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

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

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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.

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

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, BMIMCl, 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-
ucts 305 in 92–100% yields (Scheme 119). The use of indium(IV) chloride in sodium dodecylsulfate and water has also been described for these reactions.\(^{2a}\)

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 ace- tophenone required 1.0 mol% of catalyst. The trimethylsilyl enol ether of cyclohexanone and the trisopropylsilyl ether of methyl isobutrate and trimethylsilyl triflate were 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-methyloxypyrrolidines 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 \(-78^\circ\)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.

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products, 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 trflate 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,5R by X-ray diffraction analysis.

Scheme 122

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

The reaction of allenyltrimethylsilane with the 2-ethoxy- pyrrolidine 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.

Scheme 124

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

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 alllyltrimethylsilane 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).

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.

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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 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-hydroxyproprillidine was isolated. Treatment of 325 with (trimethylsilyl)oxycyclohexene and trimethylylimoxoyfurans under the same reaction conditions gave addition products in 68% and 81% yields, respectively. 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.

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

The 3-substituted N-Cbz pyrrolidines 330a–e reacted with allyltrimethylsilane, cyano(trimethylsilane), 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–e and 3-iodo-2-methoxypyrrolidines 330d were obtained in moderate to excellent yields with high 2,3-cis selectivity (Scheme 130, equation 1), while 3-azido-2-methoxypyrrolidine 330e gave the adduct 331e in 49% yield and with high 2,3-cis selectivity (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' group (R' = NHCO₂R or i). The reaction of 2-ethoxy-4-butylpyrrolidine 332 with allyltrimethylsilanes 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 2,3-trans adduct.
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).³⁶

Scheme 133

Treatment of pyrrolidine 336 with allytrimethylsilane in the presence of boron trifluoride–diethyl ether complex provided the 2,3-trans product 337 in 99% yield (Scheme 134).³⁹

Scheme 134

The 2,3-O-isopropylidene-protected pyrrolidine 340 reacted with allytrimethylsilane 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 135).³⁶ Magnesium bromide, tin(IV) chloride, dichlorodisopropylxetan-um(IV), and ytterbium(III) triflate were found to be ineffective in this reaction.³⁹

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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 allylttrimethylsilylane in the presence of boron trifluoride-diethyl ether complex (Scheme 137). The allylttrimethylsilylane 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-benzoxycyclopentylmagnesium bromide provided only the 3,5-trans adduct 348 in 58% yield (Scheme 138).72

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% yield. The prolines 328a–c (R1 = CO2Me or Cbz) gave exclusively the 2,5-cis products (Scheme 139, equation 1), whereas the prolines 328b,d (R1 = CHO or Bz) yielded the arylated adducts 349 as a mixture of isomers favouring the trans isomer (Scheme 139, equation 2).85

Scheme 138

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Scheme 139

328a R1 = CO2Me 328c R1 = Cbz
328b R1 = Bz 328c R1 = CHO
328b R1 = Bz 328c R1 = CHO
349
33–71% trans/cis = 89:11 to 48:52
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).\(^\text{69}\)

\[
\begin{align*}
&\text{[Image: Organicstannane representation]} \\
&\text{Scheme 140}
\end{align*}
\]

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.\(^\text{93}\)

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).\(^\text{88}\)

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.\(^\text{88}\)

The reactions of zinc alkynylides, prepared in situ, with 2-methoxypropyrrolidine 304 in the presence of zinc triflate afforded the corresponding 2-substituted products 357 (Scheme 144).\(^\text{82}\)

Alkynes reacted with 2-methoxypropyrrolidines 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).\(^\text{94}\)

As an extension of an earlier study,\(^\text{95}\) the reaction of the racemic 2,3-dihydroxypyrrrolidine 359 with an alkynylboronate led to the 2,3-cis product 360 in 99% yield and with high 2,3-cis selectivity (cis/trans = 98:2) (Scheme 146).\(^\text{98}\)

Organocopper reagents were treated with 3-substituted 2-methoxypropyrrolidines 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.\(^\text{96}\)

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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-acetyliminium ion, or the reaction follows an $S_N2$ mechanism.\(^{24}\)

Scheme 143

\[
\begin{align*}
\text{N} & \text{CO}_2\text{Me} \\
\text{EIMX (2.0 equiv)} & \text{Et}_2\text{O} \text{or hexane} \\
\text{Et}_2\text{O or hexane} & \text{Et}_2\text{O}_2 -72 \, ^\circ\text{C} \\
\text{Yield (%)} & \text{Et}_2\text{Zn} \\
\text{ElZn} & 74 \\
\text{ElZn} & 65 \\
\text{ElAl} & 72 \\
\text{ElAlCl} & 55 \\
\end{align*}
\]

Scheme 144

\[
\begin{align*}
\text{N} & \text{OMe} + \text{R} \xrightarrow{\text{TMEDA (1 equiv)}} \text{CH}_2\text{Cl}_2-\text{toluene} \\
\text{H}_2\text{O}, 40-50 \, ^\circ\text{C} & \text{sonication} \\
\text{Boc} & \text{Ph} \\
\text{R} & \text{TMS} \\
\text{R} & 48\% \\
\text{R} & 59\% \\
\end{align*}
\]

Scheme 145

The 3,5-disubstituted N-Boc proline 365 reacted with 2-methylpropenyl lithium 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).\(^{97}\)

Scheme 146

3.2.2.5 Carbonyl Compounds

The reaction of N-Boc-2-ethoxypropyrrolidine 309a with the $N,O$-silyketene acetal, itself prepared in situ by treatment of $N$-propionylxazolidin-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).\(^{38}\)

The 5-methoxypropyrrolidine 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 $-78 \, ^\circ\text{C}$ 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).\(^{39}\)

The titanium enolates of N-acylloxazolidinones 373a-d reacted with N-tert-butoxy carbonyl-2-ethoxypropyrrolidine (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)
The reaction of 2-alkoxypyrrolidines 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).  

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).  

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, gave the reaction products with 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).
gave the addition products 382a,b as single isomers in 82–84% yields (Scheme 155). \(^\text{100}\)

The titanium enolate of 2-pyridylthio ester 384 was treated with 2-methoxy pyrrolidine 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). \(^\text{101}\)

![Chemical structures](image)

**Scheme 155**

The boron enolates of the oxazolidin-2-ones 373a,b were treated with N-tert-butyloxycarbonyl-2-ethoxy pyrrolidine (309a) in the presence of dibutylboryl trflate (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). \(^\text{98}\)

![Chemical structures](image)

**Scheme 156**

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). \(^\text{15}\)

![Chemical structures](image)

**Scheme 157**

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). \(^\text{49}\)

![Chemical structures](image)

**Scheme 158**

3.2.2.6 Alkyl Radicals

The N-acyliminium ion 302 reacted with alkyl halides in the presence of hexabutyl distannane to give the 2-substituted pyrrolidine adducts 355 (Scheme 158). \(^\text{31,42}\)

![Chemical structures](image)

**Scheme 159**

![Chemical structures](image)

**Scheme 160**

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3.2.2.8 Active Methylene Compounds

1,3-Dicarbonyl compounds were treated with α-methoxypyrrrolidine 304 in the presence of indium(III) chloride under solvent-free conditions to afford the 2-substituted pyrrrolidines 387 (Scheme 161). Use of ethyl acetylacetone (R¹ = Me, R² = OEt), acetylacetone (R¹ = R² = Me) and diethyl malonate (R¹ = R² = OEt) gave products in 92%, 94%, and 83% yields, respectively. The use of indium(IV) chloride in sodium dodecylsulfate and water has also been described for these reactions.12b

![Chemical structure](image)

**Scheme 161**

The reaction of 3-iodo-2-methoxypyrrrolidine 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).17

![Chemical structure](image)

**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-bromoallytrimethylsilane in the presence of boron trifluoride–diethyl ether complex afforded 4,5-trans products 390 with very high selectivity (trans/cis = 87:13 to 98:2) in 85–92% yields (Scheme 163).102

![Chemical structure](image)

**Scheme 163**

3.2.3.2 Organometallic Reagents

Treatment of oxazolidinone 393 with organocupper 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).103

![Chemical structure](image)

**Scheme 165**

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

![Chemical structure](image)

**Scheme 164**

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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).  

6-Acetoxy-piperidinone 402 underwent reaction with propargyltrimethylsilane to provide the allenone product 403 in 90% yield (Scheme 171).  

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

The reaction of racemic 6-methoxy-piperidinone 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 favor of the 4,6-trans isomer (trans/cis = 57:43 to 89:11) (Scheme 173). In the same study, piperidinone 406 reacted with CH₂Cl₂/OTMS(Ph) in the
presence of scandium(III) triflate in acetonitrile to give product 407 in 88% yield and with a trans/cis ratio of 78:22.\textsuperscript{105}

### 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).\textsuperscript{106}

### 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).\textsuperscript{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.\textsuperscript{51}

Scheme 176

### 3.3.2 Reactions of N-Acylpiperidinone-Based N-Acylliminium 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).\textsuperscript{52}

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). The use of indium(IV) chloride in sodium dodecylsulfate and water has also been described for these reactions.

Scheme 178

Piperidine 412 also reacted with silicon nucleophiles in an ionic liquid (BMIInCl4) to yield the corresponding 2-substituted piperidines 413 in 65–76% yields (Scheme 179).

Scheme 179

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

Scheme 180

In a very similar study, piperidine 416a reacted with 2-[(trisopropyl)siloxyl]-5-methylfurain 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 regiosomer 422 was not obtained from the reaction of piperidine 416b (Scheme 182).

Scheme 182
adducts 424a,b and 425a,b (Scheme 183). Treatment of 423a with the silyloxynorbornene 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 silyloxynorbornene 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 allytrimethylsilane 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

Scheme 185

The reaction of bN-Boc piperidine 433 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 186).109

The N-acyl piperidines 437a,b were treated with allytrimethylsilane 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

Scheme 187

The reaction of N-Fmoc piperidine 439 with silicon nucleophiles in the presence of boron trifluoride-diethyl ether complex provided the products 440 and 441 in a
range of yields (78–96%), with good 2,6-cis selectivity. The reaction of 439 with CH$_2$CH=CH(TMS)(CH$_3$)$_2$Me afforded the corresponding 2,6-cis adduct exclusively (Scheme 190).\textsuperscript{111}

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).\textsuperscript{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).\textsuperscript{106}

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).\textsuperscript{38}

Piperidine 412 reacted with an in situ generated zinc alkynylide to give the corresponding propargylic adduct 449 in 40% yield (Scheme 195).\textsuperscript{52}

The polymer-bound racemic piperidine 431 was treated with diethylzinc in the presence of boron trifluoride–
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-propionylloxazolidine-2-one 367 with trimethyl 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}
The titanium enolates of 373a–d reacted with the N-acetyl piperidines 416a–c to afford the diastereomeric products 460 and 461 in 60–73% yields (Scheme 200).\(^{98}\)

![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).\(^{98}\)

![Scheme 201]

### 3.3.2.1.6 Alkyl Radicals

The N-aclylminium ion 447 was treated with heptyl iodide in the presence of hexabutyldistannane to give the 2-heptyl-N-acylpyperidine 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).\(^{111}\)

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).\(^{114}\)

### 3.3.2.1.8 Active Methylene Compounds

The indium(III) chloride catalysed reaction of piperidine 412 with acetylacetonate (R¹ = Me, R² = OEt), acetylacetone (R¹ = R² = Me), and diethyl malonate (R¹ = R² = 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.\(^{82b}\)
The N-acylpyrrolidines 470 reacted with 1,3-dicarbonyl compounds in the presence of copper(II) triflate and bisoazoline 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 diasteroermerically 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).^{118}
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 diastereoselectivities (Scheme 212).\textsuperscript{120}

\[ \text{Scheme 212} \]

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.\textsuperscript{94}

\[ \text{Scheme 213} \]

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).\textsuperscript{116}

\[ \text{Scheme 214} \]
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 trisopropylsilyl triflate catalysis afforded the desired products 498 in 45–89% yields (Scheme 215). In a similar study the phthalimide 497 reacted with CH₂=CHC(OTIPS)C=CH₂ (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.

In the same study, the trisopropylsilyl 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).

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).

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

Treatment of bicyclic imide 506 with sodium borohydride and then triethysilane 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).

Isoquinoline derivative 509 reacted with silicon nucleophiles in an ionic liquid, BMI-InCl₃, to give the corre-
The reaction of 511 with allytrimethylsilane 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).\textsuperscript{131}

Scheme 224

The reaction of tetraoxobispidine 519 with allytrimethylsilane 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 allytrimethylsilane under the same reaction conditions yielded the diallylated product 521 as a single isomer in 76% yield (Scheme 225).\textsuperscript{132}

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).\textsuperscript{135}

3.5.1.2 Organometallic Reagents

The addition reactions of in situ generated zinc alkynylides to isquinoline derivative 509 gave the corre-
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).  

Treatement 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).  

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).  

The α-methoxy bispinide 535 underwent reaction with Grignard reagents to afford the corresponding α-substituted bispinides 536 in 61–89% yields (Scheme 232).  

Treatement of Grignard and zinc reagents with the chiral isoquinolines derivative 537 in the presence of Ph3C•BF4• led to the formation of diastereomeric products 538 and 539 in 65–98% yields (Scheme 233).
Scheme 231

Scheme 232

Scheme 233

Treatment of quinolinidine with acyl chlorides and then organoaluminium reagents gave products 540 in yields of 60–93% (Scheme 234).\textsuperscript{119}

Scheme 234

Phthalimide 541 was treated with alkenylalanes, themselves generated by the hydrozirconation of alkynes and transmetalation to trimethylaluminium, to give products 542 in yields of 43–81% (Scheme 235).\textsuperscript{118}

Scheme 235

3.5.1.3 Enamines

Cyclic enamine ketones 543 reacted with N-acyliminium ion salts of 3,4-dihydroquinoline to provide the adducts 544 in 31–78% yields (Scheme 236).\textsuperscript{129}

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).\textsuperscript{130}
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).

![Scheme 238](image)

Scheme 238

4 Stereochemical Outcomes

A recent paper by Woerpel 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).

![Scheme 239](image)

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 σπ orbital at C-2 by the pseudo-axial σC-H orbital at C-3 (Cieplak effect). The σC-H bond is a better electron donor (more electron-rich) than the σC-O 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, NMB, 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-unsaturated case are shown in 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 (R² = 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. S₉₂-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, 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.

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

The reaction of 3,4-disubstituted pyrrolidinones 552 (R3 ≠ Ac) often gave 4,5-cis adducts (R4 = H) with high diastereoselectivities (Schemes 92, 93, 101, 102, and 103). 5,5-Disubstituted derivatives (R3 ≠ Ac, R4 ≠ H) gave products from nucleophilic addition cis to the C-4 OR3 group (Schemes 89, 94, and 105). This can be attributed to the effect of the C-4 OR3 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).

Scheme 244

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 245

In related oxocarbenium ions, the OR1 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 OR1 group may sterically impede the hydride nucleophile from

Scheme 246
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.\(^6\)

From a survey of the reactions in Section 3.2 on N-acylpyrrolidines, it is clear that 2,3-\(\textit{trans}\) products are normally favoured in the case where the 3-substituent is I (Schemes 131 and 162), NHCO-R (Scheme 131), alkyl (Scheme 147), aryl (Scheme 147) or alky (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-R, neighbouring-group participation can be used to explain the \(\textit{trans}\) 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](image)

Because the hyperconjugative donating ability of a \(\sigma_{C-H}\) bond is similar to that of a \(\sigma_{C-C}\) bond, there would be little difference in electronic stabilization 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 \(\sigma_{C-H}\) bond is a much stronger electron donor than the \(\sigma_{C-N}\) 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, cycladdition reactions, free-radical additions and nucleophilic aromatic substitution reactions. These latter reactions can be more selectively and efficiently performed using a micro-mixer. The applications of these methods to the synthesis of peptides, natural products and new pharmaceutical drugs will continue to grow over the next decade.

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References

(135) Huang, P.-Q. Synlett 2006, 1133.