Recent advances in the field of nucleophilic aromatic substitution of hydrogen

Oleg N. Chupakhin*, Valery N. Charushin

Postovsky Institute of Organic Synthesis, S. Kovalevskaya 22, Ekaterinburg 620090, Russia
Ural Federal University named after the first President of Russia B.N. Yeltsin, Mira St. 19, 620002, Russia

Abstract

Recent advances in the filed of direct C–H functionalization of aromatics and heteroaromatics through nucleophilic displacement of hydrogen in an aromatic ring are discussed.

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Introduction

One of the highlighted topics of current organic chemistry is direct C–H functionalization of aromatics without the incorporation of halogen or other functionalities, and thus corresponding to the principles of green chemistry. A large number of methods for structural modification of aromatic and heteroaromatic compounds, including the wide-spread palladium-catalyzed cross-coupling reactions, are based on the use of halogenated starting materials, although at times direct C–H functionalization can give better results. For instance, palladium-catalyzed amination of 2-chloro-5-nitropyridine results in the target amino compound in 25% yield, while the direct metal-free oxidative amination reaction of 3-nitropyridine provides a much better yield of the same compound (Scheme 1).
It is worth noting that the first approach requires incorporation of a chlorine atom into the pyridine ring, only to displace it later, and this certainly does not correspond to the principle of atom economy. On the other hand, it is well known that C–H carbons in electron-deficient aromatics are more vulnerable to nucleophilic attack than those of C–X bonds of compounds bearing a substituent X (Scheme 2).6–12 Therefore, the $\sigma^+$-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 (Scheme 2).6–14 There are a large number of examples, where substitution of hydrogen proved to occur with retention of a leaving group X, even located in an activated position in nitroarenes or heteroaromatic compounds.10–14

Several years ago the American Chemical Society, the Green Chemistry Institute, and a number of pharmaceutical corporations appealed to chemists for development of more aspirational reactions, such as the direct C–H functionalization of aromatics.15 American chemists Morton and Davis considered this field to be so important for the future, that they established the Center for selective C–H functionalization. They believe that the development of C–H functionalization techniques can change the logic of organic synthesis, and that C–H bonds have to be regarded as the favored functional groups.16

Actually, the direct functionalization of the C–H bond in aromatic compounds is now a highlighted topic for many journals. There are many aspects of C–H functionalization, including various pathways for the displacement of hydrogen through both catalytic and metal-free reactions. Within the scope of this Digest review, we intend to outline predominantly the publications of the last decade on metal-free C–H functionalization of aromatic compounds, proceeding through nucleophilic displacement of hydrogen.2–14

**Nucleophilic C–H functionalization of arenes**

There are two principal approaches for incorporating fragments of nucleophilic reagents into aromatic or related systems by displacement of the hydrogen of the C(sp$^3$–H bond. The first is based on catalytic activation of the C(sp$^3$–H bond. It involves the step of deprotonation followed by the formation of organometallic intermediates, which then react with nucleophiles to give the final products. The second approach involves a direct nucleophilic attack on an activated electron-deficient system, leading to the intermediate $\sigma^+$-adduct, followed by departure of a proton through oxidative or eliminative pathways (Scheme 3).7,17,18

Both approaches to functionalize the C(sp$^3$–H bond involve elimination of a proton, and an oxidant is needed for departure of the hydrogen. However, the sequence of steps and mechanisms of these C–H transformations are completely different, as illustrated by the recently published example taken from the chemistry of imidazole (Scheme 4).17

The first reaction is catalyzed by palladium acetate. It takes place in the presence of pyridine, as a base, and copper acetate, as oxidant, and results in the formation of indolyl-substituted imidazoles with the retention of the N-oxide moiety (Schemes 4 and 5).17

**Scheme 1.** Metal-catalyzed cross-coupling and metal free amination of nitropyridines.

**Scheme 2.** Nucleophilic attack at C–H versus C–X carbons.

**Scheme 3.** Catalytic and metal free C–H functionalization of aromatic compounds.

**Scheme 4.** C–H Functionalization of imidazoles.
The second reaction is free of metal catalysis. It occurs in the presence of acetyl chloride, proceeds faster, and results in compounds which have the same core structure as the indolyl-substituted imida-
zoles, but with the loss of the oxide group (Scheme 4). In the first case the $\text{C}($sp$^3$)$-$H bond is activated through the formation of an organopalladium intermediate, accompanied by loss of a proton. The former reacts with the nucleophilic indole to give the second organopalladium intermediate and finally, the target imidazole $N$-oxide (Scheme 5).

In the alternative approach the imidazole ring is activated for a nucleophilic attack through acylation of the nitrogen moiety, and the reaction proceeds according to the ‘Addition–Elimination’ protocol, which is rather typical for nucleophilic substitution of hydrogen as “...a fascinating subject of the last decade...”.

Indeed, the data accumulated in the literature show that $\text{SN}_1$ reactions are of fundamental value and can be used to build a variety of carbon–carbon and carbon–heteroatom bonds. This methodology involves a great variety of reactions: alkylation, alkenylation, alkylation, arylation, amination, hydroxylation, alkyoxylolation, cyanation, halogenation, as well as carboration, ferrocenylation, and others (Scheme 7).

**Strong and weak points of the $\text{SN}_2$ methodology**

In order to illustrate the synthetic opportunities of metal-catalyzed and metal-free C–H functionalizations, we have compared two approaches, the Negishi cross-coupling and the $\text{SN}_2$ reaction, used for the synthesis of the same chiral azinyl ferrocenes (Scheme 8).

Two types of chiral ferrocenes, bearing asymmetric carbon or sulfur atoms, were taken as starring materials for the synthesis of $P,N$-containing ligands. The first approach was based on the Negishi reaction, proceeding through palladium-catalyzed cross-coupling of organozinc derivatives with halogenated azines, so first, these intermediates had to be obtained before their cross-coupling. The $\text{SN}_2$ approach proved to be a much shorter pathway, affording the same compounds in better yields, and under very mild conditions (strong points), although the presence of DDQ was needed as oxidant (a week point) (Scheme 8).

The story is the same for the use of $\text{SN}_2$ reactions in the series of cyamtenunes. Once again, we have to stress the crucial role of the oxidant, since the key problem of the $\text{SN}_2$ reactions is associated with elimination of hydrogen with pair of electrons. Therefore, an appropriate oxidant (or an auxiliary group) is needed to realize the $\text{SN}_2$ reaction through either oxidative or eliminative pathways. Electrochemical nucleophilic aromatic substitution of hydrogen also appears to be a valuable alternative to induce C–H functionalization processes through activation of an aromatic ring, or to facilitate the $\text{SN}_2$ process through selective anodic oxidation of intermediate adducts.

**Oxidative $\text{SN}_2$ reactions**

An external oxidant is usually needed to perform the $\text{SN}_2$ reactions. The most plausible mechanism for oxidative $\text{SN}_2$ reactions is through transfer of an electron from $\sigma^*$-adducts followed by loss of a proton and the second electron. Effective oxidative systems for amination and alkylamination of azaaromatics, enabling one to carry out $\text{SN}_2$ reactions under mild conditions have been suggested. This has recently been exemplified by amination of triaza-pyrene (Scheme 10).

The starting electron-deficient substrate can be involved in the aromatization step. For instance, in the reaction with aromatic amines, occurring under argon atmosphere, the acridinium ion

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*[Diagram and Scheme 5, 6, 7, 8 are not fully visible in the image]*

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**Scheme 5.** Catalytic cycle for palladium-catalyzed C–H functionalization of imidazoles.

**Scheme 6.** Nucleophilic displacement of hydrogen in imidazoles.

**Scheme 7.** General character and scope of the $\text{SN}_2$ reactions.
plays the role of oxidant, thus providing aromatization of the intermediate adduct. This mechanism has been confirmed by the 
$^1$H NMR data, mathematic modeling and kinetic studies
(Scheme 11).6

The arylation of acridinium salts and other oxidative SN$_1$H reactions can be accomplished very effectively with oxygen in air at room temperature, provided that titanium dioxide TiO$_2$ is used as photocatalyst.35 When irradiated with UV light the system O$_2$/TiO$_2$ produces an electron/hole pair (e$^-$/h$^+$), and oxygen dissolved in a solution can be scavenged with exited electrons, thus affording the superoxide radicals, as very active oxidative species. Air is certainly attractive as oxidant from an ecological point of view, since the by-product is water, and it provides a better match with the atom economy and other principles of green chemistry (Scheme 12).35

Eliminative SN$_1$H reactions

Another principal version of the SN$_1$H reactions is based on eliminative aromatization of intermediate adducts. In this case, two electrons have to be taken from adducts with the help of an auxiliary anionic group (Scheme 13).6,7,10–14

There are several modes of eliminative SN$_1$H reactions. The first mode is realized, when a nucleophile bears one auxiliary group. These reactions are regarded as vicarious nucleophilic substitutions,
as suggested by Prof. Makosza (Scheme 14, for recent reviews see).10–14

If an auxiliary group is present in substrate, we deal with cine- or tele-substitutions (Scheme 15).6,7,10,11,36,37

Departure of auxiliary O-acetyl group can be illustrated by the reaction of quinoxaline N-oxide with the lithium salt of carborane (Scheme 16).38

A more complicated situation occurs when two or more auxiliary groups are available in reagents. When the lithium salt of imidazole N-oxide reacts with quinoline N-oxide, the reaction outcome depends on the reaction conditions. In the presence of DDQ the oxidative version occurs, with retention of both N-oxide functions (Scheme 17).39

Without an exogenous oxidant, a more electrophilic quinoxaline is aromatized with elimination of its N-oxide function, while in a similar reaction of quinoline N-oxide the auxiliary OAc group is eliminated from the nucleophilic fragment (Scheme 18).39

A new C–H functionalization protocol, based on the generation of nucleophilic species with two auxiliary groups in the course of the reaction, has recently been advanced (Scheme 19).40 The process is initiated by the addition of morpholine at the C–C double bond of β-nitrostyrenes, and the subsequent addition of the carbanion generated to C-6 of furazano[3,4-b]pyrazines, followed by elimination of nitrous acid and morpholine.40 It appears to be a general method for arylenethylation of aromatics, as shown by a similar C–H functionalization of other heterocyclic systems.41
Combination of the S_{N}^{H} and metal-catalyzed cross-coupling reactions

Metal-free S_{N}^{H} and metal-catalyzed cross-coupling reactions can be complementary to each other. It is nicely illustrated by transformations of 5-bromopyrimidine (Scheme 20).42–44

Actually, the Suzuki cross-coupling reaction can be used for modification of position 5 of the pyrimidine ring, which is less activated for nucleophilic attack, 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 used to obtain 4,5-disubstituted pyrimidines (Scheme 20).42–44

Some final remarks

Nucleophilic C–H modification of aromatic, heteroaromatic and related compounds can be realized through either metal-activation of C(sp^2)–H bonds or by means of nucleophilic substitution of hydrogen.

Advantages of the S_{N}^{H} methodology

As mentioned in Section Strong and weak points of the S_{N}^{H} methodology, the S_{N}^{H} approach provides a direct synthetic pathway to modify C(sp^2)–H bond in an activated aromatic ring. One of advantages of the S_{N}^{H} methodology is that it requires neither a preliminary functionalization, nor the use of transition metals (usually Pd), as catalysts. The latter is very important for the synthesis of drugs,45 and/or organic dyes for solar cells,46 in which even traces of transition metals are not permitted. This is why the direct metal-free C–H functionalization of aromatics is considered to be so aspirational for both academic and industrial chemists, by enabling them to avoid metal impurities in the target products.6–14

Scope and limitations of the S_{N}^{H} methodology

The S_{N}^{H} methodology has been applied to modify a variety of electron-deficient aromatic and heteroaromatic systems, as well as their benzo and hetero analogues (Scheme 21), by action of hundreds of C, N, O, S, Se, Si, and P-nucleophilic reagents of different nature.6–14

This methodology is an effective synthetic tool in medicinal45 and supramolecular chemistry,47–48 to modify metallabenzenes,50 arene-metal complexes,51,52 porphyrins (Scheme 22),53,54 polymers55 and free radical derivatives.56

Scheme 20. Combination of the metal free S_{N}^{H} and metal-catalyzed cross-coupling reactions of 5-bromopyrimidine.

Scheme 21. Aromatic systems entering the S_{N}^{H} reactions.

Scheme 22. Use of the S_{N}^{H} methodology to modify porphyrins.

Scheme 23. Use of the S_{N}^{H} methodology to modify calixarenes.
For instance, the S_N^1 reactions have been used to modify both the upper rim and the meso-position of calixarenes. A new example is shown in Scheme 23.

The S_N^1 reactions have found application in material science to obtain new heterocyclic ligands for metal complexes, and also compounds of the D–π–A type for dye-sensitized solar cells (Scheme 24). Indeed, compounds of this family have rather promising photophysical properties.

**Conclusion of the S_N^1 methodology to Green Chemistry**

The Nobel Prize winner professor Ryoji Noyori has claimed that in the 21st century chemists should pursue the principle of practical elegance, which means that a synthesis should be not only logical from technical point of view, but also ecologically benign. We believe that at least a number of the S_N^1 reactions do correspond nicely to this principle, as illustrated, for instance, by industrial synthesis of 4-aminodiphenylamine and other 4-nitroanilines (Scheme 25).

In this respect nucleophilic aromatic substitution of hydrogen has advantages over traditional synthetic approaches, including industrial chemistry. This is why the Flexsys America Co. was awarded with Green Chemistry Presidential Prize for development of a green synthetic route to 4-aminodiphenylamine based on the S_N^1 methodology (Scheme 25).

**Conclusion**

Nucleophilic aromatic substitution of hydrogen has been elucidating predominantly as C–H functionalization of π-deficient aromatic and heteroaromatic compounds. However, the scope of the S_N^1 reactions is not restricted by participation of electron-deficient aromatics. Neutral aromatic systems and arenes, bearing electron-donating groups, can also be activated for a nucleophilic attack through their anodic oxidation into radical-cation species, followed by addition of a nucleophile and elimination of proton (Scheme 26).

This procedure can be regarded as an additional protocol for the S_N^1 reactions, and this approach appears to be a promising area of organic synthesis.

The data of the last two decades demonstrate that the S_N^1 methodology appears to be a new chapter of aromatic chemistry, which is complementary to the advanced concept of metal-catalyzed cross-coupling reactions. These S_N^1 reactions have a common character and undoubtedly belong to the key chemical processes, thus reflecting a fundamental property of aromatic compounds.

In the scope of this digest review article, it is hardly possible to reflect all achievements in this rapidly growing field of organic chemistry. It is worth mentioning a number of recently published papers dedicated to novel applications of the S_N^1 methodology for the synthesis of heterocycles, including the reaction with Se-centered nucleophiles, leading to benzo[β]iselenophenes, and numerous S_N^1 transformations of nitroarenes, including those with P-centered diphenylphosphine anion, and incorporation of dialkyl phosphoglycine fragments, as well as new data on C–H functionalization of porphyrins, and rather exotic sapphyrins. Also it has recently been shown that even non-activated naphthalene can be involved in direct C–H functionalization by reacting with the complex of bromine with the chlorine-oxide in ionic liquids.

We have omitted a detailed consideration of mechanistic aspects of the S_N^1 reactions, which can involve electron-transfer acts and redox transformations between the following pairs ‘aromatic substrate—nucleophile’, ‘nucleophile—oxidant’, ‘intermediate σ^+-adduct—oxidant’, ‘intermediate σ^-adduct—starting aromatic substrate’ and other reacting species, which are reflected partly in books and review articles. However, we believe that the examples presented above are convincing enough to show that the S_N^1 methodology is gaining the interest of chemists (judging by a growing number of publications and research groups all over the world) as an efficient tool to build carbon–carbon and carbon–heteroatom chemical bonds between an aromatic ring and a variety of nucleophilic reagents, by using metal-free ecologically benign processes.

**References and notes**
