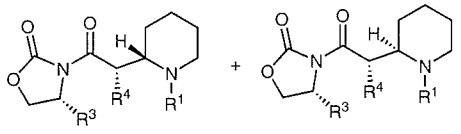
Scheme 199

The titanium enolates of **373a–d** reacted with the *N*-acyl piperidines **416a–c** to afford the diastereomeric products **460** and **461** in 60–73% yields (Scheme 200).[98]



416a R^1 = Boc, R^2 = Et
416b R^1 = Cbz, R^2 = Me
416c R^1 = CO_2Me, R^2 = Me

373a R^3 = H, R^4 = Me
373b R^3 = Bn, R^4 = Me
373c R^3 = H, R^4 = H
373d R^3 = Bn, R^4 = H

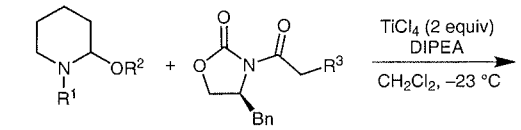


460 **461**

60–73%
460/461 = 55:45 to 66:34

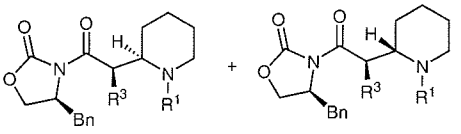
Scheme 200

In the same study the piperidines **416a–c** reacted with the titanium enolates of **378a,b** to give the corresponding products **462** and **463** in 60–73% yields (Scheme 201).[98]



416a R^1 = Boc, R^2 = Et
416b R^1 = Cbz, R^2 = Me
416c R^1 = CO_2Me, R^2 = Me

378a R^3 = Ph
378b R^3 = $(CH_2)_3Cl$



462 **463**

60–73%
462/463 = 80:20 to 92:8

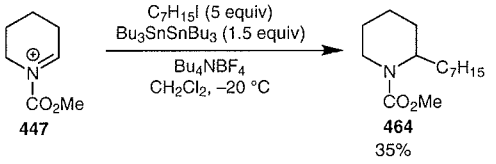
Scheme 201

3.3.2.1.6 Alkyl Radicals

The *N*-acyliminium ion **447** was treated with heptyl iodide in the presence of hexabutyldistannane to give the 2-heptyl-*N*-acylpiperidine derivative **464** in 35% yield (Scheme 202).[41,42]

3.3.2.1.7 Alkenes

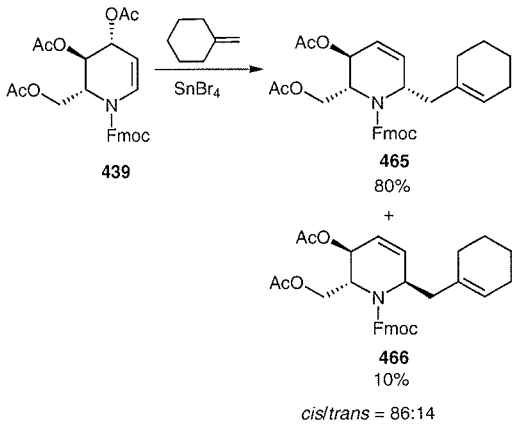
Treatment of piperidine **439** with methylenecyclohexane under catalysis by tin(IV) bromide yielded the 2,6-*cis* adduct **465** and the 2,6-*trans* adduct **466** in 80% and 10% yields, respectively (Scheme 203).[111]



447

464
35%

Scheme 202



439

465
80%

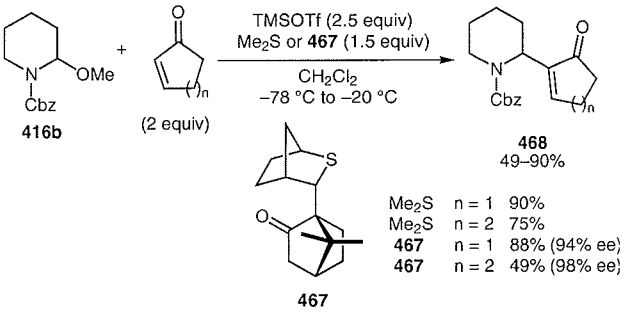
+

466
10%

cis/*trans* = 86:14

Scheme 203

Treatment of *N*-Cbz-protected 2-methoxypiperidine **416b** with cyclopentenone or cyclohexenone and dimethyl sulfide in the presence of trimethylsilyl triflate led to the formation of products **468** in 75–90% yields. The use of a chiral sulfide **467** resulted in 49–88% yields and enantioselectivities of 94–98% ee (Scheme 204).[114]



416b

(2 equiv)

468
49–90%

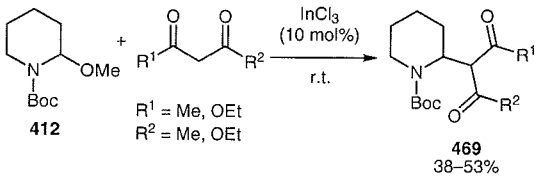
Me_2S n = 1 90%
Me_2S n = 2 75%
467 n = 1 88% (94% ee)
467 n = 2 49% (98% ee)

467

Scheme 204

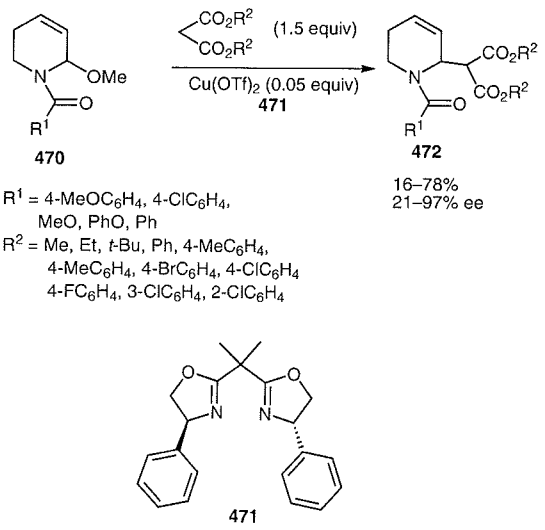
3.3.2.1.8 Active Methylene Compounds

The indium(III) chloride catalysed reaction of piperidine **412** with acetylacetonate (R^1 = Me, R^2 = OEt), acetylacetone (R^1 = R^2 = Me), and diethyl malonate (R^1 = R^2 = OEt) provided the products **469** in 53%, 38%, and 53% yields, respectively (Scheme 205).[82a] The use of indium(IV) chloride in sodium dodecylsulfate and water has also been described for these reactions.[82b]



Scheme 205

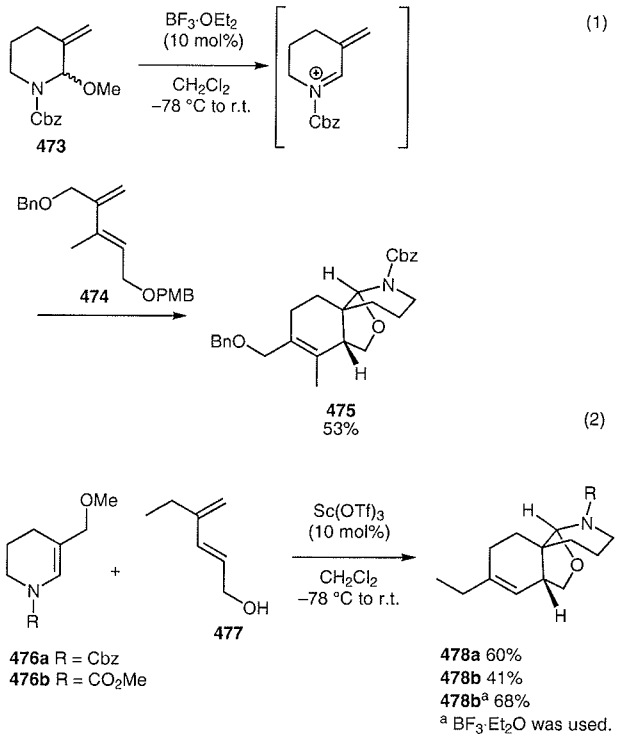
The *N*-acylpiperidines **470** reacted with 1,3-dicarbonyl compounds in the presence of copper(II) triflate and bisoxazoline ligand **471** to give products **472** in yields ranging from 16% to 78%. The highest enantioselectivity (97% ee) was obtained from the reaction of piperidine **470** (R^1 = 4-$MeOC_6H_4$) and di(4-chlorophenyl)malonate (Scheme 206).[115]



Scheme 206

3.3.2.2 Cycloaddition Reactions

The reaction of piperidine **473** with diene **474** in the presence of boron trifluoride–diethyl ether complex afforded cycloadduct **475** in 53% yield (Scheme 207, equation 1). Treatment of piperidines **476a** and **476b** with diene **477** in the presence of scandium(III) triflate afforded the corresponding cycloadducts **478a** and **478b** in 60% and 41% yields, respectively. Cycloadduct **478b** was obtained in 68% yield from the reaction of **476a** with **477** under catalysis by boron trifluoride–diethyl ether complex (Scheme 207, equation 2).[116]

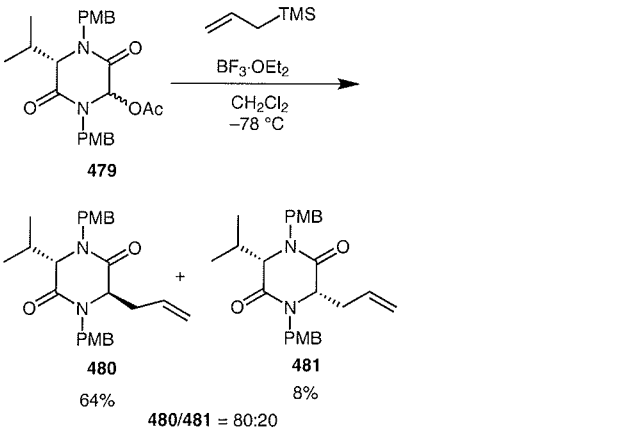


Scheme 207

3.3.3 Reactions of Piperazine-Based *N*-Acyliminium Ions with Nucleophiles

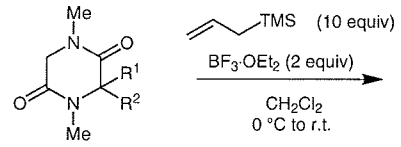
3.3.3.1 Silicon-Based Nucleophiles

Diketopiperazine **479** reacted with allyltrimethylsilane in the presence of boron trifluoride–diethyl ether complex to afford products **480** and **481** in 64% and 8% yields, respectively. The same product ratio was obtained from the reactions of diastereomerically pure 3,6-*trans* and 3,6-*cis* piperazines **479** with allyltrimethylsilane (Scheme 208).[117]

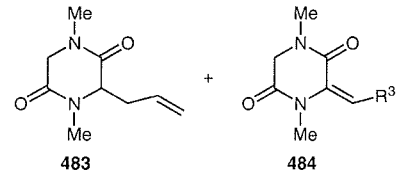


Scheme 208

The boron trifluoride–diethyl ether complex catalysed reaction of 3-methoxy-1,4-dimethylpiperazine-2,5-dione (**482a**) with allyltrimethylsilane provided allylated product **483** in 68% yield, whereas **482b** with allyltrimethylsilane under the same reaction conditions provided allylated product **483** and product **484** in 66% and 33% yields, respectively. Treatment of **482c** with allyltrimethylsilane under the same reaction conditions gave exclusively product **484** in 76% yield (Scheme 209).[48,118]



482a R^1 = H, R^2 = OMe
482b R^1 = Me, R^2 = OAc
482c R^1 = Bn, R^2 = OAc



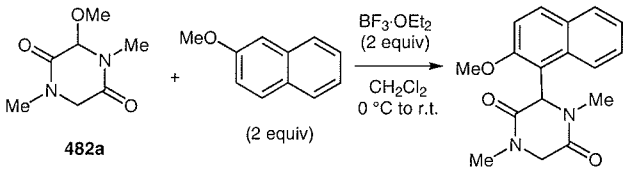
483 **484**

	Yield (%) (**483**)	Yield (%) (**484**)
a	68	0
b	66	33 (R^3 = H)
c	0	76 (R^3 = Pr)

Scheme 209

3.3.3.2 Aromatic Nucleophiles

Treatment of **482a** with 2-methoxynaphthalene in the presence of boron trifluoride–diethyl ether complex gave the corresponding arylated product **485** in 81% yield (Scheme 210).[48]



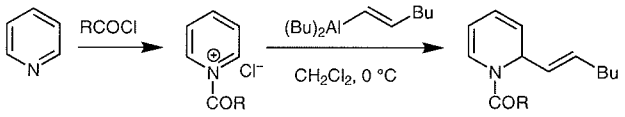
482a **485**
81%

Scheme 210

3.3.4 Reactions of Pyridine-Based *N*-Acyliminium Ions with Nucleophiles

3.3.4.1 Organometallic Reagents

The reaction of pyridine with acyl chlorides generated the *N*-acyliminium ion salt **486** which was then treated with an organoaluminium reagent to yield the corresponding adducts **487** in 90–94% yields (Scheme 211).[119]



486 **487**
90–94%

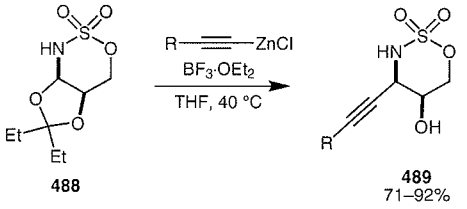
R = Bu, Ph, *c*-$C_{12}H_{14}$

Scheme 211

3.3.5 Reactions of *N,O*-Acetal Oxathiazinane *N*-Sulfonyliminium Ions with Nucleophiles

3.3.5.1 Organometallic Reagents

The reactions of *N,O*-acetal oxathiazinane **488** and related heterocycles with alkynylzinc reagents gave adducts **489** in high yields and high diastreoselectivities (Scheme 212).[120]



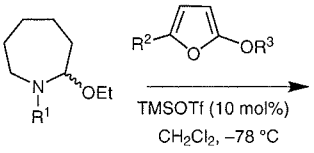
488 **489**
71–92%

Scheme 212

3.4 Seven-Membered-Ring *N*-Acyliminium Ions

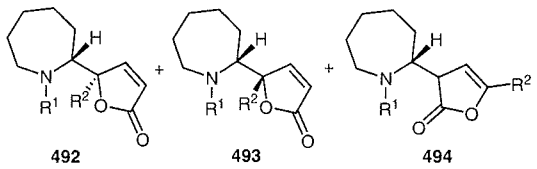
3.4.1 Reactions with Silicon-Based Nucleophiles

Treatment of the *N*-acyl-2-ethoxyazepines **490a–c** with 2-silyloxyfurans **491a,b** in the presence of trimethylsilyl triflate afforded products **492**, **493**, and **494** in 46–83% yields (Scheme 213). The reactions of azepines **490a–c** with **491a** in the presence of trimethylsilyl triflate afforded products **492** and **493** in ratios of 93:7, 85:15 and 80:20, respectively, while the reactions with **491b** yielded products **492**, **493**, and **494** in ratios of 13:45:42, 6:52:42, and 30:70:0, respectively. The regioisomer **494** was not obtained from the reaction of **490a–c** with **491a**.[84]



490a R^1 = Boc
490b R^1 = Cbz
490c R^1 = CO_2Me

491a R^2 = H, R^3 = TBS
491b R^2 = Me, R^3 = TIPS

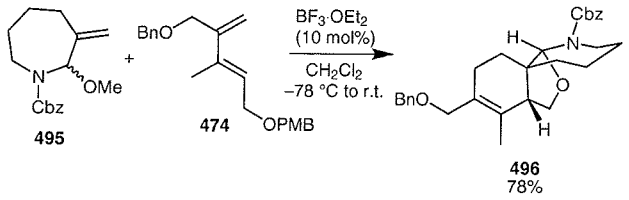


492 **493** **494**
46–83%

Scheme 213

3.4.2 Cycloaddition Reactions

Azepine **495** reacted with diene **474** in the presence of boron trifluoride–diethyl ether complex to give cycloadduct **496** in 78% yield (Scheme 214).[116]



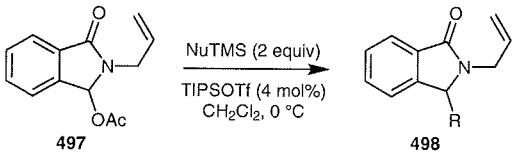
Scheme 214

3.5 Bicyclic *N*-Acyliminium Ions

3.5.1 Reactions with Nucleophiles

3.5.1.1 Silicon-Based Nucleophiles

Treatment of phthalimide **497** with silicon nucleophiles under triisopropylsilyl triflate catalysis afforded the desired products **498** in 45–89% yields (Scheme 215).[54] In a similar study the phthalimide **497** reacted with CH_2=C(OTIPS)C≡CH (2 equiv) in the presence of bis(trifluoromethane)sulfonimide (0.3 mol%) at room temperature under solvent-free conditions to give the corresponding α-substituted product in 82% yield.[63]



NuTMS	R	Yield (%)
CH_2=$CHCH_2TMS$	-CH_2CH=CH_2	88
CH_2=C(Ph)(OTMS)	-CH_2COPh	89
CH_2=C(*t*-Bu)(OTMS)	-CH_2CO*t*-Bu	87
TMSCN	-CN	82
Et_3SiH	-H	87
CH_2=C(OMe)(OTBS)	-CH_2CO_2Me	45

Scheme 215

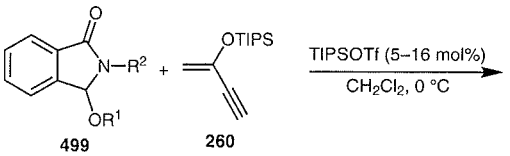
In the same study, the triisopropylsilyl triflate catalysed reactions of phthalimides **499** with **260** gave the products **500** and **501** in 45–76% yields and 13–17% yields, respectively (Scheme 216).[54]

Silicon nucleophiles reacted with phthalimide **502** in the presence of bismuth(III) triflate in acetonitrile to provide product **503** in yields of 64–84%. Lower yields were obtained when dichloromethane was used as a solvent (56–66%) (Scheme 217).[62]

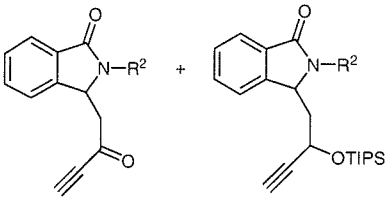
In the same study, chiral phthalimide **504** reacted with allyltrimethylsilane under bismuth(III) triflate catalysis to give product **505** in a *trans*/*cis* ratio of 75:25, and in 97% yield (Scheme 218).[62]

Treatment of bicyclic imide **506** with sodium borohydride and then triethylsilane in the presence of trifluoroacetic acid afforded products **507** and **508** in 86% yield, in a **507**/**508** product ratio of 45:55 (Scheme 219).[75]

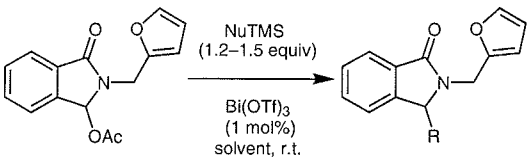
Isoquinoline derivative **509** reacted with silicon nucleophiles in an ionic liquid, BMI·$InCl_4$, to give the corre-



R^1 = H, Me, Et
R^2 = H, allyl



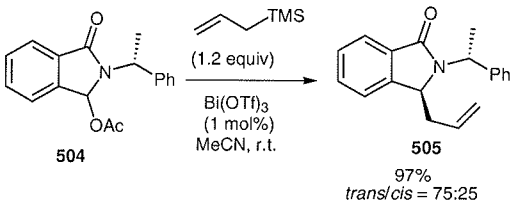
Scheme 216



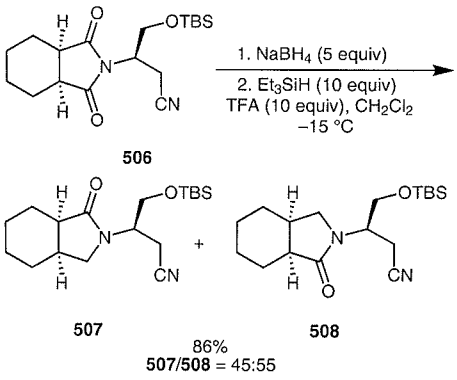
NuTMS	R	Yield (%)
CH_2=$CHCH_2TMS$	-CH_2CH=CH_2	64 (56)[a]
CH_2=C(Ph)(OTMS)	-CH_2COPh	71 (58)[a]
CH_2=C(Me)(OTMS)	-CH_2COMe	84 (66)[a]

[a] CH_2Cl_2 was used.

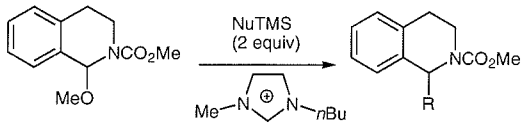
Scheme 217



Scheme 218



Scheme 219

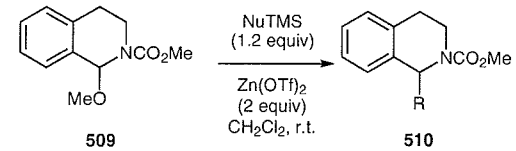


NuTMS	R	Yield (%)
CH_2=$CHCH_2TMS$	-CH_2CH=CH_2	89
CH_2=C(Ph)(OTMS)	-CH_2COPh	78
$(Me)_2C$=C(OMe)(OTMS)	-$(Me)_2CO_2Me$	79

Scheme 220

sponding α-substituted isoquinolines **510** in 78–89% yields (Scheme 220).[81]

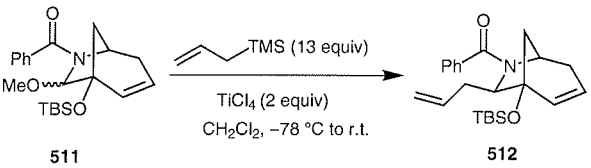
The zinc triflate mediated addition reactions of allyltrimethylsilane and 1-phenylvinyloxytrimethylsilane to the isoquinoline **509** led to the formation of the desired α-substituted adducts **510** in 72% and 80% yields, respectively (Scheme 221).[52]



NuTMS	R	Yield (%)
CH_2=$CHCH_2TMS$	-CH_2CH=CH_2	72
CH_2=C(Ph)(OTMS)	-CH_2COPh	80

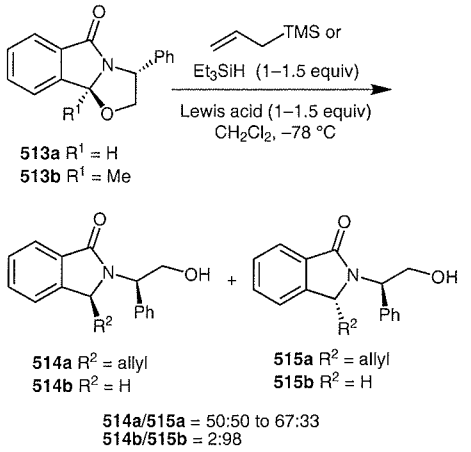
Scheme 221

The reaction of **511** with allyltrimethylsilane in the presence of titanium(IV) chloride afforded the desired α-allyl product **512** in 91% yield, as a single isomer. The stereochemistry of the product was suggested to be the result of *exo*-face attack on the intermediate *N*-acyliminium ion (Scheme 222).[121]



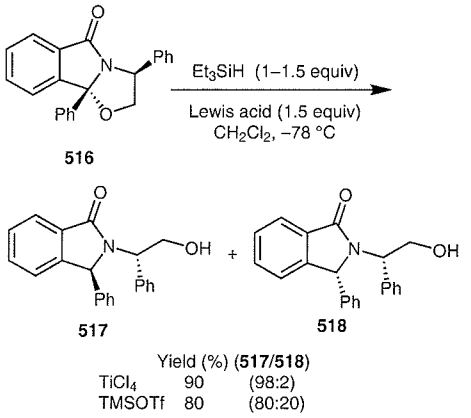
Scheme 222

The ring-opening reaction of tricyclic lactam **513a** with allyltrimethylsilane in the presence of titanium(IV) chloride, boron trifluoride–diethyl ether complex, tin(IV) chloride and trimethylsilyl triflate yielded the allylated products **514** and **515** in 86% (**514/515** = 50:50), 95% (**514/515** = 61:39), 90% (**514/515** = 60:40) and 90% (**514/515** = 67:33) yields, respectively, in favour of product **514** (Scheme 223). Lactam **513b**, however, afforded products **514b** and **515b** in a ratio of 2:98 and in 99% yield from the reaction with triethylsilane.[122]



Scheme 223

In the same study, lactam **516** reacted with triethylsilane under catalysis by titanium(IV) chloride or trimethylsilyl triflate to provide **517** and **518** in a ratio of 98:2 and 80:20 and in 90% and 80% yields, respectively (Scheme 224).[122]



	Yield (%)	(**517**/**518**)
$TiCl_4$	90	(98:2)
TMSOTf	80	(80:20)

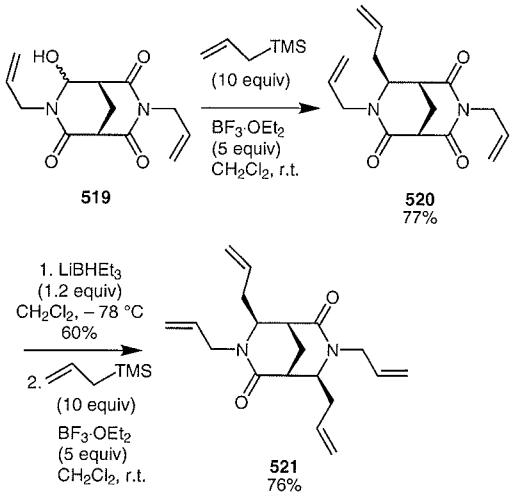
Scheme 224

The reaction of tetraoxobispidine **519** with allyltrimethylsilane in the presence of boron trifluoride–diethyl ether complex afforded product **520** as a single isomer in 77% yield. Treatment of **520** with lithium triethylborohydride and then allyltrimethylsilane under the same reaction conditions yielded the diallylated product **521** as a single isomer in 76% yield (Scheme 225).[123]

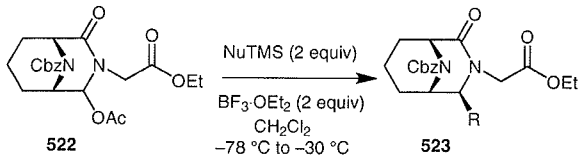
In a similar study, the boron trifluoride–diethyl ether complex catalysed reactions of bispidine **522** with silicon nucleophiles yielded products **523** in yields of 70–90% (Scheme 226).[105]

3.5.1.2 Organometallic Reagents

The addition reactions of in situ generated zinc alkynylides to isoquinoline derivative **509** gave the corre-



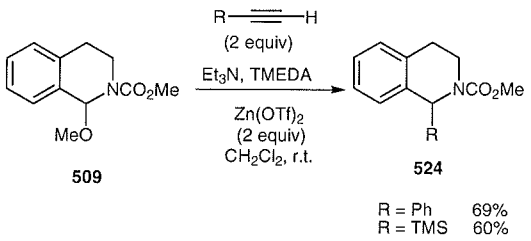
Scheme 225



NuTMS	R	Yield (%)
TMSCN	-CN	90[a]
$CH_2C(Ph)(OTMS)$	$-CH_2COPh$	70
$HC{\equiv}CCH_2TMS$	$-CH_2{=}C{=}CH_2$	90

[a] $TiCl_4$ was used.

Scheme 226

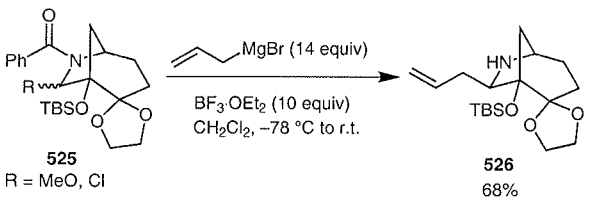


Scheme 227

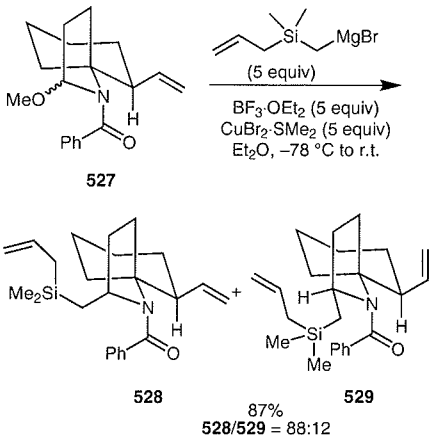
sponding products **524** in yields of 60–69% (Scheme 227).[52]

The reaction of allylmagnesium bromide with a mixture of the α-methoxy and α-chloro benzamides **525** under boron trifluoride–diethyl ether complex catalysis afforded the *exo*-allylated product **526** in 68% yield and also led to the removal of the *N*-benzoyl group (Scheme 228).[121]

Treatment of the α-methoxy lactam **527** with an organocopper reagent, generated in situ from the corresponding Grignard reagent and copper(II) bromide–dimethyl sulfide complex, led to the formation of an 88:12 mixture of products **528** and **529** in 87% yield (Scheme 229).[124]

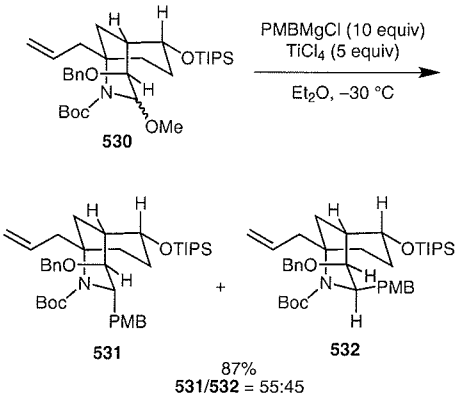


Scheme 228



Scheme 229

Treatment of **530** with 4-methoxybenzylmagnesium chloride under titanium(IV) chloride catalysis provided products **531** and **532** in a ratio of 55:45 and in 87% yield (Scheme 230).[125]

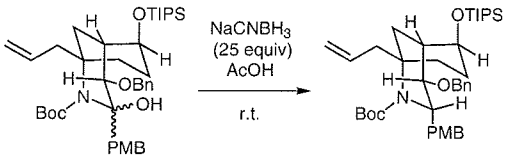


Scheme 230

In the same study, compound **533** was treated with sodium cyanoborohydride in acetic acid to give the desired product **534** as a single isomer in 69% yield (Scheme 231).[124]

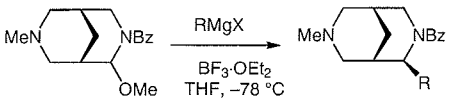
The α-methoxy bispidine **535** underwent reaction with Grignard reagents to afford the corresponding α-substituted bispidines **536** in 61–89% yields (Scheme 232).[126]

Treatment of Grignard and zinc reagents with the chiral isoquinoline derivative **537** in the presence of $Ph_3C^+BF_4^-$ led to the formation of diastereomeric products **538** and **539** in 65–98% yields (Scheme 233).[127]



533 534 69%

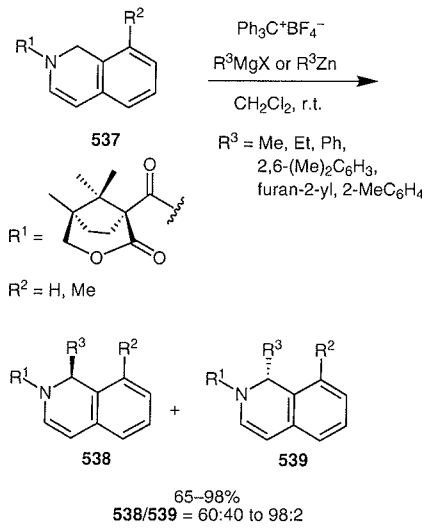
Scheme 231



535 536 61–89%

R = Me, Bn, CH_2=$CHCH_2$, CH_2=$CHCH_2CH_2$
X = Cl, Br

Scheme 232



537

R^3 = Me, Et, Ph, 2,6-$(Me)_2C_6H_3$, furan-2-yl, 2-MeC_6H_4

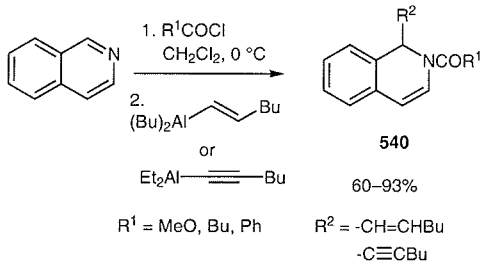
R^2 = H, Me

538 539

65–98%
538/**539** = 60:40 to 98:2

Scheme 233

Treatment of quinolidine with acyl chlorides and then organoaluminium reagents gave products **540** in yields of 60–93% (Scheme 234).[119]



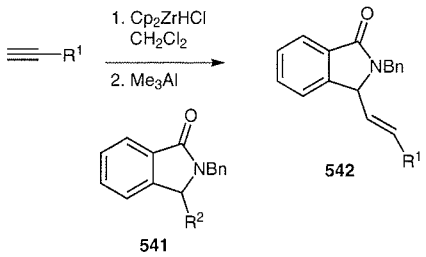
540

60–93%

R^1 = MeO, Bu, Ph R^2 = -CH=CHBu, -C≡CBu

Scheme 234

Phthalimide **541** was treated with alkenylalanes, themselves generated by the hydrozirconation of alkynes and transmetallation to trimethylaluminium, to give products **542** in yields of 43–81% (Scheme 235).[128]



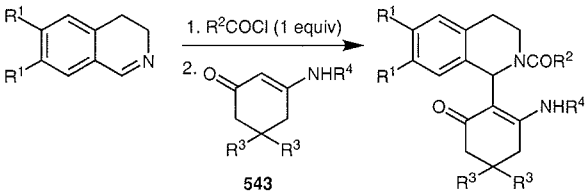
541 **542**

R^1 = Bu, *c*-C_6H_{11}, $CH_2CH_2OTBDPS$, $CH_2CH_2N(CO_2Me)Ts$
R^2 = OMe, OPiv

Scheme 235

3.5.1.3 Enamines

Cyclic enamino ketones **543** reacted with *N*-acyliminium ion salts of 3,4-dihydroquinoline to provide the adducts **544** in 31–78% yields (Scheme 236).[129]



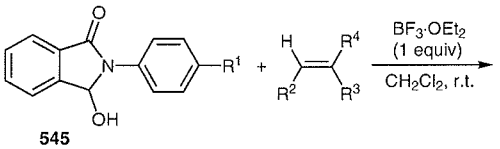
543 **544** 31–78%

R^1 = H, MeO
R^2 = Me, OEt, Ph
R^3 = H, Me
R^4 = Ph, Bn, $PhCH_2CH_2$, 3,4-$(MeO)_2C_6H_3CH_2CH_2$

Scheme 236

3.5.2 Cycloaddition Reactions

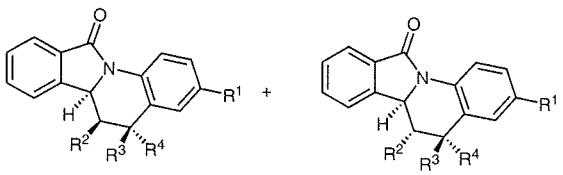
The [4+2]-cycloaddition reaction of phthalimide **545** with alkenes in the presence of boron trifluoride–diethyl ether complex led to the formation of cycloadducts **546** and **547** in yields of 45–94% as mixtures of *cis* and *trans* products in different ratios (Scheme 237).[130]



545

R^1 = H, Me, MeO

R^2 = H, Me, $C_6H_4CH_2$-, -$(CH_2)_2O$-, -$(CH_2)_3O$-
R^3 = H, Ph, Bn
R^4 = H, Me, EtO



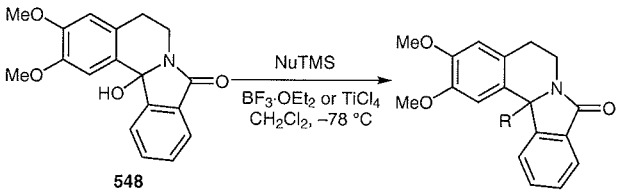
546 45–94% **547**

Scheme 237

3.6 Other Systems

3.6.1 Silicon-Based Nucleophiles

The addition reaction of silicon nucleophiles to α-hydroxylactam **548** in the presence of boron trifluoride–diethyl ether complex or titanium(IV) chloride yielded the α-substituted products **549** in yields of 69–95% (Scheme 238).[131]



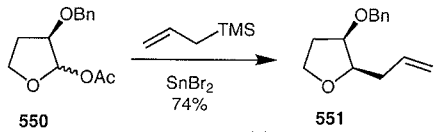
548 549

NuTMS	R
CH_2=$CHCH_2TMS$	-CH_2CH=CH_2
CH_2=$C(CH_2CH(SPh)_2)(CH_2TMS)$	-$CH_2C(Me)$=$CHCH(SPh)_2$
CH_2=C(Ph)(OTMS)	-CH_2COPh
CH_2=C(Me)(OTMS)	-CH_2COMe
CH_2=CHCH=CHOTMS	-CH_2CH=CHCHO

Scheme 238

4 Stereochemical Outcomes

A recent paper by Woerpel[132] on the stereochemical outcomes of the additions of nucleophiles to five-membered oxocarbenium ion intermediates are of relevance to our discussion here on the reactions of related five-membered-ring iminium ion intermediates. Woerpel has shown that the allylation reaction of dihydrofuran derivative **550** was *cis* selective (Scheme 239).



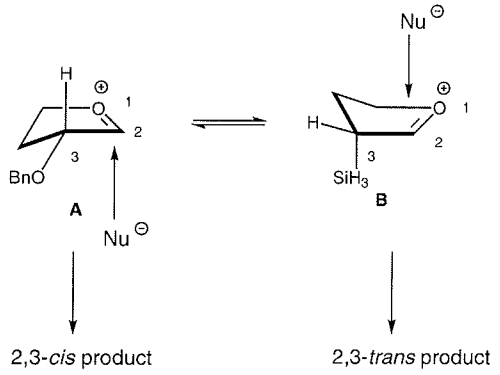
550 551

cis/*trans* = 85:15

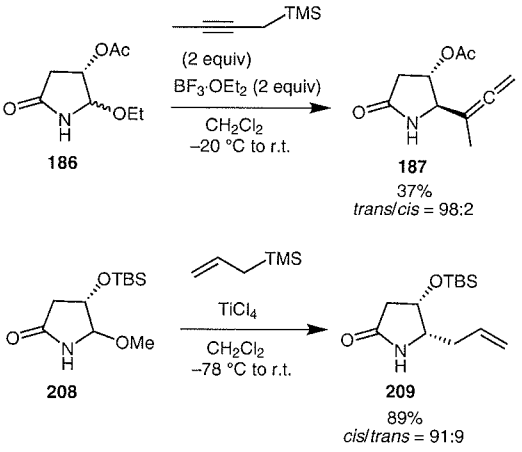
Scheme 239

This stereochemical outcome was consistent with nucleophilic attack on the oxocarbenium ion envelope conformation **A** from the 'inside' rather than on conformation **B**. Attack from the 'inside' gives rise to a more stable staggered product rather than an eclipsed product. Addition to the pseudo-equatorial conformation **A** is favoured over **B** due to stabilisation of the developing σ* orbital at C-2 by the pseudo-axial σ_{C-H} orbital at C-3 (Cieplak effect).[133] The σ_{C-H} bond is a better electron donor (more electron-rich) than the σ_{C-OBu} bond (Scheme 240).

A similar analysis on related five-membered-ring cyclic iminium ion intermediates is further complicated by the extra exocyclic or endocyclic carbonyl group, which further flattens the envelope conformation in the latter system. The N-substituent and its conformational preferences must also be considered in the latter. From a survey of the reactions in Section 3.2.1, it is clear that the nature of the O-substituent (OAc, OBn, OTBS), the N-substituent (NH, NBn, NPMB, N-allyl), the nucleophile and the Lewis acid can affect the diastereoselectivity and 4,5-*cis* to 4,5-*trans* selectivity. The examples that highlight the difference between a 4-OAc and 4-OTBS substituent in the N-unsubstituted case are shown in Scheme 241.



Scheme 240



186 187

37%

trans/*cis* = 98:2

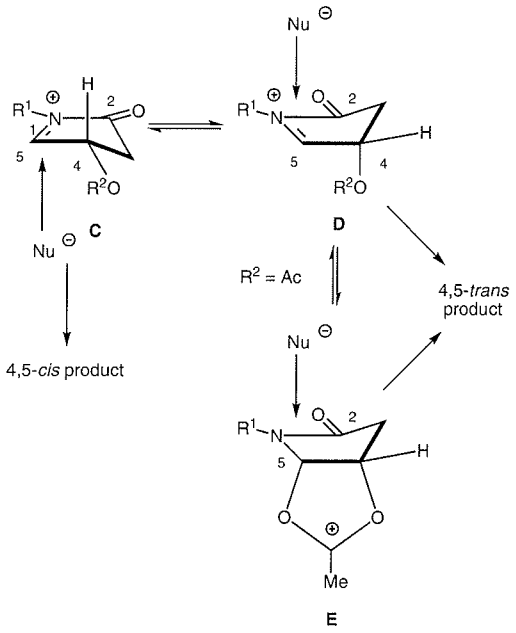
208 209

89%

cis/*trans* = 91:9

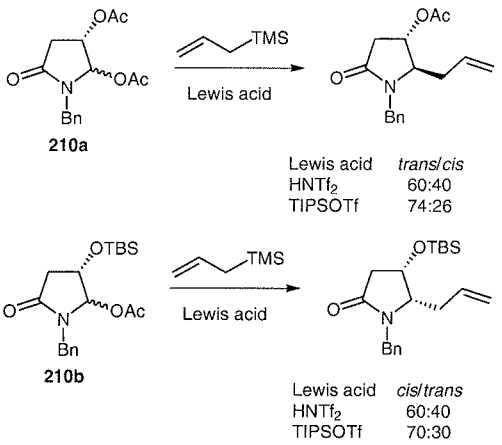
Scheme 241

Both reactions are highly diastereoselective; however, they show opposite *trans*/*cis* selectivity. The OAc derivative favours the 4,5-*trans* adduct while the OTBS derivative favours the 4,5-*cis* adduct. Thus, the OTBS derivative behaves similarly to the dihydrofuran **548** (Scheme 239) in its *cis* selectivity (Scheme 241). Indeed, the reactive envelope conformation **C** with the OTBS group (R^2 = TBS) in the favourable pseudo-equatorial orientation (Cieplak effect), can be invoked to explain this *cis* selectivity. The *trans* selectivity in the case of the OAc derivative can be rationalised by the neighbouring-group participation of the OAc group to give the bridged bicyclic cationic intermediate **E**. S_N2-like attack on this intermediate would provide the *trans* adduct (Scheme 242).



Scheme 242

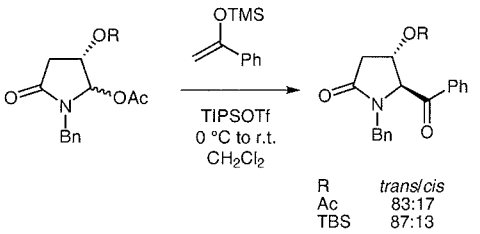
In the case of the allylation reaction of the related N-substituted pyrrolidinones,[54] the same reverse-sense *trans*/*cis* selectivity is observed between 4-OAc and 4-OTBS derivatives; however, the diastereoselectivity is considerably reduced (Scheme 243). Clearly the N-substituent is responsible for this erosion of diastereoselectivity. The influence of the N-substituent in the reactions of N-heterocyclic compounds has been well documented.[134,135]



Scheme 243

This *trans*/*cis* selectivity is also dependent upon the nucleophile, as illustrated in Scheme 244, in which the 4-OAc and 4-OTBS derivatives both favour formation of the *trans* adduct. It is possible that these reactions are under thermodynamic control.

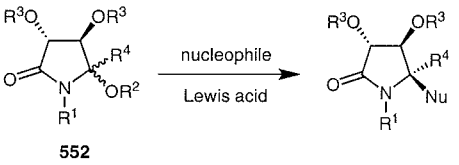
Titanium enolates are highly *trans* selective on 4-OTBS pyrrolidinone derivatives (Scheme 115). The addition of



Scheme 244

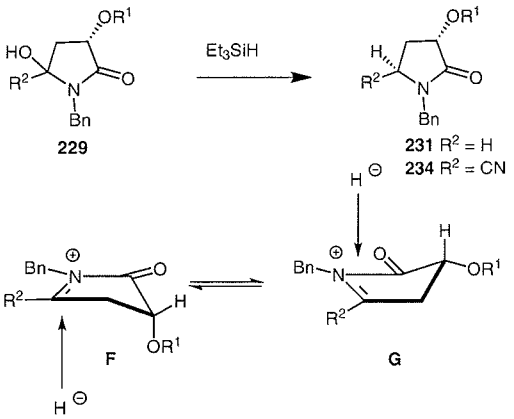
boronic acids to 4-OBn substituted pyrrolidinones are also *trans* selective (Schemes 111 and 112).

The reaction of 3,4-disubstituted pyrrolidinones **552** ($R^3 \neq$ Ac) often gave 4,5-*cis* adducts (R^4 = H) with high diastereoselectivities (Schemes 92, 93, 101, 102, and 103). 5,5-Disubstituted derivatives ($R^3 \neq$ Ac, $R^4 \neq$ H) gave products from nucleophilic addition *cis* to the C-4 OR^3 group (Schemes 89, 94, and 105). This can be attributed to the effect of the C-4 OR^3 group (Cieplak effect). In the cases where the C-3 and C-4 groups are acetate, a neighbouring-group effect by the C-3 acetate has been suggested to explain the 4,5-*cis* selectivity (Scheme 245).[79]



Scheme 245

In the case of the aminals **229**, reduction with triethylsilane and boron trifluoride–diethyl ether complex gave the 3,5-*cis* adducts (Scheme 246).

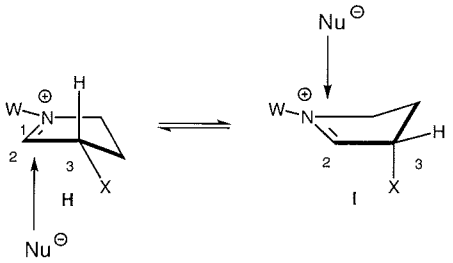


Scheme 246

In related oxocarbenium ions, the OR^1 substituent favoured the pseudo-axial orientation to help stabilise the cationic carbon of the oxocarbenium ion. A similar effect may be possible in conformation **F**; however, the OR^1 group may sterically impede the hydride nucleophile from

attacking. In conformation **F**, 1,3-allylic strain may project the *N*-benzyl group to the β-face of the iminium ion thus more effectively blocking the face to nucleophilic attack.[65]

From a survey of the reactions in Section 3.2 on *N*-acylpyrrolidines, it is clear that 2,3-*trans* products are normally favoured in the case where the 3-substituent is I (Schemes 131 and 162), $NHCO_2R$ (Scheme 131), alkyl (Scheme 147), aryl (Scheme 147) or allyl (Scheme 134). The exceptions are when the 3-substituent is OH or N_3, wherein *cis* products are formed almost exclusively (Schemes 146 and 131, respectively). When the 3-substituent is I or $NHCO_2R$, neighbouring-group participation can be used to explain the *trans* selectivity (compare with Scheme 241). When the C-3 substituent is OH, formation of a boronate intermediate can be invoked to explain the high *cis* selectivity as reported in Scheme 146. When the C-3 substituent is alkyl or N_3, steric and stereoelectronic arguments can be used to account for the stereoselectivities (Scheme 247).



Scheme 247

Because the hyperconjugative donating ability of a σ_{C-H} bond is similar to that of a σ_{C-C} bond, there would be little difference in electronic stabilisation of the transition states involving attack from the 'inside' on the pseudo-equatorial or pseudo-axial conformations **H** (X = alkyl) or **I** (Y = alkyl). Attack on conformation **H**, however, would result in unfavourable *gauche* butane interactions between the Nu and the X group, and thus attack would be expected to occur on compound **I** to give the *trans* product. When the C-3 substituent is N_3 then attack on conformation **H** would be favoured stereoelectronically since the C-3 σ_{C-H} bond is a much stronger electron donor than the σ_{C-N3} bond. Steric considerations are not important with the relatively smaller N_3 group.

Iminium ions generated from 4-substituted *N*-acylpyrrolidines give 2,4-*cis* products (Schemes 129 and 133). A reactive conformation analogous to **F** (Scheme 246) can explain the stereochemical outcome.

In general, reactions on the corresponding six-membered-ring *N*-acyliminium ion analogues have been less studied and often proceed with poorer diastereoselectivity. The stereochemical outcomes of the major products can often be rationalised as arising from axial attacks on a half-chair conformation.[134a,135]

5 Conclusions

The intermolecular addition reactions of *N*-acyliminium ions have been a major area of investigation by synthetic chemists over the past eight years. New methods to generate these cationic intermediates have been developed, including the use of new Lewis acid catalysts, polymer-supported precursors and electrochemical methods. The latter method has been successfully extended to peptide systems and can be used to prepare *N*-acyliminium ions in the absence of a nucleophile.

The reactions of *N*-acyliminium ions include the addition of nucleophiles, especially silicon-based ones, cycloaddition reactions, free-radical additions and nucleophilic aromatic substitution reactions. These latter reactions can be more selectively and efficiently performed using a micromixer. The applications of these methods to the synthesis of peptides, natural products and new pharmaceutical drugs will continue to grow over the next decade.

Acknowledgment

We thank the Australian Research Council for supporting our research in this area.

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