## 6.02

**Pyridines and Their Benzo Derivatives: Reactivity at the Ring**

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6.02.1 Introduction: General Reactivity Patterns

Substitution reactions of pyridines and their benzo derivatives continue to attract considerable attention as they play an important role in the preparation of biologically active compounds and new materials. In general, pyridine derivatives are thermally and photochemically stable, but can be attacked by electrophiles at ring nitrogen and certain carbon atoms. Strong nucleophiles can also react, generally at the α- or γ-ring carbon atoms of the pyridine ring. Patterns of general reactivity for electrophilic and nucleophilic attack are depicted in Figures 1 and 2. For a detailed discussion on reactivity, the reader is referred to the corresponding sections in CHEC(1984) and CHEC-II(1996).

Pyridines undergo radical substitution reactions preferentially at the 2-position. Yields and regioselectivity are generally higher if the reaction is carried out in an acid medium. The presence of a strongly electron-donating substituent (OH, OR, NR₂) on the pyridine ring can alter the reactivity pattern of electrophilic and radical substitution.

6.02.2 Electrophilic Attack at Nitrogen

6.02.2.1 Protonation and Salt Formation

Simple pyridines and their benzo derivatives are weak bases that form salts with strong acids. This is a very common reaction which is sufficiently described in CHEC(1984) and CHEC-II(1996) <1984CHEC(2)165, 1996CHEC-II(5)41>.
6.02.2.2 Lewis Acids


6.02.2.3 Alkyl Halides and Related Compounds

The quaternization of pyridine and its benzo derivatives using alkyl halides is well documented and these compounds have been used as versatile synthetic intermediates or as final products <2000OBC1071, 2005TL1137, 2005CHEC, 2004CHEC, 2003COR995, 2002TL7379, 2002S1530, 2001JHC909, 2001AHC269, 1997T14687>, have served as intermediates to biologically active compounds, and at times been studied for their own activity <2004OBC220, 2003JME4273, 2002CHE1098>. Chiral pyridinium-based ionic liquids have been prepared by N-alkylation of pyridines with chloromethyl(-menthyl) ether <2006TA1728>. A review on quaternary salts of pyridines and related compounds describing their synthesis, physiochemical properties, possible applications, and their biological activities has been published <2003COR995>.

Pyridinium hydrobromide perbromide salt was introduced by Djerassi and Scholz as an alternative brominating agent in 1948. Salazar and Dorta rationalized that since alkylpyridinium salts are well documented and commercially available room temperature ionic liquids, a combination of an alkylpyridinium cation with tribromide anion 1 should therefore lead to a room temperature ionic liquid bromine analogue (Equation 1).

$$\text{N}^+\text{Br}^- + \text{Br}_2 \xrightarrow{\text{no solvent}} \text{N}^+\text{Br}_3^-$$

When tested on several organic substrates, the reagent was capable of selectively monobrominating ketones along with aromatics and phenols. Anisole, for example (entry iii), required the addition of Na$_2$CO$_3$ to prevent the hydrolysis of the methoxy group whereas alkenes and alkynes were also susceptible to bromination by the reagent (entries v–vii) <2004SL1318>.

The versatility of γ-thioquinolinium salts was effectively demonstrated by Vaseux who was able to prepare, using an Eschenmoser approach, N-substituted 4-alkylidenequinolines such as 3 <1995S56>. Starting with 4(1H)-quinolinedithione, the alkylation of sulfur was accomplished using K$_2$CO$_3$ as the base, and quaternization of the quinoline nitrogen with various reactive alkyl bromides produced the desired quinolinium salts 2. A combination of R$_1$, R$_2$, and R$_3$ were investigated with variable yields. The extrusion of sulfur from the intermediates 2 using a phosphite reagent gave the desired final products 3 in reasonable yields (Scheme 1).

Several chiral N-acylpyridinium and related salts (Figure 3) have been prepared and studied as electrophiles for asymmetric nucleophilic addition reactions <2001CC1166, 2003TA1691, 1996CPB267, 2001TL6109, 2000EJO1391, 2004TA3919, 1998JOC1767>.

Expanding on established chemistry using N-acylpyridinium salts as intermediates for the preparation of N-acyldihydropyridines and dihydropyridones, Wanner and co-workers examined a method using a bicyclolactone
Table 1  Solvent-free bromination using pentylpyridiniumtribromide 1 at room temperature

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>i</td>
<td></td>
<td></td>
<td>85</td>
</tr>
<tr>
<td>ii</td>
<td></td>
<td></td>
<td>93</td>
</tr>
<tr>
<td>iii</td>
<td></td>
<td></td>
<td>90</td>
</tr>
<tr>
<td>iv</td>
<td></td>
<td></td>
<td>81</td>
</tr>
<tr>
<td>v</td>
<td></td>
<td></td>
<td>90</td>
</tr>
<tr>
<td>vi</td>
<td></td>
<td></td>
<td>84</td>
</tr>
<tr>
<td>vii</td>
<td></td>
<td></td>
<td>92</td>
</tr>
</tbody>
</table>

Scheme 1
Using $^1$H NMR spectroscopy to track the formation of the $N$-acylpyridinium salt, it was revealed that in addition to reaction concentration a great improvement in salt formation was achieved by employing trialkylsilyl triflates as additives. These conditions improved the yields of the subsequent addition reactions (Equation 2) <2000JOC9272>. Yamaguchi et al. had previously reported that certain additives such as AgOTf, NaOTf, LiOTf, AgBF$_4$, and Me$_3$SiOTf increased the reactivity of $N$-acyl salt ions generated from quinoline and chloroformates <1997TL403, 1998CL547>. They also demonstrated that addition reactions of allylsilanes to $N$-acylquinolinium salts are promoted by a catalytic amount of triflate ion to give 2-allyl-1,2-dihydro-quinoline derivatives in good yields <2001T109>.

Acid as the chiral auxiliary <2002T6757>. Using $^1$H NMR spectroscopy to track the formation of the $N$-acylpyridinium salt, it was revealed that in addition to reaction concentration a great improvement in salt formation was achieved by employing trialkylsilyl triflates as additives. These conditions improved the yields of the subsequent addition reactions (Equation 2) <2000JOC9272>. Yamaguchi et al. had previously reported that certain additives such as AgOTf, NaOTf, LiOTf, AgBF$_4$, and Me$_3$SiOTf increased the reactivity of $N$-acyl salt ions generated from quinoline and chloroformates <1997TL403, 1998CL547>. They also demonstrated that addition reactions of allylsilanes to $N$-acylquinolinium salts are promoted by a catalytic amount of triflate ion to give 2-allyl-1,2-dihydro-quinoline derivatives in good yields <2001T109>.
When first reported in 1905, the Reissert reaction demonstrated the addition of KCN to quinoline in the presence of benzoyl chloride, but many new modifications since then have employed other nucleophiles and catalytic promotion by a Lewis acid. Shibasaki reported in 2001 the first catalytic enantioselective Reissert-type reaction. Optimized reaction conditions involving an electron-rich aromatic acid chloride in a low-polarity solvent, and use of catalyst 14, were found to suppress the racemic pathway and resulted in good enantioselectivity (Scheme 2) \(<2001\text{JA}6801\>.

Transfer of the dimethylcarbamoyl group from \(N\)-acyloxypyridinium salts to pyridines and from \(N\)-acylpyridinium salts to pyridine \(N\)-oxides was studied in acetonitrile. Equations relating the reaction rates and equilibria in the \(N\)-\(O\) and \(O\)-\(N\) acyl-transfer series to the basicity of the nucleophile and leaving group were obtained. The reactions all are single stage and occur by the forced concerted \(S_n2\) mechanism \(<2004\text{RJC}1597\>.

Studies on the influence of \(N\)-acylpyridinium salt formation on the observed reaction rate have been reviewed \(<1997\text{MI}67\>.

### 6.02.2.5 Activated Alkenes

An improved preparation of precursors to cyanine dyes by means of the 1,4-addition of pyridines and quinolines to acrylamide was recently described by Deligeorgiev (Equations 3 and 4) \(<2005\text{DP}21\>.

\[
\begin{align*}
\text{Ph} & + \text{ClO}_2\text{CO}_2\text{H} \rightarrow \text{Ph} + \text{ClO}_2\text{CO}_2\text{H} \\
\text{PhMgBr} & + \text{Pr}_3\text{SiOTf} \rightarrow \text{PhMgBr} + \text{Pr}_3\text{SiOTf} \\
\text{Me}_3\text{SiOTf} & \quad \text{Yield 12 + 13(%) d.s. 12/13} \\
\text{PhMgBr} & + \text{Pr}_3\text{SiOTf} \rightarrow \text{PhMgBr} + \text{Pr}_3\text{SiOTf} \\
\text{Me}_3\text{SiOTf} & \quad \text{Yield 12 + 13(%) d.s. 12/13} \\
\end{align*}
\]
pyridinium 15 or quinolinium salt 17 in acetic acid in the presence of a catalytic amount of the respective base of the substrate with acrylamide under reflux produced salts 16 and 18 in good yield. These conditions allowed the reaction to be run in the absence of water. In all these cases, acetic acid does not only serve as a solvent but rather effectively inhibits the polymerization of the acrylamide.

\[
\begin{align*}
\text{15} + \text{AcOH} & \rightarrow \text{16} \\
\text{17} + \text{AcOH} & \rightarrow \text{18}
\end{align*}
\]

<table>
<thead>
<tr>
<th>R</th>
<th>X</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Cl</td>
<td>91</td>
</tr>
<tr>
<td>Me</td>
<td>Br</td>
<td>90</td>
</tr>
</tbody>
</table>

6.02.2.6 Halogens

\[N^*,N^*-\text{Difluoro-2,2'-bipyridinium bis(tetrafluoroborate)}\] 19, prepared in one pot by introducing BF₃ gas into 2,2'-bipyridine at 0°C followed by fluorine gas diluted with nitrogen, was shown to be a highly reactive electrophilic fluorinating agent (Equation 5) <2003JFC173>.

\[
\text{19}
\]

Synthetically useful phosphorane-derived phenyldiodonium triflates have been synthesized from the highly electrophilic pyridinium complex 20 <2002TL2359>. Similarly, benziodoxole 21 reacts with trimethylsilyl trifluoromethanesulfonate (TMSOTf) and pyridine to form a precipitate of complex 22 (Equation 6) <2002TL5735>. The first example of a pentavalent iodine complex with a chelating polydentate nitrogen ligand 24 was obtained from diacetate 23 under similar conditions (Equation 7) <2002TL5735>.

\[
\text{21} + \text{TMSOTf, CH}_2\text{Cl}_2 \rightarrow \text{22}
\]
1,2-Bis(2'-pyridylethynyl)benzenebromonium triflate 25 was prepared as shown in Equation (8) to study the transfer of Br\(^+\) to various olefinic acceptors (<2001IC3097, 2003JOC3802>).

\[
\begin{align*}
\text{pyridine} + \text{F}_2 & \xrightarrow{\text{CH}_2\text{Cl}_2, -60^\circ \text{C}} \text{N-F} \text{pyridinium salt 26} \\
\text{2-pyridylglyoxamide} & \xrightarrow{-60^\circ \text{C} \text{ to rt}} \text{31–71\%} \\
\text{pyridine chloride} & \xrightarrow{-60^\circ \text{C} \text{ to rt}} \text{10–40\%} \\
\text{pyridine carboxamide} & \xrightarrow{-60^\circ \text{C} \text{ to rt}} \text{5–8\%}
\end{align*}
\]

Similarly, the fluorine salts of 2-quinoline and 1-isoquinoline can also be harnessed to generate carboxamides 27 and 28 albeit in moderate yields (Equations 9 and 10) (<2005TL2279>).
6.02.2.7 N-Oxidation

N-Oxides, obtained by the oxidation of pyridine and its benzo analogues, are versatile intermediates in organic synthesis [2005BML883, 2003TL6643, 2003DP223, 2003CHE1263]. Reagents used for N-oxide formation include peracids, H₂O₂/AcOH, H₂O₂/manganese tetrakis(2,6-dichlorophenyl)porphyrin, H₂O₂/methyltrioxorhenium, dimethyldioxirane, bis(trimethylsilyl) peroxide, Caro’s acid, oxaziridines [2001ARK242], trifluoroacetic anhydride (TFAA)/H₂O₂–urea complex [2000TL2299], HOF/CH₃CN [1999S1427], O₂/ruthenium, [2002CC1040], H₂O₂/molecular sieves [2002JMO109], O₂/cobalt [2003AGE1265], trichloroisocyanuric acid/AcOH [2004SC247], bromamine-T/RuCl₃ [2004TL4281], and TBHP/MoCl₅ [2006RCB331].

Besides activating the ring for substitution reactions, the N-oxide moiety can serve as an effective nitrogen-protecting group. For example, in order to suppress the product of N–N bond formation (Equation 11) in favor of the desired C-4 reaction product 32, azide 31 was prepared from N-oxide 29 in two steps (Scheme 4) [2002TL6035].

When subjected to the same reaction conditions as used in Equation (11), N-oxide 31 gave the desired product 32 in a moderate yield, presumably by cyclization of the azido compound followed by thermal deoxygenation of the N-oxide intermediate (Scheme 4).
Alternatively, nucleophilic attack of the $N$-oxide 30 at the electrophilic carbon atom followed by nitrogen elimination results in formation of benzisoxazolo[2,3-$b$]isoquinoline 33 which in turn under thermolysis reaction conditions gives product 34 in 65% yield along with ca. 15% of the $p$-fluorophenol derivative 35 (Scheme 5). The latter product was successfully eliminated when the BF$_4^-$ anion of 30 was replaced by HSO$_4^-$. 

$$\begin{align*}
\text{BF}_4^- & \quad \text{CH}_3\text{CN, rt, 8 h} \quad 82\% \\
30 & \quad \text{o-dichlorobenzene} \quad \text{MW, 170 }^\circ\text{C, 30 min} \\
\text{BF}_4^- & \\
& \\
\text{33} & \\
\text{65\%} & \\
\text{34} & + \\
\text{35} & \\
\text{13\%} & \\
\end{align*}$$

Scheme 5

Although the reduction of pyridyl $N$-oxides with baker’s yeast has been reported, the reaction has not been readily employed due to the low yields and long reaction times. Baik et al. found that addition of NaOH greatly increased the efficiency of the reaction, thus producing the desired products in high yield (Equations 12 and 13) <1997TL845>. Several methods are available for the reduction of heteroaromatic $N$-oxides <2001ARK242>.

$$\begin{align*}
& \text{R} & \text{Yield (\%)} \\
& \text{H} & 95 \\
& \text{3-Br} & 96 \\
& \text{2-Me} & 87 \\
& \text{6-Me} & 93 \\
& \text{6-OMe} & 90 \\
\end{align*}$$

(12)

$$\begin{align*}
& \text{R} & \text{Yield (\%)} \\
& \text{H} & 90 \\
& \text{Br} & 86 \\
\end{align*}$$

(13)

6.02.2.8 Carbenes

Pyridine effectively stabilizes the short-lived organic carbenes 36 by forming the corresponding pyridinium ylides 37 that are far more stable than the starting carbene (Equation 14).

$$\begin{align*}
\text{36} & \quad + \\
\text{37} & \\
\text{R} & \quad H \\
\text{H} & \quad H \\
\end{align*}$$

(14)
Pyridinium tungstate 40, prepared from phenyl ethoxy carbene 38 and dihydropyridine 39, serves as an effective cyclopropanation reagent to give products 41 and 42 in 95:5 ratio and in 35% yield (Scheme 6) <1998JOM119>.

\[
\begin{align*}
\text{[C(O)W} \text{Ph})_{3} \text{]+ \text{PhMe}N} & \rightarrow \text{[C(O)W} \text{Ph})_{3} \text{]+ PhMeN} \\
38 & \quad 39 \\
\end{align*}
\]

Scheme 6

Similarly, enamines 44, and 45, react with complex 43 to give the corresponding cyclopropyl amines 46–49 (Scheme 7).

\[
\begin{align*}
\text{[C(O)W} \text{Ph})_{3} \text{]+ PhMeN} & \rightarrow \text{[C(O)W} \text{Ph})_{3} \text{]+ PhMeN} \\
43 & \quad 44 \\
\end{align*}
\]

Scheme 7

Singlet fluorocarbenes 51 substituted with diphenylphosphoryl, phenylsulfanyl, and TMS groups were generated from endo-10-fluoro-exo-10-substituted tricyclo[4.3.1.0]decadienes 50 under photolysis conditions to produce the ultraviolet–visible (UV–Vis) active ylides 52 on reaction with pyridine (Scheme 8) <2004PCA1033>.

\[
\begin{align*}
\text{Pyridines and Their Benzo Derivatives: Reactivity at the Ring} \\
11
\end{align*}
\]

Similarly, pyridine traps both carbene 55 and 56 which are effectively generated under laser flash photolysis from precursors 53 and 54, respectively. Carbene 56 was found to have greater bimolecular reactivity than analogue 55. Since singlet carbene 55 is nonplanar, the filled hybrid orbital of the carbene can now interact with the $\pi'$-system of the carbonyl. This additional stability can be attributed to the lone pairs of the carbonyl coordinating with the empty $p$ orbital of the carbene (Scheme 9) <2001JA6061, 2002TL7>.
6.02.3 Electrophilic Attack at Carbon

6.02.3.1 Halogenation

Halogenation of pyridines can be effected using a variety of reagents which are not always mild and compatible with other functionalities in the molecule. As a rule, electrophilic substitution in the pyridine ring is more facile if electron-releasing substituents are present. An indirect method of monohalogenating 2-aminopyridine at the 5-position has been reported. Pyridinium \( N \)-(2′-pyridyl)aminide 57, prepared from 2,4-dinitrophenylpyridinium halide and 2-pyridylhydrazine \(<1994\text{T}4995>\), undergoes halogenation at the 5-position when subjected to 1 equiv of \( N \)-chlorosuccinimide (NCS), \( N \)-bromosuccinimide (NBS), or \( N \)-iodosuccinimide (NIS) in 78%, 71%, and 90% yield, respectively (Equation 15) \(<1995\text{T}8649>\).

\[
\begin{align*}
\text{Scheme 8} \\
\text{53: } R &= \text{CO}_2\text{Me} \\
\text{54: } R &= \text{CN} \\
\text{55: } R &= \text{CO}_2\text{Me} \\
\text{56: } R &= \text{CN} \\
\end{align*}
\]

\[
\begin{align*}
\text{(15)} \quad \begin{array}{ccc}
\text{NXS} & X & 58:59 \\
\text{NCS} & \text{Cl} & 95:5 \\
\text{NBS} & \text{Br} & 85:15 \\
\text{NIS} & \text{I} & 100:0 \\
\end{array}
\end{align*}
\]

The 2-amino-5-halopyridines 60 were then produced from the corresponding aminides using Zn/acetic acid for the N–N bond fission (Equation 16).

\[
\begin{align*}
\text{Scheme 9} \\
\text{57} \\
\text{58} \\
\text{59} \\
\text{60} \\
\end{align*}
\]
6.02.3.1.1 Chlorination

An interesting electrophilic substitution of the pyridyl ring through a pentacovalent phosphorane was discovered and optimized by Uchida et al. Although the treatment of tris(2-pyridyl)phosphine 61 with chlorine in CH$_3$CN or CH$_2$Cl$_2$ gives the crystalline product Py$_3$P$^+$Cl Cl$^-$, it was found that the addition of methanol under refluxing conditions resulted in the formation of the coupling product 62 along with trace amounts of 5-chloro-2,2'-bipyridyl 63. Upon additional evaluation of several protic solvents, including H$_2$O, MeOH, EtOH, i-PrOH, and t-BuOH, it was found that when the chlorination of 61 was carried out in CH$_3$CN in the presence of any of these solvents the yield of the 5-chloro coupling product 63 could be increased to 61–85% (Equation 17) <1995TL4077>.

![Image of chemical structures]

Furthermore, the chlorination and bromination of the substituted starting material 64 along with tris(2-pyridyl)phosphine oxide 65 were examined (Equation 18), and the results are summarized in Table 2.

![Image of chemical structures]

**Table 2** Halogenation of phosphine 64 or phosphine oxide 65 in methanol

<table>
<thead>
<tr>
<th>Entry</th>
<th>(64 or 65)$^a$</th>
<th>R</th>
<th>$X_2$</th>
<th>66 and 67</th>
<th>Yield$^b$(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>i</td>
<td>64</td>
<td>H</td>
<td>Cl$_2$</td>
<td>3</td>
<td>77</td>
</tr>
<tr>
<td>ii</td>
<td>65</td>
<td>H</td>
<td>Cl$_2$</td>
<td>8</td>
<td>62</td>
</tr>
<tr>
<td>iii</td>
<td>64</td>
<td>4-Me</td>
<td>Cl$_2$</td>
<td>6</td>
<td>63</td>
</tr>
<tr>
<td>iv</td>
<td>64</td>
<td>6-Me</td>
<td>Cl$_2$</td>
<td>2</td>
<td>73</td>
</tr>
<tr>
<td>v</td>
<td>64</td>
<td>6-Br</td>
<td>Cl$_2$</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>vi</td>
<td>64</td>
<td>H</td>
<td>Br$_2$</td>
<td>14</td>
<td>76</td>
</tr>
<tr>
<td>vii</td>
<td>65</td>
<td>H</td>
<td>Br$_2$</td>
<td>15</td>
<td>74</td>
</tr>
<tr>
<td>viii</td>
<td>64</td>
<td>4-Me</td>
<td>Br$_2$</td>
<td>36</td>
<td>48</td>
</tr>
<tr>
<td>ix</td>
<td>64</td>
<td>6-Me</td>
<td>Br$_2$</td>
<td>22</td>
<td>69</td>
</tr>
</tbody>
</table>

$^a$Starting material (SM).

$^b$Determined by gas chromatography.

Reaction of N-fluoropyridinium triflate with a base in methylene chloride affords 2-chloropyridine as the major product along with 2-pyridyl triflate and 2-fluoropyridine. This conversion may be explained by a singlet carbene produced through proton abstraction of the N-fluoropyridinium salt <1996JFC161>.
6.02.3.1.2 Bromination

A study by Brown and Gouliaev looking at the bromination of quinoline and isoquinoline found it highly dependent on the brominating agent, the acid used, the temperature and reaction concentration, with the monobromination of isoquinoline being much more regioselective than that of quinoline. Under optimal conditions, using NBS/H$_2$SO$_4$ or N,N-dibromoisocyanuric acid (DBI)/CF$_3$SO$_3$H, 5-bromoisoquinoline can be isolated in 72% yield. The use of 2.3 equiv of NBS in concentrated H$_2$SO$_4$ leads to a 76% isolated yield of 5,8-dibromoisoquinoline. Using this procedure, 5-bromoquinoline was obtained in a modest 44% yield, while using excess reagent led to 61% yield of 5,8-dibromoquinoline <2002S83>. Regioselective bromination of 2-methoxy-6-methylpyridine using 1,3-dibromo-5,5-dimethylhydantoin (DBH) provided a high yield (85%) of 5-bromo-2-methoxy-6-methylpyridine under mild conditions. Bromination of 4-dimethylaminopyridine (DMAP) and quinoline with DBH under similar conditions afforded the C-3 brominated products in 80% and 20% yield, respectively <1997TL4415>. Regioselective mono- and dihalogenations of amino, hydroxy, and methoxy pyridines with NBS in different solvents have been studied. In most cases, the monobrominated derivatives can be obtained regioselectively and in high yields <2001S2175, 2003SL1678>.

The valuable intermediate 5-bromo-2-trifluoromethylaminopyridine 69 was prepared in one step from pyridyl methyl dithiocarbamate 68 by reaction with tetrabutylammonium dihydrogentrifluoride (TBAH$_2$F$_3$) and DBH in boiling dichloromethane (Equation 19) <1995TL563>.

\[
\text{[N\text{N}Me\text{SMe}]} \xrightarrow{\text{DBH (5 mol)}} \text{[N\text{N}CF_3\text{Me}]} \quad \text{74%}
\]

Preparation of 5-monobromo- and 5,5'-dibromo-2,2'-bipyridine (bipy) occurs in moderate yields from bipy and simple, common reagents in two steps (Scheme 10) <1995TL6471>.

\[
\text{HBr(g)} \xrightarrow{\text{MeOH}} \text{[N\text{N}Br]} \quad \text{76%}
\]

\[
\text{i, Br}_2, 180^\circ \text{C, 72 h} \quad \text{Br} \quad \text{Br} \quad \text{12} \quad : \quad \text{64}
\]

\[
\text{68} \quad \text{69}
\]

\section*{Scheme 10}

6.02.3.1.3 Iodination

Direct electrophilic iodination of simple pyridines is difficult <1996CHEC-II(5)55>; however, regioselective introduction of an iodine on a pyridine derivative can be easily accomplished via iododesilylation or iododestannylation. A few examples are given in Equations (20–24) <2005JOC2494, 2005SL1188, 1998CEJ67, 1982CPB1731, 2005CAR15>.

\[
\text{Et}_3\text{Si} \quad \text{ICI} \quad \text{CH}_2\text{Cl}_2 \quad 93\%
\]

\[
\text{Me}_3\text{Si} \quad \text{I}_2, \text{KF, PhNO}_2 \quad \text{DMF} \quad 72\%
\]

\[
\text{Me}_3\text{Si} \quad \text{ICl} \quad \text{CH}_2\text{Cl}_2/\text{CCl}_4 \quad 56\%
\]
The iodination of pyridine, quinoline, and isoquinoline via α-metalation using lithium di-tert-butyltetramethylpiperidinozincate (TMP-zincate) proceeds smoothly at room temperature using iodine as the electrophile. The chemoselective deprotonative zincation generated 2-iodopyridine \(70\) and 1-iodoisooquinoline \(71\) in 76% and 93% yield, respectively. Quinoline metalated preferentially at the 8-position to give 61% yield of the 8-iodo derivative \(72\) and 26% yield of 2-iodoisooquinoline \(73\) (Equations 25–27) \(<1999JA3539>\).

Pyridinol \(74\) undergoes regiospecific iodination at C-2 with iodine under mild basic conditions to afford diol \(75\) in good yield (Equation 28) \(<2004T11751>\). The iodination of various bromohydroxypyridines with NIS in acetonitrile is completely regioselective \(<2003SL1678>\).

6.02.3.1.4 Fluorination

The preparation of fluorinated pyridine derivatives continues to be of considerable importance due to the effect that the fluorine atom can have on the physical, chemical, and biological properties of the heterocycle. Despite this, there are few reports on the direct electrophilic fluorination of pyridines. The treatment of various quinoline derivatives with elemental fluorine in acidic reaction media afforded mono- and difluorinated products where the halogenation occurred on the benzene ring of the heterocycles \(<2004JFC661>\).
An interesting electrophilic fluorination of azinyl-N-aminides 76 with XeF$_2$, followed by alkylation of the exocyclic nitrogen, gave pyridine derivatives 77. Reductive fission of the N–N bond provided 3-fluoro-2-aminopyridines 78 (Scheme 11) <1999JOC1007>.

**Scheme 11**

### 6.02.3.2 Nitration and Sulfonation

Pyridine undergoes nitration at least $10^{22}$ times slower than benzene whereas pyridine N-oxide, pyridones, and pyridinamines can be nitrated more easily <1992H(34)2179>. The sluggish reactivity of pyridines toward electrophilic substitution can be attributed to their protonation under the reaction conditions <2005OBC538>. The first reported nitration of pyridines with dinitrogen pentoxide in sulfur dioxide solution was shown by Bakke to give 3-nitropyridines 79 in good yield (Equation 29; Table 3) <1994ACS1001, 2003PAC1403, 2005JHC463>. He proposed that this reaction proceeds by a [1,5]-sigmatropic shift of the nitro group from the 1- to the 3-position of the ring via a dihydropyridine intermediate rather than an electrophilic aromatic substitution.

![Scheme 11](image)

(Equation 29)

**Table 3** Nitration of pyridine and substituted pyridine with N$_2$O$_5$/SO$_2$

<table>
<thead>
<tr>
<th>R</th>
<th>Yield 79 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>63</td>
</tr>
<tr>
<td>2-Me</td>
<td>42</td>
</tr>
<tr>
<td>3-Me</td>
<td>29</td>
</tr>
<tr>
<td>4-Me</td>
<td>70</td>
</tr>
<tr>
<td>4-Ph</td>
<td>31</td>
</tr>
<tr>
<td>3-Ac</td>
<td>19</td>
</tr>
<tr>
<td>4-Ac</td>
<td>75</td>
</tr>
<tr>
<td>3-Cl</td>
<td>15</td>
</tr>
<tr>
<td>4-CN</td>
<td>35</td>
</tr>
<tr>
<td>Quinoline$^a$</td>
<td>16$^b$</td>
</tr>
<tr>
<td>Isoquinoline$^a$</td>
<td>28$^c$</td>
</tr>
</tbody>
</table>

$^a$Starting material.  
$^b$3-nitroquinoline.  
$^c$4-nitroisoquinoline.
More recently, Katritzky et al. were able to effectively avoid the handling of the unstable and difficult-to-obtain dinitrogen pentoxide reagent by preparing it in situ and reacting it immediately with pyridines. Since an equilibrium concentration of dinitrogen pentoxide has been proposed to exist in the nitric acid–acetic anhydride system \cite{1972CPB2678, 1973JOC2271}, a nitric acid–TFAA system was tested as a viable alternative \cite{2005OBC538}. The direct nitration of pyridine and substituted pyridines was successful by treatment of a substrate with nitric acid in TFAA (usually 12 h at 0–24 °C) followed by sodium metabisulfite solution (Equation 30; Table 4).

\begin{equation}
\text{HN}=\text{O} \quad \overset{\text{i, conc. HNO}_3}{\rightarrow} \quad \text{HN}=\text{O} \quad \text{NO}_2
\end{equation}

Table 4 Nitration of pyridine and substituted pyridines with nitric acid/TFAA and sodium metabisulfite

<table>
<thead>
<tr>
<th>R</th>
<th>Yield 79 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>83</td>
</tr>
<tr>
<td>2-Me</td>
<td>68</td>
</tr>
<tr>
<td>3-Me</td>
<td>62</td>
</tr>
<tr>
<td>4-Me</td>
<td>86</td>
</tr>
<tr>
<td>4-Et</td>
<td>25</td>
</tr>
<tr>
<td>3-Ac</td>
<td>20</td>
</tr>
<tr>
<td>4-Ac</td>
<td>83</td>
</tr>
<tr>
<td>3-Cl</td>
<td>76</td>
</tr>
<tr>
<td>4-NMe$_2$</td>
<td>32</td>
</tr>
<tr>
<td>Isoquinoline$^a$</td>
<td>37$^b$</td>
</tr>
</tbody>
</table>

$^a$Starting material.
$^b$4-nitroisoquinoline.

Nitration of 3,5-dichloro- and 3,5-difluoropyridine can be carried out via their $N$-oxides to provide the 4-nitro derivative as the major product \cite{1998J(P1)1705}. Leech reported an improved yield for the preparation of diamine 82. Using sulfuric acid and fuming nitric acid produces 4,4′-dinitro-2,2′-bipyridine-$N,N′$-dioxide 81 in 86% yield versus a previously reported yield for the nitration of 80 of 54%. The reduction of the resulting dinitro groups and the $N$-oxides was accomplished with 10% Pd/C and hydrazine hydrate to give 82 in 85% yield (Scheme 12) \cite{2004TL121}. Conversion of 2-nitroaminopyridine $N$-oxides to 2-amino-5-nitropyridine $N$-oxides occurs in the presence of sulfuric acid at 80 °C \cite{1998RJO271}.

Scheme 12
A new mild nitration employing tetramethylammonium nitrate and trifluoromethanesulfonic anhydride in CH$_2$Cl$_2$ was found to effectively mononitrate aromatics and heteroaromatics in high yields. Although pyridine 84 had been synthesized from its corresponding 2,6-dichloro-3-nitropyridine or from the direct nitration of 83 using conc. H$_2$SO$_4$ and HNO$_3$, using the milder nitronium triflate nitrating agent was equally effective but required the optimization of the reaction conditions. The conditions were modified from room temperature to reflux under a more concentrated solution in order to achieve complete conversion. Applying the reaction to microwave-assisted conditions proved fruitful but first the nitrating agent had to be prepared over 1.5 h at room temperature before its addition to the substrates and irradiation. The best conditions for converting pyridine 83 to 84 required 1.3 equiv of the nitrating agent and two irradiations, one for 10 min followed by magnetic stirring to ensure adequate reaction suspension mixing, and then by an additional 5 min of irradiation, all at 80°C (Equation 31) <2003JOC267>.

Interestingly, 3-nitropyridine can be sulfonated with Na$_2$SO$_3$ to give 2,5-disubstituted pyridine 88 (Scheme 13) <2000J(P1)1241>. The reaction proceeds through the sulfonic acid salt 85, which when treated with an acidic ion-exchange resin generates 5-hydroxyaminopyridine-2-sulfonic acid 86. Subsequent oxidation results in the nitro analogues 87 and 88 (Scheme 13) <2003OBC2710>.

In addition, the sulfonate group was found to be a good leaving group susceptible to both oxygen and nitrogen nucleophiles (Scheme 14).
Sulfonylation of 2-aminopyridine occurs at the 5-position under fairly harsh (140°C) conditions of sulfur trioxide in sulfuric acid. Subsequent C-3 bromination under mild conditions affords 89. Similarly 2-hydroxy nicotinic acid when subjected to stoichiometric 30% oleum at 140°C gave sulfonic acid 90 in 90% yield (Equations 32 and 33) <2002OPD767>.

\[
\text{H}_2\text{N} \quad \text{Br} \quad \text{SO}_3\text{H} \\
\text{HO}_2\text{C} \quad \text{HO} \quad \text{SO}_3\text{H}
\]

(Equations 32 and 33)

6.02.3.3 Diazo Coupling

The 4-aminopyridine derivative 92, prepared from the reaction of ethyl benzoylacetate and malononitrile dimer 91, undergoes the coupling reaction with aromatic diazonium salts to afford azo derivatives such as 93. Under refluxing conditions in ethanolic sodium hydroxide, these azo compounds cyclize to pyrido[3,2-c]pyridazines and pyrido[3,2-ε]-pyridazino[2',3'-α]quinazolines (Scheme 15) <2005AP329>.

\[
\text{PhCOOC} \quad \text{Ph} \quad \text{N} = \text{N} \quad \text{Cl}^- \\
\text{HO} \quad \text{NH}_2 \quad \text{O} \quad \text{NH}_2
\]

(Scheme 15)

Similarly, pyridones 94 and 96 underwent coupling with various diazonium salts to generate the azo derivatives 95 and 97 (Equations 34 and 35) <2001T6787>.

\[
\text{PhCN} \quad \text{Ph} \quad \text{N} = \text{N} \quad \text{Cl}^- \\
\text{HO} \quad \text{N} \quad \text{N}
\]

(Equations 34 and 35)
Bis-hetaryl monoazo dyes 101 and 105 were prepared respectively from pyridones 100 and 104 and the diazo analogues of thiazole 98 and thiophene 102 (Schemes 16 and 17) <2004DP1, 2004DP173>.
6.02.3.4 Acylation and Alkylation

Since the Friedel–Crafts acylation/alkylation fails with most pyridines, methods which utilize electron-rich dihydropyrindine intermediates have been developed. After the dihydropyridine undergoes electrophilic substitution, it can be readily aromatized to afford the corresponding 3-substituted pyridine <1998CHE871>. Comins and co-workers demonstrated an indirect C-5 formylation of nicotine 106 via the disilylated 1,4-dihydropyridine 107. Treatment of 107 with methyl carbonate in the presence of tetrabutylammonium fluoride (TBAF) readily acylated the nitrogen to give 108. Under Vilsmeier–Haack acylation conditions, 1-acyl-1,4-dihydronicotine 108 underwent electrophilic substitution at C-5 to give aldehyde 109. Aromatization of 109 was carried out by removal of the N-carbomethoxy group to give 110, which when subjected to elemental sulfur in refluxing toluene provided the desired nicotine-5-carbaldehyde 111 in 83% yield (Scheme 18) <2006OL179, 2006TL1449>. An entry to 3,5-disubstituted pyridines from 3-substituted pyridines via the acylation of an N-alkyl-1,4-dihydropyridine intermediate has been reported <2003TL4711>.

Nicotine can be alkylated at C-5 via the disilyl-1,4-dihydronicotine 107 using a modification of the Tsuge reaction. Addition of an aldehyde and a catalytic amount of TBAF to 107 affords the C-5 alkylnicotines 112 in moderate to good yield (Equation 36) <2006OL179>.

$$\text{(36)}$$

6.02.3.5 Oxidation

Chiral pyridinium salt 115, prepared from the reaction of Zincke salt 113 with (R)-(-)-2-phenylglycinol 114 <1992SL431, 1997JOC729>, underwent oxidation to afford 2- and 6-pyridones in high yield when treated for 1 h with potassium ferricyanide followed by potassium hydroxide. The regioselectivity was also good favoring pyridone 116 over 117 in a 90:10 ratio (Scheme 19) <1998TA2027>. Generally, an increasing percentage of oxidation at C-6 is observed when the bulkiness of the C-3 substituent increases <2000MOL1175>. 
Although a number of reagents such as Fremy’s salt, lead(II) and mercuric acetates, chromic acid, and peracids effectively oxidize isoquinoline and quinoline N-alkyl salts, potassium permanganate and active manganese dioxide are some of the mildest and most selective. Oxidation of N-methylisoquinolinium iodide in dichloroethane in the presence of KMnO$_4$ and a catalytic amount of 18-crown-6 for 3 h at room temperature led to 2-methyl-1(2H)-isoquinolinone 118b in 50% yield whereas running the reaction in CH$_3$CN afforded the desired product in 82% yield. The same procedure afforded the corresponding products 118c and 118d in good yields from the isoquinoline salts of ethyl iodide and benzyl chloride. The oxidation of the salts from acetyl chloride or ethyl chloroformate afforded upon workup the hydrolyzed pyridone 118a (Equation 37) <1996T1451>.

\[
\text{Scheme 19}
\]

Similarly, treatment of the N-alkyliminium salts of quinoline under the same oxidizing conditions resulted in formation of 1-alkyl-2(2H)-quinolinones 119 (Equation 38) <1996T1451>.

One-electron oxidation of pyridine N-oxides with lead tetraacetate gives N-oxide radical cations (Equation 39) <2002RJC729>.
Pyridine-2,3-dicarboxylic acids containing a halogen in the 5- or 6-position were prepared by oxidation of the corresponding quinolines using either ozone/H$_2$O$_2$ or catalytic RuO$_4$. Diacids substituted in the 6-position by Cl or Br, or in the 5-position by F, Cl, or Br, respectively, were isolated in 46–71% yields. The yields of 6-fluoro and 6- or 5-iodo diacids were low (<30%) (Equation 40) <2001S2495>.

\[
\text{Pyridine-2,3-dicarboxylic acids containing a halogen in the 5- or 6-position were prepared by oxidation of the corresponding quinolines using either ozone/H}_2\text{O}_2\text{ or catalytic RuO}_4.\text{ Diacids substituted in the 6-position by Cl or Br, or in the 5-position by F, Cl, or Br, respectively, were isolated in 46–71% yields. The yields of 6-fluoro and 6- or 5-iodo diacids were low (<30%) (Equation 40) <2001S2495>.
\]

6.02.4 Nucleophilic Attack at Carbon

6.02.4.1 Halogenation: Formation of a Carbon–Halogen Bond

6.02.4.1.1 Chlorination

Trichloromethylarenes are found to activate the pyridine ring via N-alkylation such that 4-chloropyridines are formed (Scheme 20) <1995TL5075>. In the case of nicotinamide, the dihydropyridine intermediate 121 undergoes an intermolecular redox reaction with hydride transferred to the benzylic position to give 122. Subsequent displacement of the C-4 chloride with nicotinamide affords the bispyridinium salts 123.

\[
\text{Conversion of 2-hydroxypyridines to 2-chloropyridines has been effected using triphenylphosphine and NCS <1999TL7477, 2001HCA1112>. Interestingly, 5-nitropyridine-2-sulfonic acid is converted to 2-chloro-5-nitropyridine in 87% yield when treated with phosphorus pentachloride (Equation 41). This reaction provides a new pathway to chloronitropyridines <2003OBC2710>.
}\]

\[
\text{An improved procedure for the preparation of 4-chloropicolinyl chloride from picolinic acid and thionyl chloride has been developed (Equation 42) <2002OPD777>. Phosphoryl chloride in the presence of triethylamine converts pyridine N-oxide into 2-chloropyridine in 90% yield <2001SC2507>.}
\]
6.02.4.1.2 Bromination
As with the reaction of 2-hydroxypyridines with NCS and triphenylphosphine cited above, the use of NBS as the halogenation reagent results in 2-bromopyridines \(<1999TL7477, 2001HCA1112\>). This reaction is also effective for the conversion of 2-quinolone to 2-bromoquinoline. In a similar fashion, the use of \(P_2O_5/\text{Bu}_4\text{NBr}\) proceeds under mild conditions to convert hydroxyheteroarenes to various bromoheteroarenes \(<2001TL4849\>). Treatment of 2-chloro-3-(hydroxymethyl)quinoline with \(\text{PBr}_3\) afforded 2-bromo-3-(bromomethyl)quinoline in high yield \(<1992JA10971\>). Bromotrimethylsilane in refluxing propionitrile converts 2-chloropyridines into 2-bromopyridines \(<2002EJO4181\>.

6.02.4.1.3 Iodination
Heteroaromatic compounds including pyridyl, quinolyl, and isoquinolyl chlorides have been converted to their corresponding iodides via acid-mediated nucleophilic halogen exchange with sodium iodide in refluxing acetonitrile \(<2003SL1801\>). Both 2-chloro- and 2-bromopyridines give the corresponding iodo derivative on treatment with in situ-generated iodotrimethylsilane \(<2002EJO4181\>). These conditions are also effective for converting 2- or 4-chloroquinoline and 1-chloroisooquinoline to their iodo derivatives.

Klapars and Buchwald developed a method for the conversion of heteroaryl bromides into the corresponding iodides using a catalyst system comprising CuI and a 1,2- or 1,3-diamine ligand. In this manner, 5-bromo-2-aminopyridine was converted to the iodopyridine \(124\) (Equation 43) \(<2002JA14844\>.

\[
\begin{align*}
\text{Br} & \quad \text{NH}_2 \\
\text{N} & \quad \text{NHMe} \\
\text{N} & \quad \text{NHMe}
\end{align*}
\]

\[
\begin{align*}
\text{I} & \quad 124
\end{align*}
\]

6.02.4.1.4 Fluorination
Nucleophilic fluorination such as halogen–fluorine exchange or Balz–Schiemann reactions of diazonium salts are common methods used to prepare various fluoropyridines \(<1984CHEC(2)216, 1996CHEC-II(5)68\>). A one-pot deaminative fluorination of aminoarenes via diazonium salts was developed using hydrogen fluoride combined with base solutions. Using this procedure, several fluoropyridines were prepared in high yield \(<1996T23\>). Selective fluorination of various pyridines and quinolines to afford the corresponding 2-fluoro derivatives can be achieved using elemental fluorine–iodine mixtures at room temperature. The reaction is suggested to proceed by fluoride attack on an \(N\)-iodo intermediate \(<1999J(P1)803\>.

Fluorination of 2,3,5-trichloropyridine with \(\text{KF}\) and \(\text{CsF}\) in an ionic liquid afforded 3,5-dichloro-2-fluoropyridine and 5-chloro-2,3-difluoropyridine in good yield \(<2004SC4301\>). Spray-dried \(\text{KF}\) in hot dimethyl sulfoxide (DMSO) containing a small amount of tetramethylammonium chloride is effective for the displacement of chlorine by fluorine in certain polyhalopyridines \(<2005CEJ1903\>). The conversion of several chloropyridines to their fluoro derivatives has been carried out at room temperature using anhydrous \(\text{TBAF}\) in DMSO \(<2006AGE2720\> or \(\text{KF}\) in sulfolane \(<2002BML411\>.

6.02.4.2 Organometallics, Enolates, and Cyanide
6.02.4.2.1 On neutral molecules
Certain pyridines react with Grignard reagents in the 1,4-manner when substituted by electron-withdrawing groups such as a carboxamide \(<2000J(P1)4245, 2005JOC2000\>\). The intermediate dihydropyridine can conveniently be oxidized to the pyridine structure. An example of this is seen in the reaction of 6-chloronicotinic acid derivative \(125\) with an excess of \(o\)-tolylmagnesium chloride, followed by oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.
(DDQ), yielding the product 126 in excellent yield (Equation 44) <1995T9531>. Trimethylsiliconide anion (Me₃Si(−)), generated from hexamethyldisilane and sodium methoxide, reacts with pyridine in hexamethylphosphoramide (HMPA) to afford 4-trimethylsilylpyridine in 92% yield <2001OL1197>.

\[
\begin{align*}
\text{CONHBu}^+ & \quad \text{(5 equiv)} \\
\text{Cl} & \quad \text{MgCl} \quad \text{(ii, AcOH or MeOH, iii, DDQ)} \\
\text{CONHBu}^+ & \quad \text{Cl} \\
\end{align*}
\]

Reactions of enolates with 2-halogenated pyridines incorporate useful functionality into the molecule. An intramolecular version is shown below (Equation 45). This is recognized as an important procedure due to the mild base required, preventing undesirable side reactions <1997TL4667, 2005JOC10186>. Malonate anion reacts with 2,3,4-trichloroquinoline to afford the C-4-substituted derivative <2006JHC117>. Displacement reactions of halopyridines with lithiated nitriles occur by aromatic nucleophilic substitution <2000SL1488, 1997H(45)1929>. Microwave irradiation assists the substitution of 2- and 3-halopyridines with the anion of phenylacetonitrile <2002T4931>. Nitro-substituted quinolines are activated toward nucleophilic addition. The anion of chloromethyl phenyl sulfone adds to a variety of nitroquinolines to give [(phenylsulfonyl)methyl]nitroquinolines <1996LA641>.

\[
\begin{align*}
\text{N} & \quad \text{SO}_2\text{Me} \\
\text{Cl} & \quad \text{r-BuOK} \quad \text{"good yield"} \\
\text{N} & \quad \text{SO}_2\text{Me} \\
\end{align*}
\]

The palladium-catalyzed, microwave-assisted conversion of 3-bromopyridine to 3-cyanopyridine using zinc cyanide in dimethylformamide (DMF) has been reported <2000JOC7984>. Substoichiometric quantities of copper or zinc species improve both conversion rate and efficiency of Pd-catalyzed cyanation reactions <1998JOC8224>. A modification of this procedure uses a heterogeneous catalyst prepared from a polymer-supported triphenylphosphine resin and Pd(OAc)₂; the nitriles were obtained from halopyridines in high yields <2004TL8895>. The successful cyanation of 3-chloropyridine is observed with potassium cyanide in the presence of palladium catalysts and tetramethylethlenediamine (TMEDA) as a co-catalyst <2001TL6707>.

A novel route to unsymmetrical trans-2-allyl-6-alkyl(alkyl)-1,2,3,6-tetrahydropyridines 127 was developed using the known 1,2-addition of RLi to pyridine followed by an allylboration of an intermediate imine formed on addition of methanol (Equation 46) <1996TL1317>.

\[
\begin{align*}
\text{N} & \quad \text{1.0 equiv MeOH} \\
\text{R} & \quad \text{HO}^- \\
\end{align*}
\]

In the Tebbe reaction with pyridine N-oxides and their benzo derivatives, regioselective attack at the α-position occurs along with the expected deoxygenation (Equations 47 and 48) <2000AGE2529>. The presumed organometallic intermediate is the titanocene methyldiene complex [Cp₂Ti=CH₂].
Preparation of 7-aryl methyl-1H-pyrrolo[3,4-c]pyridine-1,3-(2H)-diones 128 from 5-bromonicotinamide, arylacetonitriles, and lithium diisopropylamide (LDA) occurs via a pyridyne mechanism (Scheme 21). Under similar conditions, 5-chloro-3-pyridinol and arylacetonitriles afford the C-5 substitution products (Equation 49) <1998T3391>.

![Scheme 21]

6.02.4.2.2 Via pyridinium salts

The addition of nucleophiles to N-alkylpyridinium and related salts has been used extensively for the preparation of various dihydropyridines and in the synthesis of natural products <2003T2953, 2002J(P1)1141, 2001AHG269>. N-Methylquinolinium and N-methylisoquinolinium salts undergo attack by the sodium enolate of acetone at the α-carbon regioselectively (>80%) with sonochemical activation. Other methyl ketones give the desired regioisomers exclusively, though in more moderate yields (Equations 50–52) <1996JOC4830>. The C-4 addition of enolates, indolesodium, and cyanide to 1-alkyl-3-(2-quinolyl)quinolinium salts has been investigated <1998CHE1045>. Reaction of 1-methyl, 1-benzyl, and 1-benzoyl-4-ethoxycarbonylpyridinium salts with zinc and benzyl bromide
produce 4,4-disubstituted 1,4-dihydropyridines regioselectively \(<1996\text{J(P1)}2545\>\). Regioselective cyanomethylation of methylquinolinium and methylisoquinolinium iodides occurs using trimethylsilylacetonitrile in the presence of cesium fluoride \(<2000\text{JOC}907\>\).

Dimethyl acetylenedicarboxylate (DMAD) reacts with isoquinoline in the presence of ethyl bromopyruvate to yield pyrrole[2,1-\(\alpha\)]isoquinolines in excellent yields \(<2006\text{TL}6037\>\). A zwitterionic mechanism is proposed, and implies an enolate intermediate (Scheme 22). The oxidation in the final step occurs spontaneously without addition of any reagent.
The reaction of methyl nicotinate with tert-butylidemethylsilyl triflate gave the N-silylpyridinium salt which on treatment with phenyl Grignard followed by TBAF afforded the N-unsubstituted 4-phenyl-1,4-dihydropyridine <1998TL9275>. An improved preparation of N-(trimethylsilyl)pyridinium triflate, N-(triphenylsilyl)pyridinium triflate, and N-(triisopropylsilyl)pyridinium triflate involves the reaction of the corresponding allyl silanes with triflic acid followed by pyridine <1997S744>.

N-Acylpyridinium salts are more reactive than the N-alkyl derivatives and afford more stable dihydropyridine products on addition of nucleophiles. Organocuprates are utilized for entry into 2-alkynyl-substituted quinoline systems (Equation 53) <2005TL8905>. They have the advantage of superior selectivity over Grignard reagents, which yield a mixture of the 2- and 4-substituted products. The reaction has been expanded to include isoquinolines and pyridines.

\[
\begin{align*}
\text{N)-} & \text{Cl} + \text{Ph} \rightarrow \text{CuL, i-Pr}_{2}\text{NET, rt} \\
& \text{CH}_{2}\text{Cl}_{2} \\
& 90\% \\
\text{N)-} & \text{CO}_{2}\text{Et} \rightarrow \text{Ph} \\
\end{align*}
\]

The popular activation method of pyridine rings by reaction with chloroformates was not observed for reaction of N-acylated quinoline with allyltrimethylsilane until a catalytic amount of silver triflate was added. It was shown that the triflate counterion increases the electrophilicity of the N-acylquinolinium salt (Equation 54) <1997TL403, 2001T109>.

\[
\begin{align*}
\text{N)-} & \text{SiMe}_{3} \rightarrow \text{CICO}_{2}\text{Ph} \\
& \text{CH}_{2}\text{Cl}_{2} \\
& \text{AgOTf (0.1 equiv)} \\
& 84\% \\
\end{align*}
\]

The 4-silyloxyquinolinium triflates 130 are prepared in situ by reaction of N-acyl-4-quinolones 129 with TIPSOTf (TIPS = 1,1,3,3-tetraisopropylsiloxane). Addition of various Grignard or lithium reagents provide the C-2 adducts 131 (Equation 55) <1997SL313>.

\[
\begin{align*}
\text{N)-} & \text{CO}_{2}\text{R}^{1} \rightarrow 2\text{TIPSOTf} \\
& \text{CH}_{2}\text{Cl}_{2} \\
\end{align*}
\]

Benzyltrimethylstannanes react with isoquinolines and 1,6-naphthyridines in the presence of a chloroformate to afford 1-benzyl-1,2-dihydro derivatives (Equations 56 and 57) <1998TL1721, 2000TL8053>. An allyl group can be introduced at C-1 of isoquinoline using a mixture of phenyl chloroformate, iodine, and allyl bromide <2004OBC2170>. Yamaguchi and co-workers previously reported the addition of benzylstannanes to N-acylpyridinium salts <1996CHEC-II(5)76>. The CuCN·2LiBr-catalyzed organozinc addition to N-acylpyridinium salts was studied. Both dialkylzinc reagents and alkylzinc halides almost exclusively gave the C-4 addition products, with only trace amounts of the 2-substituted isomers <2003EJO4586>.

\[
\begin{align*}
\text{N)-} & \text{SnMe}_{3} \rightarrow \text{CICO}_{2}\text{Me} \\
& \text{CH}_{2}\text{Cl}_{2} \\
& 52-71\% \\
\end{align*}
\]
The reaction of pyridines with triflic anhydride affords N-trifluoromethylsulfonylpyridinium triflates in situ. These reactive pyridinium salts add phosphines, phosphates, ketones (via the enol), and electron-rich aromatics. The 1,4-dihydropyridine intermediates can be converted to 4-substituted pyridines on treatment with base <1998S195, 1999S2071, 2001OL2807, 2005OL5535>. Reaction of N-fluoropyridinium fluoride generated in situ with a series of isonitriles led to the formation of the corresponding picolinamides in good yields. A similar reaction sequence for quinoline and isoquinoline afforded the α-acetylated products at C-2 and C-1, respectively <2005TL2279>.

With N-alkyl- or N-acylpyridinium salts, the addition of isonitriles takes place efficiently when a carboxamido group is present in the 3-position. The outcome of the reaction involves the stabilization of the nitrilium intermediates by the amide, which suffers a mild dehydration providing 3-cyano-4-carbamoyl-1,4-dihydropyridines. This method also works with the corresponding N-acylquinolinium and N-acylisoquinolinium salts (Equation 58) <2006OL5789, 2004JOC3550>.

Asymmetric synthesis using N-acyl salts of pyridine and derivatives continues to be developed. The chiral N-acylpyridinium salt 132 reacts with lithiated ethyl propiolate to provide the diastereomer 133 in 70% yield and >96% de (Equation 59) <2001OL469>. The stereochemistry at C-3 is presumably due to axial protonation of the intermediate enol ether during workup.

A related example is shown by 4-methoxypyridine activated by a chiral amidine auxiliary, which on attack by a Grignard reagent provides dihydropyridone 134 (Equation 60) <2006OL2985>. Charette and co-workers have nicely developed this methodology to include the asymmetric syntheses of various substituted piperidines and natural products <2005OL2747, 2005JOC2368, 2005OL5773>.
With an amino acid-derived chiral auxiliary employed in the chloroformate, reaction of silyl enol ethers with isoquinolinium salts showed not only regiospecificity, but some stereoselectivity as well (Equation 61) \(<1999SL1154\>). The addition of ketene silyl acetals to an N-acylpyridinium salt containing a chiral 2,2-dimethyloxazolidine at C-3 gave 1,4-dihydropyridines with excellent stereoselectivity \(<2002JA8184\>\).

![Equation 61](image1)

The diastereoselective addition of prochiral metallo enolates to chiral N-acylpyridinium salt 135 has been studied \(<1999JA2651\>). Addition of the zinc enolate of 2,2-diethyl-1,3-dioxolan-4-one to a pyridine activated by a chiral chloroformate proceeded in 85% yield and with >95% de. The fixed stereochemistry of the cyclic enolate is a determining factor in the resulting relative configuration of the two new chiral centers. An acyclic transition state is proposed (Equation 62) \(<2004JOC5219\>). Chiral N-acylpyridinium salt 135 has been used as starting material for numerous asymmetric syntheses of natural products \(<2002J(P1)1141, 2002MI870, 2004JOC5219, 2005OL5227\>\).

![Equation 62](image2)

Certain indolyl and pyrrolyl Grignard reagents add to 1-acyl salts of 4-methoxy-3-(triisopropylsilyl)pyridine to give the corresponding 1-acyl-2-heteroaryl-2,3-dihydro-4-pyridones in good to high yield \(<2004JOC2863\>\). The addition of triphenylsilyl- or dimethylphenylsilylmagnesium bromide to chiral N-acyl-4-methoxypyridinium salts affords C-2-silylated 2,3-dihydro-4-pyridones in good yield and high diastereoselectivity \(<2002H(58)505\>\).

A chiral auxiliary-mediated Reissert reaction has been demonstrated. Though the diastereomeric ratios are not as high as hoped, the conditions are simple and the products are easily separated by flash chromatography (Equation 63) \(<2005TL2983\>\). A catalytic version of the asymmetric Reissert reaction with quinolines, isoquinolines, and pyridines has been developed by Shibasaki and co-workers \(<2005PAC2047, 2004JA11808\>\).

![Equation 63](image3)

6.02.4.2.3 Cross-coupling reactions
Transition metal-catalyzed cross-coupling methods are increasingly important for the synthesis of substituted pyridines and their benzo derivatives. The popular Negishi, Kumada, Suzuki, Stille, Heck, Hiyama, Sonogashira, and Kharasch cross-couplings have been utilized to prepare numerous azine derivatives. This subject has been extensively reviewed \(<1995CRV2457, 1998T263, B-2000MI183, 2002T9633, 2002J(P1)1921, 2002COR507\),
The Negishi and Kumada cross-coupling reactions have been carried out on 3,5- and 2,6-dibromopyridine. Monosubstitution can be achieved in good yield. Several substituted pyridyl amino acids have been prepared by palladium-catalyzed cross-coupling of serine-derived organozinc reagents with various halopyridines. Polyfunctional pyridines can be prepared by Pd(0)-catalyzed cross-coupling of functionalized arylmagnesium halides with chloro- or bromopyridines at temperatures as low as −40°C. N,N-Diethyl pyridyl O-sulfamates were found to be effective cross-coupling partners for Kumada–Corriu reactions.

\[
\text{Cl} \quad \text{Et} \quad \text{MgCl} \quad \text{CO}_2\text{Me}
\] +
\[
\text{Cl} \quad \text{N} \quad \text{Br}
\] →
\[
\text{Cl} \quad \text{N} \quad \text{CO}_2\text{Et}
\] ++
\[
\text{MeO}_2\text{C}
\] cat. Pd(dba)_2
\[\text{THF} \rightarrow -40^\circ\text{C}, \text{THF} \] 95%

\begin{equation}
\text{Cl} \quad \text{N} \quad \text{CO}_2\text{Et}
\end{equation}

In the Suzuki reactions of pyridine systems, the heterocycle can be used both as the electrophile and the organoborate nucleophile. Selectivity is such that either coupling partner can carry a chlorine atom on the pyridine ring as is demonstrated in the formation of bipyridyl 136 by two different routes (Scheme 23). Suzuki cross-coupling reactions of 2,4-dibromopyridine are regioselective at the 2-position with several alkenyl(aryl)boronic acids affording 2-substituted-4-bromopyridines.

\[
\text{Br} \quad \text{Cl}
\] +
\[
\text{Cl} \quad \text{Cl}
\] →
\[\text{HO-BOH} \text{Pd(PPh}_3\text{)}_4, \text{aq. Na}_2\text{CO}_3, 1,4\text{-dioxane, reflux, 18 h} \] 63%
\[
\text{Cl} \quad \text{Cl}
\] 136

\[
\text{I} \quad \text{Cl}
\] +
\[
\text{Cl} \quad \text{Cl}
\] →
\[\text{HO-BOH} \text{Pd(PPh}_3\text{)}_4, \text{aq. Na}_2\text{CO}_3, 1,4\text{-dioxane, reflux, 18 h} \] 66%

Scheme 23

A short synthesis of 2-aryl-6-chloronicotinamides via regioselective Suzuki coupling of 2,6-dichloronicotinamide with aryl boronic acids was reported. Regioselectivity was attributed to chelation of the palladium(0) species to the carbonyl of the amide group (Equation 65). The Suzuki coupling reaction has been applied to the preparation of small combinatorial libraries using 5-bromonicotinic acid as a scaffold on three different types of solid support. Alkyl groups can be introduced by the B-alkyl Suzuki–Miyaura reaction using an alkyl borane and a pyridyl halide. Methylation can be carried out using methylboron reagents such as methylboronic acid, methylboranes derived from 9-borabicyclo[3.3.1]nonane (9-BBN), and trimethylboroxine.

\[
\text{Cl} \quad \text{Cl} \quad \text{NHR} + \text{Ar(B(OH)}_2 \quad \text{cat. PXpd}_2 \quad \text{K}_2\text{CO}_3, \text{MeOH}
\] →
\[
\text{Cl} \quad \text{NHR}
\] cat. PXpd_2 = Bu'_4Cl_6P_2Pd_2
\[19-61\%

\begin{equation}
\text{Cl} \quad \text{NHR}
\end{equation}
Suzuki cross-coupling with 2,3-dibromoquinoline shows preferential reaction at C-2 providing 2-aryl-3-bromoquinolines <1999SC3959>. Palladium-catalyzed coupling of arylboronic acids to 1,3-dichloroisooquinoline takes place exclusively at the 1-position to give 1-aryl-3-chloroisooquinolines <1997J(P1)927>. The cross-coupling at C-4 of 4-iodonicotine derivative 137 and amino boronate ester 138 afforded 139 which is an intermediate in a short synthesis of (S)-brevicolline (Equation 66) <2006OL3549>.

\[
\text{Cl} \quad \text{Me}^+ \quad \text{N} \quad \text{I} \quad \text{Br} \quad \text{H} \\
\text{N} \quad \text{O} \quad \text{CO}_2\text{Me} \quad \text{H}_{\text{NBOC}} \quad \text{NHBOC} \\
137 + 138 \quad \text{10\% Pd}_2\text{dba}_3 \quad \text{20\% Xantphos} \quad \text{1.5 equiv Cs}_2\text{CO}_3 \quad \text{1.4-dioxane, 110 °C} \quad \text{77\%} \\
\text{N} \quad \text{Me}^+ \quad \text{N} \quad \text{Br} \quad \text{Cl} \\
\text{N} \quad \text{O} \quad \text{CO}_2\text{Me} \quad \text{NHBOC} \\
139
\]

The Stille reaction is very tolerant of most functional groups, making it effective for the preparation of complex pyridine derivatives (Equation 67) <2004EJO1891>. It is possible to generate the organostannane in situ through the palladium-mediated reaction of a pyridyl halide or triflate with hexamethylditin <1995TL9085, 2001JOC1500>.

\[
\text{Br} \quad \text{MeO} \quad \text{N} \quad \text{CO}_2\text{Me} \quad \text{N} \quad \text{Br} \\
\text{N} \quad \text{CO}_2\text{Me} \quad \text{NHBOC} \quad \text{Pd(Ph}_3\text{)}_4, \text{1,4-dioxane} \quad \text{reflux, N}_2, \text{overnight} \quad \text{63\%} \\
\text{N} \quad \text{CO}_2\text{Me} \quad \text{N} \quad \text{Br} \quad \text{MeO} \\
\text{NBOC} \quad \text{BOC} \\
140 \quad 2-\text{(NHBOC)}\text{C}_2\text{H}_5\text{SnMe}_3 \quad 18\%
\]

The dibromopyridine 140 underwent successive Sille and Negishi cross-couplings to afford bipyridine 141 (Scheme 24) <2002S1564>. Several 6-heteroaryl-3-methylpyridines were prepared from 3-picoline by a one-pot lithiation-stannylation-Stille reaction sequence <2001TL1879>. The Stille cross-coupling reaction has been used profusely for the preparation of substituted pyridines, bipyridines, poly(bipyridines), and terpyridines <2004CRV2667>. Conditions have been found for the Stille and Heck cross-couplings of 4-chloroquinolines <2003JOC7077, 2003JOC7551>.

\[
\text{Br} \quad \text{N} \quad \text{Br} \quad \text{CO}_2\text{Et} \\
\text{N} \quad \text{Br} \quad \text{CO}_2\text{Et} \\
140 + \text{Bu}_3\text{Sn} \quad \text{Pd(Ph}_3\text{)}_4 \quad \text{toluene} \quad 60\% \\
\text{Br} \quad \text{N} \quad \text{Br} \quad \text{CO}_2\text{Et} \\
\text{N} \quad \text{CO}_2\text{Et} \\
141
\]

\[
\text{Br} \quad \text{N} \quad \text{Br} \quad \text{CO}_2\text{Et} \\
\text{N} \quad \text{CO}_2\text{Et} \\
\text{MeZnCl} \quad \text{THF, Pd(Ph}_3\text{)}_4 \quad 80\% \\
\text{141}
\]

Scheme 24
The inter- and intramolecular Heck reactions provide other routes to substituted pyridines <B-2000MI183>. Although electron-deficient 2-bromopyridines are resistant to substitution under Heck conditions, the aminopyridine 142 affords a high yield of the adduct 143 (Equation 68) <1998T6311>. The intermolecular Heck reaction of a 3-pyridyltriflate with ethyl acrylate is accelerated by LiCl <1999SL804>. An efficient Heck vinylation of 3-substituted-2-bromo-6-methylpyridines with methyl acrylate has been developed <2005T4569>.

\[
\begin{align*}
\text{NHCOCBu}^+ & \quad \text{Pd(OAc)}_2, \text{Ph}_3\text{P} \\
\text{142} & \quad \text{NaOAc}, 130^\circ \text{C} \\
\text{143} & \quad 98\%
\end{align*}
\]

Equation 68

A regioselective tandem Heck-lactamization was developed for a multi-kilogram preparation of drug intermediate 145 from trihalopyridine 144 (Equation 69) <2006JOC8602>.

\[
\begin{align*}
\text{Br} & \quad \text{Pd(OAc)}_2 \\
\text{144} & \quad \text{NaOAc, KBr, 100^\circ C} \\
\text{145} & \quad 80\%
\end{align*}
\]

Equation 69

The intramolecular Heck reaction is a versatile method for the formation of pyridine-containing heterocycles, synthetic intermediates, and natural products <2004COR781, 2003CRV2945, 1999H(51)1957>. A few examples are depicted in Equations (70)–(72) <1996H(43)1641, 1999JOC3461, 2001OL4255>.

\[
\begin{align*}
\text{Ph} & \quad \text{Pd(OAc)}_2 \\
\text{N} & \quad \text{NaOAc, K}_2\text{CO}_3 \\
\text{DMF, 100^\circ C} & \quad 80\%
\end{align*}
\]

Equation 70

\[
\begin{align*}
\text{OMe} & \quad \text{Pd(OAc)}_2 \\
\text{N} & \quad \text{K}_2\text{CO}_3 \\
\text{DMF, 90^\circ C} & \quad 68\%
\end{align*}
\]

Equation 71

\[
\begin{align*}
\text{HO} & \quad (\text{Ph}_3\text{P})_2\text{Pd(OAc)}_2 \\
\text{K}_2\text{Ac, CH}_3\text{CN} & \quad 100^\circ \text{C} \\
\text{64%}
\end{align*}
\]

Equation 72

The Hiyama cross-coupling of organosilanes is attractive as the intermediates are often easy to prepare and the silicon by-products are environmentally benign. A one-pot synthesis of 2-aryl-3-methylpyridines from 2-bromo-3-methylpyridine was developed (Scheme 25) <2003JOM58>. Both 2- and 3-bromopyridine cross-couple with phenyltrimethoxysilane to afford the corresponding phenylpyridines in good yield <1999OL2137>.

Gros and co-workers have shown that the presence of electron-withdrawing substituents on the pyridine ring of 2-trimethylsilylpyridines provides sufficient activation to allow them to be useful partners in the Hiyama cross-coupling.
The reaction can be performed at room temperature with various heteroaryl halides (Equation 73) <2005OL697>. It was found that (2-pyridyl)allyldimethylsilanes are pyridyl-transfer reagents in palladium-catalyzed coupling reactions of aryl iodides in the presence of silver oxide as an activator <2006OL729>.

\[
\begin{align*}
\text{Cl}_2(\text{Et})\text{Si} & \\
\rightarrow & \\
\text{Ar} & \\
\end{align*}
\]

Scheme 25

The Sonogashira reaction has been routinely used to prepare alkynylpyridine derivatives <B-2000MI183, 1997(JP)709, 1998BML2169, 2005OL1793>. With dihalopyridines, bisalkenylation is easily achieved using excess alkyne. There have been several examples of regioselective monocetylenation of polyhalopyridines with the α-position being preferentially substituted in most cases <2005T2245>. A modification of the Sonogashira reaction starting with a TMS-substituted alkyne was used to prepare pyridine derivative 146 (Equation 74) <2003BML351>. A copper-free Sonogashira alkynylation of 3-amino-2-chloropyridines was used in an efficient azaindole synthesis <2006OL3307>.

\[
\begin{align*}
\text{Cl} & \\
\rightarrow & \\
\text{Cl} & \\
\end{align*}
\]

The Sonogashira coupling reaction of 2,4-dibromoquinoline with trimethylsilylacetylene is regioselective for the 2-position affording quinoline derivative 147 in high yield (Equation 75) <2003JOC3736>. The regioselectivity is reversed with 2-bromo-4-iodoquinoline due to the greater reactivity of the aryl-iodide bond toward oxidative addition with palladium (Equation 76) <2005TL6697>. Conditions were found for the regioselective Sonogashira alkynylation of 4-chloro-6-iodo(bromo)quinolines to afford 6-alkyl-4-chloroquinolines in high yields <2004RCB189>.

The Sonogashira coupling reaction of 2,4-dibromoquinoline with trimethylsilylacetylene is regioselective for the 2-position affording quinoline derivative 147 in high yield (Equation 75) <2003JOC3736>. The regioselectivity is reversed with 2-bromo-4-iodoquinoline due to the greater reactivity of the aryl-iodide bond toward oxidative addition with palladium (Equation 76) <2005TL6697>. Conditions were found for the regioselective Sonogashira alkynylation of 4-chloro-6-iodo(bromo)quinolines to afford 6-alkyl-4-chloroquinolines in high yields <2004RCB189>.
There have been several advances in iron-catalyzed cross-coupling reactions. This method works very well for the coupling of alkyl Grignard reagents to electron-deficient aryl- and heteroaryl chlorides and tosylates as well as electron-rich heteroaryl triflates. In their synthesis of muscopyridine, Fürstner and Leitner prepared intermediate 149 from pyridyl triflate 148 by the iron-catalyzed sequential addition of two different Grignard reagents (Scheme 26).

Stille and Suzuki couplings of bromopyridines are effective in the synthesis of various bipyridines and terpyridines. By use of various palladium-catalyzed coupling reactions, 2,6-dichloro-4-iodopyridine can be converted to a number of 2,4,6-trisubstituted pyridines. Palladium-catalyzed cross-couplings can be carried out on halopyridine N-oxides and halo-N-alkylpyridinium salts in good yields. Bipyridines are conveniently prepared by palladium- or nickel-catalyzed homocoupling of halopyridines.

6.02.4.3 Heteroatom Nucleophiles

6.02.4.3.1 Nucleophilic addition

Heteroatom nucleophiles react with pyridine in its neutral or activated pyridinium form. When the nitrogen has been fluorinated, the product of nitrile/isonitrile addition is an imidazopyridine (Equation 77).

The proposed mechanism for formation of 151 is shown in (Scheme 27). Proton abstraction by the hydride base from the activated 2-position of the N-fluoropyridinium triflate yields a highly reactive carbene which undergoes attack by the acetonitrile solvent. The resulting nitrilium ylide eliminates fluoride and subsequently adds the isonitrile with cyclization. Finally, reduction by the hydride reagent and aromatization provide the imidazopyridine 151. The undesired amide 152 is a product of hydrolysis of the intermediate nitrilium compound.
Pyridine $N$-oxides are converted to tetrazolo[1,5-$a$]pyridines in good to excellent yield by heating a pyridine and sulfonyl or phosphoryl azide in the absence of solvent (Scheme 28) \( <2006\text{JOC}9540 > \).

An attempt to generate an amino-aryl carbene 154 from the alkylated phenanthridium salt 153 (Equation 78) \( <2006\text{TL}531 > \) was unsuccessful due to steric interactions. The actual reaction with a variety of strong, sterically hindered bases/nucleophiles is shown (Equations 79–81). The mesityllithium products proved that a carbene intermediate is not possible. Unlike $t$-butyl alcohol and hexamethyldisilazane, trimethylbenzene, the conjugate acid of mesityllithium, is not prone to carbene insertion reactions. Electronically this is explained by the planar nature of 153 which serves to lower the lowest unoccupied molecular orbital (LUMO) energy of the iminium moiety.
Under biphasic conditions, the reaction of benzylamine or piperidine with the quinolinium salt 155 gave adducts 156 in high yields. Addition of the amine nucleophile takes place exclusively at the C-4 position of the quinolinium salt. On treatment of 156 with acetyl chloride, the corresponding carboxamides are produced in near quantitative yields along with the regeneration of quinolinium salt 155 (Scheme 29). Intramolecular attack of a C-3-tethered amine onto pyridinium salts provides a novel route to nitrogen heterocycles via a ring-opening mechanism. An oxidative double phosphorylation of N-alkylpyridinium salts was effected through the use of dialkyl phosphates, DDQ, and triethylamine. Moderate to good yields of 2,6-diphosphonylated-1,2-dihydropyridines were obtained in a one-pot reaction involving tandem nucleophilic addition/oxidation processes.

Scheme 29

The base combination of sodium amide and sodium tert-butoxide in tetrahydrofuran (THF) containing a secondary amine converts halopyridines into aminopyridines via a pyridyne intermediate (Equation 82). The regioselectivity varies depending upon the position and type of pyridine substituents.

Amination of 3-nitropyridine with potassium permanganate in liquid ammonia, or an aliphatic amine, affords the 2-amino-pyridine 157 (Equation 83). The nitropyridine 158 is aminated at C-6 with O-methylhydroxylamine in the presence of ZnCl to give 159 in high yield (Equation 84).
6.02.4.3.2 Nucleophilic substitution

Substitution reactions of halopyridines with heteroatom nucleophiles have been commonly used for the preparation of numerous pyridine derivatives. A number of monographs and review articles have covered this useful chemistry. The order of reactivity is position 4 > 2 > 3. The halide in 2- and 4-halopyridines is quite easily substituted by nucleophiles such as hydrazine, thiolate anions, and alkoxides. Reaction at the 3-position is more difficult, but use of a higher temperature in DMSO or DMF often effects substitution. The substitution reactions are more facile if an activating group is present on the ring. For example, treatment of 2-bromonicotinamides with secondary amines in refluxing THF affords the corresponding 2-amino derivatives in good yields. The heteroarenium salts are readily available in quantitative yield by treating pentachloropyridine, or tetrachloropyridine, and DMAP in 1,2-dichlorobenzene at 80 °C. Activation of chloropyridines by heteroarenium substituents allows sequential substitutions by O-, N-, and S-nucleophiles.

6.02.4.3.3 Metal-catalyzed coupling reactions

The palladium-catalyzed amination of halopyridines has been developed into a useful method for the preparation of various aminopyridine derivatives. Excellent regioselectivity can be obtained on amination of polyhalopyridines. Reaction of piperazine derivative and 5-bromo-2-chloropyridine catalyzed by a palladium–Xantphos complex predominately gives the 5-amino-2-chloropyridine in high yield. The corresponding amination of 2,5-dibromopyridine exclusively affords the 2-amino-5-bromopyridine (Scheme 31).

The synthesis of macrocycles containing two pyridine and two polyamine fragments was carried out by the Pd-catalyzed amination of 2,6-dihalopyridines.

Intermolecular palladium-catalyzed coupling of halopyridines and alcohols is a mild and versatile method for the preparation of pyridine ethers. Complex molecules containing heterocycles and sensitive functionality can be prepared in high yield. A general palladium-catalyzed coupling of aryl bromides and thiols is also effective in the pyridine series.
The copper-mediated C(aryl)–O, C(aryl)–N, and C(aryl)–S bond formation can be used as an alternative to many palladium-catalyzed transformations <2003AGE5400, 2006T4435>.
6.02.4.4 Chemical Reduction

Chemical reduction of pyridines can be achieved with hydride, dithionite, dissolving metal reagents, or hydrogenation. The pyridine nucleus can be activated to reduction by conversion to a pyridinium species (1984CHEC(2)165, 1996CHEC-II(5)80).

6.02.4.4.1 Hydride reduction

The methyl ester of nicotinic acid is selectively reduced to the 1,2-dihydropyridine 166 in a vast improvement over previous methods (Equation 87) (2001OL201). Low temperatures and choice of pyridinium-activating agent are crucial to avoid 1,4-dihydropyridine formation. A modification of Fowler’s dihydropyridine synthesis was used to prepare the N-acyldihydropyridine 167 (Equation 88) (2006OL2961).

\[
\begin{align*}
\text{Kanomata et al.} & \text{ carried out the reduction of N-alkylpyridinium salt 168 via hydride transfer from diolate 169 to afford mainly the 1,4-dihydropyridine 170 (Equation 89) (1998AGE1410).} \\
\text{Hydride transfer by isopropanol to quinoline is catalyzed by a pentamethylcyclopentadienyl (Cp\textsuperscript{+}) iridium complex, resulting in regioselective reduction to 1,2,3,4-tetrahydroquinoline 171. The yield is optimized by use of acid, and N-alkylation by the isopropyl group is eliminated by including water (Equation 90) (2004TL3215). A possible mechanism is thought to involve iridium hydride as the reducing reagent.}
\end{align*}
\]

6.02.4.4.2 Dithionite reduction

Sodium dithionite reduction of pyridinium salts, usually substituted with electron-withdrawing groups in the 3- or 3,5-positions, chiefly affords the corresponding 1,4-dihydropyridines. The regioselectivity of formation of the dithionite adducts and mechanisms of decomposition have been studied (2005T10331, 2000TL1235). The sodium...
Dithionite reduction of pyridinium salts 172 and 174 gave the 1,4-dihydropyridines 173 and 175, respectively (Equations 91 and 92) <1997JOC729, 2002T7869>.

Lavilla and co-workers developed a dithionite reduction of α-substituted N-alkylpyridinium salts to afford the corresponding 1,4-dihydropyridines or piperidines. In the absence of NaHCO₃, full reduction occurred to give the piperidine derivatives in high yield (Scheme 32) <2005TL3513>.

Scheme 32

6.02.4.4.3 With free electrons
Pyridines are readily reduced under dissolving metal conditions to provide dihydro or perhydro derivatives <B-2000MI217, 1996CHEC-II(5)82>. Donohoe et al. have examined the partial reduction of a series of pyridines containing electron-withdrawing groups. Conditions were found such that the intermediate anion from the reduction of 176 could be alkylated with electrophiles to afford 1,2-dihydropyridines 177 containing a quaternary center at C-2 (Equation 93) <2001J(P1)1435>.

A two-electron reduction of activated pyridinium salt 178 forms an intermediate enolate 179, which, upon quenching with a number of electrophiles, yields dihydro-4-pyridones 180 after hydrolysis. These compounds are notable because they contain a variety of groups α to the nitrogen (Table 5; Equation (94) <2005OL435, 2006OBC1071>.)
One-electron electrochemical reduction of pyridinium salts 181 yields mixtures of four isomeric dimers 182–185. The two most abundant products are 182 and 183 (Equation 95) <2002J(P1)542>.

\[
\text{OMe} \quad \text{I}^- \xrightarrow{\text{Li, DBB, THF}} \begin{array}{c}
\text{OMe} \\
\text{PMB}
\end{array}
\]
\[
\xrightarrow{-78^\circ \text{C}} \begin{array}{c}
\text{OMe} \\
\text{PMB}
\end{array}
\]
\[
\xrightarrow{+2e^-} \begin{array}{c}
\text{OMe} \\
\text{PMB}
\end{array}
\]
\[
\xrightarrow{\text{R-X, } -78^\circ \text{C}, 3 \text{ h} \text{ then } \text{H}_3\text{O}^+, -78^\circ \text{C} \text{ to rt}} \begin{array}{c}
\text{O} \\
\text{PMB}
\end{array}
\]

(94)

One-electron electrochemical reduction of pyridinium salts 181 yields mixtures of four isomeric dimers 182–185. The two most abundant products are 182 and 183 (Equation 95) <2002J(P1)542>.

In the presence of Zn/CuI couple in a protic medium under sonochemical activation, pyridinium salt 186 and α-chloroacrylates afford the 4-substituted 1,4-dihydropyridines 187. The mechanism likely involves the one-electron reduction of 186, and addition of the radical to the olefin to generate a new radical whose reduction, proton abstraction, and Zn-promoted reductive cleavage of the C–Cl bond complete the conversion (Equation 96) <2004COR715>.

\[
\begin{array}{c}
R \quad \text{CONH}_2, \text{CONHMe}
\end{array}
\]

(95)

6.02.4.4 Hydrogenation
A common and often efficient method for the preparation of saturated piperidines is the catalytic reduction of pyridines, pyridine N-oxides, or pyridinium salts <2001CHE797, 2003T2953>. Reduction of the naphthylpyridyl alcohol 188

\[
\begin{array}{c}
\text{OMe} \\
\text{PMB}
\end{array}
\]

(96)
with molecular hydrogen over PtO₂ yields a 90:10 mixture of *erythro*-189 and *threo*-190 piperidines in quantitative yield (Equation 97) <2003JOC7308>. Activation of the ring is achieved with HCl and optimal *erythro* formation is observed at lower temperature (−10°C). Recrystallization from diethyl ether gives pure *erythro* in 60% yield.

Partial hydrogenation of ethyl nicotinate under heterogeneous catalytic conditions in EtOH, or in THF/Ac₂O, affords the corresponding vinylogous amides 191 and 192, respectively. This method can also be applied to 3-acetyl- and 3-benzoylpyridine (Scheme 33) <2006EJO4343>.

Scheme 33

An efficient procedure for the reduction of pyridine *N*-oxides to piperidines using ammonium formate and palladium on carbon has been developed (Equation 98) <2001JOC5264>. The reaction conditions are mild and can also be applied to the *N*-oxides of quinoline and isoquinoline.

Deuterated ammonium formate is found to reduce 4-carboxylpyridine *N*-oxide in the presence of a palladium catalyst. Incorporation of a minimum of five deuteriums in the ring is achieved in good yield (Equation 99) <2004TL8889>.

In recent years, a few stereoselective methods for the asymmetric hydrogenation of pyridines and related heterocycles have been developed <2005OBC4171>. A chiral auxiliary method starts with a oxazolidinone-substituted pyridine which on reduction with H₂/Pd(OH)₂ in acetic acid affords the corresponding piperidine in good yield and high enantiopurity. The chiral auxiliary is cleaved during the reaction and can be recovered (Equation 100) <2004AGE2850>.
Application of the known iridium-catalyzed hydrogenation of imines to the pyridine system results in excellent yields and good ee’s when reaction conditions, catalysts, and activated pyridines are optimized. Among the findings are the use of molecular iodine to oxidize the Ir(I) to Ir(III) in situ, choice of ligand, and that of a variety of 2-methylpyridines, activated and unactivated, only the N-acyliminopyridinium ylide 193 was hydrogenated (Equation 101) <2005JA8966>. The conditions shown for synthesis of 194 are optimal.

\[
\begin{align*}
R &= \text{Me, CF}_3, \text{CONMe}_2 \\
\text{Ir} &\rightarrow \text{Ir}^{\text{III}} \text{ in situ}
\end{align*}
\]

\[
\text{COD} = 1,5\text{-cyclooctadiene}
\]

\[
\text{Ar} = 4\text{-fluorophenyl}
\]

6.02.5 Free Radical Attack at Carbon

6.02.5.1 Halogenation

The direct free radical chorination or bromination of pyridines is effected at high temperatures (220–500 °C) or by irradiation <1996CHEC-II84, B-2000MI217>. Attack at the α-position predominates. A recent process for producing 2-chloropyridine combines pyridine with chlorine in the vapor phase in the presence of a catalyst which generates free radicals <2002USP6369231>. Free radical bromination of bipyridyl using Barton chemistry is used in order to unambiguously assign the structures purported to be 5,5'-dibromo-2,2'-bipyridine and 5-bromo-2,2'-bipyridine (Equations 102 and 103) <1995TL6471>. This method employs a radical decarboxylative bromination. Azobisisobutyronitrile (AIBN) is the radical initiator and BrCCl₃ is the chain carrier. The reaction is performed in one pot as isolation of the intermediate thiohydroxamic ester is not necessary.
6.02.5.2 Alkylation, Arylation, and Acylation

Radical alkylations of pyridines and quinolines preferentially occur at positions 2 and 4. Protonation of the ring nitrogen influences the regioselectivity by favoring C-4 substitution.

Pyridine is attacked by the adamantyl radical to give a mixture of C-2 and C-4 isomers (Equation 104). The analogous reaction of ethyl isonicotinate gave mainly the 2-substituted derivative.

Using a modified Minisci reaction, the 4-position of the quinoline ring in alkaloid 195 (camptothecin) was substituted to afford the highly active antitumor agent 196 (karenitecin) (Equation 105).

Various intramolecular aryl radical reactions of pyridine derivatives have been developed. An early example of this type is found in a short synthesis of camptothecin 195. The tetracyclic intermediate 197 was cyclized by a free radical reaction to afford the natural product (Equation 106).
Radical cyclization of the 4-pyridone 198 occurs to give isoindolinone 199 with loss of a chlorine atom (Equation 107) <2003T3009>. Intramolecular free radical arylations of isoquinolin-1-ones have been reported <2000OL2535>. Various intramolecular radical additions to pyridines and quinolines at the 2-, 3-, and 4-positions have been shown to be facile processes <1997TL137, 2000J(P2)1809, 2001TL9061, 2001TL2907, 2001JOC2197, 2003T3009, 2004OL3671>. Occasionally, rearrangements are observed. The free radical cyclization of 200 produced the product 201 via the ipso-substitution mechanism proposed in Scheme 34 <2003T3009>.

\[
\begin{align*}
\text{Cl} & \quad \text{Br} \\
\text{N} & \quad \text{O} \\
\text{C} & \quad \text{C} \\
198 & \quad \text{Me}_3\text{Si}_3\text{SiH, AIBN} \\
\text{benzene, } & \Delta \\
43\% \\
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{O} \\
\text{N} & \quad \text{O} \\
\text{C} & \quad \text{C} \\
200 & \quad \text{1,5-ipso} \\
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{O} \\
\text{N} & \quad \text{O} \\
\text{C} & \quad \text{C} \\
201 & \quad \text{1,6-ipso} \\
\end{align*}
\]

Scheme 34

A new process for the homolytic acylation of protonated heteroaromatic bases has been developed by Minisci et al. An N-oxyl radical generated from N-hydroxyphthalimide by oxygen and Co(II) abstracts a hydrogen atom from an aldehyde. The resulting nucleophilic acyl radical adds to the heterocycle which is then rearomatized via a chain process. Under these conditions, quinoline and benzaldehyde afford three products (Equation 108) <2003JHC325>. A similar reaction with 4-cyanopyridine gives 2-benzoyl-4-cyanopyridine in 96% yield.

\[
\begin{align*}
\text{PhCHO} & \quad \text{N-hydroxyphthalimide} \\
\text{TFA, Co(acac)}_2, & \text{Co(acac)}_3 \\
12\text{h, PhCN} & \quad \text{41\%} \\
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{O} & \quad \text{O} \\
\text{Ph} & \quad \text{Ph} \\
41\% & \quad \text{34\%} \\
\end{align*}
\]
6.02.6 Thermal and Photochemical Reactions and Those Involving Cyclic Transition States

The mechanisms of ring-expansion and ring-opening reactions of quinolyl and isoquinolyl nitrenes generated by flash vacuum thermolysis (FVT) are proposed \(^{<2003JOC1470>}\). Tetrazoles 202 and 203 were used as the starting materials. The subsequent decomposition to and observation of azides 204 and 205 and nitrenes 206 and 207 through a common carbodiimide 208 was achieved through the use of different, and subsequently increasing, FVT temperatures (Scheme 35). The intermediates were isolated in an argon matrix and characterized by infrared spectroscopy. Interestingly, the same nitrenes were observed for the matrix photolysis reactions of tetrazoles 202 and 203.

![Scheme 35]

Carbenes 210 generated from the triazoloquinoline 209 by FVT rearrange into a seven-membered ring ketenimine 211, similar to carbodiimide 208. The ketenimine similarly rearranges to 1-naphthylnitrene 212 and nitrone derivatives 213, 214, 215, and 216 (Scheme 36) \(^{<2004JOC2033>}\).

Similar products were found in the thermolysis of triazoloisoquinoline 217, again through carbene 218, ketenimine 219, and nitrene 220, to the cyanoindenes 215 and 216 as well as 2-aminonaphthalene 221 and 1,2'-azonaphthalene 222 (Scheme 37).
In a modified Graebe–Ullman reaction, pyridylbenzotriazole 223 was converted to α-carboline 224 in an efficient manner but in moderate yield (Scheme 38) <2006OL415>. Microwave irradiation was the energy source for both α-carboline synthesis and the preparation of 223. The advantages of this procedure are that the starting materials are commercially available and lower reaction times are used resulting in fewer undesirable side products. The style of microwave oven, amount of pyrophosphoric acid, power level, and time were all optimized.

A 2-pyridone ring can be a building block for the synthesis of isoquinoline derivatives by acting as a dienophile in a Diels–Alder reaction. An electron-withdrawing group at C-4 is necessary for reaction with various substituted 1,3-butadienes (Equation 109) <2000CPB1814>.
A phase-selective photochemical reaction of 2-pyridones is observed. Irradiation of 225 in benzene gives mainly rearrangement products 226, whereas, in the solid state, [4+4] photocycloaddition to the photodimer 227 occurred in quantitative yield (Scheme 39) <2004OL683>. The stereochemistry of the photodimer was exclusively the trans-anti-configuration, as shown. This is presumably due to π–π-stacking and dipole–dipole interactions between the pyridones. Intermolecular photocycloaddition of 2-pyridone mixtures can be selective and lead to useful quantities of [4+4] cycloaddition cross-products <1999JOC950>.

Photochemical cycloaddition of 2-cyanofuran with 2-alkoxy-3-cyanopyridine results in the formation of [4+4] photoadducts 228 and 229. The latter compound is seen to arise through the intermediate 230 (Scheme 40) <2004TL4437>. Mechanistic studies show that the photoadditions proceed from the singlet-excited state of the pyridine. The preference for the formation of 228 over 229 is explained by the two heteraromatics approaching each other such as to avoid proximity of their electronegative heteroatoms.

An intramolecular [4+4] photocycloaddition of a 2-pyridone with a furan ring yields the complex 1,5-cyclooctadiene 231 <2006OL3367>. The proposed transition state conformation leading to the realized (and desired) cis,syn-product is...
shown (Equation 110). The isopropyl group on the cyclopentane of the pyridone demonstrated stereocontrol and the isopropyl group on the nitrogen of the pyridone was found to be necessary. The $N$-unsubstituted pyridine yielded only 25% of the desired cis,syn-product, the majority being the trans,syn-isomer.

Irradiation of isoquinolinium hydroxytris(pentafluorophenyl)borate 232 resulted in C$_6$F$_5$ transfer to the isoquinolinium cation to yield 2-methyl-1-(2,3,4,5,6-pentafluorophenyl)-1,2-dihydroisoquinoline 233 <2005JOC10653>. The mechanism is proposed to be due to a photoinduced electron transfer from the singlet state of the $N$-methylisoquinolinium cation, confirmed using fluorescence quenching (Scheme 41).
Photolysis of 3-substituted pyridinium salt 234 in aqueous base provides the highly functionalized bicyclic aziridine 236, albeit in low yield (20%) \( <2005\text{JOC5618} > \). Fortunately, the two regioisomers can be separated chromatographically. The reaction presumably proceeds through indiscriminant hydroxide addition onto an intermediate allylic cation 235. Compound 236 can be carried on to the desired acetamidocyclopentene derivative 237 in three steps and 80% yield (Scheme 42).

![Scheme 42]

Further Developments

References

Pyridines and Their Benzo Derivatives: Reactivity at the Ring


Pyridines and Their Benzo Derivatives: Reactivity at the Ring


Biographical Sketch

Professor Daniel L. Comins received his B.A. degree in chemistry in 1972 from the State University of New York at Potsdam and his Ph.D. in 1977 from the University of New Hampshire under the direction of Robert E. Lyle. During 1977–79, he was a postdoctoral associate in the laboratories of Professor A. I. Meyers at Colorado State University working on the total synthesis of the antitumor alkaloids \( N \)-methylmaysenine and maysine. He joined the faculty of Utah State University in 1979, became an associate professor in 1984, and moved to North Carolina State University as a full professor in 1989. His research interests include heterocyclic chemistry, synthetic methodology, and total synthesis of natural products. In 1995 and again in 1999, he was elected to the Advisory Board of the International Society of Heterocyclic Chemists. He is or has been a member of the editorial advisory boards of *Progress in Heterocyclic Chemistry*, *Letters in Organic Chemistry*, *ARKIVOC*, and *Current Topics in Medicinal Chemistry*. Professor Comins is currently an associate editor of the *Journal of Organic Chemistry*. In 1998, he became a Japan Society Promotion of Science (JSPS) Research Fellow. Recently, he was the recipient of the 2005 North Carolina ACS Distinguished Lecturer Award.

Sean O’Connor was born in Portsmouth, New Hampshire (United States), in 1947. He received his B.S. with special attainments in chemistry from Washington and Lee University. He completed his M.S. at the University of South Carolina with Professor R. L. Cargill and his Ph.D. from Clemson University with Professor R. A. Abramovitch. He has been a postdoctoral associate in the laboratories of Professor D. L. Comins (Utah State University) and Professor R. E. Gawley (University of Miami). He worked as an industrial chemist for 20 years in the aerospace, biotechnology, and pharmaceutical fields and relocated to Clemson University in August 2005, where he is a lecturer in the chemistry department.
Rima S. Al-awar earned her B.S (1988) and Ph.D. (1993) degrees from North Carolina State University under the direction of Prof. Daniel L. Comins. Upon completing her postdoctoral studies with Prof. Michael T. Crimmins at the University of North Carolina at Chapel Hill, she joined Eli Lilly and Company as a senior organic chemist in 1995. As a research scientist in Discovery Chemistry Research and Technologies, she worked on oncology projects including the natural product cryptophycin and several kinase-based inhibitors. She is currently a head in Chemistry Process Research and Development.