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**STRATEGY OF C-H FUNCTIONALIZATION IN THE DESIGN OF
PHARMACOLOGICALLY ACTIVE COMPOUNDS AND FUNCTIONAL
MATERIALS**

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A key vector in the modern organic chemistry development is the targeted design of molecular systems to create effective drugs based on them, as well as “smart” materials for molecular electronics. A special place among the organic and hybrid substances is occupied by azaheterocyclic compounds, on the basis of which effective chemical pharmaceuticals to be used in the diagnosis and treatment of infectious, oncological, cardiovascular, neurodegenerative and other socially significant diseases are known. At the same time, azaheterocyclic compounds, due to their unique electronic, electrochemical, photophysical, coordination and other properties, are attractive building blocks for the development of organic electronics materials, primarily sensors, nonlinear optics, spintronics, catalysis and other actively developing areas.

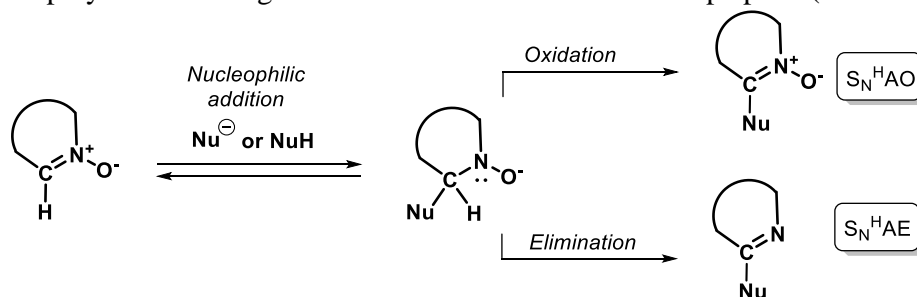
Among the known synthetic approaches, the methodology of direct C–H functionalization is one of the most progressive strategies that has shown effectiveness in the targeted modification of organic compounds of various classes [1-3]. This approach considers the C–H fragment as an independent functional group that, under certain conditions, can be modified under the influence of various reagents that carry a certain functional load. The use of C–H functionalization methods and approaches, in particular nucleophilic hydrogen substitution reactions (S_N^H), allows one to avoid the introduction of

halogens or other auxiliary groups into azaheterocyclic substrates at preliminary stages, as well as in some cases of using metal complex catalysis. The competitive advantage of this strategy compared to the classical methods used for constructing carbon-carbon and carbon-heteroatom bonds is that these techniques are focused on optimizing synthetic schemes by reducing the number of intermediate stages, minimizing losses and by-products, eliminating the use of harmful substances in laboratory and industrial processes.

The current work is a systematic study of the possibilities of the direct C(sp²)-H functionalization strategy as an effective synthetic tool for the targeted design of azaheterocyclic systems of aromatic and non-aromatic nature for the preparation of promising organic and hybrid materials based on them.

Nucleophilic hydrogen substitution reactions (S_N^H) uncatalyzed by transition metals in azaheterocyclic systems

The concept of reactions of nucleophilic substitution of hydrogen (S_N^H) was first proposed and developed as an independent scientific direction in the work of the Ural School of synthetic chemists. S_N^H Methodology, being a basic synthetic tool for obtaining new functional derivatives of five- and six-membered azaheterocycles, allowed the targeted construction of complex bi- and polyfunctional organic assemblies for multifunctional purposes (Scheme 1).



Scheme 1 – General scheme of nucleophilic hydrogen substitution reactions (S_N^H) uncatalyzed by transition metals in azaheterocyclic systems (using the example of functionalization of azaheterocyclic N-oxides)

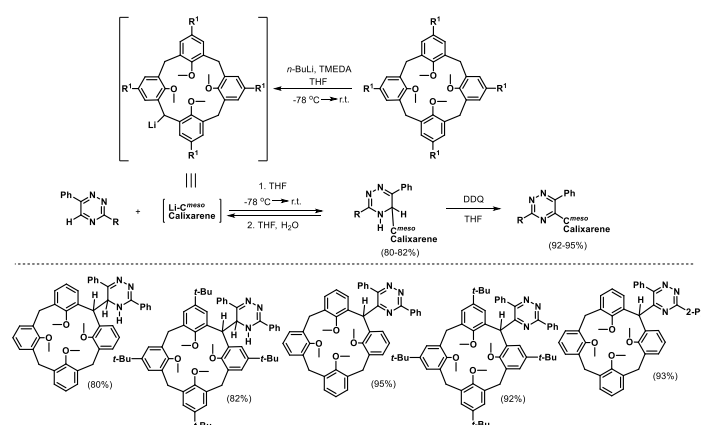
According to the generally accepted concepts, reactions of nucleophilic substitution of hydrogen (S_N^H) proceed in two stages. At the first stage, the nucleophilic reagent is added to the azaheterocyclic substrate with the formation of σ^H-adducts, and at the second stage, these intermediates are converted to SNH-products. The aromatization of σ^H-adducts can be carried out in two ways: oxidative and eliminative pathways. In this regard, S_N^H reactions should be classified as transformations occurring either according to the “Addition-Oxidation” (S_N^HAO) or according to the “Addition-Elimi-

nation” (S_N^H AE) scheme. It is worth noting that to implement the first type of transformation, the presence of an oxidizing reagent in the system is necessary. The elimination pathway of aromatization requires the presence of an auxiliary group in the heterocyclic substrate or in the nucleophilic reaction participant (vicary nucleophilic substitution).

The C–H/C–M (M=Li, MgX) coupling reactions proceeding according to the nucleophilic substitution of hydrogen (S_N^H) scheme were used for the synthesis of azaheterocyclic systems functionalized with fragments of nitroxyl radicals, calixarenes, thiophene, imidazole, and pentafluorobenzene.

Calixarenes are of great importance in supramolecular chemistry; increased interest in this class of macrocyclic structures is due to the wide possibilities of their practical use [4]. Thus, effective ionophore receptors for the selective extraction of metal ions, catalysts, chemosensors, transmembrane ion carriers, materials for nonlinear optics, biologically active substances and drug delivery systems based on calixarenes are known. The uniqueness of the applied properties of calixarenes is associated with their complex structural organization. The most common approach in the design of new functionally substituted calixarenes is modification of the macromolecule at the upper (OH group) and lower (at the $C(sp^2)$ –H bond of the aromatic ring) rim.

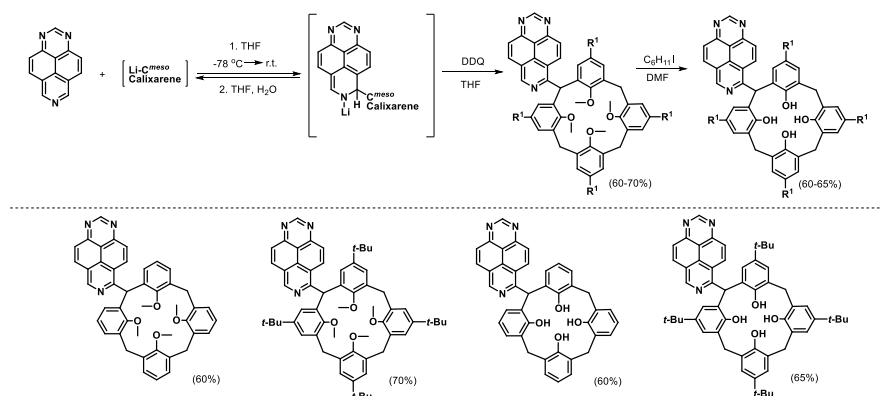
The methodology of nucleophilic hydrogen substitution (S_N^H reaction) in azines and their N-oxides was used for the first time to obtain new azaheterocyclic calixarene derivatives containing azaheterocycle fragments at the *meso*-position using 2-lithium-25,26,27,28-tetramethoxycalix[4]arenes as nucleophilic reagents (Scheme 2) [5]. The coupling products of lithio-calixarenes with triazines, σ^H -adducts, were obtained in yields of 80–82%. Next oxidative aromatization of adducts was carried out in THF at room temperature using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) as an oxidant to give the corresponding S_N^H products in yields of 92–95%.



Scheme 2— C–H/C–Li coupling of 1,2,4-triazines with lithium derivative of tetramethoxycalixarenes

Studies on the reactivity of substrates based on polycyclic azaaromatic hydrocarbons, in particular 1,3,7-triazapyrene derivatives, in the processes of interaction with lithium derivatives of calixarenes as nucleophiles were also carried out. The increased interest in such compounds is due to the wide possibilities of using derivatives of polycyclic azaaromatic hydrocarbons in sensors and molecular electronics, in particular as working elements of organic photovoltaics (OPVs), organic light-emitting diodes (OLEDs) and organic field-effect transistors (OFETs).

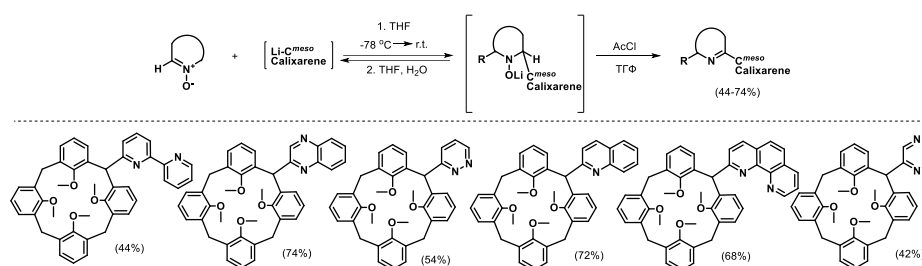
To synthesize 1,3,7-triazapyrenes functionally substituted with a calix[4]arene fragment, a synthetic strategy that included a series of sequential transformations of the macrocycle, namely the preparation of calixarenes with protected hydroxyl groups, mesolithiation followed by the reaction of nucleophilic hydrogen substitution (S_N^H) in 1,3,7-triazapyrene using lithiumcalix[4]arene as a nucleophilic reagent, oxidation of the resulting unstable σ^H -adduct under the action of DDQ and subsequent removal of the protecting group under the action of cyclohexyl iodide in DMF was used (Scheme 3) [6]. As a result, new 1,3,7-triazapyrene derivatives modified with a tetramethoxycalix[4]arene fragment were obtained in 60-70% yields and the corresponding tetrahydroxycalix[4]arenes 28 in 60-65% yields.



Scheme 3 – Synthesis of 1,3,7-triazapyrene derivatives, modified with a tetramethoxycalix[4]arene fragment, and the corresponding tetrahydroxycalix[4]arenes

To expand the applicability of the proposed approach to other azaheterocyclic substrates, the interaction of the lithium derivative of tetramethoxycalix[4]arene with non-activated azaheterocycles based on mono-(pyridine, quinoline, isoquinoline, 2,2'-bipyridine) and diazines (pyrazine, quinoxaline, pyridazine) was studied [7]. As a result, it was found that the reactivity of these substrates was not sufficient to form the desired functional derivatives. To solve this problem, structurally diverse N-oxides of mono- and

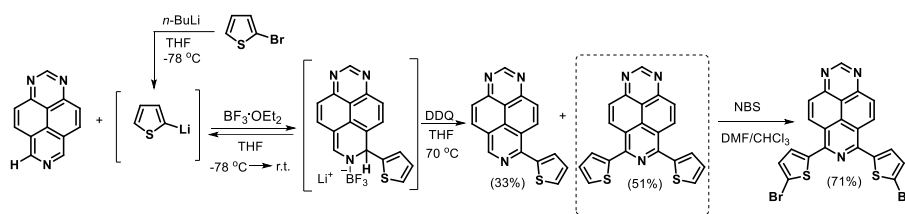
diazines with mono-, bi-, and tricyclic structures were introduced in reactions with lithium calixarene (Scheme 4). These transformations are a two-stage process, the implementation of which is carried out according to the S_N^H AE scheme. At the first stage, the nucleophilic reagent is added to the C=N bond of azine-N-oxide with the formation of low-stable intermediate compounds - σ^H -adducts. At the second stage, the elimination of the oxygen-containing fragment takes place along with the proton at sp^3 -hybridized carbon atom of the azaheterocycle with the formation of aromatized S_N^H products. The use of AcCl at the aromatization stage makes it possible to obtain reaction products in yields of 44-74%.



Scheme 4 – Non-catalyzed transition metal C–H/C–Li combinations of azine-N-oxides with the lithium derivative of tetramethoxycalixarenes

The synthesis of mono- and disubstituted 1,3,7-triazapyrenes containing functional blocks that improve their fluorescent properties (quantum yield, lifetime, solvatochromism, etc.) is an important task in the creation of organic photoluminescent materials. One of the most frequently used structural elements in the development of photoactive materials with desired properties is the thienyl functional block. In particular, thiophene derivatives are used in various fields of molecular electronics such as organic light-emitting diodes (OLEDs), organic photovoltaics (OPVs), and organic field-effect transistors (OFETs). It is also known that intermolecular S–S interaction enhances the effect of intermolecular charge transfer in the solid state. In addition, the design of organic molecules characterized by intramolecular charge transfer effects (e.g., push-pull fluorophores) is one of the widely used strategies to create organic fluorescent chemosensors for the detection of nitroaromatic compounds. The properties of this series of compounds can be easily modeled by changing the structure of the main substituent of the chemosensor, as well as the nature and position of the functional groups. It should be noted that the development and application of chemical sensors based on small molecules seems relevant for the detection of nitroaromatic compounds, both for assessing health or environmental risks, and for monitoring and studying the condition of soils and groundwater.

For the synthesis of mono- and bis-thienyl-substituted 1,3,7-triazapyrenes, the strategy of oxidative nucleophilic hydrogen substitution (SNHAO) in heteroarenes was used, in particular the BF_3 -catalyzed reaction of C-H/C-Li coupling of 1,3,7-triazapyrene with 2-thienyllithium (Scheme 12) [8]. In accordance with the proposed mechanism, in the first stage, triazapyrene is activated by $\text{BF}_3 \cdot \text{OEt}_2$ with the generation of the corresponding quaternary salt, which further reacts with 2-thienyllithium to form the unstable σH -adduct. This intermediate, under the action of an oxidizing agent, is converted into the corresponding monosubstituted product, which can also react with another 2-thienyllithium molecule to form 6,8-di(thienyl-2-yl)-1,3,7-triazapyrene. In order to demonstrate the potential of the synthesized compounds for further functionalization, bromination of the thiophene fragment of 6,8-di(thienyl-2-yl)-1,3,7-triazapyrene was carried out using NBS (Scheme 5). As a result, 6,8-bis(5-bromothiophen-2-yl)-1,3,7-triazapyrene was obtained in 71% yield.

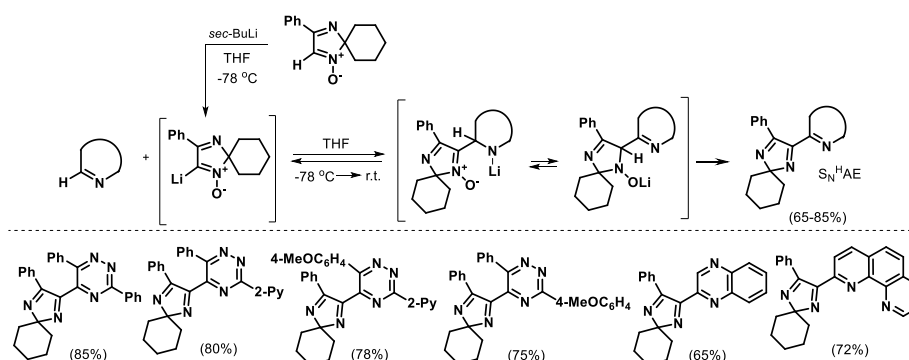


Scheme 5 – BF_3 -catalyzed oxidative C-H/C-Li coupling of 1,3,7-triazapyrene with 2 thienyllithium

Molecular systems containing a biheterocyclic scaffold, in particular azine derivatives functionalized with an imidazole moiety, are of interest as promising pharmacoactive compounds capable of selectively binding to biomolecule receptors. In addition, imidazoles derivatives are considered today as critical building blocks in modern light-emitting and liquid crystalline materials, solar cells, dyes and pigments.

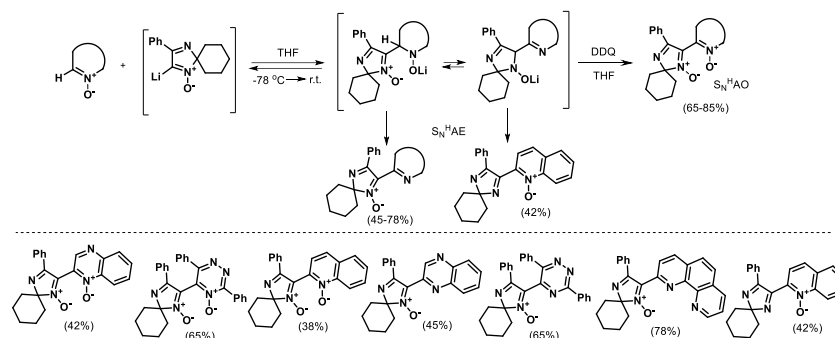
For the synthesis of functionally substituted azaheterocycles, a simple and convenient approach was developed based on $\text{S}_\text{N}^\text{H}$ reactions of the lithium derivative of aldonitrone with azines (Scheme 6) [9]. It is known that nitrones, containing a proton at the α -carbon atom relative to the N-oxide group, exhibit acidic properties and, when interacting with organometallic bases (s-BuLi, LDA), form the corresponding lithium derivatives. The relative stability of the resulting intermediates, which are dipole-stabilized carbanions, is due to both the electron-withdrawing effect of the N^+-O^- group and the possibility of the formation of a thermodynamically favorable intramolecular coordination bond $\text{O} \cdots \text{Li}$. During the investigation of the proposed $\text{S}_\text{N}^\text{H}$ approach, it was found that the lithium derivative reacted smoothly with π -

deficient azaheterocyclic substrates. This transformation should also be considered as a two-step S_N^H process leading to previously unknown 2*H*-imidazolyl-containing azine derivatives. At the first stage, the nucleophilic addition of the lithium derivative to the HC=N bond of azine occurs with the formation of σ^H -adducts. These intermediates have limited stability and can exist in two tautomeric forms. At the second stage, an elimination reaction occurs with the formation of heterocyclic derivatives without an N-oxide fragment in the structure, in this case the process should be classified as a vicary hydrogen replacement.



Scheme 6 – C–H/C–Li Coupling of azines with the lithium derivative of 2*H*-imidazole-1-oxide

It should be noted that in the case of using less electrophilic non-activated monoazines (pyridine, quinoline) in reactions with organolithium compound, the formation of the corresponding C–C coupling products was not detected. To achieve the goal of obtaining biheterocyclic assemblies, the synthetic possibilities of using N-oxides in this reaction were investigated (Scheme 7) [10]. Thus, it was found that the lithium derivative of cyclic aldonitrone interacted not only with the N-oxide of 1,2,4-triazines, but also with the activated forms of quinoxaline, 1,10-phenanthroline and quinoline. These transformations lead to the formation of two different types of products: compounds with two N-oxide fragments and heterocycles containing N^+-O^- in the structure of imidazole and azine. Intermediate products formed at the addition stage can exist in two tautomeric forms. These intermediates correspond to S_N^H AO products, their structure is determined by the conditions of the aromatization stage. In the absence of an oxidizing agent, compounds are formed, containing one N^+-O^- group in an azole or azine substrate, which is due to the greater stability of the corresponding tautomeric forms of intermediates.



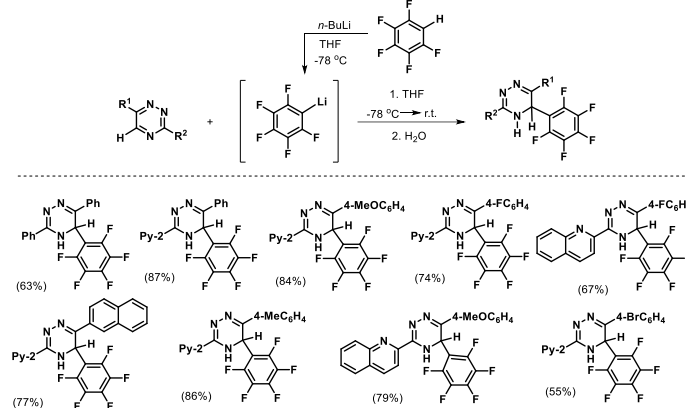
Scheme 7 – Non-catalyzed transition metal C–H/C–Li coupling of azine-N-oxides with the lithium derivative of 2*H*-imidazole-1-oxide

Heterocyclic compounds containing polyfluoroaromatic fragments are substances with high potential for practical applications [11]. The increased interest in these derivatives is due to the fact that the inclusion of fluorine atoms or fluorine-containing groups in organic structures increases their stability to oxidative and other undesirable degradation processes, improves lipophilicity, as well as transport functions, including penetration through the blood-brain barrier. The presence of an electronegative fluoroaryl moiety leads to increased photoluminescence efficiency, minimization of self-quenching, and a decrease in the difference in HOMO/LUMO energy levels, which, in turn, is of key importance in the design of advanced photoactive materials. In addition, the inclusion of organofluorine fragments into the structure of organic molecules can be used to tune their properties due to the spatial and electronic effects of organofluorine substituents in the structure of the target compound. Today, the use of fluoroaryl synthons is actively used in the development of promising drugs (antibiotics, anti-inflammatory, antihypertensive, anticancer and antifungal drugs), effective plant protection products, modern materials for molecular electronics, especially in field-effect transistors (FET) and organic light-emitting diodes (OLED), photocells organic thin film transistors (OTFT), radio frequency identification (RF-ID) sensors, etc.

To create new polyfluoroaryl-substituted azaheterocyclic compounds, a strategy of direct, non-C–H/C–Li transition metal-catalyzed combinations of azaheterocyclic substrates (azines, azine-N-oxides, and non-aromatic substrates) with pentafluorophenyllithium, as well as accompanying structural transformations, was developed.

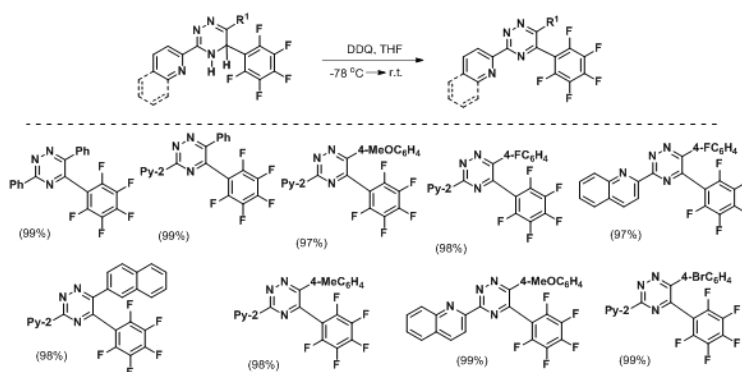
The S_N^H reaction methodology was successfully applied to the direct functionalization of azaheterocyclic substrates based on 1,2,4 - triazines 1 under the action of pentafluorophenyllithium as a nucleophilic reagent obtained from pentafluorobenzene and *n*-BuLi [12, 13]. It is worth noting that the lithium derivative is a relatively stable compound due to the electron-

withdrawing nature of the fluorine atoms in the aromatic ring (Scheme 8). Synthetic studies have shown that at the first stage, stable dihydro compounds, σ^H -adducts, are formed in yields of 55-87%.



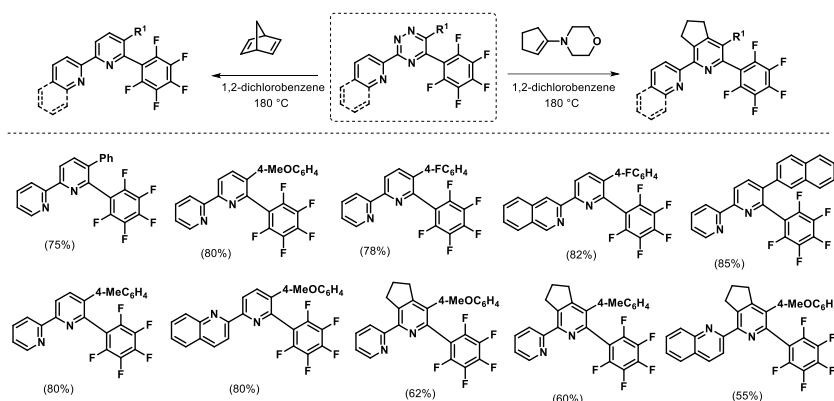
Scheme 8 – Addition of pentafluorophenyllithium to 1,2,4-triazines in the synthesis of polyfluoroarylated azaheterocyclic systems

To obtain the corresponding S_N^H products, intermediates were subjected to oxidative aromatization using various quinone-based oxidizing agents. The best results (97-99% yield) were achieved using DDQ (Scheme 9). Thus, the capabilities of the methodology of oxidative nucleophilic substitution of hydrogen (S_N^H) in the design of polyfluoroarylated azaheterocyclic systems have been demonstrated, which in turn deserve both independent attention for the creation of promising materials based on them, and as objects for further functionalization.



Scheme 9 – Oxidation of pentafluorophenyl-substituted dihydro-1,2,4-triazines in the synthesis of polyfluoroarylated azaheterocyclic systems

The next step towards the target polyfluoroarylated 2,2'-bipyridines was the use of the aza-Diels-Alder reaction for the synthesized functionally substituted 1,2,4-triazines using 2,5-norbornadiene while boiling the reaction mass in 1,2-dichlorobenzene (Scheme 10). As a result, a series of 2,2'-bipyridine ligands were obtained in 75-85% yields. Using 1-morpholinocyclopentene as a dienophile, cyclopenta[c]pyridines were obtained by boiling the reaction mass in 1,2-dichlorobenzene in yields of 55-62%. It was also found that pentafluorophenyl-substituted triazines and their 2,2'-bipyridine analogues could also be prepared beginning from 1,2,4-triazine-4-oxides.

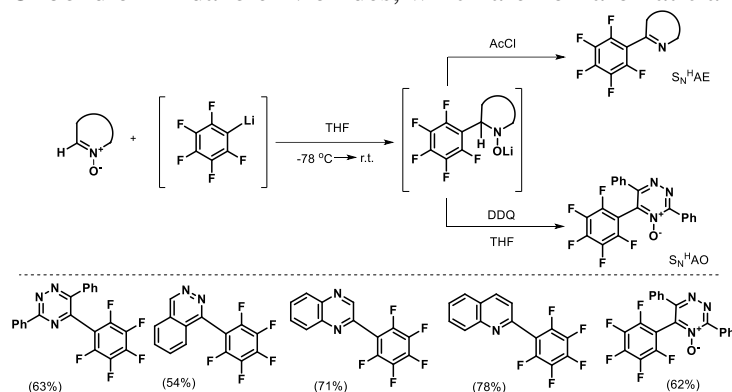


Scheme 10 – Synthesis of polyfluoroarylated 2,2'-bipyridines and their structural analogues

In the case of C-H functionalization of mono-, di- and triazine-N-oxides, the lithium derivative at the first stage adds to the $C=N^+-O^-$ bond of azine-N-oxides with the formation of σ^H -adducts, which can then be converted into various pentafluoroarylation products depending on the conditions used in the aromatization step (Scheme 11) [14]. It was found that pentafluorophenylazines were formed in 54-78% yield as a result of elimination aromatization. The C-C coupling conditions were also optimized using various deoxygenating agents such as $AcCl$, Ac_2O and TFFA. The highest triazine yield (65%) was achieved when the reaction mixture was treated with $AcCl$ as a deoxygenating reagent. In addition, to obtain C-C combination products of azine-N-oxides while preserving the N^+-O^- group, the patterns of oxidative aromatization were studied. Pentafluorophenyl-substituted 1,2,4-triazine-1-oxide was found to be the only product of the reaction of 3,6-diphenyl-1,2,4-triazine-4-oxide with lithium derivative in the presence of DDQ.

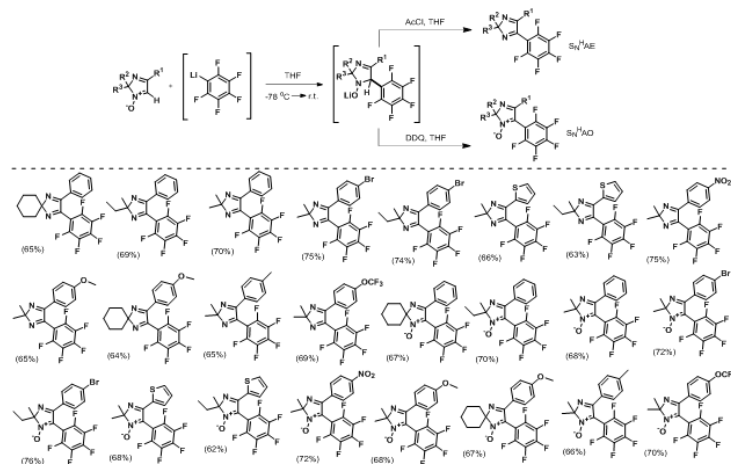
New pentafluoroaryl-substituted 2*H*-imidazole derivatives were synthesized as a result of C-H/C-Li couplings of 2*H*-imidazol-1-oxides with pentafluorophenyllithium obtained in situ from pentafluorobenzene (Scheme 12)

[15]. According to modern concepts of nucleophilic hydrogen substitution reactions (S_N^H), at the first stage pentafluorophenyllithium attacks the $HC=N^+-O^-$ bond of imidazole-N-oxides, which are non-aromatic azahe



Scheme 11— C–H/C–Li Coupling of azine-N-oxides with pentafluorophenyllithium

terocycles containing a carbon center active for nucleophilic C–H functionalization C(5), with the formation of unstable σH -adducts, which could be converted into the corresponding S_N^H -products of two types - compounds formed either according to the “Addition-Elimination” (SNHAE) scheme or according to the “Addition-Oxidation” scheme (SNHAO). Thus, in the presence of a deoxygenating agent in the reaction mixture, the conversion of intermediates into pentafluorophenyl-modified SNHAE products in yields of 64-75%; in the presence of an external oxidant, the transformation proceeds according to the SNHAO scheme to obtain products containing an N-oxide group in yields of 62-76%.



Scheme 12 - Synthesis of 2*H*-imiazol-1-oxides with pentafluorophenyllithium according to the Addition-Hydrolysis (S_N^H AE) or Addition-Oxidation (S_N^H AO) scheme

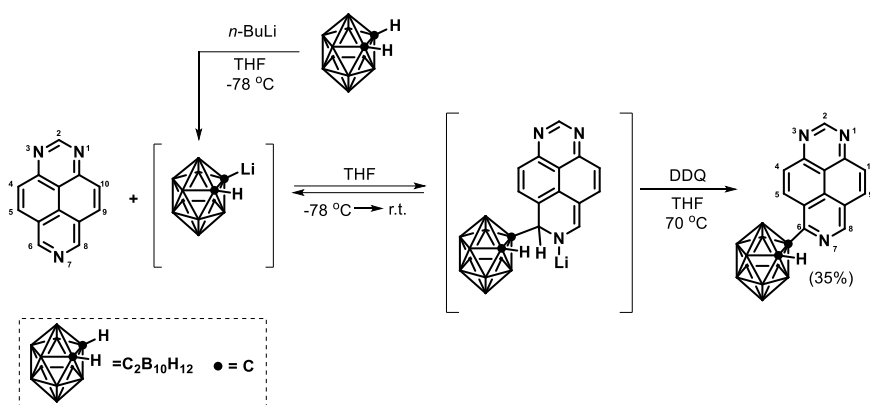
Dicarba-*closo*-dodecaboranes (carboranes) belong to organoboron polyhedral *closo* clusters, which can be considered as non-classical three-dimensional aromatic compounds [16]. The regular icosahedral structure of carboranes is formed by 12 node atoms (10 boron atoms and two carbon atoms), which are equidistant from the center and carry 26 electrons involved in the formation of bonds between the vertices. Due to the unique structural and physicochemical properties of carboranes, including their thermal and chemical stability, these organoboron compounds are of great importance for the development of materials for visualizing malignant tumors, agents for boron neutron capture therapy (BNCT), ligands of biomolecular receptors, immunostimulants, catalysts, luminescent materials, supramolecular structures. In addition, organoboron derivatives containing both hydrophilic (heterocyclic) and lipophilic (carborane) fragments play a key role in the delivery of BNCT agents to tumor cells and their accumulation in concentrations sufficient for the treatment of malignant neoplasms.

To obtain promising azaheterocyclic assemblies containing an organoboron functional block, coupling of azaheterocyclic substrates with carboranyl lithium not catalyzed by C–H/C–Li transition metals are currently considered as an effective strategy. The synthetic availability of lithium carboranes is due to the fact that dicarba-*closo*-dodecaboranes exhibit C–H acidic properties and, under the action of bases, form mono- and dilithium derivatives, which are highly active nucleophilic synthons for the construction of new functionally substituted organoboron assemblies.

Among the many compounds formed by azinyl functional blocks, molecular systems based on azapyrene are of particular interest in the series of fused polycyclic heteroarenes. The increased interest in compounds of this class is due to the fact that the inclusion of nitrogen atoms in the structure of pyrene and its analogues affects the electronic characteristics of molecular systems, making it possible to obtain organic semiconductors, redox-active compounds and key building blocks of molecular devices, as well as physiologically active substances that exhibit activity as DNA intercalators and antitumor agents.

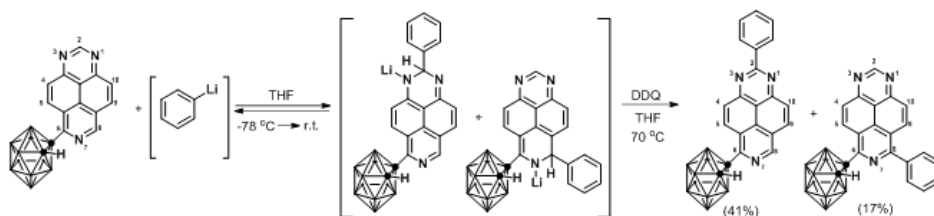
To synthesize the target functionally substituted derivatives of 1,3,7-triazapyrene, we used the methodology of direct C–H functionalization of azaheterocyclic substrate under the influence of carboranyl lithium, formed in situ from o-carborane and *n*-BuLi (Scheme 13) [17]. This transformation is realized in two stages. At the first stage, the nucleophilic reagent adds to the azomethine (–CH=N–) bond to form the anionic σ^H -adduct. Subsequent rearomatization of intermediate 63 leads to the formation of a stable S_N^H product. It is worth noting that rearomatization of the triazapyrene fragment

requires an external oxidizing agent, so this process can be classified as nucleophilic addition-oxidation (S_N^H AO) hydrogen substitution.



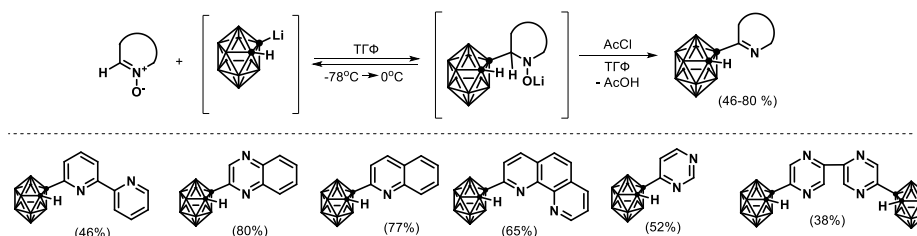
Scheme 14 - Synthesis of carboranyl-substituted derivative of 1,3,7-triazapyrene

Carboranyl-substituted triazapyrene is a C(6)-monosubstituted derivative, the structure of which contains two azomethine fragments with electrophilic centers C(2) and C(8) of the azapyrene ring, which are available for further nucleophilic functionalization as a result of oxidative S_N^H transformations. Substituted isomeric triazapyrene carborane molecules are known to have valuable photophysical properties due to the diversity of both electronic and spatial interactions between the triazapyrene ring and the introduced functional blocks. To synthesize disubstituted derivatives, further modification of mono derivative was carried out using the S_N^H reaction with phenyllithium (Scheme 15). While carboranyl lithium reacts selectively at the C(6) position of 1,3,7-triazapyrene, the coupling of mono derivative with phenyllithium occurs at both the C(2) and C(8) positions. As a result, two regioisomers (2-phenyl-1,3,7-triazapyrenylcarborane and 8-phenyl-1,3,7-triazapyrenylcarborane) were obtained in yields of 41% and 17%, respectively.



Scheme 15 – Synthesis of carboranyl-substituted derivative of 1,3,7-triazapyrene

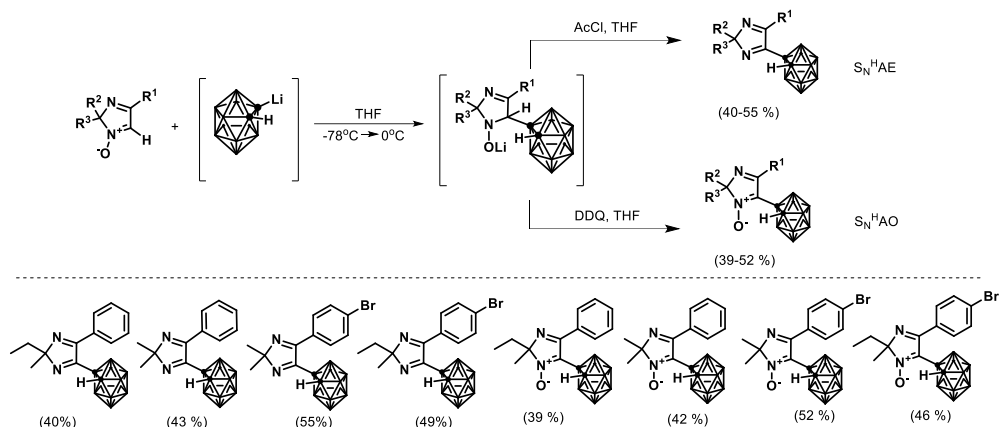
To obtain carboranyl-substituted azaheterocyclic compounds based on other azines, the C(sp²)-H functionalization methodology of azine-N-oxides was used as the main synthetic approach. Thus, it was found that N-oxides of mono- and diazines reacted with carboranyl lithium through the mechanism of nucleophilic hydrogen substitution, which was realized according to the “Addition-Hydrogen Ejection” (S_N^HAE) scheme with the formation of the corresponding azinyl-substituted *o*-carboranes (Scheme 16) [18]. In this case, at the first stage, the nucleophilic reagent is added to the HC=N⁺-O⁻ bond of azine-N-oxides to obtain the corresponding dihydro compounds - anionic σ^H-adducts. At the second stage, deoxygenative aromatization of intermediates occurs under by the action of acylating agents to form products in 46-80% yields. In the case of pyrazin-N-oxide, the symmetric dimeric compound 5,5'-bis(1,2-dicarba-closo-dodecaboran-1-yl)-2,2'-bipyrazine is formed in 38% yield.



Scheme 16 - Synthesis of carboranyl-substituted azinyl derivatives

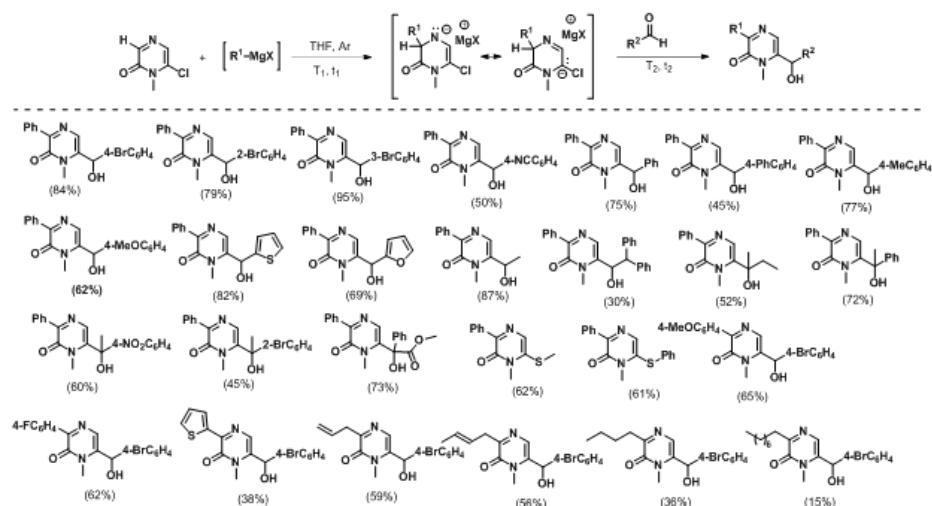
Non-catalyzed by transition metal catalyzed C-H/C-Li couplings are widely used in the chemistry of π-deficient (hetero)aromatic systems as a convenient and efficient synthetic approach. These transformations have been successfully applied to the synthesis of various mono-, di- and triazinyl-modified carboranes via direct C-H/C-Li coupling of non-aromatic 2*H*-imidazole-1-oxides with carboranyl lithium.

Cross-coupling reactions of 2*H*-imidazole-1-oxides with carboranyl-lithium lead to carboranyl-substituted imidazoles, their structures are determined by the implemented mechanism of S_N^H transformations: “Addition-Elimination” (S_N^HAE) or “Addition – Oxidation” (S_N^HAO), respectively (Scheme 17) [19]. In accordance with modern concepts of S_N^H transformations, the first stage of both transformations, S_N^HAE and S_N^HAO, includes the reversible formation of unstable anionic σ^H-adducts as a result of the nucleophilic attack of carbonyllithium on the CH=N⁺-O⁻ bond of 2*H*-imidazole-1-oxides. The second stage of the process can be implemented in both elimination and oxidative variants to obtain the corresponding carboranylated 2*H*-imidazoles.



Scheme 17— C–H/C–Li Coupling of 2*H*-imidazole-1-oxides with carboranyl lithium

To obtain new functionally substituted pyrazin-2(1*H*)-one derivatives, an original synthetic strategy for combinations of 1-methyl-6-chloropyrazin-2(1*H*)-one with organomagnesium compounds not catalyzed by C–H/C–MgX transition metals was developed [20]. This approach is based on double functionalization of N-protected pyrazin-2(1*H*)-ones, implemented by the telenucleophilic hydrogen substitution (S_N^{tele}) mechanism, including interaction with nucleophilic reagents and subsequent interaction with electrophiles (Scheme 18).

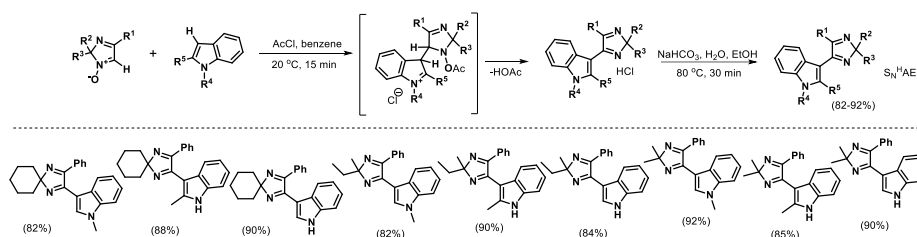


Scheme 18 – Reactions of telenucleophilic hydrogen substitution in 1-methyl-6-chloropyrazin-2(1*H*)-one to obtain new 3,6-disubstituted-1-methylpyrazin-2(1*H*)-ones.

According to the proposed reaction mechanism, in the first stage, the organomagnesium compound reacts with the pyrazinone substrate to form the anionic σ^H -adduct, which then reacts with various electrophiles to obtain the target 3,6-disubstituted-1-methylpyrazine-2(1*H*)-ones.

Reactions of C–H/C–H non-transition metal-catalyzed combinations of non-aromatic substrates with nucleophilic reagents, proceeding according to the nucleophilic hydrogen substitution (S_N^H) scheme, were used to synthesize new 2*H*-imidazoles derivatives functionalized with fragments of π -excess aromatic compounds.

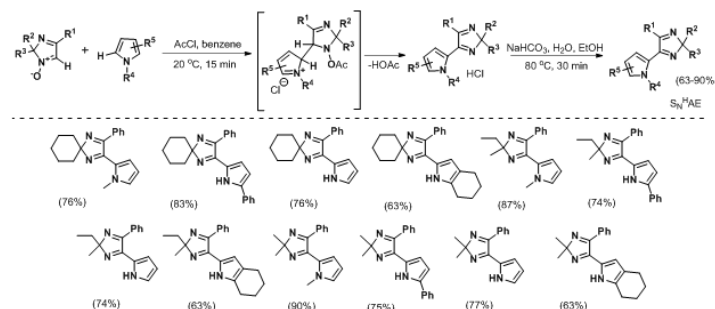
To synthesize new functionally substituted 2*H*-imidazole derivatives functionalized with fragments of π -excess azaheterocyclic compounds, methods for C(sp²)–H functionalization in non-aromatic azaheterocyclic substrates (2*H*-imidazole-1-oxides) using indoles, pyrroles and their functional derivatives were developed [21]. In particular, by the reaction of nucleophilic substitution of hydrogen (S_N^H) in cyclic aldonitrones under the action of indoles, the products of C–H/C–H coupling uncatalyzed by transition metals were obtained in 82–92% yields under mild conditions (Scheme 35). Thus, it was found that the nucleophilic attack of indoles on the unsubstituted carbon C(5) of imidazole 1-oxide occurred in the presence of acetyl chloride as a reagent activating the electrophilic substrate and is a two-stage process. At the first stage, nucleophilic indoles are added to the activated nitrones with the formation of unstable σ^H -adducts. The elimination of acetic acid from intermediate at the second stage leads to the S_N^H products in the form of hydrochlorides. Their precipitation from reaction solutions shifts the dynamic equilibrium towards the direct reaction, which provides good yields of indolyl-substituted imidazoles. Subsequent hydrolysis of salts under the action of NaHCO₃ in aqueous ethanol leads to the target indolyl-substituted imidazoles in almost quantitative yields.



Scheme 19 – Non-transition metal catalyzed C–H/C–H coupling of 2*H*-imidazole-1-oxides with indoles

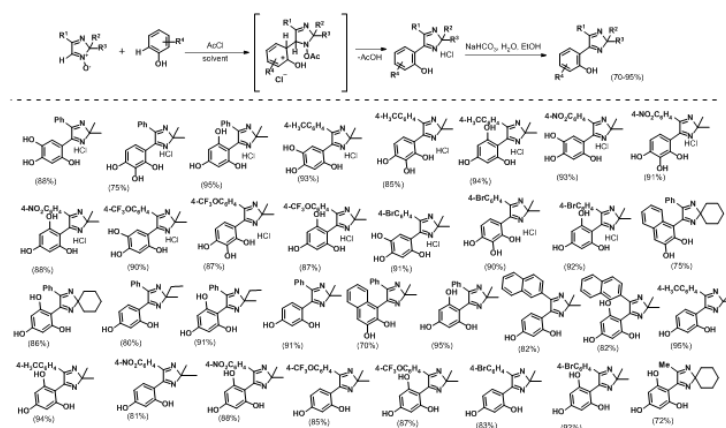
The possibilities of nucleophilic hydrogen substitution reactions according to the “Addition-Elimination” (S_N^H AE) scheme in cyclic aldonitrones were demonstrated using pyrrole derivatives of various structures as C-nucleophilic reagents under similar conditions (Scheme 20) [22]. In this case,

the products of C–C couplings were isolated in the form of stable hydrochlorides, which were quantitatively converted into the corresponding free forms 99 upon interaction with an aqueous-ethanol solution of NaHCO₃.



Scheme 20 – Non-transition metal C–H/C–H coupling of 2*H*-imidazole-1-oxides with pyrroles

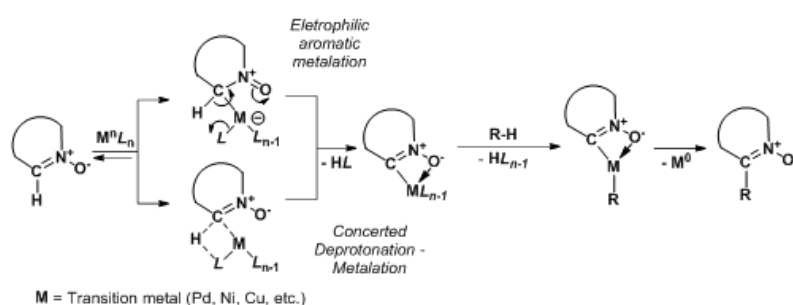
New azaheterocyclic compounds containing phenolic functional blocks were synthesized using direct uncatalyzed by transition metals C–H/C–H coupling reactions of 2*H*-imidazole-1-oxides with phenols (Scheme 21) [23]. In this case, reactions of nucleophilic hydrogen substitution in non-aromatic cyclic aldonitrones were realized according to the “Addition–Elimination” (SNHAE) scheme through the stage of formation of σ H-adducts with the formation of new phenol derivatives in the form of hydrochloride salts, which in some cases could be converted into the corresponding bases. To obtain the target phenolic derivatives of imidazoles in free form, NaHCO₃ (5% solution in water) was used as a mild base, preventing the formation of the corresponding sodium phenolates. Thus, a series of new phenolyl-substituted azaheterocyclic derivatives with yields of 70-95% were synthesized for the first time.



Scheme 21—Non-transition metal catalyzed C–H/C–H couplings of 2*H*-imidazole-1-oxides with phenols

Transition metal-catalyzed cross-dehydrogenative coupling reactions of non-aromatic azaheterocyclic systems

Cross-dehydrogenative couplings (CDC) reactions catalyzed by transition metals are a convenient synthetic tool in the targeted synthesis of bi- and polyfunctional organic compounds by modifying the free C–H bond of the starting organic substrate. Reactions of this type made it possible, within the framework of the dissertation work, to obtain a number of previously unknown functionally substituted azaheterocyclic systems of non-aromatic nature by constructing new C–C and C–N bonds (Scheme 22).



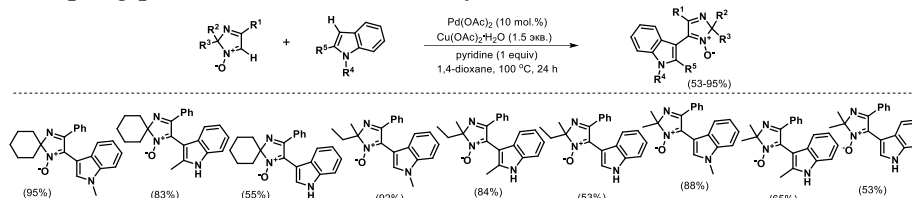
Scheme 22 – General scheme of metal-catalyzed reactions of cross-dehydrogenative combinations involving non-aromatic azaheterocyclic systems (using the example of functionalization of azaheterocyclic N-oxides)

According to generally accepted concepts, the key stage of cross-dehydrogenative combinations is the formation of an organometallic intermediate as a result of the interaction of the initial C–H substrate with a catalytic agent based on the salt form of the transition metal. The relative stability of the intermediate determines the possibility of implementing the entire functionalization process, and two possible mechanisms for generating the intermediate product are distinguished: electrophilic aromatic metalation and synchronous deprotonation - metalation. Subsequent interaction of the intermediate with a second participant in the reaction, in particular a nucleophilic reagent, leads to the formation of the target product, which is accompanied by the release of the transition metal in a reduced form.

C–H/C–H coupling reactions proceeding according to the scheme of cross-dehydrogenative transformations catalyzed by transition metals were used to synthesize new azaheterocyclic systems based on 2*H*-imidazole, functionalized with fragments of pyrroles, indoles, thiophenes and their derivatives.

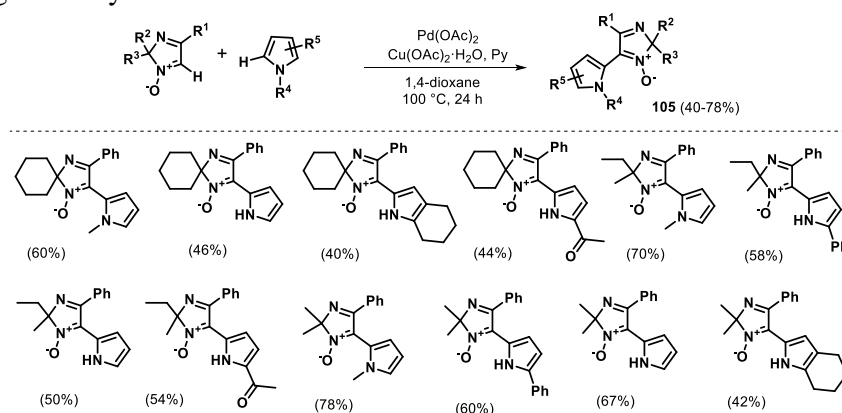
It was found that cyclic nitrones containing a hydrogen atom in the α -position to the N^+-O^- group of the azomethine fragment, which can be considered as non-aromatic analogs of azine N-oxides, enter into palladium-

catalyzed oxidative C–C coupling reactions with various indoles (Scheme 39) [24]. The reactions were carried out in 1,4-dioxane using pyridine as a base and a ligand stabilizing the organometallic intermediate, palladium(II) acetate as a catalyst and copper(II) acetate as an oxidizing agent. As a result, the C–C coupling products were obtained in yields of 53-95%.



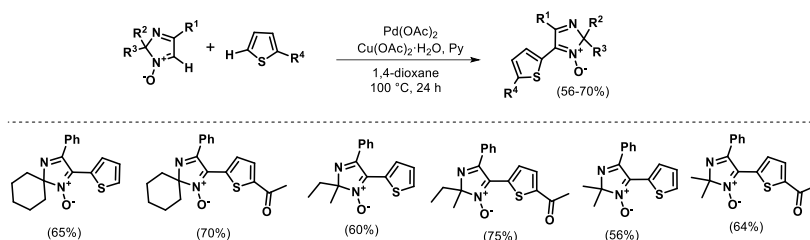
Scheme 23 – Palladium-catalyzed oxidative couplings of 2*H*-imidazole-1-oxides with indoles

To obtain new C(5)-modified 2*H*-imidazole derivatives with a pyrrole moiety, Pd(II)-catalyzed C–H/C–H couplings of cyclic nitrones with various π -excess heterocycles, namely pyrroles, were carried out (Scheme 24) and thiophenes 106 a,b (Scheme 41), containing both electron-donating and acceptor substituents [25]. The oxidative C–C coupling reactions used allowed to synthesize a number of previously unknown biheterocyclic assemblies containing an N-oxide group in the structure of the imidazole fragment in yields of 40-78%.



Scheme 24 — Palladium-catalyzed oxidative couplings of 2*H*-imidazole-1-oxides with pyrroles

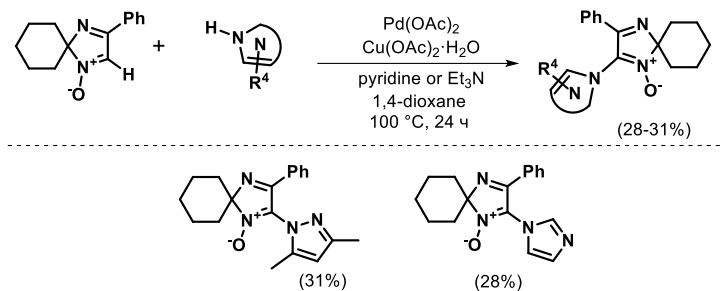
Reactions with thiophenes were carried out under similar conditions to those used for couplings of 2*H*-imidazole-1-oxides with indoles. For the reaction of 2*H*-imidazole-1-oxides with thiophenes. As a result, it was shown that the maximum yield of product was achieved when the reaction is carried out for 24 *h*, when the reagents were taken in the following proportions: 2*H*-imidazole-1-oxide (1.0 *mmol*), thiophene (2.0 *mmol*), palladium acetate (0.1 *mmol*), copper acetate (1.5 *mmol*).



Scheme 25 – Palladium(II)-catalyzed oxidative couplings of 2*H*-imidazole-1-oxides with thiophenes

Metal-catalyzed cross-dehydrogenative C–H/N–H coupling reactions have been used to synthesize novel 2*H*-imidazole-based azaheterocyclic molecular systems functionalized with azole moieties. As a result of these transformations, new biheterocyclic derivatives were obtained, which are mainly of interest as potential bioactive molecules.

The formation of a previously unknown product of C–N coupling was discovered in the reaction of 2*H*-imidazole-1-oxide with 1*H*-imidazoles under the conditions of Pd-catalyzed oxidative C–H/C–H coupling of aldonitrones with five-membered NH-containing heterocycles: 10 *mol.*% Pd(OAc)₂, 1.5 equiv Cu(OAc)₂·H₂O, 1.5 equiv base/stabilizing ligand (pyridine or NEt₃); boiling in 1,4-dioxane for 24 *h* (Scheme 26) [26]. It was found that in the case of imidazole, the use of pyridine as an auxiliary reagent is most suitable, while for the 3,5-dimethylpyrazole coupling, higher yields are achieved when NEt₃ is used.

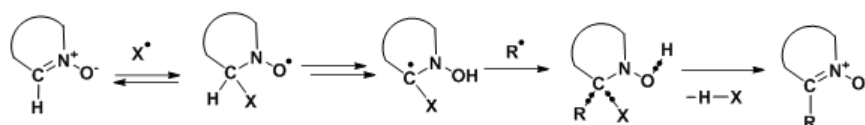


Scheme 26 – Palladium-catalyzed cross-dehydrogenation C–N couplings of aldonitrones with 1*H*-imidazoles

Radical-induced C–H/C–N reactions of cross-dehydrogenative couplings of non-aromatic azaheterocyclic systems based on 2*H*-imidazole-1-oxide

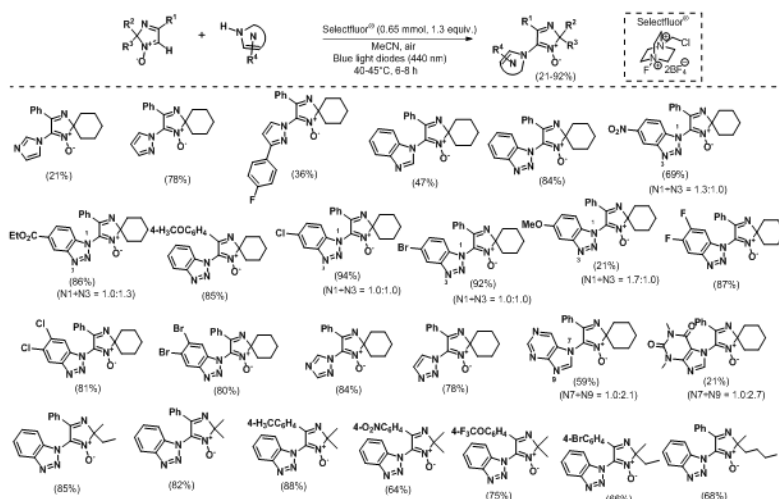
Cross-dehydrogenative couplings (CDC) reactions, in which radical initiators play a key role, currently deserve special attention as convenient and effective methods for the preparation of bi- and polyfunctional organic

compounds. In this work, reactions of this type were used to obtain a number of previously unknown functionally substituted azaheterocyclic systems of non-aromatic nature by constructing new C-N bonds (Scheme 27). According to generally accepted ideas, this type of cross-dehydrogenative combinations involves the activation of the C-H bond under the action of the radical particle X^\bullet , which acts as the initiator of the process. The activated radical heterocyclic substrate further interacts with the coupling partner, resulting in the formation of an adduct, the elimination of the HX molecule from which leads to the desired functionally substituted product.



Scheme 27 – General scheme of radical-induced reactions of cross-dehydrogenative combinations involving non-aromatic azaheterocyclic systems (in a simplified form using the example of functionalization of azaheterocyclic N-oxides)

In the course of the study, the possibilities of the Selectfluor®-induced C(sp²)-H azolation reaction of cyclic nitrones under visible light irradiation conditions were studied [27]. Thus, combinations of cyclic aldonitrones with various NH-azoles/azoloazines were carried out. As a result, bifunctional products containing a new C-N bond were obtained in yields of up to 94% (Scheme 28).



Scheme 28 – Radical-induced cross-dehydrogenative C-N couplings of aldonitrones with azoles

In summary, original synthetic approaches have been proposed and implemented, combined with a strategy of direct C(sp²)-H functionalization

of azaheterocyclic substrates of aromatic and non-aromatic nature, as well as accompanying structural transformations for the creation of promising organic compounds containing various functional blocks in their structure (calixarenes, polyfluoroarenes, carboranes, polyphenols, etc.). This chapter presents the main results of synthetic studies, studies of the structural, physicochemical and other properties of the obtained compounds, as well as information about the practical value of the developed approaches and the possibilities of practical use of the obtained compounds.

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**С-Н ФТОРИНГОВЫЕ ПРОЦЕССЫ НА АРОМАТИЧЕСКИХ И НЕАРОМАТИЧЕСКИХ СУБСТРАТАХ
И ИХ ПРИМЕНЕНИЕ В СИНТЕЗЕ
ОСОБЕННОСТИ**

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В.Н. ДАВЫДОВ, О.Н. ДИКИН**

Ակնարկը նվիրված է արդի օրգանական քիմիայի զարգացման կարևորագույն ուղղություններից մեկին՝ մոլեկուլային համակարգերի նպատակաուղղված նախագծմանը և ստեղծմանը: Նմանատիպ համակարգերը անհրաժեշտ են ազահետերոցիկլային միացությունների հիման վրա նոր դեղերի, ինչպես նաև մոլեկուլային էլեկտրոնիկայում կիրառվող «խելացի» նյութերի ստեղծման համար: C-H ֆունկցիոնալացման եղանակը, որը որպես սինթեզի ինքնուրույն ուղղություն առաջարկվել և մշակվել է Ուրալյան դպրոցի քիմիկոսների կողմից, հնարավորություն է ընձեռում խուսափելու հալոգենների կամ այլ ֆունկցիոնալ խմբերի ներմուծումից ռեակցիաների նախնական փուլերում, որի շնորհիվ իրականացվում է ջրածնի ատոմի անմիջական նուկլեոֆիլ տեղակալում ($\text{S}_\text{N}^\text{H}$): Ներկայացված աշխատանքը նվիրված է ազահետերոցիկլային համակարգերի $\text{C}(\text{sp}^2)\text{-H}$ ուղիղ ֆունկցիոնալացման նպատակաուղղված հետազոտությանը, որի շնորհիվ հնարավոր է ստանալ տարբեր՝ այլ եղանակներով անհասանելի արոմատիկ և ոչ արոմատիկ բնույթի հեռանկարային օրգանական և հիբրիդային նյութեր:

СТРАТЕГИЯ C-H ФУНКЦИОНАЛИЗАЦИИ ПРИ СОЗДАНИИ ФАРМАКОЛОГИЧЕСКИ АКТИВНЫХ СОЕДИНЕНИЙ И ФУНКЦИОНАЛЬНЫХ МАТЕРИАЛОВ

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Обзор посвящен важнейшему направлению развития современной органической химии – целенаправленному проектированию молекулярных систем, которые необходимы для создания на их основе эффективных лекарств, а также «умных» материалов для молекулярной электроники на базе азаетероциклических соединений. Среди известных синтетических подходов методология прямой C–H-функционализации является одной из наиболее прогрессивных. Концепция реакций нуклеофильного замещения водорода была впервые предложена и развита как самостоятельное научное направление в работах уральской школы химиков-синтетиков. Использование методов и подходов функционализации C–H, в частности, реакций нуклеофильного водородного замещения (S_N^H), позволяет избежать введения галогенов или других вспомогательных групп в азаетероциклические субстраты на предварительных стадиях. Настоящая работа посвящена систематическому исследованию возможностей стратегии прямой функционализации $C(sp^2)$ –H как эффективного синтетического инструмента направленного конструирования азаетероциклических систем ароматической и неароматической природы для получения перспективных органических и гибридных материалов на их основе.

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