

Graphical Abstract

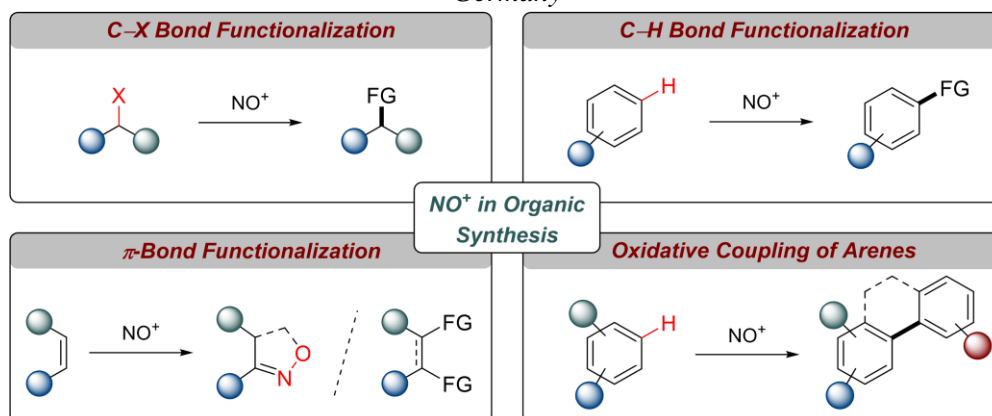
Reactive nitrogen species: nitrosonium ions in organic synthesis

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Reactive nitrogen species: nitrosonium ions in organic synthesis

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ABSTRACT

Nitrosonium ions are versatile and mild oxidants, which were successfully employed in organic transformations. The applications cover different fields, such as the functionalization of carbon-carbon and carbon-heteroatom bonds, functionalization of unsaturated bonds and the oxidative coupling of arenes, catalyzed by nitrosonium ions. Due to the ability of nitrosonium ions to modify various types of bonds with different modes of action, a variety of applications has been established, which addresses current challenges in organic chemistry research. By considering additional points, such as safety of reagents, by-product formation, employed solvents and energy consumption, several aspects of green and sustainable chemistry can be addressed. Within this review, synthetic applications of nitrosonium ions under transition metal-free reaction conditions are summarized.

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1. Introduction

Transition metal-free chemistry has observed steadily increasing interest in the past decades.^[1] Several approaches of synthetic organic chemistry are covered within this field. Organocatalysis is the most prominent representative. Additionally, radical chemistry, photochemistry, electrochemistry, and oxidative coupling have emerged as modern approaches for metal-free synthesis.^[2] Metal-free reactions serve as a powerful alternative, since transition metal-catalyzed reactions are to some extent still limited in application and face particular challenges. Pharmaceuticals, which are often synthesized applying transition metal-catalysis, might be contaminated with residual metal impurities. Removal of those impurities can be challenging, expensive and time intensive.^[3] Metal-based impurities might alter the physical properties of organic molecules, which potentially causes problems in material science applications.^[4] Toxicity, high prices, oxygen and moisture sensitivity are downsides associated with transition metal catalysts.^[5] In the context of C–H bond functionalization, a sacrificial oxidant in stoichiometric amounts is often required.^[6] However, metal-free approaches face disadvantages as well. Regioselectivity issues are common drawbacks and the requirement of stoichiometric amounts of high molecular weight oxidants is detrimental, since some organic oxidants are toxic, explosive or corrosive.^[2]

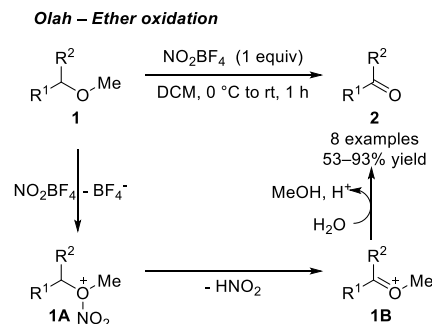
This literature survey is an overview with emphasis on the application of nitrosonium ions as reagents and catalysts in organic synthesis. The structure and properties of nitrosonium ions have been well reviewed in the past.^[7] Nitrosonium ions are reactive intermediates and found wide application in organic chemistry. The nitrosonium ion is a strong single-electron oxidant with an oxidation potential of $E^\circ = 1.28$ V (vs SCE in MeCN).^[8] Nitrosonium ions can be generated using nitrosonium salts with different counterions (e.g. BF_4^- , PF_6^- , HSO_4^- , ClO_4^-), nitrous acid, nitrogen-oxygen gases (e.g. NO_x , N_2O_3 , N_2O_4), nitrites and pre-functionalized ionic liquids.^[9] A common method to generate nitrosonium ions is the treatment of sodium nitrite with strong acids (e.g. acetic acid, trifluoroacetic acid, triflic acid). Nitrosonium salts are inexpensive, stable and safe in handling, which makes them attractive reagents in organic chemistry.^[10] Additionally, reactive nitrogen species can be found in every living cell and undertake important functions as messenger molecules and as transient post-translational protein modifications.^[11]

Classically, enolizable C–H bonds undergo nitrosation in the presence of nitrosonium salts.^[12] Nitrosonium ions react with primary, secondary and tertiary amines under N–N bond formation.^[7b] Additionally, nitrosonium salts were also applied for the diazotization of anilines.^[13] Diazonium salts are important precursors for radical reactions, transition metal-catalyzed reactions and substitution reactions.^[14] However, *tert*-butyl nitrite (TBN) has superseded nitrosonium salts for N–N bond formation due to its superior solubility in organic solvents, facile handling and functional group tolerance.^[15] Under certain conditions, the nitrosonium ion is able to form stable complexes with sterically demanding alkenes, aromatic compounds and heteroatom-centered ligands.^[7a]

2. Oxidative carbon-carbon and carbon-heteroatom bond functionalization

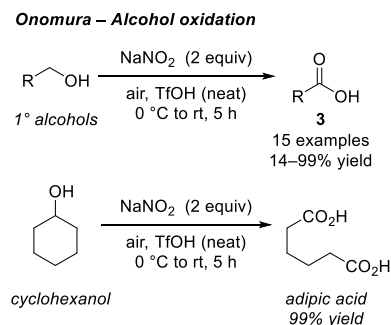
Due to the oxidative character of nitrosonium ions, a great number of applications are based on the oxidative functionalization of carbon-heteroatom bonds. For numerous applications of nitrosonium salts, George Olah holds a pioneer

position. Olah's group reported the C–O bond activation of methyl ethers (**1**) with nitronium tetrafluoroborate for the synthesis of ketones (**2**) (Scheme 1). Initially, the nitrosonium ion activates the ether bond by forming intermediate **1A**. Reductive elimination of nitrous acid leads to the formation of intermediate **1B** and subsequent hydrolysis gives the desired ketone (**2**).^[16]



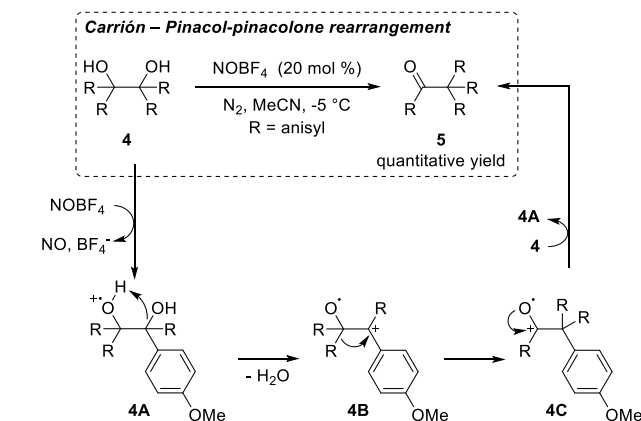
Scheme 1 Olah's oxidation of methyl ethers.

This work served as a template for several other oxidation reactions. Using the same conditions, alcohols, silyl protected alcohols, and stannyl-protected alcohols were converted to the corresponding carbonyl analogues.^[17] The mixture of NaNO_2 -TfOH is capable to oxidize primary alcohols to the corresponding carboxylic acids (**3**). Additionally, cyclohexanol was converted to adipic acid in one step (Scheme 2).^[18] Later, Wu and co-workers developed the removal of TBS and THP protecting groups from alcohols using nitrosonium tetrafluoroborate as catalyst.^[19] The method was also suitable for the deprotection of aliphatic and phenolic hydroxy groups.



Scheme 2 Conversion of primary and secondary alcohols to carboxylic acids.

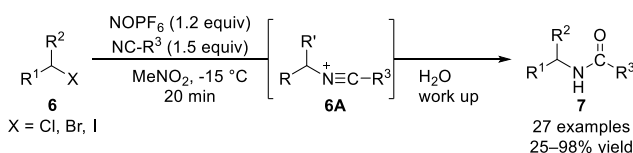
In 1993, Carrión and co-workers reported the pinacol-pinacolone rearrangement initiated by substoichiometric amounts of nitrosonium tetrafluoroborate (Scheme 3).^[20] This reaction represents an interesting application, since other oxidants usually favor the glycol cleavage. According to the proposed mechanism, a single-electron-transfer (SET) initiates the reaction to form **4A**. Elimination of water delivers intermediate **4B**, which is followed by 1,2-migration of the anisyl group to afford **4C**. Radical transfer of **4C** to pinacol (**4**) leads to the formation of pinacolone (**5**) and allows the propagation of the reaction. The oxidation potential of pinacol **4** was determined with cyclic voltammetry. A potential of 1.32 V and 1.46 V (vs Ag/Ag^+ in MeCN) was determined, which supports the proposed SET process. Consequently, no product was formed when the anisyl groups were replaced by *para*-chlorophenyl groups.



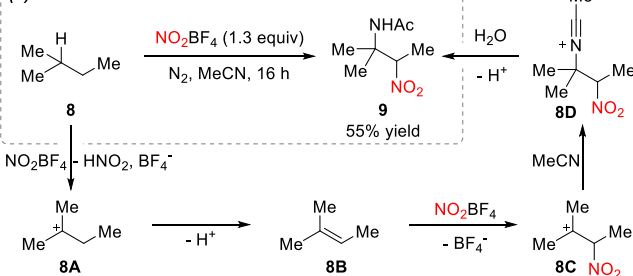
Scheme 3 Oxidative pinacol-pinacolone rearrangement using sodium tetrafluoroborate as initiator.

Olah and co-workers reported the oxidative displacement of alkyl halides (**6**) with stoichiometric amounts of nitronium tetrafluoroborate (Scheme 4a). It was proposed that the nitronium ion oxidizes the halide to generate a better leaving group. Different nitriles were used as trapping reagents. Aqueous work up of **6A** yielded the corresponding amides **7** via a Ritter-type reaction.^[21] Bach and co-workers reported comparable results (Scheme 4b). The employment of secondary alkyl halides yielded *vicinal* nitro amides through activation of the halide. Interestingly, 2-methylbutane (**8**) as a substrate yielded the same product *via* hydride abstraction at the tertiary carbon atom. According to the proposed mechanism, **8A** is formed upon oxidation of the tertiary C–H bond. Elimination leads to formation of **8B** and the nitronium ion is attacked by the double bond. Finally, **8C** is scavenged by the solvent to form **8D**. Aqueous work up gives the *vicinally* functionalized product **9**.^[22] Further, oxidation of propellanes and other simple alkanes was successfully reported in the following years.^[23]

(a) Olah – Ritter-type amination



(b) Bach – Vicinal C–N bond formation

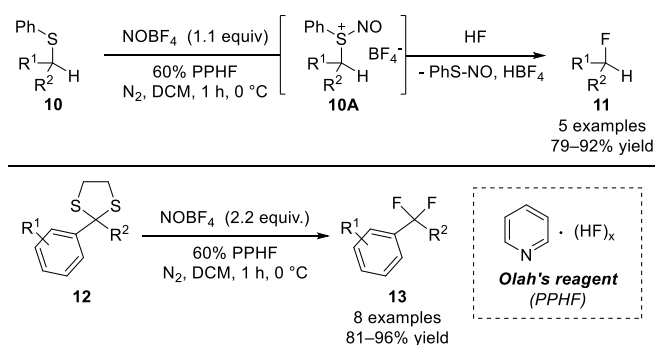


Scheme 4 Oxidative functionalization of carbon-halide and $\text{C}_{\text{sp}^3}\text{--H}$ bonds. (a) Ritter-type amination of secondary alkylhalides. (b) Vicinal C–N bond formation by oxidation of inert $\text{C}_{\text{sp}^3}\text{--H}$ bonds.

In addition, Olah's group reported the oxidative fluorination of thioethers (**10**) and dithiolanes (**12**) (Scheme 5).^[24] Initially, *S*-nitrosation for the formation of **10A** leads to the activation of the C–S bond, followed by the nucleophilic attack of fluoride to form **11**. PPHF (hydrogen fluoride pyridine) serves as fluoride source in this reaction. The method allowed the mono-functionalization of thioethers as well as the synthesis of *geminal* difluorinated

products (**13**) using thioacetals (**12**). In the absence of a fluoride donor, the sulfides are converted to the corresponding ketones.^[25]

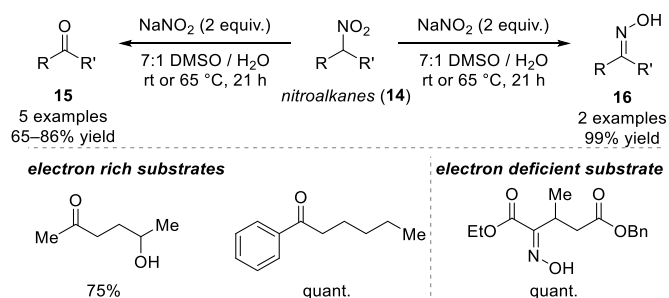
Olah – Fluorination of thioethers and dithiolanes



Scheme 5 Fluorination of thioethers and dithiolanes using nitronium tetrafluoroborate.

The conversion of nitroalkanes (**14**) to ketones (**15**) and oximes (**16**) with sodium nitrite was reported by Mioskowski and co-workers (Scheme 6).^[26] The authors proposed the *in situ* formation of nitronium ions, which are involved in the oxidation of the starting materials. The synthesis of ketones or oximes from secondary nitroalkanes is also known as Nef reaction.^[27] Despite the synthetic applicability, the mode of action of sodium nitrite, in particular the exact role of the nitronium ion could not be conclusively uncovered yet. However, conversion of oximes to ketones is known to involve nitronium species.^[28]

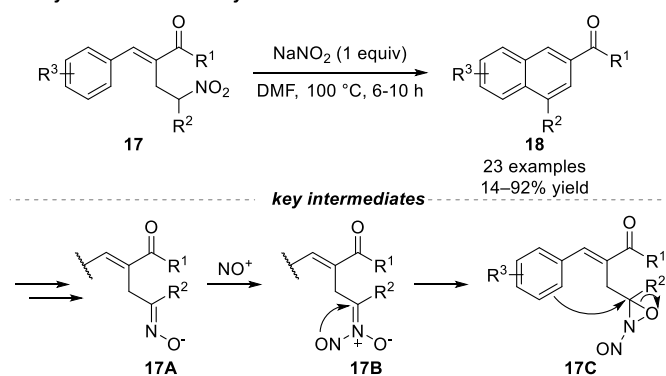
Mioskowski – Synthesis of ketones and oximes



Scheme 6 Synthesis of ketones and oximes from nitroalkanes.

Using related reaction conditions, Reddy and co-workers reported the synthesis of naphthalenes **18** from arylated nitroalkanes **17** (Scheme 7).^[29] The authors proposed a Friedel-Crafts-like reaction mechanism upon functionalization of the nitroalkane. Oxime **17A** was proposed as intermediate, which undergoes nitrosation in order to form **17B**. Intramolecular nucleophilic attack and formation of **17C** induces the Friedel-Crafts-type reaction. Afterwards, elimination of 1,2-dihydroxydiazene as leaving group occurs and the product is formed. The diazene further decomposes to water and nitrous acid. The scope of the reaction covered a broad number of naphthalenes and carbazoles, demonstrating good functional group tolerance.

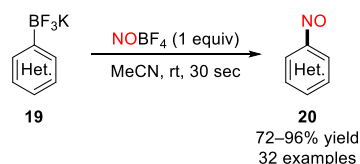
Reddy – Friedel-Crafts alkylation



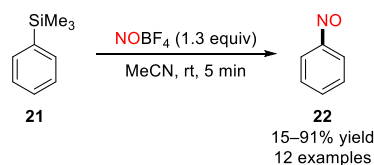
Scheme 7 Friedel-Crafts-like synthesis of naphthalenes.

In 2014, Molander and Cavalcanti reported the efficient nitrosation of aromatic boronates (**19**) with nitrosonium tetrafluoroborate (Scheme 8a).^[30] The reported reaction conditions allowed the synthesis of a broad number of nitroso arenes (**20**), including challenging heteroarenes. For the majority of substrates, the formation of products occurred within 30 seconds. The transformation is also suitable for aryl boronic acids and aryl boronic esters, but with reduced yields. In 2018, Hilt and co-workers reported a related transformation for the nitrosodesilylation of **21** (Scheme 8b).^[31] A shared feature of both methods is the fast reaction rate. According to the proposed mechanism for both approaches, a shared pathway for the nitrosation exists *via ipso*-substitution of the leaving group. Precise control of the amount of nitrosonium salt was crucial in order to avoid poly-nitrosation. By using trimethylsilyl-substituted fluorobenzene as model substrate, ¹⁹F-NMR studies revealed that more equivalents of nitrosonium tetrafluoroborate lead to the addition of a second nitronium ion to the nitroso group.

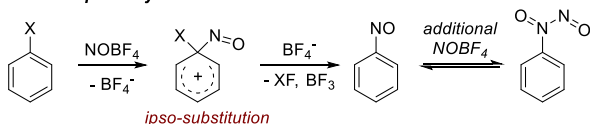
(a) Molander – Nitrosation



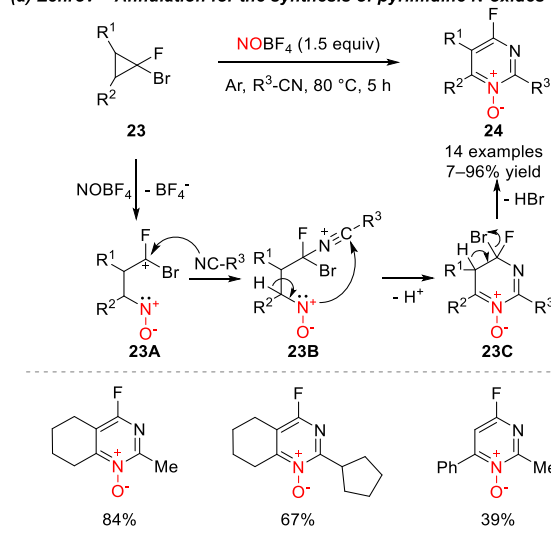
(b) Hilt – Nitrosodesilylation



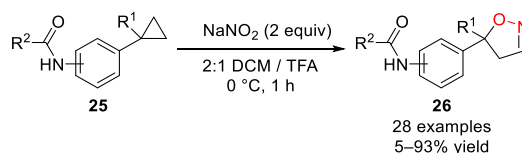
common pathway for both reactions

Scheme 8 Nitrosation of weak C_{sp}²-heteroatom bonds. (a) Nitrosation of heteroaryl borates with nitrosonium tetrafluoroborate. (b) Synthesis of nitrosobenzene *via* nitrosodesilylation.

Zefirov and co-workers converted the halogenated cyclopropanes **23** to fluorinated pyrimidine *N*-oxides (**24**) under incorporation of a nitrosonium ion and an organic nitrile molecule (Scheme 9a).^[32] According to the proposed mechanism, the nitrosonium ion reacts with the strained C–C bond of the cyclopropanes **23**. Ring opening gives the positively charged intermediate **23A**, which is subsequently scavenged by the nitrile to form **23B**. Nucleophilic attack at the nitrile carbon leads to the formation of **23C**. Finally, aromatization with elimination of HBr affords the pyrimidine *N*-oxide **24**. Trofimova reported the functionalization of cyclopropyl substituted anilines **25** (Scheme 9b). Oxidative addition of the nitrosonium ion to the cyclopropane unit yielded isoxazolines **26**.^[33] Sodium nitrite served as source for nitrosonium ions, since they were generated *in situ* under the acidic reaction conditions. However, undesired nitration, formation of benzoxazines, and formation of quinolines as by-products limited the synthetic applicability. In analogy to the work of Trofimova's group, synthesis of halogenated isoxazoles was reported by Zyk and co-workers.^[34]

(a) Zefirov – Annulation for the synthesis of pyrimidine *N*-oxides

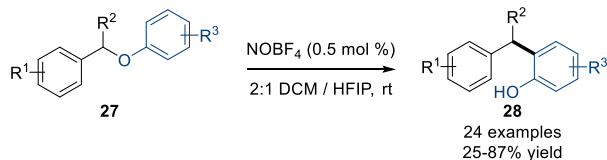
(b) Trofimova – Ring opening of cyclopropanes

Scheme 9 Oxidative C–C bond functionalization of cyclopropanes. (a) Nitrosation of *geminal*-bromofluorocyclopropanes for the synthesis of pyrimidine *N*-oxides. (b) Synthesis of aniline-fused isoxazolines.

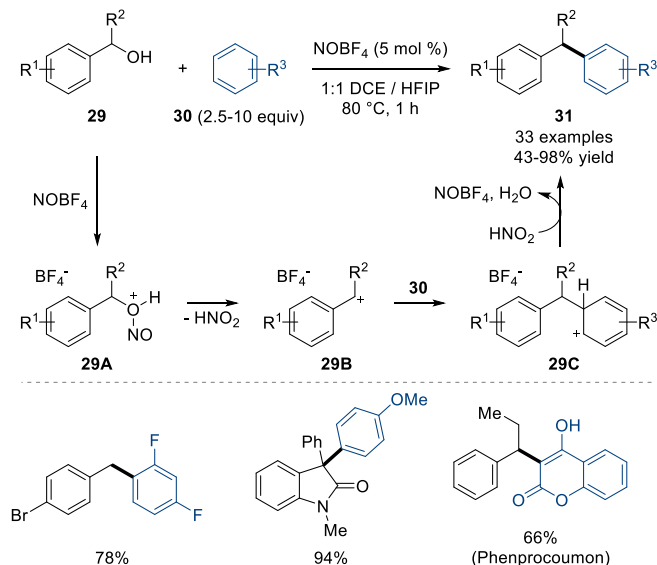
In 2018, Antonchick and co-workers studied the intramolecular rearrangement of benzyl aryl ethers (**27**) using nitrosonium tetrafluoroborate as catalyst (Scheme 10a).^[35] The reaction proceeded *via* an intramolecular Friedel-Crafts reaction upon C–O bond activation, initially discovered by Tarbell and co-workers.^[36] Based on these results, an intramolecular variant was developed (Scheme 10b). Under adjusted reaction conditions, the coupling of various benzyl alcohols (**29**) with arenes (**30**) for the synthesis of diarylmethanes (**31**) was performed.^[35] According to the proposed mechanism, nitrosonium tetrafluoroborate activates the benzylic alcohol (**29A**). Under reductive elimination of nitrous acid, the benzyl cation **29B** is formed. Subsequently, the intermediate reacts with arene **30** to form the desired product *via* an electrophilic aromatic

substitution (**29C**). The nitrosonium ion is regenerated upon protonation of nitrous acid by HBF_4 . This Friedel-Crafts type reaction allows the efficient coupling of non-activated starting materials and avoids the usage of commonly utilized organo halides. A broad scope for both variants was demonstrated, even covering the synthesis of drug molecules in a straightforward manner.

(a) Antonchick – Rearrangement of benzyl aryl ether



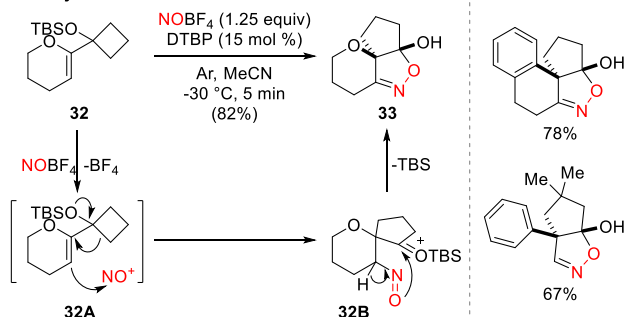
(b) Antonchick – Metal-free benzylation of arenes



Scheme 10 Nitrosonium ions in C-O bond activation. (a) Catalytic intramolecular rearrangement of benzyl aryl ethers. (b) Intermolecular benzylation of arenes with benzyl alcohols.

Recently, Tu's group reported the incorporation of nitrosonium tetrafluoroborate using silyl allyl ethers **32** (Scheme 11).^[37] The developed reaction conditions allowed the synthesis of different polycyclic oximes (**33**) in good yields and short reacting times *via* a semipinacol rearrangement. According to the proposed mechanism, the nitrosonium cation reacts with the enolic double bond (**32A**), inducing the C-C bond migration of the cyclobutan moiety to form intermediate **32B**. The TBS-protecting group is released upon H-elimination and intramolecular attack, whereupon the final product **33** is formed with high relative stereoselectivity. Depending on the ring size, the reaction stopped without intramolecular cyclization, giving access to polycyclic ketones instead of oximes.

Tu – Synthesis of oximes

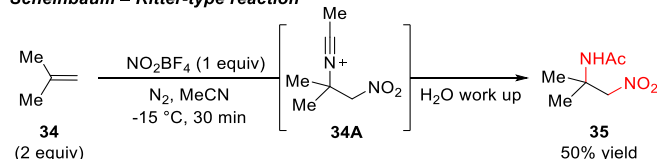


Scheme 11 Tu's synthesis of oximes *via* ring opening of cyclobutanes. DTBP = di-*tert*-butylpyridine.

3. Functionalization of π -bonds

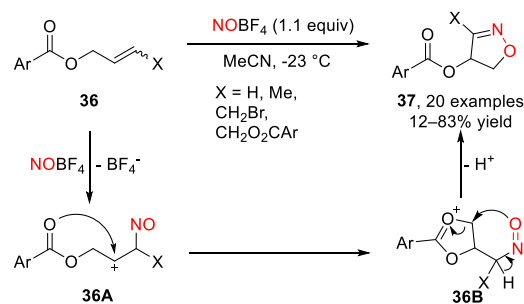
The reactivity of nitrosonium and nitronium ions towards various π -bonds has been studied in the past decades. Functionalization occurs under incorporation of the nitrosonium ion into the target structure or in a catalytic fashion. In 1971, Scheinbaum and co-workers reported the Ritter-type functionalization of propylene (**34**) and butene (Scheme 12).^[38] The product formation results from the addition of the nitronium ion to the alkene and subsequent nucleophilic attack of the solvent. Hydrolysis converts the intermediate **34A** to the corresponding amide **35**. In the absence of a scavenging nucleophile, nitrosonium salts act as initiators for alkene polymerization.^[39]

Scheinbaum – Ritter-type reaction

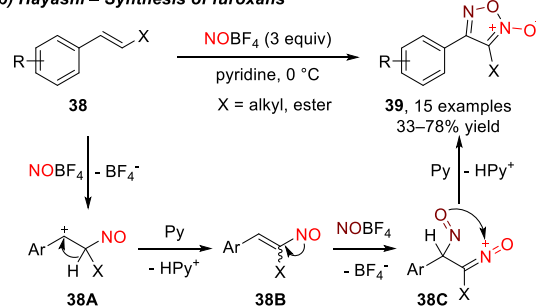


Scheme 12 Ritter-type functionalization of propylene with nitronium tetrafluoroborate.

(a) Kim – Synthesis of 2-isooxazolines



(b) Hayashi – Synthesis of furoxans

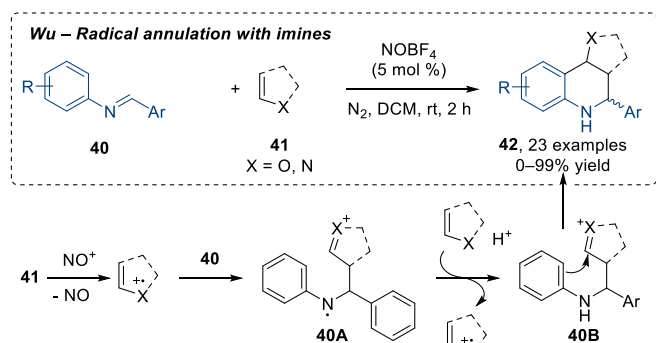


Scheme 13 Functionalization of π -bonds under incorporation of nitrosonium ions. (a) Synthesis of 2-isooxazolines using unsaturated aryl ether. (b) Synthesis of furoxanes in pyridine.

Kim and co-workers applied nitrosonium tetrafluoroborate for the synthesis of 2-isooxazolines (**37**) using unsaturated aryl ethers **36** (Scheme 13a).^[40] According to the proposed mechanism, the double bond attacks the nitrosonium ion to generate the positively charged intermediate **36A**. The neighboring ester group scavenges the positive charge to form cyclic intermediate **36B**. Finally, intramolecular attack of the nitroso group forms the isoxazoline **37**. The developed strategy was later applied by Macritchie within the synthesis of racemic Brevioxime.^[41] Hayashi and co-workers achieved the incorporation of two nitrosonium ions for the regioselective synthesis of furoxans **39**

(Scheme 13b). Regioselectivity was reasoned through the stability of the benzylic cation **38A** and steric effects favouring the deprotonation by pyridine at the less hindered position to form **38B**. Intermediate **38B** reacts with a second equivalent of the nitrosonium ion to form **38C**, which undergoes ring closure to form furoxanes **39**.^[42] The same results were achieved using the NaNO_2 -AcOH system.^[43]

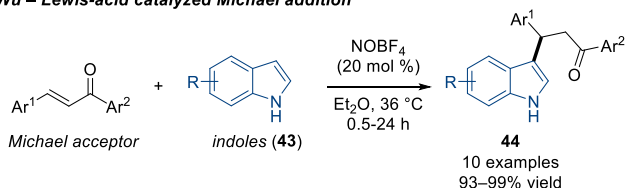
Wu and co-workers contributed with an interesting example of a radical annulation reaction of imines (**40**) with electron-rich alkenes (**41**) (Scheme 14).^[44] In this Povarov-type reaction, the nitrosonium cation acts as an initiator and not as a catalyst. The nitrosonium ion oxidizes the vinyl starting material through a SET, followed by a nucleophilic attack of imine **40**. The formed intermediate **40A** undergoes radical transfer with another molecule of the vinyl starting material in order to form intermediate **40B** and to propagate the reaction. In the last step, intramolecular attack takes place to form the annulated product **42**. Analogously, the coupling of **41** with oximes was reported by the same group.^[45]



Scheme 14 Nitrosonium initiated Povarov-type reaction of imines with electron-rich alkenes.

Later on, the same group studied an alternative mode of action for nitrosonium tetrafluoroborate. Nitrosonium ions were found to efficiently catalyze the Michael addition of indoles (**43**) with α,β -unsaturated ketones for the synthesis of C3-alkylated indoles **44** (Scheme 15).^[46] Within this reaction, nitrosonium tetrafluoroborate acts as an oxophilic Lewis-acid, underlining the variability of nitrosonium salts to promote different types of transformation.

Wu – Lewis-acid catalyzed Michael addition

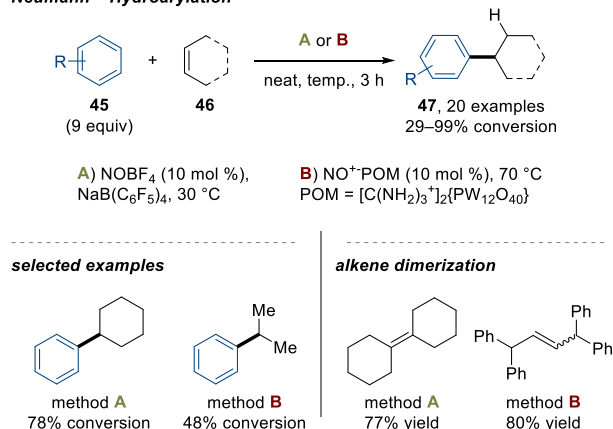


Scheme 15 Michael addition of indoles to enones catalyzed by nitrosonium tetrafluoroborate.

In 2008, Neumann and co-worker reported the catalytic hydroarylation of alkenes (**46**) with simple arenes (**45**) for the synthesis of **47** (Scheme 16). Within this study, the authors generated a soluble nitrosonium catalyst by adding an organic counter ion to the reaction. For some examples a more reactive heterogeneous phosphotungsten catalyst (POM) proved to give better results. In the absence of an arene as coupling partner, alkene dimerization was identified as the outcome of the reaction by GC-MS analysis. Unfortunately, no mechanism for this

transformation was proposed, although it was assumed that alkene dimerization included a double bond nitrosation step.^[47]

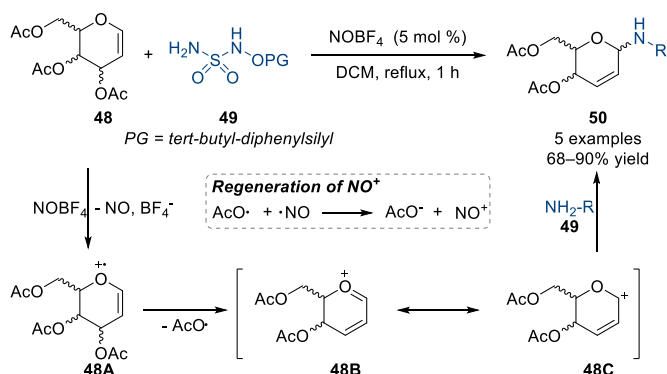
Neumann – Hydroarylation



Scheme 16 Catalytic functionalization of alkenes with homogeneous and heterogeneous nitrosonium catalysts.

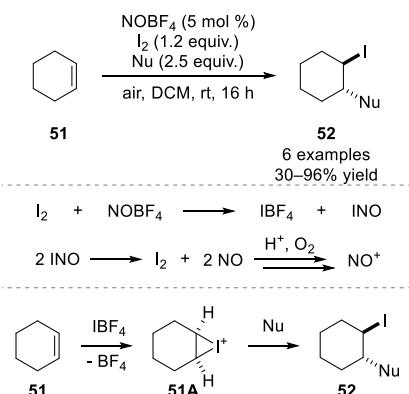
Winum and co-workers reported the catalytic Ferrier rearrangement achieving *N*-glycosylation of glycals (**48**) (Scheme 17).^[48] Five glycals were converted into 2,3-unsaturated glycosides **50**, albeit without selectivity for the formation of the anomeric center. According to the mechanism, a SET process initiates the transformation to generate the oxocarbenium radical **48A**. Elimination of an acetate radical leads to formation of **48B** and upon charge delocalization, intermediate **48C** reacts with the hydroxysulfamide (**49**) to form the unsaturated glycoside **50**. The released acetate radical regenerates the nitrosonium ion to maintain the catalytic activity. Importantly, the obtained products revealed inhibitory activities against different isoforms of the enzyme carbonic anhydrase.

Winum – Catalytic Ferrier *N*-glycosylation

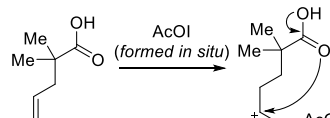


Scheme 17 Catalytic Ferrier rearrangement for the catalytic *N*-glycosylation of glycals.

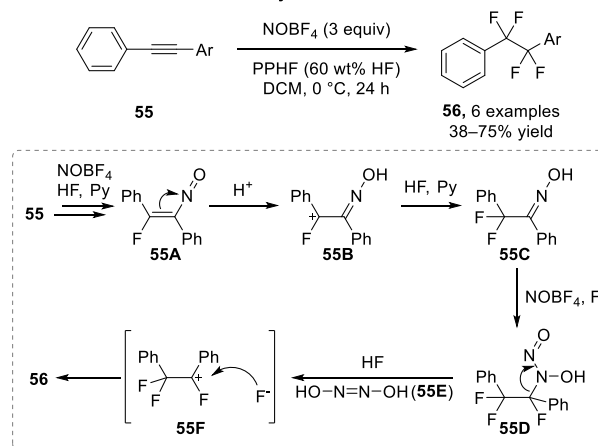
Another pioneer in the field of nitrosonium salt chemistry was Finn Radner. His group reported the *vicinal* iodo-functionalization of cyclohexene (**51**) using nitrosonium tetrafluoroborate as catalyst (Scheme 18).^[49] According to the proposed mechanism, the nitrosonium ion oxidizes elemental iodine to generate highly electrophilic IBF_4 . The activation of iodine leads to addition of the I^+ species to cyclohexene (**51**) to form halonium ion intermediate **51A**, which undergoes *trans*-selective ring opening with various nucleophiles to form **52**. Iodine, acetate, nitrile- and thiocyanate were successfully applied as nucleophiles. Importantly, ambient oxygen served as terminal oxidant in the reaction.

Radner – Vicinal iodo-functionalization**Scheme 18** 1,2-Iodo-functionalization of cyclohexane.

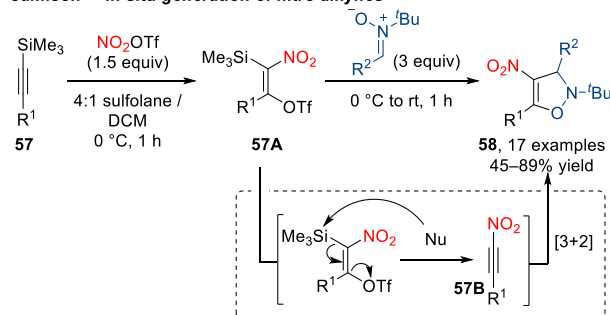
Later, Liu and co-workers developed iodo-cyclizations of alkenes and alkynes (**53**) for the synthesis of lactones (**54**) (Scheme 19). Acetyl hypoiodite (AcOI) was proposed as key intermediate in accordance to the work by Radner.^[50] Sodium nitrite serves as the source for nitrosonium ions and ambient air as oxidant to regenerate the reactive nitrogen species.

Liu – Iodo-cyclization**Key intermediate****Scheme 19** . Catalytic iodo-cyclization for the synthesis of lactones.

In 1994, Olah and co-workers reported the fluorination of diarylacetylenes **55**. PPHF (Olah's reagent) was applied as source for fluoride nucleophiles (Scheme 20).^[51] According to the proposed mechanism, the nitrosonium ion adds to the triple bond leading to the first attack of fluoride to form intermediate **55A**. Formation of intermediate **55B** induces the formation a benzylic cation, which also reacts with fluoride. Nitrosation of the oxime **55C** and subsequent fluorination of **55D** is followed by elimination of 1,2-dihydroxydiazene (**55E**) in order to form **55F**. The diazene further decomposes to water and nitrous acid. Thereby, fluoride attacks the benzylic cation of **55E** to give the perfluorinated product **56**.

Olah – Perfluorination of acetylenes**Scheme 20** Fluorination of diarylacetylenes.

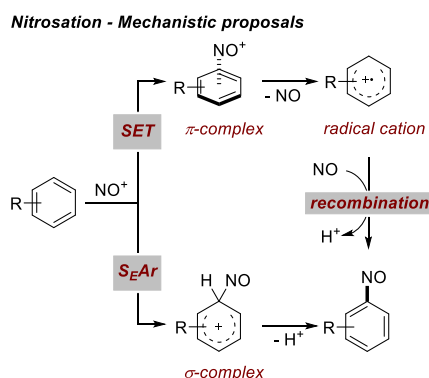
Recently, the generation of silyl triflates **57A** derived from trimethylsilyl alkynes **57** as equivalents of nitro alkynes was reported by Jamison and co-worker in batch and continuous flow (Scheme 21).^[52] Nitro alkynes suffer from poor stability and the application in organic synthesis appeared to be illusive. Jamison's group reported that treatment of alkynes **57** with a solution of nitronium triflate in sulfolane leads to the *in situ* formation of nitro alkynes **57B**, which smoothly undergo [3+2] cycloaddition with nitrones to form stable 4-nitro-4-isoxazolines (**58**). Online NMR spectroscopy indicated the formation of a silyl triflate **57A** as a key intermediate. The application of a flow reactor bypasses the danger of working with hazardous and potentially explosive intermediates for the synthesis of useful heterocycles.

Jamison – In situ generation of nitro alkynes**Scheme 21** Silyl triflates as nitro alkyne equivalents for the synthesis of heterocycles in batch and continuous flow.**4. C–H bond functionalization of arenes**

C–H bond functionalization represents a highly efficient approach in order to increase molecular complexity.^[53] Step-intensive pre-functionalization of starting materials is avoided, since abundant carbon-hydrogen bonds are functionalized in a direct manner. Therefore, the step- and atom-economy is dramatically improved and the amount of produced waste is decreased.^[54] Due to its advantages, the construction of carbon-carbon and carbon-heteroatom bonds through functionalization of C–H bonds has observed tremendous attention in the past decades.^[55] However, the selective functionalization of inert and abundant C–H bonds is still demanded. Oxidative functionalization of $\text{C}_{\text{sp}}^2\text{--H}$ and $\text{C}_{\text{sp}}\text{--H}$ bonds is considered to be easier than functionalization of the inert $\text{C}_{\text{sp}}^3\text{--H}$ bonds.^[56] The strong and localized C–H bonds in saturated molecules have no

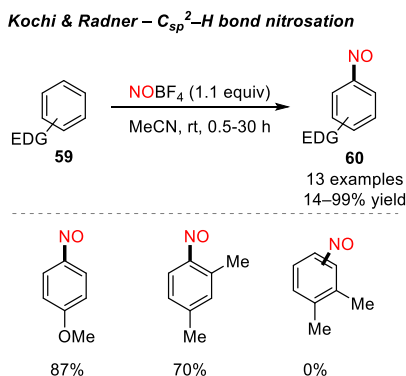
empty low energy orbitals or filled high energy orbitals that could readily participate in chemical reactions.^[57] Many methods for C–H bond functionalization utilize transition metal-catalysts, which are not unrestrictedly applicable, due to the aforementioned reasons. Consequently, metal-free reaction methodologies for C–H bond functionalization represent an efficient and sustainable strategy for the functionalization of organic molecules. Several points for *green and sustainable* chemistry can be fulfilled by combining both approaches.^[58]

In 1946, Ingold and Huges considered the nitronium cation as a reactive electrophile for aromatic nitration reactions.^[59] In the following years an alternative mechanism based on a SET process and recombination of the radical species was discovered (Scheme 22).^[60] Nowadays, the possibility for a SET mechanism is supported by theoretical calculation.^[61] The co-existence of the polar mechanism and the SET mechanism for the nitrosation of activated arenes was proposed by other groups.^[62]



Scheme 22 Proposed pathways for aromatic nitrosation of arenes.

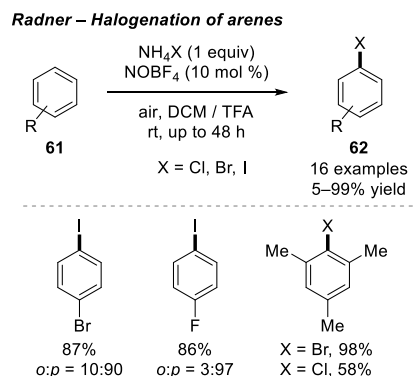
In-depth mechanistic studies by Kochi and Radner for the C–H bond nitrosation translated into a general methodology for the functionalization of anisole derivatives and poly-methylated arenes (**59**) (Scheme 23).^[63] Typically, the nitrosated products **60** were isolated as single regioisomers. Interestingly, *meta*-xylene underwent the nitrosation with good yields, while no product was formed when *ortho*-xylene was used as substrate. A strong kinetic isotope effect was determined and UV/Vis spectroscopy allowed the identification of a charge-transfer-complex. The experimental findings support the nitrosation *via* a radical pathway. Nitration of arenes can be achieved under the same reaction conditions using nitronium- instead of nitrosonium tetrafluoroborate.^[64]



Scheme 23 Nitrosation of anisole derivatives and poly-methylated arenes.

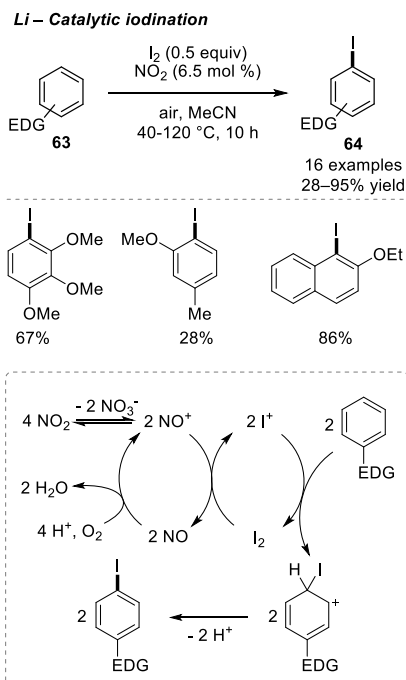
In the following years, nitration of phenols was achieved using various inorganic and organic nitrates.^[65] Treatment of 18-crown-6 ether with gaseous N₂O₄ gives a stable nitrosonium complex, which was applied for the nitration of phenols as well.^[66] In the following years, *tert*-butyl nitrite (TBN) replaced nitrosonium salts in the nitration of arenes due to the aforementioned advantages.^[67] Recently, Düssel and König reported the photocatalytic nitration of anilides.^[68] Sodium nitrite served in this reaction as the source for NO₂ radicals. However, the course of reaction does not include the formation of reactive nitronium or nitrosonium species.

In 1988, Radner and co-workers were the first to report the catalytic iodination of simple arenes (**61**) using NOBF₄ as catalyst under aerobic conditions (Scheme 24).^[69] The reaction proceeds in a Friedel-Crafts fashion through the oxidation of iodide to I⁺ species, followed by electrophilic aromatic substitution for the synthesis of iodoarenes (**62**) (also see Scheme 18). This system was also applied for bromination and chlorination, using NH₄Br and NH₄Cl, respectively. Based on control experiments, the *in situ* formation of I⁺ species and the regeneration of the nitrosonium ions by ambient oxygen was proposed. The distribution of regioisomers was in accordance to expected trends for an electrophilic aromatic substitution. Inspired by the pioneering work of Radner, several groups reported the combination of sodium nitrite and strong Brønsted-acids for the sustainable halogenation of arenes, enolizable C–H bonds, and alkenes.^[70] In accordance to the proposed mechanism by Radner, these transformations proceed *via* the *in situ* generation of nitrosonium ions and oxidation of the halogens to generate electrophilic species.



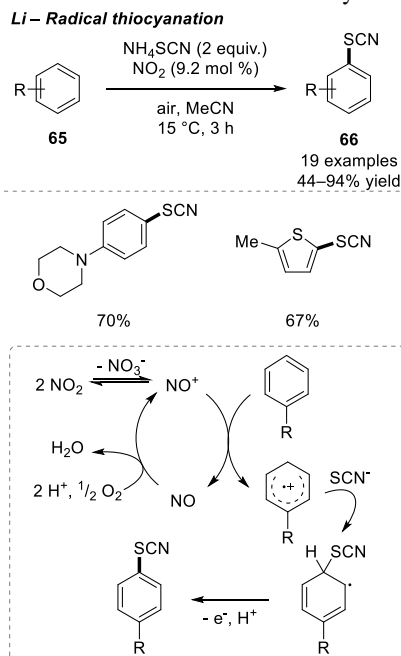
Scheme 24 Radner's aerobic and catalytic halogenation of arenes.

Li and co-workers reported a related transformation for the efficient iodination of electron-rich arenes **63** yielding iodoarenes **64** (Scheme 25).^[71] Interestingly, gaseous nitrogen dioxide was applied as catalyst for the transformation. According to the proposed mechanism, nitrogen dioxide is in equilibrium with nitrosonium species. The nitrosonium ion oxidizes iodine, which undergoes electrophilic aromatic substitution with the arene. The formed nitrogen dioxide is re-oxidized by ambient air to maintain the catalytic activity. To proof the involvement of nitrosonium ions, the reaction was repeated with nitrosonium tetrafluoroborate in substoichiometric amounts. The identical outcome was observed, suggesting the generation of nitrosonium ions during the course of reaction. Additionally, no biaryl formation took place in the absence of iodine, which suggested that only iodine was oxidized.



Scheme 25 Nitrogen dioxide-catalyzed electrophilic iodination of anisole derivatives.

Later, the same group expanded the developed reaction to the oxidative thiocyanation of electron-rich arenes **65** by employing gaseous nitrogen dioxide as the catalyst (Scheme 26).^[72] The reaction proceeds through generation of a radical cation intermediate, which reacts with the thiocyanate. Subsequent oxidation and rearomatization affords the corresponding arylthiocyanate **66**. The developed reaction proceeds analogously with nitrosonium tetrafluoroborate as the catalyst.



Scheme 26 Radical thiocyanation of electron-rich arenes.

5. Non-directed coupling of arenes under aerobic conditions

The formation of radical species *via* single-electron-transfer (SET) processes is a key step for the non-directed functionalization of aromatic compounds (Figure 1). The radical

cation reacts with a second nucleophilic arene (often itself). A second oxidation step is followed by rearomatization to give the biaryl product. This process allows the two-fold C–H bond functionalization, since no leaving group is required on both coupling partners. The ability of nitrosonium salts to oxidize electron-rich arenes to radical cations has been studied intensively in the past decades.^[73] Shine and Bandlish were the first to isolate and characterize stable radical cation salts generated by treating polycyclic aromatic compounds with stoichiometric amounts of nitrosonium tetrafluoroborate.^[74]

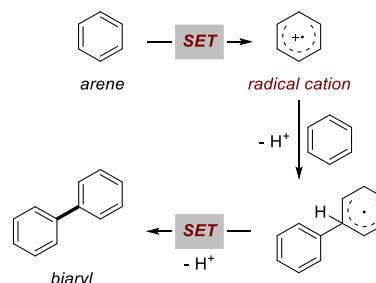
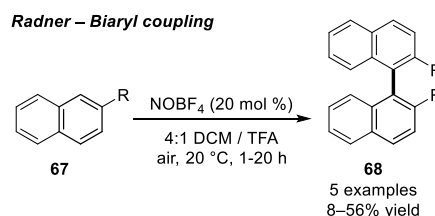


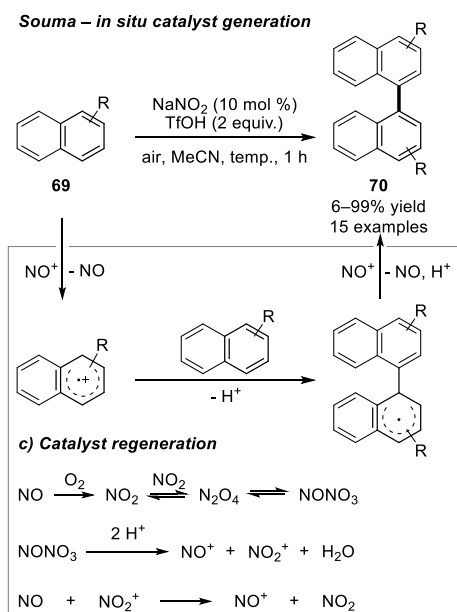
Figure 1 Non-directed C–H bond functionalization of arenes *via* SET for the generation of radical intermediates.

Despite the insights into the oxidation processes mediated by nitrosonium salts, practical application for oxidative coupling of arenes using nitrosonium ions are comparably less intensively studied. The first example of a nitrosonium ion catalyzed coupling reaction of naphthalenes **67** was reported by Radner's group in 1988 (Scheme 27). The homo-coupled products **68** were obtained by employing ambient oxygen as the terminal oxidant.^[75] The formation of π -complexes and subsequent radical cation formation for the biaryl coupling was later confirmed by Shubin's group by means of NMR-studies. This study provided the first evidence for a common pathway of nitrosation and biaryl coupling of arenes.^[76]

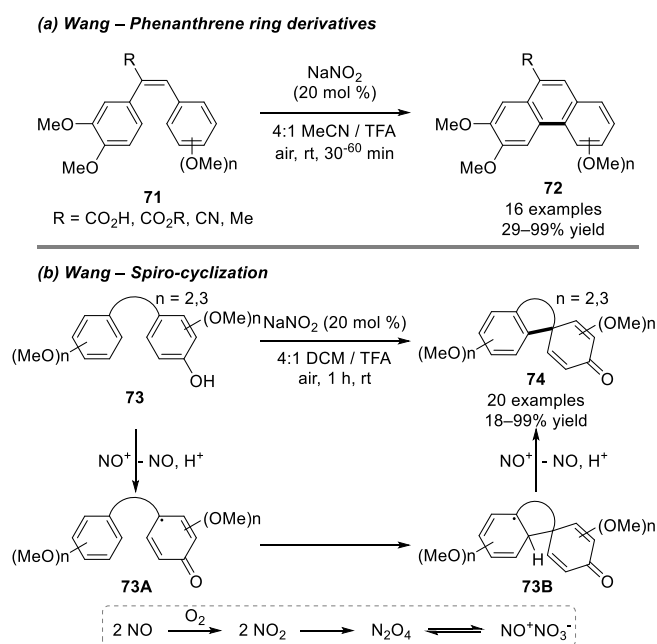


Scheme 27 First catalytic biaryl coupling.

Souma and co-workers continued the initial studies on the non-directed biaryl coupling of naphthalenes (**69**) for the synthesis of binaphthalenes (**70**) (Scheme 28).^[77] Treatment of NaNO_2 with triflic acid allowed the *in situ* generation of reactive nitrosonium species. Depending on the reactivity of the naphthalene, the temperature had to be adjusted to avoid decomposition of starting material. Ambient oxygen maintained the catalytic cycle. Importantly, loading of acid was crucial to suppress undesired nitration of the starting material and the product.^[64] A conclusive cycle for the regeneration of nitrosonium ions was proposed (Scheme 28c). Formed nitrogen monoxide is oxidized by ambient oxygen to form nitrogen dioxide. Nitrogen dioxide is in equilibrium with dinitrogen tetroxide, which undergoes disproportionation to form labile nitrosonium nitrite. In the presence of a strong acid, protonation takes place to release a nitrosonium ion, a nitronium ion and water. The nitrosonium ion is able to oxidize nitrogen monoxide, whereupon nitrogen dioxide is able to re-enter the catalytic cycle.^[78]



Scheme 28 *In situ* generation of nitrosonium ions for the catalytic coupling of naphthalenes. (c) Proposed catalytic cycle.



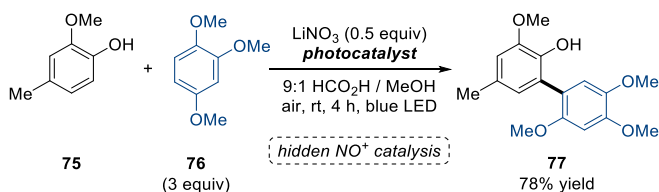
Scheme 29 Catalytic intramolecular biaryl coupling (a) Sodium nitrite catalyzed aerobic synthesis of polymethoxyphenanthrene rings. (b) Nitrosonium catalyzed spiro-cyclization of phenols.

Oxidative biaryl coupling catalyzed by nitrosonium ions remained untouched for several decades. In 2012, Wang and co-workers reported the synthesis of electron-rich phenanthrene rings **72** via intramolecular C–C bond formation employing **71** as starting material (Scheme 29a).^[79] The scope for the oxidative coupling reaction was extended to the intermolecular homo-coupling of 1,2,4-trimethoxybenzene. Additionally, the same group reported the catalytic intramolecular arene-phenol coupling of **73** under aerobic conditions for the synthesis of spiro-cyclohexadienones **74** (Scheme 29b).^[80] According to the proposed mechanism, a SET-process and subsequent deprotonation initiates the reaction to form a hexadienone radical

(**73A**). Intramolecular attack to form **73B** is followed by a second SET process and rearomatization yields the spirocyclic dienone motif. Oxidation of the starting material leads to the formation of nitrogen monoxide, which is oxidized by ambient air. Two molecules of nitrogen dioxide dimerize to form dinitrogen tetroxide. Finally, dinitrogen tetroxide is in equilibrium with nitrosonium nitrite, which serves as source for nitrosonium ions. The proposed regenerative cycle for the nitrosonium ion is in agreement with the aforementioned studies by Radner and Souma (Scheme 28). The synthesis of different scaffolds has been reported, however highly reactive poly-methoxylated starting materials are mandatory to achieve coupling.

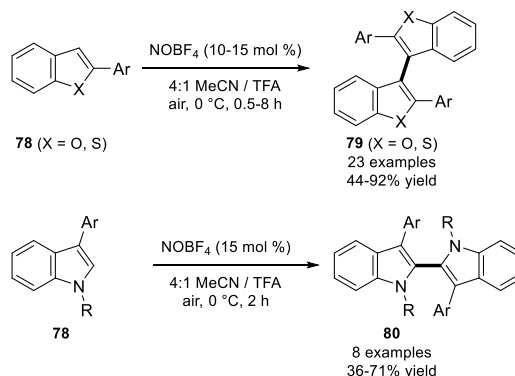
König and co-workers reported an attempt for a selective cross-coupling reaction of phenol **75** with electron-rich arene **76** under photochemical reaction conditions (Scheme 30). Initially, LiNO_3 was hypothesized to serve as a radical donor under photochemical conditions. However, systematic optimization revealed that neither the photocatalyst nor blue light was required for the synthesis of **77**. In fact, it was found that LiNO_3 serves as a source for nitrosonium ions, which mediate the transformation,^[81]

König – Nitrosonium-mediated phenol-arene coupling



Scheme 30 Attempts for the oxidative coupling of phenols and arenes.

Antonchick – Oxidative coupling of electron-rich heteroarenes

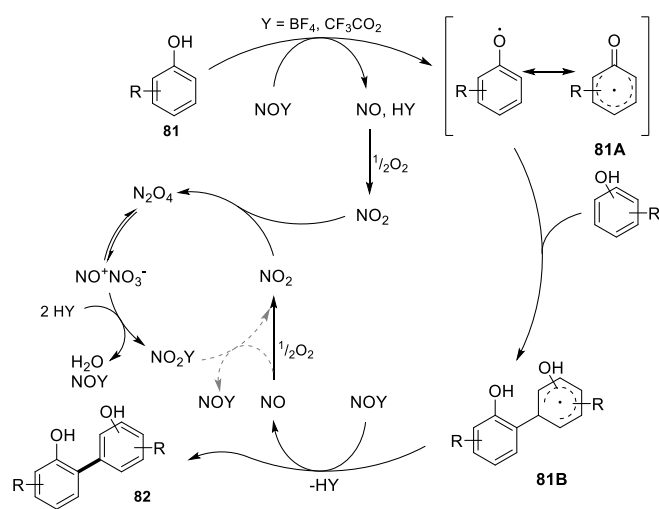
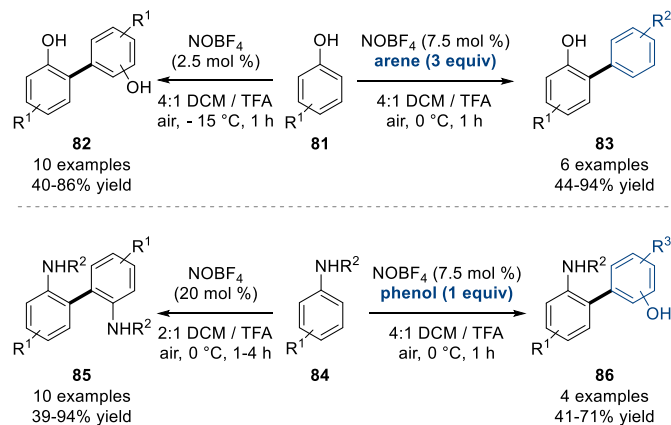


Scheme 31 Oxidative coupling of arylated heteroarenes using ambient oxygen as terminal oxidant.

Recently, Antonchick and co-workers actively expanded the scope of oxidative coupling reactions of arenes catalyzed by nitrosonium ions. Towards novel applications of nitrosonium ions as catalysts, the coupling of arylated heteroarenes was studied (Scheme 31). Guided by the oxidation potential of the substrates, the oxidative coupling of arylated benzofurans and structurally related heterocycles was studied. 2-Arylated benzofurans and benzothiophenes (**78**) were successfully converted into the corresponding 3,3'-dimers (**79**) in high yields and short reaction times. Functional groups were well tolerated, covering different steric and electronic properties. Additionally, 3-arylated indoles (**78**) underwent the dimerization process smoothly, giving access to biologically active dimeric compounds (**80**). Mechanistic studies revealed that the reaction

proceeds *via* the formation a radical cation intermediate, analogously to the proposal of Souma and Wang (Scheme 28 and Scheme 29). It was also found that ambient oxygen serves as terminal oxidant and water is produced as the stoichiometric by-product. Thereby, the developed reaction conditions served as mild and efficient substitute for known methods.

Antonchick – Oxidative homo- and cross-coupling



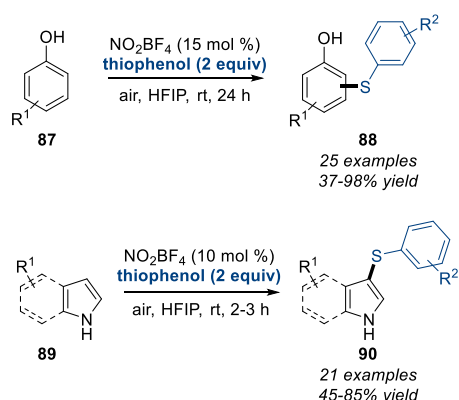
Scheme 32 Nitronium salts as efficient catalyst for C–H/C–H cross-coupling reactions.

The cross-coupling of arenes represents a great challenge, due to the high tendency of electron-rich arenes to preferentially undergo homo-coupling under oxidative reaction conditions. In the past decades several approaches for the selective cross-coupling of phenols have been developed. Most notably, Pappo and co-workers developed a predictive model for the cross-coupling of phenols with arenes and phenols.^[82] Based on this remarkable work, Antonchick and co-workers applied nitronium ion catalysis for the selective homo- and cross-coupling of phenols (81) and protected anilines (84) (Scheme 32).^[83] Notably, the unprecedented phenol-anilide cross-coupling was achieved within this study. According to the proposed mechanism, the substrates are oxidized by means of homolytic heteroatom-hydrogen bond cleavage to form 81A. Intermediates 81A react with a second equivalent of the substrate, or a nucleophilic arene in the case of cross-coupling, by means of radical electrophilic aromatic substitution and subsequent rearomatization generates intermediate 81B. A second oxidation step by nitronium tetrafluoroborate leads to aromatization and formation of the products 82 or 83 respectively. Nitrogen

monoxide, which is formed upon oxidation of the starting material, is oxidized by molecular oxygen, forming nitrogen dioxide. Nitrogen dioxide dimerizes to form dinitrogen tetroxide, which is in equilibrium with nitrosonium nitrate by means of disproportionation. Nitrosonium and nitronium ions are released under the acidic reaction conditions and water is generated as by-product. Finally, the nitronium ion is able to oxidize nitrogen monoxide instead of molecular oxygen to maintain the catalytic cycle. Control experiments supported, that phenols and protected anilines share a similar mechanism.

Antonchick's group was the first to disclose the carbon-heteroatom bond formation *via* C–H bond functionalization of arenes, using reactive nitrogen species as catalysts.^[84] Beside phenols and anilines, thiophenols represent another class of aromatic compounds entailing weak heteroatom-hydrogen bonds, which allowed the C–H/S–H cross-dehydrogenative coupling by a radical-radical recombination pathway. Under optimized conditions, various phenols (87) were efficiently coupled with thiophenols. The developed reaction conditions were also applied for the cross-coupling of indoles and pyrroles (89) and thiophenols under mild conditions (Scheme 33). The transformations shared the same feature of employing ambient oxygen as the oxidant in order to maintain the catalytic activity of the nitronium salt. Notably, a distinct recombination selectivity between phenols and indoles was revealed. On the one hand, phenols react with disulfides, which are formed upon oxidative dimerization of the thiophenols. On the other hand, indoles react directly with thiophenols, without formation of disulfides prior to the coupling step.

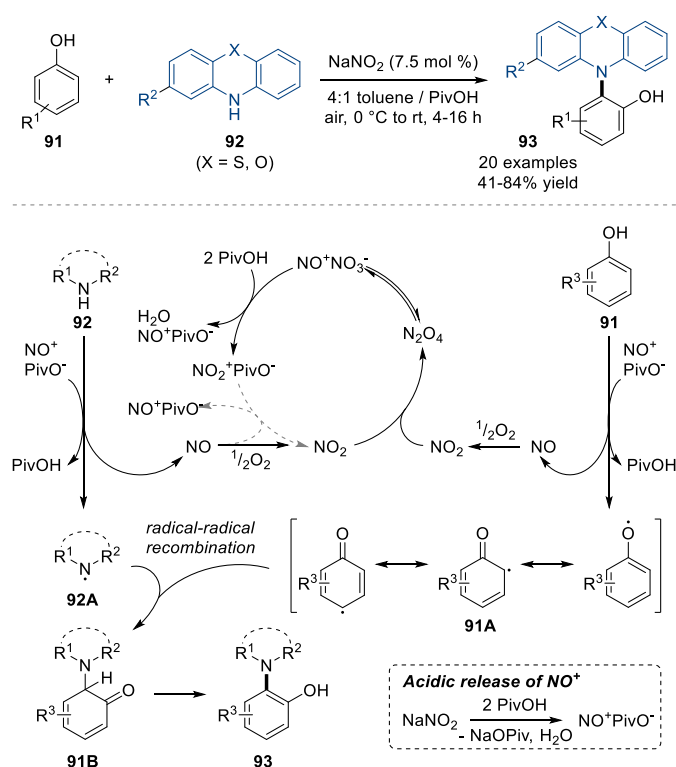
Antonchick – Catalytic carbon-sulfur bond formation



Scheme 33 Nitronium salts as efficient catalysts for C–H/S–H cross-dehydrogenative coupling reactions of phenols and indoles with thiophenols.

In the same study, Antonchick and co-workers disclosed the catalytic C–H bond amination of phenols (91) with phenothiazines (92).^[84] Strikingly, sodium nitrite served as source for nitronium ions under the acidic reaction conditions (Scheme 34). The optimized reaction conditions omitted the use of halogenated solvents and reagents. Thereby, the C–H/N–H cross-coupling for the synthesis of 93 was achieved under mild and environmentally benign reaction conditions, meeting the criteria for green and sustainable chemistry.^[58] According to the proposed mechanism, sodium nitrite is converted to nitrosonium pivalate under the acidic reaction conditions. The nitrosonium ion is capable of oxidizing both starting materials *via* homolytic heteroatom-hydrogen bond cleavage in order to form radical intermediates 91A and 92A. Delocalization of the phenoxy radical is followed by subsequent radical-radical recombination

to form intermediate **91B**. The formed intermediate **91B** undergoes rearomatization to form product **93**. The regeneration of nitrosonium ions was assumed to work analogously to the previously developed transformation. It should be noted that a radical-propagation step *via* radical transfer from **92A** to phenols **91** was proposed as an alternative pathway. However, the radical-radical recombination and regeneration of nitrosonium species would occur in the same manner.^[85]



Scheme 34 Sustainable C–H/N–H cross-coupling for the C–H bond amination of phenols.

6. Conclusion

In summary, the application of nitrosonium ions in organic synthesis offers diverse and versatile applications, covering the functionalization of carbon-heteroatom bonds, unsaturated bonds and the functionalization of aromatic C–H bonds for the non-directed coupling of arenes. The usefulness of nitrosonium ions roots in their mild oxidation properties accompanied with the ability to functionalize various types of bonds with different modes of action. Although nitrosonium salts are well known for a long time, it is still possible to address current challenges in organic synthesis by means of the development of novel and efficient reaction methodologies. Due to the safe handling, scalability and exclusion of any specialized equipment, nitrosonium ion catalysis might serve as alternative for technically more restricted methods. Several aspects of green and sustainable chemistry can be addressed by additionally considering aspects, such as safety of reagents, by-product formation, employed solvents and energy consumption. This might have the greatest potential for the development of novel applications for the oxidative coupling of arenes, which already has been shown to efficiently employ ambient air as oxidant and to produce water as by-product. However, the summarized transformation often require the presence of stoichiometric

amounts of nitrosonium salts, halogenated solvents or counterions, which are undesirable from an economical and environmental point of view. Consequently, future work in the field of nitrosonium ion catalysis has to point overcome these drawbacks by using environmentally benign solvents and nitrosonium ions sources, such as sodium nitrate. Nitrosonium ion catalysis can serve as powerful vehicle to rapidly discover novel reactivities, due to the facile handling and operationally simple reaction set up. Therefore, much emphasis should be pointed to the discovery of novel substrates enabling unprecedented transformation catalyzed by nitrosonium ions. Thereby, the application of nitrosonium ion catalysis can truly contribute to the progress of the field of oxidative transformations in organic chemistry.

7. References

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