Russian Chemical Reviews **84** (12) 1191 – 1225 (2015) © 2015 Russian Academy of Sciences and Turpion Ltd

DOI 10.1070/RCR4462

Organolithium compounds in the nucleophilic substitution of hydrogen in arenes and hetarenes †

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The review considers the most typical examples of the direct non-activated non-catalytic C – C bond formation in arenes and their metal complexes activated by electron-withdrawing substituents in the aromatic nucleus and in hetarenes (azines and their N-oxides, porphyrins, *etc*.) upon the reactions with aliphatic and (hetero)aromatic (hetero)organolithium nucleophiles. Particular attention is given to the direct introduction of nitroxide radicals and (hetero)organic moieties into mono-, di- and triazines and their N-oxides. The influence of the structures of the (hetero)aromatic substrate and the (hetero)organolithium nucleophile on the reaction pathway and rate and on the structure of the reaction product is analyzed.
The bibliography includes 237 references.

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I. Introduction

The nucleophilic aromatic substitution of hydrogen (S_N^H) is one of the most rapidly developing and promising areas of research in organic synthesis.[1–3] The S_N^H reactions have a great synthetic potential due to the fundamental property of C – H bonds in π-deficient arenes and hetarenes, namely, high susceptibility to nucleophilic attack resulting, under certain conditions in the presence of nucleophiles of different nature, in the cleavage of a C – H bond and its replacement by a C – X bond, where X = $C(sp^3)$, $C(sp^2)$, C(sp), O, N, S, P and so on. The nucleophilic attack at the unsub-

† Dedicated to Academician N S Zefirov on the occasion of 80th birthday.

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Received 22 April 2014
Uspekhi Khimii **84** (12) 1191 – 1225 (2015); translated by T N Safonova

stituted carbon atom in π-deficient arenes and hetarenes can be used to avoid preliminary introduction of leaving groups, such as Hal, OR, SO_2R (R = Alk, Ar), NO_2, *etc*., into the aromatic nucleus, thus opening new possibilities for the direct introduction of substituents into the aromatic nucleus and offering considerable advantages compared to conventional nucleophilic aromatic substitution ($S_N^{ipso}Ar$).

The present review covers the literature on this subject, including studies of the non-catalytic C–C bond formation, which is of great importance in organic synthesis, in reactions of π-deficient systems with organolithium compounds performed by research groups of the Institute of Organic Synthesis and the Ural Federal University under the supervision of Academician O N Chupakhin. These processes can substantially extend the potential of Suzuki, Sonogashira, Heck and other cross-coupling reactions,[4–8] which are known to proceed with reagents bearing a halogen atom and a metal-containing moiety in the presence of transition metal complexes as catalysts. To the best of our knowledge, no attempts have been made in recent years to arrange systematically, classify and integrate reactions of nucleophilic substitution of hydrogen involving organolithium compounds within a single publication. Our goal is to fill in this gap to a certain degree.

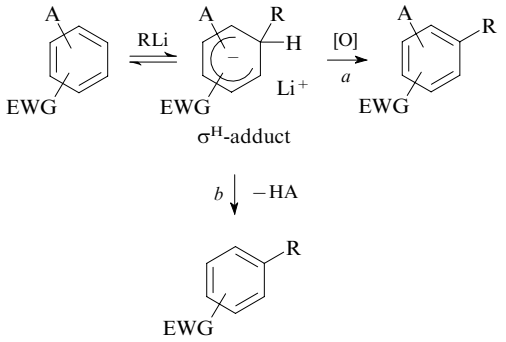
The nucleophilic substitution of hydrogen occurs *via* an addition–elimination (AE) mechanism and involves the steps of formation of σ^H-adducts and their aromatization. Electron-withdrawing groups (EWG) in the (hetero)aromatic substrate facilitate the first step, which is characterized by the reversibility of the reaction of π-deficient arenes and hetarenes with nucleophiles. The resulting σ^H-adducts are susceptible to dissociation and can undergo further transformations, including aromatization. Stability of these adducts varies in a broad range. Thus, the known species range from very unstable, which are difficult to detect by spectroscopic methods, to easy-to-isolate intermediates, which are not subjected to dehydrogenation even under drastic conditions. In the latter case, the reaction stops at the first step. Stability of the adducts is determined not only by solvation effects but also by structural (both electronic and steric) features of the reaction partners. The determination and elucidation of the characteristic features of nucleophilic attack at the C–H bond in π-deficient systems shed light on many features of S_N^H reactions, such as the role of the oxidizing agent and auxiliary groups, the mediated substitution of hydrogen, transhetarylation processes, concentration dependences an so on. Since the release of a hydride anion is thermodynamically unfavourable (as opposed to *ipso*-substitution of good leaving groups eliminated as anions), S_N^H reactions proceed *via* other aromatization paths. Scheme 1 outlines two types of aromatization of σ^H-intermediates that are formed in the stage of nucleophilic addition:

— oxidative aromatization of σ^H-adducts (path *a*);

— auto-aromatization of σ^H-adducts (path *b*);

The latter type of aromatization occurs *via* several paths but always in the absence of an external oxidant. The hydrogen abstraction can take place simultaneously with the elimination of the auxiliary group A that is present in the substrate. In this case, both the hydrogen atom and the auxiliary group A are eliminated from the starting moiety of the σ^H-adduct. These reactions are referred to as the *cine*- or *tele*-substitution (see Scheme 1, path *b*).

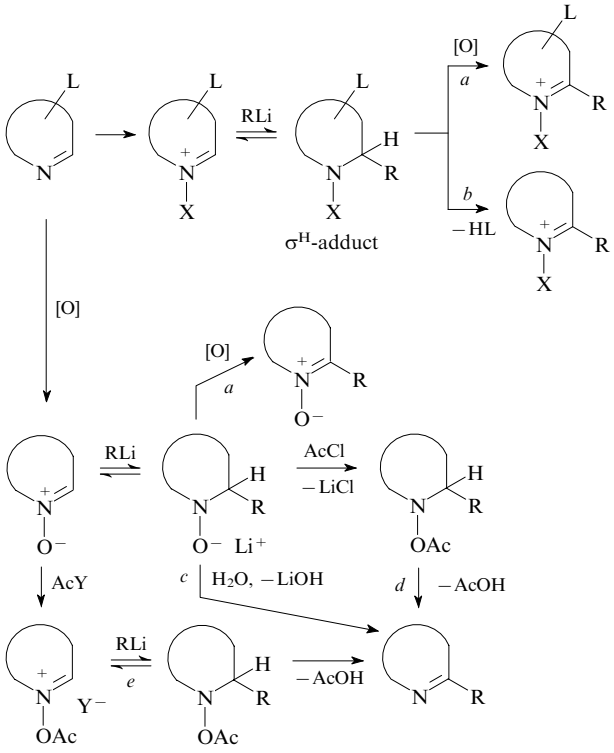
Scheme 1



EWG = NO_2, CN, CO_2Alk, SO_3H, *etc*.;
A = Hal, OAlk, SAlk, CN, NO_2, *etc*.; R = Alk, Ar

In another type of auto-aromatization, the auxiliary leaving group is formed after the addition of a nucleophile. The hydrogen abstraction simultaneously with the N–O bond cleavage is most commonly used for the aromatization of σ^H-adducts in the case of aromatic N-oxides (Scheme 2, paths *c* and *d*). In essence, this reaction also involves the mediated nucleophilic substitution of hydrogen. Meanwhile, the oxidative aromatization with the retention of the N-oxide moiety is also possible for such reactions.

Scheme 2



L is a substituent or a ligand; X, R = Alk, Ar; Y^- is an anion

Examples of the application of organolithium or -magnesium compounds as nucleophiles in the synthesis using yet another type of auto-aromatization, in which an auxiliary group is introduced into the σ^H-adduct by a nucleophile (so-called vicarious nucleophilic substitution [9]), are lacking in the literature.

II. Direct introduction of alkyl and aryl moieties into (het)arenes *via* nucleophilic substitution of hydrogen

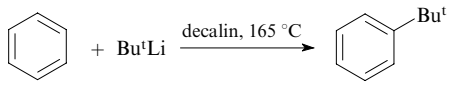
II.1. Reactions of unactivated arenes

II.1.a. Unsubstituted aromatic compounds

The nucleophilic substitution reactions of benzene and its analogues are usually difficult to initiate because the nucleophilic addition to such systems results in a loss of a relatively high aromatic delocalization energy, while neither electron-withdrawing susbtituents nor heteroatoms that stabilize the formation of anionic σ-complexes are present in the aromatic nucleus. Nevertheless, several S_N^H reactions of unactivated arenes are described in the literature. In particular, the alkylation of benzene and naphthalene with alkyllithium was reported (Schemes 3 and 4).[10–12]

It is noteworthy that benzene can be subjected to nucleophilic monoalkylation. Thus, the treatment with *tert*-butyllithium in decalin at 165 °C gave *tert*-butylbenzene, although in low yield.[10]

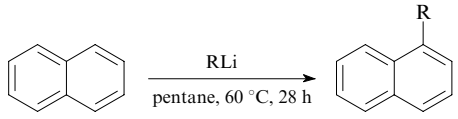
Scheme 3



(15%)

Under similar conditions, the reaction of naphthalene with n-butyllithium and sec-butyllithium affords the corresponding 1-butylnaphthalenes (see Scheme 4). The reaction with *tert*-butyllithium produces a mixture of mono- and dialkylnaphthalenes, the monoalkylation occurring mainly at position 1 (~95%) followed by the introduction of a substituent at position 3, 6 or 7.[10–12]

Scheme 4



R = Bu^n (15%), Bu^s (20%), Bu^t (30%–45%)

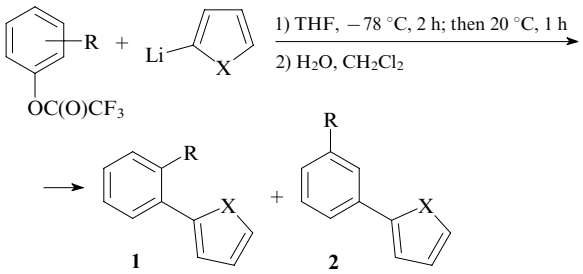
Monobutylphenanthrene was synthesized in 50% yield by the alkylation of phenanthrene with *tert*-butyllithium.[10]

The reaction mechanism is unclear because there are few examples of the alkylation of arenes with lithioalkanes and no special studies. However, the fact that prolonged heating of the reactants without using an inert atmosphere is required for the reaction to proceed suggests that this reaction occurs *via* oxidative nucleophilic substitution of hydrogen (see Scheme 1, path *a*).

II.1.b. Auto-aromatization of σ^H-adducts in nucleophilic substitution

The reactions of trifluoroacylated phenols with lithiofuran or -thiophene that occur *via* the *cine*-substitution (see Scheme 1, path *b*) accompanied by the elimination of trifluoroacetic acid for afford products of the nucleophilic substitution of hydrogen (Scheme 5).[13] The reactions of 4-phenyl- or 2-methylphenyl trifluoroacetates with a Li reagent give a mixture of *ortho* (**1**) and *meta* isomers (**2**), whereas the reaction of 2-methoxy derivatives produces only *meta* isomer **2** (R = OMe).

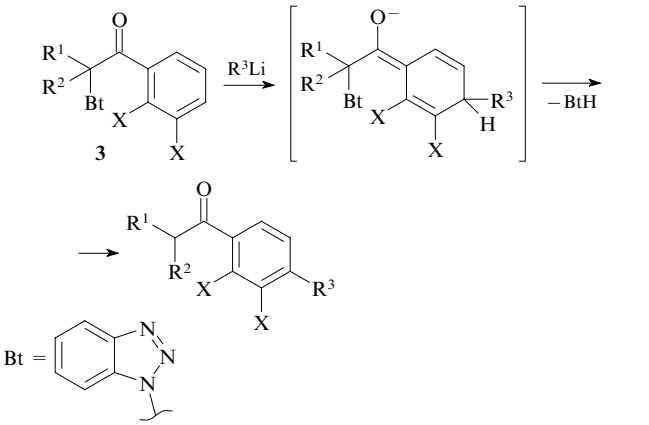
Scheme 5



R	X	Ratio **1** : **2**	Yield (%)
H	O		52
2-Me	O	32 : 68	54
2-OMe	O	0 : 100	58
4-Ph	O	58 : 42	52
H	S		49
2-Me	S	43 : 57	54
2-OMe	S	0 : 100	35

The *tele*-substitution in the nucleophilic alkylation of α-(benzotriazol-1-yl) ketones **3** was described by Katritzky *et al.*[14] (Scheme 6).

Scheme 6



R^3	R^1	R^2	X or X–X	Yield (%)
Bu^n	Bt	Bt	H	78
Bu^s	Bt	Bt	H	62
Bu^t	Bt	Bt	H	49
Bu^n	Bt	Bt	benzo	76
Bu^t	Bt	Ph	H	62
Bu^t	4-MeC_6H_4	Pr^i	H	46
Bu^t	2-MeC_6H_4	Ph	H	72
Bu^s	Ph	Ph	H	69
Bu^t	Ph	Ph	H	48

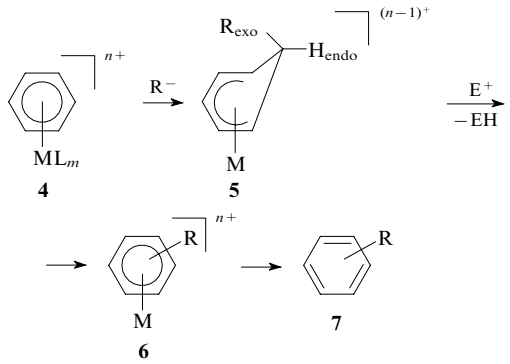
II.2. Reactions of metal arene complexes

II.2.a. Nucleophilic substitution using an oxidant for aromatization of σ^H-adducts

The coordination of arenes to transition metals is known to increase the electron density of the aromatic ring and enhance the susceptibility to nucleophilic attack.[15–23] In recent years, the use of such complexes in organic synthesis was described in a number of reviews.[24–26]

Actually, the reactions of metal arene complexes **4** with carbanions afford quite stable adducts **5**, which usually contain the substituent R in the *exo* position and the cyclohexadienyl moiety opposite to the coordinated metal ion (Scheme 7).[17, 18, 23, 27] Attempts to eliminate the hydrogen ion from complex **5** by treating the latter with the triphenylmethyl cation or other electrophiles are not always successful because the electrophilic attack at the *endo*-oriented hydrogen atom (H_{endo}) in complex **5** is sterically hindered. Meanwhile, the reactions resulting in the elimination of H_{endo} and accompanied by the decomposition of metal arene complex **6** to substituted arenes **7** are described in numerous publications.[18, 23, 28–31]

Scheme 7

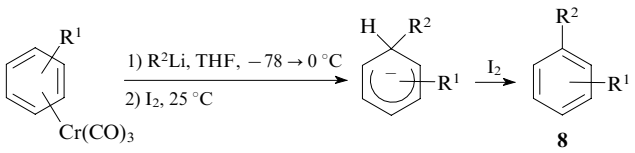


L is a ligand, E is an electrophile

In general terms, this process can be considered as nucleophilic aromatic substitution of hydrogen. The use of different types of metal arene complexes shows that this procedure is a powerful synthetic tool for the preparation of substituted arenes.

Tricarbonylchromium is one of the most suitable groups for activating nucleophilic substitution of hydrogen in arenes. This group readily adds to the benzene ring and can be removed in the last reaction step.[16, 23, 27, 31–37] The coordination of transition metals (including chromium) by arenes offers a unique possibility of the wide use of nucleophilic substitution of hydrogen in arenes. Meanwhile, it should be taken into account that such reactions proceed in the presence of a suitable oxidant. Such oxidants have a dual function. They not only remove a hydrogen atom next to the sp^3-carbon atom in the cyclohexadienyl intermediate but also oxidize the chromium complex to form the aromatic nucleus. Actually, the treatment of arene chromium tricarbonyl complexes with alkyl- or aryllithium and then with iodine affords alkyl- or aryl-substituted products **8** usually in good yields (Scheme 8, Table 1).

Scheme 8



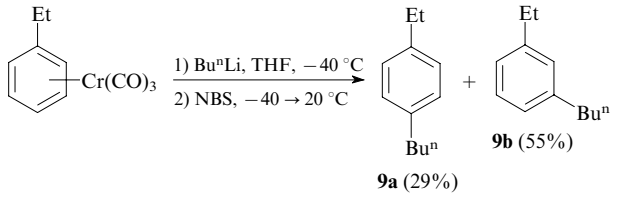
The complexation of arenes with tricarbonylchromium is successfully applied for the introduction of cyanomethyl, isobutyronitrile, n-butyl, *tert*-butyl and phenyl groups into the benzene ring (see Table 1). Limitations refer to such types of lithium reagents as methyllithium, ethyllithium or n-propyllithium. Being strongly basic, these reagents can mediate competitive hydrogen–lithium exchange in the benzene ligand resulting, after the treatment with iodine, in the formation of iodobenzene.[34, 36] The hydrogen–lithium exchange can be avoided by changing the reaction conditions. This was demonstrated by the alkylation of (η^6-ethylbenzene)tricarbonylchromium with n-butyllithium at −40 °C followed by the oxidation with *N*-bromosuccinimide (NBS) to form a mixture of *meta*- and *para*-ethyl-substituted n-butylbenzenes **9a**,**b** (Scheme 9).[37]

The formation of *meta* isomers as the major products (the percentage of *ortho* isomers is 0%–10%; of *para* isomers, not higher than 0%–2%) from methyl-, ethyl-

Table 1. Substitution of hydrogen in η^6-arenetricarbonyl complexes of chromium upon the activation of the carbanion and using I_2 as the oxidant (see Scheme 8).

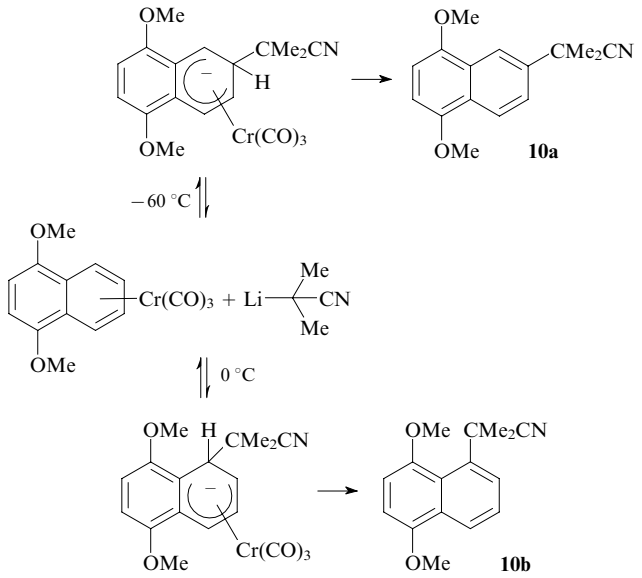
Arene	Li-Reagent	Product **8**	Yield (%)	Ref.
Benzene	$LiCH_2CN$	Phenylacetonitrile	68	34
	$LiCMe_2CN$	Phenylisobutyronitrile	94	34
	Bu^tLi	*tert*-Butylbenzene	68	31
	2-Lithio-1,3-dithiane	2-Phenyl-1,3-dithiane	93	34
	$4\text{-}MeC_6H_4Li$	4-Methylbiphenyl	71	34
	$LiCH_2CO_2Bu^t$	*tert*-Butyl phenylacetate	87	34
	$LiCMe_2CO_2Bu^t$	*tert*-Butyl dimethylphenylacetate	91	34
Toluene	$LiCH_2CN$	*o*-Tolylacetonitrile	30	16
		m-Tolylacetonitrile	56	16
	LiCHMeCN	*o*-Tolylisopropionitrile	12	16
		m-Tolylisopropionitrile	70	16
	$LiCMe_2CN$	*o*-Tolylisobutyronitrile	1	16
		m-Tolylisobutyronitrile	94	16
	2-Lithio-1,3-dithiane	2-*o*-Tolyl-1,3-dithiane	49	16
		2-*m*-Tolyl-1,3-dithiane	45	16
Ethylbenzene	Bu^nLi	1-n-Butyl-3-ethylbenzene	55	37
		1-n-Butyl-4-ethylbenzene	29	37
Chlorobenzene	$LiCMe_2CN$	*o*-Chlorophenylisobutyronitrile	2	33
		m-Chlorophenylisobutyronitrile	56	33

Scheme 9



and chloro-substituted benzenes (see Table 1) suggests that the transition state in the reaction giving the η^5-cyclohexadienyl intermediate is a pentadienyl anion. The *meta*-directing effect of electron-donating substituents is rather easy to explain because these substituents have the least destabilizing effect if they are in *meta* positions of the cyclohexadienyl system.[16, 23, 27, 31 – 35, 37] Nevertheless, the results of the reaction depend on the conditions used. For example, isomers **10a**,**b** are produced by alkylation of (dimethoxynaphthalene)tricarbonylchromium with lithium isobutyronitrile at different temperatures (Scheme 10).

Scheme 10

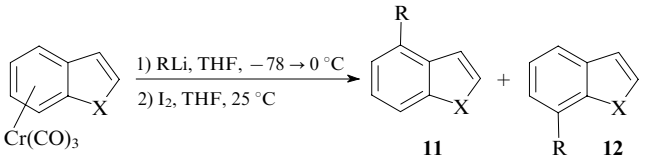


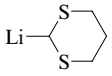
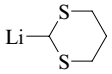
Reactions of complexes of indole and benzofuran, which are coordinated through the six-membered ring to tricarbonylchromium, with organolithium compounds in the presence of an oxidant give products of nucleophilic substitution of hydrogen **11** and **12** (Scheme 11).[16]

In (η^6-arene)tricarbonylmanganese complexes, arenes are also highly reactive toward different nucleophiles, including methyl- and phenyllithium.[38] However, in most cases it is impossible to oxidize intermediate derivatives of (η^5-cyclohexadienyl)tricarbonylmanganese(I).

Compared with neutral chromium complexes cationic complexes of iron and manganese can strongly activate arene ligands to nucleophilic attack. Nevertheless, such compounds are of less importance in organic synthesis because, due to their high reactivity, other reaction products are formed, resulting in lower yields of S_N^H products. Moreover, no general methods are available for the removal of coordinated metals and their separation from substituted arenes.[35]

Scheme 11

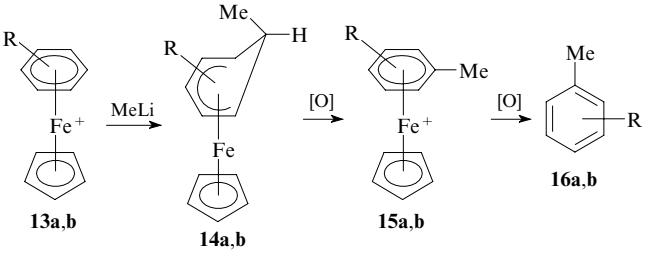


X	RLi	Ratio **11** : **12**	Yield **11** + **12** (%)
NH	$LiCH_2CN$	75 : 25	43
NH	$LiCMe_2CN$	97 : 3	73
NH	$LiCMe_2CO_2Bu^t$	97 : 1	92
NH		14 : 86	68
O	$LiCMe_2CN$	73 : 27	71
O		86 : 14	42

Reactions of η^6-arene-η^5-cyclopentadienyliron fluoroborates **13a**,**b** with nucleophiles under oxidation conditions proceed like reactions of Cr complexes.[39] The oxidation of intermediate adducts **14a**,**b** affords η^5-cyclopentadienyliron complexes **15a**,**b**, which are oxidized to the corresponding substituted arenes **16a**,**b** even under mild conditions (Scheme 12).[30]

The reaction pathway depends on the nature of substituents. Thus, complex **13a** containing a chlorine atom in the benzene ring adds methyllithium predominantly at the *ortho* position (the isomer ratio *ortho* : *meta* : *para* = 4 : 1 : 0) due to the inductive effect of the substituent, whereas the reaction of anisole analogue **13b** occurs predominantly at the *meta* position.[29]

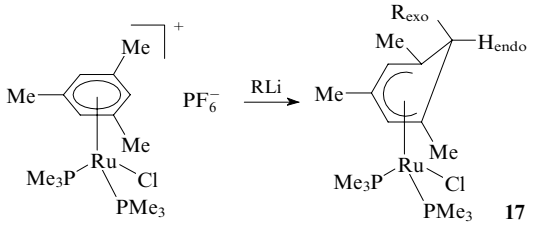
Scheme 12



R = Cl (**a**), OMe (**b**)

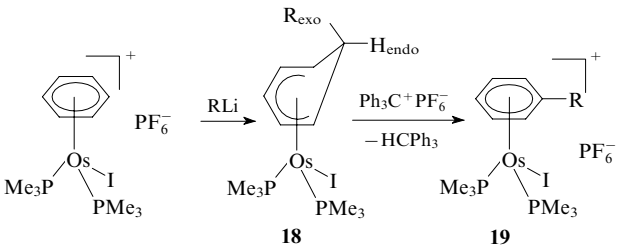
Alkyllithium compounds react with benzeneruthenium(II) and benzeneosmium(II) complexes to form quite stable cyclohexadienyl complexes **17** and **18** (Schemes 13 and 14).[17, 18, 40]

Scheme 13



R = Me, Ph

Scheme 14



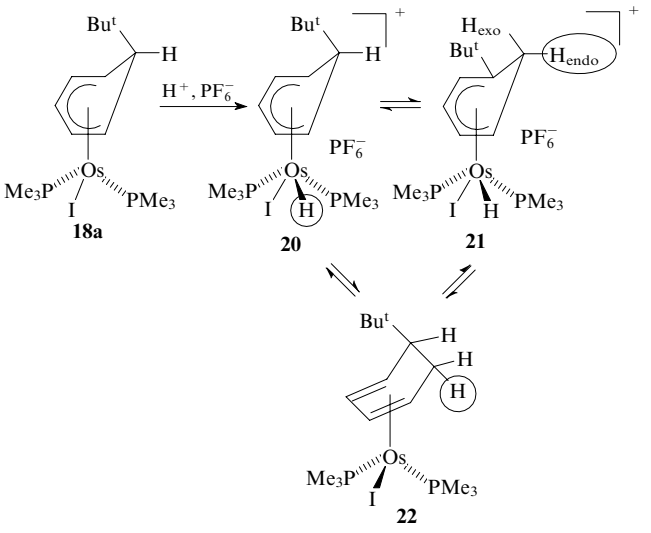
R = Me, Et, Pr^n, Bu^n, Bu^t, Ph

Structural studies of compounds **17** and **18** by ^{1}H and ^{31}P NMR spectroscopy and the X-ray diffraction data for osmium complex **18a** (R = Bu^n) showed that the cyclodienyl moiety adopts an envelope conformation with the n-butyl group attached in the *exo* position at the sp^3-carbon atom.[17]

The oxidation of osmium cyclohexadienes **18** containing the group R in the *exo* position and the hydrogen atom in the *endo* position with triphenylmethyl hexafluorophosphate (trityl hexafluorophosphate) in acetone readily proceeds at room temperature and is completed in a few minutes to form yellow or orange osmium arene salts **19** in nearly quantitative yield (see Scheme 14).[18] The most probable mechanism of this oxidation reaction involves the formation of isomeric cyclohexadienyl complexes, in which the alkyl group at the sp^3-carbon atom is absent because of its migration.

This is confirmed by experimental data for (*exo*-6-*tert*-butyl-η^5-cyclohexadienyl)iodobis(trimethylphosphine)osmium(II) **18a**, which is more stable than complexes **19** containing n-alkyl groups and is oxidized with trityl hexafluorophosphate in dichloromethane at 55 °C in 5 h (Scheme 15). The NMR study showed that the protonation of osmium complex **18a** with trifluoroacetic acid in the presence of NH_4PF_6 occurs at the osmium ion to form hydride complex of osmium(IV) **20**, which is isomerized to compound **21**. The isomerization proceeds through intermediate complex **22**. This suggests the reversible proton transfer between the osmium ion and the cyclohexadienyl moiety. Cyclohexadienyl complex **22** contains the CH_2 group, in which the *exo*-hydrogen atom is more susceptible to oxidation.[18] It should be noted that several such isomerization reactions were observed for cyclohexadienyl complexes of tricarbonylchromium, -manganese and -molybdenum.[41]

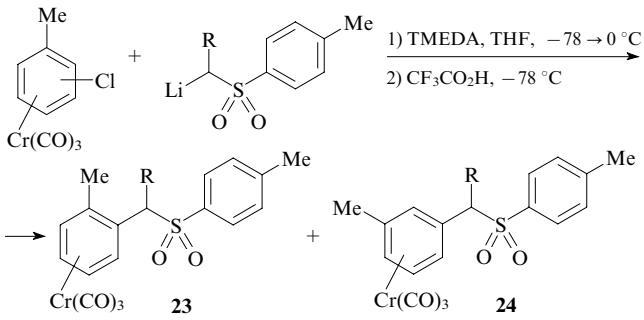
Scheme 15



II.2.b. Auto-aromatization of σ^H-adducts in nucleophilic substitution

Aromatization of adducts that are formed after the attack of organolithium compounds on the arene chromium tricarbonyl complex can be accompanied by the elimination of an atom or a good leaving group from the arene, *i.e.* proceed as the *cine*- or *tele*-substitution.[42] For example, chlorotoluene(tricarbonyl)chromium complexes react with 4-lithioethyl(or methyl) tolyl sulfone in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) to give predominantly *cine*- and(or) *tele*-substitution products **23** and **24** (Scheme 16).[43, 44]

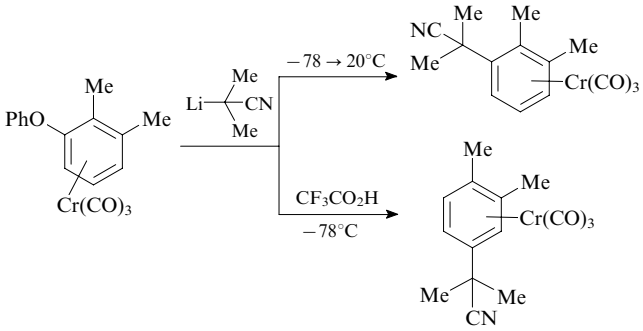
Scheme 16



Position of Cl in complex $ClC_6H_4Me \cdot Cr(CO_3)_3$	R	Yield (%)	
		23	**24**
para	Me	69	17
meta	Me	38	38
ortho	Me	0	81
para	H	0	72
meta	H	20	20
ortho	*H*	*3*	*65*

Depending on the conditions used, the reaction of the 2,3-dimethyl-1-phenoxybenzene chromium tricarbonyl complex with 2-lithioisobutyronitrile gives *tele*- and *ipso*-substitution products (Scheme 17).[45, 46]

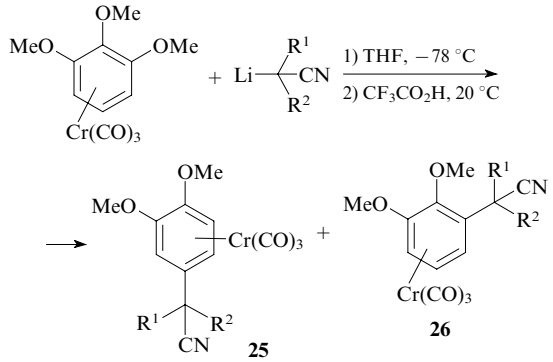
Scheme 17



For example, the reaction of the 1,2,3-trimethoxybenzene complex results only in the *tele*-substitution to form isomeric 3,4-dimethoxyphenylisobutyronitrile complexes **25** and **26** (Scheme 18).[47] The similar *tele*-substitution of

methoxy groups was observed in chiral arene chromium tricarbonyl complexe.[48]

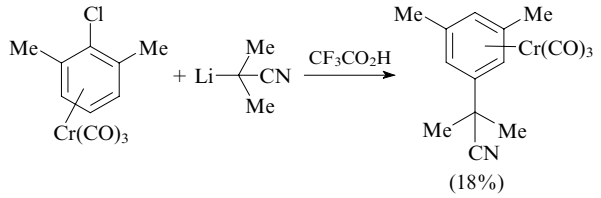
Scheme 18



R^1	R^2	Yield (%)	
		25	**26**
H	H	42	22
H	Me	78	5
Me	Me	98	–

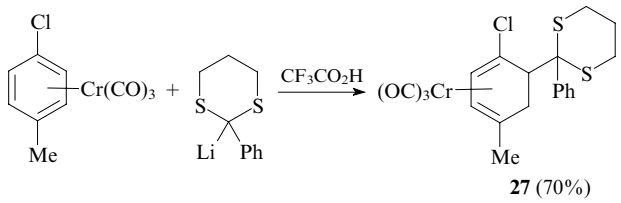
A halogen atom can also act as a leaving group, for example, in the aromatization of the corresponding σ^H-adduct that is formed in the reaction of 2,6-dimethylchlorobenzene chromium tricarbonyl complex with 2-lithio-2-methylpropionitrile (Scheme 19).[49]

Scheme 19



Stable intermediate **27** was isolated in the reaction of the 4-chlorotoluene chromium tricarbonyl complex with 2-lithio-2-phenyl-1,3-dithiane (Scheme 20), which is additional evidence of the addition – elimination mechanism of the reaction.[50]

Scheme 20



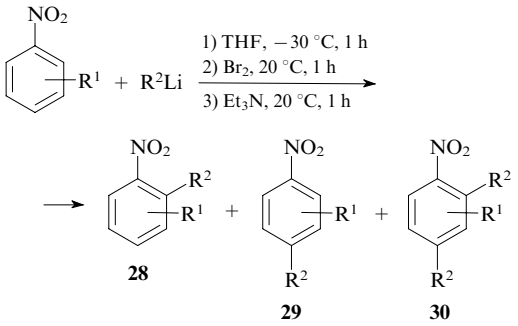
II.3. Reactions of nitroarenes

The S_N^H reactions in arenes activated by the nitro group remain the subject of extensive research. There are numerous publications concerned with the chemistry of nitroarenes,[51 – 54] the formation of anionic σ-complexes[55 – 58] and substitution of nucleofugal groups.[59] The nucleophilic substitution of hydrogen in aromatic systems containing nitro groups attracts considerable attention.[1, 54, 60 – 72]

It is believed that S_N^H reactions with nitroarenes proceed *via* a two-step addition – elimination mechanism.[54, 62] Nevertheless, in some cases the authors did not take into account the fact that these transformations can involve the formation of charge transfer complexes, radical ion salts and other species. In fact, the reactions of nitroarenes with nucleophilic reagents are often accompanied by the formation of charge transfer complexes although convincing experimental evidence of their existence was obtained only in a few cases.[73]

Nitrobenzene and its derivatives are easily C-alkylated with methyl- or butyllithium in the presence of an oxidant.[74] The reaction proceeds at *ortho* and *para* positions with respect to the nitro group to give a mixture of alkylnitroarenes **28** – **30** (Scheme 21). A decrease in steric accessibility of the reaction centre in the case of the *tert*-butyl substituent compared with the methyl group leads to an enhancement of the regioselectivity of the reaction.

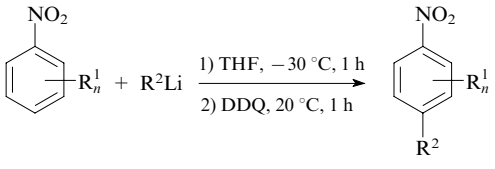
Scheme 21



R^1	R^2	Yield (%)		
		28	**29**	**30**
H	Me	32	20	7
2-Me	Bu^n	10	45	3
2-Me	Bu^t	4	30	0
4-Et	Me	52	0	0

The reactions of compounds, which contain two substituents at the *ortho* position with respect to the nitro group or the second nitro group at position 3(5) of the aromatic ring, with *tert*-butyllithium afford only *para*-substitution products **29**, although the total yield of these products is lower (Scheme 22).[74] A similar result was obtained in the reaction of *m*-dinitrobenzene with methyllithium.

Scheme 22

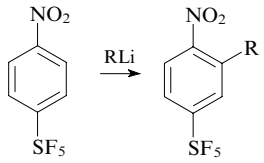


DDQ is 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

R^1_n	R^2	Yield (%)
2,6-Me_2	Bu^n	23
2-Me-5-NO_2	Bu^n	12
3-NO_2	Me	5

The presence of the SF_5 group (called the 'substituent of the future' [75]) in nitroarenes, on the one hand, increases the susceptibility of the benzene ring to nucleophilic attack due to its electron-withdrawing character comparable with that of the trifluoromethyl group and, on the other hand, increases the regioselectivity of the reaction due to steric factors (the size of the SF_5 group is comparable with that of the *tert*-butyl group). Thus, the reactions of 1-nitro-4-pentafluorosulfanylbenzene with methyl- and n-butyllithium give exclusively *ortho*-substituted products **31a**,**b** (Scheme 23), whereas the reactions of 1-nitro-3-pentafluorosulfanylbenzene with methyllithium afford *ortho*- and *para*-substituted products **32a**,**b**, with the former compound being the major product (Scheme 24).[76]

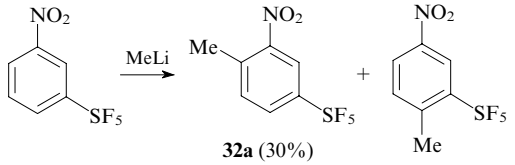
Scheme 23



31a,**b**

R = Me (**a**, 64%), Bu^n (**b**, 61%)

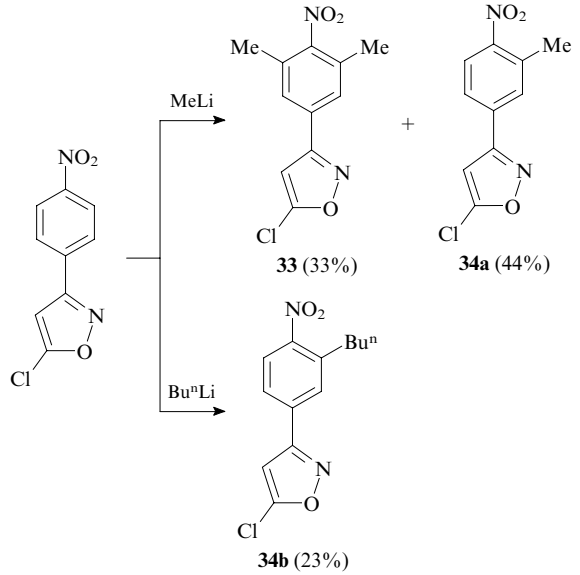
Scheme 24



32a (30%) **32b** (15%)

The isoxazole ring in the *para* position with respect to the nitro group in 5-chloro-3-(4-nitrophenyl)isoxazole is not subjected to nucleophilic attack in the reaction with methyllithium but it is favourable for the formation of disubstituted (**33**) and monosubstituted (**34a**) products in yields of up to 44% (Scheme 25),[77] whereas the reaction with n-butyllithium gave only monosubstituted product **34b** in low yield.

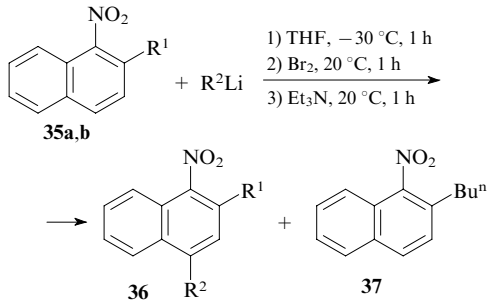
Scheme 25



33 (33%) **34a** (44%) **34b** (23%)

The annulation of an aromatic or heteroaromatic ring with nitroarenes leads to their higher susceptibility to the action of organolithium compounds because the *in situ* generated σ^H-adducts are more stable. This results in higher yields of products **36** and **37** synthesized by the nucleophilic alkylation of 1-nitronaphthalenes **35a**,**b** [R^1 = H (**a**), Me (**b**)], the regioselectivity of the reaction also being higher (Scheme 26).[74]

Scheme 26

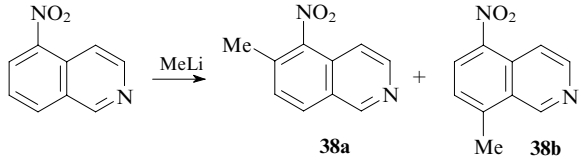


35a,**b** **36** **37**

R^1	R^2	Yield (%)	
		36	**37**
H	Bu^n	48	25
Me	Me	66	
Me	Bu^n	70	

The reaction of methyllithium with 5-nitroisoquinoline leads exclusively to the substitution in the benzene ring and the formation of compounds **38a**,**b** (total yield is 40%); the ratio of *ortho* to *para* isomers is 2.5 : 1 (Scheme 27).[78]

Scheme 27



38a **38b**

II.4. Reactions of monoazines

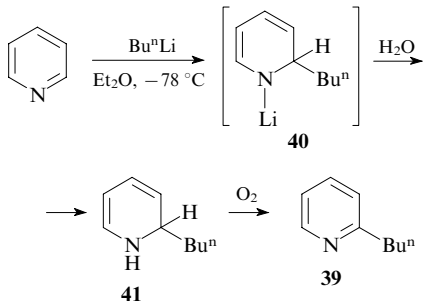
In azines, the endocyclic nitrogen atom of the pyridine type performs the same function as the nitro group in arenes, activating the heteroaromatic ring towards nucleophilic attack. Depending on the nature of the substituents in the azine ring, the aromatization of the σ-adducts that are formed in the reaction with organolithium compounds can occur *via* several mechanisms.

II.4.a. Oxidative nucleophilic substitution

The use of organolithium compounds for the substitution of hydrogen in the azine ring provides one of the simplest approaches to the formation of a new C–C bond. As early as 1930, it was shown [79] that these derivatives react with pyridine to form adducts at the C(2) atom, and the aromatization of the latter affords 2-substituted pyridines. For example, 2-n-butylpyridine (**39**) was synthesized in good yield by the reaction of pyridine with n-butyllithium (Scheme 28). The reaction proceeds through the formation of intermediate σ^H-adduct **40**, which is transformed, after hydrolysis, to compound **41**. In some reactions, these

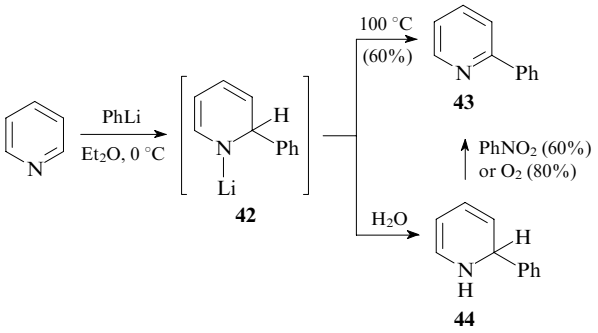
adducts were isolated and identified by ^{1}H and ^{13}C NMR spectroscopy.[80–83]

Scheme 28



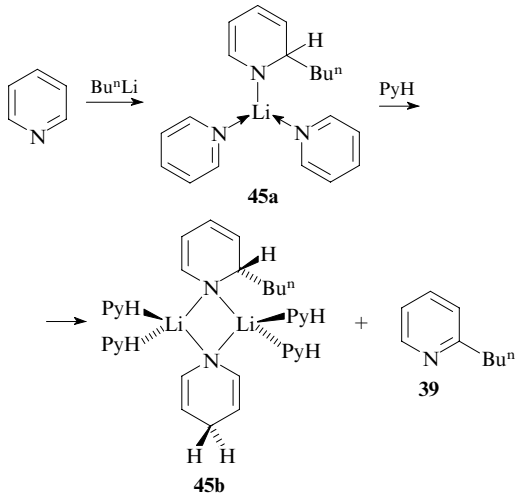
At 0 °C pyridine reacts with the aromatic analogue of MeLi — phenyllithium — to form adduct **42**, which was obtained as a lithium derivative (Scheme 29).[81] Upon heating, this adduct is transformed into 2-phenylpyridine (**43**), and the hydrolysis of this adduct gives dihydro derivative **44**, which can be rather easily oxidized to 2-phenylpyridine.[84, 85]

Scheme 29



It was hypothesized that the reaction proceeds through the formation of lithium hydride; however, it was later shown that adduct **45a** is formed as an intermediate in this reaction (Scheme 30).[86, 87]

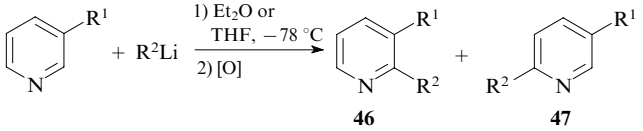
Scheme 30



The treatment of adducts **45a** with pyridine (4 equiv.) gives 2-n-butylpyridine and air-stable dimer **45b** composed of 1,2- and 1,4-dihydropyridine moieties (in a ratio of 1 : 1) and four pyridine molecules (PyH).[82] Formally, the reaction with the participation of adduct **45a** involves the reduction of pyridine with lithium hydride that is generated upon the formation of 2-n-butylpyridine. However, lithium hydride was not detected among the reaction products. These results provide evidence that 2-alkylpyridine is generated in the reaction of adduct **45a** with pyridine.‡

In recent years, this reaction has been widely used for the synthesis of substituted pyridines and other azines. The alkylation or arylation of pyridine with organolithium nucleophiles usually proceeds at the α position. σ^{H}-Adducts can be dehydrogenated with different oxidants — from oxygen to nitrobenzene. This reaction with 3-alkylpyridines produces a mixture of 2,3- and 2,5-substituted pyridines **46** and **47** (Scheme 31; a dash indicates that the yield was not reported in the original paper).[88–92]

Scheme 31

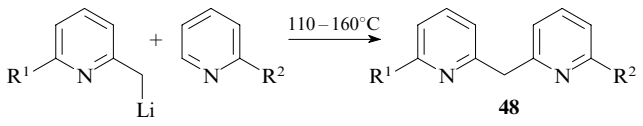


R^1	R^2	Ratio **46** : **47**	Yield **46** + **47** (%)
Me	Me	84 : 16	28
Me	Pr^i	20 : 80	–
Me	Ph	94 : 6	48
Et	Ph	87 : 13	42
Pr^i	Ph	76 : 24	32
Bu^t	Me	1 : 99	61
Bu^t	Ph	5 : 95	24
cyclo-C_6H_{11}	Ph	65 : 35	–
Ph	Ph	16 : 84	35
OMe	Ph	100 : 0	21
NH_2	Ph	100 : 0	24

Under more severe conditions (two-fold excess of R^2Li at −70 °C), different degrees of nucleophilic alkylation of pyridine can be achieved when using different excesses of an alkyllithium reagent. For example, 2,6-disubstituted pyridines were synthesized by the reaction of pyridine with *tert*-butyllithium.[90–92] Under yet more severe conditions (heating in the presence of an excess of R^2Li to room temperature), the reaction produces 2,4,6-tris(*tert*-butyl)pyridine.[90]

The reaction of organolithium compounds with pyridine and its derivatives was used to synthesize pyridylmethanes — polydentate N-donor ligands **48**–**52** (Schemes 32–34).[93, 94]

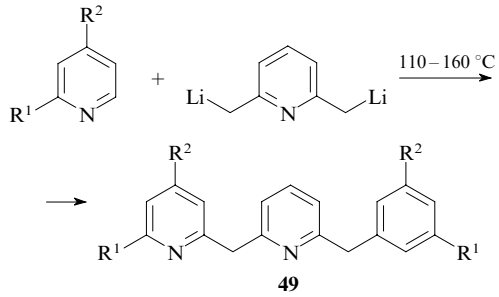
Scheme 32



$R^1 = R^2 = H$ (45%), Me (45%); $R^1 = H$, $R^2 = Me$ (40%)

‡ These data also account for the formation of 2-alkylpyridines in the synthesis of 6-substituted *trans*-2-allyl-1,2,3,6-tetrahydropyridines from pyridine, alkyllithium and triallylborane.[83]

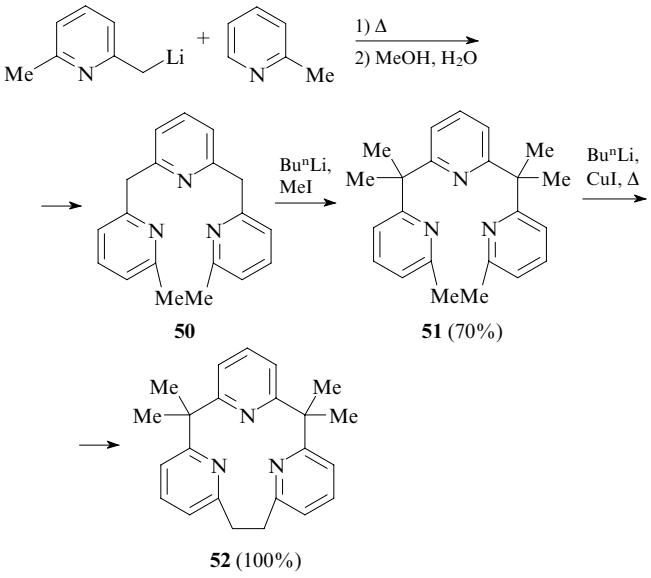
Scheme 33



49

$R^1 = R^2 = H$ (45%); R^1 = Me: $R^2 = H$ (65%), Bu^t (50%)

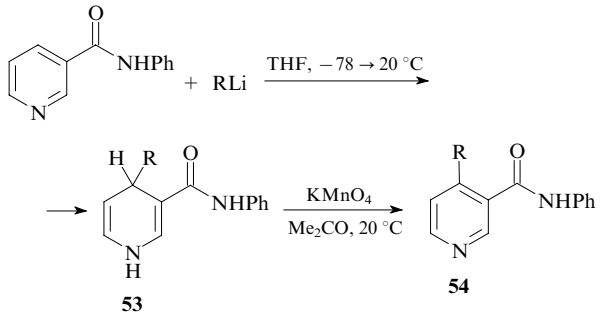
Scheme 34



50 **51** (70%) **52** (100%)

At low temperatures, it is possible to introduce alkyl substituents at the γ position of the pyridine ring. For example, the reaction of *N*-phenylnicotinamide with alkyllithium gives 1,4-dihydro adducts **53**, which are easily oxidized with potassium permanganate to form 4-substituted nicotinamides **54** (Scheme 35).[95]

Scheme 35



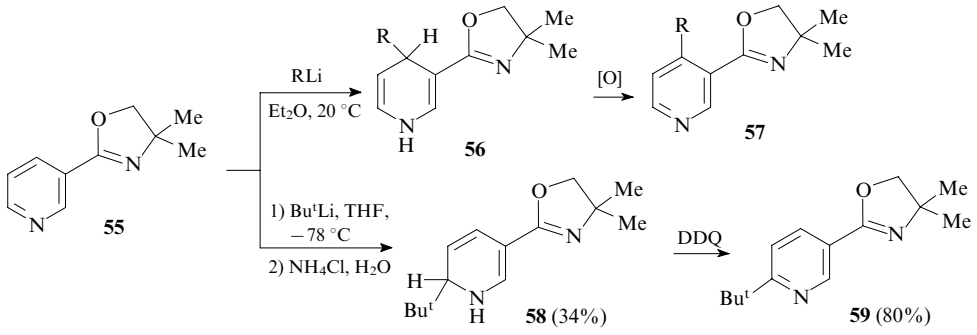
53 **54**

R = Me (59%), Bu^n (91%), Ph (74%)

Depending on the reaction conditions, pyridyloxazoline **55** forms exclusively α- or γ-substitution products. For example, the reaction with alkyl- or aryllithium in diethyl ether at room temperature affords dihydro adducts **56**, which, after the oxidation with atmospheric oxygen, give compounds **57** as products of nucleophilic substitution of hydrogen at position 4 of pyridine (Scheme 36).[96–99] The reaction with *tert*-butyllithium at −78 °C produces adduct **58**, which gives the corresponding 6-*tert*-butyl derivative **59** in 80% yield after the oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.[95]

The regioselectivity of the nucleophilic attack in pyridines **60a**,**b** containing the chiral oxazoline moiety at position 3 depends on the nature of substituents in the azole. For instance, 4-substituted compounds **61** are obtained as the major products by alkylation of methoxy derivative **60a**, whereas the reaction of its hydroxy analogue **60b** affords 6-substituted pyridines **62** (Scheme 37).[100] Meyers and Natale [100] attributed this difference to the chelating effect of the OMe substituent in compound **60a**, which directs attack of the organolithium nucleophile to position 4 in pyridine, and the absence of this effect in hydroxy derivative **60b** due to the formation of the OLi salt.

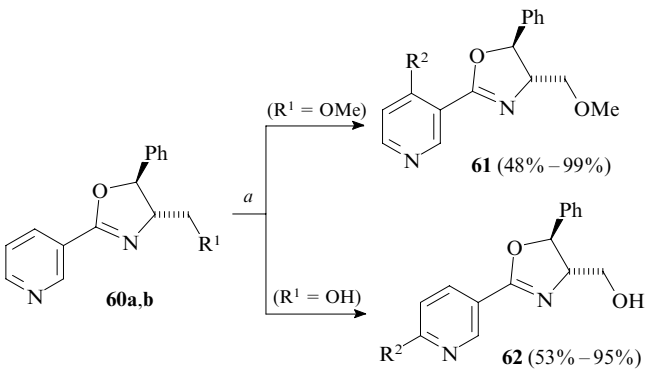
Scheme 36



55 **56** **57** **58** (34%) **59** (80%)

R	Yield of **56** (%)	Oxidation conditions	Yield of **57** (%)	R	Yield of **56** (%)	Oxidation conditions	Yield of **57** (%)
Me	69	$KMnO_4$, acetone, 25 °C	48	Bu^s	74	DDQ, benzene, 25 °C	55
		DDQ, benzene, 25 °C	27	Bu^t	75	The same	71
		O_2, 25 °C	52	Ph	78	$KMnO_4$, acetone, 25 °C	41
Bu^n	78	$KMnO_4$, acetone, 25 °C	45			DDQ, benzene, 25 °C	50
		DDQ, benzene, 25 °C	83				

Scheme 37

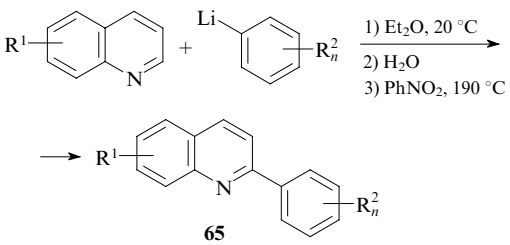


R^2 = Me, Ph, Bu^n;
(*a*) 1) R^2Li (2 equiv.), THF, −78 °C; 2) NH_4Cl, H_2O; 3) DDQ

The addition of organolithium derivatives to quinolines and isoquinolines results in the formation of the corresponding dihydro derivatives, which can be isolated and characterized. The oxidation of these adducts gives substituted aromatic compounds. Thus, the reaction of quinoline with 2-lithioanisole produced σ^H-adduct **63**, which was oxidized to 2-(2-methoxyphenyl)quinoline (**64**) upon heating with nitrobenzene under drastic conditions (Scheme 38).[84]

A similar result, *viz*., the formation of 2-dimethylaminophenylquinolines **65**, was observed for quinoline derivatives (Scheme 39). 9-Diethylaminophenylacridine and 3-diethylaminophenylbenzo[*f*]quinoline were synthesized by the same method in 61% and 56% yields, respectively.[101]

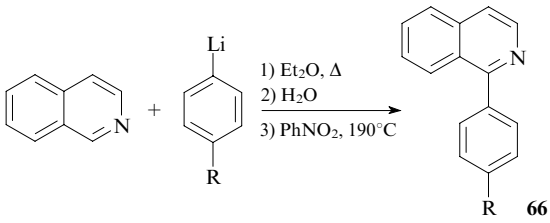
Scheme 39



R^1	R^2_n	Yield (%)
H	4-NMe_2	27
6-Cl	4-NMe_2	30
6-OMe	4-NMe_2	22
8-Me	4-NMe_2	26
H	2-NMe_2	35
H	2-NMe_2-5-Me	26
8-Me	2-NMe_2	35
8-Me	2-NMe_2-5-Me	28
H	3-NMe_2	7
8-Me	3-NMe_2	26

As early as 1947, Gilman and Gainer[102] reported the reaction of isoquinoline with aryllithium derivatives and the subsequent oxidation of the adducts to 2-arylisoquinolines **66** (Scheme 40). Nitrobenzene was also used as the catalyst.

Scheme 40



R = NH_2 (70%), NMe_2 (55%), Me (55%), SH (20%)

With the aim of synthesizing new ligands for chiral catalysts, Pena-Cabrera *et al.*[103] selectively introduced optically active alkyllithium reagents into 1,10-phenanthroline and isolated (1*R*)-camphor derivative **67** and *endo*-borneol derivative **68**. Compound **67** is formed *via* the *in situ* lithiation of camphor hydrazone with *sec*-butyllithium or of iodide with *tert*-butyllithium followed by the reaction with 1,10-phenanthroline at −78 °C. Compound **68** is produced as a result of the double bond migration in the lithium derivative of camphor in the reaction with 1,10-phenanthroline at room temperature. (1*R*)-Nopinone derivative **69** was synthesized in a similar way. In this case, compound **70**, which does not contain a double bond, was isolated as a by-product (Schemes 41 and 42).

Scheme 41

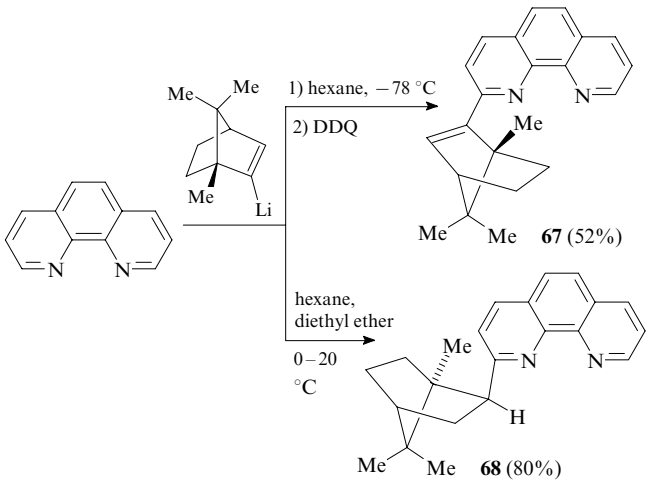


Table 2 gives the recently reported examples of the synthesis of aryl-substituted monoazines by nucleophilic substitution of hydrogen using organolithium reagents.

Scheme 38

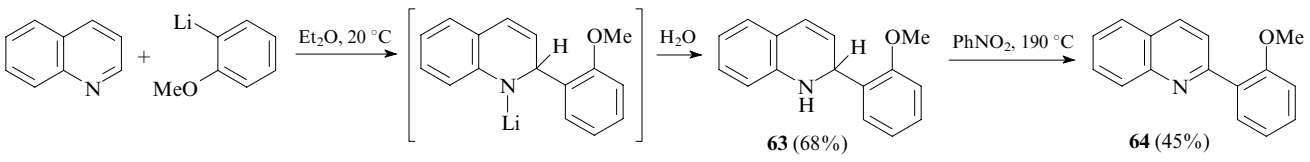


Table 2. Examples of the synthesis of aryl- and alkyl-substituted derivatives of monoazines using lithium reagents.

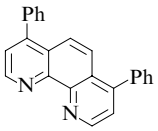
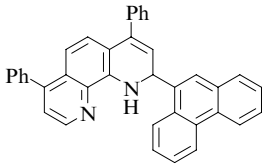
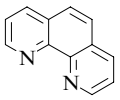
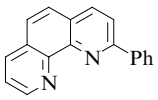
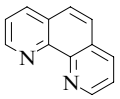
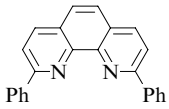
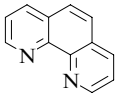
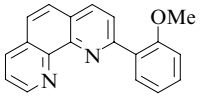
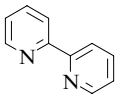
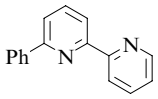
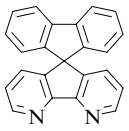
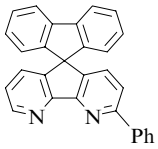
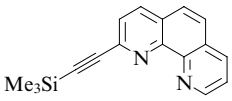
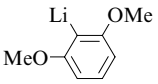
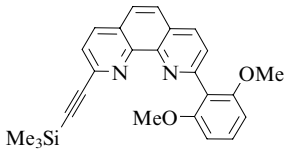
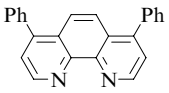
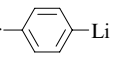
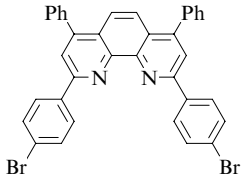
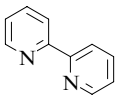
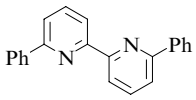
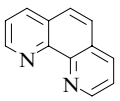
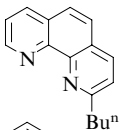
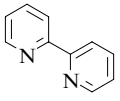
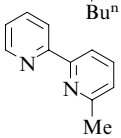
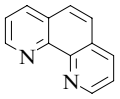
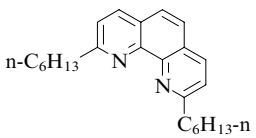
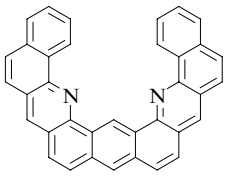
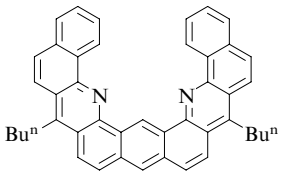
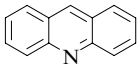
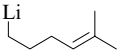
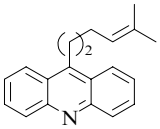
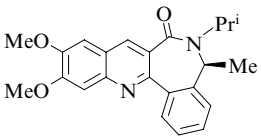
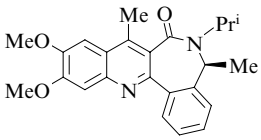
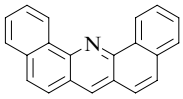
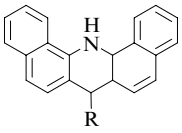
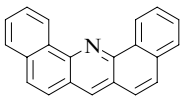
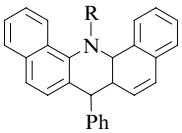
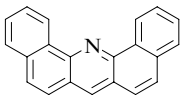
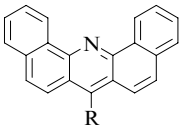
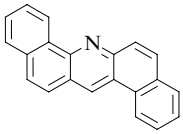
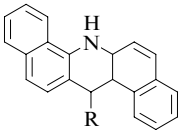
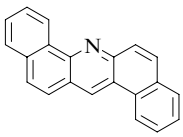
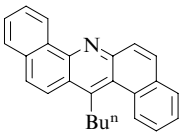
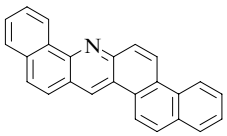
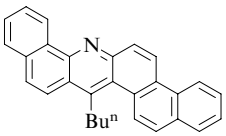
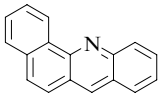
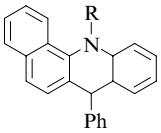
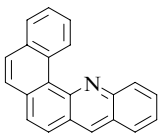
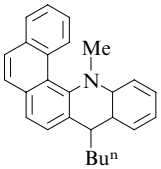
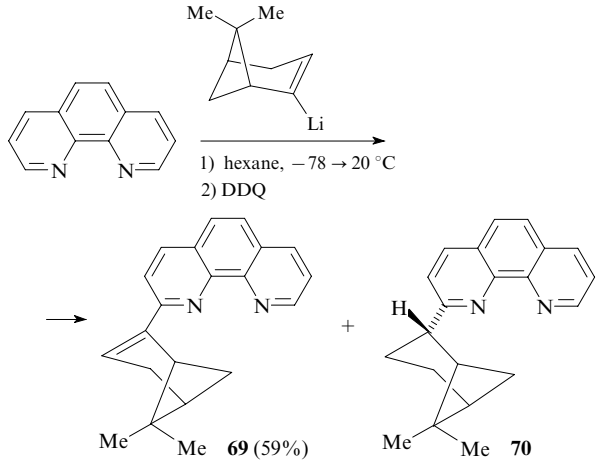
Substrate	Reagent	Product	Oxidant	Yield (%)	Ref.
	9-Lithiophenanthrene		–	80	104
	PhLi		MnO_2	99	105
	PhLi		MnO_2	78	106
	2-MeC_6H_4Li		–	See [b]	107
	PhLi		$KMnO_4$	55	108
	PhLi		MnO_2	93	109
			MnO_2	74	110
			MnO_2	50	111
	PhLi		–	See [b]	112
	Bu^nLi		MnO_2	98	105
	MeLi		$KMnO_4$	30	113
	n-$C_6H_{13}Li$		MnO_2	78	106

Table 2 (continued).

Substrate	Reagent	Product	Oxidant	Yield (%)	Ref.
	Bu^nLi – TMEDA		–	28	114
			$PhNO_2$	31	115
	MeLi		NCS [a]	See [b]	116
	RLi (R = Me, Bu^n, Bu^s)		–	94 (R = Me), 73 (R = Bu^n), 63 (R = Bu^s)	117 – 119
	PhLi – EtBr or PhLi – MeI			58 (R = Et), 55 (R = Me)	119
	RLi (R = Me, Bu^n, Bu^s)		DDQ	See [b]	117 – 119
	RLi (R = Me, Bu^n, Bu^s)		–	94 (R = Me), 80 (R = Bu^n), 76 (R = Bu^s)	117 – 119
	Bu^nLi		DDQ	80	117 – 119
	Bu^nLi		DDQ	70	117 – 119
	PhLi – ROH (R = H, D, Me, Et)		–	42 – 75	119
	Bu^nLi – MeI		–	See [b]	119

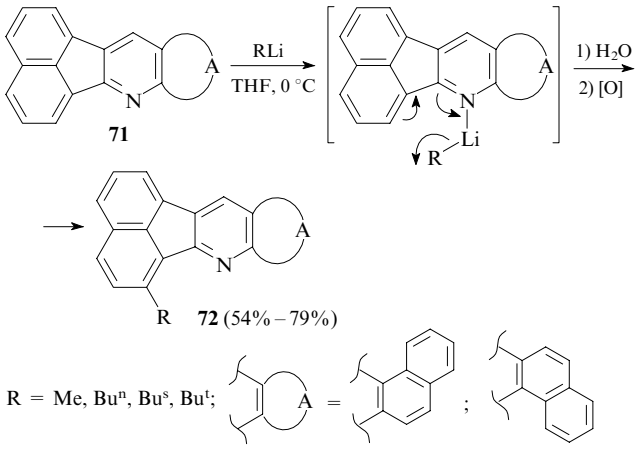
Note. Here and in Table 4, a dash indicates that the special oxidant was not used. [a] NCS is *N*-chlorosuccinimide; [b] the yield is not reported in the original publication.

Scheme 42



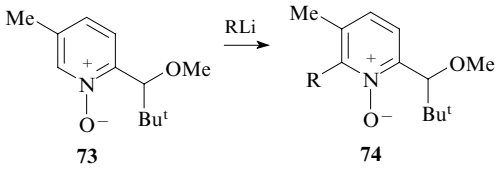
The reaction of polycyclic azaarenes **71** with organolithium reagents deserves special notice (Scheme 43).[117–119] In all cases, the nucleophilic attack occurs not at the pyridine ring but at the six-membered aromatic ring annulated to the cyclopentane moiety. These reactions afforded products **72** in moderate yields. In the authors' opinion, this is attributed to the structural features of the starting molecule. Thus, the annulation of the acenaphthene ring results in the formation of a cavity, and the immediate effect of the closely spaced pyridine nitrogen atom directs nucleophilic attack to this position. It is noteworthy that in all other similar examples, the attack of an organolithium compound occurs on the pyridine moiety to give the corresponding addition or substitution products[117–119] (see Table 2).

Scheme 43



The introduction of the N-oxide function into the azine ring facilitates the nucleophilic attack and offers additional opportunities for subjecting the resulting σ^H-adducts to aromatization *via* the oxidation pathway. However, monoazine N-oxides are used much more rarely as substrates in the reactions with organolithium reagents. For example, the deprotonation of pyridine *N*-oxide **73** with n-butyl- and *tert*-butyllithium produces the corresponding C-alkylation products **74** as by-products in yields up to 23% (Scheme 44), the dehydrogenation products at this position being the major ones.[120]

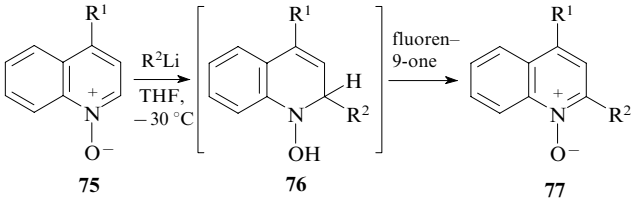
Scheme 44



R = Bun (23%), But (11%)

The reaction of quinoline *N*-oxides **75** with alkyl- or aryllithium compounds produces stable σ^H-adducts **76**, which can be efficiently oxidized with fluoren-9-one to the corresponding 2-substituted quinoline *N*-oxides **77** (Scheme 45).[121]

Scheme 45

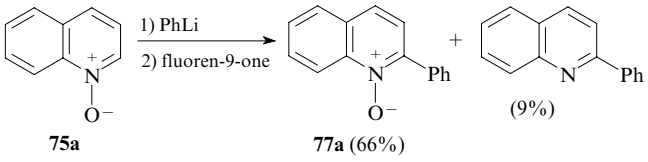


R^1 = H: R^2 = Bun (85%), But (43%), Ph (66%), 2-Th (69%);
R^1 = Me: R^2 = Bun (70%), But (28%), Ph (37%), 2-Th (48%);
R^1 = OMe: R^2 = Bun (55%), But (25%), Ph (43%), 2-Th (34%);
R^1 = Cl: R^2 = Bun (5%), But (0%), Ph (34%), 2-Th (44%);
R^1 = NO_2: R^2 = Bun (5%), But (0%), Ph (6%), 2-Th (20%);
Th is thienyl

II.4.b. Other pathways of aromatization of σ^H-adducts

In some cases, the aromatization of σ^H-adducts in the reactions of azine N-oxides with organolithium reagents occurs not only *via* the oxidation pathway but also *via* deoxygenation. For example, the reaction of quinoline oxide **75a** with phenyllithium gave 2-phenylquinoline oxide **77a** along with 2-phenylquinoline in a yield of up to 9% (Scheme 46).[121]

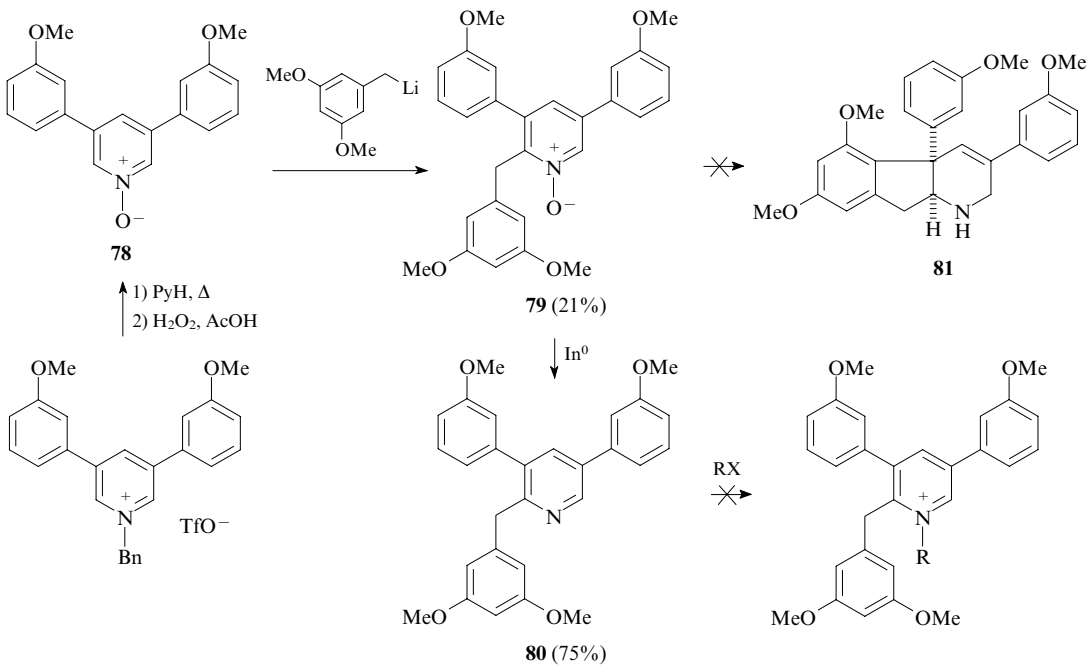
Scheme 46



The criteria of the selection of the appropriate lithium reagent and the azine component can find practical application. For example, the reaction of pyridine *N*-oxide **78** with benzyllithium was considered[122] as a facile procedure for the generation of the indeno-tetrahydropyridine core of the naturally occurring anticancer alkaloids haouamines A and B. However, attempts to further transform 2-benzylpyridine *N*-oxide **79** and 2-benzylpyridine **80**, either directly or indirectly, into indenotetrahydropyridine **81** failed (Scheme 47).

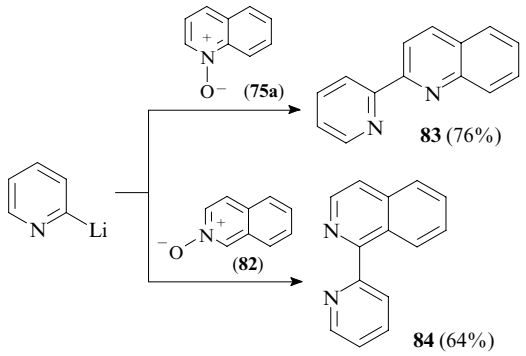
Apart from alkyl- and aryllithium reagents, hetaryllithium derivatives can also be subjected to nucleophilic substitution with azines. These reactions can be used for the alternative synthesis of polynuclear heterocyclic systems.

Scheme 47



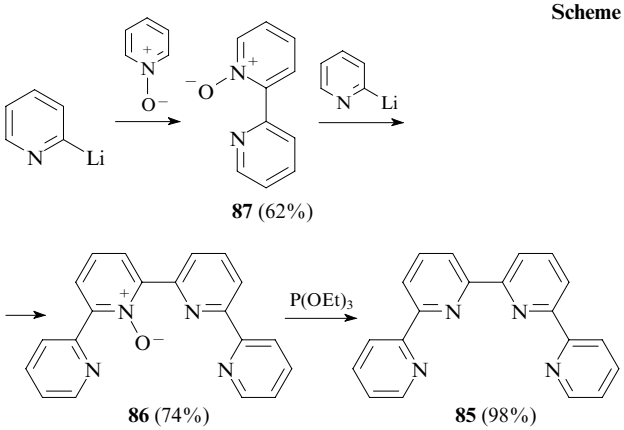
For instance, the direct introduction of pyridyllithium into quinoline oxide (**75a**) and isoquinoline oxide (**82**) gave benzannulated derivatives of 2,2′-bipyridine **83** and **84**, which are promising ligands for coordination of metal cations (Scheme 48).[123]

Scheme 48



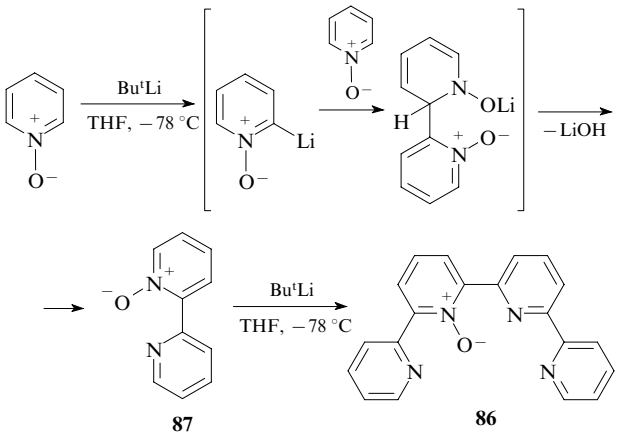
The same researchers proposed [123] a method for the synthesis of 2,2′:6′,2″:6″,2‴-quaterpyridine (**85**) and its N-oxide **86** by the stepwise reaction of pyridyllithium: first with pyridine *N*-oxide and then with dimerization product **87** (Scheme 49).

Scheme 49



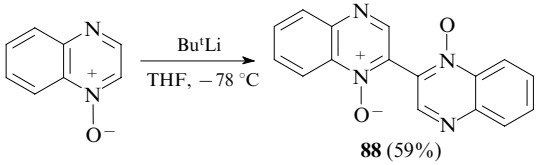
The formation of dimerization product **87** is evidenced by the fact that 2,2′:6′,2″:6″,2‴-tetrapyridine *N*-oxide **86** can be directly prepared by the stepwise reaction of pyridine *N*-oxide with *tert*-butyllithium, which is successively added to the reaction mixture (two 0.5 equiv. portions) (Scheme 50).

Scheme 50



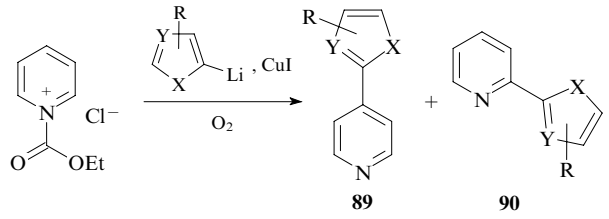
Similarly, the dimerization of quinoxaline *N*-oxide in the presence of 0.5 equiv. of *tert*-butyllithium affords 2,2′-biquinoxaline *N*-oxide **88** (Scheme 51).[123]

Scheme 51



Unlike the introduction of the N-oxide function, the N-acylation (as well as N-sulfonation, N-alkylation and N-arylation) of the pyridine ring not only activate the latter to nucleophilic attack but also can influence the regioselectivity of nucleophilic addition. For example, the direction of the formation of C(2)- and C(4)-adducts in reactions of hetaryllithium derivatives with pyridinium salts was explained [125] in terms of the Pearson principle of hard and soft acids and bases (HSAB).[124] Thus, soft nucleophiles form C(4)-adducts **89**, whereas hard nucleophiles give C(2)-isomers **90** (Scheme 52).

Scheme 52

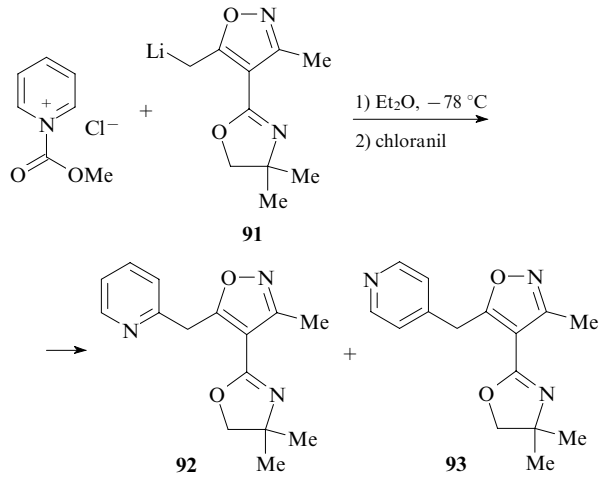


X	Y	R	Yield (%)	
			89	**90**
O	CH	H	49	0
O	CH	5-Me	44	0
O	CH	5-Et	41	0
O	CH	3-Br	40	0
S	CH	H	0	67
S	CH	5-Me	0	47
S	CH	5-Et	0	45
S	CH	5-Br	0	49
S	CH	4-Br	51	0
NMe	N	H	0	46
NSO_2Ph	CH	H	0	54
NMe	CH	H	45	0

More recently, Lai *et al.*[126] prepared substitution products at positions of 2 and 6, as well as at position 4, of the pyridine ring.

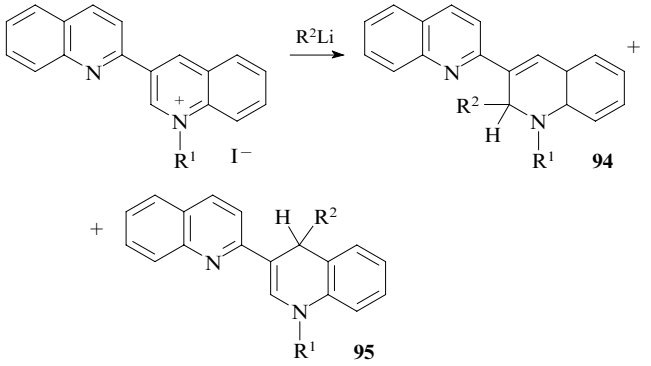
The reaction of alkyllithium derivative **91** with the pyridinium salt is not regioselective: it gives two substitution products **92** and **93** in a total yield of 75% (Scheme 53).[127]

Scheme 53



Salts of the benzannulated analogue of pyridine — quinolinium — do not show high regioselectivity in the reactions with alkyl- and aryllithium reagents as well. Thus, products **94** and **95** were isolated in ratios from 1 : 1 to 1.5 : 1.[128] However, the reactions with lithium acetylenide give C(2)-adducts **94** as the only products (Scheme 54, Naph is naphthyl) regardless of the substituent size.

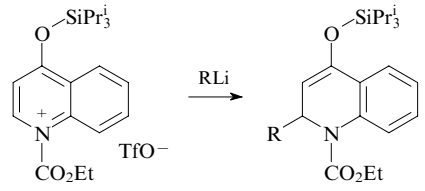
Scheme 54



R^1	R^2	Yield (%)	
		94	**95**
Me	Me	51	49
Me	Ph	61	39
Me	1-Naph	65	35
Me	PhCH≡C	100	0
Et	PhCH≡C	100	0
Bu^n	PhCH≡C	100	0

In the presence of a substituent at position 4 of the (benzo)pyridine ring, the nucleophilic attack occurs only at position 2. For example, the reaction of (trifluoromethyl)-sulfonates (triflates) **96** with organolithium derivatives produced 2-alkyl- and 2-phenyldihydroquinolines **97** (Scheme 55).[129]

Scheme 55

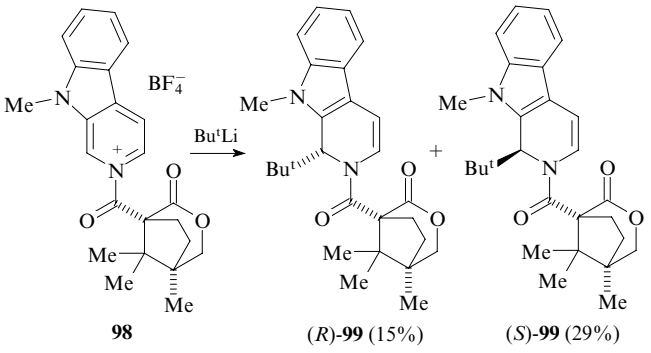


R = Me (55%), Bu^t (80%), Ph (57%); Tf = SO_2CF_3

The reaction of chiral *N*-acyl-β-carbolinium tetrafluoroborate **98** with *tert*-butyllithium affords two diastereomeric addition products **99**, with the *S* isomer being the major product. The direction of nucleophilic attack (*si* face) and the configuration of the major diastereomer are determined by the effect of the chiral acyl substituent (Scheme 56).[130]

Unusual results were obtained in attempting to generate carbenes by the reaction of 5-phenathridinium triflate **100** with sterically hindered bases.[131] The reaction of compound **100** with mesityllithium (Mes = 2,4,6-$Me_3C_6H_2$) gives not only α-addition product **101a** but also the addition product at the annulated benzene ring — unstable quinone derivative **101b** (**101a** : **101b** = 40 : 60).

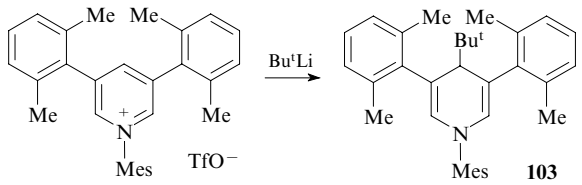
Scheme 56



The reaction of salt **100** with lithium bis(trimethylsilyl)-amide (LiHMDS) yields stable adduct **102** (Scheme 57).

Attempts to generate carbenes by the reaction of 1,3,5-triarylpyridinium salts with *tert*-butyllithium led to the formation of only C(4)-adduct **103** in 39% yield rather than the C(2)-adduct (Scheme 58).[132]

Scheme 58

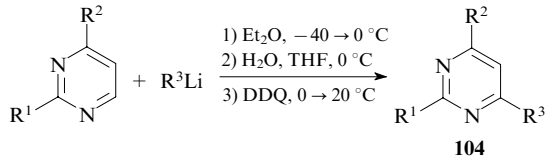


II.5. Reactions of diazines

II.5.a. 1,3-Diazines

The introduction of an additional nitrogen atom into the six-membered pyridine ring results in that many diazines readily react with alkyl- and aryllithium compounds to form stable dihydro adducts, which can be transformed into the corresponding substitution products. For example, the nucleophilic attack in the reaction of pyrimidines with organolithium compounds occurs at position 4 to give adducts, which are easily aromatized to compounds **104** upon the treatment with potassium permanganate or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (Scheme 59, Table 3).[133, 134]

Scheme 59



The nucleophilic attack at position 2 of pyrimidine occurs much more rarely, usually when position 4 is occupied. A series of 2-substituted pyrimidines were synthesized by the reaction of 5-aryl-4,6-dichloropyrimidines using 2,3-dichloro-5,6-dicyanobenzoquinone as the oxidant.[138, 139]

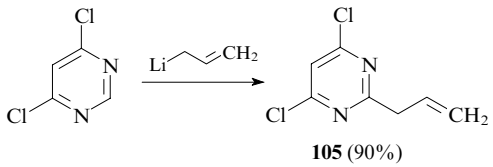
Table 3. (Het)arylation/alkylation products of 1,3-diazines **104** (see Scheme 59).

R^1	R^2	R^3	Yield (%)	Ref.
H	H	Ph	64	133
H	H	4-MeC_6H_4	51	133
H	H	4-$MeOC_6H_4$	45	133
H	H	Mes	25	133
H	H	2,6-$(MeO)_2C_6H_3$	18	133
H	H	2-Th	46	133
H	H	2-Fu	53	133
H	H	Thiazol-2-yl	30	133
H	H	Benzothiazol-2-yl	27	133
Cl	H	Thiazol-2-yl	83	134
SMe	SMe	Me	85	135
SMe	SMe	Bu^n	77	135
SMe	SMe	Ph	83	135
SMe	SMe	2-$MeOC_6H_4$	70	135
SMe	SMe	2-Th	76	135
SMe	SMe	3-Th	76	135
SMe	SMe	Thiazol-2-yl	52	135
Cl	Cl	Bu^i	63	136
SMe	H	4-Biphenyl	85	137
SMe	H	1-Naph	95	137
SMe	Ph	Ph	100	137
Cl	H	Me	84	138

Note. Fu is furyl.

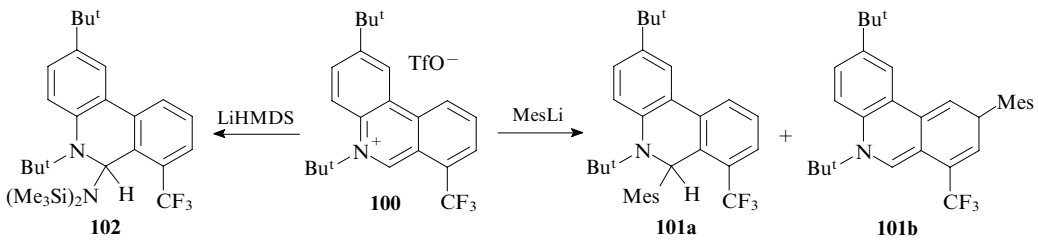
The reaction of 4,6-dichloropyrimidine with allyllithium produces exclusively 2-allyl-substituted pyrimidine **105**, with the chlorine atoms remaining intact in the product (Scheme 60).[140]

Scheme 60

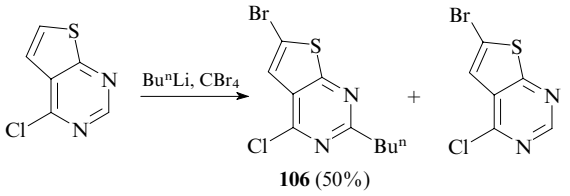


2-Bromo-6-n-butyl-4-chlorothieno[2,3-*d*]pyrimidine (**106**) was obtained as the second product in attempting to brominate 4-chlorothieno[2,3-*d*]pyrimidine with n-butyllithium in tetrabromomethane. The mechanism of the formation of this product was not proposed, but it can be attributable to the direct nucleophilic attack at unsubstituted position 2 of the pyrimidine ring (Scheme 61).[141, 142]

Scheme 57



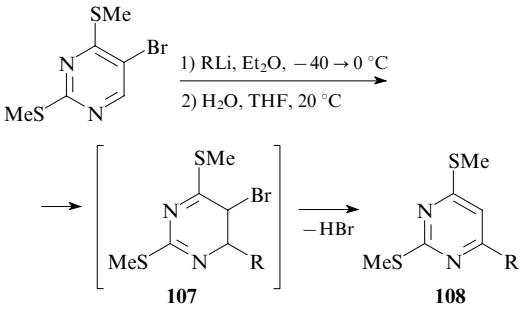
Scheme 61



II.5.b. Auto-aromatization of σ^H-adducts in nucleophilic substitution

The reaction of 5-bromo-2,4-di(methylsulfanyl)pyrimidine with organolithium compounds proceeds *via* the *cine*-substitution mechanism (see Scheme 1, path *b*).[135] In this case, intermediate σ^H-adducts **107** undergo aromatization through the elimination of HBr to form the corresponding pyrimidines **108** (Scheme 62).

Scheme 62



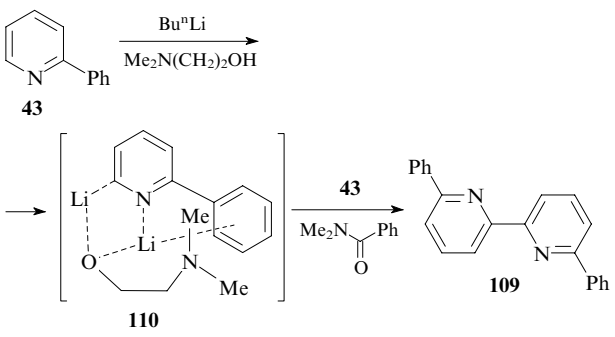
R = Ph (82%), 2-MeOC$_6$H$_4$ (3%), 2-Th (90%), 3-Th (33%), thiazol-2-yl (77%)

II.5.c. Synthesis of bi- and ter(aza)pyridines by di- and trimerization of azines and diazines

In some cases, the reactions of azines and diazines with alkyl- or aryllithium compounds do not afford substitution and addition products; instead they proceed through mediated C-lithiation of the azaheterocycle accompanied by the attack of the lithium heteroaromatic compound on the free heterocyclic molecule to give dimeric homocoupling products.[143] This synthetic approach is often applied to prepare symmetrical 2,2′-bipyridines and their aza analogues.

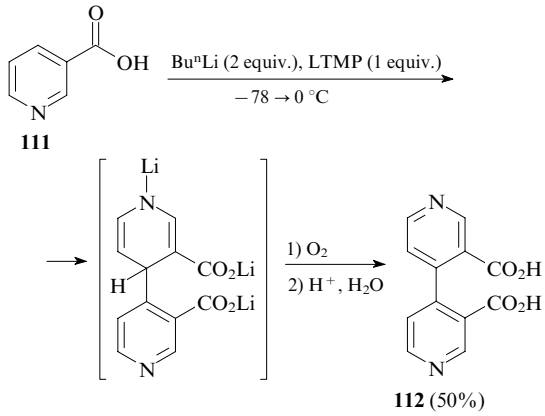
For example, in the presence of *N,N*-dimethylaminoethanol as the chelating reagent, 2-phenylpyridine (**43**) forms dimer **109** in low yield (3.4%). Chandran *et al.*[144] suggested the initial formation of intermediate **110** (Scheme 63).

Scheme 63



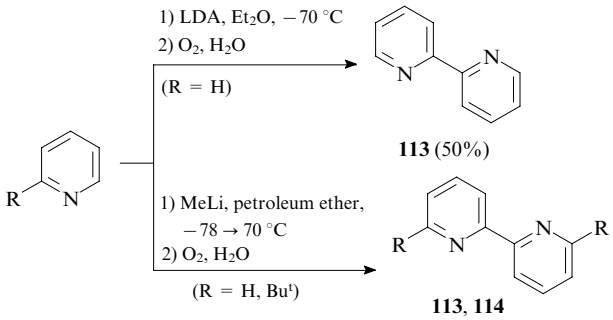
Attempts to deprotonate nicotinic acid (**111**) organolithium reagents [Bu^{n}Li and then lithium 2,2,6,6-tetramethylpiperidide (LTMP)] resulted in the formation of the dimerization product — 4,4′-bipyridine-3,3′-dicarboxylic acid (**112**) (Scheme 64).[145]

Scheme 64



The treatment of pyridine and its 2-*tert*-butyl derivative with lithium diisopropylamide (LDA) and methyllithium gave 2,2′-bipyridines **113** and **114** (Scheme 65).[88,146]

Scheme 65

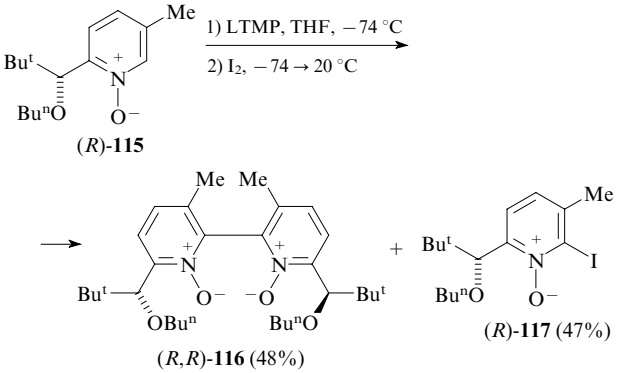


R = H (**113**, 9%), Bu^t (**114**, 30%)

Similarly, the reactions of pyridine, quinoline and isoquinoline with superbases (for example, lithium diisopropylamide) produce 2,2′-dimers in yields of up to 55%.[146]

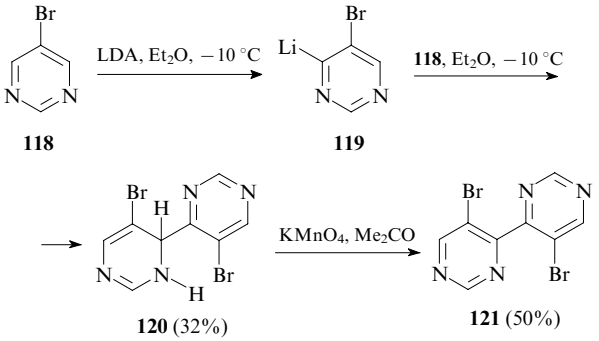
The reaction of pyridine *N*-oxide **115** containing a chiral carbon atom in the substituent at position 2 with lithium 2,2,6,6-tetramethylpiperidide followed by the oxidation with elemental iodine afforded dimerization [(*R*,*R*)-**116**] and iodination [(*R*)-**117**] products (Scheme 66).[120]

Scheme 66



In the presence of lithium diisopropylamide, the reaction of 5-bromopyrimidine (**118**) results in the *in situ* generation of 5-bromo-4-lithiopyrimidine (**119**), which reacts with the second molecule of the starting compound **118**.[147] This gives rise to dimer **120**, which undergoes aromatization to form bipyrimidine **121** (Scheme 67).

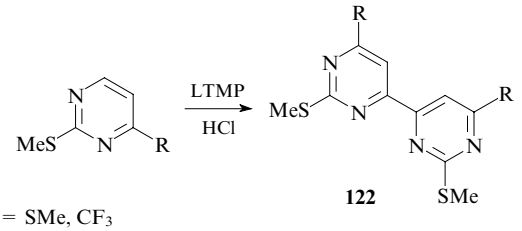
Scheme 67



118 **119** **120** (32%) **121** (50%)

The formation of minor dimeric products **122** was observed also upon lithiation of 2-(methylsulfanyl)-4-(trifluoromethyl)pyrimidine[148,149] or 2,4-di(methylsulfanyl)-pyrimidine (Scheme 68).[150]

Scheme 68



122

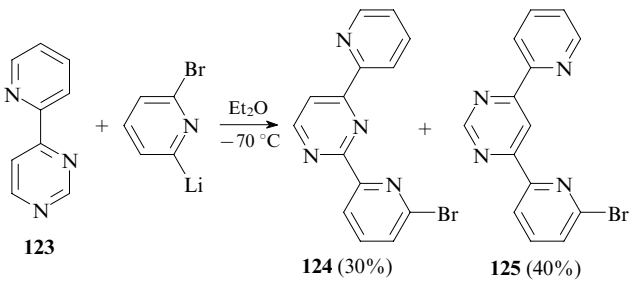
R = SMe, CF_3

The lithiation of 2-chloroquinoxaline produced 2,2′-dichloro-3,3′-biquinoxaline in a yield of up to 59%.[151,152]

The synthesis of a trimer based on 1,3-diazine and pyridine can also be considered in this section.

Like the reaction of pyridines with 2-pyridyllithium reagents giving rise to oligopyridine systems (see Schemes 49 and 50), the reaction of 6-bromo-2-pyridyllithium with 4-(2-pyridyl)pyrimidine (**123**) affords 2,4-bis(2-pyridyl)pyrimidine **124** and 4,6-bis(2-pyridyl)pyrimidine **125**, with the latter being the major product (Scheme 69).[153]

Scheme 69



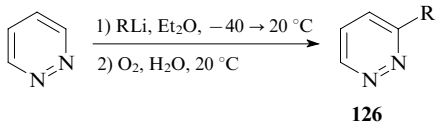
123 **124** (30%) **125** (40%)

II.5.d. 1,2-Diazines

Numerous examples of nucleophilic substitution of hydrogen in pyridazines are given in the review by Pozharskii and Gulevskaya.[154] This section deals with the most interesting reactions of pyridazines with organolithium compounds and reactions described in the literature since the publication of the review.

Unactivated unsubstituted pyridazine reacts with alkyllithium reagents under mild conditions to form 3-substituted pyridazines **126** (Scheme 70).[155] The reaction with *tert*-butyllithium was performed in pentane; other reactions, in diethyl ether.

Scheme 70

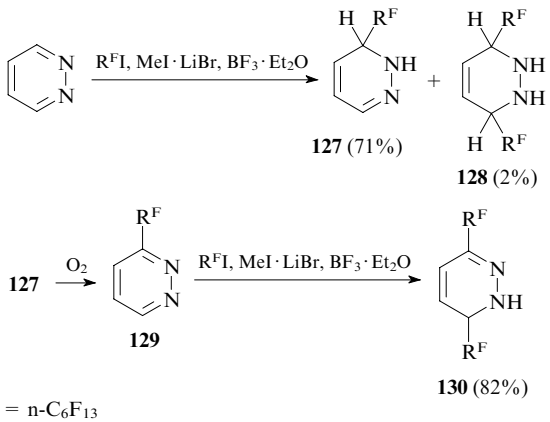


126

R = Bu^n (51%), Ph (17%), Bu^t (65%)

Uno *et al.*[156] developed a procedure for the direct introduction of organic perfuloro moieties into pyridazines. This procedure involves the nucleophilic addition of perfluoroalkyllithium reagents, which are generated *in situ* from perfluoroalkyl iodides and a methyllithium–lithium bromide complex, to activated pyridazine (Scheme 71). Dihydropyridazine adducts **127** (tetrahydropyridazines **128** are by-products) are quantitatively oxidized in air to the corresponding 3-perfluoroalkylpyridazines **129**, which can be again subjected to this reaction to form products **130**.

Scheme 71



127 (71%) **128** (2%) **129** **130** (82%)

R^F = n-C_6F_{13}

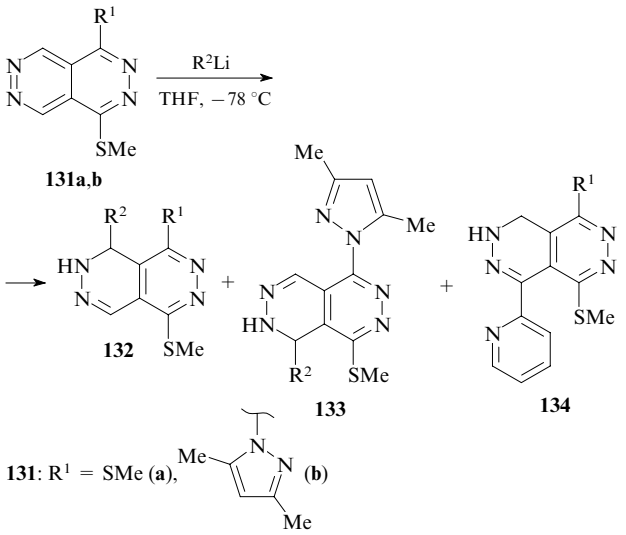
Nagy *et al.*[157] studied annulated bispyridazine — 2,3,6,7-tetraazanaphthalene **131** — as an isosteric analogue of 1,2,4,5-tetrazine (see below). It was shown that, despite the presence of good leaving groups in the azine ring, compounds **131a**,**b** react with alkyl- and (het)aryllithium reagents to form stable addition products **132**–**134**. In the presence of two different substituents in one of the pyridazine rings (compound **131b**), the addition products at the unsubstituted carbon atom in the second ring are generated with moderate regioselectivity (Scheme 72).

The reactions of phthalazines **135a**,**b** with methyllithium proceed in a similar way to give addition products **136a**,**b** (Scheme 73).[158]

In the presence of trimethylchlorosilane, pyridazine-containing complexes of the composition [{μ-(pyridazine-N^1:N^2)}Fe_2(μ-CO)$(CO)_6$] react with aryllithium reagents to

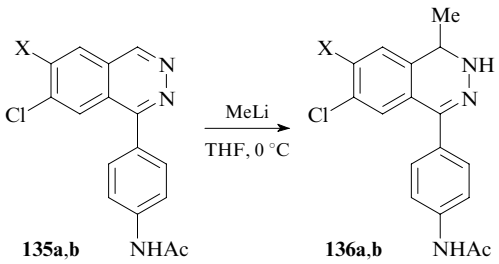
form siloxycarbene metal complexes **137**.[159] The annulation of the benzene ring leads apparently to an increase in the electrophilicity of the pyridazine ring and(or) a decrease in steric accessibility of the carbonyl group.

Scheme 72



R^2Li	Products [yield (%)]	
	from substrate **131a**	from substrate **131b**
PhLi	**132** (91)	**132** (35) + **133** (11)
Bu^nLi	**132** (65)	**132** (18) + **133** (9)
Bu^nCuLiI	**132** (61)	0
4-$MeOC_6H_4Li$	**132** (43)	**132** (18)
2-$MeOC_6H_4Li$	**132** (51)	**132** (46) + **133** (19)
1-NaphLi	**132** (52)	**132** (45)
2-NaphLi	**132** (33)	**132** (74)
2-ThLi	**132** (90)	**132** (45)
2-PyLi	**134** (18)	**132** (11) + **133** (35)
PhLi + TMEDA	0	**132** (36)

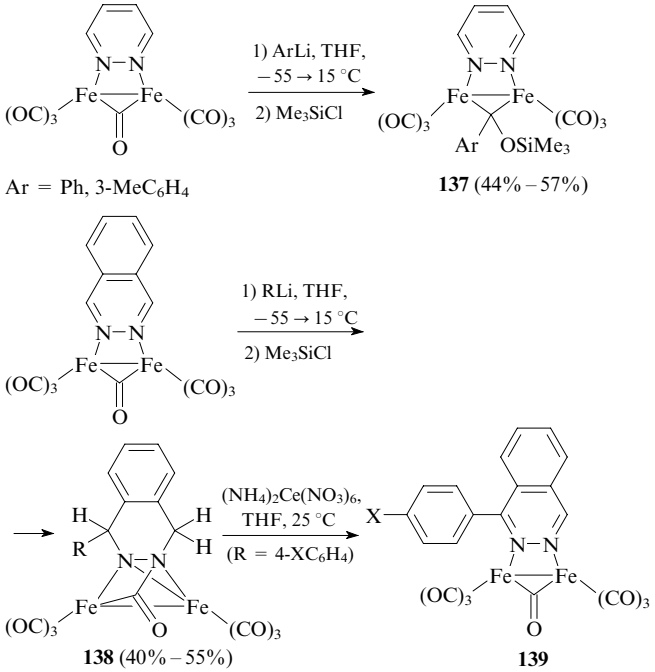
Scheme 73



X = H (**a**, 51%), Cl (**b**, 58%)

The reactions of the related metal complex [{μ-(phthalazine-N^2:N^3)}Fe_2(μ-CO)$(CO)_6$] with aliphatic and aromatic organolithium compounds produce stable σ-adducts **138**. These reactions give rise to a diiron carbonyl complex with a radically new arrangement of the μ-CO group, which is no more bridging; besides, new C–N bonds are formed. Aromatization of complexes **138** affords S_N^H-products **139** (Scheme 74).[160]

Scheme 74



138: R = Me, 4-XC_6H_4 (X = H, Me, OMe, CF_3, Ph);
139: X = Me (38%), OMe (31%)

II.5.e. 1,4-Diazines

In most cases, the reactions of 1,4-diazines — pyrazines — with alkyl- and aryllithium derivatives proceed *via* the usual pathways with the nucleophilic addition at position 2 of pyrazine. It should be noted that the nucleophilic *tele*-substitution giving products **140** and **141** occurs in 2,3- and 2,6-dichloropyrazines upon the treatment with lithiodithiane (Scheme 75).[161]

Scheme 75

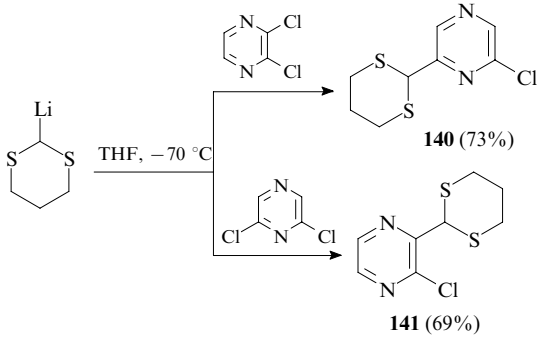


Table 4 gives examples of such reactions performed in recent years.

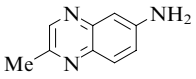
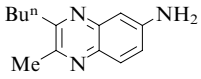
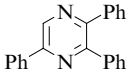
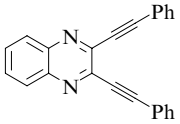
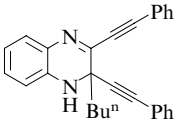
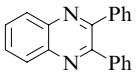
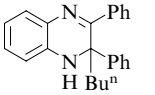
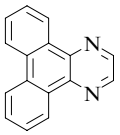
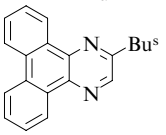
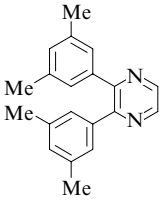
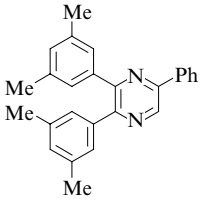
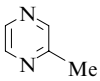
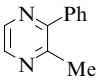
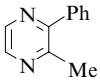
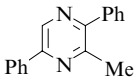
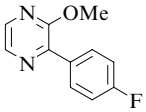
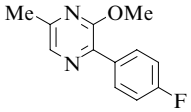
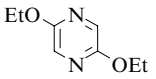
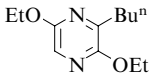
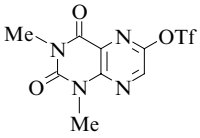
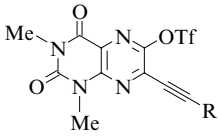
II.6. Reactions of triazines

II.6.a. 1,3,5-Triazines

Reactions of triazines with organolithium compounds are much more rare in the literature. Therefore, it is expedient to list all these reactions in the present review.

Due to the symmetrically arranged nitrogen atoms of the pyridine type, *sym*-triazine **142a** (R^1 = H, X = N, Y = CH) can be subjected to nucleophilic attack at each

Table 4. Reactions of pyrazines with organolithium compounds.

Azine	RLi	Product	Oxidant	Yield (%)	Ref.
	Bu^nLi		MnO_2	75	162
	PhLi		MnO_2	56	163 – 165
	Bu^nLi		–	23	166
	Bu^nLi		–	81	167, 168
	Bu^sLi		MnO_2	31	169
	PhLi		MnO_2	26	170
	PhLi		–	22	171
	PhLi		–	12	165
	MeLi		–	15	172
	Bu^nLi		Air	75	173
	R—≡—Li (R = H, Ph)		CuI (catalyst)	40 – 72	174

carbon atom in the ring to form addition products — stable σ^H-adducts **143** (Scheme 76, path *a*).[175, 176]

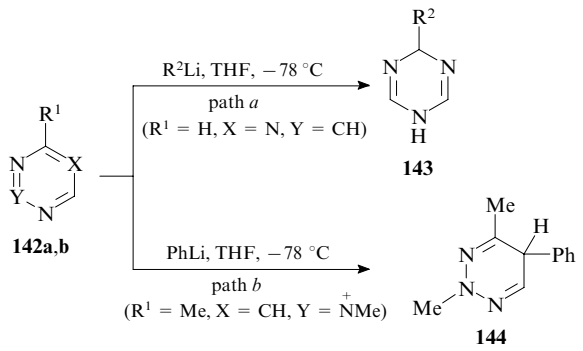
II.6.b. 1,2,3-Triazines

Apart from azaphilic addition products at the N(2) atom or the transformation products of the triazine ring resulting from the N(2)- or C(4)-nucleophilic attack, the reaction of 2,4-dimethyl-1,2,3-triazine **142b** (R^1 = Me, X = CH, Y = N^+Me) with phenyllithium gives 5-phenyl-2,5-dihydro-1,2,3-triazine **144** — the nucleophilic addition product at the C(5) atom (see Scheme 76, path *b*).[177] No other examples of S_N^H reactions with 1,2,3-triazines were found in the literature.

II.6.c. 1,2,4-Triazines

As opposed to 1,3,5-triazines, the C(5) atom in 1,2,4-triazines and their N-oxides containing a good leaving group or an unsubstituted carbon atom at position 5 of the ring is most reactive towards nucleophilic attack.

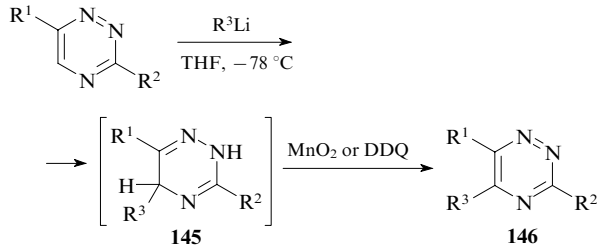
Scheme 76

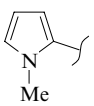


R^2	Yield of **143** (%)	Ref.
Me_3SiCH_2	76	175
Bu^n	60	175, 176
Me	37	175, 176
Bu^t	57	175
$(Me_3Si)_2CH$	80	175, 176
Ph	24	175, 176

Thus, the reactions of 3-methyl- or 3-methylsulfanyl-1,2,4-triazines with (het)aryl- or alkyllithium derivatives afford adducts **145**, which can be subjected to aromatization with a soft oxidant (MnO_2 or DDQ) to form 3-methyl- or 3-methylsulfanyl-5-R-1,2,4-triazines **146** (Scheme 77).[178–180] In some cases, the yield of compounds **146** can be increased to 66%–70% using an excess of an oxidant (for example, up to 10 equiv. of MnO_2).[178]

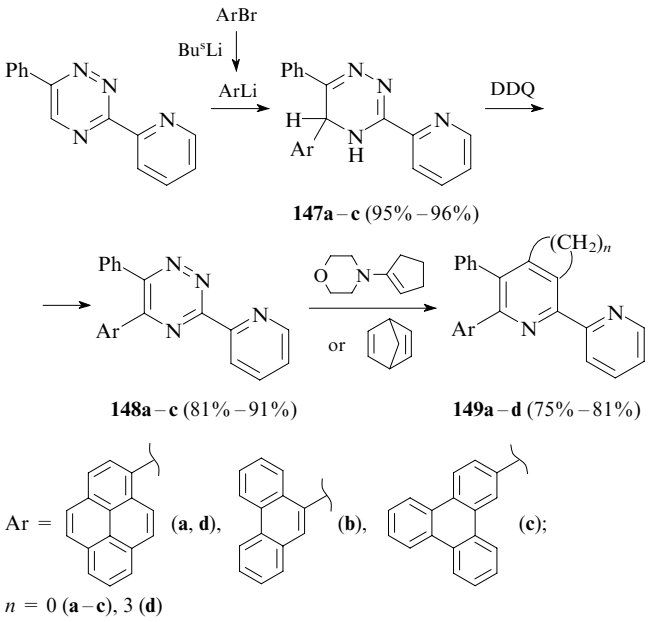
Scheme 77



R^1	R^2	R^3	Yield (%)	Ref.
H	SMe	2-Py	70	178
H	SMe	2-Fu	66	178
H	SMe	Ph	60	178
Ph	SMe	Pr^i	26	179
Ph	Me		29	180

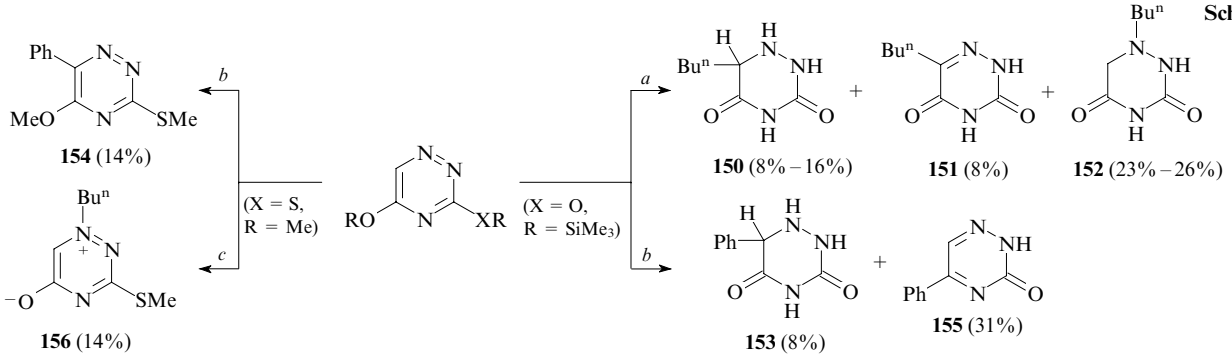
The transformation of the 1,2,4-triazine ring into the pyridine moiety is a well-known synthetic approach to various pyridine derivatives, including 2,2′-bipyridines.[181–185] On the other hand, pyridine is less susceptible to aryllithium reagents. Kovalev *et al.*[186] developed a facile synthetic approach to new photoluminescent ligands of the 2,2′-bipyridine series containing fragments of polynuclear aromatic compounds at position 5. Thus, stable σ-adducts **147a–c** were prepared by the reaction of 6-phenyl-3-(2-pyridyl)-1,2,4-triazine with lithium derivatives of polyaromatic compounds, which were generated *in situ* upon the treatment of appropriate bromoarenes with Bu^sLi. The aromatization of these σ-adducts with DDQ gave 5-aryl-3-(2-pyridyl)-1,2,4-triazines **148a–c**. The subsequent aza-Dields–Alder reaction of products **148a–c** with 1-morpholinocyclopentene produced target 2,2′-bipyridines **149a–c** (Scheme 78). In the reaction with compound **148a**, 2,5-norbornadiene (product **149d**) was also used as a dienophile.

Scheme 78



The reactions of 3,5-disubstituted 1,2,4-triazines with organolithium reagents can afford substitution products at the C(5) or C(6) atom depending on the nature of substituents at position 5. n-Butyllithium, being a weaker nucleophile, gives C(6)-addition (**150**, **151**) and N(1)-alkylation (**152**) products (Scheme 79).[187] The reaction with phenyllithium involves the competitive substitution of hydrogen at position 6 to form addition (**153**) or substitution (**154**)

Scheme 79

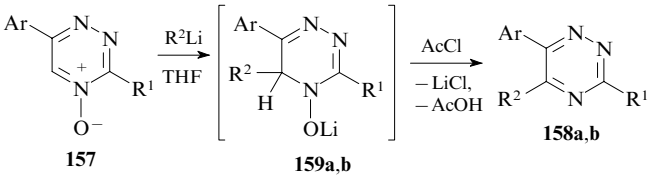


(*a*) Bu^nLi, THF, −100 °C; (*b*) PhLi, $B(OEt)_3$, THF, −100 °C; (*c*) Bu^nLi, $B(OEt)_3$, THF, −100 °C

products, as well as the substitution at position 5 of the triazine ring to form product **155**, provided that there is a good leaving group (trimethylsilyloxy). It should be noted that the reaction of 5-methoxy-3-methylsulfanyl-1,2,4-triazine with n-butyllithium yields exclusively zwitterion **156**.

The reactions of lithium derivatives of arenes and hetarenes with 1,2,4-triazine 4-oxides **157** also proceed *via* nucleophilic substitution of hydrogen giving 5-(het)aryl-1,2,4-triazines **158**a,**b** (Scheme 80).[188] The reaction takes place in the presence of the acylating agent (acetyl chloride). Therefore, σ^H-adducts **159a**,**b** undergo aromatization *via* elimination of acetic acid.

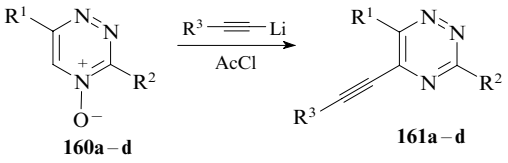
Scheme 80



R^1 = 4-ClC_6H_4, Ar = R^2 = Ph (**a**, 65%);
Ar = 4-ClC_6H_4, R^1 = Ph, R^2 = 2-Py (**b**, 30%)

Under similar conditions, triazine *N*-oxides **160a**–**d** react with lithium derivatives of acetylenes as nucleophiles to form 5-alkynyl-1,2,4-triazines **161a**–**d**, which can be considered as an alternative to the Sonogashira cross-coupling reaction (Scheme 81).[189, 190]

Scheme 81

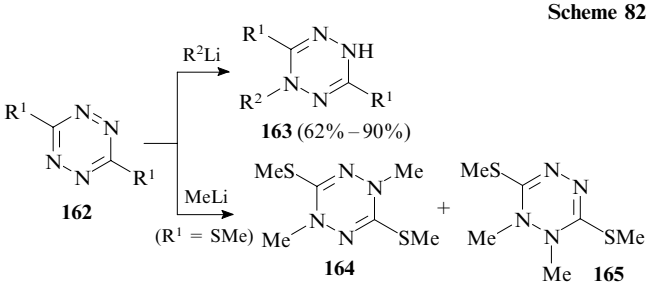


R^1 = 4-MeC_6H_4: R^2 = 2-Py, R^3 = $SiMe_3$ (**a**, 43%); R^2 = H, R^3 = Ph (**b**, 65%); R^1 = R^2 = R^3 = Ph (**c**, 70%); R^1 = Ph, R^2 = R^3 = 4-MeC_6H_4 (**d**, 63%)

II.7. Reactions of tetrazines

No examples of reactions of 1,2,3,4-tetrazines and 1,2,3,5-tetrazines with organolithium reagents were found in the literature. 1,2,4,5-Tetrazines **162** are the most commonly used representatives of tetrazines. Reactions of azines **162** with organolithium compounds (Scheme 82) as hard nucleophiles give predominantly products of the so-called azaphilic addition — alkylation or arylation at one (products **163**) or two nitrogen atoms in the ring (compounds **164** and **165**).[191]

Scheme 82



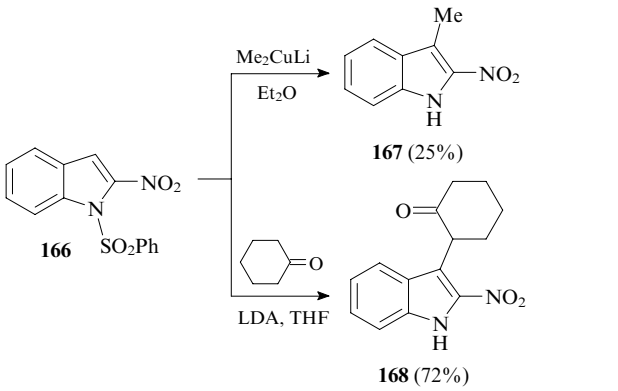
R^1 = 3-Py, 3,5-dimethylpyrazol-1-yl, SMe; R^2 = Me, Bu^n, Ph

II.8. Reactions of five-membered azaheterocycles

Five-membered azaheterocycles are highly aromatic compounds due to which they are prone to electrophilic substitution. Meanwhile, nucleophilic substitution or addition reactions with monoheteroatomic derivatives (furan, thiophene, pyrrole) are difficult to initiate. Therefore, in order to increase the electrophilicity of the five-membered ring, it is necessary to introduce additional electron-withdrawing groups, for example, the pyridine nitrogen atom or a nitro group.

Thus, the methylation of 1-benzenesulfonyl-2-nitroindole (**166**) with lithium dimethylcuprate proceeds *via* the *tele*-substitution mechanism to form 3-methylindole **167** and is accompanied by elimination of the benzenesulfonyl group (Scheme 83).[192] The reaction of the *in situ* generated lithium derivative of cyclohexanone with 2-nitroindole **166** results in the substitution of hydrogen giving product **168**.[193]

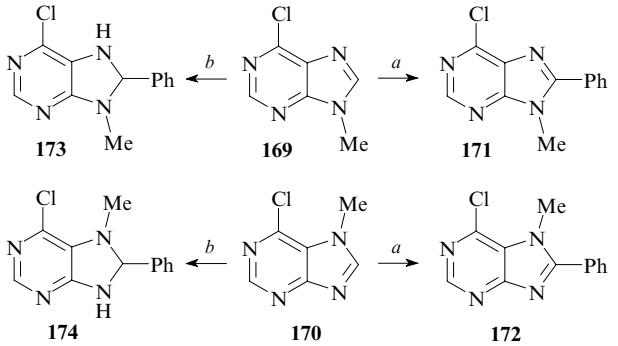
Scheme 83



Under the conditions of the reaction of synthetic purine analogues with organolithium reagents, the imidazole ring is more susceptible to nucleophilic attack than, for example, the diazine ring. For instance, *N*-methyl-6-chloropurines **169** and **170** react with phenyllithium in the presence of tris(dibenzoylmethide)iron [$Fe(DBM)_3$]

s the oxidant to form exclusively 8-phenylpurines **171** and **172**. In the absence of the oxidant, the reaction proceeds *via* a stepwise mechanism, and intermediate dihydropurines **173** and **174** can be isolated in the individual state (Scheme 84).[193]

Scheme 84



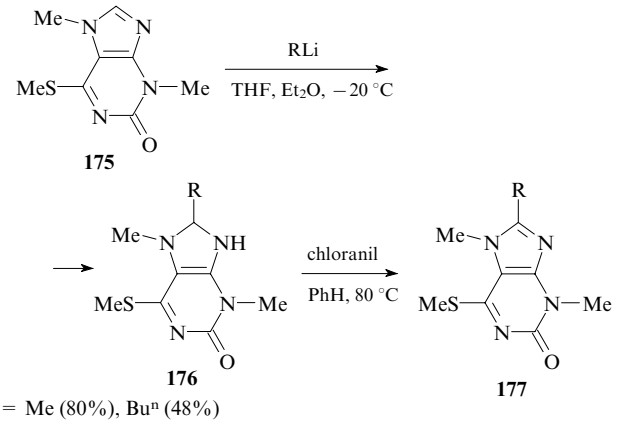
(*a*) PhLi, $Fe(DBM)_2$, THF, −25 → 25 °C; (*b*) PhLi, THF, −25 → 25 °C

6-Chloro-9-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)purine reacts with n-butyllithium in a similar way to form the corresponding 8-butyl-substituted purine nucleoside.[194]

The reactions of 3,7-dimethyl-6-methylsulfanyl-2-oxopurine (**175**) with alkyllithium reagents afford 8-substituted

purines **176** and **177**. As in the transformations shown in Scheme 84, the leaving groups in the azine ring are not replaced (Scheme 85).[195]

Scheme 85

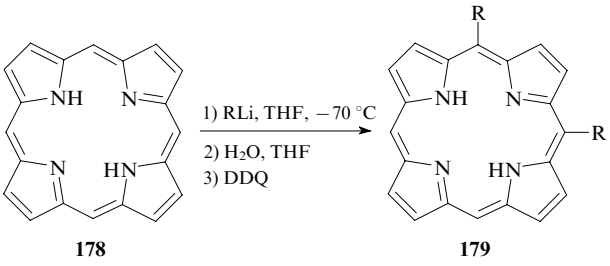


R = Me (80%), Bu^n (48%)

II.9. Reactions of porphyrins

Being aromatic compounds, porphyrins are prone to nucleophilic substitution of hydrogen upon the treatment with such nucleophiles as organolithium compounds.[196–208] The reaction occurs at the *meso* position of the porphyrin ring. For example, unsubstituted porphyrin **178** readily reacts with phenyl- and n-heptyllithium to form 2,10-diphenyl- or di-n-heptylporphyrins **179** (Scheme 86).[204] In this case, the reaction products were obtained in yields much higher compared with the conventional assembly of the porphyrin ring from pyrrole or tripyrrolylmethane and the appropriate aldehydes.[199]

Scheme 86



R = n-C_7H_{15} (61%), Ph (74%)

The sequence of reactions performed by Feng *et al.*[203] as applied to octaethylporphyrin **180a** involves the addition of the organolithium compound (n-butyllithium), hydrolysis of adduct **181a** and oxidation of porphodimethene **182a** using DDQ (Scheme 87). The total yield of *meso*-substituted porphyrin **183a** is 50%.

This approach was used to prepare a large series of *meso*-substituted octaethylporphyrins **183**, the reaction being possible for both free porphyrins and their complexes with metals (Scheme 88, Table 5).[201,205,206,209] The yield of substitution products depends on the nature of the organolithium nucleophile. For example, the reactions with the use of n-butyl- or *sec*-butyllithium as the nucleophile afford the *meso*-substituted products in 50% and 11% yields, respectively, while the reactions with *tert*-butyllithium or isopropyllithium do not proceed.[209]

Table 5. Products generated by the reactions of octaethylporphyrin and its metal complexes with organolithium compounds (see Scheme 88).

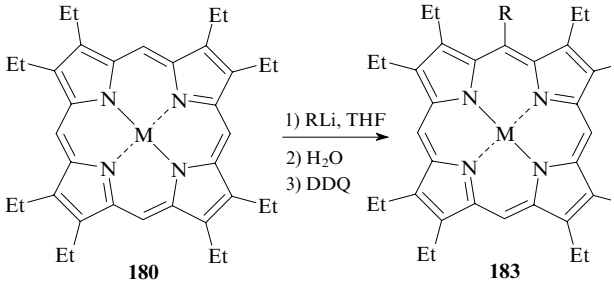
M	RLi	Yield of **183** (%)	Ref.
2 H	Bu^{n}Li	50	210
2 H	MeLi	39	211
2 H	Bu^{s}Li	11	212
2 H	HC≡C(CH$_2$)$_3$Li	48	205
2 H	PhLi	90, 100	205, 210
2 H	4-H$_2$NC$_6$H$_4$Li	72	205
2 H	4-BrC$_6$H$_4$Li	56	205
2 H	4-(HC≡C)C$_6$H$_4$Li	72	205
Ni	Bu^{n}Li	28	209
Ni	Bu^{s}Li	82	209
Zn	Bu^{n}Li	40	210
Cu	Bu^{n}Li	75	210
Co	Bu^{n}Li	40	210
Ni	1,3-Dioxan-2-yllithium	70	210
Ni	HC≡C(CH$_2$)$_3$Li	65	205
Ni	PhLi	65	210
Ni	4-BrC$_6$H$_4$Li	40	210
Ni	4-H$_2$NC$_6$H$_4$Li	59	205
Ni	2,5-Me$_2$C$_6$H$_3$Li	65	210

Compounds with a substituent at one of the porphyrin *meso* positions (compounds **184**) give 5,10- and 5,15-regioisomers **185** and **186** (Scheme 89, Table 6).

Tetrabenzoporphyrins **187** react with RLi in a similar way to form products **188** and **189** (Scheme 90).[205]

Under these conditions, the reactions of organolithium compounds with 5,15-disubstituted porphyrins **190**, both in

Scheme 88



Scheme 87

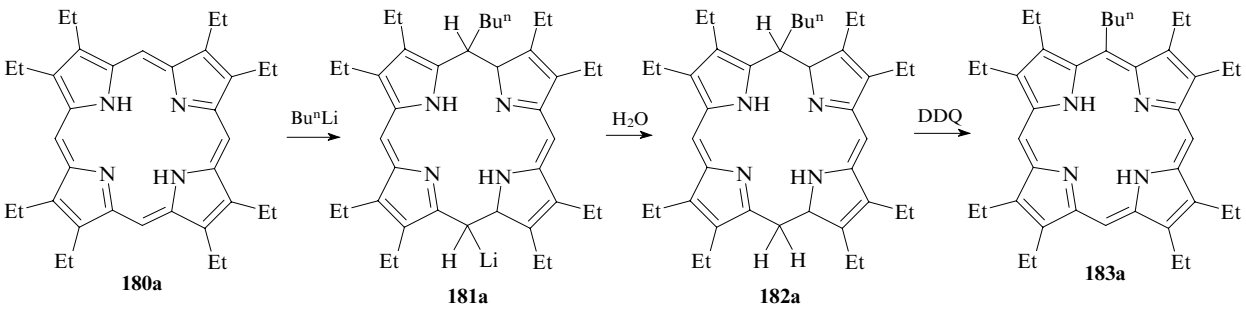
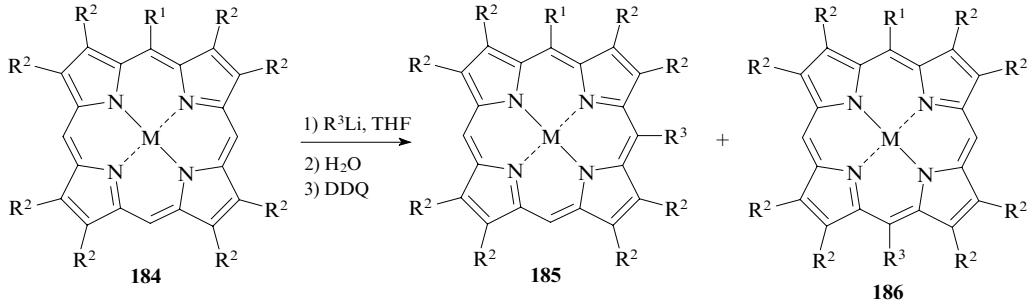


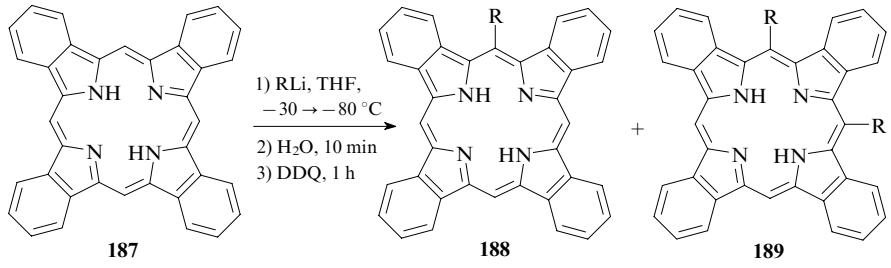
Table 6. Products generated by the reactions of *meso*-substituted porphyrins and their metal complexes with organolithium compounds (see Scheme 89).

Starting porphyrin			R^3Li	Yield (%)		Ref.
M	R^1	R^2		**185**	**186**	
2 H	Ph	Et	PhLi	84	3	209
2 H	Ph	Et	4-(HC≡C)C_6H_4Li	61	0	205
2 H	4-(HC≡C)C_6H_4	Et	4-(HC≡C)C_6H_4Li	65	0	205
Ni	Bu^n	Et	Bu^nLi	24	14	209
Ni	Ph	Et	Bu^nLi	71	14	209
Ni	Ph	Et	PhLi	97	0	209
Zn	Ph	Et	PhLi	90	0	209
2 H	Pent-3-yl	H	PhLi	69	0	213
2 H	Pent-3-yl	H	n-C_6H_{13}Li	59	0	213
2 H	4-$MeOC_6H_4$	H	n-C_6H_{13}Li	32	11	213
2 H	Bu^t	H	PhLi	7	17	213

Scheme 89

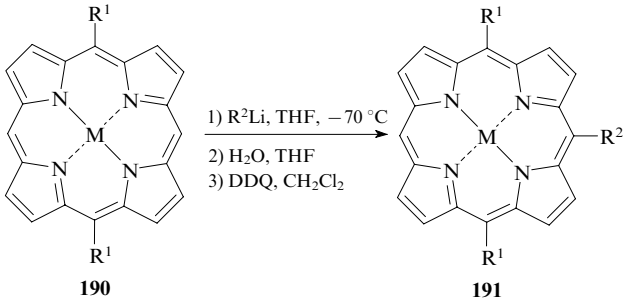


Scheme 90



R	Yield (%)	
	188	**189**
Bu^n	43	13
n-C_6H_{13}	38	9

Scheme 91



the form of free bases and as complexes with nickel, proceed *via* the substitution of hydrogen at position 10 of the porphyrin ring to yield 5,10,15-trisubstituted products **191** (Scheme 91, Table 7).[197, 200, 202, 207, 208, 214]

In the case when the oxidation with DDQ is performed immediately after the addition of an organolithium compound, without the hydrolysis step, the reaction proceeds *via* another pathway. Thus, the nucleophilic substitution of hydrogen is accompanied by dimerization to biporphyrins **192** (Scheme 92).[197, 200, 215]

Heteroaromatic substituents in the porphyrin ring can act as additional coordinating moieties for organolithium reagents. For example, the direct *meso*-alkynylation of β,β′-dipyridylporphyrins **193** with alkynyllithium derivatives leads to the coordination of β,β′-dipyridyl substituents to the organolithium reagent and intensification of the nucleophilic attack at the porphyrin *meso* position to give products **194**. The substitution and addition products at the pyridine rings are not formed (Scheme 93).[216]

III. Direct introduction of heterooragnic moieties into (het)arenes involving *in situ* generated lithium derivatives

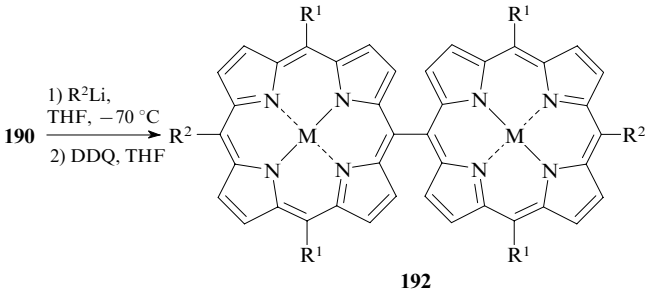
III.1. Reactions with carboranes

In the previous sections, it was shown that the complexes (η^6-arene)$Cr(CO)_3$ react with aliphatic and aromatic lithium reagents *via* the addition and substitution of hydrogen in the aromatic ring. There are a few examples of the use of lithium derivatives of carboranes in these reactions. For example, the chromium complex of 1,2-dichlorobenzene **195a** reacts with 1-lithio-2-methylcarborane **196a** (Scheme 94; B atoms are shown as unlabelled vertices of

Table 7. Products generated by the reactions of di-*meso*-substituted porphyrins and their metal complexes with organolithium compounds (see Scheme 91).

M	R^1	R^2	Yield of **191** (%)	Ref.
2 H	Bu^n	PhLi	74	200
2 H	Ph	Pr^iLi	30	200
2 H	Ph	Bu^nLi	94	200
2 H	Ph	Bu^sLi	15	200
2 H	Ph	PhLi	89	200
2 H	Ph	4-$H_2NC_6H_4Li$	82	202
2 H	Ph	4-$Me_2NC_6H_4Li$	78	202
2 H	Ph	4-HOC_6H_4Li	75	202
2 H	Ph	3-HOC_6H_4Li	30	202
2 H	Ph	3-$MeOC_6H_4Li$	83	202
2 H	Ph	4-(1,3-Dioxolan-2-yl)-phenyllithium	86	202
2 H	Ph	4-(HC≡C)C_6H_4Li	85	202
2 H	Ph	3-$Me_2NC_6H_4Li$	75	202
Ni	Ph	1,3-Dioxan-2-yllithium	73	202
Ni	Bu^n	PhLi	95	200
Ni	Ph	Pr^iLi	52	200
Ni	Ph	Bu^sLi	65	200
Ni	Ph	Bu^tLi	53	200
Ni	Ph	PhLi	92	200
Ni	4-MeC_6H_4	n-$C_6H_{13}Li$	92	210

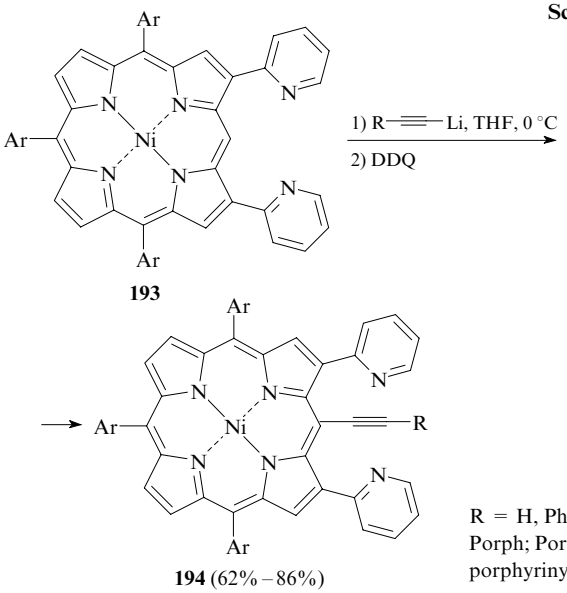
Scheme 92



192

R^1 = Bu^n, R^2 = Ph (55%); R^1 = Ph: R^2 = Bu^n (75%), Ph (79%); M = 2 H, Zn, Ni

Scheme 93



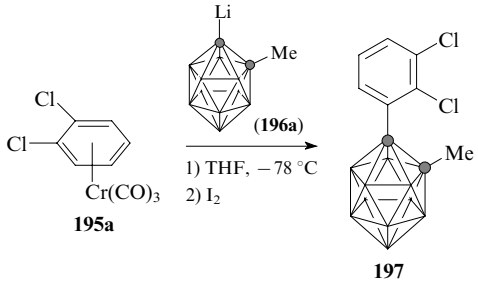
193

194 (62%–86%)

R = H, Ph, $SiMe_3$, Porph; Porph is porphyrinyl

the dodecahedron, and C atoms are indicated by grey circles).[217] The subsequent aromatization of the adduct with elemental iodine affords 1-(2,3-dichlorophenyl)-2-methyl-*ortho*-carborane **197**. The reaction was unexpectedly accompanied by the substitution of hydrogen rather than chlorine.

Scheme 94

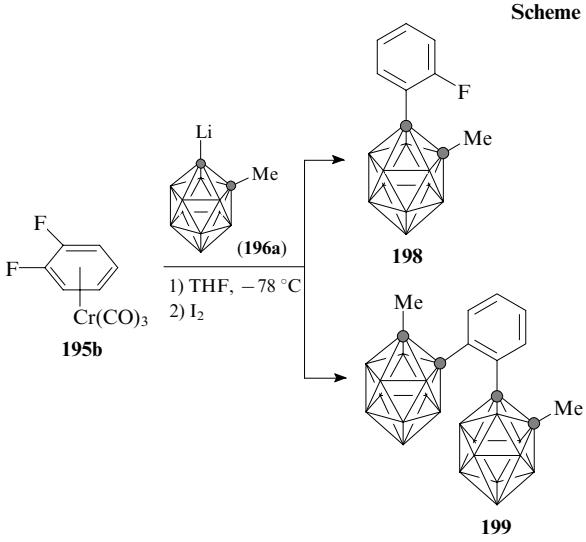


195a

197

Meanwhile, in the reaction of the related compound containing fluorine atoms instead of chlorine (compound **195b**), the expected substitution of fluorine takes place to form mono- (**198**) or disubstituted (**199**) products (Scheme 95).

Scheme 95



195b

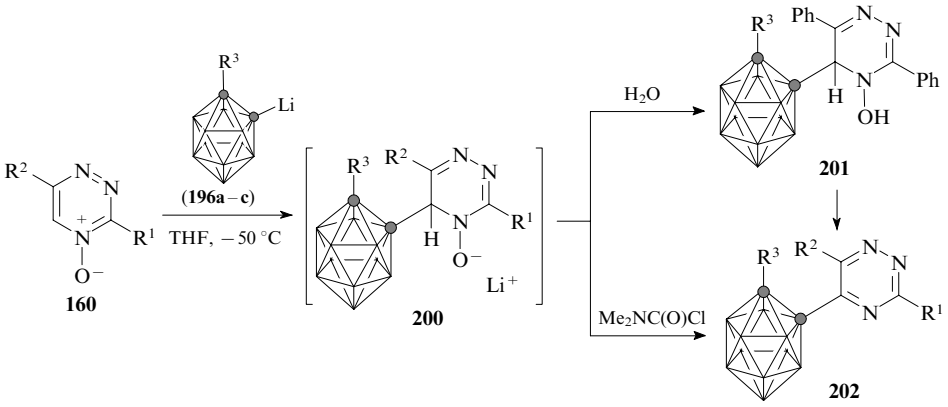
198

199

The direct introduction of a fragment of an organoboron compound giving rise to a new C–C bond was described in the literature.[218–220] 1,2,4-Triazine 4-oxides **160** were found to easily react with 1-lithio-*ortho*-carborane (**196b**), 1-lithio-2-phenyl-*ortho*-carborane (**196c**) and 1-lithio-2-methyl-*ortho*-carborane (**196a**) in tetrahydrofuran at low temperatures to give σ^H-adducts **200**, which can be isolated in the free state. For example, the treatment of the reaction mixture with water produced 1-(4-hydroxy-3,6-diphenyl-4,5-dihydro-1,2,4-triazin-5-yl)-2-phenyl-1,2-dicarba-*closo*-dodecaborane (**201**), which was characterized by spectroscopic methods. However, these compounds are usually unstable and easily undergo aromatization accompanied by elimination of a water molecule and the formation of 1,2,4-triazinylcarboranes **202** (Scheme 96).

The aromatization occurs even more easily with the use of mild acylating agents, such as dimethylcarbamoyl chloride and acetic anhydride. In these reactions, σ^H-adducts were not isolated and the acylating agent was added directly to the reaction mixture. It should be noted that the lithiation of unsubstituted carborane occurs without stereochemical control of the possible formation of dilithiocarborane *via* lithiation of both carbon atoms in the carborane

Scheme 96

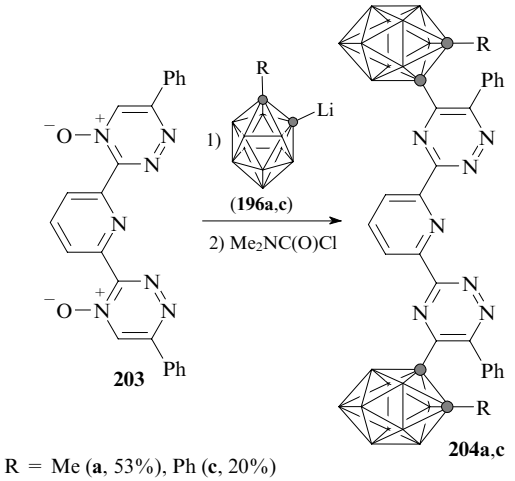


R^1	R^2	R^3	Yield of **202** (%)
Ph	Ph	H	40
Ph	Ph	Ph	37
4-MeC_6H_4	4-MeC_6H_4	Ph	39
Ph	4-MeC_6H_4	Ph	21
Ph	2-Py	Me	48
Ph	2-Py	Ph	56

ring. However, only monotriazinylcarborane **202** was isolated from the reaction mixture.

Under these conditions, 2,6-bis(1,2,4-triazinyl)pyridine di-*N*-oxide **203** easily reacts with lithio-*ortho*-carboranes to produce 2,6-bis[5-(2-R-1,2-dicarba-*closo*-dodecaboran-1-yl)-6-phenyl-1,2,4-triazin-3-yl]pyridines **204** (Scheme 97).[220]

Scheme 97



R = Me (**a**, 53%), Ph (**c**, 20%)

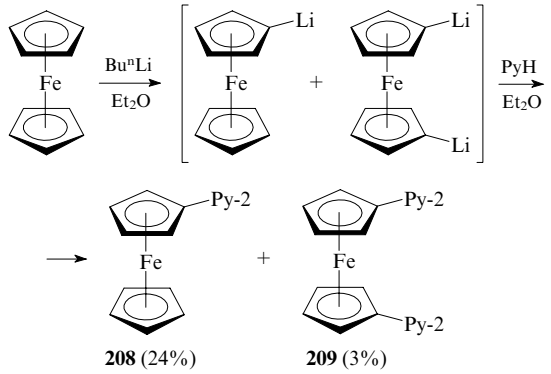
The reaction of the C-lithium derivative of unsubstituted *meta*-carborane as a nucleophile proceeds in a similar way.[220] Thus, the reaction of 1,2,4-triazine 4-oxide **205a** with monolithiated *meta*-carborane, taken in equivalent amounts, followed by the treatment of the reaction mixture with acetic anhydride gives 1-(3,6-diphenyl-1,2,4-triazin-5-yl)-1,7-dicarba-*closo*-dodecaborane **206** (Scheme 98). The use of a twofold excess of *tert*-butyllithium with respect to 1,2,4-triazine 4-oxide **205b** and subsequent treatment of the reaction mixture with dimethylcarbamoyl chloride results on the synthesis of 1,7-bis(triazinyl)-*meta*-carborane **207**.

III.2. Reactions with ferrocenes

The synthesis and chemical transformations of ferrocenes were considered in detail in the review paper.[221] This section describes the most interesting examples of the reactions of (di)lithioferrocenes with azines.

Thus, the reaction of a mixture of lithio- and dilithio-substituted ferrocenes with pyridine in diethyl ether gives 2-pyridylferrocene (**208**) and 1,1′-bis(2-pyridyl)ferrocene (**209**) as a by-product (Scheme 99).[222, 223] The mixture is easily separated by chromatography on alumina.

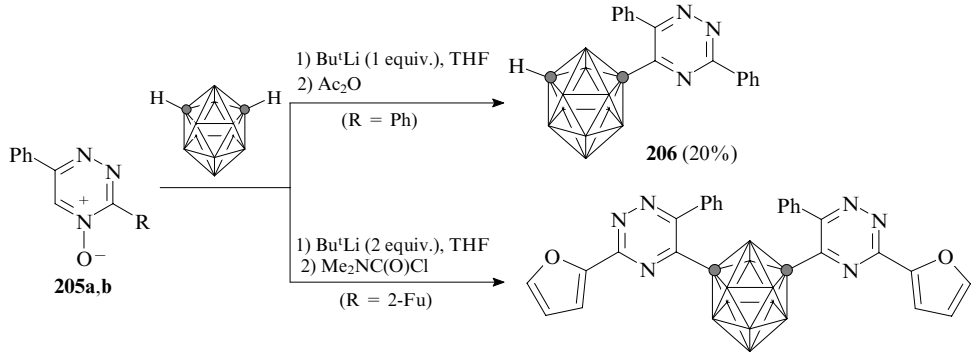
Scheme 99



Quinolinylferrocenes were synthesized in a similar way.[223, 224]

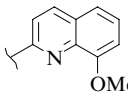
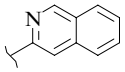
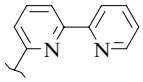
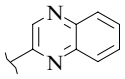
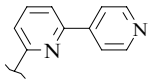
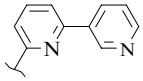
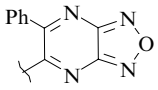
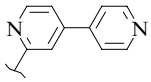
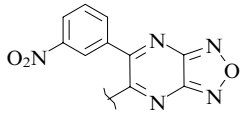
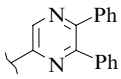
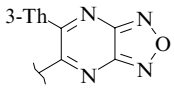
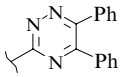
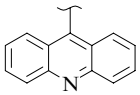
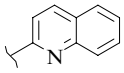
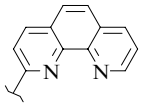
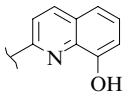
The reactions of ferrocenyllithium with 2,2′-, 2,3′-, 2,4′- and 4,4′-bipyridines, as well as with 1,10-phenanthroline in diethyl ether at 18 °C afford the corresponding monosubstituted ferrocene derivatives.[225, 226]

Scheme 98



R = Ph (**a**), 2-Fu (**b**)

Table 8. Products generated by the reaction of azines with ferrocenyllithium (see Scheme 100).

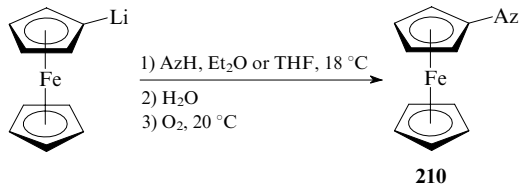
Azinyl (Az)	Yield (%)	Ref.	Azinyl (Az)	Yield (%)	Ref.
	24 32 45	222 223 227		70	227
	27	223		50	227
	40 62	225 227		54	227
	25	225			
	30	225		75	228
	22	225		70	228
	60	227			
	56	227		60	228
	47	227		68	227
	21 3	222 223		35 68	225 227
	58 45	226 227			

It was also shown that other mono-, di- and triazines (AzH) react with ferrocenyllithium in THF without additional activation to furnish S_N^H-products **210** in rather high yields (Scheme 100, Table 8).

Under these conditions, the reactions of dilithioferrocene stabilized by TMEDA with appropriate azines produce 1,1′-bis[6-(2,2′-dipyridyl)]ferrocene in 20% yield and 1,1′-bis[2-(1,10-phenanthrolyl)]ferrocene in 14% yield.[225]

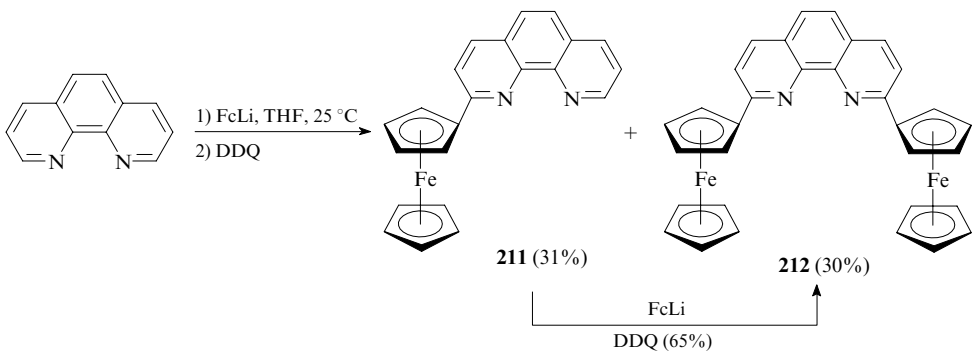
1,10-Phenanthroline reacts with ferrocenyllithium (FcLi) to form 2-ferrocenyl-1,10-phenanthroline (**211**) and(or) 2,9-bis(ferrocenyl)-1,10-phenanthroline (**212**). The latter was synthesized in 30% yield directly from unsubstituted 1,10-phenanthroline using a threefold excess of ferrocenyllithium in the presence of DDQ (this reaction also gives compound **211** in 31% yield), and the yield can reach 65% in the reaction of monosubstituted product **211** with an excess of ferrocenyllithium (Scheme 101).[229]

Scheme 100



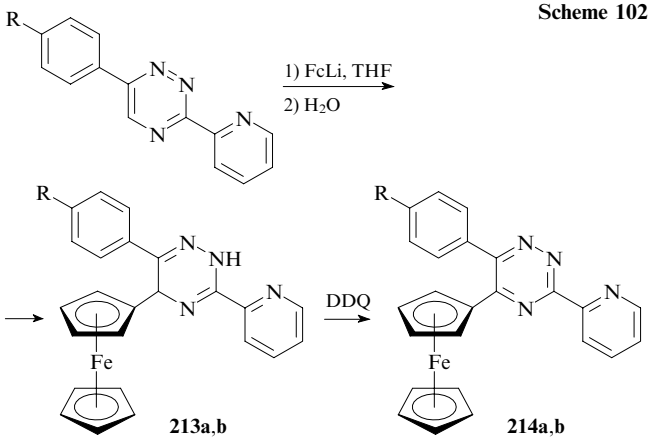
210

Scheme 101



In the reaction with the use of 1,2,4-triazines as substrates for nucleophilic attack of the lithium derivative on ferrocene, intermediate σ^H-adducts **213** were isolated in the individual state (yields 75%–76%) and they were quite stable. The aromatization of these adducts with DDQ gave S_N^H-products **214** in high yields (91%–92%) (Scheme 102).[230]

Scheme 102

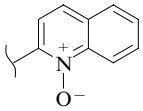
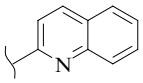
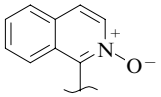
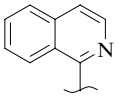
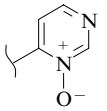
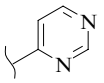
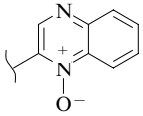
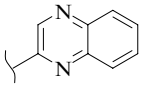
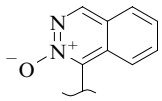
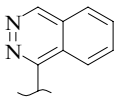
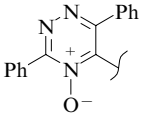
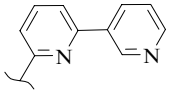


R = H (**a**), OMe (**b**)

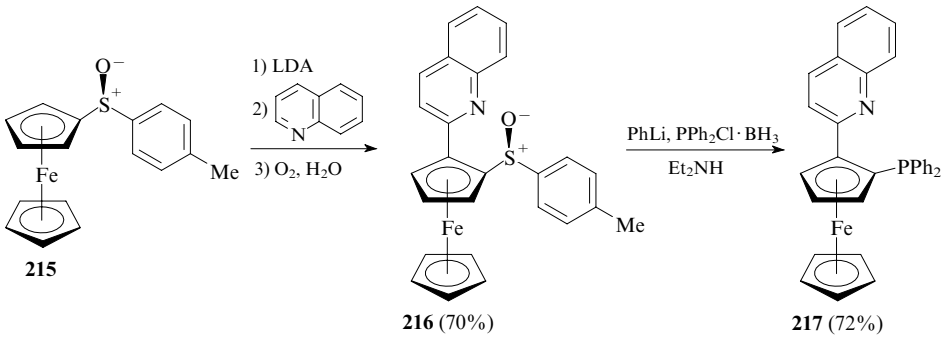
The development of methods for the preparation of new types of ligands involved in highly efficient catalysts for asymmetric synthesis is of considerable interest in modern synthetic chemistry. These catalysts can be used to prepare a single stereoisomer, which is particularly important, for example, in the synthesis of biologically active compounds. Chiral ferrocene derivatives that can serve as catalysts for Pd-catalyzed cross-coupling reactions have attracted great attention in the past decades. These catalysts include P,S-, P,O-, P,P-, P,N-bidentate ligands that combine asymmetric centres and planar chirality. Planar chiral ferrocenes are most often synthesized from molecules with pre-introduced asymmetric moieties.

The synthesis of chiral ligands based on ferrocenes containing asymmetric sulfur atoms in the side chain, for example of (*S*)-ferrocenyl *p*-tolyl sulfoxide (**215**), was documented.[231] Ferrocenyllithium generated from bromoferrocene was subjected to the reaction with (*S*)-(−)-menthyl *p*-toluenesulfinate at −78 °C to furnish ferrocenyl sulfoxide. The reaction proceeded stereoselectively and gave *S* isomer **215** in good yield (80%) with high enantiomeric excess (*ee* ⩾ 99%). Ferrocenyl sulfoxide **215** was subjected to direct 1,2-lithiation with LDA in dry THF for 40 min to form the corresponding lithium intermediate, and the latter easily reacted with quinoline at −78 °C to yield planar

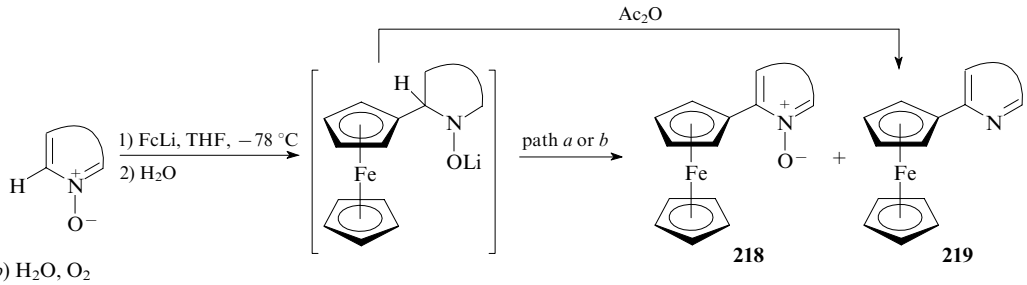
Table 9. Products generated by the reaction of azine N-oxides with ferrocenyllithium (see Scheme 104).[232]

	Yield of **218** (%)			Yield of **219** (%)		
				Method A		Method B
	path *a*	path *b*		path *a*	path *b*	
	65	55		14	30	55
	34	44		10	23	48
	35	24		7	15	38
	60	51		12	25	52
	35	23		4	15	35
	36	24		6	18	38
				8	20	42
				12	24	50

Scheme 103



Scheme 104



(*a*) DDQ; (*b*) H_2O, O_2

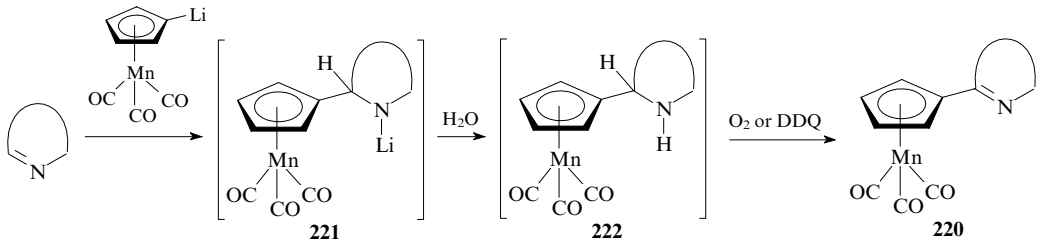
chiral derivative **216** (Scheme 103). Compound **216** can be transformed into ligand **217**.

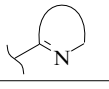
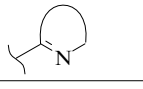
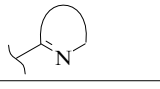
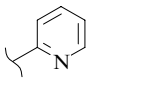
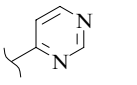
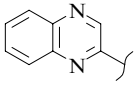
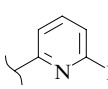
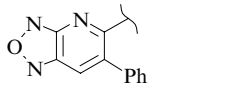
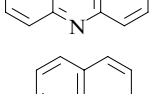
The reactions of azine *N*-oxides with ferrocenyllithium can give two types of products.[232] Thus, the reactions in the presence of such oxidants (method A) as DDQ or atmospheric oxygen (paths *a* and *b*, respectively) afford mixtures of products of substitution (**218**) and aromatization *via* deoxygenation (**219**). The ratio of the reaction products depends on the nature of the azine. In the presence of acetic anhydride (method B), the aromatization occurs *via* the deoxygenation mechanism and gives product **219** (Scheme 104, Table 9).

III.3. Reactions with cymantrenes

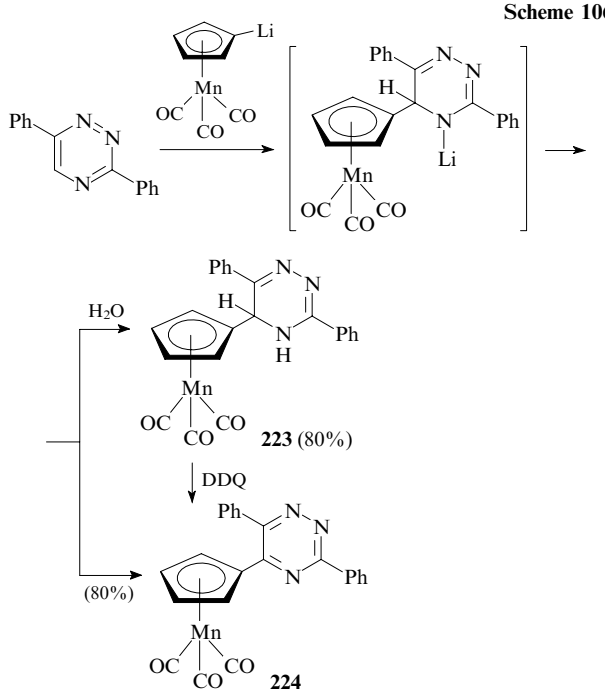
Reactions of cyclopentadienyltricarbonylmanganese (cymantrene) with heteroarenes have not been known earlier. Therefore, data on hybrid azine – cymantrene structures are virtually absent in the literature. It was found[233] that cymanthrenyllithium can react with azines in THF at −78 °C in 1.5 h to form stable hetarylcymantrenes **220** (Scheme 105). According to the currently accepted mechanism of S_N^H reactions, the first step involves the addition of cymanthrenyllithium to azine giving σ^H-adducts **221**, which are hydrolyzed with water from the solvent (or atmospheric air) to dihydro compounds **222**. This reaction proceeds without additional activation of hetarene. The second step is the oxidative aromatization of σ^H-adducts of mono- and diazines — dihydroazines **222**. This process takes place spontaneously upon the contact of intermediates **221** with air. Meanwhile, the use of a mild oxidant such as DDQ instead of atmospheric oxygen made it possible to increase the yield of the products, on the average, by 20%.[228, 233]

Scheme 105



	Yield (%)		Yield (%)		Yield (%)		Yield (%)
	40		51		60		54
	45		56		55		
	50		50		60 [231]		45

Scheme 106



As opposed to unstable σ^H-adducts of mono- and diazines with cymanthrenyllithium, as well as to ferrocenyl derivatives, stable adduct **223** can be isolated in the case of 1,2,4-triazine. This adduct can undergo aromatization in THF in the presence of DDQ at room temperature to give triazinylcymantrene **224** in quantitative yield (Scheme 106).[233]

III.4. Reactions with nitroxide radicals

Nitroxide radicals are used to study mechanisms of chemical reactions, as spin labels and spin probes, as paramagnetic models in biophysics and medicine, polymer stabilizers and so on.

Stability of nitroxide radicals is determined by the degree of unpaired electron delocalization within the bonds of substituents and steric hindrance in the vicinity of atoms with high spin density, for example, as a result of the direct introduction of nitrogen-containing substituents.

For this purpose, the aldonitrone lithium derivative, which was generated from N-oxide **225** and lithium hexamethyldisilazide, was introduced into 1,2,4-triazines and their N(4)-oxides.[234] In the case of 3,6-diphenyl-1,2,4-triazine *N*-oxide (**160c**), intermediate **226** was subjected to oxidative aromatization to furnish product **227** with the retention of N-oxide functions in the aldonitrone moiety and the triazine ring. Besides, intermediate adduct **226** can undergo aromatization to heterocyclic compound **228a** (82% yield) with a loss of N-oxide functions (Scheme 107). Besides, related compounds **228b–d** were synthesized directly from appropriate 1,2,4-triazines.

The lithium derivative of radical **229** reacts with 1,2,4-triazines in a similar way.[235] Intermediate adducts **230** undergo aromatization either *via* deoxygenation to form monoxides **231** or through the oxidation to imidazole-*N*-oxyl *N*-oxides **232** (Scheme 108).

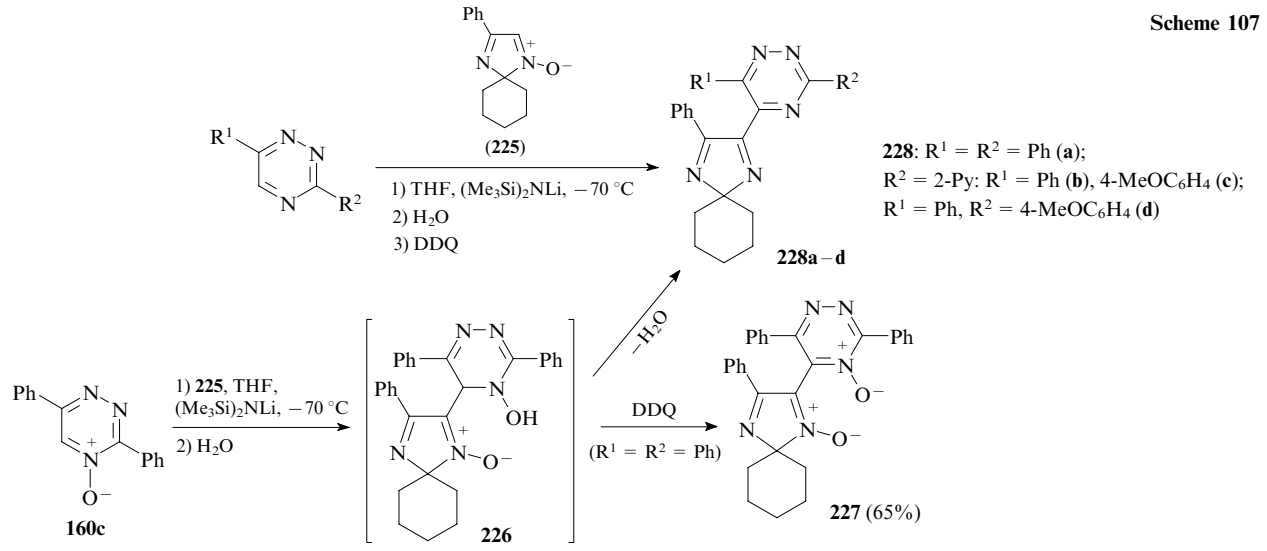
Derivatives of nitroxide radicals with vicinal paramagnetic moieties located on a heterocyclic matrix are worthy of special mention. These compounds have attracted considerable interest since they can be used as a basis for the construction of metal heterospin clusters with exchange interaction channels between nitroxide fragments in a certain configuration located at adjacent C atoms of the heterocycle. Radicals **233** were synthesized for the first time *via* nucleophilic attack of lithium derivative **229** on mono-, di- and triazine *N*-oxides. Under these conditions, quinoxaline 1,4-dioxide forms biradical **234** (Scheme 109).[236]

More recently, it was found[237] that not only heteroaromatic triazine and pyrazine N-oxides, but also dihydropyrazines, which do not have a cyclic conjugated system of π-bonds (for example, compound **235**), can react with lithium derivatives of nitroxide radicals *via* the S_N^H mechanism. Most likely, this reaction also proceeds through the formation of unstable intermediate **236**, the subsequent aromatization *via* elimination being mediated by a water molecule that is released from this intermediate. The absence of the second N-oxide function in the diamagnetic moiety of derivative **237a** (R = Me) (Scheme 110) confirms the proposed mechanism. The oxidative aromatization with DDQ affords a mixture of three compounds — major product **238** and by-products **237b** (R = H) and **239**.

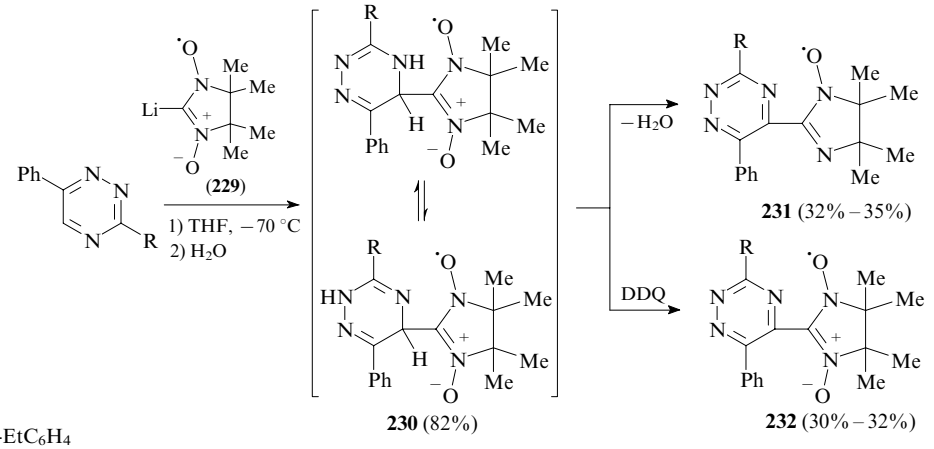
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The data summarized in this review clearly demonstrate considerable potential of the direct non-catalytic C–C bond formation in reactions of π-deficient systems (arenes

Scheme 107

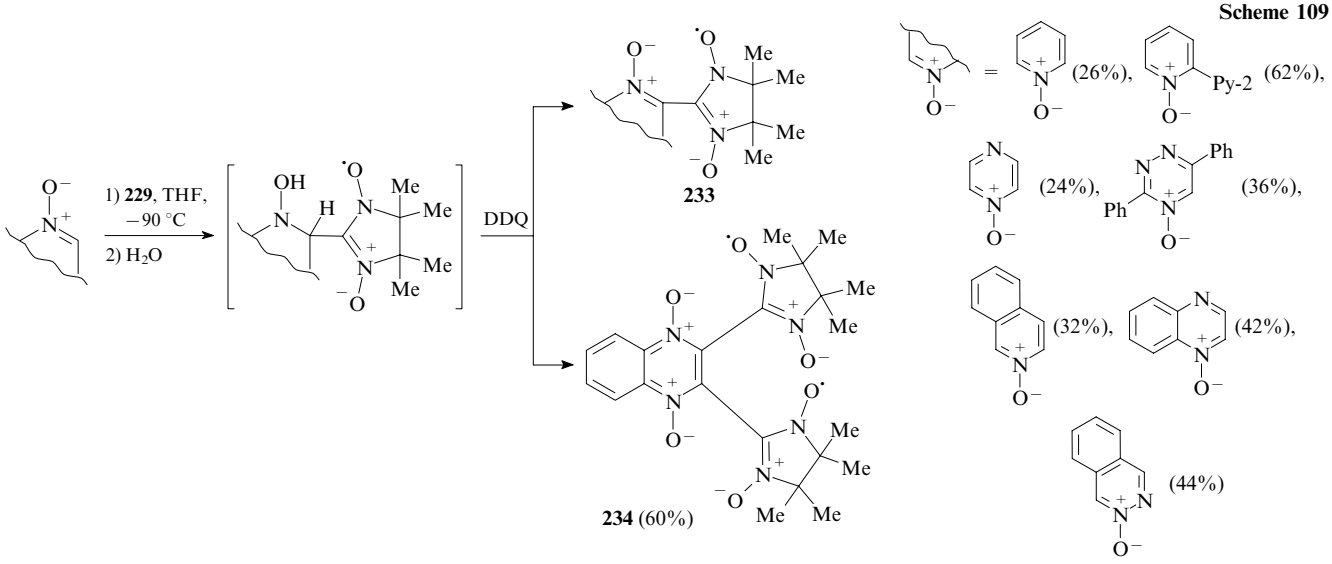


Scheme 108

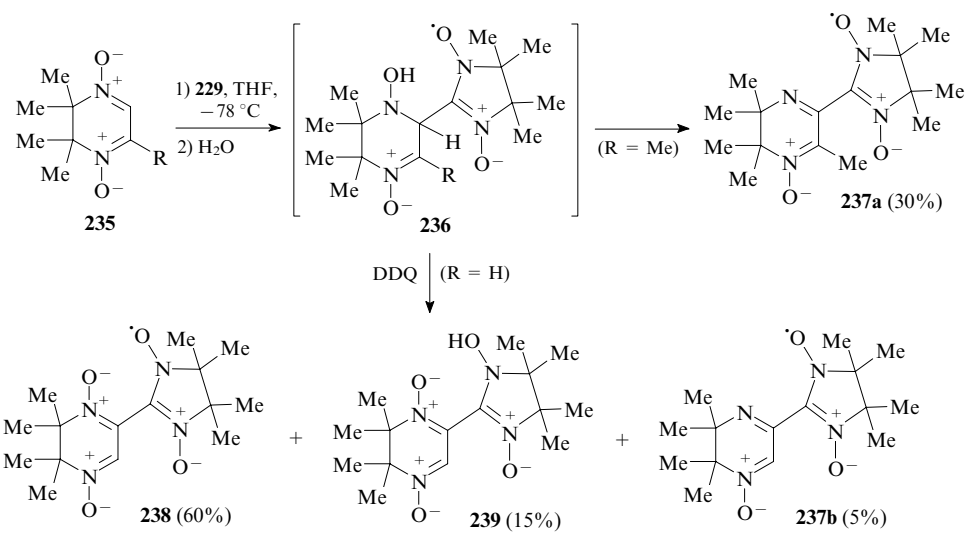


R = Ph, 4-EtC$_6$H$_4$

Scheme 109



Scheme 110



and hetarenes) with organolithium compounds, including (hetero)organolithium reagents and even nitroxide radicals. These processes can considerably extend the scope of cross-coupling reactions and, for certain compounds, can completely replace the latter reactions. In some cases, stable intermediate σ^H-adducts can be isolated as individual compounds, characterized and, depending on the structure, subjected to transformations into S_N^H products *via* different aromatization pathways. Besides, stable σ^H-adducts can serve as chiral reagents for the preparation of catalysts for asymmetric synthesis or biologically active compounds.

This review article was supported by the Russian Science Foundation (Agreement No. 15-13-10033).

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