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FUNCTIONALIZATION OF THE PYRIDINE RING. 1. REACTIONS WITH CARBON–CARBON BOND FORMATION (REVIEW)

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A review is presented for advances in the direct introduction of alkyl, alkenyl, alkynyl, aryl, and hetaryl substituents into the pyridine ring over the past 15 years.

Pyridine derivatives have great importance in biological metabolism. The role of these compounds in the pharmaceutical industry, agricultural chemistry, veterinary medicine, and industry is not less important. Modern organic chemistry provides a broad arsenal of methods for the preparation of various pyridine derivatives. One such approach involving the synthesis of the ring from acyclic fragments has long been known but rather often proves far from general. Another pathway, which has been developed extensively in the past few years, involves the functionalization of an existing pyridine ring. This approach appears especially attractive in light of the many methods for the activation of the pyridine aromatic system and feasibility of further modification of the introduced groups. It is precisely for this reason that we dedicate the following review series to this approach.

In the first review in this series, we examine reactions of pyridine and its derivatives leading to carbon–carbon bond formation upon the introduction of alkyl, alkenyl, alkynyl, aryl, and hetaryl substituents. The methods for introducing these substituents into the pyridine ring are quite similar and, thus, they should be classified on the basis of the starting compounds.

1. INTRODUCTION OF CARBON SUBSTITUENTS INTO THE PYRIDINE RING BY REPLACEMENT OF A HYDROGEN ATOM

Our general theoretical understanding of the chemical properties of pyridine indicates two pathways for formation of a carbon–carbon bond with the pyridine ring: aromatic radical substitution and nucleophilic substitution. Radical processes have been studied extensively in recent years, while there have been only a few studies on nucleophilic substitution in this context.

1.1. Radical Substitution Reactions

Radical reactions may be used to replace hydrogen atoms in the pyridine ring by alkyl, aryl, and hetaryl substituents but such reactions are mostly nonregioselective, which significantly reduces their synthetic usefulness.

The radical sources may be various alkyl, aryl, or hetaryl compounds, capable of generating stable radicals by chemical, thermochemical, or photochemical methods. Organic peroxides, which generate radicals upon thermolysis or photolysis are among the most common radical sources. Thus, for example, the thermal decomposition of a peroxide, $[Me(CH_2)_{10}CO_2]_2$ in acetic acid at 70°C leads to formation of the $Me(CH_2)_9CH_2^{\cdot}$ radical, which alkylates pyridines at $C_{(2)}$ and $C_{(4)}$ according to the following scheme [1]:

M. V. Lomonosov State University, Moscow 119899. Translated from Khimiya Geterotsiklicheskikh Soedinenii, Nos. 11-12, pp. 1536-1602, November-December, 1994. Original article submitted November 4, 1994.

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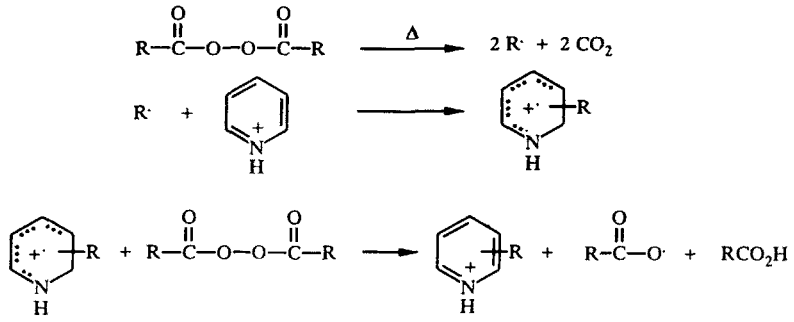
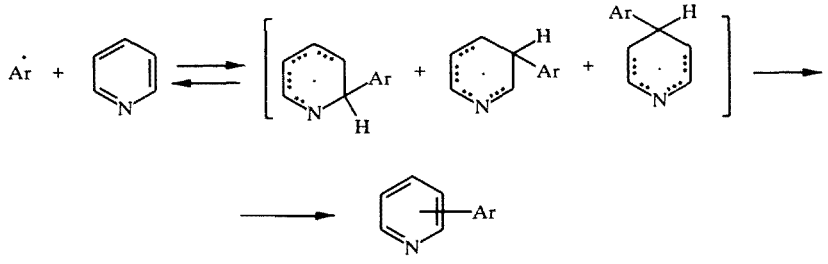


A study of the effect of pH of the medium on this reaction showed that protonation of pyridine enhances the rate of addition of the alkyl radical to the ring but diminishes the rate of reaction of the intermediate radical with peroxide.

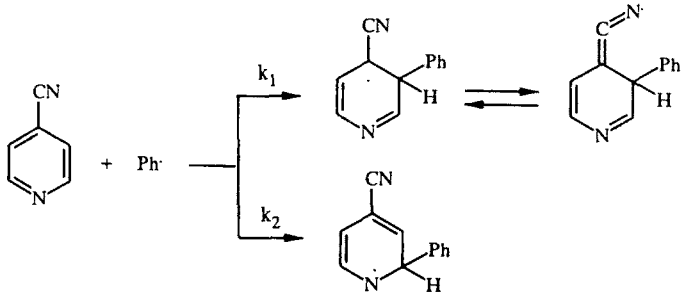
A mixture of α-, β-, and γ-isomers is formed upon the photochemical arylation of pyridine by p-tolyl peroxide [2].

The generation of p-tolyl radicals may also be achieved using p-tolyl iodide, di-p-tolylsulfone, di-p-tolylsulfoxide, and di-p-tolyl sulfide [2].



The homolytic arylation of 4-methylpyridine by p-RC_6H_4· radicals also leads to formation of isomeric substituted pyridines, whose ratio is not sensitive to the polarity of the radical in media with different acidity and basicity [3]. Aromatic radicals have been found to behave as electrophiles relative to 4-methylpyridine. In the arylation of the 4-methylpyridinium cation, the aryl radical acts as a nucleophile and the ratio of the isomeric reaction products and its rate depend on the nature of substituent R in the para position of the aryl radical [3].

The presence of an electron-withdrawing substituent in the pyridine molecule or pyridinium ion has no effect on the direction of arylation [4]. The reactivity and regioselectivity for nonprotonated pyridines are a function of the stability of the intermediate radical adduct. The polar effect is slight in this case. Thus, $k_2 < k_1$.



For protonated pyridines, in which polarity is greatly enhanced, the polar effect due to charge separation in the transition state has a significant effect on the reactivity and regioselectivity. The position with lowest electron density is attacked more rapidly ($k_3 > k_4$). The phenyl radical displays marked nucleophilic nature.

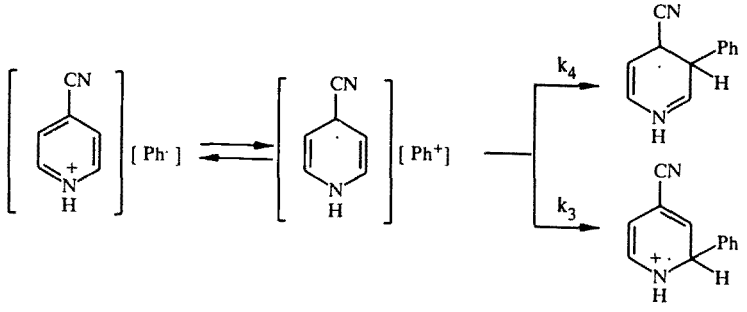
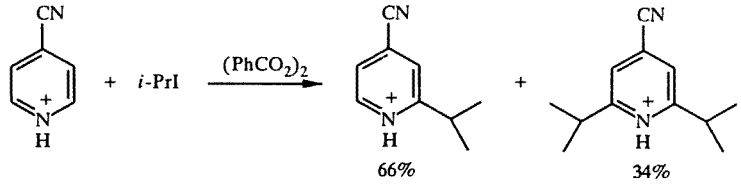


TABLE 1. Alkylation of 4-X-Substituted Pyridines

X	R	Alkylpyridine content, %		Conversion, %	Yield, %
		2-mono-	2,6-di-		
CN	*i*-Pr	67	33	86	95
CN	*c*-Hex	62	38	92	93
CN	*t*-Bu	58	42	96	94
Ac	*i*-Pr	68	32	85	95
Me	*c*-Hex	100	—	35	99

The rates of formation of bonds at the β position hardly changes ($k_1 \cong k_4$), while the rate of bond formation at the α and γ positions are significantly enhanced upon protonation ($k_3 > k_2$). The polar nature of this effect is also indicated by the increase in the rate of addition at the α position when there are electron-withdrawing substituents at the γ position.

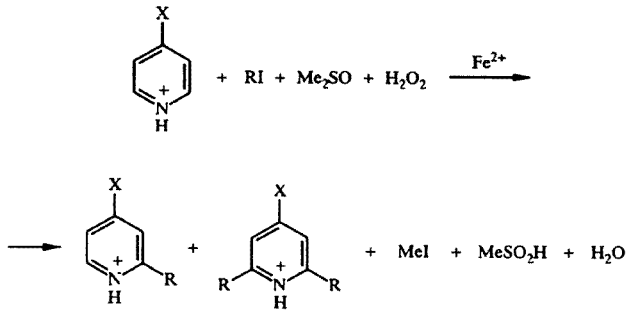
Organic halides may also serve as a source of free radicals. Thus, alkyl iodides together with benzoyl peroxide serve as convenient sources of nucleophilic radicals for the selective homolytic alkylation of protonated pyridines at the α positions [5]. These reactions proceed with high yield in acetonitrile, acetic acid, and benzene at 60-80°C in the presence or absence of small amounts of ferric salts.



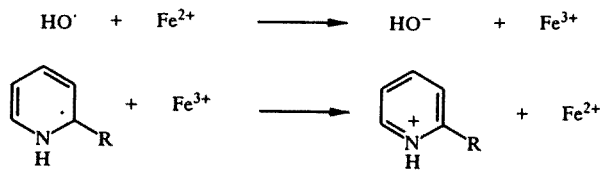
Hydrogen peroxide in DMSO in the presence of ferrous salts may initiate the homolytic alkylation of pyridines instead of benzoyl peroxide [6]. A combination of polar and enthalpy factors accounts for the high selectivity of this reaction. The abstraction of iodine from an alkyl iodide by a methyl radical (generated from DMSO) is a key step in this reaction:

(1)

This method is successful because slight changes in the energy of the C–I bond (related to the structure of the R group) lead to considerable change in the reaction rate and equilibrium state. Thus, the rate constants for key step (1) are: R = Et (20.1), i-Pr (468), and t-Bu ($1.7 \cdot 10^4$). This process for 4-substituted pyridines leads to 2-monoalkyl- and 2,6-dialkylpyridines (Table 1).



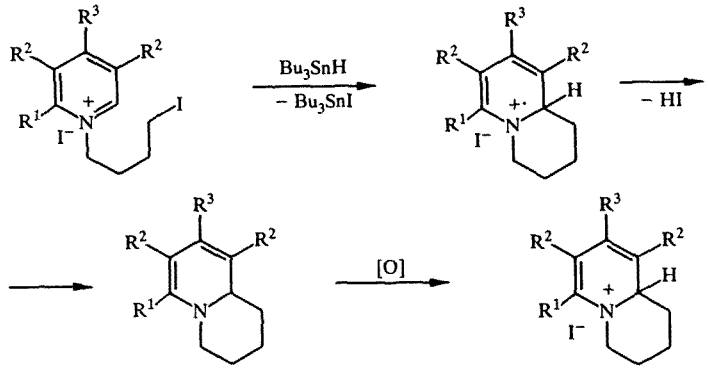
The role of the ferrous salt involves oxidation of the pyridine radical formed as follows:



In an intramolecular variant of alkylation by alkyl iodides, radicals are generated using tributyltin hydride [7].

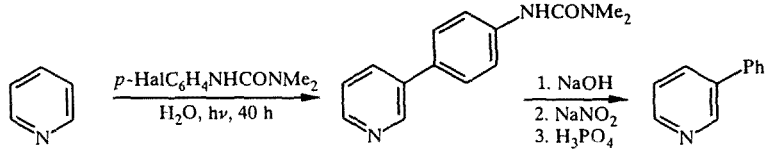
TABLE 2. *tert*-Butylation of Substituted Pyridines

$[Cu^{2+}]$ mole/liter	$[H_2SO_4]$ mole/liter	Content, %				Isomer ratio	
		I	II	III	IV	I : II	III : IV
tert-Butylation of 4-cyanopyridine at 25°C							
0	1,50	94,70	1,98	1,99	1,28	47,8	1,50
0	0,025	87,4	3,7	6,0	2,9	23,6	2,1
0,0025	1,50	88,7	7,4	2,47	1,3	12,0	1,9
tert-Butylation of 4-cyanopyridine at 57°C							
0	1,50	92,50	0,99	4,30	2,44	93,0	1,76
0,0025	1,50	79,12	10,20	3,80	6,70	7,7	0,56
tert-Butylation of I at 25°C					25 °C		
0	1,50			93,3	6,7		13,94
0,0025	1,50			52,1	35,9		1,45



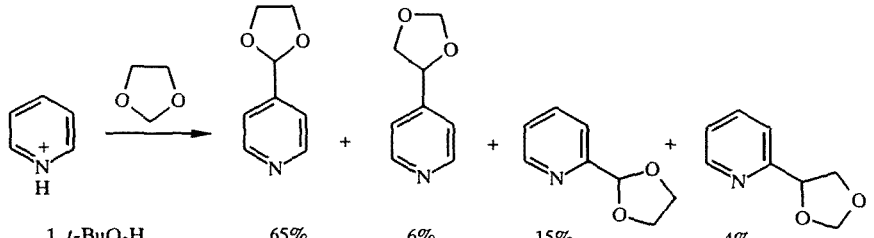
$R^1 = R^2 = R^3 = H$ (60%), $R^2 = R^3 = H$, $R^1 = Me$ (58%), $R^1 = R^2 = H$, $R^3 = Me$ (58%), $R^1 = R^3 = H$, $R^2 = Me$ (67%)

Aromatic halides may also be used to prepare free radicals. For example, the photoarylation of pyridine by (p-halophenyl)dimethylurea gives only the β-isomer in high yield [8].



Hal = Cl (92%), Br (83%)

Four isomeric compounds were isolated from the products of the alkylation of protonated pyridine (sulfuric acid, pH 5) by 1,3-dioxolane initiated by the t-BuOOH−$FeSO_4$ system [9]:

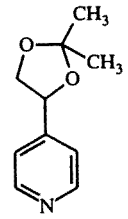


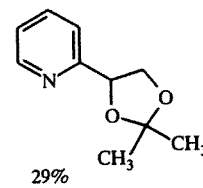
1. *t*-BuO_2H, $FeSO_4$, H_2SO_4	65%	6%	15%	4%
2. H_2O_2 − $FeSO_4$	38%	22%	11%	20%

The isomer ratio depends on the nature of the initiator. The reaction does not proceed at all in the absence of initiator. This finding indicates the radical nature of the reaction. Only two isomers are formed under analogous conditions when 2,2-dimethyl-1,3-dioxolane is used:

TABLE 3. Temperature Effect on the tert-Butylation of 4-Cyanopyridine

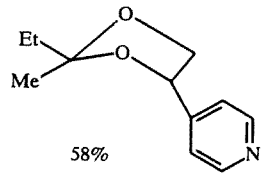
T, °C	Content, %		
	I	II	IV
18	94,35	4,39	1,26
90	96,30	1,56	2,14


61%


29%

In all the cases presented, the reactivity of $C_{(4)}$ of the pyridinium cation is greater than for $C_{(2)}$ relative to nucleophilic radicals.

A mixture of stereoisomers may be formed in the reaction with 2-methyl-2-ethyl-1,3-dioxolane in addition to positional isomers. Under the conditions studied (pH 5), trans-2-methyl-2-ethyl-4-(4-pyridyl)- and trans-2-methyl-2-ethyl-4-(2-pyridyl)-1,3-dioxolanes are the major alkylation products [9].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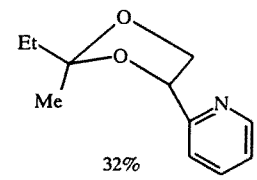

32%

The cis forms of these compounds probably undergo acid-catalyzed isomerization to the thermodynamically more stable trans isomers.

When the pyridine ring has electron-withdrawing substituents, the orientation of radical alkylation depends on the position of this substituent and differs for the protonated and nonprotonated forms [10]. Thus, alkylation proceeds selectively at $C_{(5)}$ (para position relative to the electron-withdrawing substituent) for 2-substituted pyridine derivatives:

X = COMe, CO_2Et, CN; R· =

Carrying out this reaction in the presence of sulfuric acid radically alters the orientation and the 4- and 6-substituted isomers are the major alkylation products along with an admixture of the 4,6-disubstituted product.

Alkylation of 4-substituted pyridines proceeds less selectively. Pyridine base gives mainly the 3-substituted isomer with a trace of the 2-alkylated product, while the cation mainly gives 2-monoalkyl- and 2,6-dialkylpyridines [10].

The reaction of 2,4-diacetylpyridine with the dioxanyl radical proceeds exclusively at $C_{(5)}$:

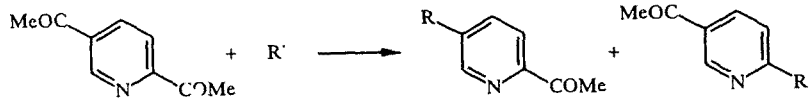
Two ipso-substitution products are formed in the case of 2,5-diacetylpyridine:

TABLE 4. Rates of the Homolytic Butylation of Pyridines

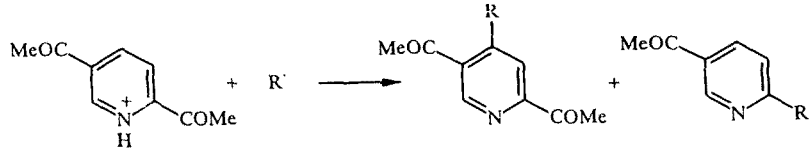
Compound	Rate	
	n-Bu	*t*-Bu
Relative homolytic butylation rates		
4-Methoxypyridine	1	1
4-Methylpyridine	3	28
Py	10	194
Absolute homolytic butylation rates at 57°C		
4-Cyanopyridine	$8,9 \cdot 10^5$	$6,3 \cdot 10^7$
4-Acetylpyridine	$6,8 \cdot 10^5$	$4,6 \cdot 10^6$
Py	$4,4 \cdot 10^4$	$3,3 \cdot 10^4$
4-Methylpyridine	$1,3 \cdot 10^4$	$4,8 \cdot 10^3$
4-Methoxypyridine	$4,4 \cdot 10^3$	$1,7 \cdot 10^2$

TABLE 5. Alkylation of Protonated Pyridine

Radical source	Reaction product	Yield relative to pyridine consumed, %
MeCOOH	2-Methylpyridine	34
	4-Methylpyridine	28
EtCOOH	2-Ethylpyridine	27
	4-Ethylpyridine	25
PrCOOH	2-Propylpyridine	37
	4-Propylpyridine	28
i-PrCOOH	2-*i*-Propylpyridine	25
	4-*i*-Propylpyridine	38
BuCOOH	2-Butylpyridine	31
	4-Butylpyridine	31

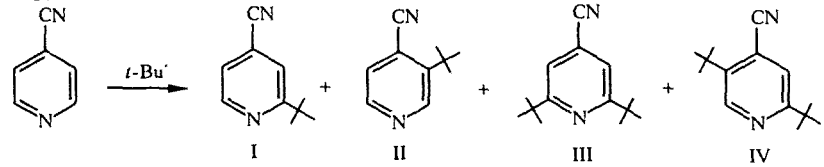


Upon protonation of this pyridine derivative, the attack proceeds at $C_{(4)}$ with ipso replacement of the 2-acetyl group:



As noted above [4], the change in the substitution regioselectivity upon protonation is attributed to a change in the nature of the transition state [10].

Kinetic studies of the n-butylation and tert-butylation of protonated pyridines (4-cyano-, 4-acetyl-, 4-methoxypyridines, and pyridine itself) permitted a detailed evaluation of the effect of various factors on the regioselectivity of homolytic alkylation by nucleophilic radicals [11]. Thus, the tert-butyl radical is more active than the n-butyl radical for activated pyridines such as 4-cyano- and 4-acetylpyridines. This clearly demonstrates the predominant role of polar effects relative to steric and enthalpy effects (Table 2).



I II III IV

Comparison of these results indicates that the activities of the α and β positions in 4-cyanopyridine and I differ significantly. The activity of the α position in 4-cyanopyridine in all cases is greater than for the β position, while the activities of both positions are comparable for 4-cyano-2-tert-butylpyridine (I) in the presence of cupric salts. The steric hindrance to protonation of I probably accounts for this behavior.

TABLE 6. Alkylation of 4-Cyanopyridine

Radical source	Alk	Yield, %	
		2-Alkylation	2,6-Dialkylpyridine
MeCOOH	Me	81	6
EtCOOH	Et	74	19
PrCOOH	Pr	48	10
i-PrCOOH	*i*-Pr	71	24
BuCOOH	Bu	49	2

TABLE 7. Radical Alkylation of Pyridine by Alkylmercury Chlorides

R	Yield of isomer mixture, % (method for yield determination)	Ratio of 2- and 4-Isomers	R	Yield of isomer mixture, % (method for yield determination)	Ratio of 2- and 4-Isomers
Et	64 (PMR)	2,0	*i*-Pr	72 (PMR)	1,6
n-Bu	73 (GLC)	2,4		89* (GLC)	3,1
n-Hex	85* (GLC)	1,9	c-Hex	69 (isolated)	3,1
$Me_3CCH_2CH_2$	64 (PMR)	2,5	2-Norbornyl	90 (isolated)	4,1
Me_3CCH_2	54 (PMR)	1,9	*t*-Bu	94 (PMR)	1,4
c-$C_5H_9CH_2$	77 (PMR)	1,9		98* (GLC)	6,0

*Reaction in the presence of 1,4-diazabicyclo[2.2.2]octane.

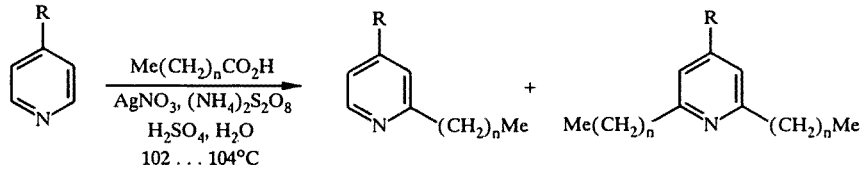
The reversibility of tert-butylation is a very significant finding. The effect of reversibility on regioselectivity should increase with increasing temperature (Table 3).

Indeed, the I:II ratio is 18 at 18°C, while it increases to 62 at 90°C. These results incontrovertibly indicate the reversibility of the addition of the tert-butyl radical to 4-cyanopyridine.

Comparison of the relative and absolute rates of n-butylation and tert-butylation of various substituted pyridines (Table 4) shows that the tert-butyl radical is more reactive for activated pyridines such as 4-cyano- and 4-acetylpyridines than the n-butyl radical. This finding may be attributed only to polar factors, while steric and enthalpy factors play a large role for n-butylation.

We should note that the tert-butyl radical is always more selective than the n-butyl radical but may be either more or less reactive depending on the electronic features of the aromatic system. The tert-butyl radical is more reactive when polar effects predominate over steric and thermodynamic effects [11].

The use of alkyl- and arylcarboxylic acids in the presence of silver nitrate is a specific method for the homolytic alkylation of protonated pyridine and pyridine derivatives with electron-withdrawing substituents [12-16]. The radicals in this case are generated upon the oxidative decarboxylation of the corresponding acids.



Alkylation of the pyridinium cation under these conditions (Table 5) proceeds about equally at $C_{(2)}$ and $C_{(4)}$ [12].

2-Alkyl-4-cyanopyridines are mainly formed from 4-cyanopyridine along with a trace of 2,6-dialkyl-4-cyanopyridines [12] (Table 6).

The following scheme for the generation of alkyl or aralkyl radicals may be given for the oxidative decarboxylation of phenylacetic acid [16]:

$$S_2O_8^{2-} + 2\,Ag^+ \longrightarrow 2\,SO_4^{2-} + 2\,Ag^{2+}$$

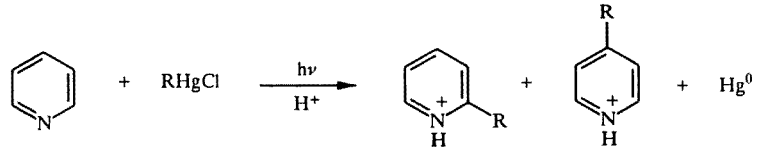
$$PhCH_2COOH + 2\,Ag^{2+} \longrightarrow PhCH_2^{\cdot} + CO_2 + H^+ + Ag^+$$

$$PhCH_2COO^- + SO_4^{-\cdot} \longrightarrow PhCH_2^{\cdot} + CO_2 + SO_4^{2-}$$

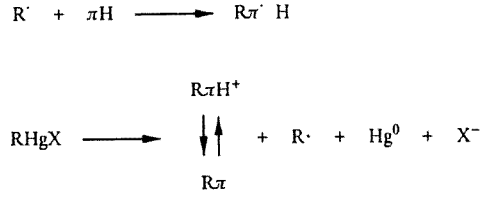
TABLE 8. Arylation of Pyridine by Diazonium Salts

R	Total yield of isomeric arylpyridines, %	Isomer yields, %			Reference
		2-	3-	4-	
H	40				[23]
m-F	48	18	10	6	[23]
p-F	38	3	2	1	[23]
m-NO_2	50	8	5	2	[23]
o-OMe		32	3	20	[23]
p-OMe		29	3	4	[24, 25]
3,4-$(OMe)_2$					[26]
4-Pyridyl	40	25		15	[27]

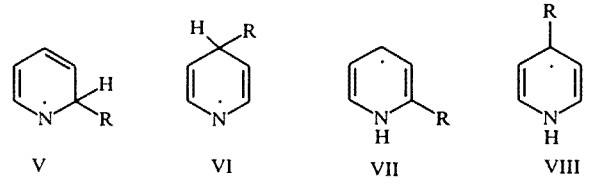
Alkylmercury halides may serve as a convenient source of free radicals [17-19]. For example, the photolysis of tert-butylmercury chloride in the presence of pyridinium cations proceeds with intermediate formation of radical–cations. The pyridinium radical–cation readily loses a proton to give a substituted pyridine radical, which is then oxidized by the alkylmercury halide. The alkylation leads to a mixture of 2- and 4-tert-butylpyridines in 94% yield. The isomer ratio varies from 0.48 to 1.1 depending on the reaction conditions [17]. The isomer ratio was studied in detail for a large series of alkylmercury halides [19] (Table 7).



A high ratio of the 2- and 4-isomers indicates that the attack of R· proceeds mainly at unprotonated pyridine since the pyridinium cation is known to undergo alkylation mainly at $C_{(4)}$ [20]. However, this does not completely rule out radical attack at the pyridinium cation and Py···Hg(R)Cl complex. Thus, the reaction was carried out in the presence of 1,4-diazabicyclo[2.2.2]octane in order to prevent the electrophilic dissociation of RHgCl by the pyridinium cation. Since the addition of 1,4-diazabicyclo[2.2.2]octane when R = Bu enhances the yield of the alkylation products, virtually without altering the isomer ratio, there is clearly no alkylation of the pyridinium cation. The relationship between PyH^+, Py···Hg(R)Cl, and Py is more complex for the more nucleophilic tert-butyl radical.



The initial attack of pyridine by radical R· leads to azacyclodienyl radicals V and VI, which may lose a proton to give radical–anions ($R\pi^{-\cdot}$) or undergo isomerization (presumably upon reaction with PyH^+ or Py) to give radicals VII and VIII ($R\pi^{\cdot}H$). Radicals VII and VIII are readily oxidizable.

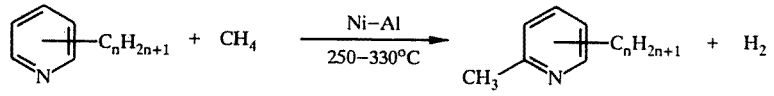


Evidence for this scheme is found in the ratio of 2- and 4-isomers for various R· radicals: 1.9 for Bu, 3.1 for i-Pr, 4.1 for 2-norbornyl, and 6.0 for t-Bu. These ratios indicate that the more electron-donating radicals give a greater yield of the 2-isomer [19].

The data on the radical alkylation of pyridine bases by alkanes are extremely limited. There have been only two studies devoted to the α-methylation of pyridines on a heterogeneous nickel–aluminum catalyst [21, 22].

TABLE 9. Photoalkylation of Pyridine by Esters

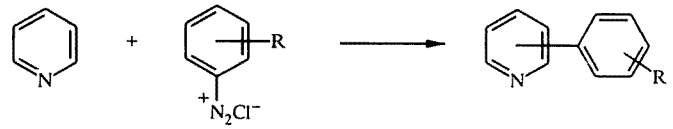
R	Total yield of alkylpyridines, %	Isomer yields, %		
		α-	β-	γ-
$CH_3(CH_2)_6$	66	35	11	20
$CH_3CO(CH_2)_2$	86	40	15	31
$Ph(CH_2)_2$	80	53	11	16
c-C_5H_{11}	94	42	12	40
c-Hex	95	42	15	38
2-Norbornyl	92	52	12	28
1-Adamantyl	80	38	13	29



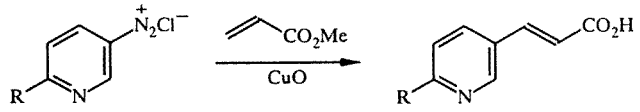
15...40%

The use of ethane and propane in this reaction also leads to α-methylpyridines, probably due to cracking of the hydrocarbons under the reaction conditions [21].

Various arylazo compounds are often used as the source of aryl radicals. The use of aryldiazonium salts for these purposes leads, as a rule, to low yields of mixtures of isomeric alkylpyridines, some of which may be separated chromatographically or isolated as picrates [23-27] (Table 8).

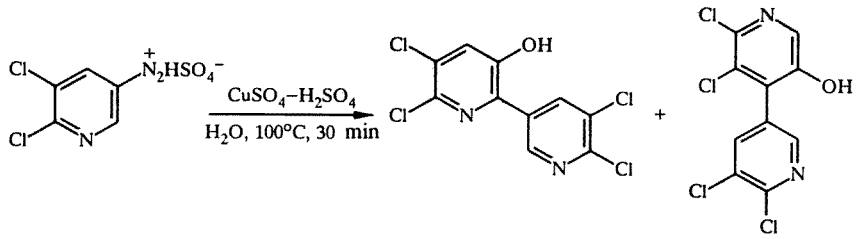


An alternative possibility is the use of pyridyldiazonium salts [28, 29]. Thus, the reaction of 3-pyridyldiazonium salts with methyl acrylate in the presence of CuO permits the introduction of a vinyl group into the pyridine ring [28]:



R = Cl (9%), OMe (26%), OEt (31%), OPr (23%), OC_5H_{11} (22%), OPh (21%), SEt (11%)

Treatment of 5,6-dichloro-3-pyridyldiazonium sulfate with cupric sulfate in sulfuric acid gives a mixture of dipyridines in 74% yield [29].

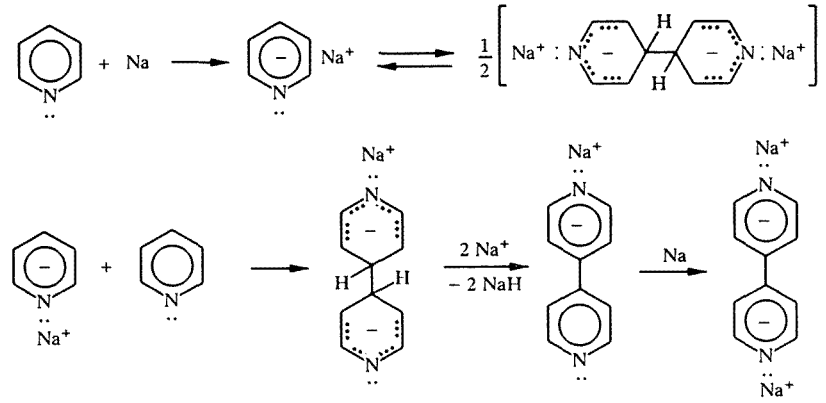


4- and 2-Pyridyl N-oxide radicals are also generated upon the diazotization of 4- and 2-aminopyridine N-oxides by amyl nitrite [30]. These electrophilic radicals readily pyridylate thiophenes, furans, and pyrroles in acetic acid.

In addition to the use of pyridine diazonium salts, there are also other methods for generating pyridine radical–ions such as those for the synthesis of dipyridines [31-35]. Thus, 4,4′-dipyridines are formed upon the action of alkali metals on pyridine [31]. This reaction proceeds through the formation of radical–anions, dimerization of these intermediates, and, finally, aromatization of the coupling products to give diaryls:

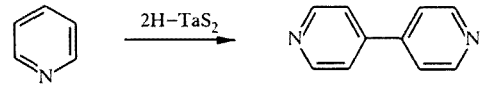
TABLE 10. Arylation of Pyridine by O-Acyloximes

Ar	Yields of isomeric arylpyridines, %		
	α-	β-	γ-
Ph	37	24	19
2-Pyridyl	45	25	15
3-Pyridyl	44	21	18
4-Pyridyl	44	23	20
2-Pyrazinyl	41	30	15

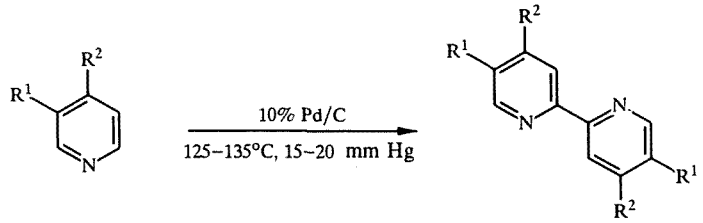


The formation of $Py^{+\cdot}$ and $Pic^{+\cdot}$ mother radical–cations occurs upon the radiolysis of pyridine and picoline using ^{60}Co γ radiation. This process for pyridine leads to 2,2′-, 2,4′-, and 4,4′-dipyridines and for 2-picoline, to pyridylpicolylmethanes, 4,4′- and 3,3′-dipicolines, and a small amount of dipyridylethane [32].

The dimerization of pyridine by the action of the hydrogen–tantalum sulfide system also proceeds through radical–cation formation [35].



The reductive coupling of substituted pyridines over Pd/C in vacuum yields a series of 2,2′-dipyridines with low yields [34].



$R^1 = COMe, R^2 = H; R^1 = CN, R^2 = H; R^1 = CO_2Et, R^2 = H; R^1 = H, R^2 = COMe$

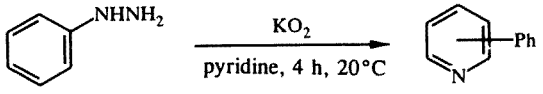
The oxidative dimerization of pyridine to give 4,4′-dipyridyls in a sealed tube with atmospheric oxygen at 300°C proceeds with yields of only 12-15% [33].

After a brief diversion related to the participation of pyridyl radicals in the introduction of carbon substituents into the pyridine ring, we shall return to an examination of the arylation and alkylation of pyridines due to radical generation from azo compounds.

Complex mixtures containing products of the radical arylation and coupling of pyridine are formed in the reaction of substituted phenylhydrazines with potassium superoxide (KO_2) in pyridine [36]. The composition of the reaction mixture depends significantly on the structure of the starting phenylhydrazine. Thus, isomeric phenylpyridines are the major products in the case of unsubstituted phenylhydrazine:

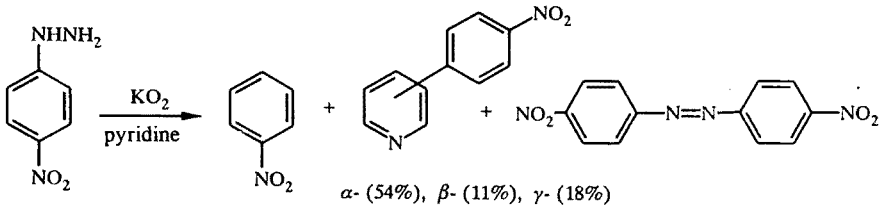
TABLE 11. Preparation of Oxoalkylpyridines

n	R	Catalyst	XIII:XIV isomer ratio	Yield, %
3	H	$Pb(OAc)_4$	2,75 : 1	63
		$Mn(OAc)_3$	3,00 : 1	63
4	H	$Pb(OAc)_4$	2,50 : 1	55
3	Me	$Pb(OAc)_4$		67



2-Ph + 3-Ph (71%), 4-Ph (21%)

The reaction of p-nitrophenylhydrazine is more complex:

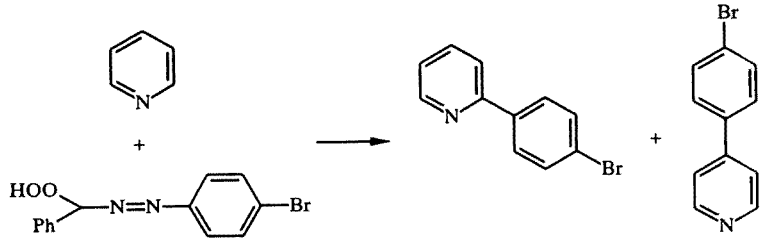


α- (54%), β- (11%), γ- (18%)

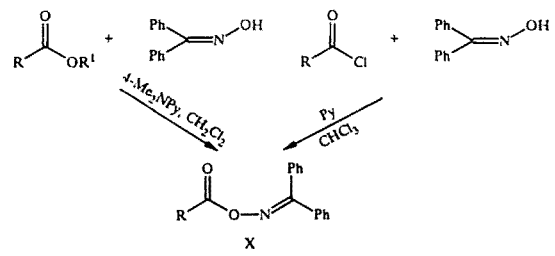
2,4-Dinitrophenylhydrazine does not arylate pyridine under these conditions at all. In the case of 2,5-dichlorophenylhydrazine, two isomeric (2,5-dichlorophenyl)pyridines were isolated in 15 and 16% yield from the complex reaction mixture. The structures of the isolated products could not be elucidated.

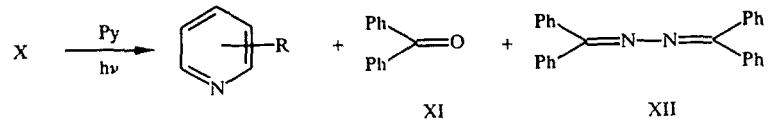
The reaction of pyridine with the hydrazide of benzoic acid and with KO_2 gave 2,2′- (14%), 2,4′- (17%), and 4,4′-dipyridyls (1%). The formation of these products may be attributed to the recombination of 2- and 4-pyridyl radicals arising due to hydrogen abstraction from pyridine by intermediate radical species since KO_2 does not react directly with pyridine [36].

Under mild conditions, azoperoxide IX reacts with pyridine to give 2- and 4-aryl derivatives in low yield among a whole series of other products [37].



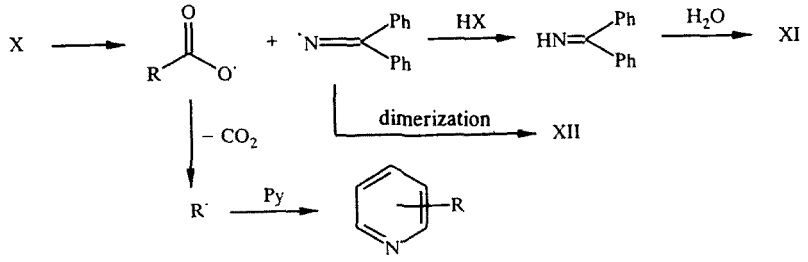
The photolysis of esters of aliphatic carboxylic acids and benzophenone oxime leads to the selective generation of primary, secondary, and tertiary aliphatic radicals, which form mixtures of α-, β-, and γ-alkylpyridines in high yield [38] (Table 9).



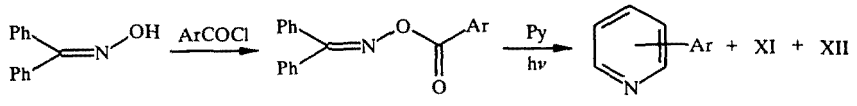


XI XII

The isomer ratio reflects the reactivity of the pyridine base relative to free radicals. The β position is least active ($\alpha > \gamma > \beta$). The scheme for radical generation and formation of the reaction products may be given as follows:



Esters of oximes and aromatic carboxylic acids behave similarly [39] (Table 10).



The isomers may be separated by crystallization of the picrates. As in the formation of alkylpyridines, 2-isomers are formed in low yield. However, the selectivity is lower and the activities of the β and γ positions are comparable.

1.2. Alkylation of Pyridines by Alcohols

The catalytic alkylation of pyridines by alcohols is a separate section since it is not confined within the distinct boundaries of a single mechanism and the direction of the process is largely a function of the nature of the catalyst.

Thus, the α-methylation of pyridines by methanol upon γ-irradiation catalyzed by nickel nitrate under mild conditions ($\sim 20°C$) likely proceeds through the γ-initiated coordination of methanol and pyridine at an Ni^{2+} ion [40]. The second step involves formation of a pyridine–methanol adduct and subsequent dehydration of this adduct. Co^{2+} salts accelerate the α-methylation of pyridine. Under the same conditions, γ-picoline forms 2,4-lutidine as the major product with maximum yield of 8% [40]. The liquid-phase alkylation of pyridine by methanol in the presence of Raney nickel proceeds with higher yields [41].

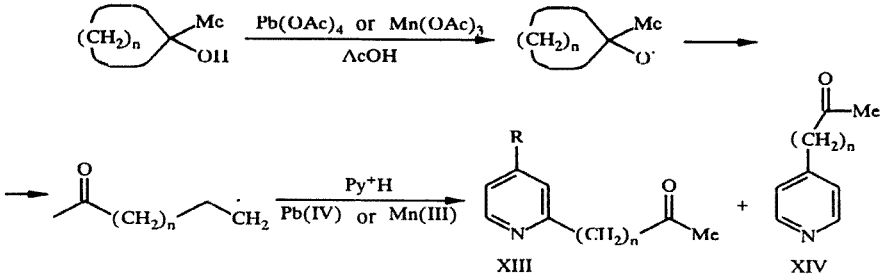
The orientation of the alkylation of pyridines by alcohols using zeolites as catalysts depends on whether the zeolites are X- or Y-type and the nature of the metal [42-44]. Nickel-containing Y-type zeolites have high catalytic activity, which reaches a maximum at 350°C in the alkylation of pyridine by methanol (78% pyridine conversion and 77 and 23% selectivity for the formation of 2-picoline and 2,6-lutidine, respectively) [42]. The use of Na^+-, K^+-, Rb^+-, and Cs^+-exchanged X- and Y-type zeolites leads to low selectivity and the formation of side-chain alkylation products, namely, 2- and 4-ethyl- and 2- and 4-vinylpyridines in addition to picolines and lutidines [43]. β-Methylation is observed over H^+- and Li^+-exchanged zeolites, while α- and γ-methylation (with predominance of the former) is found for alkaline–earth zeolites [44]. Thus, the yields of α-, β-, and γ-picolines using HY-zeolite are 3, 12, and 3%, respectively, while the use of BaY-zeolite gives these picolines in 23, 4, and 8% yield, respectively. The analogous alkylation is observed when ethanol is used.

The homogeneous liquid-phase alkylation of isomeric picolines by methanol or ethanol is achieved by the addition of catalytic amounts of ammonium halides and leads to products of alkylation of the side-chain and α-positions. This reaction proceeds at 320-350°C in a nitrogen stream. The fraction of side-chain alkylation products increases with increasing temperature.

The use of oxoalkyl radicals formed from tertiary cycloalkanols by the action of $Pb(OAc)_4$ or $Mn(OAc)_3$ opens a new pathway for the synthesis of oxoalkylpyridines (Table 11) [46]:

TABLE 12. Alkylation of Pyridine by Diethylmagnesium in the Presence of Crown Ether

Crown ether	Reaction time, h	Isomer yields, %	
		2-	4-
12-Crown-4	24	0,54	<0,01
15-Crown-5	24	6	16
15-Crown-5	48	9	26
15-Crown-5	72	13	37
18-Crown-6	24	0,43	<0,01

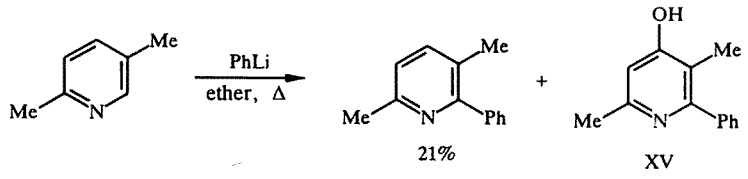


XIII XIV

1.3. Nucleophilic Substitution of Hydrogen in the Pyridine Ring

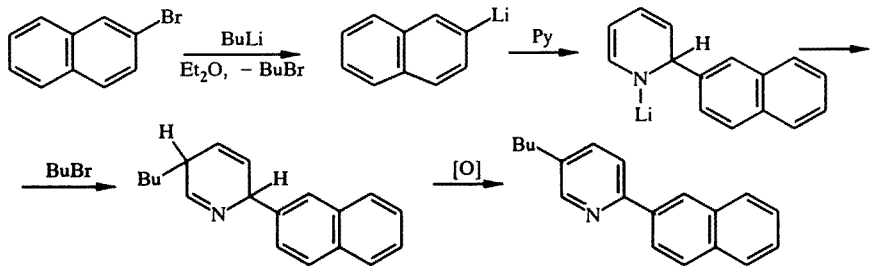
Strong C-nucleophiles are generally used for the introduction of carbon substituents into the pyridine ring by nucleophilic substitution of hydrogen atoms. Aryl and alkyl organometallic compounds serve as the source of these nucleophiles.

Thus, the arylation of 2,5-lutidine by phenyllithium leads to the corresponding α-phenyl derivative [47]:



The side-reaction involving formation of 4-hydroxypyridine XV is likely related to γ-lithiation of 3,6-dimethyl-2-phenylpyridine.

A similar reaction permits the introduction of a 2-naphthyl substituent at $C_{(2)}$ in pyridine [48]:

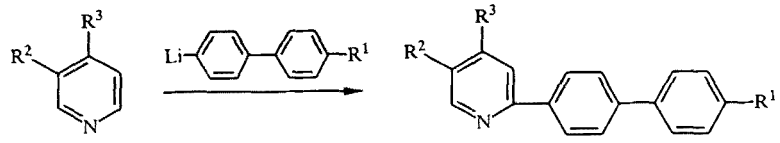


The addition of organometallic compounds to the pyridine ring leads to the formation of the N-lithium derivative of 1,2-dihydropyridine and subsequent loss of lithium hydride or oxidation of the intermediate gives the substitution product. The 1,2-dihydropyridine intermediate is capable of reaction with electrophiles, which leads after oxidation to a 2,5-disubstituted pyridine. Thus, treatment of a mixture of 2-bromonaphthalene and pyridine in ether gives 5-butyl-2-(2-naphthyl)-pyridine.

TABLE 13. Reaction of 4-Trimethylstannyl-N-acylpyridinium Salts with Grignard Reagents

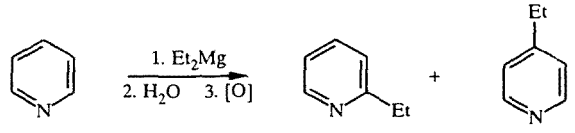
R	R^1	Yield of XIX, %	R	R^1	Yield of XIX, %
Pr	PhO	68	*c*-Hex	CH_2Ph	39
Ph	PhO	70	Bu	Et	54
Bu	PhO	50	Et	$PhCH_2O$	44
c-Hex	PhO	57	Pr	EtO	49
c-Hex	EtO	49			

Substituted diphenyls are introduced into the α-position of the pyridine ring for the synthesis of polyaromatic derivatives with liquid crystal properties. Lithium derivatives of the diphenyls are used [49-51]:



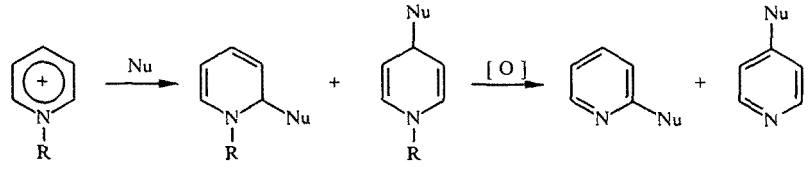
R^1 = Alk, CN, R^2 = Alk, OAlk, OCOCHClCHMeEt, R^3 = Alk

A specific effect of 15-crown-5 on the orientation of the nucleophilic substitution in the alkylation of pyridine by diethylmagnesium has been reported [52, 53]. Thus, while 1,2-addition of the organomagnesium reagent occurs as the major process in the absence of this crown ether, the formation of 1,4-dihydro species becomes predominant in the presence of the crown ether. In both cases, oxidative aromatization leads to ethylpyridines (Table 12).



2. REACTIONS OF PYRIDINIUM SALTS

The addition of C-nucleophiles (organometallic reagents, stabilized carbanions, and aromatic nucleophiles) to N-alkyl-, N-aryl-, and N-acylpyridinium salts serves as an efficient method for the introduction of various carbon substituents into the pyridine ring. In the general case, such addition may proceed at the α- or γ-positions of the ring to give 1,2- and 1,4-dihydropyridines, respectively.



R=Alk, Ar, Ac, OAc, $SiAlk_3$, O–X

As a rule, dihydropyridines readily undergo aromatization by the action of various oxidizing agents to give 2- and 4-substituted pyridines. The regioselectivity of such reactions has long been the subject of both theoretical analysis [54] and practical investigation [55].

On one hand, according to theoretical concepts, addition to the α- or γ-positions of the pyridine ring depends significantly on the hardness of the nucleophile [56] (hard nucleophiles attack mainly $C_{(2)}$, while soft nucleophiles attack mainly $C_{(4)}$). On the other hand, addition at the α- and γ-positions is considered possible in the case of kinetic control, while addition only at the γ-position is possible in the case of thermodynamic control [57, 58]. In the latter case, if the nucleophile is sufficiently stable, rapid addition and elimination lead to an equilibrium, in which the thermodynamically more stable 1,4-dihydro isomer becomes predominant. The stability of dihydropyridines depends also on the nature of the substituents at the nitrogen atom and on the pyridine ring as well as on the type of nucleophile.

TABLE 14. Reaction of N-Phenoxycarbonylpyridinium Salts with Grignard Reagents

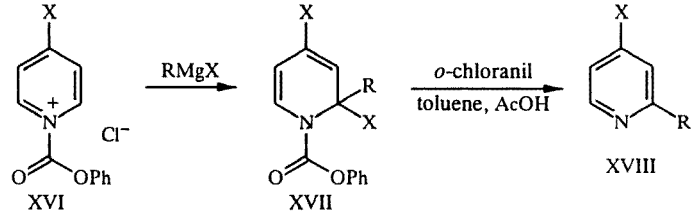
R^1	R^2	XX:XXI Isomer ratio	Reference	R1	R^2	XX:XXI Isomer ratio	Reference
CO_2Me	Ph	79 : 21	[61]	Br	Ph	52 : 9	[62]
CO_2-Pr-*i*	Ph	87 : 13	[61]	Br	*p*-ClC_6H_4	48 : 5	[62]
CO_2-Bu-*t*	Ph	83 : 17	[61]	Br	p-$MeOC_6H_4$	48 : 11	[62]
CO_2Me	Me	40 : 60	[61]	Br	*o*-MeC_6H_4	28 : 20	[62]
CO_2Me	Bu	43 : 57	[61]	Br	1-Нафтил	29 : 24	[62]
CO_2Me	*c*-Hex	16 : 84	[61]	Br	2-Нафтил	49 : 9	[62]
CO_2Me	Ph	84 : 16	[61]				

TABLE 15. Reaction of N-Phenoxycarbonyl-3-(trialkylstannyl)pyridinium Salts with Grignard Reagent

R	R^1	XXII:XXIII Isomer ratio	Total yield, %	R	R^1	XXII:XXIII Isomer ratio	Total yield, %
Bu	*c*-Hex	72 : 28	63	Bu	*m*-EtC_6H_4	77 : 23	77
Bu	*i*-Pr	61 : 39	67	*c*-Hex	*c*-Hex	95 : 5	62
Bu	Ph	99 : 1	80				

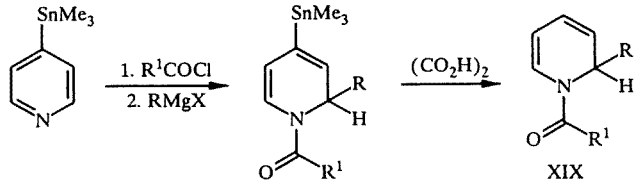
N-Alkoxycarbonylpyridinium salts have found greatest use.

The addition of alkyl and aryl Grignard reagents for 4-substituted N-phenoxycarbonylpyridinium salts proceeds regiospecifically at the α-position [59]:



X = Cl, Br; R = Pr (46%), c-Hex (36%), Ph (55%), Et (46%), Hex (64%), CH_2=CH (54%), 1-naphthyl (53%), i-Pr (42%) (The yield of 2-substituted pyridines XVIII is given)

The presence of a trimethylstannyl substituent at $C_{(4)}$ leads to an analogous effect. This substituent is readily eliminated from the addition product upon the action of oxalic acid (Table 13) [60]:



We should note the possibility of using not only N-phenoxycarbonylpyridinium salts but also alkoxycarbonylpyridinium and acylpyridinium salts.

Alkyl and aryl Grignard reagents add to N-phenoxycarbonylpyridinium salts lacking substituents at $C_{(2)}$ and $C_{(4)}$ to give a mixture of 1,2- and 1,4-dihydropyridines, whose aromatization by o-chloranil or sulfur leads to 2- and 4-substituted pyridines (Table 14) [61-63].

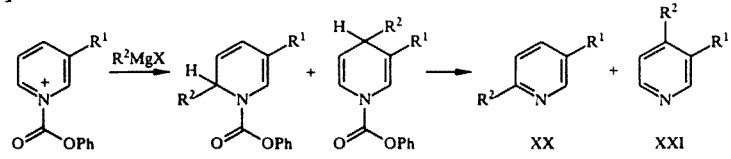


TABLE 16. Effect of the Acyl Group and Structure of the Grignard Reagent on the Regioselectivity in Alkylation and Arylation

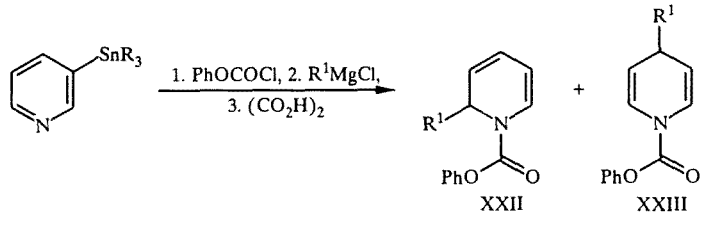
R^1MgX	R^2	XXIV:XXV Isomer ratio	Total yield, %	R^1MgX	R^2	XXIV:XXV Isomer ratio	Total yield, %
EtMgBr	Me	70 : 30	76	PhMgCl	Ph	73 : 27	77
EtMgBr	EtO	64 : 36	73	PhMgCl	*t*-Bu	52 : 48	66
EtMgBr	*t*-Bu	52 : 48	73	*i*-PrMgCl	Me	51 : 49	56
PhMgCl	Me	93 : 7	70	*i*-PrMgCl	EtO	41 : 59	82
PhMgCl	EtO	93 : 1	80	*i*-PrMgCl	*t*-Bu	13 : 87	80

TABLE 17. Effect of Added CuI on the Regioselectivity of the Reaction of N-Phenoxycarbonylpyridinium Salts with Grignard Reagents

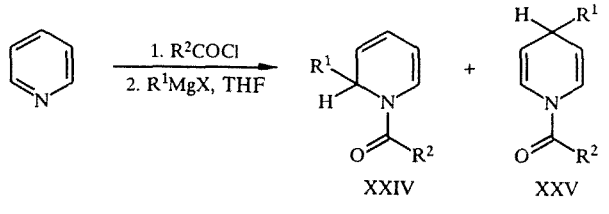
R^2	XX:XXI Isomer ratio	Total yield, %	Yield of purified XXI, %	R^2	XX:XXI Isomer ratio	Total yield, %	Yield of purified XXI, %
Me	1 : 99	58	48	c-Hex	4 : 96	49	41
Bu	7 : 93	52	44	Ph	5 : 95	64	60

These results show that, in all cases, mixtures of 1,2- and 1,4-dihydropyridines are formed but the ratio of these products depends largely on steric factors due to both the substituents in the pyridine ring and the Grignard reagent. For example, sterically nonhindered Grignard reagents give mainly 6-aryl-3-bromopyridines XX (R^1 = Br, R^2 = Ar) (49-52%) with 9% yield of 4-isomer XXI and less than 4% yield of 2-aryl-3-bromopyridine, while the use of bulky reagents with o-tolyl and 1-naphthyl groups enhances the content of the 4-isomer [62].

The effect of the nature of the substitution in the pyridine ring may be demonstrated in the reaction of 1-(phenoxycarbonyl)-3-trialkylstannylpyridinium salts (Table 15) [63].



In the general case for 1-acylpyridinium salts, the reaction regioselectivity depends on the structure of the Grignard reagent and nature of the acyl group (Table 16) [64]:



Additional evidence for the significant effect of steric factors on the regioselectivity lies in the finding that use of bulky substituents in N-tert-butylmethylsilylpyridinium salts XXVI leads to attack at $C_{(4)}$ with almost complete regioselectivity (≥99%). The resultant 1,4-dihydropyridines XXVII are readily oxidized by atmospheric oxygen to give 4-substituted pyridines XXVIII in 58-70% yield [65, 66].

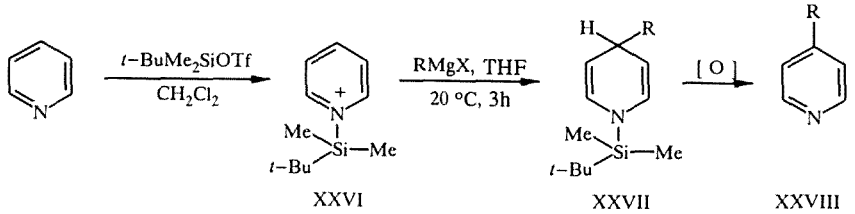
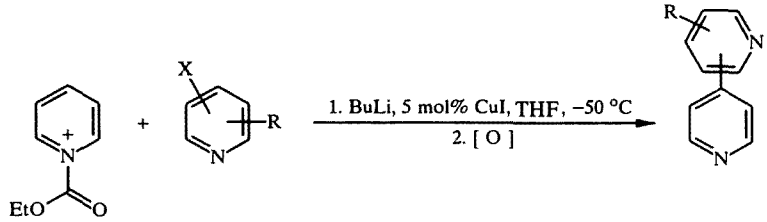


TABLE 18. Effect of CuI on the Hetarylation of 4-Ethoxycarbonylpyridinium Salts

X	R	Yield, %	Reference	X	R	Yield, %	Reference
3-Br	5-OMe	54	[70]	2-Br	6-OMe	58	[73]
3-Br	5-OCH_2Ph	59	[70]	2-Br	6-OCH_2Ph	62	[73]
3-Br	H	12	[71]				

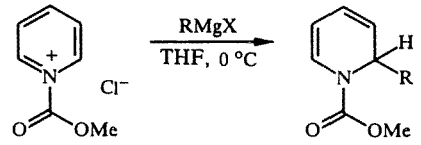
The addition of Grignard reagents in the presence of ~5 mole % CuI proceeds regioselectively at $C_{(4)}$ [61, 63, 64, 67-69]. This may be demonstrated, for example, by the change in the ratio of the resultant pyridines XX and XXI ($R^1 = CO_2Me$) (Table 17).

The addition of CuI has a similar effect on the reaction of N-ethoxycarbonylpyridinium salts with lithium derivatives of various heterocycles, which permits the selective preparation of 4-hetarylpyridines (Table 18) [70-74].



This method was also used for introducing five-membered heterocycle residues at $C_{(4)}$: 2-furyl (49%), 5-methyl-2-furyl (44%), 2-ethyl-5-furyl (41%), 3-bromo-2-furyl (40%), and 3-thienyl (51%) [74].

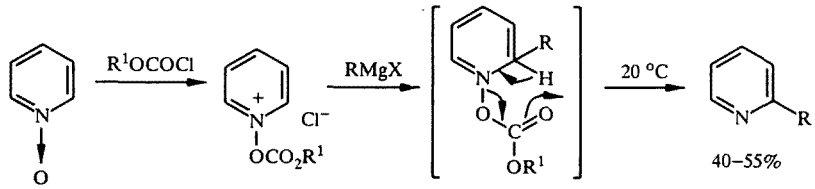
In contrast to alkyl and aryl Grignard reagents capable of giving products of 1,2 and 1,4 addition to N-acylpyridinium salts in various ratios depending on the structure of the reagents and reaction conditions, alkenyl and alkynyl Grignard reagents give only 1,2-dihydropyridines (regioselectivity > 99%) [70].



R = CH_2=CH (81%), (*E*)-HexCH=CH (71%), BuC≡C (85%), PhC≡C (85%), Me_3SiC≡C (99%)

As noted by Akiba et al. [65], soft reagents attack predominantly $C_{(4)}$, while hard reagents attack $C_{(2)}$ of the pyridine ring. Thus, unsaturated Grignard reagents, which are harder than alkyl Grignard reagents, selectively form 1,2-dihydropyridines [75, 76].

Other reasons account for the regioselectivity of 1,2-addition of various Grignard reagents to N-(alkoxycarbonyl)-oxypyridinium salts XXIX obtained from pyridine N-oxides [77, 78].



XXIX XXX

R=Ph, *o*-$MeOC_6H_4$, C≡C–$SiMe_3$, CH_2=CH

This reaction differs from reactions of other pyridinium salts in that aromatization of the intermediates occurs due to spontaneous loss of a monoalkyl ester of carbonic acid. The possibility of forming a six-membered transition state in intermediate XXX accounts for the ~98% selectivity of attack at $C_{(2)}$ and not at $C_{(4)}$. In the latter case, such a transition state is impossible.

The use of allylzinc bromides with ring-substituted salts XXIX leads to 2-allylpyridines in 35-60% yield [78].

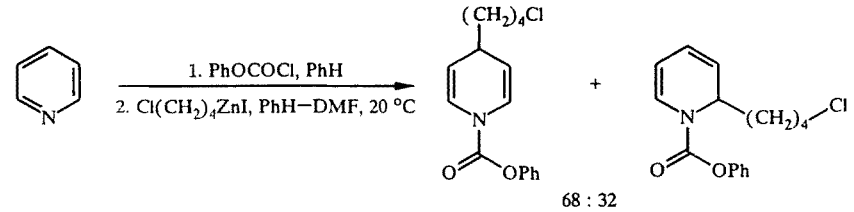
The addition of alkylzinc iodides to N-phenoxycarbonylpyridinium salts, as in the case of Grignard reagents, may give both 1,2 and 1,4 addition products [79].

TABLE 19. Reaction of 1-Ethoxycarbonylpyridinium Salts with Alkyl and Aryl Cuprates

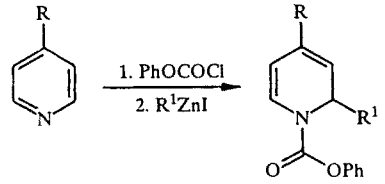
R	Total yield, %	XXXI:XXXII Isomer ratio	Yield of XXXIII, %	R	Total yield, %	XXXI:XXXII Isomer ratio	Yield of XXXIII, %
$CH_3(CH_2)_3$	89	99,5 : 0,5	68	$CH_3CH_2CHCH_3$	83	99,7 : 0,3	38
$CH_3(CH_2)_5$	85	99,7 : 0,3	66	Ph	94	99,0 : 1,0	59
$Ph(CH_2)_2$	81	100 : 0	55				

TABLE 20. Reaction of N-Alkoxycarbonylpyridinium Salts with Allyltributylstannane

R	R^1	Yield, %	Regioselectivity, %	R	R^1	Yield, %	Regioselectivity, %
Me	H	87	93	Me	3-Me	74 (2- : 6- =75 : 25)	93
Et	H	84	95	Me	3-Cl	87	94
CH_2CCl_3	H	84	91	Me	3-Br	87	91
$CH_2CH{=}CH$	H	64	95	Me	3-OAc	96	86
Me	6-Me	65	99	Me	3-CHO	88(2- : 6- =76 : 24)	
Me	4-Me	66	89				

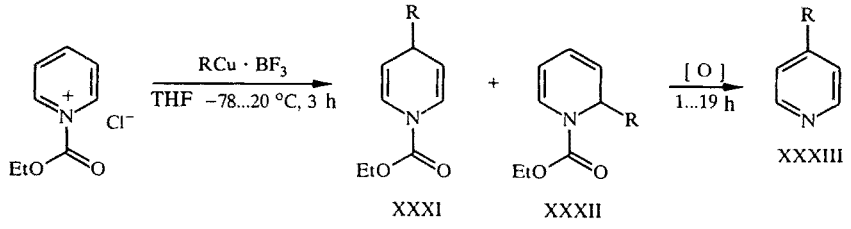


The introduction of bulky substituents at $C_{(4)}$ of the starting pyridine permits the regioselective preparation of 1,2-dihydropyridines [79].



R = *t*-Bu, R^1 = Bu (71%), $Cl(CH_2)_4$ (81%), $EtO_2(CH_2)_2$ (46%), $EtO_2C(CH_2)_3$ (35%), R = Ph, R^1 = Bu (57%), $EtO_2C(CH_2)_2$ (66%), $EtO_2C(CH_2)_3$ (47%)

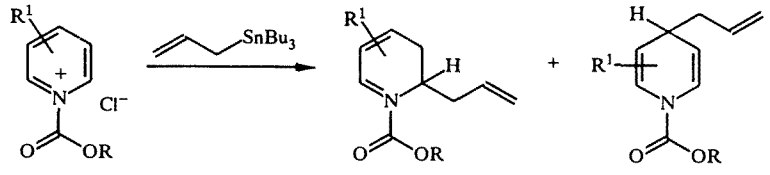
In contrast to organomagnesium and organozinc reagents, BF_3 complexes of alkyl or aryl cuprates react with 1-ethoxycarbonylpyridinium salts with ≥99% regioselectivity at $C_{(4)}$ to give the corresponding 1,4-dihydro derivatives in 81-94% yield. These products oxidize readily by the action of oxygen to give 4-alkyl- or 4-arylpyridines (Table 19) [66, 80].



The regioselectivity of the reaction of N-alkoxycarbonylpyridinium salts with organotin reagents, in contrast to the examples discussed above, depends exclusively on the structure of these reagents [81, 82]. The use of allyltributylstannane leads to 1,2-dihydropyridines XXXIV with high selectivity (Table 20) [81].

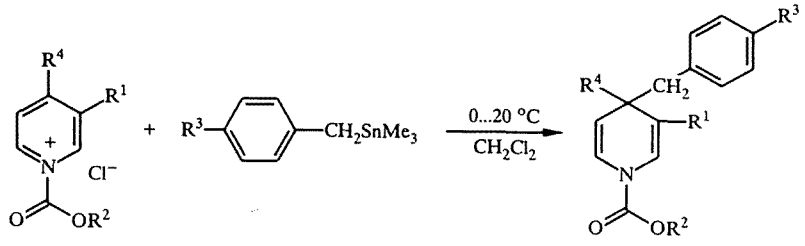
TABLE 21. Addition of Trimethylbenzylstannanes to Pyridinium Salts

Compound XXXV	R^1	R^2	R^3	R^4	Yield, %
a	H	Me	H	H	68
b	H	CH_2CCl_3	H	H	100
c	Cl	Me	H	H	77
d	Br	Me	H	H	70
e	CHO	Me	H	H	92
f	CN	Me	H	H	90
g	OAc	Me	H	H	55
h	OAc	CH_2CCl_3	H	H	63
i	H	Me	Me	H	56
j	CHO	Me	Me	H	90
k	Cl	Me	Me	H	78
l	Br	Me	Me	H	75
m	H	Me	OMe	H	56
n	CHO	Me	OMe	H	91
o	Cl	Me	OMe	H	69
p	Br	Me	OMe	H	83
q	H	Me	H	CN	98
r	H	Me	H	CHO	90
s	H	Me	Me	CN	99
t	H	Me	Me	CHO	91
u	H	Me	OMe	CN	99



XXXIV

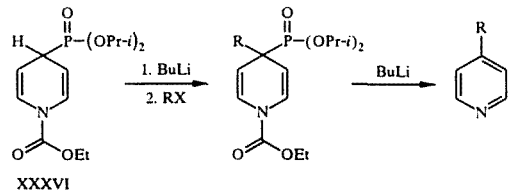
The finding of exclusive 1,4 addition in going to trimethylbenzyltin and its para derivatives was completely unexpected (Table 21) [82].



XXXVa–v

These results indicate that the reaction of N-methoxycarbonylpyridinium chloride (R^2 = Me) with trimethylbenzyltin smoothly gives 4-benzyl-N-methoxycarbonyl-1,4-dihydropyridine in 68% yield. The use of the more strongly electron-withdrawing 2,2,2-trichloroethylcarbonyl group raises the yield of XXXVb to 100%. The yield is also enhanced when there are electron-withdrawing groups at $C_{(3)}$ of the ring (for example, XXXVc–XXXVf), which indicates that the reaction is ionic, while the retention of formyl, nitrile, and acetoxy groups at this position indicates high chemoselectivity. The retention of high regioselectivity even when there is a substituent at $C_{(4)}$ of the starting salt (XXXVq–XXXVv) is especially unusual.

Another method for the regioselective alkylation at $C_{(4)}$ involves the prior introduction of a bulky diisopropylphosphonyl group into this position with subsequent treatment of the resultant diisopropyl 1-ethoxycarbonyl-1,4-dihydropyridine 4-phosphate (XXXVI) with butyllithium and an alkyl halide [83]. The key feature of this scheme is the use of the phosphonyl group as a substituent, which efficiently stabilizes the anion and is a good leaving group.



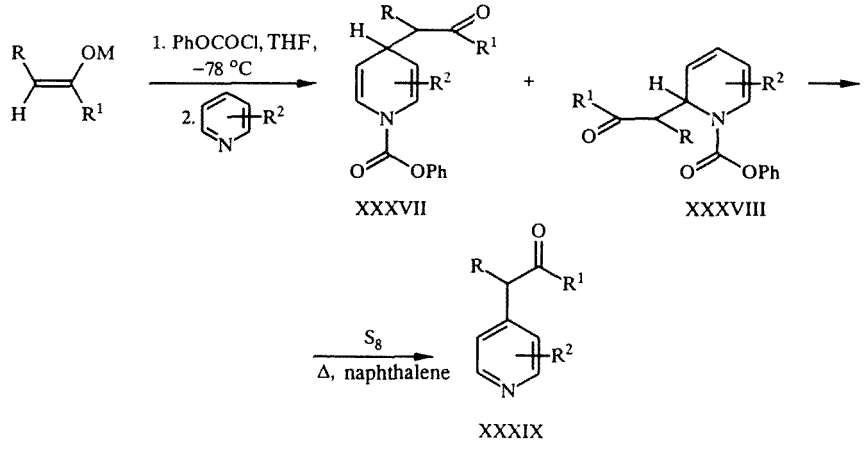
XXXVI

R X = MeI (74%), EtBr (76%), CH_2=$CHCH_2Br$ (70%), BuBr (78%), $PhCH_2Br$ (87%)

TABLE 22. Reaction of Pyridinium Salts with Enolates

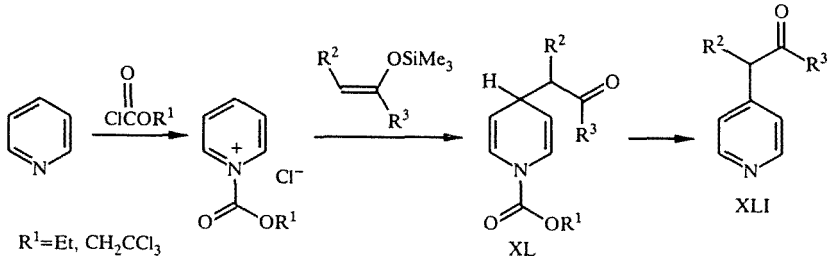
R	R^1	M	R^2	Yield of XXXVII+XXXVIII, %	XXXVII:XXXVII ratio	Yield of XXXIX, %
H	Me	Li	H	71	52 : 48	32
H	Me	$Ti(OPr\text{-}i)_3$	H	81	74 : 26	62
H	Me	$Ti(OPr\text{-}i)_4^-Li^+$	H	90	87 : 13	71
Me	Et	$Ti(OPr\text{-}i)_3$	H	78	93 : 7	65
$-(CH_2)_5-$		$Ti(OPr\text{-}i)_3$	H	91	87 : 13	57
$-(CH_2)_5-$		$Ti(OPr\text{-}i)_4^-Li^+$	H	93	92 : 8	62
Me	Ph	$Ti(OPr\text{-}i)_3$	H	74	98 : 2	59
H	Ph	$Ti(OPr\text{-}i)_3$	H	73	92 : 8	52
Me	OEt	$Ti(OPr\text{-}i)_3$	H	64	73 : 27	59
Me	OEt	$Ti(OPr\text{-}i)_4^-Li^+$	H	71	88 : 12	63
H	Ph	$Ti(OPr\text{-}i)_4^-Li^+$	2-Me	52	92 : 8	67
H	Ph	$Ti(OPr\text{-}i)_4^-Li^+$	3-Me	86	88 : 12	53

In addition to organometallic compounds, other C-nucleophiles such as enolates [84], enol ethers [85, 86], stabilized carbanions [87], aromatic π-nucleophiles [88], and π-excess heterocyclic compounds [89-91] may be used in reactions with N-acylpyridinium salts. Thus, while the use of lithium enolates in the reaction with N-phenoxycarbonylpyridinium salts gives a mixture of equal amounts of 4- and 2-(β-oxoalkyl)dihydropyridines, going to titanium enolates permits the selective introduction of a substituent at $C_{(4)}$ (Table 22) [84].



4-Substituted pyridines XXXIX are formed in good yields under aromatization conditions (sulfur in naphthalene at reflux), while the minor products, 1,2-dihydropyridines XXXVIII, decompose.

Trimethylsilyl ethers of enols react with N-ethoxycarbonylpyridinium chloride at $C_{(4)}$ with high regioselectivity. The yield of 1-ethoxycarbonyl-4-(2-oxoalkyl)-1,4-dihydropyridine XL is 42-87%. The use of 2,2,2-trichloroethoxycarbonyl salts gives yields of 80-100%. Dihydropyridine XL is aromatized by the action of O_2 or silver nitrate to give 4-(2-oxoalkyl)-pyridine XLI in 30-65% yield [85]:



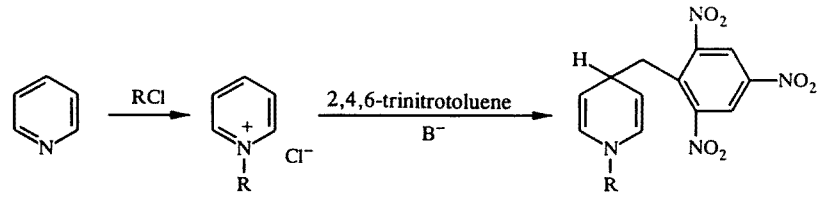
The reaction with 2,4,6-trinitrotoluene in the presence of base, which proceeds in low yield, may be given as an example of a reaction of N-acylpyridinium salts XLII with stabilized carbanions [87]:

TABLE 23. Photochemical Reaction of 2-Iodopyridine with Aromatic Compounds

R	Yield, %	Conversion, %	Isomer ratio		
			ortho	*meta*	*para*
CO_2Me	12	30	18	39	43
Cl	26	40	35	27	38
Me	37	30	40	26	34
OMe	67	90	51	13	36
OH	48	50	81	2	17

TABLE 24. Photochemical Reaction of 2-Halopyridines with Five-Membered Heterocycles

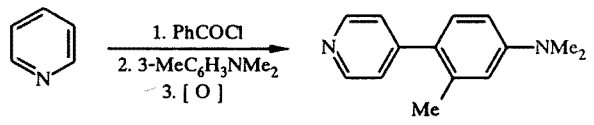
X	Y	Yield, % (compound)	Conversion, %	X	Y	Yield, % (compound)	Conversion, %
I	O	42 (XLIV)	70	I	NMe	28(XLIV)	59
Br	O	32(XLIV)	55	Br	NMe	29(XLIV)	45
I	NH	32(XLIV)	42	I	S	49(XLIV)	40
Br	NH	41(XLIV)	27			38(XLV)	



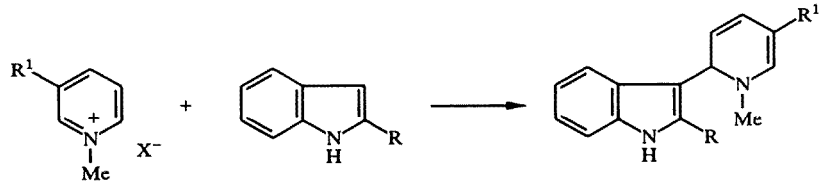
XLII

R=PhOC (36%), $PhSO_2$ (13%)

The use of electron-donating 3-dimethylaminotoluene in the presence of copper has been proposed for use in the introduction of a substituted aromatic ring at $C_{(4)}$ of the pyridinium salt [88].



The hetarylation of alkylpyridinium salts is accomplished using π-excess indole in basic media [89-91] (according to recent refined data, this reaction proceeds at $C_{(2)}$ of the pyridinium salt [91]).



R = CH_2COCH_3, R^1 = CH=$CHCO_2Me$ (50%), R = Me, R^1 = CHO (26%), R = Me, R^1 = H (95%), R = Me, R^1 = CH = $CHCO_2Me$ (80%)

Definite interest is also found in another method for the introduction of carbon substituents based on the selective α-lithiation of 4-substituted 1-alkoxycarbonyl-1,4-dihydropyridines with subsequent treatment with electrophiles according to the following scheme [69]:

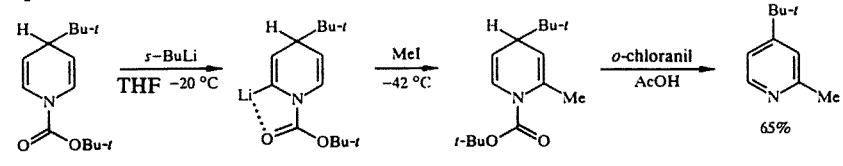


TABLE 25. Photochemical Reaction of 4-Iodopyridine with Five-Membered Heterocycles

X	Yield of XLVI, %	X	Yield of XLVI, %
O	34	NMe	69
NH	56	S	29 (2- : 3- = 87 : 13)

TABLE 26. Photochemical Reaction of 4-Iodopyridine with 4-Amino- and 4-Dimethylaminopyridines

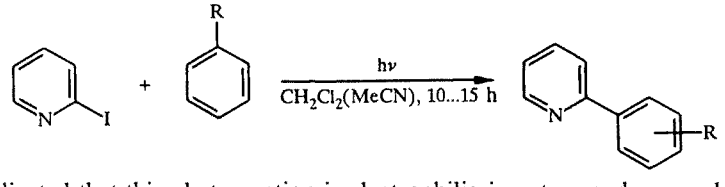
R	Yield, %	Isomer ratio		
		2-	4-	6-
H	41	84	16	
Me	45	51	20	29

3. REACTIONS OF HALOPYRIDINES

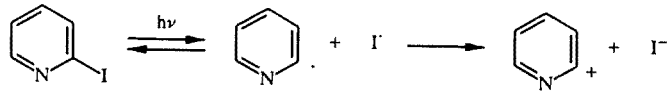
In light of their availability and high reactivity, halopyridines are commonly used as precursors for various pyridine derivatives. A number of synthetic methods have been developed for the substitution of the halide atom in a pyridine ring by alkyl, alkenyl, alkynyl, aryl, and hetaryl substituents. The yields of the desired products are close to quantitative and the techniques for carrying out these reactions and isolating the final products are usually extremely simple.

The carbon–halogen bond, especially in the α- and γ-positions of the pyridine ring, is sufficiently labile and capable of participating in nucleophilic substitution, exchange of halogen by metal, and also homolytic dissociation upon irradiation.

The capacity of the carbon–halogen bond to undergo photolytic dissociation is used in the photochemical synthesis of various 2-aryl- and 2-hetarylpyridines. The irradiation of a mixture of 2-iodopyridine and various benzene derivatives leads to isomeric 2-phenylpyridines (Table 23) [92].

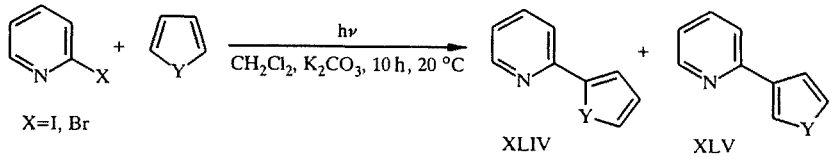


The isomer ratio indicated that this photoreaction is electrophilic in nature and proceeds through cation XLIII formed upon electron transfer [92].



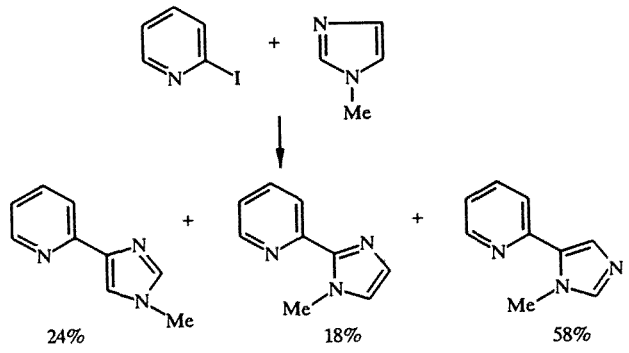
XLIII

Under analogous conditions, the irradiation of a mixture of 2-iodopyridine and various five-membered aromatic compounds gives 2-hetaryl-substituted pyridines (Table 24) [93]:

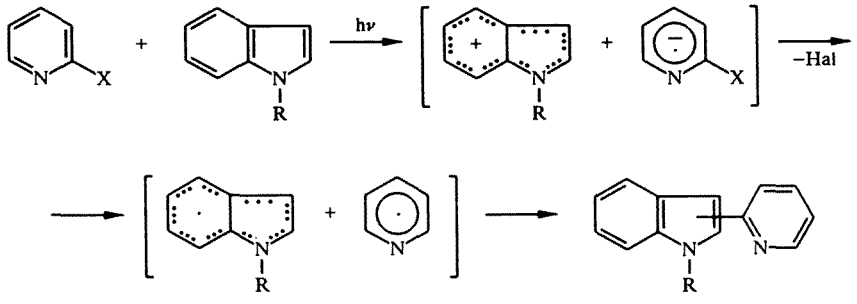


XLIV XLV

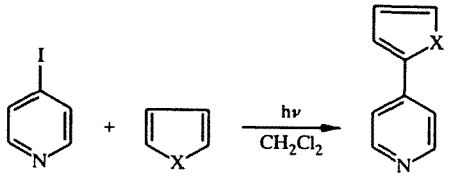
The photoreaction with N-methylimidazole leads to the formation of three regioisomers [93].



Low regioselectivity is observed also in the photochemical arylation of 2-bromopyridine by indole [94]. The composition of the isomer mixture suggests an electron-transfer mechanism. The dependence of the regioselectivity on the polarity of the medium is slight.



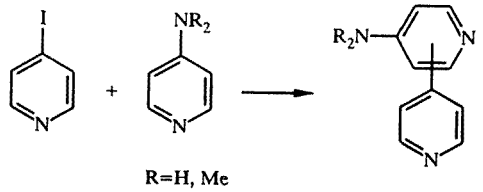
Such conversions upon irradiation are also found for 4-iodopyridine. The photoreaction of 4-iodopyridine with five-membered heterocycles selectively gives 4-(2-hetaryl)pyridines (Table 25) [95].



XLVI

X=O, NH, NMe, S

The reaction with six-membered heterocycles such as pyridine and pyrazine is quite difficult. Thus, the photolysis of a mixture of 4-bromopyridine and pyridine in methylene chloride is accompanied by the formation of dipyridines in ~6% yield. The photochemical hetarylation using 4-iodopyridine and 4-amino- or 4-dimethylaminopyridines as the substrate is more successful (Table 26) [95].



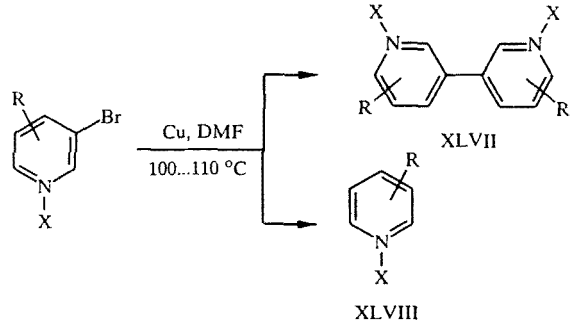
R=H, Me

A cyano group in the pyridine ring is capable of undergoing free-radical substitution upon irradiation. The photolysis of 2,4-cyanopyridine in the presence of an alkene in a nonpolar solvent leads to 2-cyano-4-allylpyridine. The formation of a new ring between $C_{(5)}$ and the carbon atom of the CN group at $C_{(4)}$ involving the alkene is observed in polar solvents. Such a change in the direction of the chemical transformations of 2,4-dicyanopyridine in the presence of an alkene upon irradiation depending on the polarity of the medium is probably related to the difference in the stabilization of the intermediates in solvents of different polarity [96].

TABLE 27. Transformations of 3-Bromopyridines under Ullmann Reaction Conditions

R	X	Yield, %		R	X	Yield, %	
		XLVII	XLVIII			XLVII	XLVIII
2-NO_2	—	75		6-CN	—		90
4-NO_2	—	68		2-(C=O)	H	10	
4-NO_2	O	78		4-(C=O)	H		
5-NO_2	—		92	H	O		90
6-NO_2	—		83				

The most well-known method for the preparation of various aryl- and hetarylpyridines, including dipyridines, is based on the Ullmann reaction. However, only 2-halopyridines usually undergo this reaction, while the yields of the desired products are only moderate. Various modifications of the Ullmann reaction have been reported, which permit enhancement of the yield of aryl- and hetarylpyridines. This problem has been examined in quite a few communications such as the work of Fanta [97]. Success in the Ullmann reaction with 3-bromopyridine requires the presence of an electron-withdrawing substituent such as a nitro, cyano, or N-oxide group in the pyridine ring or N-protonation. This method may be used to obtain, for example, 2,2′-dinitro-, 4,4′-dinitro-, 1,1′-dioxo-4,4′-dinitro-, and 2,2′-dioxo-3,3′-dipyridines [98]. Only the hydrodebromination product is formed in the reactions of 5-nitropyridine, 6-nitropyridine, 6-cyano-3-bromopyridine, and 3-bromopyridine N-oxide (Table 27).

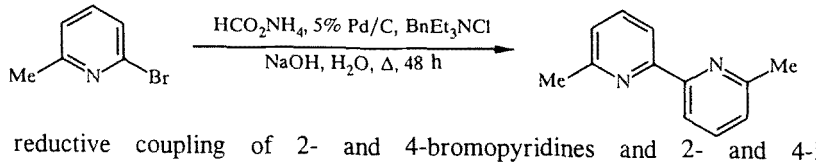


Significant activity of the halogen substituent in the Ullmann reaction is observed when a nitro group is present at the adjacent position.

Ultrasonic irradiation of a solution of 2-bromopyridine in THF in the presence of lithium leads to a mixture of 65% 2,2′-, 5% 2,4′-, and 30% 4,4′-dipyridines. 3-Bromopyridines undergo only hydrodebromination under these conditions [99].

The many examples of the preparation of dipyridines as the result of catalytic reductive homocoupling of halopyridines indicates that homogeneous and heterogeneous nickel and palladium catalysts are most frequently used for these purposes.

The reduction of 2- or 4-bromo-6-methylpyridines by ammonium formate using palladium on charcoal and benzyltriethylammonium chloride as a phase transfer catalyst gives 2,2′- and 4,4′-dipyridines in 50% yield [100].



The electrolytic reductive coupling of 2- and 4-bromopyridines and 2- and 4-iodopyridines in the DMF–Et_4NOTs–Pd cathode system with catalysis by bis(triphenylphosphine)palladium chloride is very efficient for the preparation of dipyridines [101].

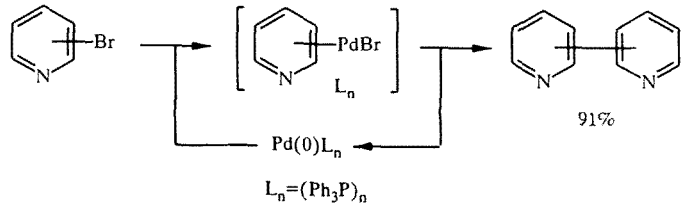
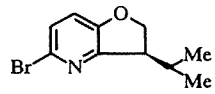
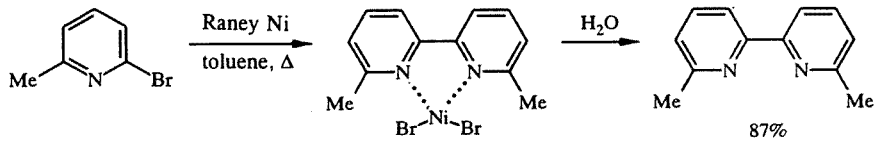


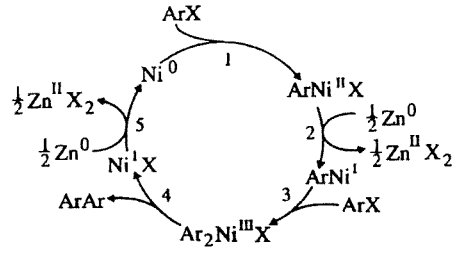
TABLE 28. Reductive Coupling of Halopyridines

$(R)_n$	X	Reaction conditions	Yield, %		Reference
			XLIX	L	
H	2-Br	$NiCl_2$, PPh_3, Zn, DMF, 50 °C	68		[104]
3-OMe	2-Br		75		[104]
6-OMe	2-Br		86		[104]
H	3-Br		80		[104]
2-OMe	3-Cl		51		[104]
5-OMe	3-Cl		88		[104]
6-OMe	3-Br		56		[104]
H	4-Cl		82		[104]
3,4-$(OMe)_2$	2-Br		87		[105]
3-OH	2-Br		55		[106]
3-OH, 6-Me	2-Br		42		[106]
H	2-Cl		70		[107]
			63		[108]
H	2-Br	$NiBr_2(Ph_3P)_2$, Zn, Et_4NI, THF	72		[103]
H	2-Cl		60		[103]
H	3-Br		73		[103]
3-CO_2Me	2-Cl		53		[103]
5-CO_2Me	3-Br		69		[103]
6-OMe	2-Cl		90		[103]
H	2-Br	NaH, *t*-BuONa, $Ni(OAc)_2$, Ph_3P, DMF, 30...60 °C	65	25	[109]
H	3-Br		78	20	[109]
H	2-Cl		68	30	[109]
H	3-Cl		90	6	[109]
H	4-Cl		86	10	[109]
6-OMe	2-Cl		79	18	[109]

High yields are achieved when Raney nickel is used as the catalyst for the reductive homocoupling of halopyridines [102].



The reductive homocoupling with catalysis by Ni(0) has found common use for the preparation of symmetrical dipyridines (Table 28). This catalyst is usually generated *in situ* by the reduction of bis(diphenylphosphino)nickel chloride using zinc powder or sodium hydride. This catalyst is effective for iodine, bromine, and chlorine derivatives of pyridine. The mechanism for the catalytic process may be represented as follows [103]:



$$ArX + Ni^0L_2 \longrightarrow ArNi^{II}XL_2$$

$$2\,ArNi^{II}XL_2 \longrightarrow Ar_2Ni^{II}L_2 + Ni^{II}X_2L_2$$

$$Ar_2Ni^{II}L_2 \longrightarrow Ar{-}Ar + Ni^0$$

TABLE 29. Cross-Coupling of Halopyridines with Grignard Reagents

$(X)_n$	R	L	Yield of LIII,* %	Reference
3-Br	4-(EtO)C_6H_4	Ph_3P	78	[111]
4-Br	2-(THPOCH$_2$)C_6H_4	Ph_3P	75	[112]
4-Cl	2-(THPOCH$_2$)C_6H_4	Ph_3P	55	[112]
2-Cl	TCH*[2]	dppe*[3]	65	[113]
2,6-(Cl)$_2$	TCH	dppe	36(31)	[113]
2-Br	Bu	dppp*[4]	47	[114]
2-Br	2-Thienyl	dppp	78	[114]
3-Br	Bu	dppp	47	[114]
2,6-(Cl)$_2$	Bu	dppp	63	[114]
2,6-(Cl)$_2$	2-Thienyl	dppp	11	[114]
3,5-(Cl)$_2$	Bu	dppp	42(9)	[114]
3,5-(Cl)$_2$	2-Thienyl	dppp	11	[114]
2-Br	Me_3SiCH_2	dppp	72	[114]
3-Br	Me_3SiCH_2	dppp	35	[114]
2,6-(Cl)$_2$	Me_3SiCH_2	dppp	69(11)	[114]
2-Br	1-Methyl-2-pyrrolyl	dppb*[5]	71	[115]

*The monocoupling product yield is given in parentheses.

*[2]TCH) tricyclo[4.1.0.0^{2,7}]hept-1-yl.

*[3]dppe) bis(diphenylphosphino)ethane.

*[4]dppp) bis(diphenylphosphino)propane.

*[5]dppb) bis(diphenylphosphino)butane.

The catalytic cycle includes the following steps:

1) oxidative addition of Ni(0) at the Ar−X bond,

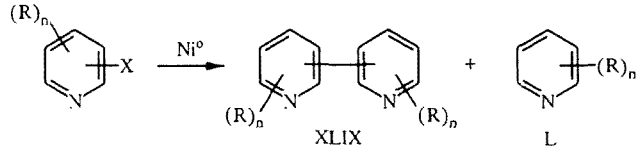
2) electrochemical reduction of $ArNi^{II}$ to $ArNi^{I}$ with the participation of zinc,

3) oxidative addition of $ArNi^{I}$ to ArX,

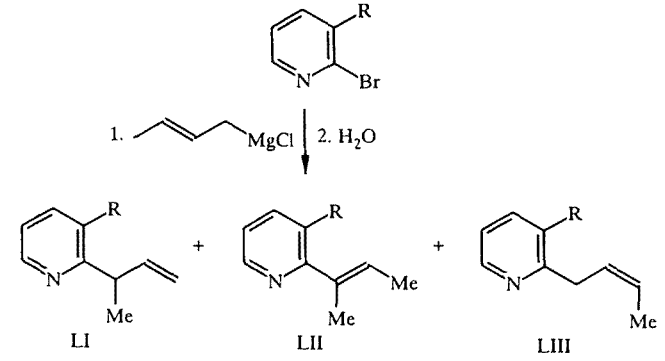
4) reductive elimination of the resultant diphenyl, and

5) reduction of Ni^{I} to Ni^{0}.

Carrying out this reaction in the presence of Et_4NI facilitates the reductive homocoupling, probably as a consequence of iodide ion activation of the electrochemical reduction of the Ni^{2+} ion by zinc.



Halopyridines readily undergo coupling with organolithium and organomagnesium compounds. These reactions are convenient methods for introducing carbon substituents into the pyridine ring. Thus, the reaction of 2-butenylmagnesium chloride with 2-bromopyridine and 2-bromo-3-picoline proceeds as follows [110]:

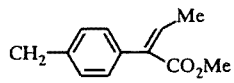


R=H (60%); Me (78%, 99% isomeric purity) R=H (14%) R=H (15%)

TABLE 30. Cross-Coupling of Halopyridines with Grignard Reagents

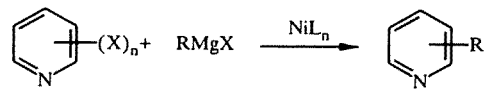
LVI	R	L	Yield of LVII, %	LVI	R	L	Yield of LVII, %
$R^1 = R^2 = Ph$	Me	PPh_3	89	$R^1 = R^2 = p$-$MeOC_6H_4$	Me	PPh_3	61
$R^1 = R^2 = Ph$	Ph	PPh_3	87	$R^1 = R^2$ = 2-furyl	Me	PPh_3	44
$R^1 = R^2 = Ph$	Bu	dppp	86	$R^1 = R^2$ = 2-thienyl	Me	PPh_3	26
$R^1 = R^2 = Ph$	*c*-Hex	dppp	86	$R^1 = Ph$, R^2 = 2-thienyl	Me	PPh_3	23

TABLE 31. Cross-Coupling of Halopyridines with Organozinc Compounds

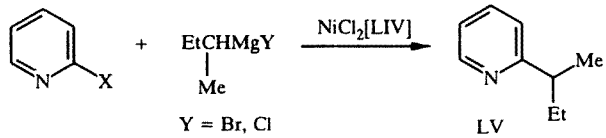
X	R	Catalyst	Yield, %	Reference
2-I	CF_2=CF	—	64	[120]
2-Br	Ph	$Pd(PPh_3)_4$	99	[121]
3-Br	Ph	$Pd(PPh_3)_4$	0	[121]
2-Br	1-R-Imidazol-2-yl*	$Pd(PPh_3)_4$	*	[122]
2-Br	Ph	$Pd(PPh_3)_4$	90	[123]
2-Br	Hex	$Pd(PPh_3)_4$	85	[123]
2-Br	Hex—C≡C	$Pd(PPh_3)_4$	79	[123]
3-Br	Ph	$Pd(PPh_3)_4$	0	[123]
3-Br	1-Methylpyrrol-2-yl	$Pd(PPh_3)_4$	66	[115]
2-Br	$R(CH_2)_n$ *2	$Pd(PPh3)_2Cl_2$	30...60	[124]
3-Br		Niacac $(Me_2CHCH_2)_2AlH$	70	[125]

* R = Me (90%), CH_2OEt (93%), SO_2NMe_2(60%).
*2 n = 2...4, R = Cl, $EtCO_2$.

Carrying out this reaction in the absence of excess Grignard reagent at 0°C prevents isomerization of LI to LII and leads to allyl derivative LI with 99% isomeric purity [110]. The use of nickel phosphine complexes as catalysts for the coupling of halopyridines significantly improves the synthetic utility of this reaction (Table 29).



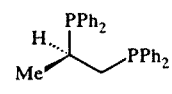
The cross-coupling of halopyridines with alkyl Grignard reagents using chiral phosphines such as LIV as ligands gives chiral alkylpyridines [116].



Y = Br, Cl

LV

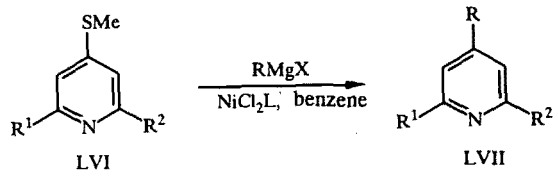
X	Yield of LX, %	Optical purity, % (absolute configuration)
2-Cl	70	1,6 (R)
2-Br	80	3,6 (S)
3-Br	65	16,4 (R)
3-Cl	50	0 (R)
4-Br	80	3,0 (R)
4-Cl	85	14,0 (R)



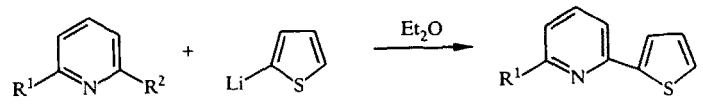
(R)-Prophos

LIV

The analogous cross-coupling with Grignard reagents catalyzed by nickel phosphine complexes is found for 4-(alkylthio)pyridines (Table 30) [117].

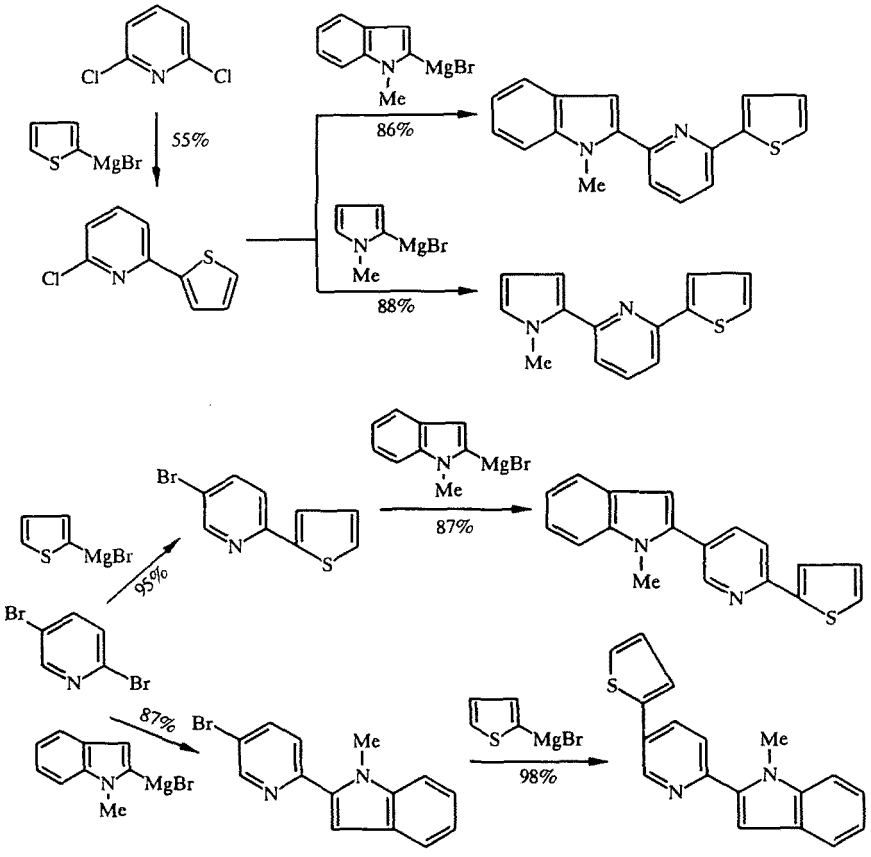


In some cases, the cross-coupling of organolithium derivatives of five-membered heterocycles with α-fluoro- and α-chloropyridines is useful for the preparation of hetarylpyridines [118].



R^1 = H, R^2 = F (58%); R^1 = R^2 = Cl (36%)

Palladium phosphine complexes may be used as catalysts for the cross-coupling of halopyridines with Grignard reagents. Minato et al. [119] have reported the synthesis of various mixed heteroaromatic trimers containing a pyridine ring.



The cross-coupling of organozinc compounds with halopyridines using palladium and nickel complexes as catalysts has been very useful for the preparation of new carbon–carbon bonds with the pyridine ring (Table 31). Most of such reactions have yields close to quantitative, which makes these reactions advantageous relative to the corresponding reactions with organomagnesium and organolithium compounds.

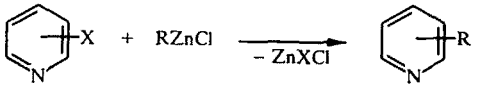
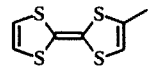
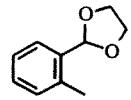
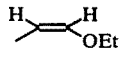


TABLE 32. Cross-Coupling of Halopyridines with Organomercury Compounds

X	R	Y	Yield, %	
			LVIII	LIX
2-I	H	S	92	9
2-I	6-Me	O	87	10
3-Br	6-NO_2	S	75	15
3-I	H	S	70	—

TABLE 33. Cross-Coupling of Halopyridines with Organotin Compounds

X	$(R')_n$	R	Catalyst	Yield, %	Reference
3-Br		4-Methyloxazol-2-yl	$Pd(PPh_3)_4$	100	[129]
2-Br		4,4-Dimethyloxazol-2-yl	$Pd(PPh_3)_4$	85	[129]
3-Br		4,4-Dimethyloxazol-2-yl	$Pd(PPh_3)_4$	82	[129]
3-Br		1-Triisopropylsilyl-pyrrol-3-yl	$Pd(PPh_3)_4$	88	[130]
2-Br			$Pd(PPh_3)_4$	82	[131]
2-Br		3-Formylthien-2-yl	$Pd(PPh_3)_4$	60	[132]
2-Br		CH=CH—$CH_2CH(OEt)_2$	$Pd(PPh_3)_4$	98	[133]
3-I		CH=CH—$CH_2CH(OEt)_2$	$Pd(PPh_3)_4$	65	[133]
2-Br	3-CO_2Et, 4-Me	*p*-$MeOC_6H_4$	$Pd(PPh_3)_4$	94	[134]
3-Br			$Pd(PPh_3)_4$	58	[135]
2-Br		2-Pyridyl	$Pd(PPh_3)_4$	77	[136]
3-Br		2-Pyridyl	$Pd(PPh_3)_4$	63	[136]
2-Br		3-Pyridyl	$Pd(PPh_3)_4$	59	[136]
2-Br		3-Methylisoxazol-5-yl	$Pd(PPh_3)_2Cl_2$	64	[137]
3-Br		3-Methylisoxazol-5-yl	$Pd(PPh_3)_2Cl_2$	60	[137]
2-Br		2-Methylmercapto-5-pyrimidyl	$Pd(PPh_3)_2Cl_2$	72	[138]
3-Br			$Pd(PPh_3)_2Cl_2$	65	[138]
4-Br			$Pd(PPh_3)_2Cl_2$	67	[138]
2-Br	3-NO_2		$Pd(PPh_3)_2Cl_2$	96(*E*)	[139]
2-Br			$Pd(PPh_3)_2Cl_2$ Et_4NCl	62(*Z*)	[140]
3-Br			$Pd(PPh_3)_2Cl_2$ Et_4NCl	72(*Z*)	[140]
4-Br	2,6-$(Me)_2$		$Pd(PPh_3)_2Cl_2$	70(*Z*)	[140]
3-Br	4-CO_2Et		$Pd(PPh_3)_2Cl_2$ Et_4NCl	66(*Z*)	[141]
3-Br	2-CO_2Et		$Pd(PPh_3)_2Cl_2$ Et_4NCl	76(*Z*)	[141]
3-Br	6-NO_2	CH_2=CH—	$Pd(MeCN)_2Cl_2$	89	[142]

Halogen may be replaced as the leaving group by triflate. The reaction of 3-pyridine triflate with furanzinc chloride leads to 3-(2-furyl)pyridine in 81% yield [126].

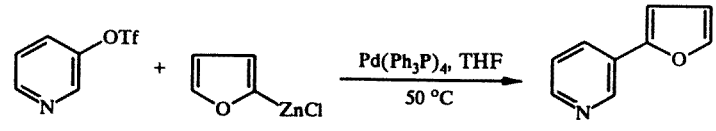


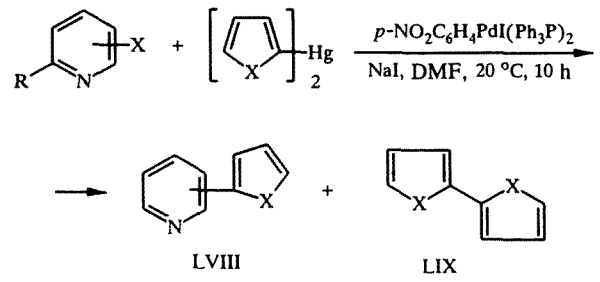
TABLE 34. Cross-Coupling of Halopyridines with Arylborate Esters [151]

R	X	Yield, %	
		LXI	LXII
2-NH_2	5-Br	87	13
2-EtO	5-Br	91	7
2-NO_2	5-Br	97	3
H	2-I	7	2

TABLE 35. Cross-Coupling of Halopyridines with Aryl- and Hetarylboric Acids

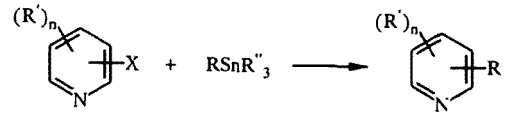
$(R)_n$	X	Ar	Catalyst	Yield, %	Reference
5-CO_2Me	3-Br	*m*-$NO_2C_6H_4$	$Pd(PPh_3)_4$	92	[143]
		Ph		98	[143]
		m-MeC_6H_4		98	[143]
		o-MeC_6H_4	$Pd(OAc)_2[P(o\text{-}Tol)_3]_2$	81	[143]
		o-$NO_2C_6H_4$		61	[143]
		o-$MeOC_6H_4$		70	[143]
		2,4,6-$Me_3C_6H_4$	$Pd(PPh_3)_4$	0	[143]
		2-Furyl	$Pd(OAc)_2[P(o\text{-}Tol)_3]_2$	86	[143]
		3-Furyl		83	[143]
	3-Cl	Ph	$Pd(dppb)Cl_2$	71	[146]
6-Ph	3-Cl	Ph		83	[146]
2-NO_2	2-Cl	Ph		73	[146]
3-OH	2-Cl	Ph		15	[146]
3-CO_2Et, 4-Me	2-Br	Ph	$Pd(PPh_3)_4$	58	[134]
3-CO_2Et, 4-Me	2-Br	*m*-$MeOC_6H_4$		82	[134]
	2-Br	2-Formyl-3-thienyl		78	[132,147]
	2-Br	4-Formyl-3-thienyl		85	[132,147]
	3-Cl	Ph	$Pd(dppb)Cl_2$	71	[148]
	3-Cl	Ph	$Pd(PPh_3)_4$	0	[148]
3-NO_2	2-Cl	Ph	$Pd(dppb)Cl_2$	73	[148]
	2,5-$(Cl)_2$	Ph		83	[148]
3-NO_2	2-Cl	4-Pyridyl		75	[148]
3-OH	2-Cl	Ph		15	[148]
2-OH	5-Cl	Ph		0	[148]
3-$CONH_2$	2-Cl	Ph		0	[148]
	2-Br	Ph	$Pd(PPh_3)_4$	53	[149]
	3-Br	Ph		86	[149]
	3-I	Ph		84	[149]
	3-Cl	Ph		0	[149]
	4-Br	Ph		86	[149]
2-OMe	5-Br	Ph		65	[149]
2-OH	5-Br	Ph		0	[149]
3-OH	2-Br	Ph		57	[149]
2-NH_2,3-Me	5-Br	Ph		79	[149]
2-NO_2	5-Br	Ph		88	[149]
2-NO_2, 3-Me	5-Br	Ph		76	[149]
	2,6-$(Br)_2$	3-Thienyl		51	[150]
	2,6-$(Br)_2$	3-Furyl		50	[150]
	2,6-$(Br)_2$	2-Thiazolyl		52	[150]

The reaction of organomercury compounds and bromo- and iodopyridine derivatives with palladium phosphine complexes as catalysts is used for the preparation of furyl- and thienylpyridines (Table 32) [127, 128].



LVIII LIX

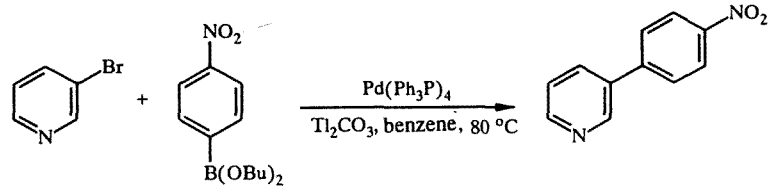
We should note that the cross-coupling of organomercury compounds is usually accompanied by the formation of homocoupling products LIX and, furthermore, requires use of a nucleophilic catalyst such as NaI. These disadvantages may be eliminated by using organotin compounds (Table 33). Furthermore, the cross-coupling of organotin compounds proceeds using palladium catalysts without phosphine ligands such as $(MeCN)_2PdCl_2$, Li_2PdCl_4, and $PdCl_2$.



LX

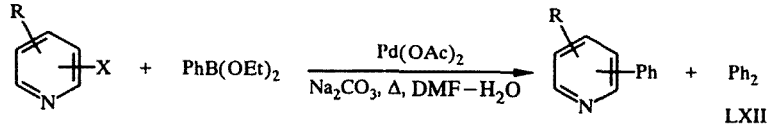
R''=Me, Bu

The major disadvantage of the methods for formation of new carbon–carbon bonds in aromatic substrates using the cross-coupling of organomercury and organotin compounds lies in the high toxicity of these organometallic derivatives. Thus, organoboron derivatives, especially arylboric and hetarylboric acids and their esters are most attractive for the modification of haloaromatic compounds (Tables 34 and 35). The cross-coupling of arylboric acids proceeds under mild conditions with high yields. Furthermore, the use of these compounds significantly simplifies the product isolation procedure. The cross-coupling of arylboric acids is carried out in the presence of bases such as $NaHCO_3$, Na_2CO_3, or amines since the dianion of the arylboric acid is formed as a reaction intermediate. This hypothesis was offered by Tompson and Guadino [143] in light of the finding that neither diphenylboric acid or triphenylboron undergoes the cross-coupling reaction, while butyl esters react only in the presence of water, i.e., under conditions facilitating their hydrolysis. However, Sato [144] reported a successful attempt to carry out the cross-coupling of dibutyl p-nitrophenylborate with 3-bromopyridine in benzene with $Pd(PPh_3)_4$ as the catalyst in the presence of thallium carbonate.



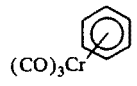
The maximum yields of the cross-coupling products are achieved when the reactions are carried out in mixtures of water and an organic solvent. In this case, the time required for the maximum yield is markedly reduced, probably since water facilitates the transmetallation step, which may be rate-limiting in the catalytic cross-coupling of organoboron compounds. Furthermore, carrying out these reactions in mixtures of water and an organic solvent permits us to use readily available palladium(II) salts such as $Pd(OAc)_2$ without additional use of phosphine ligands as precursors of the Pd^0 catalyst [145].

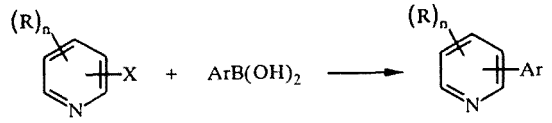
We should note that the reaction is more sensitive to steric hindrance in the arylboric acid than in the halogen derivative. The reactions of ortho-substituted arylboric acids proceed very slowly and with low yield. Di-ortho-substituted arylboric acids hardly undergo the cross-coupling reaction, especially with sterically hindered halopyridines [145].



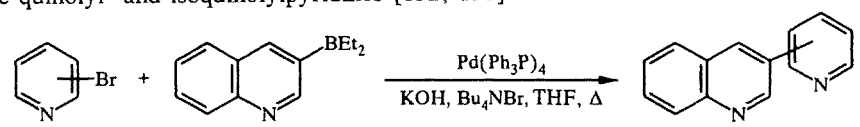
LXI LXII

TABLE 36. Reactions of Pentafluoropyridinium Salts with Organosilicon Compounds

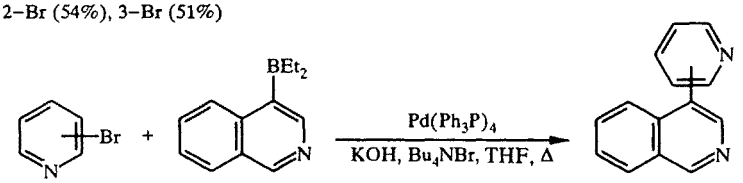
R	Reaction conditions	Yield, %
PhC ≡ C	DMF, KF	75
$PhCH_2$	DMSO, CsF	45
	DMSO, CsF	40



The cross-coupling of diethyl(3-quinolyl)- and 2-(4-isoquinolyl)boranes with bromopyridines has been proposed for the preparation of isomeric quinolyl- and isoquinolylpyridines [152, 153].

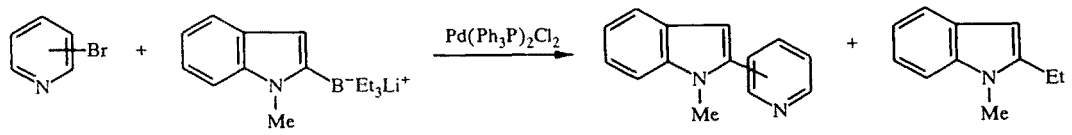


2-Br (54%), 3-Br (51%)



2-Br (60%), 3-Br (64%)

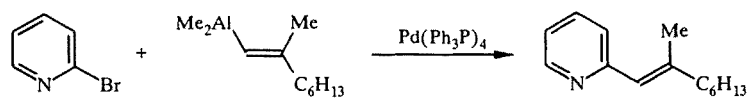
Lithium triethyl(1-methylindol-2-yl) borate undergoes cross-coupling with bromopyridines in the presence of $Pd(PPh_3)_2Cl_2$ [154].



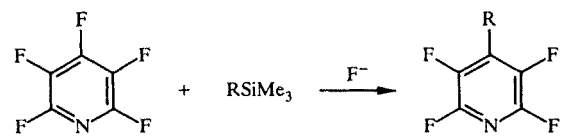
LXIII LXIV

Br	Yield, %	
	LXIII	LXIV
2	60	20
3	70	10

Reactions of organoaluminum and organosilicon compounds (Table 36) with halopyridines have been reported. These reactions lead to the formation of a new carbon–carbon bond but only a few examples of such reactions are known [156].

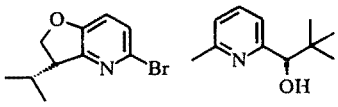


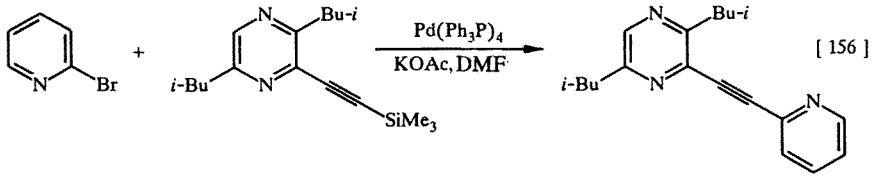
[123]



[155]

TABLE 37. Condensation of Halopyridines with Terminal Acetylenes

$(R')_n$	X	R	Catalyst	Yield, %	Reference
	4-Br		$Pd(PPh_3)_4$, CuI, Et_3N	60	[165]
2,6-$(CO_2R)_2$ R = Me, Et	4-Br	Ph	$Pd(OAc)_2$, Ph_3P, CuI	60	[166]
	2-Br		$Pd(PPh_3)_2Cl_2$ CuI, Et_3N	60	[167]
	2-Br	CH_2OH	$Pd(PPh_3)_2Cl_2$ CuI, Py	89	[168]
	2-Br	CH=CHSEt	$Pd(PPh_3)_2Cl_2$ CuBr, Et_3N	90	[169]
	3-Br	CH=CHSEt	$Pd(PPh_3)_2Cl_2$ CuBr, Et_3N	80	[169]
	2-Cl	Bu	$Pd(PPh_3)_2Cl_2$ CuI, KOAc	61	[163]
	3-I	$CH_2CH(OEt)_2$	$Pd(PPh_3)_2Cl_2$ CuI, Et_3N	63	[170]
4,6-$(Me)_2$	2-I	$CH_2CH(OEt)_2$	$Pd(PPh_3)_2Cl_2$	38	[170]
2-Me, 6-Ph	4-I	$CH_2CH(OEt)_2$	$Pd(PPh_3)_2Cl_2$	51	[170]
5-NO_2	2-Br	Ph	$Pd(PPh_3)_2Cl_2$ CuI, KOAc	70	[171]
3,6-$(Me)_2$, 5-NO_2	2-Br	CH_2OH	$Pd(PPh_3)_2Cl_2$ CuI, KOAc	80	[171]
	2-Br	C_8H_{17}	$Pd(PPh_3)_2Cl_2$ CuI, KOAc	60	[171]
	2-Br	2-Methyl-5-pyridyl	$Pd(PPh_3)_2Cl_2$ CuI, KOAc	80	[171]
5-NO_2	2-Cl	2-Methyl-5-pyridyl	$Pd(PPh3)_2Cl_2$ CuI, KOAc	60	[171]
5-NO_2	2-Br	2-Methyl-5-pyridyl	$Pd(PPh_3)_2Cl_2$ CuI, KOAc	80	[171]
5-NO_2	2-Cl	3-Quinolyl	$Pd(PPh_3)_2Cl_2$ CuI, KOAc	80	[171]
5-NO_2, 3,6-$(Me)_2$	2-Br	2-Methyl-5-pyridyl	$Pd(PPh_3)_2Cl_2$ CuI, KOAc	70	[171]
5-NO_2	2-Cl	2-Methyl-5-pyridyl	$Pd(PPh_3)_2Cl_2$ CuI, KOAc	72	[171]
	3,5-$(Br)_2$	2-Pyridyl	$Pd(PPh_3)_2Cl_2$ CuI, KOAc	65	[171]
			$Pd(PPh_3)_4$, CuBr, Et_3N	75	[108]



[156]

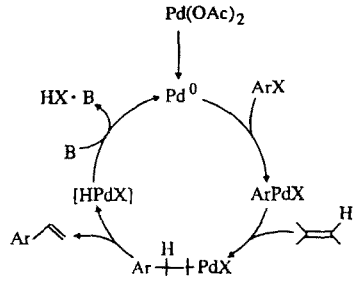
The arylation of olefins by aryl halides (Heck reaction) with Pd^0 catalysis is an efficient method for the formation of a carbon–carbon bond [157]. This reaction is carried out in the presence of base, while inorganic palladium salts and palladium on charcoal are used as the catalyst. The catalytic cycle of the Heck reaction involves several steps:

1) oxidative addition of Pd^0 at the Ar–X bond,

2) addition of the organopalladium compound to the olefin,

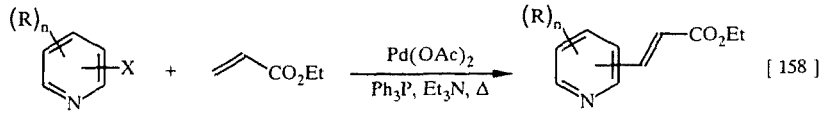
3) elimination of HPdX, and

4) regeneration of Pd^0 by the reaction of HPdX with the base.



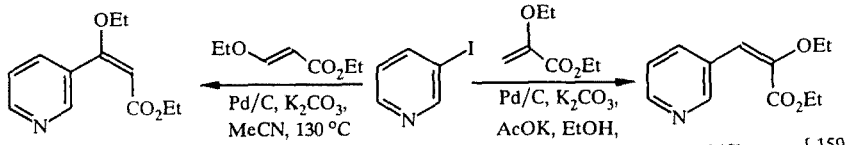
B = base

Although the Heck reaction is a convenient method for the direct introduction of an alkenyl substituent into the aromatic ring, it usually gives only moderate yields in the case of pyridines.



[158]

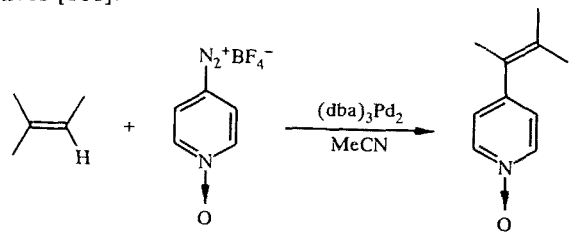
$(R)_n$	X	Yield, %	$(R)_n$	X	Yield, %
3-NH_2	2-Br	67	4-NH_2,2,6-$(Me)_2$	3-I	74
3-NH_2,4,6-$(Me)_2$	2-Br	70	3-NO_2,2,6-$(Me)_2$	4-I	57
4-NH_2	3-Br	65	2-NH_2	3-I	78



43% 24% [159]

This reaction is greatly facilitated by carrying it out in a mixture of water and an organic solvent or even in water. For example, styrene is arylated by 3-bromo-6-methylpyridine in aqueous media in the presence of palladium phosphine complexes such as $Pd(PPh_3)_2Cl_2$ and $Pd(o\text{-}TolI_3P)_2Cl_2$ and tributylamine to give phenylpyridylethylene in 65-75% yield [160]. The slight solubility of the starting compounds in water does not hinder the arylation reaction, which probably proceeds on the phase separation boundary.

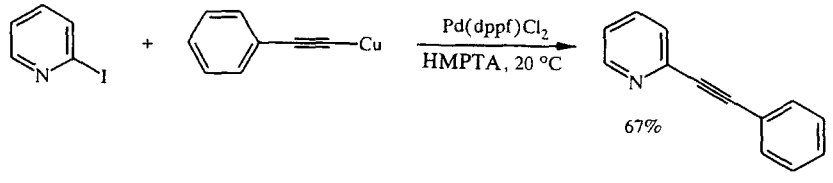
The arylation of olefins is possible not only using halogen derivatives but also using pyridyldiazonium salts. Thus, 4-pyridyldiazonium N-oxide tetrafluoroborate in the presence of tris(dibenzylidenacetone)dipalladium reacts with olefins to give the corresponding vinyl derivatives [161].



dibenzylidenacetone

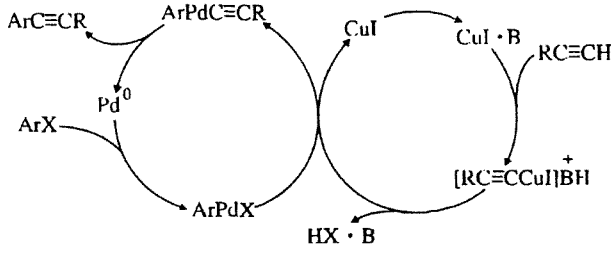
Olefin	Yield, %	Olefin	Yield, %
Cyclopentene	76	Indene	18
Styrene	59	Cyclohexene	45
Ethylacrylate	7		

Bumagin et al. [162] have proposed a method for the preparation of phenylpyridylacetylene based on the coupling of copper phenylacetylide with 2-iodopyridine catalyzed by $Pd(dppf)Cl_2$ (dppf = 1,1′-bis(diphenylphosphino)ferrocene). The use of $PhPdI(PPh_3)_2$ as the catalyst proved much less effective.



67%

This method for obtaining pyridylacetylenes requires the prior preparation of organocopper compounds, which is more complicated than acetylenic condensation directly using a terminal acetylene. Acetylenic condensation catalyzed by the Pd^0-Cu^I-base system is an efficient method for replacement of halogen in an aromatic ring by an acetylene group. This method is applicable for obtaining various pyridylacetylenes in high yield. Initially, this method was developed for aryl iodides and aryl bromides but recently, there have been quite a few examples of the use of aryl chlorides. This significantly expands the synthetic scope of the reaction, especially for obtaining various pyridine derivatives since iodo- and bromopyridines are much less available than chloropyridines. The use of β-chloropyridines in acetylenic condensation has not been achieved, while β-bromopyridine readily undergoes such reactions [163]. The step involving transmetallation with the organopalladium compound in acetylenic condensation features an intermediate obtained *in situ* in catalytic amounts from the terminal acetylene by the action of base and cuprous iodide. A possible reaction mechanism involves two conjugated catalytic cycles:

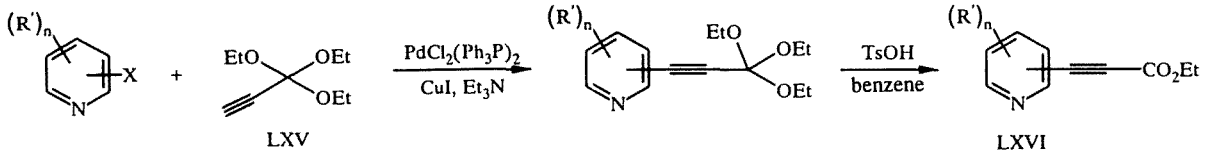


B = base

The kinetics and regioselectivity of acetylenic condensation has been examined in detail by Singh and Just [164].

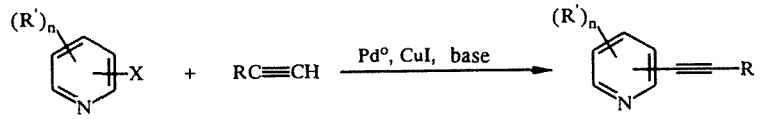
The condensation of terminal acetylenes and halopyridines (Table 37) has yielded a series of pyridylacetylenes, some of which hold promise as starting compounds for liquid crystal preparation.

Sakamoto et al. [170] have proposed a synthesis for pyridylpropiolates based on the reaction of bromo- and iodopyridines with 3,3,3-triethoxy-1-propyne (LXV).

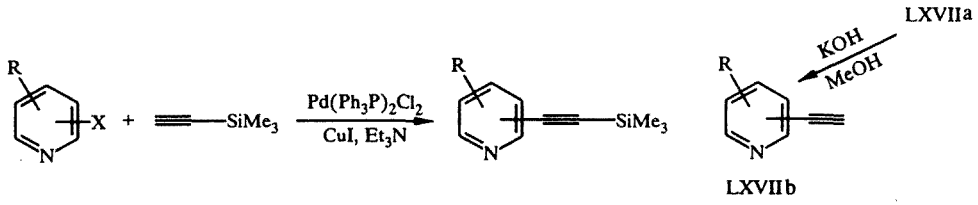


LXV LXVI

$(R')_n$	X	Yield, %	$(R')_n$	X	Yield, %
4,6-$(Me)_2$	2-I	73	6-Me,2-Ph	4-I	61
	3-Br	63			

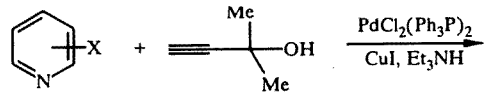


The most efficient method for obtaining terminal pyridylacetylenes from the corresponding halides involves the coupling of the halides with trimethylsilylacetylene [172, 173] or 2-methyl-3-butyn-2-ol [174, 175] with subsequent treatment of the coupling product with KOH in methanol or NaOH in toluene, respectively.

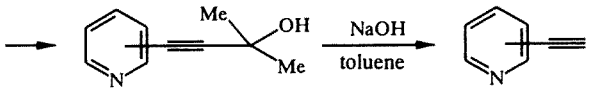


LXVIIb

R	X	Yield, %		Reference	R	X	Yield, %		Reference
		LXVIIa	LXVIIb				LXVIIa	LXVIIb	
H	2-Cl	80	67	[172]	H	3-Br	80	58	[172]
H	2-Br	100	53	[172]	4-MeO	2,3-$(Br)_2$	70	52	[173]



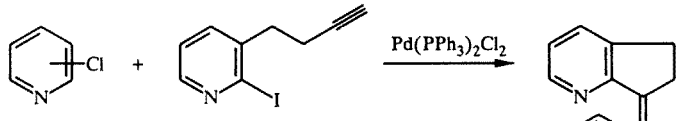
LXVIIIa



LXVIIIb

X	Yield, %		Reference
	LXVIIIa	LXVIIIb	
2-Br	80	90	[174]
4-Br	70	90	[175]

Treatment of 4-(o-iodophenyl)-1-butyne with chloropyridines in the presence of catalytic amounts of $Pd(PPh_3)_2Cl_2$ leads to the formation of pyridyl derivatives of (Z)-1-indanylidenes [176].



2–Cl (66%), 3–Cl (53%)

In conclusion, we should recall that halopyridines are convenient synthetic precursors for pyridine derivatives containing alkyl, alkenyl, alkynyl, aryl, and hetaryl substituents. Recent organic synthetic methods based on the use of palladium(0) and nickel(0) complexes as catalysts open new possibilities for the functionalization of the pyridine ring.

4. REACTIONS OF HETEROORGANIC PYRIDINE DERIVATIVES

Heteroorganic pyridine derivatives are used as precursors of various pyridine derivatives containing alkyl, alkenyl, alkynyl, aryl, and hetaryl substituents. The problem of the selective introduction of the heteroorganic group into the pyridine ring arises in this case. In this chapter, we briefly treat the selective metallation of pyridines. The direct metallation of π-electron-deficient aromatic compounds including pyridines and the derived strategy for functionalization of the aromatic ring have been examined in detail by Undheim and Benneche [177].

Organolithium compounds occupy a special place among heteroorganic pyridine derivatives used for the preparation of functional derivatives and are commonly used in the formation not only of carbon–carbon bonds but also of carbon–heteroelement bonds. The reported methods for the preparation of organolithium pyridine derivatives have been examined by Yale [178]. The preparation of organolithium compounds based on the direct lithiation of the aromatic ring exploiting activation by a directing group permits high selectivity in the functionalization of the pyridine ring. The selectivity of the direct metallation depends significantly on the nature of the directing group, solvent used, and lithiation agent. Direct metallation upon activation by the directing group sometimes competes with the addition of organolithium compounds to the π-electron-deficient pyridine ring (see chapter 1 [179, 180]):

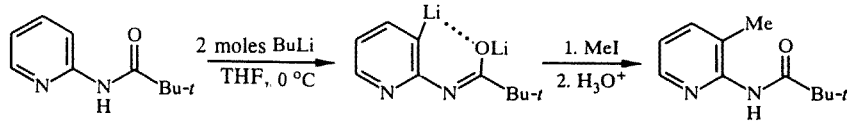
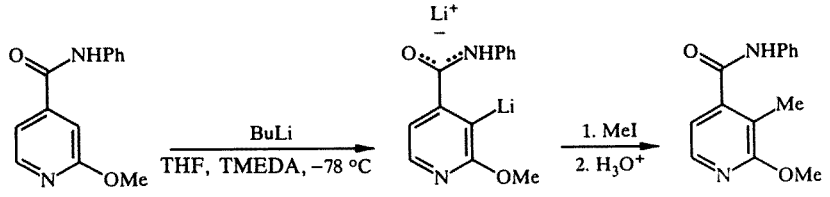


TABLE 38. Reactions of 2-Pyridylcopper with Methyl β-Phenylvinyl Ketone and Ethyl Cinnamate

R	Reagents	Yield of LXX, %	R	Reagents	Yield of LXX, %
Me	2-$C_5H_4NCu \cdot SBu_2$, LiI	49	Me	2-$C_5H_4NCu \cdot PBu_3$, LiI	73
	$(2\text{-}C_5H_4N)_2CuLi$, LiI	85		2-C_5H_4NCu	0
	$(2\text{-}C_5H_4N)_2CuLi$	74	OEt	2-$C_5H_4NCu \cdot SBu_2LiI$	0
	(2-C_5H_4N)PhCuLi, LiI	81		$(2\text{-}C_5H_4N)_2CuLi$, LiI	82
	(2-C_5H_4N)PhCuLi	72		(2-C_5H_4N)PhCuLi, LiI	85

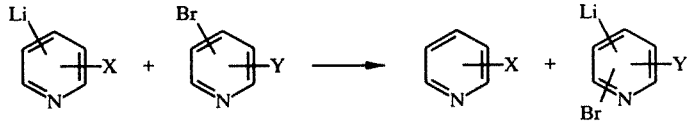
The use of a secondary carboxamide substituent as the directing group provides for exceptional regioselective ortho-metallation and subsequent electrophilic substitution in the pyridine ring [181, 182]. Epsztajn et al. [183] have reported that the N-phenylamide group is the most suitable orienting group. For example, the lithiation of 2-methoxy-4-(phenylaminocarbonyl)pyridine XLIX proceeds selectively at $C_{(3)}$.



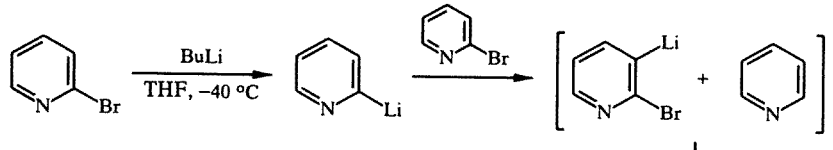
LXIX

Analogously, 4-methoxy-3-methyl-2-(phenylaminocarbonyl)pyridine is formed by the lithiation of 4-methoxy-2-(phenylaminocarbonyl)pyridine and subsequent treatment of the lithium derivative with methyl iodide.

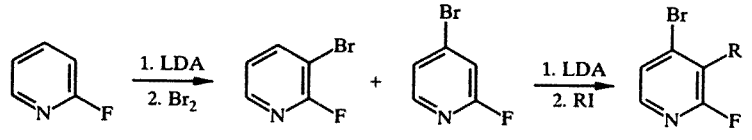
An alternative method for the formation of pyridinelithium derivatives is based on the metal−halogen exchange reaction [178]. Since halogen−lithium exchange occurs rather rapidly and under mild conditions, the formation of pyridinelithium derivatives usually is not accompanied by significant side-reactions. The selection of special reaction conditions permitted the preparation of pyridinelithium derivatives completely different from those formed as the result of rapid halogen−lithium exchange. The formation of unusual pyridinelithium derivatives is observed as the result of homotransmetallation (X = Y) or heterotransmetallation (X ≠ Y) [184, 185].



The displacement of lithium from one position to another is observed as the result of intermolecular processes and leads to isomerization of the lithium derivatives to more stable species and/or the conversion of a mixture of various bromine derivatives to a single compound. Several examples of such processes for obtaining various pyridine derivatives are given below [184, 185].



R=Me (70%); $CH_2CH{=}CH_2$ (60%)

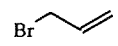
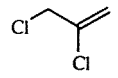
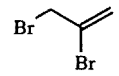
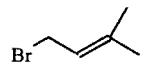
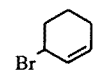
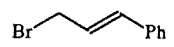
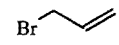
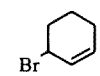
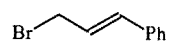


R=Me (60%); $CH_2CH{=}CH_2$ (70%)

TABLE 39. Reaction of 2- and 3-Pyridylcopper Triphenylphosphine Complexes with Iodobenzenes

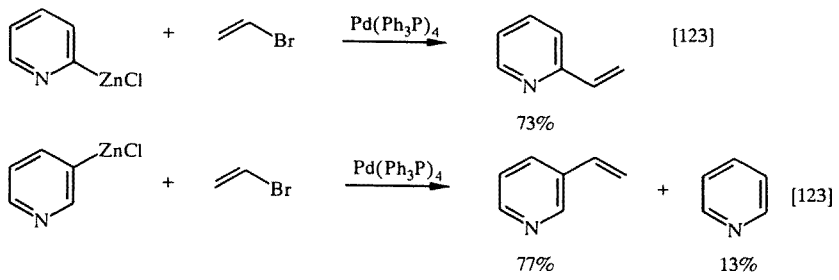
$(R)_n$	Yield of LXXI, %	$(R)_n$	Yield of LXXI, %
H	62	2,3,4-$(Me)_3$	58
2-MeO	76	2,4,6-$(Me)_3$	57
3,5-$(MeO)_2$	72	2-Me	32

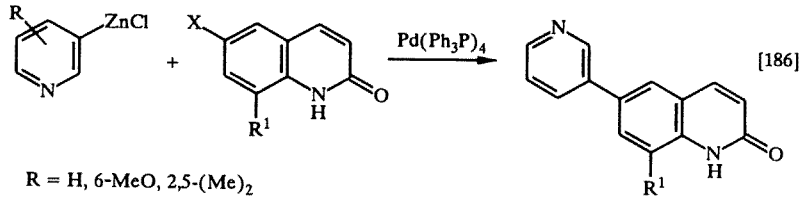
TABLE 40. Reactions of Lithium Trialkyl (3- and 4-Pyridyl) Borates with Allyl Halides

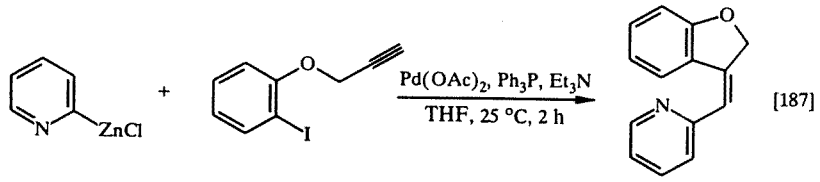
Position of BR_3Li^+	Reagent	Yield of LXXVIII, %	Reference
3		72	[193, 194]
		9	[193]
		55	[193, 194]
		44	[193]
		70	[193, 194]
		40(23)*	[193, 194]
4		48	[194]
		52	[194]
		30(20)*	[194]

*The yield of the rearranged product $C_5H_4N-\overset{Ph}{\underset{}{\langle}}=$ is given in parentheses.

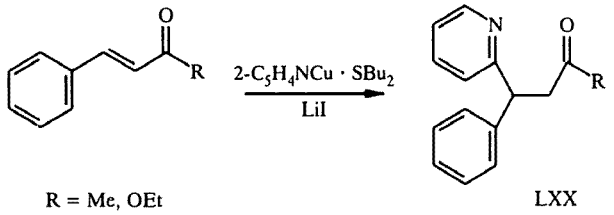
Organozinc compounds are formed upon the treatment of organolithium pyridine compounds with zinc chloride. The reaction of the organozinc products with various electrophilic reagents is a convenient method for the preparation of a range of pyridine derivatives containing carbon substituents in high yield. The formation of side-products is minimal. The reactions of pyridylzinc chlorides with electrophilic reagents such as halohydrocarbons requires catalysis by palladium complexes:





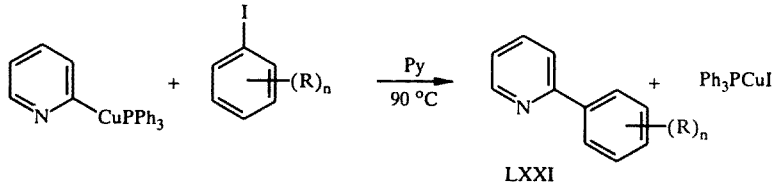


Organocopper pyridine derivatives obtained from pyridyllithium and cuprous iodide deserve special attention. 2-Pyridylcopper complexes with dibutyl sulfide and tributylphosphine, lithium di(2-pyridyl) cuprate, and lithium (2-pyridyl)-(phenyl) cuprate are capable of conjugated addition to α,β-unsaturated carbonyl compounds. Thus, Malmberg and Nilsson [188] have described the reaction of pyridyl organocopper compounds with 3-buten-2-one and ethyl 3-phenylpropionate (Table 38). α,β-Unsaturated ketones are more reactive than esters of α,β-unsaturated carboxylic acids.



R = Me, OEt LXX

2- or 3-Pyridylcopper with triphenylphosphine may be used for the preparation of arylpyridines. The reaction of these compounds with substituted iodobenzenes leads to the formation of various phenylpyridines (Table 39) [189, 190].



LXXI

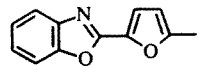
The most likely mechanism for this reaction is related to formation of copper(III) complexes through cis addition of iodobenzene to the 2-pyridylcopper triphenylphosphine complex, leading to adducts LXXII and LXXIII.

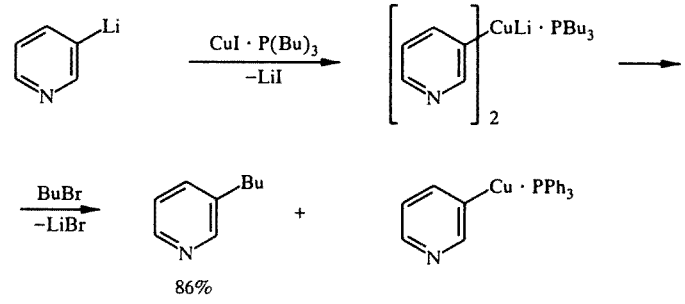
LXXII LXXIII

Adduct LXXII is converted upon reductive cis elimination to phenylpyridine, while adduct LXXIII is converted to the starting compound.

The introduction of a carbon substituent at $C_{(3)}$ of the pyridine ring is an important problem in the synthetic chemistry of pyridine since most of the existing methods based on the use of both halopyridines and organometallic derivatives give only moderate yields. However, a number of methods have recently been proposed, which permit introduction of a carbon substituent at $C_{(3)}$ of the pyridine ring using organocopper and organoboron derivatives. Thus, the complex of lithium di(3-pyridyl)cuprate with triphenylphosphine may serve as a convenient precursor for 3-alkylpyridines. For example, the following synthetic scheme has been proposed for the preparation of 3-butylpyridine [191]:

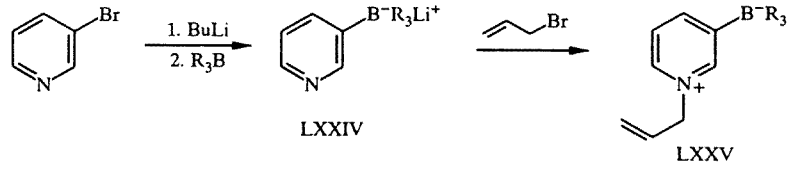
TABLE 41. Reaction of Diethyl(3-pyridyl)borane with Halides

Ar	X	Yield, %	Ar	X	Yield, %
2-Pyridyl	Cl	82	3-Quinolyl	Br	77
2-Pyridyl	Br	85	1-Isoquinolyl	Cl	70
3-Methyl-2-pyridyl	Br	83	2-Pyrimidyl	Cl	47
6-Methoxycarbonyl-2-pyridyl	Br	77	2-Thienyl	Br	75
	Br	63	1-Alkyl-3-indolyl	Br	39
6-Chloro-2-pyridyl	Cl	37	1-Tosyl-5-indolyl	Br	47
3-Pyridyl	Br	82		Br	62



86%

Trialkyl(3-pyridyl) borates are also used for the introduction of a substituent at $C_{(3)}$.

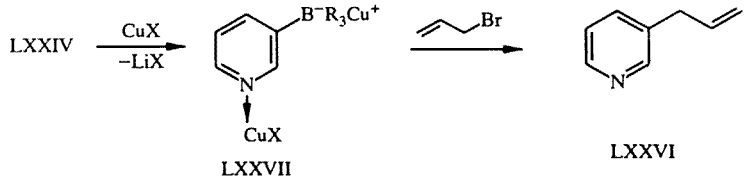


LXXIV

LXXV

64%

Lithium trialkyl(3-pyridyl) borate LXXIV reacts with allyl bromide to give betaine LXXV [192]. However, only 3-allylpyridine LXXVI is formed when the reaction of borate LXXIV is carried out with allyl bromide in the presence of cuprous salts. This change in the course of the reaction is related to coordination of copper at the nitrogen atom and formation of copper borate LXXVII.

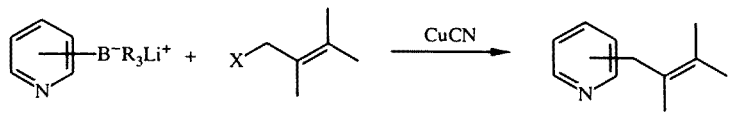


LXXVII

LXXVI

X = Cl (39%), Br (48%), I (43%), CN (64%)

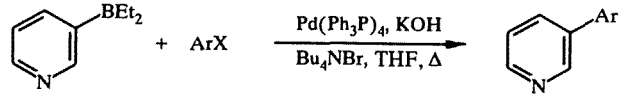
This method has yielded a series of 3- and 4-allylpyridine derivatives [193, 194].



The palladium-catalyzed cross-coupling of diethyl(3-pyridyl)borane LXXVIII [195] with halogen derivatives of aromatic heterocycles in the presence of base is used for the preparation of β-hetarylpyridines [196] (Table 41).

TABLE 42. Reactions of 2-Pyridylsulfoxides with Organometallic Compounds

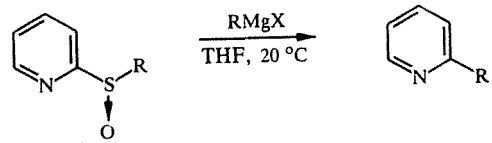
R	R^1M	Yield of 2-benzylpyridine LXXXI, %	R	R^1M	Yield of 2-benzylpyridine LXXXI, %
CH_2Ph	PhMgBr	98	Me	$PhCH_2MgCl$	79
CH_2Ph	MeMgBr	83	Ph	$PhCH_2MgCl$	71
CH_2Ph	BuLi	46			



LXXVIII

5. USE OF SULFOXIDES, PHOSPHONIUM SALTS AND PHOSPHINE OXIDES

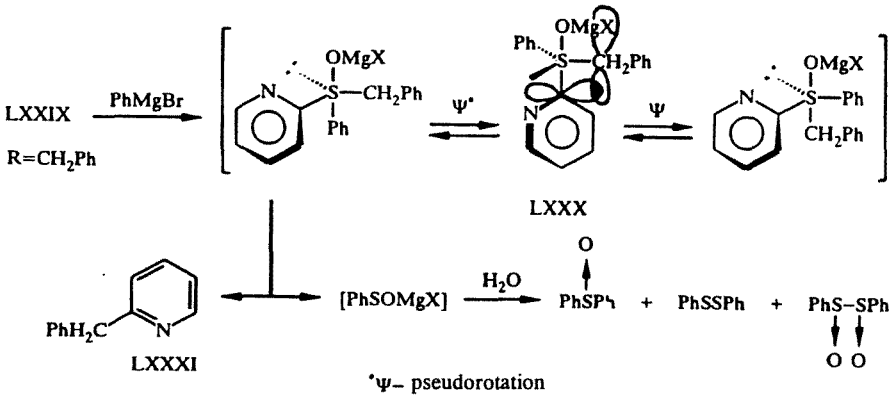
The action of Grignard reagents on pyridylsulfoxides is a reaction holding theoretical interest, which results in the introduction of a carbon substituent into the pyridine ring [197-199].



LXXIX

R = CH_2Ph, CH(Me)Ph

The formation of intermediate LXXX was predicted in the nucleophilic attack of a Grignard reagent at the tricoordinated sulfur atom in sulfoxide LXXIX. If the bonding orbitals of the polarized basal and electronegative apical bonds overlap effectively in the sulfurane intermediate, a bond is formed subject to apical–apical or apical–basal ligand exchange, which should lead to coupling of the basal and apical ligands [197]. Since the coupling takes place intramolecularly, both ligands should retain their starting configuration during this process:



The above scheme shows that the reaction of sulfoxide LXXIX (R = CH_2Ph) with phenylmagnesium bromide and sulfoxide LXXIX (R = Ph) with benzylmagnesium bromide leads to 2-benzylpyridine, i.e., only benzylpyridines LXXXI are formed when there is a benzyl group in the starting sulfoxide or Grignard reagent (Table 42).

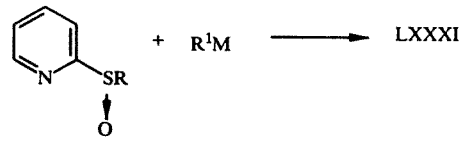
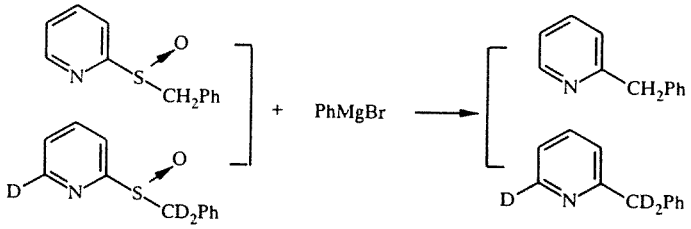


TABLE 43. Synthesis of Dipyridines

Grignard reagent	Sulfoxide	Dipyridine LXXXII	Yield, %
2-C_5H_4NMgBr	2-C_5H_4NSOPh	2,2'-dipyridine	75
2-C_5H_4NMgBr	2-(6-Cl)C_5H_4NSOMe	6-Cl-dipyridine	43
2-C_5H_4NMgBr	3-C_5H_4NSOMe	2,2'-dipyridine	23
		2,3'-dipyridine	37
2-C_5H_4NMgBr	4-C_5H_4NSOPh	2,4'-dipyridine	58
2-C_5H_4NMgBr	2-C_9H_6NSOEt	2-(2-pyridyl)quinoline	62
3-C_5H_4NMgBr	2-C_5H_4NSOPh	2,3'-dipyridine	63
3-C_5H_4NMgBr	3-C_5H_4NSOPh	No reaction	
3-C_5H_4NMgBr	4-C_5H_4NSOPh	3,4'-dipyridine	25
		4,4'-dipyridine	14
3-C_5H_4NMgBr	2-C_9H_6NSOEt	2-(3-pyridyl)quinoline	67
4-C_5H_4NMgBr	2-C_5H_4NSOPh	2,4'-dipyridine	63
4-C_5H_4NMgBr	4-$C_5H_4NSOTol$-*p*	3,4'-dipyridine	13
		4,4'-dipyridine	25
4-C_5H_4NMgBr	4-$C_5H_4NSOTol$-*p*	4,4'-dipyridine	50
4-C_5H_4NMgBr	2-C_9H_6NSOEt	2-(4-pyridyl)quinoline	56

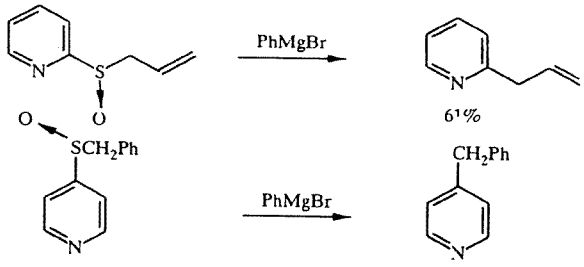
The coupling requires that the benzyl and 2-pyridyl groups are at an angle of 90° to the sulfur atom in the starting σ-sulfurane intermediate LXXX.

Special experiments demonstrated the intramolecular nature of this reaction:

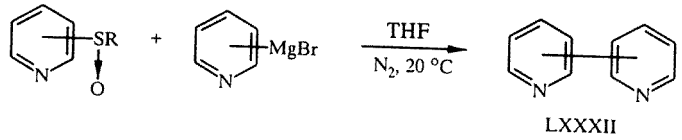


The retention of configuration was confirmed by experiments with optically active sulfoxide LXXIX (R = MeC*HPh) [197].

This reaction may be extended to other pyridylsulfoxides [197]:



This method has been applied for the synthesis of dipyridines (Table 43) [198, 199] according to the following scheme:



LXXXII

In this case, two nitrogen heterocycles are combined in intermediate sulfurane LXXX, while the phenyl group does not participate in the reaction.

TABLE 44. Reactions of Phosphine Oxides with Organolithium and Organomagnesium Compounds

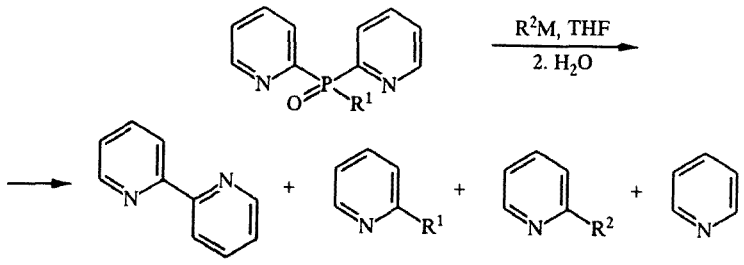
R^1	R^2M	Yield, %			
		2,2'-pyridine	2-R^2-pyridine	2-R^1-pyridine	Pyridine
2-Pyridyl	MeMgI	4	—	—	15
2-Pyridyl	PhMgBr	60	0,2	—	15
2-Pyridyl	PhMgI	65	0,2	—	29
2-Pyridyl	2-PyLi	82			
2-Pyridyl	2-Thi-Li	65	—	—	25
2-Pyridyl	$PhCH_2MgCl$	23	9	—	8
2-Pyridyl	p-$MeC_6H_4CH_2MgCl$	37	5	—	7
2-Pyridyl	p-$ClC_6H_4CH_2MgCl$	31	6	—	8
$PhCH_2$	MeMgI	41	—	2	6
$PhCH_2$	PhMgBr	30	0,2	—	36

TABLE 45. Reactions of Phosphonium Salt LXXXIII with Water and Methanol Under Various Conditions

X	Reaction conditions	Yield, %		X	Reaction conditions	Yield, %	
		2,2'-dipyridine	Pyridine			2,2'-dipyridine	Pyridine
H	H_2O, 60 °C, 2,5 h	47	64	4-Me	H_2O, 60 °C, 2,5 h	42	31
	H_2O/HCl, 20 °C, 30 min	64	17		H_2O/HCl, 20 °C, 30 min	73	68
	H_2O/HCl, reflux, 10 h	73	80	6-Me	H_2O, 60 °C, 2,5 h	39	64
	MeOH, 20 °C, 72 h	26	20		H_2O/HCl, 20 °C, 30 min	73	20
					H_2O/HCl, reflux, 10 h	87	68

Comparison of the reactivity of Grignard reagents shows that the 3-isomers should be more stable. Thus, the reaction between 2-C_5H_4NMgBr and 3-C_5H_4NMgBr gives a sulfurane, which leads to the 2,3-coupling product due to pseudorotation or the reaction between 2-C_5H_4NSOPh and 3-C_5H_4NMgBr gives symmetrical 2,2'-dipyridine due to equilibrium (2-C_5H_4NSOPh should be more reactive than the 3-isomer relative to 2-C_5H_4NMgBr).

Analogous ligand coupling also occurs at the phosphorus atom in phosphine oxides and phosphonium salts containing at least two pyridyl groups. Thus, Newkome [200] has described the formation of 2,2'-dipyridine upon treating bis(6-substituted) 2-pyridylphosphine oxides with sodium ethylate. The same product is obtained in the reaction of phosphine oxides with Grignard reagents (Table 44) [201].

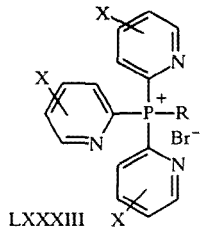


Uchida et al. [201] have proposed that both the coupling and exchange of the ligands occurs within the pentacoordinated phosphorus intermediate.

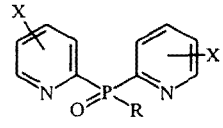
This reaction was then extended to phosphonium salts and phosphoxides but by the action of nucleophiles on these reagents in neutral or, even, acid media [202]. Thus, for example, benzyltri(2-pyridyl)phosphonium bromide (LXXXIII R = CH_2Ph) undergoes rapid alkaline hydrolysis at room temperature to give benzyldi(2-pyridyl)phosphine oxide (LXXXIV, R = CH_2Ph) and pyridine in good yield. However, ligand coupling occurs upon dissolving salt LXXXIII in water at 20°C, i.e., 2,2'-dipyridyl and benzyl(2-pyridyl)phosphine oxide LXXXV are formed in addition to oxide LXXXIV and pyridine. This reaction is accelerated by the addition of dilute hydrochloric acid, which leads predominantly to ligand coupling products (Table 45).

TABLE 46. Rearrangement of 2-[(2E)-3R-allyloxy]pyridines

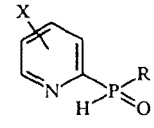
Solvent	Reaction mixture composition, %			
	R = Me		R = Ph	
	LXXXIXa	XC	LXXXIXb	XC
Tetrachloroethylene	29	0	98	2
Diglynze	51	32	91	9
DMF	34	19	82	18
H_2O	24	76	—	—
No solvent	—	—	100	0



LXXXIII

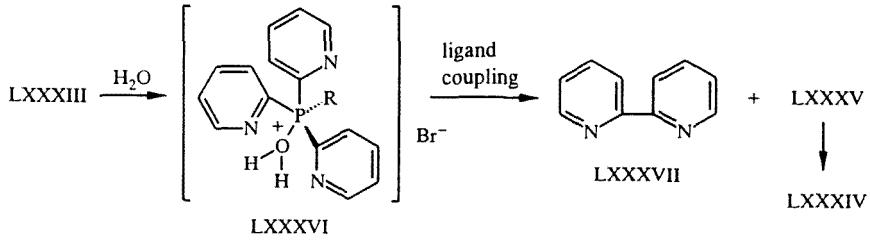


LXXXIV



LXXXV

Pentacoordinated intermediate LXXXVI is formed upon the nucleophilic attack of water at the phosphorus atom. The equatorial 2-pyridyl group in this intermediate should couple with the axial 2-pyridyl group in order to give dipyridyl.



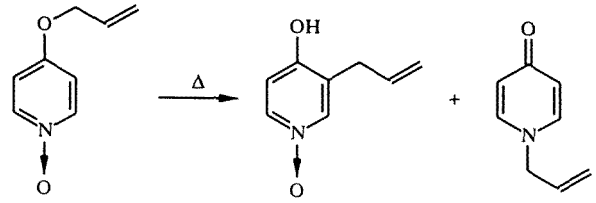
LXXXVI

Coupling of the 2-pyridyl and benzyl groups is not observed in this reaction for salt LXXXIII (R - CH_2Ph) since this group cannot occupy an axial position in aqueous media.

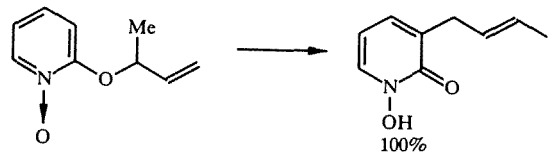
We should note the similarity of the mechanisms for intramolecular ligand coupling in isosteric sulfur and phosphorus molecules.

6. PREPARATION OF ALLYLPYRIDINES FROM OXYGEN-CONTAINING DERIVATIVES

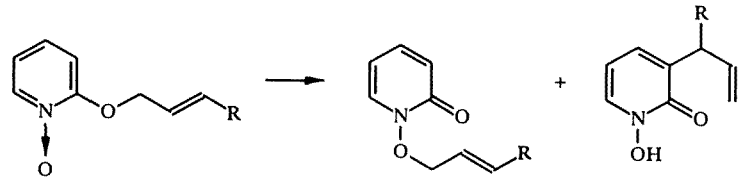
The sigmatropic rearrangements of 4- and 2-allyloxypyridine N-oxides permit introduction of an allyl substituent at $C_{(3)}$ of the pyridine ring [203, 204]. Thus, heating 4-allyloxypyridine N-oxide in vacuum leads to 4-hydroxy-3-allylpyridine N-oxide along with N-allyl-4-pyridone.



The rearrangement of 2-(2-buten-3-yloxy)pyridine N-oxide in tetrachloroethylene, DMF, or water at 100°C gives the 3,3-sigmatropic shift product, namely, 1-hydroxy-3-(buten-2-yl)-2-pyridone, regioselectively in high yield [204].



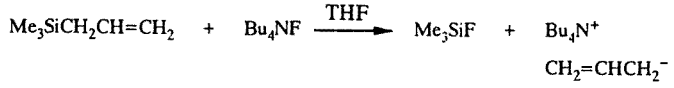
In contrast, the rearrangement of isomeric 2-[(2E)-3-methylallyloxy]pyridine N-oxide gives the products of 1,4- and 3,3-sigmatropic arrangements, LXXXIX and CL, respectively. The phenyl analog displays analogous behavior (Table 46).



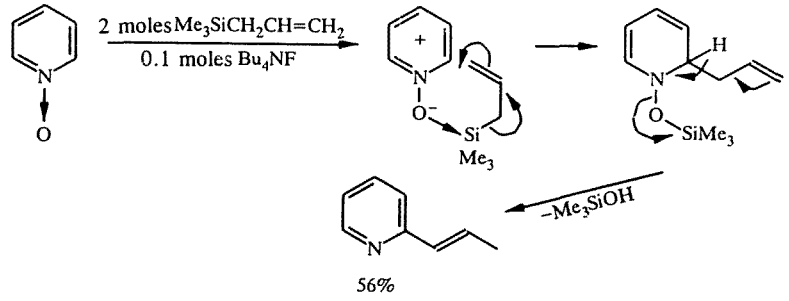
LXXXVIII LXXXIXa, b XCa, b

LXXXIX, XC a R=Me; b R=Ph

Pyridine N-oxide is readily alkylated by the action of allyl- or benzyltrimethylsilane and fluoride ions [205].

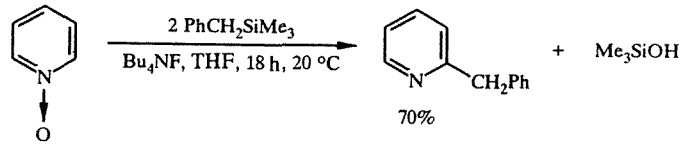


Since allyltrimethylsilane forms hard trimethylsilyl fluoride upon treatment with Bu_4NF and tetrabutylammonium salt with the soft allyl anion, the authors carried out the reaction of two equivalents of allyltrimethylsilane with pyridine N-oxide in the presence of 0.1 equivalent Bu_4NF.



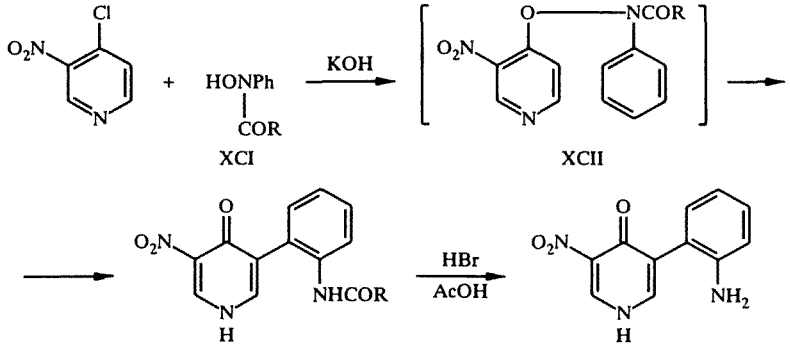
56%

Benzylation proceeds analogously.



70%

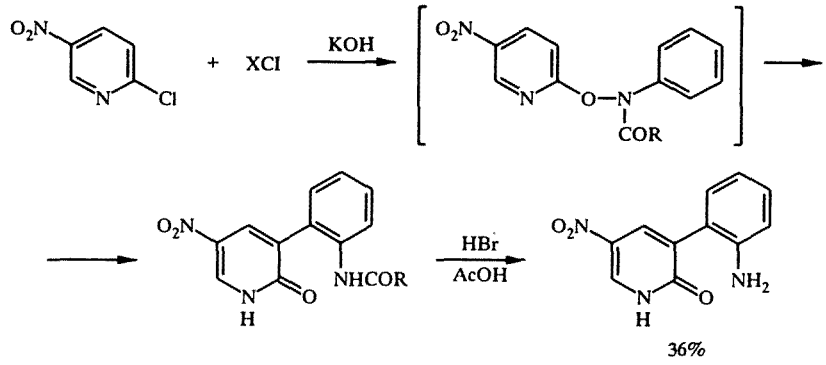
An unusual rearrangement also using pyridine oxygen derivatives permits arylation of the β ring position [206]. Thus, the reaction of 4-chloro-3-nitro- and 2-chloro-5-nitropyridines with benzyl-N-hydroxy-N-phenylcarbamate (XCI) leads to the introduction of a 2-aminophenyl group into pyridine. This reaction apparently proceeds through rearrangement of intermediate XCII by analogy to the benzidine rearrangement:



XCI XCII

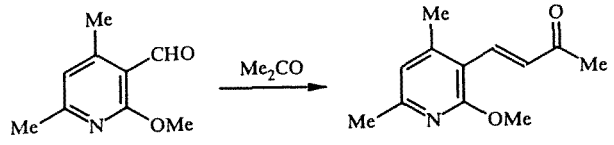
87%

R=OCH_2Ph, Me

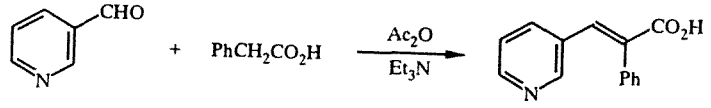


7. SYNTHESES OF ALKENYL- AND ALKYNYLPYRIDINES USING CARBONYL DERIVATIVES

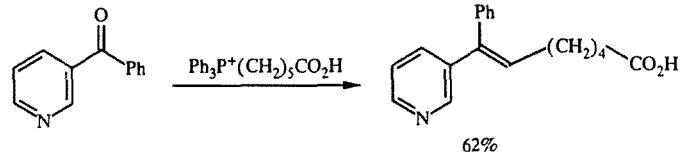
In addition to the direct introduction of unsaturated substituents into the pyridine ring, another approach exists for the preparation of vinyl- and ethynylpyridines using carbonyl substituents. Thus, for example, an ordinary Knoevenagel condensation gives an α,β-unsaturated ketone from 4,6-dimethyl-2-methoxy-3-pyridinaldehyde and acetone [207].



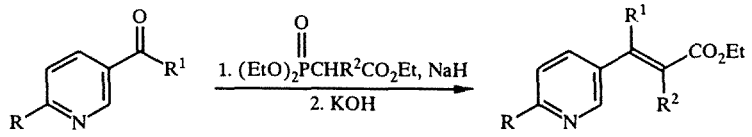
A similar condensation proceeds with phenylacetic acid in acetic anhydride in the presence of triethylamine [208].



The use of the Wittig reaction is also standard. The reaction of 3-benzoylpyridine with $Ph_3P^+(CH_2)_5CO_2HBr^-$ gives a 1:1 mixture of E and Z unsaturated pyridines, which readily isomerizes in hydrobromic acid to give the pure E isomer [209].

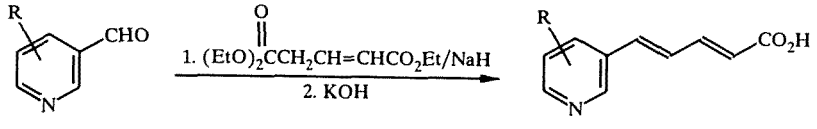


The use of 3-acetylpyridine and pyridine-3-aldehyde in this reaction led to a series of 3-pyridylacrylic acids [208].



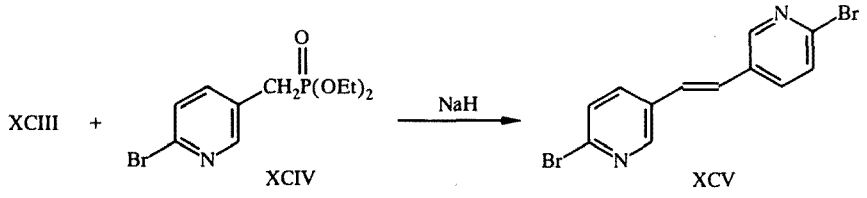
R = H, R^1 = Me, R^2 = H (23%), R = R^1 = H, R^2 = Me (74%), R = R^1 = H, R^2 = Et (23%), R = R^1 = H, R^2 = Pr (33%), R = R^1 = H, R^2 = Ph (31%), R = R^2 = Me, R^1 = H (21%)

A diene is analogously introduced into a pyridine molecule using the Wittig reaction [208]:



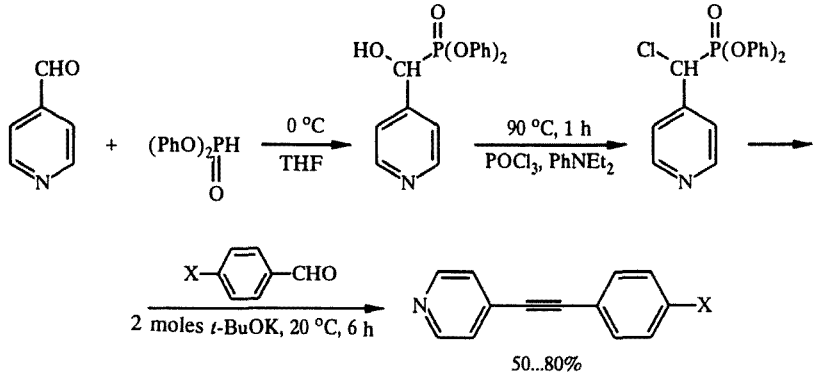
XCIII

The Wadsworth–Emmons reaction [210] of pyridinecarbaldehyde XCIII with pyridinephosphoryl esters XCIV in dioxane in the presence of sodium hydride leads to dipyridylethylenes XCV [211].



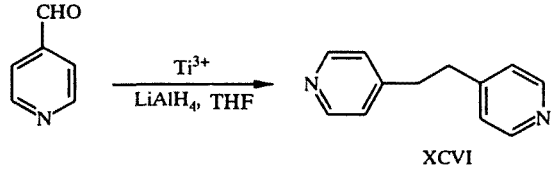
R = Cl (63%), Br (40%), SMe (65%)

A modification of the Horner–Emmons reactions [212] converts 4-pyridinecarbaldehyde into 4-pyridylphenylacetylene according to the following scheme [213]:



50...80%

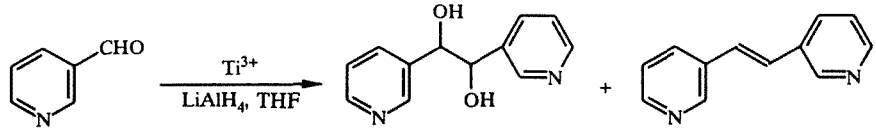
The dicarbonyl coupling of 4-pyridinecarbaldehyde in the presence of low-valence titanium yields 1,2-bis(4-pyridyl)-ethane (XCVI) due to a symmetrical process even in the presence of benzaldehyde. 4,4′-Diazastilbene is probably formed in the first step. This product is readily reduced to XCVI over 1 h in 70% yield and, thus, is not isolated from the reaction [214].



XCVI

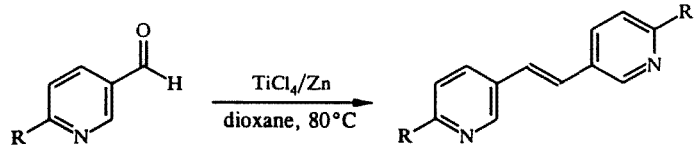
25%

The extent of oxidation of the products depends on the position of the formyl group in the pyridine ring. Thus, a mixture of a glycol and the corresponding diazastilbene is formed in the case of 3-pyridinecarbaldehyde:



24% 28%

This reaction with 6-substituted 3-pyridinaldehyde gave only distilbenes in moderate yield [211].

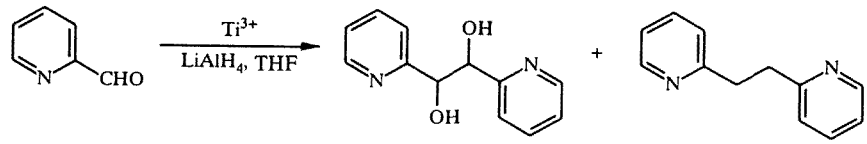


R = OMe (40%), SMe (30%)

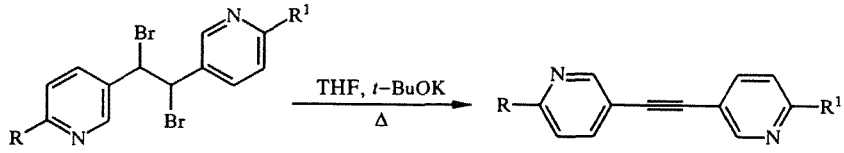
TABLE 47. Dehydrobromination of Dibromopyridylethanes

R	R^1	Yield, %	
		dibromide	dipyridylacetylene
Br	Br	60	40
Br	Cl	63	53
OMe	OMe	60	70
Me	Me	80	50

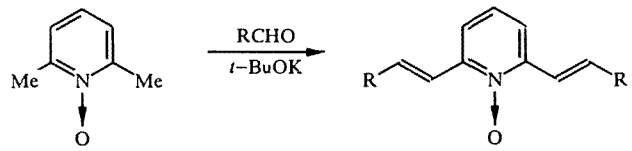
Under analogous conditions, 2-pyridinaldehyde forms a mixture of a glycol and the product of complete reduction:



Pyridylethylenes may be converted by the usual bromination–dehydrobromination scheme into dipyridylacetylenes (Table 47) [211].

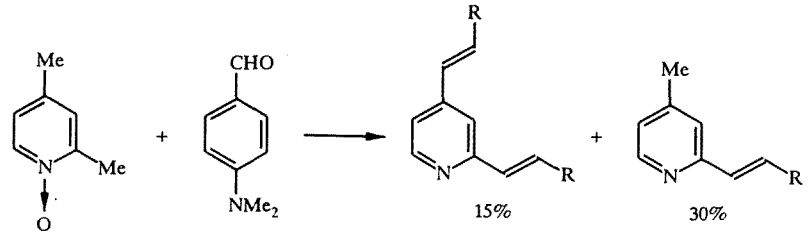


An alternative possibility for the use of condensation reactions for the modification of substituents in the pyridine ring is the use of pyridines as the methylene component rather than the carbonyl component. Such condensations of CH-acid alkyl substituents of activated pyridines are well known. Thus, we present here only one example related to the condensation of lutidine N-oxides with aromatic heterocyclic aldehydes in the presence of potassium tert-butylate [215]. The products of condensation at both methyl groups were obtained for 2,6-lutidine N-oxide.



R = 4-$MeOC_6H_4$ (23%), 4-$Me_2NC_6H_4$ (89%), 2-thienyl (19%), 3-thienyl (26%)

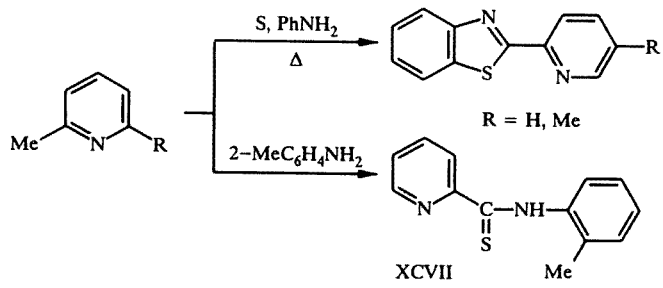
This reaction with 3,4-dimethylenedioxybenzaldehyde gave 17% monosubstitution product and 17% disubstitution product. The condensation of 2,4-lutidine N-oxide with p-dimethylaminobenzaldehyde leads to a mixture of the products of condensation at both methyl groups even when one equivalent of aldehyde is used.



The use of pyridinaldehydes and thiophenaldehydes in acetic anhydride in the presence of potassium acetate and iodine as the catalyst gives analogous mixture.

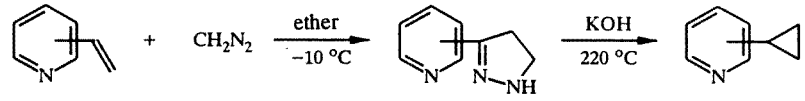
8. SYNTHESES OF HETARYLPYRIDINES USING ALKYL, ALKENYL AND ALKYNYL DERIVATIVES

The hetaryl substituent may be introduced directly into the pyridine ring using various cross-coupling reactions. Another approach to the synthesis of hetarylpyridines involves construction of the heterocyclic ring using substituents already present in the pyridine molecule. Thus, the oxidative condensation of α-methylpyridines in the presence of sulfur and aniline gave 2-(2-benzothiazolyl)pyridines [216].

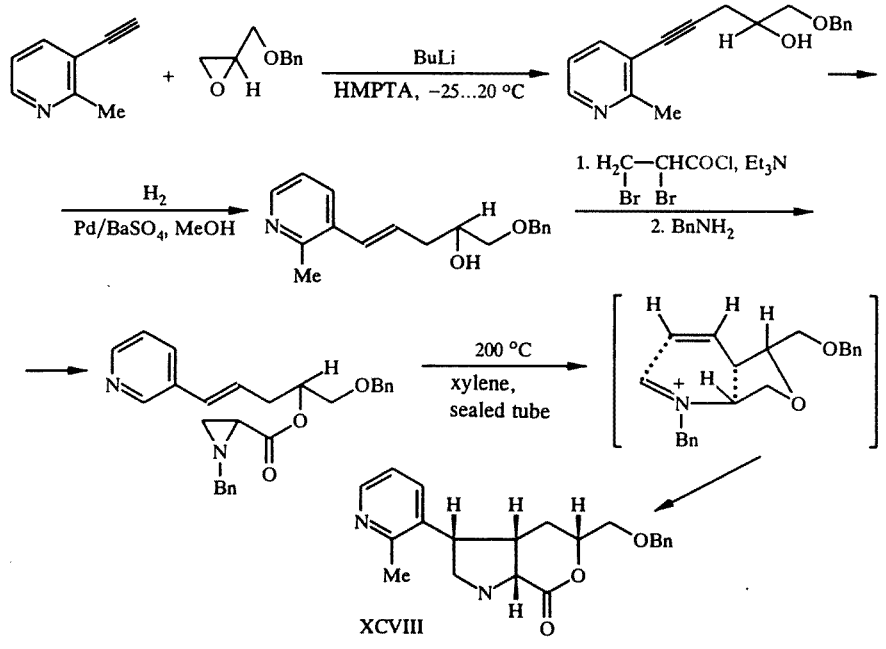


Thioamides XCVII, which probably serve as intermediates in this reaction, were isolated when o-toluidine was used.

The cycloaddition of diazomethane to 2- and 4-vinylpyridines is a pathway for obtaining 3-pyrazolinylpyridines, which may then be converted to 2- and 4-cyclopropylpyridines [217].

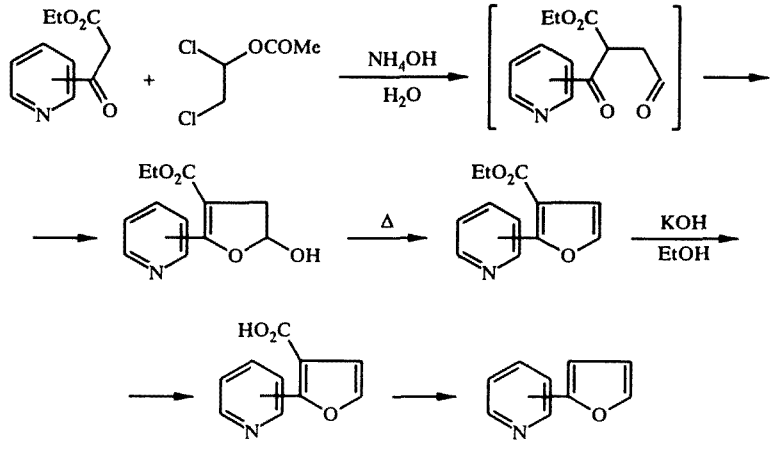


Acrolylic acid B, a pyridine neurotoxin, was synthesized enantioselectively by using 2-methyl-3-ethynylpyridine in a key step according to the following scheme [218]:



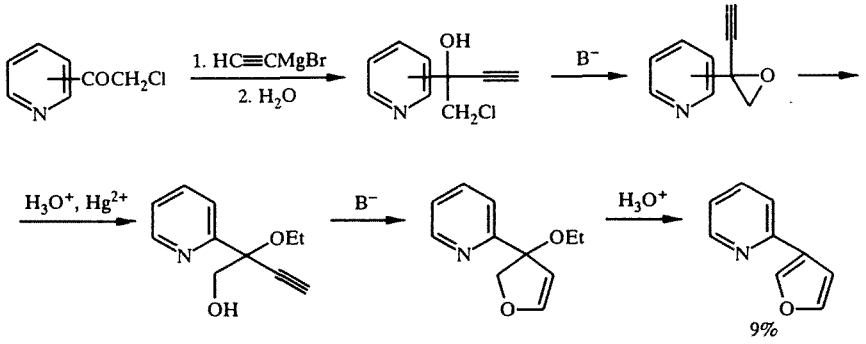
PMR analysis indicated that XCVIII was obtained as the cis isomer.

The well-known Feist–Benari method for furan synthesis using pyridine-containing 1,3-dicarbonyl compounds leads to the following isomeric 2-furylpyridines in high yield [219]:

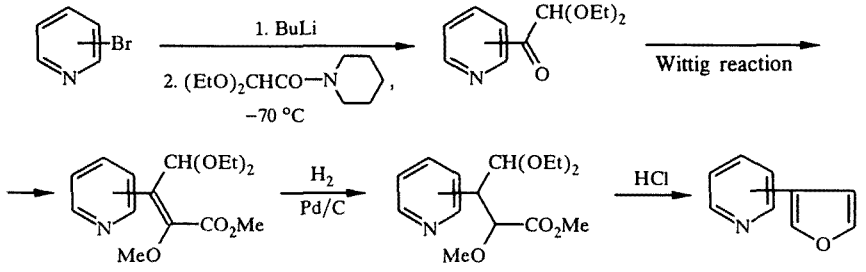


2-Py (80%), 3-Py (86%), 4-Py (88%)

Attempts to synthesize 3-furylpyridines using chloroacetylpyridines led to only low yields of the desired products:



This encouraged the authors to propose a more successful synthetic pathway:



2-Py (49%), 3-Py (40%), 4-Py (42%)

Thus, all the various existing methods for the introduction of carbon substituents into the pyridine ring have been discussed in this review.

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