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**Conference paper**

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# Nucleophilic C–H functionalization of arenes: a new logic of organic synthesis

## Expanding the scope of nucleophilic substitution of hydrogen in aromatics

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**Abstract:** Direct metal-free C–H functionalization of arenes with nucleophiles is a new chapter in the chemistry of aromatics. Comprehensive studies on nucleophilic substitution of hydrogen in arenes (the $S_N^H$ reactions), including mechanisms, intermediates, mathematic and electrochemical modeling, kinetics, electron-transfer, etc. have shown that this is not the hydride ion, but C–H proton is departed, and this process is facilitated by the presence of an appropriate oxidant or an auxiliary group. The $S_N^H$ reactions, as a part of the general C–H functionalization concept, change the logic of organic synthesis. They open new opportunities, avoiding incorporation of good leaving groups or other auxiliaries in an aromatic ring, as a prefunctionalization step, thus providing a better correspondence to the principles of green chemistry.

**Keywords:** arenes and hetarenes; C–H functionalization; dye-sensitizers for solar cells; eliminative and oxidative mechanisms; intermediate adducts; medicinal chemistry; Mendeleev XX; nucleophilic displacement of hydrogen.

## Introduction

Structural modifications of aromatic systems have always been a subject of considerable interest to many chemists. There are several principal ways to modify the structure of aromatic compounds. The classic approach is electrophilic aromatic substitution of hydrogen (Fig. 1) [1]. This type of C–H functionalization of aromatics is usually associated with aggressive electrophilic reagents (nitrous and sulfuric acids, halogens, etc), drastic conditions and a huge amounts of wastes, while sustainable development requires application of new chemical methodologies, based on the principles of green chemistry [2].

Transition-metal-catalyzed cross-coupling reactions (Buchwald–Hartwig, Heck, Kumada, Stille, Suzuku–Mijaura, Sonogashira, and others) have improved the situation considerably, providing chemists with a new tool to functionalize C–X (X-halogen) and C–H chemical bonds, however they cannot avoid a criticism, since most of these catalytic methods are based on using aryl halogenides, as starting materials. Besides that, transition metals (usually Pd) are rather expensive and toxic, and even traces of transition metals are not allowed to be impurities in drugs, organic solar cells and other high-tech materials (Fig. 2) [3].

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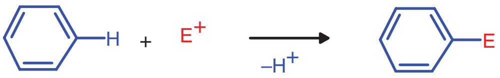


**Fig. 1:** C–H functionalization of aromatics through electrophilic displacement of hydrogen.

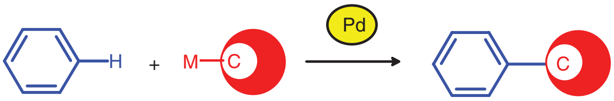


**Fig. 2:** Functionalization of aromatics through metal-catalyzed cross-coupling reactions.

In this communication we wish to discuss a relatively new synthetic methodology which is based on direct nucleophilic C–H functionalization of aromatic and heteroaromatic compounds, regarded formally as the displacement of the hydride ion (Fig. 3) [4–15].

More that 40 years passed since the first examples of reactions, leading to nucleophilic substitution of hydrogen in aromatic compounds, had been analyzed systematically and published in *the Russian Chemical Reviews* [16]. At that time text-books on organic chemistry claimed that "… hydrogen in an aromatic ring is not displaced with nucleophiles" [17]. The following decades brought a great deal of data concerning these $S_N^H$ reactions; a number of review articles, several monographs and hundreds of original papers have been published [see 4–15 and references therein]; this field became "…*the fascinating subject*…" [18], and one of the highlighted topics for many international journals. Many research groups all over the world (Poland, Belgium, Germany, Spain, Japan, USA, Russia and other countries) joined the field of nucleophilic C–H functionalizations, thus showing importance of the subject and its international recognition, which is reflected now in adavanced text-books on organic chemistry, for instance the Chapter 13 of the text-book [1] (Aromaic substitution, nucleophilic and organometallic) contains the sub-section "Hydrogen as leaving group".

The data accumulated show that, indeed, the $S_N^H$ reactions are of great fundamental and practical value, and can be used to modify a variety of nitro-, aza- and heteroaromatic compounds, including their benzo annelated analogues, as well as quinones, azinones, porphyrins, azulenes and arene-metal-complexes (Fig. 4), through the nucleophilic displacement of hydrogen and the formation of new carbon–carbon and carbon–heteroatom bonds (Fig. 5). The $S_N^H$ methodology involves a lot of reactions, such as nucleophilic alkylation, alkenylation, alkynylation, amination, hydroxylation, alkoxylation, cyanation, cyanomethylation, halogenation, sulfurization, as well as cymantrenylation, carboranylation, ferrocenylation and others [4–16].

Nucleophilic C–H functionalization of aromatic compounds is one of the key topics of current organic chemistry [4–16]. The scheme of the $S_N^H$ reactions (Fig. 3) looks rather simple, however, a hydrogen atom has a poor tendency for elimination as the hydride ion, and nucleophilic C–H functionalization appears to be a more complicated process. It involves a number of elementary acts, and can be realized through various multi-step pathways "addition-oxidation" or "addition-elimination" in the presence of an outer oxidant or through departure of an auxiliary group from the intermediate $\sigma^H$-adduct (Fig. 5).

Actually the metal-free cross-coupling between an aromatic substrate and nucleophile takes place as a reversible addition step, resulting in the formation $\sigma^H$-adducts, followed by their dehydrogenation into stable $S_N^H$ products (Fig. 5) [5]. Scale of stability of $\sigma^H$-adducts is varied to a great extent. Some of them are easily

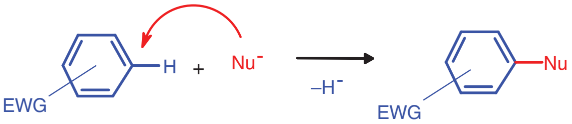


**Fig. 3:** C–H functionalization of aromatics through nucleophilic displacement of hydrogen.

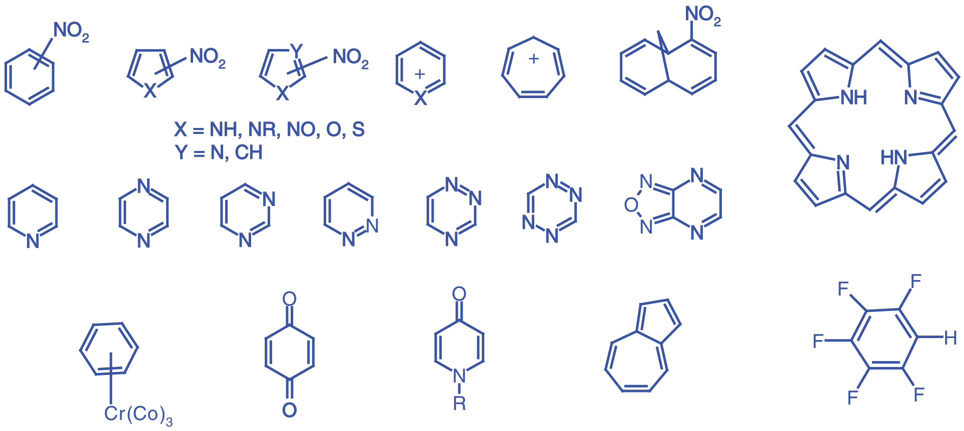


**Fig. 4:** Examples of aromatic and heteroacromatic compounds, as well their benzo annelated systems, quinones, azulenes and arene-metal complexes, entering the $S_N^H$ reactions.

oxidized, and in this case the $S_N^H$ reaction can be arranged as one-pot process. In other events intermediate $\sigma^H$-adducts are stable enough to be isolated from the reaction mixture, followed by their dehydrogenation into the final $S_N^H$ products, as a result of two successive reactions (Fig. 5) [5].

In the frames of this short review article we wish to present the results of our recent studies in the field of nucleophilic C–H functionalization of arenes and hetarenes, and also to show the scope and value of this synthetic methodology. More attention will be paid to the series of heterocyclic compounds, since due to a lower aromaticity of heteroaromatics intermediate heterocyclic $\sigma^H$-adducts used to be more stable than their carbocyclic analogues, and, therefore, they can be elucidated by NMR and other physical methods, including X-ray analysis. Some of these intermediate dihydro compounds are so stable, that they can find further applications [5].

There are a variety of catalytic methods which are used by chemists to modify the structure of aromatic and heteroaromatic compounds [3]. Many of them are based on using halogenated starting materials or intermediates. In particular, palladium-catalyzed cross-coupling reactions proved to be efficient synthetic tool to construct rather complicated organic molecules. This method is so popular among chemists that they use it even in those cases when other methods give better results. For instance, palladium-catalyzed amination of chloropyridine results in the target compound in a poor yield, while metal-free oxidative amination reaction, being in fact the cross-dehydrogenative coupling (CDC), provides much better yield of the same compound (Fig. 6) [19]. Besides that, the first approach suggests that a chloro atom has first to be incorporated into the

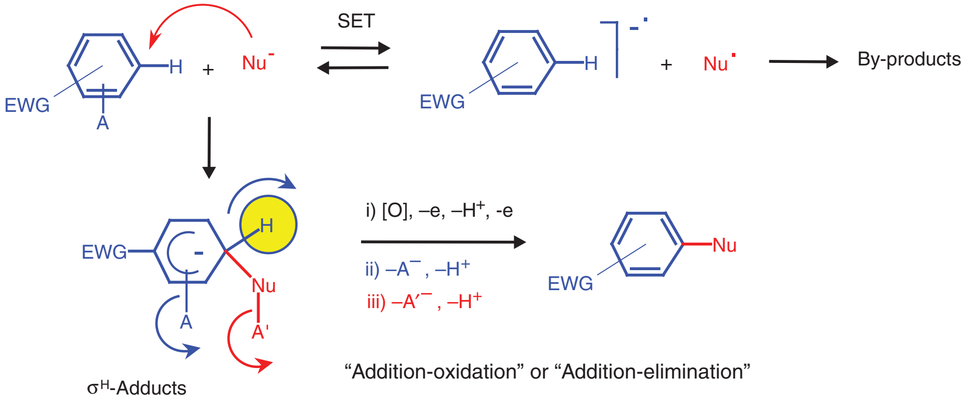


**Fig. 5:** General scheme for nucleophilic displacement of hydrogen in aromatic compounds.

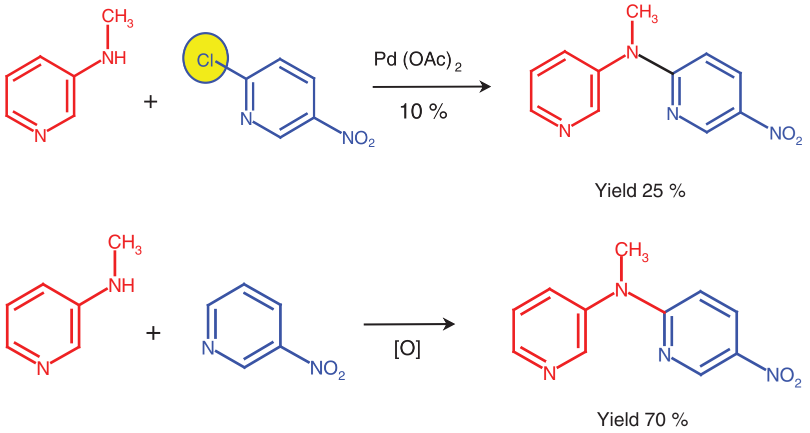


**Fig. 6:** Metal-catalyzed cross-coupling and metal free cross-dehydrogenative coupling of nitropyridines with 3-(methylamino) pyridine.

pyridine ring, just in order to be displaced later, and this procedure does not correspond to the principles of green chemistry [2].

Meanwhile, one of the key tasks of organic chemistry is to find direct routes for C–H functionalization of aromatics, avoiding incorporation of halogen or other functionalities in order to correspond the principles of green chemistry! American Chemical Society, Green Chemistry Institute, and pharmaceutical corporations have appealed to develop more aspirational reactions, such as direct C–H functionalization of aromatics [20].

## The general features of the $S_N^H$ reactions

It is well known that C–H carbons in electron-deficient aromatics are more vulnerable for a nucleophilic attack than those of C–X bonds bearing a substituent X (Fig. 7) [4–15]. Therefore, the $\sigma^H$-adducts, rather than the Meisenheimer complexes are expected to be formed, although appropriate conditions for elimination of hydrogen atom with pair of electrons have to be found (Fig. 7) [4–15].

It has been well established that addition of a nucleophile at C–H in an aromatic ring proceeds faster than at C–X, so nucleophilic substitution of hydrogen in arenes is faster, than displacement of a halogen atom. As a consequence, the generally accepted mechanism of the $S_NAr$ reactions has recently been corrected [21]. Indeed, there are many examples where a nucleophile attacks first an unsubstituted C–H carbon, instead of conventional nucleophilic displacement of halogen. In such cases a halogen atom appears to protect the attached carbon of the C–X bond from a nucleophiic attack. Indeed, a chloro atom in 1-chloro-4-nitrobenezene

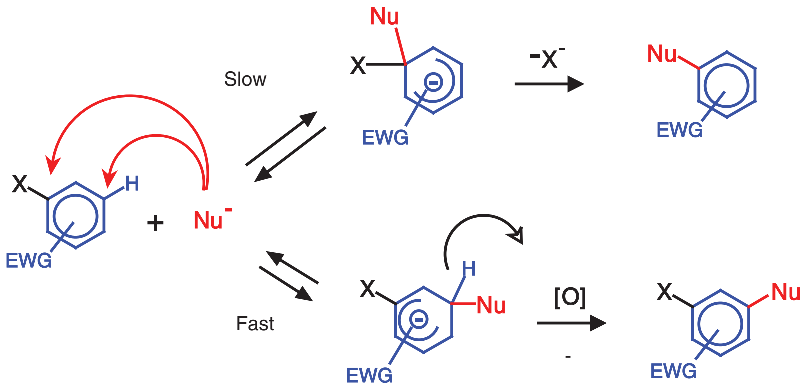


**Fig. 7:** Nucleophilic attack on C–H versus C–X carbons of an aromatic ring.

has to be regarded as the protecting group, directing a nucleophilic attack predominantly at C-3 carbon with retention of halogen at C-1 (Fig. 8) [9–13]. Since this chloro atom at C-1 can be displaced with nucleophiles, it enhances opportunities for functionalization of 1-chloro-4-nitrobenzene.

Such examples indicate that it is a high time to change the logic of organic chemistry. In fact, halogen atoms and other good leaving groups, which are usually displaced by nucleophiles, have to be regarded as protecting substituents, directing a nucleophilic attack at C–H bond. American chemists Daniel Morton and Huw Davies consider this field so important for the future, that they suggested to establish the center for selective C–H functionalization [22].

The data accumulated in the literature [4–16] show that, when designing synthetic ways to rather complicated aromatic molecules, and constructing C–C or C–X bonds (where X–heteroatom) with participation of nucleophilic reagents, it is not necessary at all to use preliminary derivatization of these molecules by introduction of chloro (halogen) or other auxiliary groups into an aromatic ring. It is advised to consider first an opportunity to incorporate the target nucleophilic fragments through direct nucleophilic displacement of the C–H bond in arenes and hetarenes. Even in the event, that an electron-defficient aromatic compound bears a halogen atom in an activated position, it is possible to exploit first the nucleophilic displacement of hydrogen of the C–H bond, rather than halogen or other auxiliary groups, as illustrated by the example given in Fig. 8.

Finally, if an aromatic substrate does not contain any electron-withdrawing group (EWG), for instance, the nitro or aza groups (examples of structures are shown in Fig. 4), and, contrary to that, it bears an electron-donating group (EDG), the $S_N^H$ methodology can also be exploited. In this case the new logic of organic synthesis suggests to consider an opportunity of electrochemical activation of an aromatic system through the anodic oxidation, followed by the nucleophilic C–H functionalization through displacement of hydrogen (Fig. 9) [14, 23–26].

This promising approach, using an anode as a “green oxidizing agent”, has recently been applied for C–H functionalization of 1,2- and 1,4-dihydroxybenzenes, as exemplified by electro-induced nucleophilic substitution of hydrogen in pyrocatechol (Fig. 10) [26]. Also it is worth mentioning that thorough mechanistic studies of electrochemical oxidation of intermediate $\sigma^H$-adducts derived from nitroaromatic compounds have been performed [27, 28].

As mentioned above, the key problem of the $S_N^H$ reactions is associated with *elimination of hydrogen with pair of electrons* ($H^- = 2e + H^+$), which can be realized either oxidative or eliminative pathways (Fig. 11) [4–15, 23, 29]. External oxidant is usually needed to perform the $S_N^H$ reaction, as illustrated by nucleophilic C–H

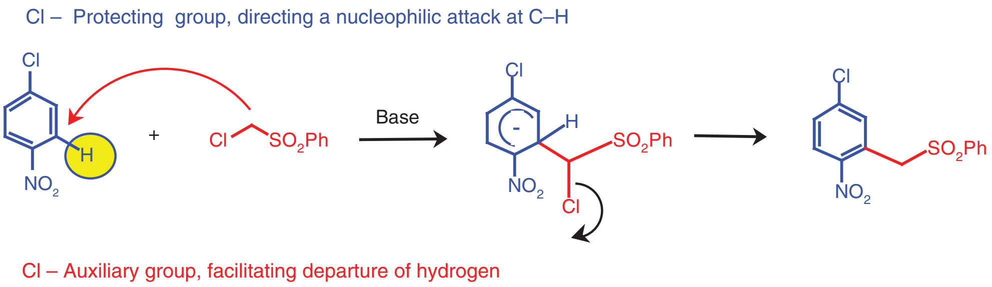


**Fig. 8:** C–H functionalization of 1-chloro-4-nitrobenzene with the vicarious C-nucleophile.

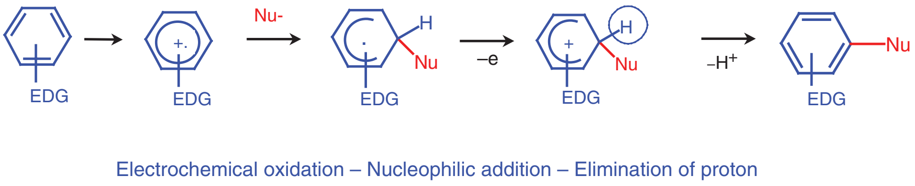


**Fig. 9:** Electrochemical activation of aromatics for nucleophilic C–H functionalization.

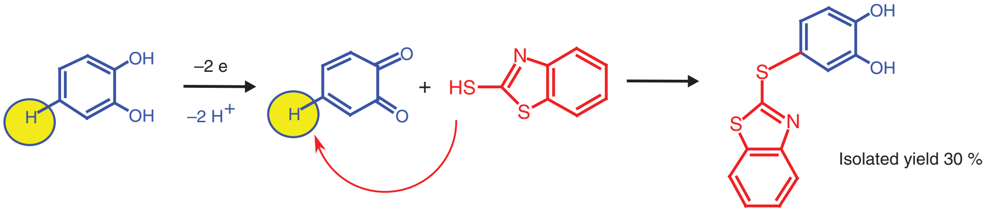


**Fig. 10:** Electrochemical C–H functionalization of pyrocatechol.

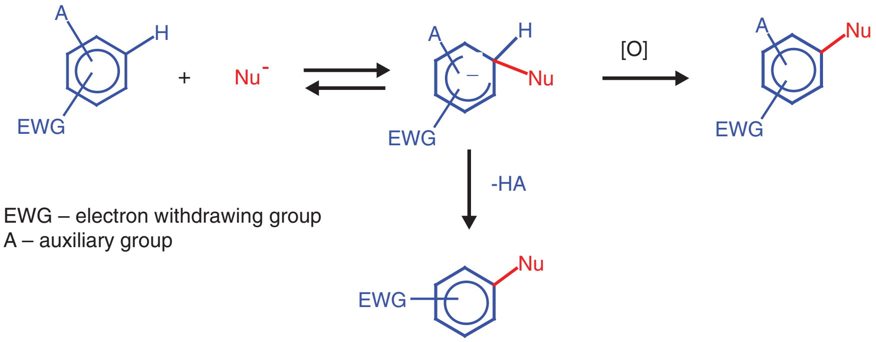


**Fig. 11:** Two principal modes of the $S_N^H$ reactions, depending on aromatization ways.

functionalization of triazolo[*a*]annulated 8-azapurins, proceeding in the presence of such specific oxidant, as phenyliododiacetate (Fig. 12) [30].

The most plausible mechanism for oxidative $S_N^H$ reactions is realized through transfer of electron from $\sigma^H$-adducts followed by departure of proton and one more electron $(H^- = e + H^+ + e)$ [26]. In some $S_N^H$ reactions the starting material acts as oxidant. For instance, in the reaction of acridinium salts with aromatic amines the acridinium cation is an effective oxidant, which provides aromatization of the intermediate adduct. This mechanism has been proved by kinetic studies (Fig. 13) [29].

Also oxidation with air oxygen at room temperature can be arranged effectively, provided titanium dioxide $TiO_2$ is used in this reaction as heterogeneous photocatalyst (Fig. 14) [31]. When irradiated with UV light the system $O_2/TiO_2$ produces electron/hole pair $(e^-/h^+)$, and oxygen dissolved in solution can be scavenged with exited electrons, thus affording the superoxide radicals, as very active oxidative species. Use of air oxygen is certainly attractive from ecological point of view, since it provides a better correspondence to atom economy and other principles of green chemistry [2].

Another principal mode of the $S_N^H$ reactions is the eliminative aromatization of intermediate adducts. In this case, two electrons are taken from adducts with the help of an auxiliary group.

There are several modes of eliminative $S_N^H$ reactions. The first case is that a nucleophile bears an auxiliary group. These reactions are regarded as *Vicarious nucleophilic substitutions of hydrogen*, as suggested by Prof. M. Makosza (Fig. 15) [9–13].

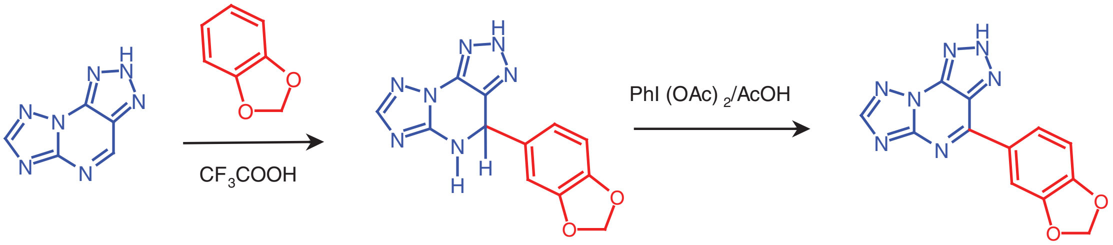


**Fig. 12:** Nucleophilic C–H functionalization of azapurins.

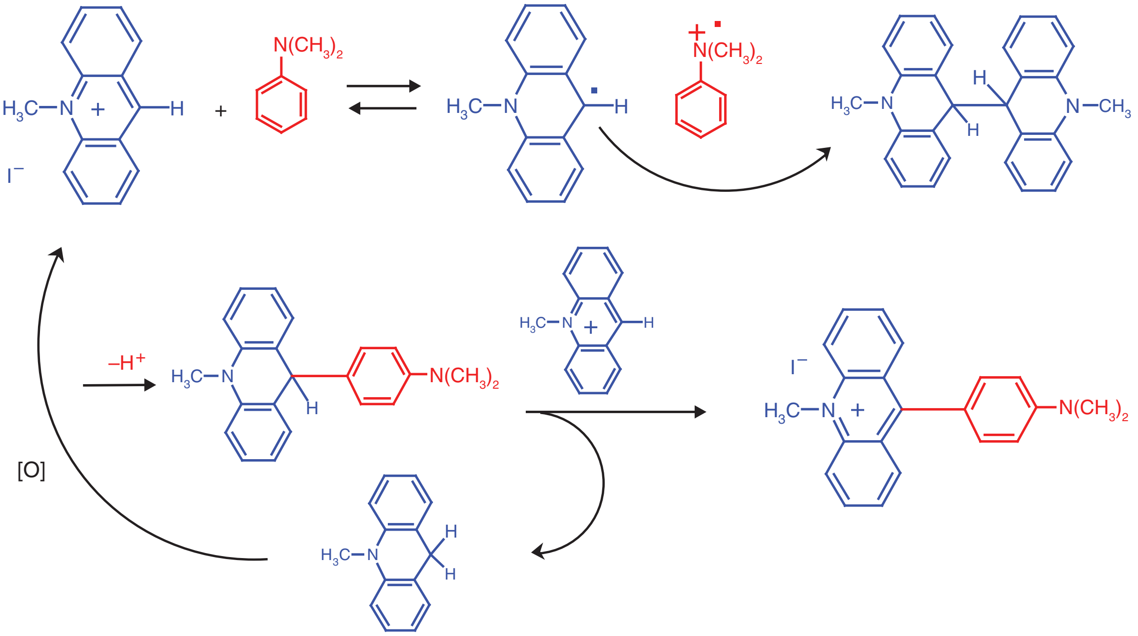


Fig. 13: C–H functionalization of acridium salts.

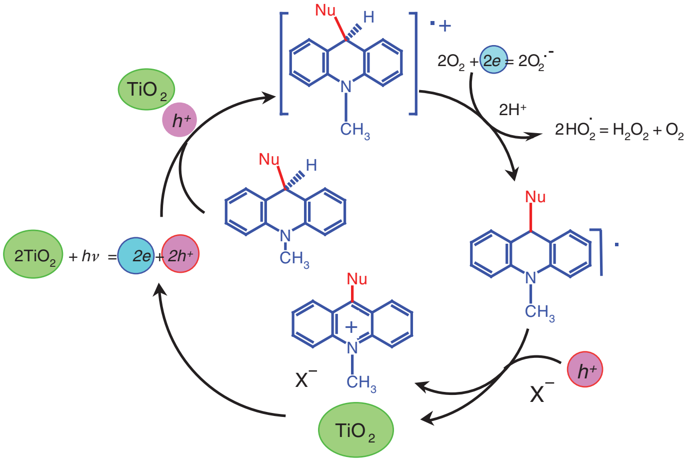


Fig. 14: Catalytic oxidation of intermediate adducts in nucleophilic C–H functionalization of acridium salts.

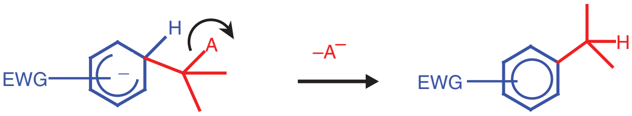


Fig. 15: Vicarious nucleophilic substitution of hydrogen.

If an auxiliary group is present in aromatic substrate, we deal with *tele*- or *cine*-substituions, as exemplified by displacement of hydrogen in amination of 1,7-naphthiridines (Fig. 16) [6] and C–H functionalization of azine-N-oxides (Fig. 17) [32].

A more complicated situation is when two or several auxiliary groups are present in reagents. A new C–H functionalization protocol has been suggested to incorporate arylalkenyl fragments. It is based on using

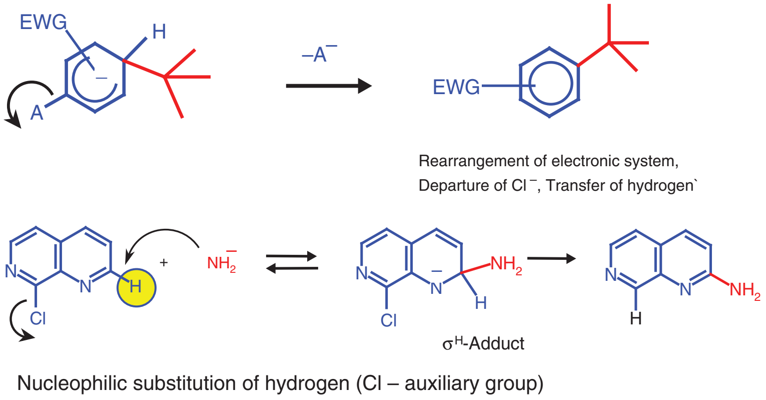


**Fig. 16:** *Tele*-amination of naphthyridines.

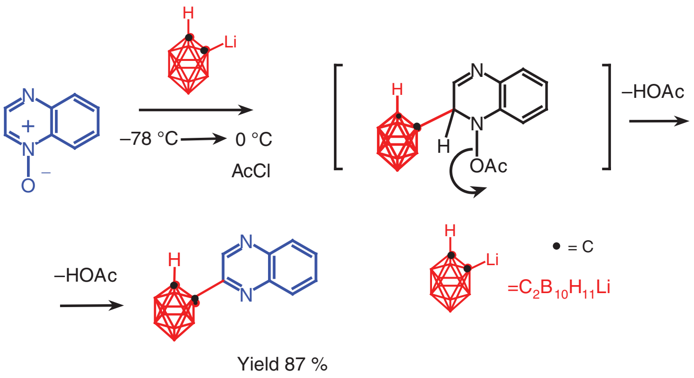


**Fig. 17:** Eliminative carboranylation of azine-N-oxides.

nucleophilic species, containing two auxiliary groups, which are generated in the course of the reaction. The process is initiated by the addition of morpholine at the C–C double bond of *β*-nitrostyrenes, and the subsequent addition of the generated carbanion to C-6 of furazano[3,4-*b*]pyrazines, followed by elimination of nitrous acid and morpholine (Fig. 18) [33].

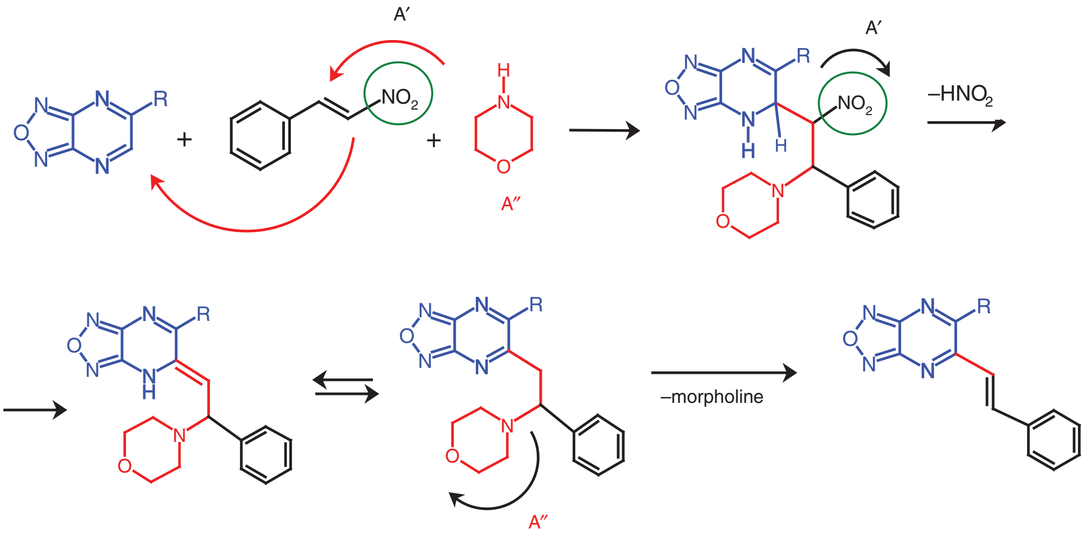


**Fig. 18:** Metal-free arylalkenylation of azaaromatic compounds.

In fact, oxidative and eliminative procedures are complementary to each other, as illustrated by the synthesis of 2-oxoindoles by using the intramolecular displacement of hydrogen. It is worth noting, that these derivatives are hardly accessible by other methods (Fig. 19) [34, 35].

## Use of the $S_N{}^H$ methodology in material science

The next few examples are entitled to demonstrate that metal-free $S_N{}^H$ reactions and metal-catalyzed cross-coupling reactions might be complementary to each other (Fig. 20) [36, 37]. Actually, the Suzuki cross-coupling reaction can be used for modification of C-5 position of the pyrimidine ring, which is less activated for nucleopilic attack than C-4, while the $S_N{}^H$ methodology is effective for nucleophilic C–H functionalization of position 4. It is worth mentioning that various combinations of these two types of C–C coupling reactions, Addition-oxidation or addition-elimination, and also various sequences of steps can be realized to obtain 4,5-disubstituted pyrimidines (Fig. 20) [36–44].

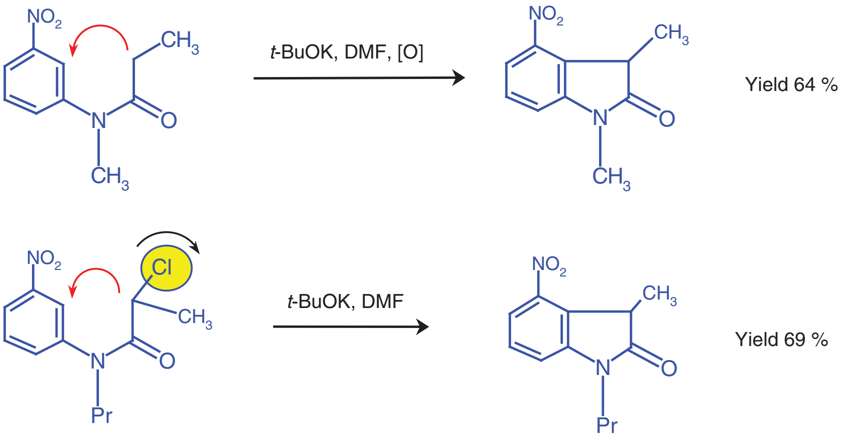


**Fig. 19:** Oxidative and eliminative C–H functionalization of nitroaromatics in the synthesis of 2-oxoindoles.

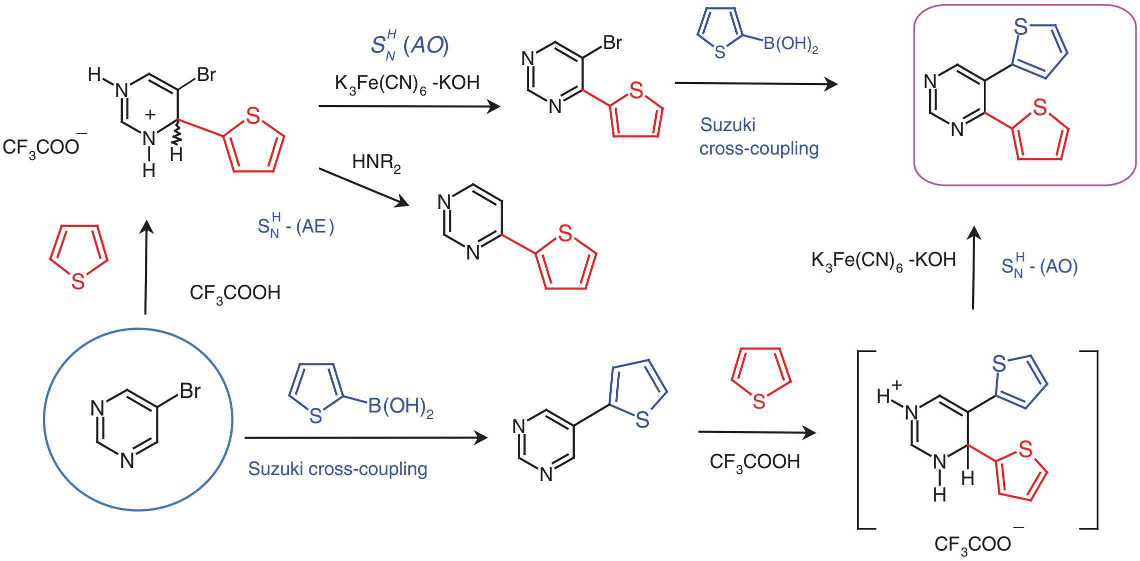


**Fig. 20:** Combination of the metal free $S_N{}^H$ and metal-catalyzed cross-coupling reactions of 5-bromopyrimidine.

These $S_N^H$ reactions have found application in material science to obtain new fluorescent compounds, which can be used as organic sensors for detection of nitroaromatic explosives [37, 38], and also as compounds of the D-A type for dye-sensitized solar cells (Fig. 21) [39, 40]. Indeed, compounds of this family have rather promising photophysical properties [39–44].

## Use of the $S_N^H$ methodology in medicinal chemistry

The characteristic feature of the $S_N^H$ reactions is that they take place without catalysis by transition metals. This is why the metal-free C–H functionalization reactions are of special interest for medicinal chemists.

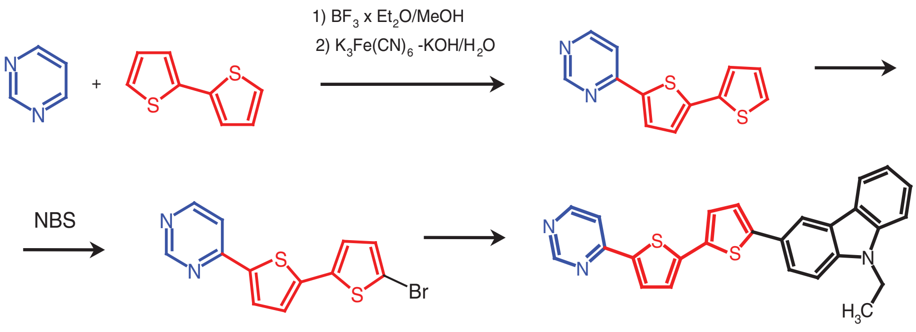
It has already been mentioned above that the advantage of the $S_N^H$ methodology is that it requires neither a preliminary functionalization, nor use of transition metals (usually Pd), as catalysts. It is very important for the synthesis of drugs, where even traces of transition metals are not permitted. This is why this methodology is so aspirational for both academic and industrial chemists, thus enabling them to avoid impurities of metals in the target products.

Use of the $S_N^H$ methodology in the chemistry of antibacterial fluoroquinolones is illustrated by intramolecular sybstitution of hydrogen, leading to the tricyclic pyrazolo[2,3-*a*]quinoline system (Fig. 22) [45].

The construction of antivirals of the indole family is a good example of vicarious cyanomethylation of nitroaromatics, as illustrated by the synthesis of Eudistomin C, the antiviral agent of marine origin (Fig. 23) [46].

The next example exploits the oxidative version of the $S_N^H$ methodology in the synthesis of potential drugs of the coumarine family. Being activated with the Lewis acid coumarins become electrophilic enough to react with nucleophilic thiophens to give $\sigma^H$ adducts, which can be oxidized with DDQ into C–H/C–H coupling products (Fig. 24) [47].

On the other hand, 5,7-dihydroxycoumarins can be regarded as nucleophilic species, capable of C–H/C–H cross-coupling with highly electron-deficient azines. A simple, selective and environmental friendly method has recently been developed in our laboratory to modify 7-nitroquinoxalin-2-ones (Fig. 25) [48].



NBS = N-Bromosuccinimide

**Fig. 21:** Use of the $S_N^H$ methodology to obtain compounds for dye-sensitized solar cells.

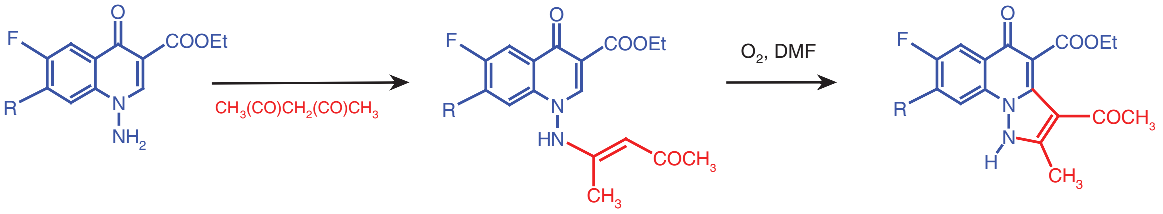


**Fig. 22:** Use of the $S_N^H$ methodology to modify the structure of fluoroquinolones.

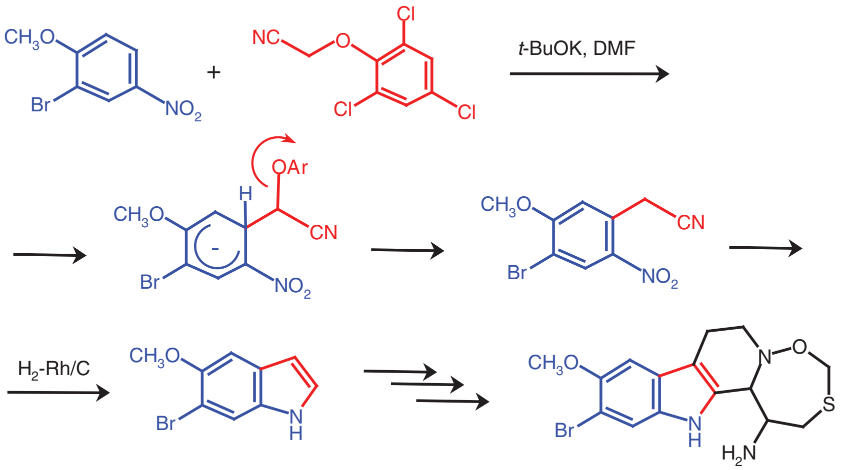


Fig. 23: Use of the $S_N^H$ methodology for the synthesis of Eudistomin C.

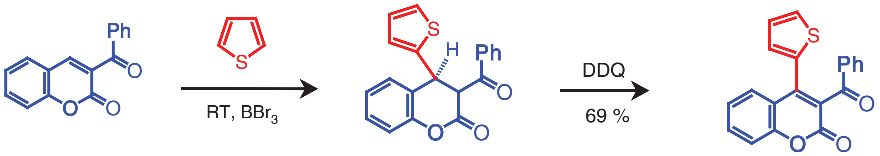


Fig. 24: Use of the $S_N^H$ methodology for C–H functionalization of coumarins.

A similar approach has been used for C–H/C–H cross coupling of 6-ntroazolopyrimidines with quercetin [49]. Also a number of antimycobacterials of the pyrimidine family have recently been obtained by using the $S_N^H$ methodology [50–52].

## Other applications of the $S_N^H$ methodology

In the 21st century chemists should pursue the principle of practical elegance, which means that a synthesis should be not only logical and perfect from technical point of view, but also ecologically benign. In this

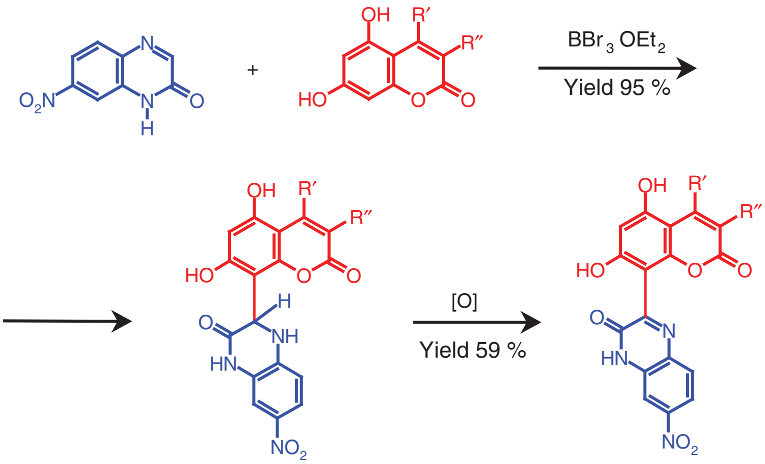


Fig. 25: C–H functionalization of azaaromatic compounds by action of dihydroxycoumarins.

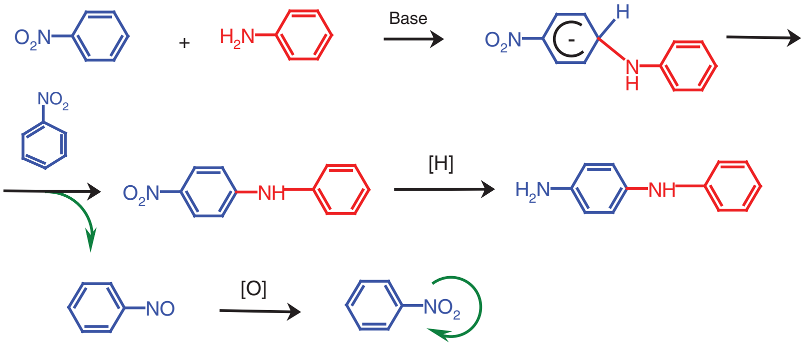


**Fig. 26:** Industrial application of the $S_N^H$ methodology.

respect $S_N^H$ methodology has advantages over traditional chemistry, including industrial applications. For instance, a new method for the synthesis of 4-aminodiphenylamine, the well-known anti-aging agent for rubber materials (Fig. 26) has been developed [53, 54]. In contrast to the traditional approach, which suggests incorporation of chlorine atom followed by its displacement, this approach exploits the $S_N^H$ methodology (Fig. 26) [53–56].

Amination of nitrobenzene with benzamide is also a good example of green chemistry based on use of the $S_N^H$ methodology [55, 56].

## Final remarks

In the frames of this communication we have tried to provide agruments that metal free C–H functionalization through nucleophilic displacement of hydrogen is a powerful synthetic methodology of great practical value. We believe that it is a high time to draw attention of both academic and industrial chemists to this methodology, based on using "chlorine-free" ecologically benign process and "green oxidizing agents", such as air oxygen and anodic oxidation. Research studies in the field of the $S_N^H$ reactions are currently in progress, as evidenced by numerous examples, presented in this paper, including electrochemical version of the $S_N^H$ reactions [23–28], and anodic dehydro-aromatization of intermediate $\sigma^H$-adducts [27, 28, 57]. Further development of experimental methods and mechanistic studies of the $S_N^H$ reactions are expected to enhance synthetic potential of metal-free C–H functionalizations, thus providing a progress in this promising field of organic synthesis.

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