doi:10.2533/chimia.2024.32 Chimia 78 (2024) 32–39

Simplifying Nitration Chemistry with Bench-stable Organic Nitrating Reagents

Subrata Patra, Vasiliki Valsamidou and Dmitry Katayev*

Abstract: Nitro compounds play a crucial role in academia and industries, serving as building blocks for the synthesis of drugs, agrochemicals, and materials. Nitration, a fundamental process in organic synthesis, has undergone significant evolution since the 19th century. While electrophilic nitration dominates historically, recent decades have seen a focus on new reagents and their reactivity modes for achieving mild and robust synthesis of nitro compounds. Our group has a longstanding interest in developing cost-effective, readily available, recyclable nitrating reagents derived from organic scaffolds. These reagents serve as a controllable source of nitryl radical and nitronium ion species, enabling mild and practical nitration of hydrocarbons with exceptional functional group tolerance. This account details the development of nitrating reagents and their diverse applications in catalytic nitration across various classes of organic molecules.

Keywords: Nitration · Nitronium ion · Nitryl radicals · Organic nitrating reagent · Photoredox

Subrata Patra was born in West Bengal, India. He completed his MSc in chemistry in 2017 from the Indian Institute of Technology Guwahati (IITG), India, under the guidance of Prof. T. Punniyamurthy. In 2017, he moved to the University of Alberta, Canada, and joined the group of Prof. Jeffrey M. Stryker. In 2021, he moved to Switzerland to the laboratory of Prof. D. Katayev at the University of Bern to conduct his doctoral studies. His current research involves the development of photo-/electro- and mechanochemical strategies for the selective functionalization of unsaturated hydrocarbons.

Vasiliki Valsamidou was born in Munich, Germany. She studied chemistry at LMU Munich and completed her MSc in late 2022 from the group of Prof. D. Didier on electro- and photocoupling reactions with boronic ester species. Prior to that, she also worked in the fields of organometallic chemistry (group of Prof. Paul Knochel), pharmaceutical (group of Dr. O. Thorn-Seshold), and inorganic chemistry (group of Prof. W. Schnick). In April 2023 she moved to Bern, Switzerland, where she joined the group of Prof. D. Katayev for her doctoral studies to investigate novel nitrating reagents and develop functional group transfer methodologies.

Dmitry Katayev studied at D. I. Mendeleev University of Technology (Higher Chemical College of the Russian Academy of Sciences (Moscow)) where he obtained his MSc in Chemistry and Chemical Engineering. He received his doctorate degree in the group of Prof. E. P. Kündig at the University of Geneva (Switzerland). Awarded a fellowship by the Swiss National Science Foundation (SNSF), he joined the research group of Prof. L. J. Gooßen at TU Kaiserslautern (Germany) as a postdoctoral researcher. In 2015, he joined the group of Prof. A. Togni at ETH Zürich (Switzerland) under an SNSF return fellowship. He was later awarded the SNSF Ambizione grant and the Holcim Stiftung, which allowed him to launch his independent research at ETH Zürich in 2018. As a recipient of the SNSF Eccellenza Professorial Grant, he joined the Department of Chemistry of the University of Fribourg as an Assistant Professor in early 2021. Shortly after, in October 2022, he joined as Assistant Professor with Tenure Track in Organic Chemistry at the University of Bern.

*Correspondence: Prof. D. Katayev, E-mail: dmitry.katayev@unibe.ch
Department für Chemie, Biochemie und Pharmazie, University of Bern, Bern, CH-3012 Bern

1. Introduction

Nitro compounds play a crucial role in synthesizing nitrogen-containing molecules and hold immense significance in chemical sectors such as pharmaceuticals, dyes, energetic materials, and fertilizers (for selected examples see Fig. 1A). In synthetic chemistry, the nitro group acts as a pivotal precursor to various compounds, including amines, hydroxylamines, aldehydes, carboxylic acids, isocyanates, and diverse heterocycles.[1] The progress in organometallic chemistry has empowered the utilization of the nitro group as a leaving entity in cross-coupling reactions.[1d]

Recently, nitro compounds have found application in the field of drug development and are incorporated into a wide range of biologically active molecules, contributing to the development of anti-infective drugs and agents for the treatment of diseases such as trypanosomatids.[2] Their metabolic pathways and *in vivo* nitration of biomolecules are of significant interest.[3] Innovations in synthetic applications of the nitro group have gone beyond classical redox transformations. This includes the exploration of denitrative cross-couplings, radical processes, and asymmetric organocatalytic transformations.[4] Global researchers drive nitration chemistry towards more efficient and environmentally conscious methodologies with recent advances in continuous flow nitration, decarboxylative nitration, C(sp^2)–H nitration catalyzed by transition metals, *ipso*-nitration reactions, and nitrative difunctionalizations.[5] There is a growing presence of comprehensive review articles focusing on the synthesis of nitro compounds *via* nitration of aliphatic and (hetero)aromatic compounds, offering the chemical community valuable synthetic tools for the construction of C–C, C–N, C–O and C–S chemical bonds as alternative strategies to conventional techniques.[6] Despite nearly 200 years

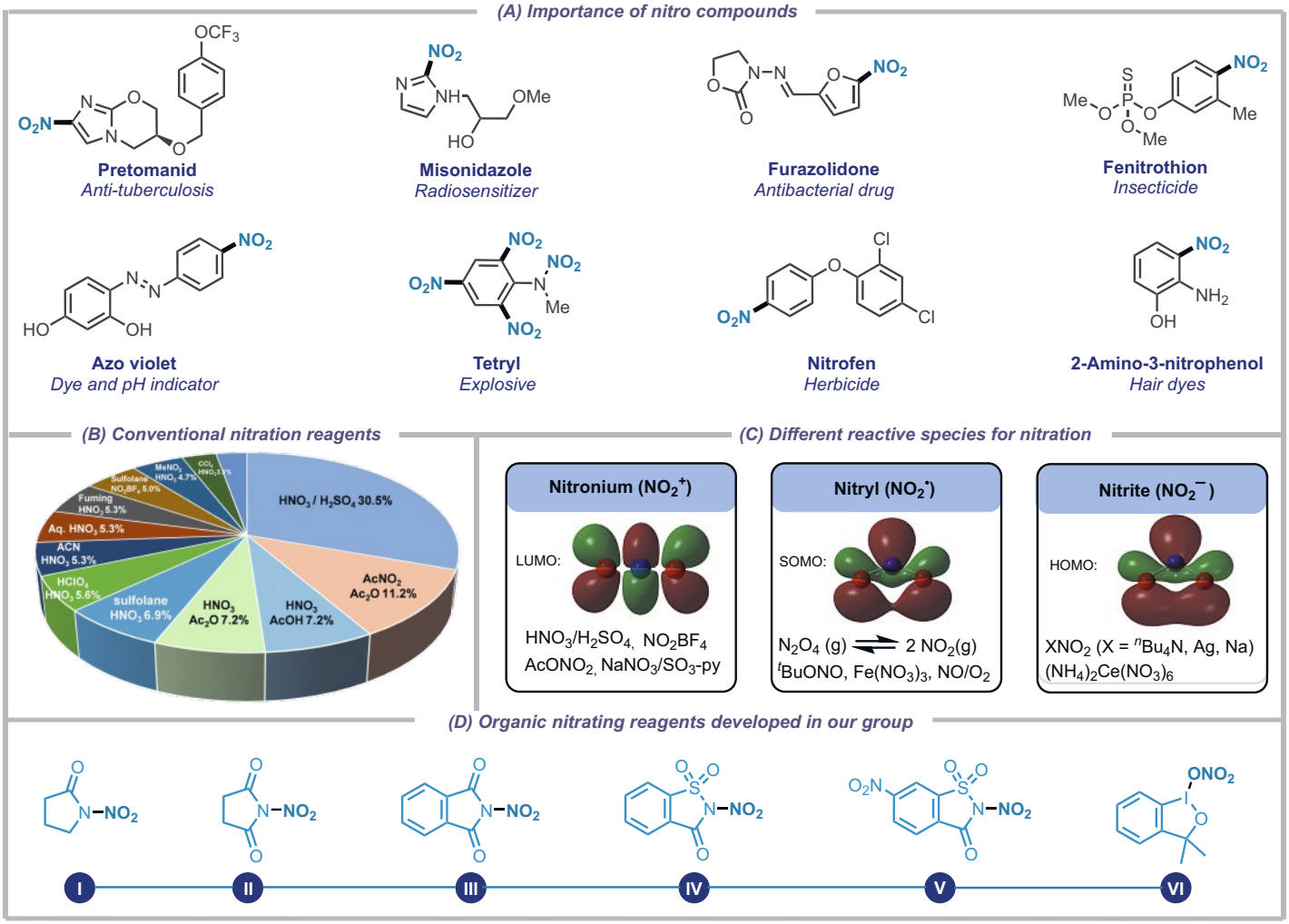


Fig. 1. Introduction: (A) Importance of nitro compounds; (B) Conventional nitration reactions; (C) Different reactive species for nitration; (D) Organic nitrating reagents developed in our group.

of nitration history, there's persistent room for improvement, particularly in developing selective, mild, and sustainable nitration processes. Particular attention is paid to the compounds that enable nitration reactions, nitrating reagents, which are categorized into inorganic (*e.g.* nitric acid) and organic molecules. While well-acknowledged progress is seen in inorganic reagents, the study of organic nitrating reagents remains limited despite their 120 year history.[7] This account summarizes the design and synthesis of organic nitrating reagents developed by our group, elucidating their application in catalytic nitration processes of unsaturated hydrocarbons, aromatic and (hetero)aromatic compounds.

2. Radical Nitration

Driven by the prevalence of the nitro group in drug-like molecules and recognizing its synthetic importance in various functional group interconversions, we have introduced a new class of organic, bench-stable, inexpensive, and recyclable NO_2-transfer reagents based on heterocyclic scaffolds and various synthetic limitations associated with classical electrophilic nitration have been successfully overcome (Fig. 2). N-Nitropyrrolidinone I was first prepared by Coburn and Ungnade in 1965, whereas Kauffman and Burger revealed the synthesis of molecules II and III in 1954.[8] However, their exact structures (N–NO_2 *vs* O–NO_2 bonds) and modes of reactivity as potential nitration reagents remained unexplored until recently. After drastically improving synthetic approaches, we studied their physical and chemical properties by TGA-DSC, SC-XRD, IR, and DFT methods. In particular, the solid state-structures revealed the presence of a weak N–NO_2 bond in their structures, suggesting a single-electron transfer (SET) mechanism as a highly promising strategy for liberating nitryl radicals from these molecules. This assumption was further supported by our cyclic voltammetry measurements (reagent-II, –1.39 V *vs* SCE), ensuring N–N mesolytic bond fragmentation *via* an exergonic, irreversible, and reductive SET process. Interestingly, molecules II and III are bench-stable solids and resistant to decomposition in various protic and aprotic solvents.

Our journey toward exploring the potential of these molecules as nitrating reagents began in 2019 with the disclosure of a chemo- and regioselective diversification of alkenes and alkynes mediated by photoredox reaction conditions. N-Nitrosuccinimide (II) emerged as the most effective reagent to deliver nitryl radicals in the presence of 2.5 mol% Ru-based photocatalyst and blue light irradiation for 12 h, affording *e.g.* β-nitroalkenes (Scheme 1)[9] in excellent yields under exceptionally mild conditions. The process tolerates both terminal and highly substituted alkenes. A net-neutral radical/polar crossover mechanism is outlined in Scheme 1 and was supported by a range of control experiments including photo-induced EPR spectroscopy, kinetic isotope effect studies, UV-Vis spectroscopy, Stern-Volmer quenching, and DFT calculations. These findings strongly advocate in favor of a radical mechanism. At the outset, N-nitrosuccinimide (II) engages into a single electron reduction initiated by the excited state of a photocatalyst, leading to NO_2 radical species. Subsequently, $^{\bullet}NO_2$ reacts with an olefine molecule through Giese-type addition,[10] followed by an oxidation step with the photosensitizer. The *in situ* generated nitroalkyl cation intermediate undergoes β-elimination, ultimately resulting in the formation of the desired nitroalkene product.

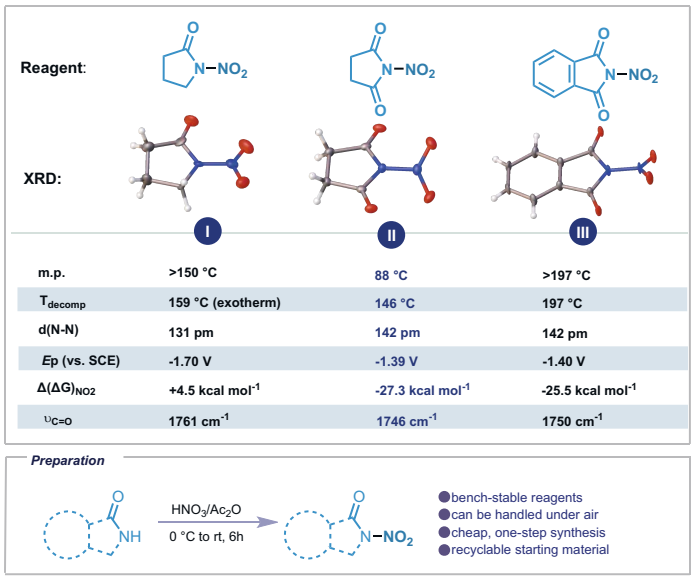
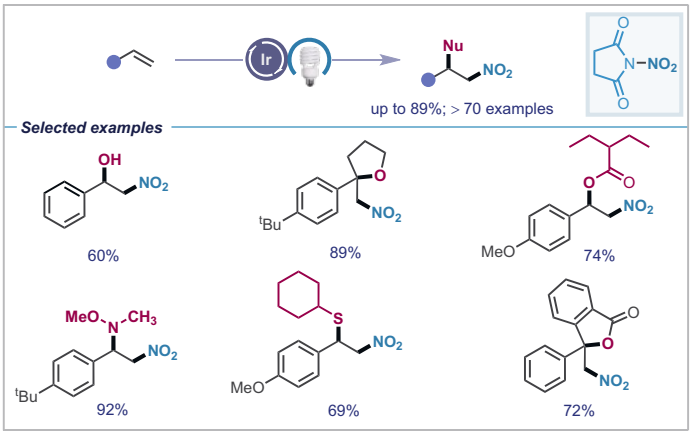
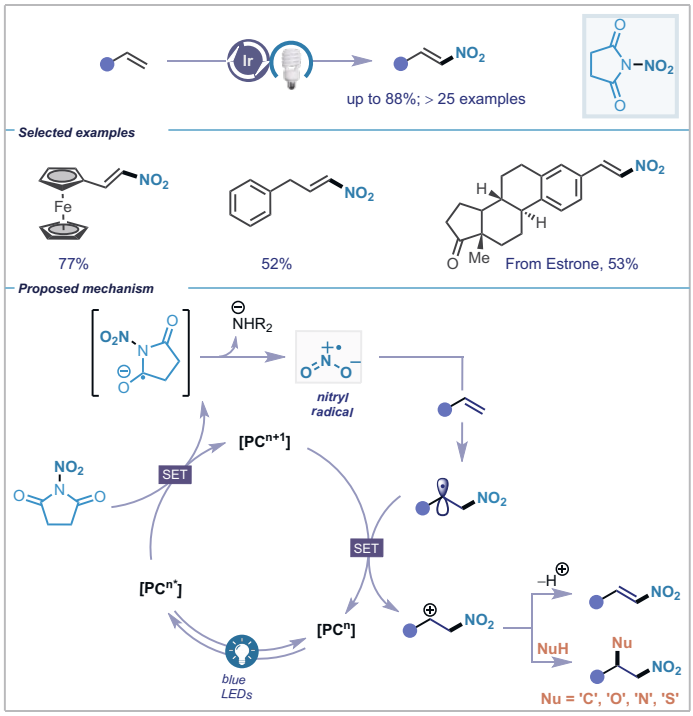


Fig. 2. Bench-stable organic nitrating reagents.

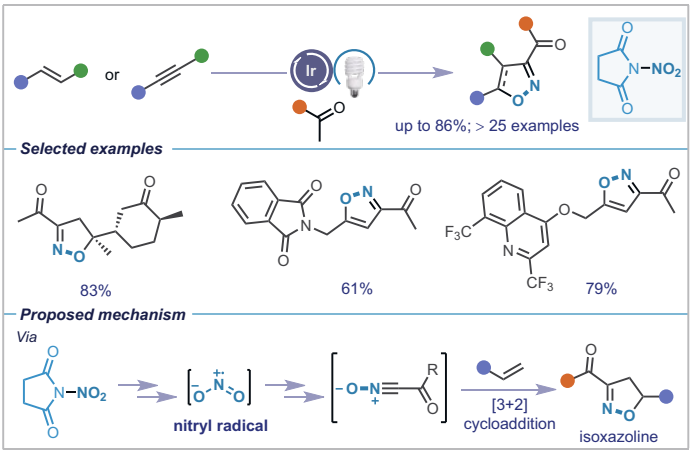
By conducting the reaction in the presence of external protic nucleophiles, we were able to introduce highly efficient and widely applicable nitrative difunctionalization protocols (Scheme 2).[9,11,12] For example, in the presence of water, nucleophilic addition to the benzylic cation intermediate yields β-nitrohydrins, representing a much simpler alternative to the nitro-aldol (Henry) reaction. Aliphatic thiols typically display pronounced nucleophilic characteristics, which can often lead to side reactions like the hydrothiolation of alkenes. Interestingly, our mild light-mediated protocol has exhibited an efficient nitrothiolation with decent chemical yields. Such aliphatic alkenes reactivity has been underexplored in photocatalytic difunctionalization reactions. The demand to access vicinal diamines is highly sought, owing to their privileged role in medicinal chemistry. The development of the nitrative-amination of olefins would be an excellent concept for the preparation of orthogonally-substituted unprotected vicinal diamines. Our exploration through various optimization studies unveiled that elevating the nucleophilicity of amines suppresses side processes, conceptualizing the first nitroamination reaction. Finally, our light-driven protocol also tolerates a vast scope of alcohols and carboxylic acids, including several complex molecules. To illustrate the ease of operation and scalability, the procedure was extended to a 10.0 mmol scale in continuous flow under standard conditions. Another remarkable application of our nitrating reagents was the development of a one-pot synthesis of isoxazolines and isoxazoles, a key motif of diverse natural products and pharmaceuticals. From a synthetic perspective, isoxazole derivatives are valuable and easily unmasked molecules, providing straightforward access to β-hydroxy nitriles, γ-amino alcohols, and β-hydroxy ketones. Nitrile oxides, key intermediates for preparing isoxazoline and isoxazole derivatives *via* cycloaddition reactions, are typically prepared through a harsh two-step sequence involving an oxime and an exogenous oxidant. Given this, we explored the possibility of a simple procedure to feature either isoxazolines or isoxazoles directly from unsaturated hydrocarbons and our reagent (Scheme 3).[9]



Scheme 2. Photocatalytic nitrative difunctionalization of alkenes using N-nitrosuccinimide.



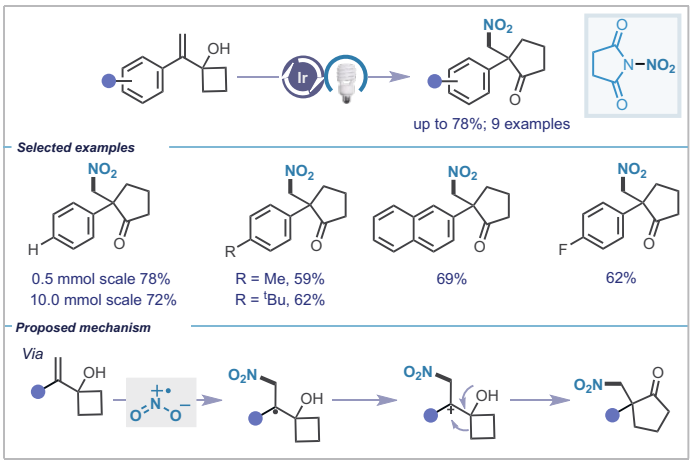
Scheme 1. Proposed mechanism for the formation of β nitroalkenes and nitrative difunctionalization of alkenes.



Scheme 3. One-step preparation of isoxazolines and isoxazoles.

This approach facilitates the *in situ* generation of a nitrile oxide from a ketone partner, as evidenced by the formation of the corresponding furoxan when conducted in the absence of a dipolarophile. Under photoredox conditions, the generation of a nitryl radical from N-nitrosuccinimide initiates the α-nitration of acetone, resulting in an *in situ* oxidation that produces 3-acetyl nitrile

oxide (Scheme 4). The ensuing 1,3-dipolar cycloaddition with a compatible dipolarophile consistently yields the desired heterocycle in a single operational step, employing a mild, regioselective, and versatile protocol with wide-ranging chemoselectivity.

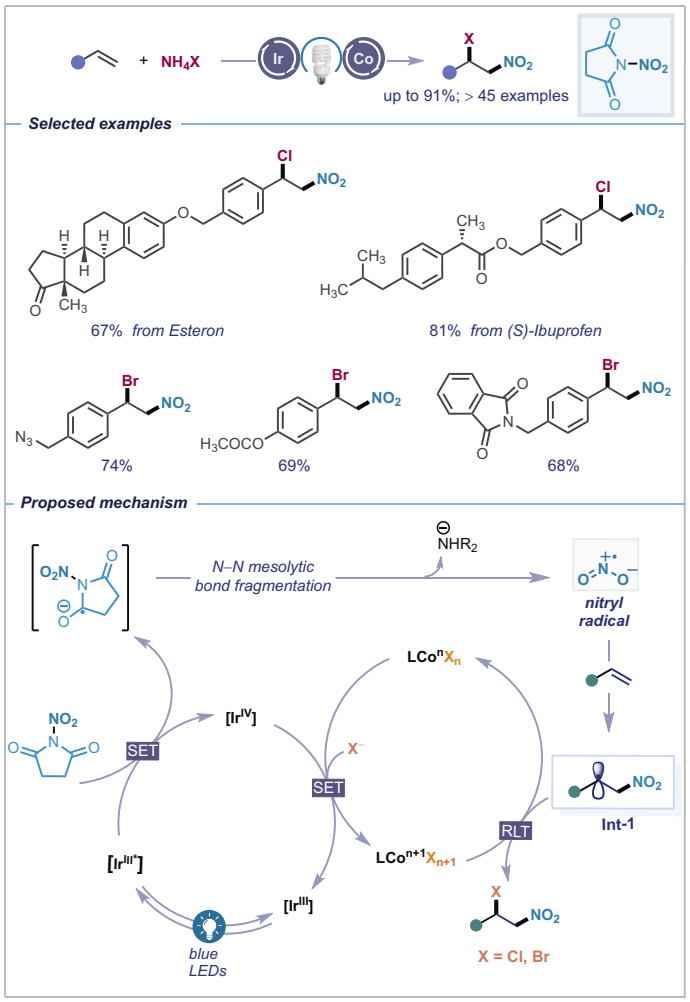


Scheme 4. Proposed mechanism for the semipinacol-type rearrangement.

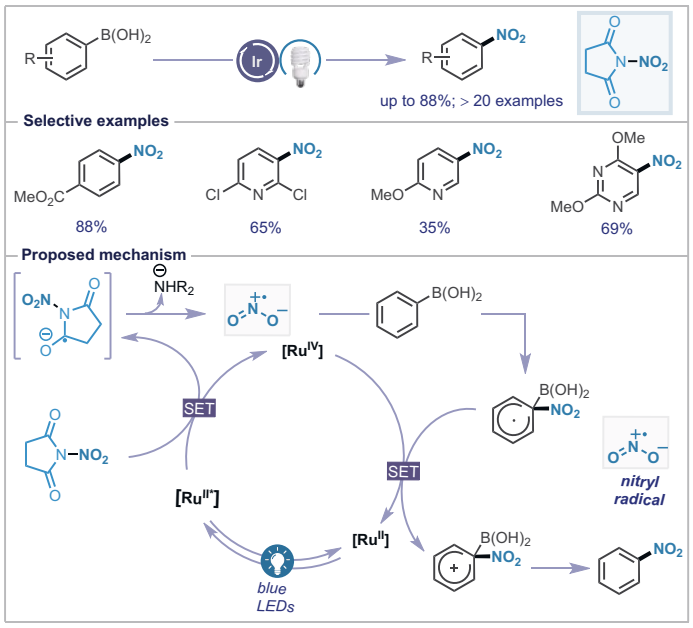
Rearrangement reactions have drawn significant attention in synthetic chemistry, emerging as powerful tools for constructing all-carbon quaternary centers. Recent progress in semipinacol-type rearrangements of allylic alcohols allows the synthesis of β-functionalized ketones while simultaneously forming new Csp^3-FG bonds in a single chemical operation. In the context of pertinent endeavors, we were able to extend the scope of semipinacol-type transformations by creating a novel pathway triggered by nitryl radicals (Scheme 4). This route leads to densely functionalized NO_2-containing cyclic molecules under mild and visible light-mediated photoredox conditions, utilizing N-nitrosuccinimide as a redox-active nitrating reagent.

Metallaphotoredox catalysis represents a rising technology in organic synthesis to construct simultaneously multiple chemical bonds. In the realm of nitration chemistry, we recently designed a modular dual photoredox and cobalt catalysis paradigm for the difunctionalization of unsaturated hydrocarbons, that allowed the challenges that emerged to be overcome with a nitrative photoredox net-neutral radical/polar crossover pathway (Scheme 5).[12] In particular, we were able to unlock the synthesis of challenging 1,2-halonitroalkane substrates through the novel cobalt-mediated radical ligand transfer (RLT) pathway. This collaborative interplay between a photocatalyst and a high-valent cobalt metal center operates under mild reaction conditions, enabling one-step synthesis of 1,2-chloronitro- and 1,2-bromonitroalkanes. Moreover, the method exhibits exceptional functional group tolerance and exclusive regioselectivity across a variety of olefins. This synergistic catalysis proved highly effective in the late-stage functionalization of bioactive molecules, displaying an unparalleled nitrative difunctionalization of extensively functionalized olefin scaffolds. Based on various control experiments, and mechanistic investigations, cobalt-mediated RLT mechanism was proposed (Scheme 5). The generated nitryl radical from reagent II under photoredox conditions undergoes a Giese-type addition to the β-position of olefin to form the stabilized benzyl radical intermediate Int-1 which then undergoes a cobalt-assisted radical ligand transfer step with the contemporary formation of the product and regeneration of a low-valent cobalt catalyst.

Progressing beyond the functionalization of unsaturated linear hydrocarbons, our exploration of these organic nitrating reagents



Scheme 5. Dual photoredox and cobalt catalyzed synthesis of 1,2-chloronitro- and 1,2-bromonitroalkanes.



Scheme 6. Nitryl radical-driven *ipso*-nitration of (hetero)aryl boronic acids.

in catalytic transformations has expanded thanks to the development of regioselective synthesis of nitro (hetero)aromatic compounds. This was made possible by designing an *ipso*-nitration protocol of readily available aryl boronic acids, which proceeds

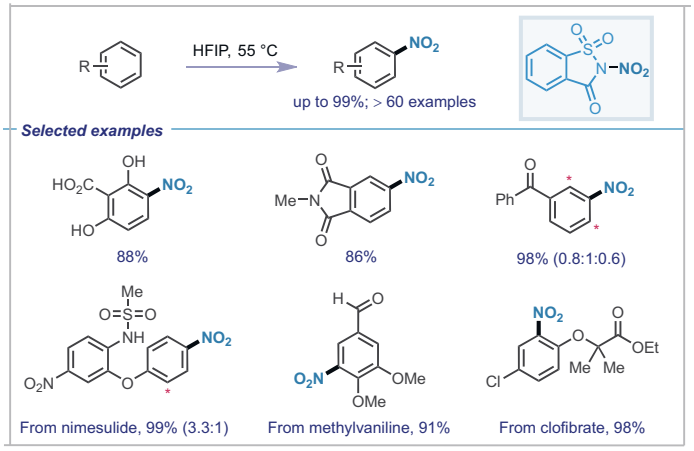
under photoredox conditions and employs N-nitrosuccinimide (II) as the nitrating agent.[13] The proposed catalytic pathway for nitryl radical assisted *ipso*-nitration is illustrated in Scheme 6. Initial excitation of the photocatalyst, followed by oxidative quenching with reagent II, generates the NO_2 radical species through mesolytic N–N bond cleavage. Subsequent addition to the *ipso*-carbon of phenylboronic acid (R = H), followed by the oxidation/deprotonation steps of the cyclohexadienyl radical results in the final nitro adduct. Complementary, *ipso*-nitration of (hetero)arylboronic acids can also be achieved by using another nitrating reagent as a source of electrophilic nitronium ion. This methodology will be further detailed in the subsequent chapter.

3. Electrophilic Nitration

Among the many methods developed to transfer and install a nitro group on desired scaffolds, the generation of nitronium ions NO_2^+ stands as the one of the most frequently employed techniques (Fig. 1, B). In particular, the electrophilic aromatic substitution reaction (SEAr) using 'mixed acid' approach (HNO_3/H_2SO_4) is one of the earliest investigated transformations[14] and continues to find use in both laboratory and industrial applications. However, the harsh conditions of this protocol constitute a significant drawback, increasing the number of side products due to oxidation and hydrolysis, thereby limiting the number of tolerated functionalities and the potential for late-stage nitrations. To avoid the use of mineral acid, other electrophilic nitrating reagents based on acyl nitrates, nitryl halides, or nitronium salts have been implemented.[7] However, these methods also have disadvantages such as sensitivity to moisture or air and susceptibility to thermal decomposition.

In the last years, the interest for electrophilic nitration using organic reagents has increased significantly, and N-nitramine based molecules have captured the attention of researchers. While they also suffer from high moisture sensitivity and limited nitration capabilities, they inspired us for the design of a $R_2N–NO_2$ scaffold, that would circumvent all the disadvantages of their predecessors. In 2019 we disclosed the synthesis of N-nitrosaccharin molecule and its application as a mild reagent for the electrophilic nitration of a wide range of arenes and heteroarenes (Scheme 7).[15] This saccharin-based reagent is easily accessible, inexpensive, bench-stable, and recyclable. The aromatic nitration with this reagent can be efficiently achieved using 10 mol% magnesium perchlorate [$Mg(ClO_4)_2$] as a Lewis acid catalyst at 85 °C in acetonitrile or by simply carrying out the reaction in HFIP 1,1,1,3,3,3-hexafluoroisopropanol at 55 °C. Very good to excellent yields with expected *o*- and *p*-patterns were achieved with monosubstituted arenes containing both electron-donating and electron-withdrawing substituents. Several acid sensitive molecules including methyl benzoate and benzophenone were subjected to our nitration protocols without undergoing hydrolysis of the ester or ketone moieties. Additionally, an unprecedented manifold of substituted (hetero) aromatic and biologically active compounds were successfully nitrated, resulting in excellent yields. Experimental and theoretical analyses of the reaction strongly suggest an electrophilic mechanistic pathway. Finally, reagent optimization revealed that the introduction of an electron-withdrawing group at the aromatic unit of the reagent, such as a nitro group, effectively increases the reaction rate (Fig. 3).

With this powerful tool in hand, we next turned our attention to *ipso*-nitrations. This type of functionalization was usually applied when the aggressive 'mixed acid' protocols had to be avoided, *e.g.* in the *ipso*-nitration of organometallic compounds, carboxylates, or aryl (pseudo)halides using palladium or copper catalysts.[16] Albeit preventing the formation of isomeric mixtures and of hydrolyzed and oxidized byproducts, the problem of poor functional group tolerance and generation of acidic or metal waste still remained prevalent. Our organic nitrating reagents were



Scheme 7. Direct (hetero)aromatic nitration using electrophilic N-nitrosaccharin reagent.

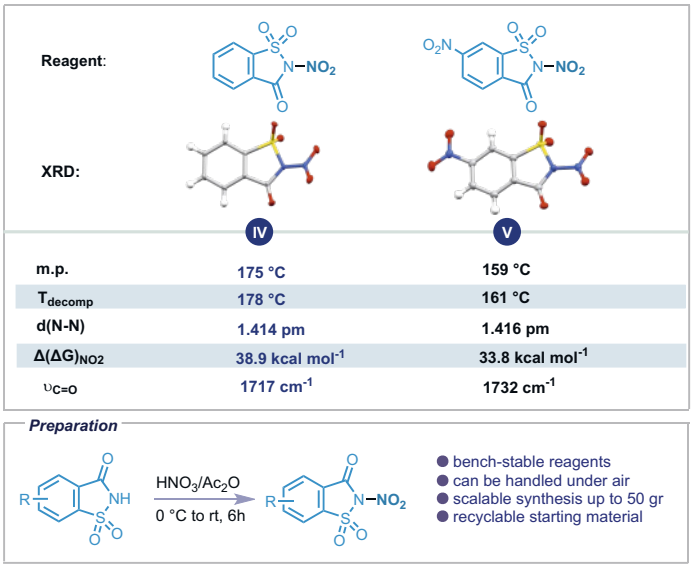
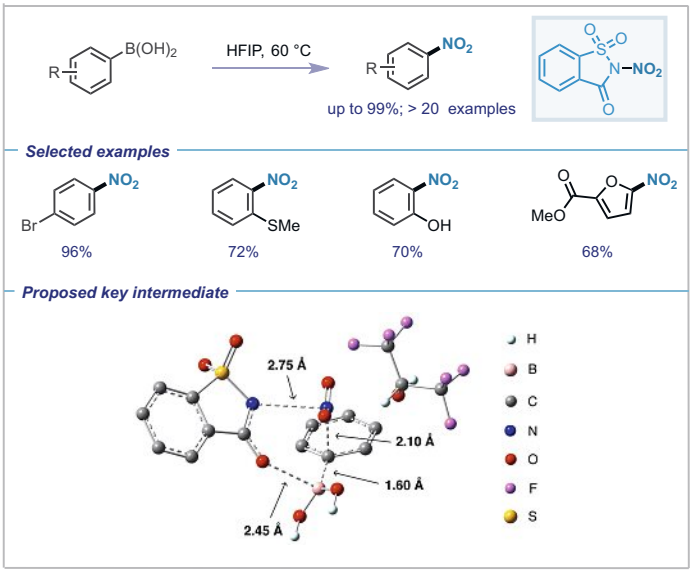


Fig. 3. Bench-stable organic nitrating reagents for electrophilic nitration.

therefore promising candidates to overcome these challenges. In 2020 we demonstrated the suitability of reagent IV for the effective *ipso*-nitration of aryl boronic acids (Scheme 8), which we selected for their excellent stability to air and moisture, structural diversity, and commercial availability.[13] We utilized the already well-established conditions involving HFIP as an assisting solvent and activator at 60 °C. This enabled us to convert electron-rich and electron-poor arylboronic acids and even heteroalrylboronic acids into their nitrated counterparts in a chemo- and regioselective manner. Halogen substituents, as well as hydroxyl and ester groups, were well tolerated and afforded good to excellent yields, independently of their *ortho*-, *meta*- or *para*-orientation. In all cases, no polynitration by-products were observed, and the reaction displayed scalability up to 10 mmol without a decrease in chemical yield. Notably, DFT studies revealed a transition state with a high-level of organization, whereby HFIP assists the cleavage of the $N–NO_2$ bond (Scheme 8).

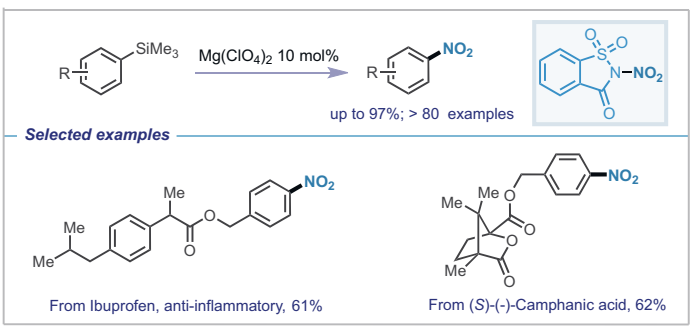
Encouraged by this reactivity, we further extended the concept of *ipso*-nitration to encompass challenging aryltrimethylsilanes (Scheme 9).[17] These compounds are known for their low toxicity, high stability, excellent solubility, and their convenient preparation. In a similar manner to the arylboronic acids, the *ipso*-nitration of these compounds proceeded smoothly under air in the presence of catalytic amounts of Mg-based Lewis acid in acetonitrile at



Scheme 8. *Ipso*-nitration of (hetero)arylboronic acids using N-nitrosaccharin as electrophilic nitrating reagent.

elevated temperature. The reaction tolerated various electron-donating and electron-withdrawing aryl substituents in *ortho*-, *meta*- and *para*-positions. An extensive range of 5- and 6-membered heterocycles, *e.g.* pyridine, thiophene, coumarin, and carbazole, bearing a trimethylsilyl group reacted with moderate to excellent yield. Importantly, when the reaction is performed in the presence of functional groups such as pinacol boronate, phosphonate, triflate, and sulfoxide, the *ipso*-nitration takes place exclusively with the trimethylsilyl substituent. To further explore the chemoselectivity of our protocol, we evaluated aromatic compounds containing heavier tetrels (-GeR_3 and -SnR_3) to our reaction conditions and achieved successful nitration. We then assessed their reactivity against trimethylsilyl containing compounds and revealed a preference for their *ipso*-substitution. Contrary to that, the nitration in an intermolecular competition between Ar-$SiMe_3$ and Ar-$B(OH)_2$ can be controlled by the addition of HFIP. While the substitution of the boronic acid moiety occurs in the presence of HFIP, only *ipso*-nitration of the trimethylsilyl group was observed without its addition. All these findings suggest that by manipulating the leaving groups and fine-tuning reaction conditions using N-nitrosaccharin, there is substantial potential for utilizing these concepts in orthogonal synthesis.

In summary, we have demonstrated the efficacy and versatility of our organic nitrating reagent IV by achieving mild and sustainable nitration reactions in an electrophilic aromatic substitutive manner, while tolerating remarkable number of functional groups.



Scheme 9. Regioselective *ipso*-nitration of silanes using N-nitrosaccharin reagent.

4. Nitrooxylating Reagent

Organic nitrate-carrying drugs have repeatedly shown enhanced activity against diseases like malaria,[18] Alzheimer's,[19] and diabetes[20] and a reduced likeliness to cause side effects compared to other known pharmacophores. Additionally, the nitrooxy group can serve as convenient handle for various functionalizations in organic synthesis, since the weak O–NO_2 bond can be easily cleaved or entirely displaced by nucleophiles. However, synthetic methods to access organic nitrates have predominantly employed harsh reaction conditions such as 'mixed acid' (HNO_3/H_2SO_4), strong oxidants (*e.g.* dinitrogen pentoxide), or moisture sensitive, heat sensitive, or highly hazardous reagents, resulting in low functional group tolerance, poor selectivity, and limited scopes.[21] To overcome these synthetic hurdles, in 2020 we introduced a novel hypervalent iodine-based reagent (Fig. 4) that enables a direct and selective nitrooxylation of enolizable C-H bonds with a wide nitrate ester scope. This bench stable and mild reagent is user-friendly, easy to synthesize, versatile, and allows two modes of activation: with Brønsted and Lewis acids or under photoredox catalysis.

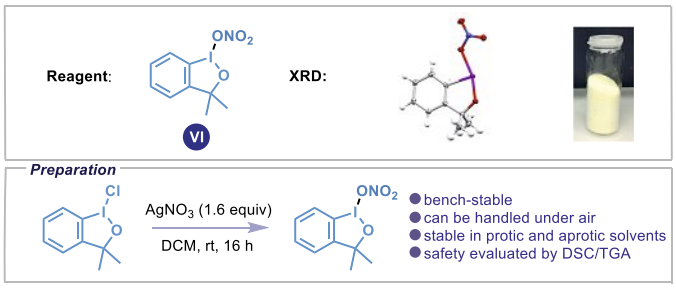
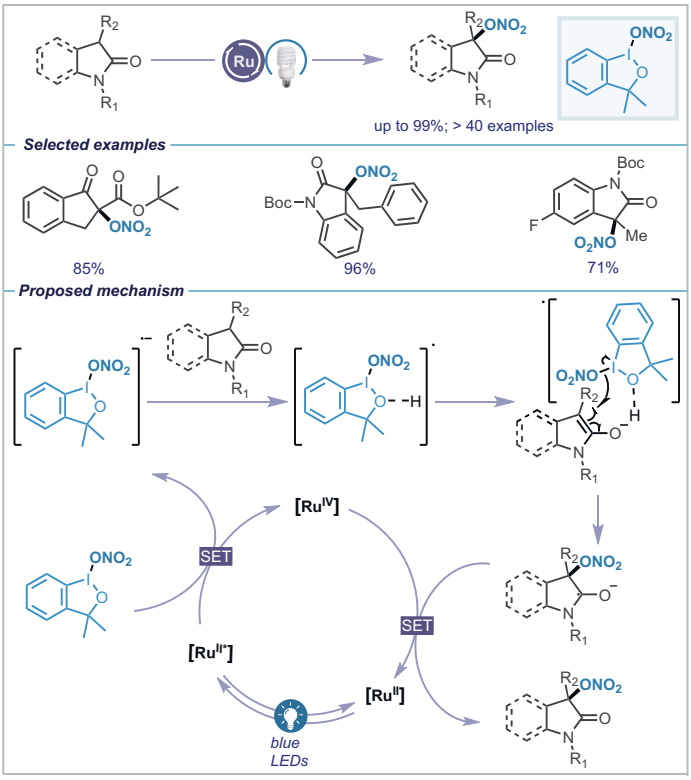


Fig. 4. Design and synthesis of hypervalent iodine-based nitrooxylating reagent.

Its initial application in organic synthesis was demonstrated through the direct C–H nitrooxylation of β-keto esters (Scheme 10).[22] The reaction proceeded at room temperature in the absence of catalyst or exogenous base and tolerated a variety of deactivating and activating substituents, providing the corresponding products in good to excellent yields. When employing less acidic acyclic β-keto esters, 1,3-diketones or malonates, the protocol was adjusted through the addition of 10 mol% CuOAc. Experimental mechanistic assessments suggested no inhibition of the reactivity in presence of radical scavengers, whereas the addition of base completely suppressed the reaction, proving the necessity of protonation/Lewis acid coordination to the hypervalent iodine-based reagent.

Building up on the reactivity of this reagent, the photoreductive catalytic pathway was next illustrated on oxindoles, which are abundant scaffolds in many natural products and bioactive compounds. Even though no formation of nitroxylated product was observed under previously employed acidic conditions, when submitted to high-intensity blue LEDs and a catalytic amount of $[Ru(bpy)_3](PF_6)_2$, good to excellent yields were achieved. The presence of a sterically demanding isopropyl group or a benzyl group at position C3 of oxindole was tolerated, just like activating and deactivating substituents at both the oxindole core and the benzyl group, as well as various N-protecting groups. Pulse radiolysis was used to investigate the mechanism, revealing the generation of a reducing radical intermediate. This constitutes one of the rare examples in which the reduction of such hypervalent iodine-based reagent does not lead to a fragmentation and liberation of a free radical. Considering the scarcity of elegant methods to access organic nitrates, in contrast to the sustained interest in their development and applications, we believe that the mechanistic insights and studies of the physical properties of this hypervalent iodine-based reagent are important



Scheme 10. Proposed mechanism for nitrooxylation reaction.

steps toward a more convenient and facile introduction of the NO_3 group onto various organic scaffolds and the elucidation of the biological effects of this still largely unexplored functional group.

5. Conclusions

Substantial progress in organic nitrating reagents and nitration chemistry has occurred mainly in the last two decades and is now gaining momentum. The recent emphasis on crafting reagents specifically for nitrating applications holds the promise of revealing innovative, stable organic nitrating reagents with unique activation mechanisms. This strategic approach may offer a solution to longstanding challenges in nitrating chemistry, achieving chemo-, regio- and stereoselective nitration of organic molecules and making nitration a suitable transformation in total synthesis. Herein, we have highlighted our group's focus on catalytic nitration and nitrooxylation to enhance the value of common feedstock chemicals. While these initial findings are promising, further exploration is necessary to address key challenges in these research areas. Currently, our research group focuses on utilizing stable organic nitrating reagents for nitrative difunctionalization reactions through metallaphotoredox catalysis, employing either radical ligand transfer or reductive cross-coupling reactions. Simultaneously, we are exploring electrochemical[23] and mechanochemical nitration concepts, which can add further significant value to the field of nitro compounds.

Acknowledgements

We express our sincere gratitude to the ETH Zurich, the University of Fribourg, the University of Bern, and the Swiss National Science Foundation (PCEFP2_186964) for their unwavering support of our research initiatives. D.K. acknowledges the Schweizerischer Nationalfonds zur Förderung der Wissenschaftlichen Forschung (Swiss National Science Foundation, SNSF) for the financial support (PCEFP2_186964). D. K. expresses gratitude to all present and past members of the Katayev group for their valuable contributions to the research topics discussed in this account.

Received: November 30, 2023

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The definitive version of this article is the electronic one that can be found at https://doi.org/10.2533/chimia.2024.32