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Transformative reactions in nitroarene chemistry: C–N bond cleavage, skeletal editing, and N–O bond utilization

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Nitroarenes are highly versatile building blocks in organic synthesis, playing a pivotal role in various reactions. Common transformations involving nitroarenes include nucleophilic aromatic substitution (S_NAr) reactions, where the nitro group functions both as a potent electron-withdrawing group that activates the aromatic ring and as a leaving group facilitating the substitution. Additionally, the direct transformation of nitro groups, such as reduction-driven syntheses of amines and carboxylic acids, as well as *ipso*-substitution S_NAr reactions, have been extensively explored. Interactions between *ortho*-nitro groups and neighboring substituents also provide unique opportunities for selective transformations. However, beyond these well-established processes, direct transformations of nitro groups have been relatively limited. In recent years, significant advancements have been made in alternative methodologies for nitro group transformations. This review focuses on the latest progress in novel transformations of nitroarenes, with emphasis on three major categories: (i) functional group transformations involving C–N bond cleavage in nitroarenes, (ii) skeletal editing *via* nitrene intermediates generated by N–O bond cleavage, and (iii) the utilization of nitroarenes as an oxygen source through N–O bond cleavage. These developments under-score the expanding utility of nitroarenes in modern organic synthesis.

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1. Introduction

Nitroarenes a crucial class of compounds in organic chemistry, valued for their high reactivity and versatility in diverse chemical transformations. The presence of the nitro group ($-NO_2$) imparts unique electronic properties to the aromatic ring, making nitroarenes indispensable intermediates across a broad range of synthetic applications.[1] Traditionally, nitroarenes have been utilized in nucleophilic aromatic substitution (S_NAr) reactions, where the electron-withdrawing nature of the nitro group facilitates the substitution of leaving groups, particularly at the *ortho*- and *para*-positions (Fig. 1A).[2] These reactions often proceed *via* the formation of a Meisenheimer complex, a delocalized anionic intermediate that stabilizes the transition state and promotes reaction progression. Additionally, the nitro group itself can act as a leaving group in *ipso*-substitution S_NAr reactions, highlighting its dual functionality as both an activating and a leaving group.[3] Another unique transformation is vicarious nucleophilic substitution (VNS), in which the leaving group is present on the nucleophile rather than the aromatic ring, resulting in the formal substitution of a hydride on the aromatic ring.[4] These transformations further demonstrate the functional versatility of nitroarenes in synthetic methodologies, underpinned by their ability to enable selective functionalization, particularly in adjacent positions. Interactions between *ortho*-nitro groups and neighboring substituents, such as hydrogen bonding or chelation effects, can also facilitate regioselective transformations, broadening the scope of nitroarene reactivity.[1a] In addition to their role in S_NAr reactions, nitroarenes are commonly employed in reductions, where the nitro group is converted into valuable functional groups such as amines and carboxylic acids.[5] The reductive transformation of nitroarenes has been extensively studied and remains one of the most widely used methods for generating amine-containing compounds.

While traditional transformations of nitroarenes—primarily substitution and reduction—are well-explored, the past decade has witnessed remarkable advancements in alternative transformation methods. Notably, novel approaches in C–N and N–O bond cleavage, often catalyzed or mediated by nitrene intermediates, have introduced efficient and sustainable routes to complex molecular architectures. These innovations not only expand the synthetic utility of nitroarenes but also align with the growing demand for greener and more selective methodologies in organic synthesis.

In this review, we focus on three emerging areas of nitroarene chemistry that have garnered considerable attention

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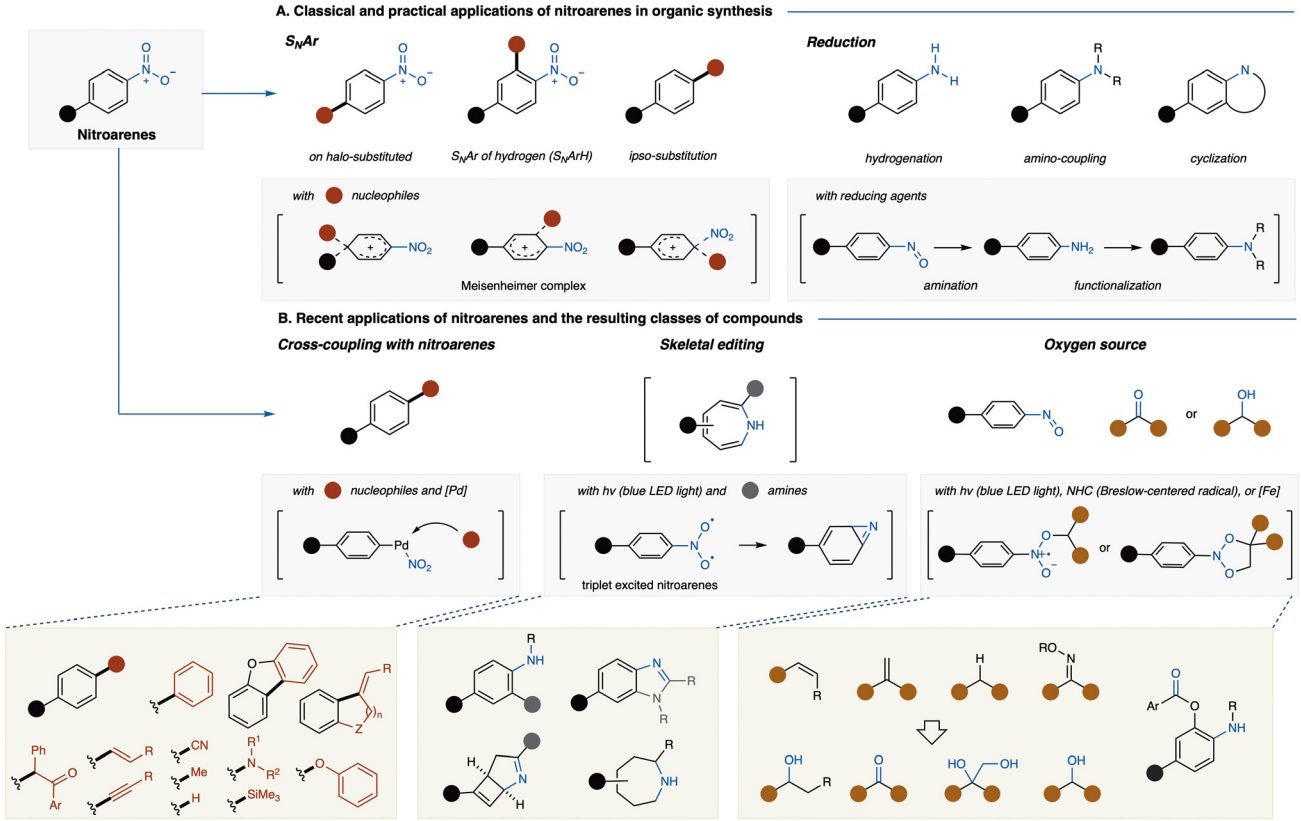

Fig. 1 Synthetic applications of nitroarenes in organic chemistry. (A) Traditional and widely used applications of nitroarenes in nucleophilic aromatic substitution (S_NAr) and reduction reactions for the synthesis of amines, carboxylic acids, and functionalized aromatic compounds. (B) Emerging applications of nitroarenes in modern synthetic methodologies, including denitrative cross-coupling, skeletal editing, and oxygen transfer reactions, along with examples of the resulting compound classes.

(Fig. 1B): (i) functional group transformations involving C–N bond cleavage, particularly through palladium-catalyzed cross-coupling with nucleophiles; (ii) skeletal editing using triplet excited-state nitroarenes,[6] which proceed *via* diazirine intermediates; and (iii) the utilization of nitroarenes as an oxygen source through N–O bond cleavage. These three cutting-edge reactions share the common feature of utilizing inexpensive nitroarenes, but their reaction sites differ entirely. Denitrative

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coupling targets the carbon adjacent to the nitro group, skeletal editing leverages the nitrogen atom of the nitro group, and oxygen transfer reactions utilize the oxygen atoms of the nitro group. However, they all share the clever exploitation of the electronic polarization inherent in aromatic nitro compounds. These transformations represent a significant shift in how nitroarenes can be applied in modern organic synthesis, offering new strategies for molecular editing and functionalization. By exploring these recent developments, this review aims to provide a comprehensive overview of the expanding utility of nitroarenes and their potential for future applications in synthetic organic chemistry.

2. Functional group transformations involving C–N bond cleavage in nitroarenes

Cross-coupling reactions utilizing haloarenes are well-established and widely employed in organic synthesis, serving as a foundational tool for constructing diverse organic compounds.[7] Over the years, numerous cross-coupling methodologies have been developed, enabling access to a broad range of molecular architectures. However, recent attention has increasingly shifted towards identifying alternative electrophiles that minimize halogen-containing waste, a major byproduct of traditional haloarene couplings.[8] Aromatic nitro compounds have emerged as promising alternatives, and transition metal-catalyzed denitrative couplings have been increasingly reported (Fig. 2A).

In 2011, Wu and Chen reported a rhodium-catalyzed denitrative cross-coupling reaction between electron-deficient nitroarenes and aryl boronic acids.[9] This work was followed by several studies documenting etherification and sulfidation reactions of nitroarenes using various transition metal catalysts. However, these metal-catalyzed denitrative couplings have primarily been limited to nitroarenes bearing electron-withdrawing substituents, with transformations largely restricted to the formation of C–O or C–S bonds, thereby limiting the broader utility of nitroarenes as aryl electrophiles.[10]

A breakthrough came with the work of Nakao and co-workers, who demonstrated that Pd/BrettPhos catalysts could effectively activate C–NO_2 bonds in nitroarenes, enabling Suzuki–Miyaura coupling (Fig. 2B).[10a] This catalytic system has since proven effective in facilitating C–NO_2 bond cleavage,

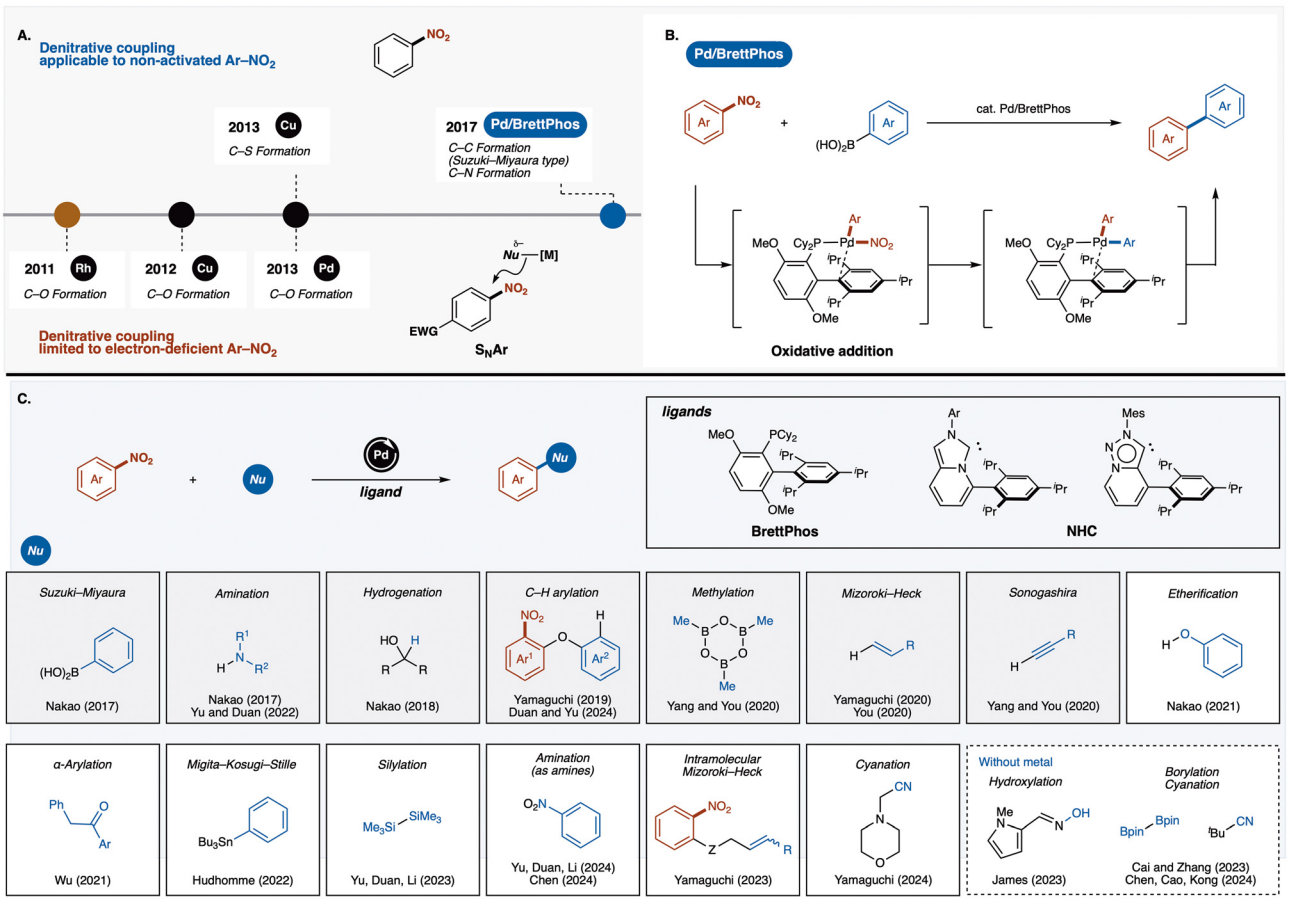


Fig. 2 Advances in catalytic denitrative transformations of nitroarenes. (A) Timeline highlighting key developments in catalytic denitrative reactions of nitroarenes. (B) Pd-Catalyzed Suzuki–Miyaura coupling enabled by C–NO_2 bond activation. (C) Structures of effective ligands and representative nucleophiles utilized in denitrative coupling reactions.

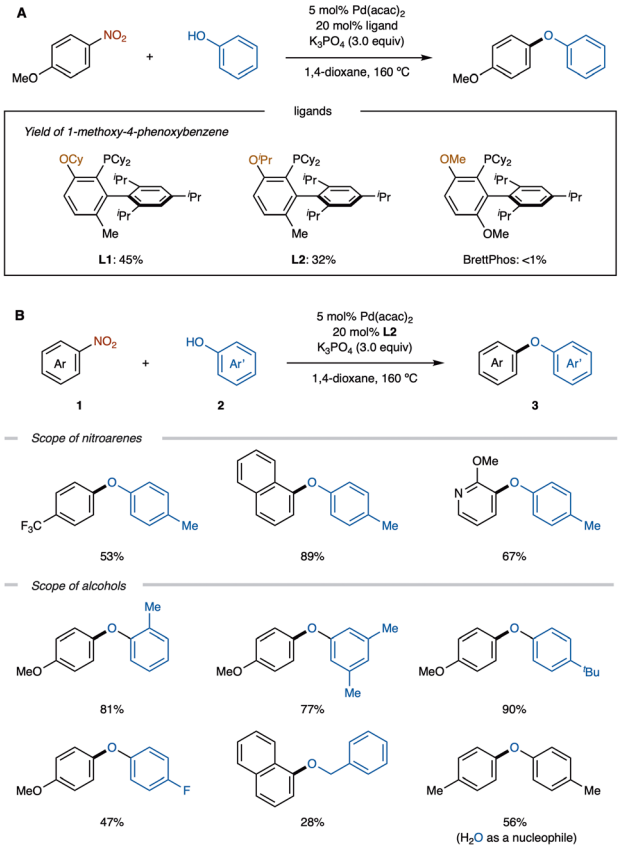
expanding the synthetic potential of nitroarenes in cross-coupling reactions. Subsequent studies have highlighted the utility of N-heterocyclic carbene (NHC) ligands, including imidazopyridine-based and pyridine-fused triazolylidene carbenes, which have shown significant efficacy in C–NO_2 bond activation.[11] Diverse denitrative transformations of nitroarenes, including amination,[10b] hydrogenation,[10c] intramolecular C–H arylation,[10d] methylation,[10e] Mizoroki–Heck reaction,[10fg] and Sonogashira coupling,[10h] have been reported (Fig. 2C). A comprehensive summary of these transformations up to 2021 was provided by Yamaguchi group.[12a] In this review, we focus on denitrative coupling reactions involving a range of nucleophiles reported since 2021, with particular attention to recent advances in reactions that proceed without the use of transition metal catalysts.[12b]

2.1. Etherification

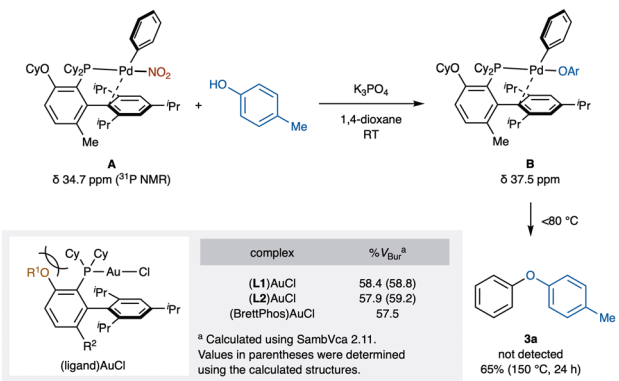
Diaryl ethers are essential structural motifs commonly found in natural products and bioactive molecules.[13] Methods for their synthesis typically involve Ullmann reactions catalyzed by copper or iron, as well as Pd-catalyzed Buchwald–Hartwig etherifications.[14] However, these conventional methods rely on haloarenes as substrates, which can present environmental concerns due to halogenated byproducts. As a complementary, halogen-free approach, etherification from aromatic nitro compounds has been developed, notably by a Nakao group (Scheme 1A).[15] Using $Pd(acac)_2$/**L1** catalyst system with K_3PO_4 as a base, nitroarenes **1** were reacted with arenols **2** to afford diaryl ethers **3** in good to moderate yields.

An extensive ligand screening revealed that ligands **L1** and **L2**, characterized by bulky substituents on the oxygen atom, demonstrated catalytic activity in this transformation, whereas BrettPhos, a commonly used ligand in denitrative coupling reactions, showed no activity (Scheme 1A). This method proved effective for various nitroarenes, including those with electron-donating and electron-withdrawing substituents, converting them into the corresponding diaryl ethers **3** (Scheme 1B). Additionally, substrates such as 1-nitronaphthalene and 2-methoxy-3-nitropyridine were successfully applied in this reaction. In terms of alcohol substrates, not only substituted arenols but also benzyl alcohol and even water were compatible, demonstrating the method's versatility.

The Nakao group further investigated the nitrite–phenoxide exchange step by adding premixed *p*-cresol and K_3PO_4 to a solution of **A** in 1,4-dioxane-d_8 (Scheme 2). After stirring the mixture at room temperature for 24 h, a new signal was observed in the ^{31}P NMR spectrum, shifted 3 ppm downfield from that of **A**. Although the product could not be fully characterized, this signal is presumed to correspond to the formation of (**L1**)Pd^{II}(Ph)(O-*p*-tol) (**B**) as diaryl ether **3a** was detected upon heating the complex to 80 °C. The thermal stability of this complex below 80 °C suggests that reductive elimination is the rate-determining step. Additionally, the $\%V_{bur}$ values were calculated for each ligand to evaluate the steric hindrance around the metal center.[16] These findings support the observation that reactions are less favorable with bulkier ligands and



Scheme 1 Pd-Catalyzed denitrative etherification. (A) Reaction conditions and ligand screening for the etherification of nitroarenes with arenols (Nakao group). (B) Substrate scope of nitroarenes and alcohols applicable to Pd-catalyzed etherification.



Scheme 2 Mechanistic studies of the nitrite–phenoxide exchange and reductive elimination steps.

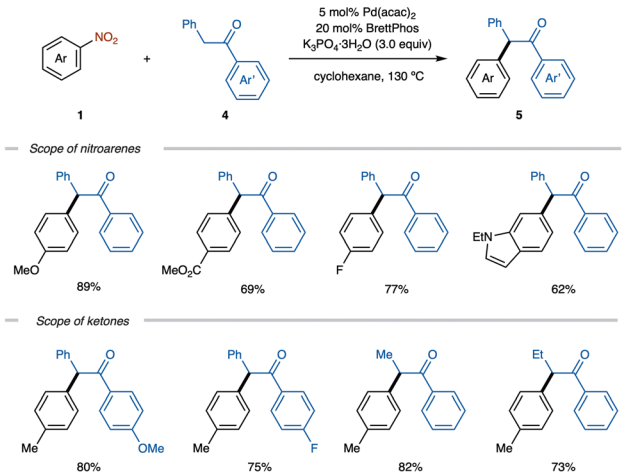
suggest a correlation between the progression of reductive elimination and the steric bulk of the ligands.

2.2. α-Arylation of ketones

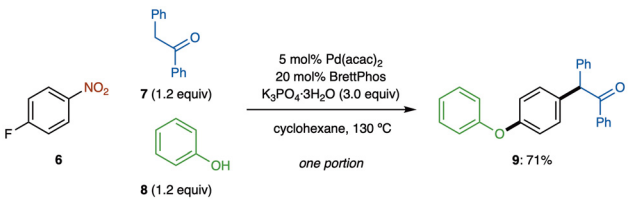
Catalytic α-arylation of carbonyl compounds with aryl halides is an efficient strategy for the direct synthesis of α-aryl carbonyl

compounds, which serve as pivotal intermediates in pharmaceuticals and π-conjugated materials.[17] Recently, Wu reported the α-arylation of ketone **4** using nitroarenes **1** as arylating agents under a Pd/BrettPhos catalytic system in the presence of K_3PO_4, affording a variety of α-arylated carbonyl compounds **5** (Scheme 3).[18] his methodology demonstrated good compatibility with various functional groups. The reaction tolerated a broad range of ketones **4**, from aryl phenyl ketones to alkyl phenyl ketones, illustrating the versatility of the α-arylation process.

Utilizing the inherent reactivity of 4-halonitrobenzene in S_NAr reactions, a one-pot, three-component denitrative α-arylation was performed (Scheme 4). Specifically, 4-fluoronitroarene (**6**), 1,2-diphenylethan-1-one (**7**), and phenol (**8**) were subjected to Pd/BrettPhos catalytic conditions, enabling a sequential one-pot S_NAr and denitrative α-arylation to afford **9** in a good yield.



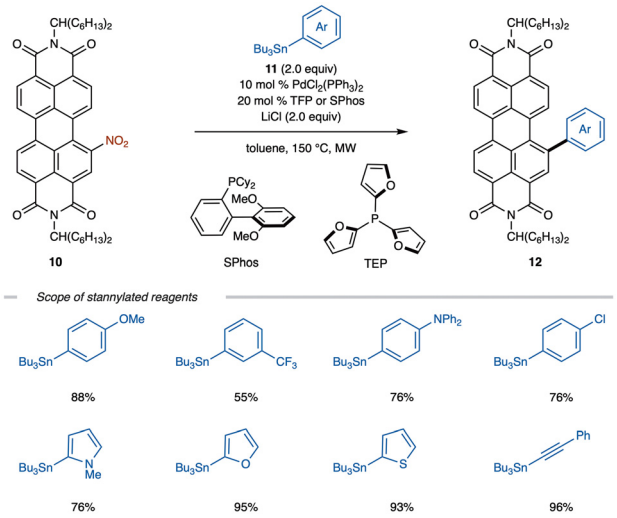
Scheme 3 Pd-Catalyzed α-arylation of ketones with nitroarenes (Wu group).



Scheme 4 Three-component coupling by S_NAr/denitrative α-arylation.

2.3. Migita–Kosugi–Stille coupling

The Migita–Kosugi–Stille reaction has become a cornerstone in organic synthesis for constructing carbon–carbon single bonds.[19] This base-free, transition metal-catalyzed reaction between organostannanes and organic electrophiles is one of the most efficient and widely used methods for synthesizing highly functionalized molecules. Its outstanding selectivity, robust functional group tolerance, and broad applicability



Scheme 5 Denitrative Migita–Kosugi–Stille coupling of nitoroarenes (Hudhomme group).

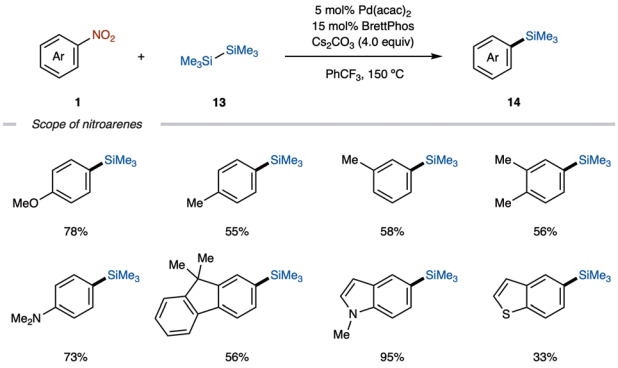
make it indispensable for various applications, such as the synthesis of natural products and the development of conjugated polymers for electronic devices.

In 2022, the Hudhomme group reported a Pd-catalyzed biaryl synthesis of nitroarenes **10** with arylstannanes **11** in the presence of LiCl (Scheme 5).[20] This study focuses on the functionalization of perylene–diimide (PDI) derivatives **10**, which are anticipated to exhibit unique electronic properties in organic electronics.[21] Accordingly, the nitroarene substrates are limited to a select few examples, primarily compound **10** and its analogues. Conversely, the reaction tolerates a diverse array of organostannanes, enabling the synthesis of a wide range of PDI derivatives **12**, including those containing heteroaromatic rings and alkynes.

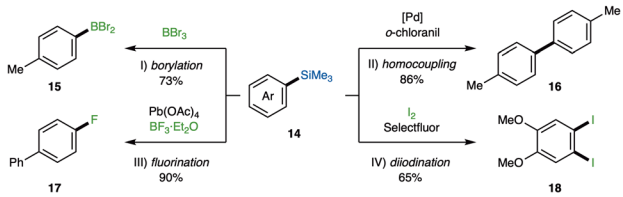
2.4. Silylation

In organic synthesis chemistry, silicon-containing compounds are valuable intermediates due to their ability to introduce a variety of functional groups.[22] Despite numerous advancements in C–Si bond formation, denitrative silylation of aromatic nitro compounds has remained a significant challenge. In 2023, Yu, Duan and Li reported a method for denitrative silylation of aromatic compounds using a palladium catalyst in combination with **1** and disilane **13** (Scheme 6).[23] They identified hexamethyldisilane (**13**) as an effective silylation reagent, which, under Pd/BrettPhos catalysis with K_3PO_4 as a base, produced silylated arenes **14** in good yields. This protocol demonstrated broad applicability across a range of nitroarenes, including heteroarenes, under the optimized conditions.

To showcase the synthetic versatility of the aryl silane products **14**, Scheme 7 illustrates several representative transformations of aryl silanes into valuable building blocks. Borylation of **14** with BBr_3 afforded dibromo(*p*-tolyl)borane (**15**) in 73% yield (I). Oxidative homocoupling of **14** using a palladium



Scheme 6 Pd-Catalyzed denitrative silylation of nitroarenes (Duan and Li group).



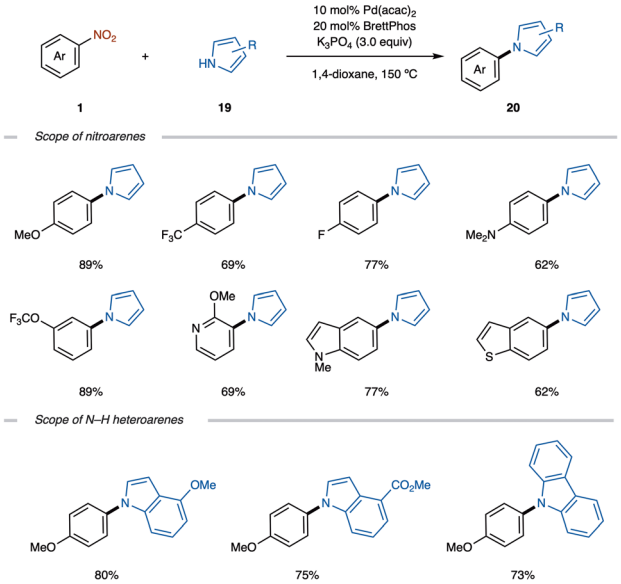
Scheme 7 Derivatizations of aryl trimethylsilane compounds.

catalyst and *o*-chloranil yielded biaryl **16** in 86% yield (II). Additionally, **14** was successfully converted into fluoroarene **17** and diiodinated product **18**, demonstrating the transformation of the C(sp^2)–Si bond into the C(sp^2)–halogen bond (III and IV).

2.5. Buchwald–Hartwig amination

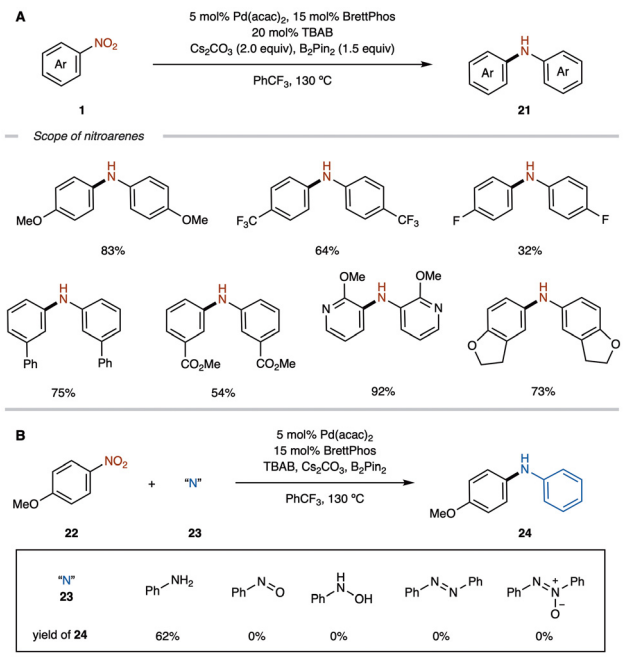
The Buchwald–Hartwig amination, a Pd-catalyzed coupling of aryl halides with amines, is well-established method for synthesizing substituted arylamines.[24] Traditionally, the synthesis of arylamines from nitroarenes has required multiple steps, including nitro group reduction followed by *N*-substitution. To simplify this process, the Nakao and Wu groups independently developed Buchwald–Hartwig amination methods for nitroarenes.[11b] However, these methods did not address the *N*-arylation of N–H heteroarenes.

In response, Yu and Duan developed a Buchwald–Hartwig amination oprotocol for nitroarenes with N–H heteroarenes (Scheme 8).[25] Using Pd(acac)$_2$/BrettPhos catalyst system and K_3PO_4 as a base, nitroarenes **1** were coupled with N–H heteroarene **19** to give *N*-arylated heterocycles **20** in moderate to good yields. The reaction tolerated various nitroarenes **1** with electron-donating and electron-withdrawing substituents, successfully converting them into the corresponding arylamines **20**. Other nitroarenes, including 2-methoxy-3-nitropyridine and 5-nitroindole, also proved compatible with the reaction conditions. For the amine component, a range of N–H heteroarenes, including pyrrole, indole, and carbazole, were effective substrates.



Scheme 8 Pd-Catalyzed denitrative amination of nitroarenes with N–H heteroarenes (Yu and Duan group).

More recently, the Li group achieved the formation of C(sp^2)–N bonds *via* a Buchwald–Hartwig-type amination using synthetically upstream nitroarenes **1** as the sole starting materials, by reducing a portion of the nitroarenes *in situ* to amines (Scheme 9A).[26] Using Pd/BrettPhos as the



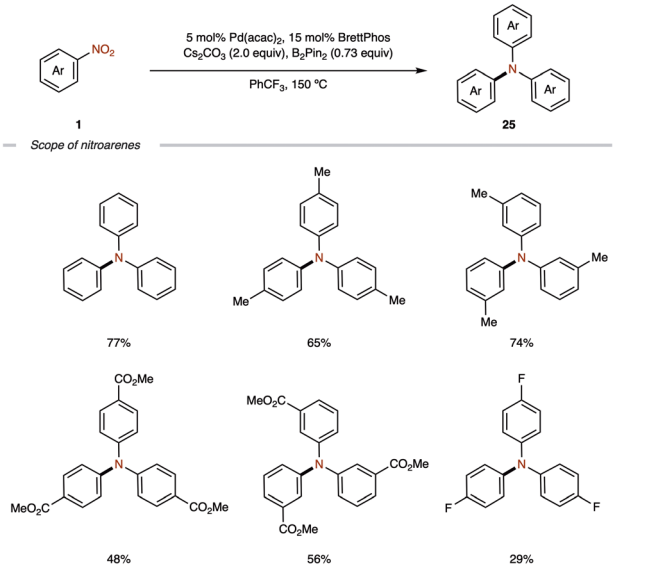
Scheme 9 Pd-Catalyzed denitrative amination of nitroarenes as sole starting materials (Li group). (A) In situ reduction of nitroarenes **1** to amines for C(sp^2)–N bond formation, yielding symmetrical diarylamines **21**. (B) Investigation of potential intermediates, with aniline identified as a key intermediate for diarylamine formation **24**.

optimal catalyst and B_2pin_2 as the most effective reductant, they successfully synthesized the desired diarylamine **21**. Nitroarenes **1** bearing both electron-donating and electron-withdrawing substituents afforded symmetrical diarylamines **21** in good yields. Additionally, nitroarenes containing heteroaromatic rings, such as pyridine and benzofuran, were effectively converted to the corresponding hetero diarylamines **21**.

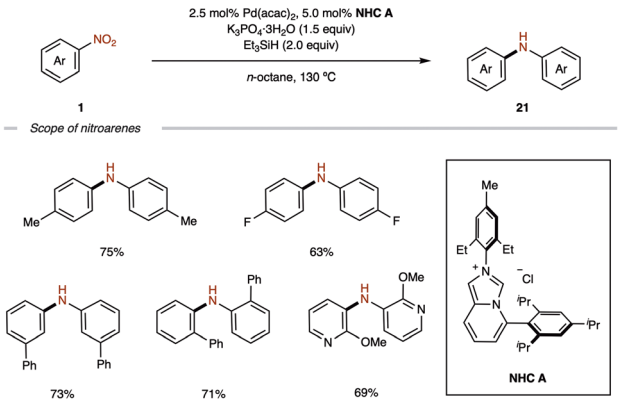
To investigate potential intermediates, they tested compounds **23** including aniline, nitrosobenzene, *N*-phenylhydroxylamine, azobenzene, and azoxybenzene in reactions with nitroarene **22** in the absence of the reductant B_2pin_2 (Scheme 9B). Only aniline led to the formation of the desired diarylamine product **24**, achieving a yield of 62%. These results strongly support the hypothesis that arylamine is likely a key intermediate in this transformation.

In addition, by adjusting the equivalents of the reductant B_2pin_2, they successfully synthesized symmetrical triarylamines **25** directly from nitroarenes **1** (Scheme 10). This reaction was compatible with nitroarenes bearing both electron-donating and electron-withdrawing substituents.

Almost concurrently, Chen and co-workers developed a method for synthesizing diarylamines *via* the reduction and coupling of nitroarenes **1** using palladium catalysts with NHC ligands (Scheme 11).[11g] They identified Pd/NHC **A** complex as the optimal catalyst, with Et_3SiH serving as the most effective reductant for nitroarenes **1** in this transformation, affording the desired diarylamine **21**. This reaction consistently produced symmetrical diarylamines **21** in good yields from nitroarenes **1** containing both electron-donating and electron-withdrawing substituents.



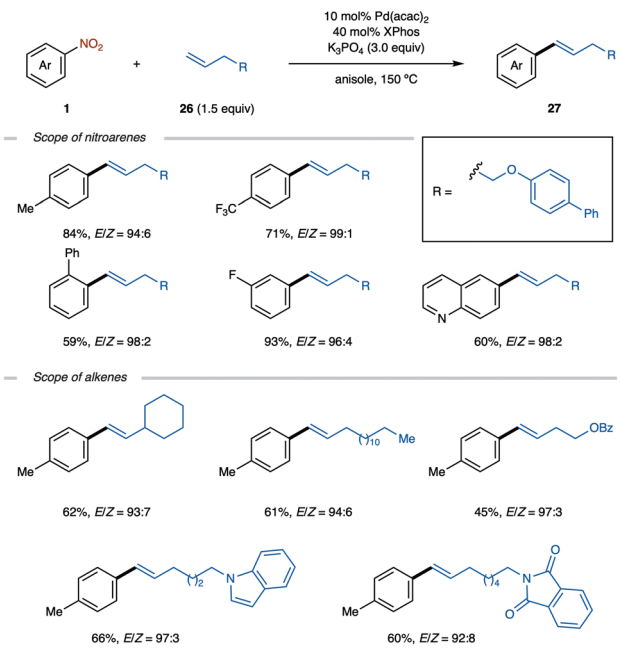
Scheme 10 Substrate scope of nitroarenes to form symmetrical triarylamines.



Scheme 11 Pd-Catalyzed denitrative amination using nitroarenes as the sole starting material (Chen group).

2.6. Mizoroki–Heck reaction

The Mizoroki–Heck reaction between aryl halides and alkenes is a well-established method for constructing aryl alkenes.[27] Recently, Yamaguchi and You introduced a Pd-catalyzed denitrative Mizoroki–Heck reaction.[10f,g] Although denitrative Mizoroki–Heck reactions have been explored, their scope has generally been limited to activated alkenes, such as acrylates and styrenes. Expanding this methodology, the Wu group developed a palladium-catalyzed regioselective Mizoroki–Heck reaction using unactivated alkenes **26** and nitroarenes **1**. (Scheme 12).[28] The authors reoptimized previously reported conditions for use with unactivated alkenes, employing anisole as the solvent to facilitate the reaction at higher temperatures. This practical protocol enabled the synthesis of a wide range of denitrative alkenylated products **27** with high *E*/*Z* selectivity.



Scheme 12 Denitrative Mizoroki–Heck reaction of nitroarenes with unactivated alkenes (Wu group).

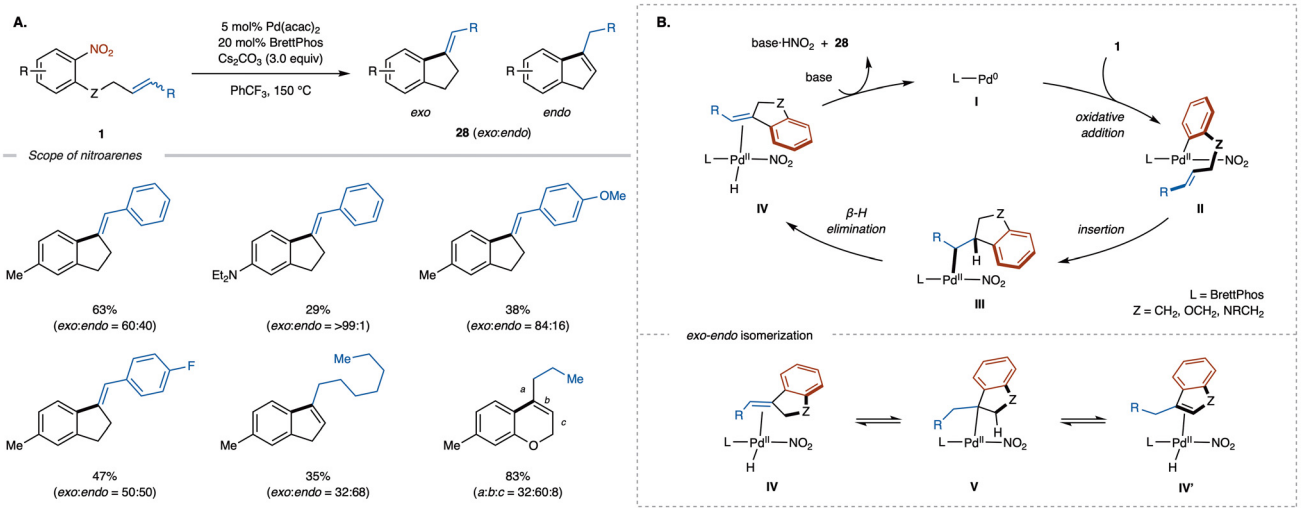


Fig. 3 Denitrative intramolecular Mizoroki–Heck reaction (Yamaguchi group). (A) Substrate scope. (B) Plausible mechanism.

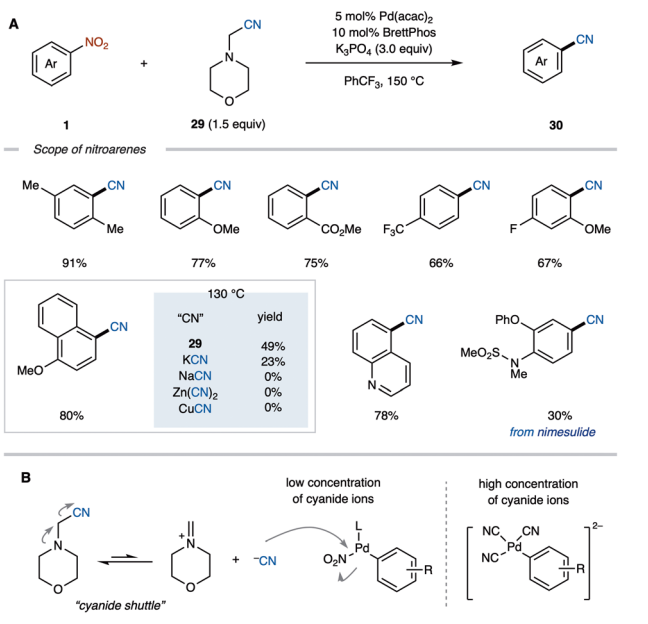
More recently, the Yamaguchi group reported a Pd-catalyzed denitrative intramolecular Mizoroki–Heck reaction of nitroarenes **1** (Fig. 3A).[29] Since a tethered-alkene group can be introduced onto the nitroarene core through nucleophilic aromatic substitution (S_NAr), this denitrative approach provides a convergent synthetic route to benzo-fused cyclic compounds **28.** They found that a combination of $Pd(acac)_2$, BrettPhos and Cs_2CO_3 as the base provided the desired cyclized products **28** in moderate yields.

Based on previous reports, they proposed the following mechanism for intramolecular Mizoroki–Heck reaction (Fig. 3B). The reaction begins with oxidative addition of Pd(0) species **I** to nitroarene **1**, generating intermediate **II.** Intramolecular carbopalladation then forms the alkyl–Pd(II) species **III**, which undergoes β-hydrogen elimination to produce intermediate **IV.** Subsequent base-assisted reductive elimination regenerates the active Pd(0) species **I**, while product **28** dissociates from **IV.** Under high-temperature conditions, *exo–endo* isomerization of the cyclic olefin can occur *via* a reversible Pd–H migratory insertion between **IV** and **IV′**, facilitated by β-hydrogen elimination of **V.**[30]

2.7. Cyanation

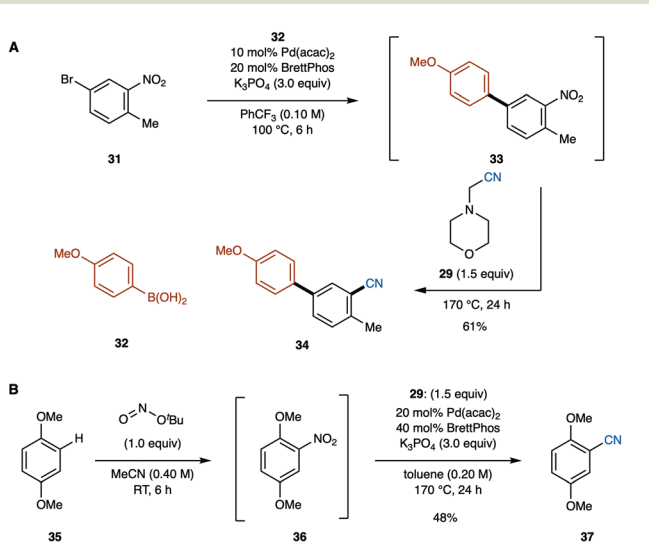
Aryl nitriles are essential intermediates in the development of pharmaceuticals and organic electronic materials, playing a key role in the synthesis of therapeutic compounds such as citalopram, used for treating major depression, and etravirine, used for HIV treatment.[31] The cyanation of nitroarenes offers a pathway to aryl nitriles; however, traditional methods typically require multiple steps, including reduction, diazotization, and the Sandmeyer reaction. In 2024, the Yamaguchi group reported a single-step, Pd-catalyzed denitrative cyanation using nitroarenes **1** as electrophilic partners and aminoacetonitriles **29** as non-metal cyanating agents.[32a]

Traditionally, transition-metal-catalyzed cyanation reactions rely on metal cyanides as the cyanide source, which generate hazardous HCN and metal waste. Organic cyanide sources, such as morpholin-4-ylacetonitrile (**29**), offer a safer alternative. Using $Pd(acac)_2$/BrettPhos as the catalytic system and a base, nitroarenes **1** react with **29** to afford aryl nitriles **30** in moderate yields (Scheme 13A). In addition to its safety profile, this organic cyanide reagent serves as a "cyanide shuttle", gradually releasing cyanide ions into the reaction mixture (Scheme 13B). Notably, reactions using metal cyanides can be hindered due to catalyst deactivation by excess cyanide.[33] In contrast, the gradual release from the organic cyanide source may allow for more effective cyanation of less reactive aromatic electrophiles, such as aryl esters, which typically undergo oxidative addition more slowly than haloarenes.[34]



Scheme 13 Pd-Catalyzed denitrative cyanation of nitroarenes (Yamaguchi group) (A) one-step cyanation of nitroarenes with aminoacetonitrile **29** (B) Role of aminoacetonitriles as cyanide shuttles, gradually releasing cyanide ions for effective cyanation.

Since nitro groups are generally stable under conventional cross-coupling conditions, they conducted a sequential cross-coupling of **31** (Scheme 14A). Initially, Suzuki–Miyaura coupling of **31** with **32** produced biaryl **33** smoothly. The resulting nitroarene **33** was then subjected to the current C–C bond-forming cyanation with **29**, affording **34** in 61% yield over two steps. In another example, a sequential aromatic C–H cyanation was performed without the need for a chelation directing group (Scheme 14B).[35] A previously reported aromatic C–H nitration of **35** followed by the present denitrative cyanation of the resulting **36**, successfully generated **37** in a moderate yield. More recently, Chen, Cao, and Kong reported a one-step synthesis of aryl nitriles *via* electrochemically driven denitrative cyanation of nitroarenes.[32b] See Scheme 20 for further details.

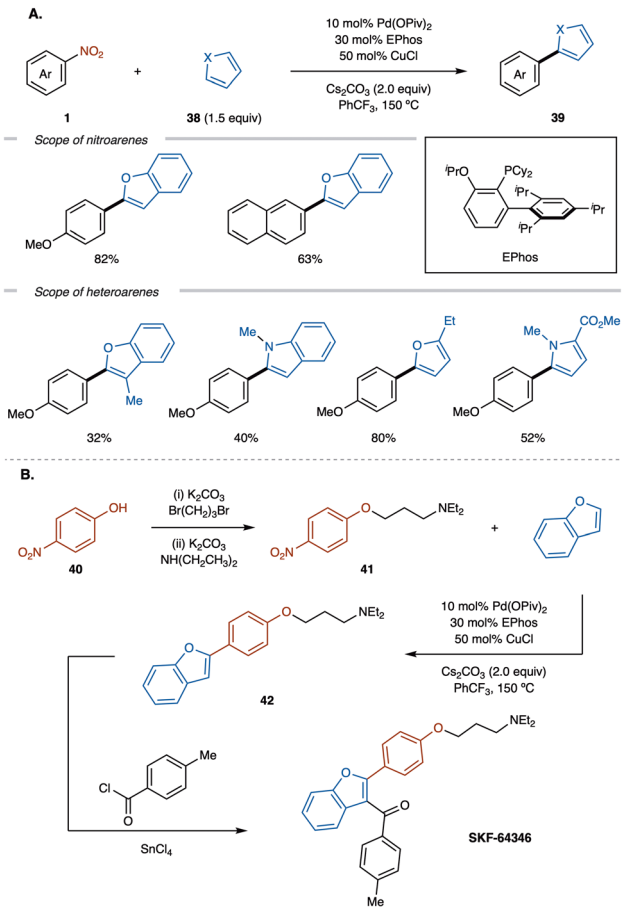


Scheme 14 Sequential coupling reactions Involving nitroarenes (A) sequential Suzuki–Miyaura coupling and denitrative cyanation of nitroarene (B) sequential C–H nitration followed by denitrative cyanation.

2.8. α-C–H Arylation of heteroarenes

α-Arylated heteroarenes are essential structural motifs in natural products, pharmaceuticals, and functional materials.[36] Heteroarenes such as indoles and pyrroles with α-aryl groups substituents are particularly valuable frameworks in drug discovery, where the α-aryl group is often critical for pharmacological activity.[37] In 2019, Yamaguchi and Nakao reported a Pd-catalyzed denitrative intramolecular C–H arylation of nitroarenes.[10d] Recently, Yu achieved an intermolecular C–H arylation of nitroarenes **1** and heteroarenes **38** using a Pd/EPhos catalyst in the presence of Cs_2CO_3 and CuCl (Scheme 15A).[38] This method proved applicable to various nitroarenes **1** and heteroarenes **38**, including benzofuran, indole, furan, and pyrrole, resulting in the formation of the corresponding diaryl products **39**.

With this Pd-catalyzed intermolecular C–H arylation method established, the Yu group applied it to the synthesis of SKF-64346, a compound with therapeutic potential for



Scheme 15 Intermolecular α-C–H arylation of heteroarenes with nitroarenes (Yu group) (A) Pd-catalyzed intermolecular C–H arylation (B) synthesis of SKF-64346.

Alzheimer's disease (Scheme 15B).[39] The synthesis began with a two-step S_{N2} reaction of nitroarene **40** to produce alkoxynitroarene **41**. This intermediate was then subjected to Pd-catalyzed denitrative intermolecular C–H arylation with benzofuran, followed by Friedel–Crafts acylation under acyl chloride and $SnCl_4$ conditions, ultimately yielding SKF-64346.

2.9. Denitrative coupling without metal catalyst

Recent studies have reported metal-free denitrative coupling reactions. Unlike metal-catalyzed processes, which rely on the oxidative addition of nitroarenes to metals as a driving force, these reactions proceed *via* radical functionalization through the formation of aryl radicals. It should be noted that dearomative/denitrative cyclization reactions are also known without metal catalyst;[40] however, these reactions are not covered in this review.

2.9.1. Hydroxylation. Phenols and their derivatives are essential in modern organic synthesis, serving as key building blocks and structural components in natural products, biologically active compounds, pharmaceuticals, and functional materials.[41] Snyder and colleagues demonstrated that nitroarenes could be converted to arenols *via* substitution with oxime anions, providing a feasible approach for the hydroxy-

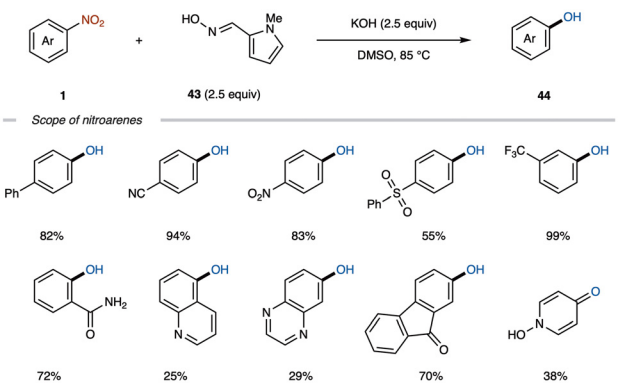
lation of nitroarenes.[42] However, this is the only reported method that does not require nitroarenes to bear strongly electron-withdrawing substituents. In a related advance, James and co-workers developed a metal-free method for the direct conversion of nitroarenes **1** to arenols **44** in a single step (Scheme 16).[43] This protocol involves reacting various nitroarenes **1** with a readily prepared oxime reagent **43** in the presence of potassium hydroxide as a base and DMSO as the solvent, affording arenols **44** in moderate yields.

The James group investigated the formation of arenol **46** by reacting oxime **43** with 4-nitrobiphenyl **45** in the presence of the radical and redox scavenger Galvinoxyl (Scheme 17A). The significant inhibition of arenol **46** formation suggested a radical chain mechanism. Furthermore, repeating the reaction with sodium metal, a sacrificial single-electron donor, increased the yield of arenol **46**, indicating that the reaction likely proceeds *via* one-electron reduction.

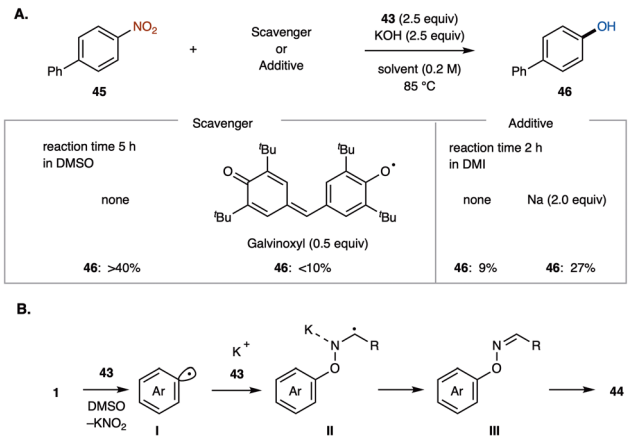
Based on these observations, they proposed the following denitrative hydroxylation mechanism (Scheme 17B). The radical-nucleophilic substitution ($S_{RN}1$) chain reaction is proposed to begin with the interaction between oxime **43** and nitroarene **1**, leading to the formation of aryl radical **I**.[44] This aryl radical then reacts with the oxime anion **43** to form radical anion **II**. Subsequently, radical anion **II** transfers an electron to nitroarene **1** *via* intermolecular electron transfer, regenerating aryl radical **I** and releasing coupling product **III**, which fragments *in situ* to produce the observed arenol **44**.

2.9.2. Borylation and cyanation. Aryl boronic esters are valuable synthetic intermediates, highly regarded for their versatility in a wide range of transformations and significant applications in chemical biology and drug discovery.[45] Cai and Zhang group recently developed the first electrochemical borylation of nitroarenes (Scheme 18).[46] In this process, nitroarene **1** was borylated using B_2pin_2 (**47**) and *t*-BuONO under various electrochemical conditions, yielding the desired aryl boronic esters **48** in moderate to high yields, with excellent tolerance for a broad range of functional groups.

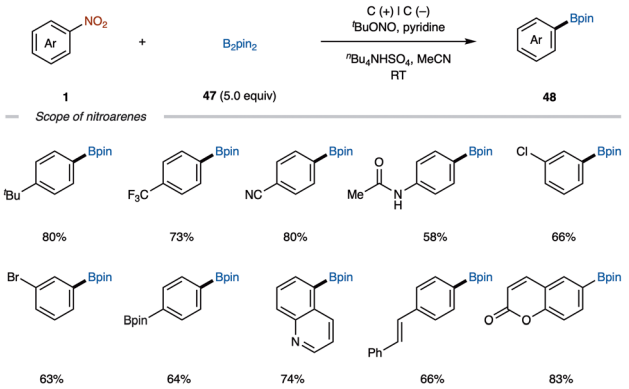
Based on mechanistic studies, they proposed a borylation mechanism (Scheme 19). Initially, nitrobenzene **1** undergoes



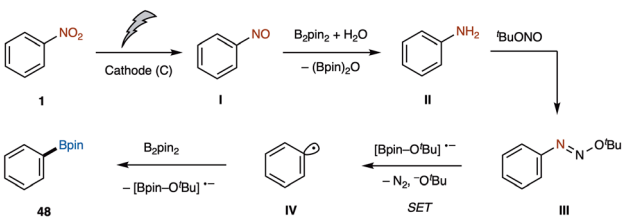
Scheme 16 Metal-free denitrative hydroxylation of nitroarenes (James group).



Scheme 17 Mechanistic studies of metal-free denitrative hydroxylation. (A) Radical trapping experiments. (B) Plausible mechanism.



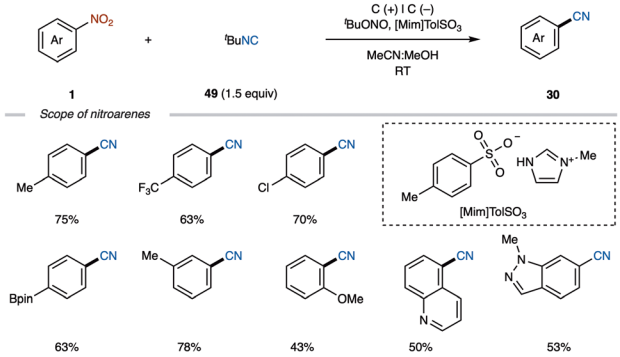
Scheme 18 Electrochemical borylation of nitroarenes (Cai and Zhang group).



Scheme 19 Plausible mechanism.

electron transfer at the cathode, combining with protons to form nitrosobenzene **I**, which then reacts with B_2pin_2 and H_2O to give aniline **II** and $(Bpin)_2O$. Subsequent diazotization of **II** with *t*-BuONO generates phenyldiazonium salt **III**, which undergoes single electron transfer (SET) to release N_2, *tert*-butoxide anion, and phenyl radical **IV**. Finally, radical **IV** reacts with B_2pin_2 and the *tert*-butoxide anion to form the borylated product **48**.

Subsequently, Chen, Cao, and Kong reported the electrochemical cyanation of nitroarene **1** (Scheme 20).[47] By reacting



Scheme 20 Electrochemical cyanation of nitroarenes (Chen, Cao, and Kong groups).

nitroarene **1** with *t*-BuNC (**49**), *t*-BuONO, and [Min]$TolSO_3$ as the ionic liquid under various electrochemical conditions, they successfully synthesized the desired aryl nitriles **30** in moderate to high yields, with excellent tolerance for a wide range of functional groups. They proposed that in this reaction, nitroarenes **1** are electrochemically reduced to anilines, which subsequently form aryl radical intermediates. These radicals then react with *t*-BuNC, the radical trapping agent, to yield the aryl nitriles **30**.

While denitrative coupling has significantly broadened the synthetic utility of nitroarenes, challenges remain in expanding substrate generality, particularly for electron-rich nitroarenes, and in minimizing catalyst loadings to improve sustainability. Additionally, the high reaction temperatures often required for these transformations present a significant obstacle. Developing catalysts with higher activity and efficiency is crucial to address this issue. Future advancements could focus on designing more robust catalytic systems or exploring photocatalytic approaches to enhance reaction efficiency and selectivity under milder conditions.

3. Skeletal editing of nitroarenes using nitrene precursors

Recent advancements in organic synthesis have increasingly focused on molecular rearrangement and skeletal editing, enabling selective and systematic modification of molecular frameworks by adding or removing atoms. The development of new redox-active organophosphorus catalysts has broadened the scope of nitroarene transformations, enhancing both functional group tolerance and substrate generality, and enabling more efficient and selective skeletal rearrangement reactions. Furthermore, it has been discovered that nitroarenes can be photochemically reduced to nitrenes using blue LED irradiation, facilitating skeletal editing reactions that not only leverage classic principles but also significantly expand functional group compatibility and applicability across diverse substrates. This section discusses these recent advancements and the unique mechanisms underlying these transformations.

3.1. *o*-Phenylenediamine synthesis

The incorporation of amine groups onto aromatic rings is essential in medicinal chemistry and synthetic applications, especially given that anilines are key components of numerous bioactive compounds. Developing methods for their efficient synthesis holds considerable societal impact.[48] Among nitrogen-containing aromatic compounds, *ortho*-phenylenediamines represent a particularly valuable yet challenging derivatives due to their presence in many high-impact pharmaceuticals.[49] Traditional synthetic methods for these derivatives often require multi-step sequences, beginning with *ortho*-halogenation of nitroarenes or *ortho*-nitration of haloarenes, typically involving a minimum of four steps.[50] Recent strategies using C–H activation and functionalization *via* metal or radical species have provided partial solutions to these synthetic challenges.[51] However, these methods still necessitate the installation and removal of directing groups, adding complexity and limiting practical applications due to the increased number of synthetic steps.

In 2023, Radosevich introduced a novel strategy for the reductive C–H amination of nitroarenes **1**, enabling tandem C- and N-functionalization to synthesize 2-aminoanilides **51** and benzimidazoles **52** from readily available starting materials (Fig. 4A).[52] Using a redox-active organophosphorus catalyst (**P·[O]**) and $PhSiH_3$ as the terminal reductant, nitroarenes **1** were reacted with secondary amines **50** at 120 °C, followed by the addition of acyl chloride, affording aniline derivatives **51** in moderate to good yields. When primary amines **50** were used, benzimidazoles **52** were obtained in similar yields. The reaction demonstrated compatibility with a variety of nitroarenes containing electron-donating and electron-withdrawing substituents, as well as a range of primary and secondary amines, including morpholine. Based on previous studies, it was proposed that the redox-active organophosphorus catalyst could facilitate complete deoxygenation of the nitroarene *via* a P(III)/P(V) cycle, leading to the formation of a high-energy arylnitrene intermediate **I** (Fig. 4B).[53] Phenylnitrene **I**, typically generated *via* photolytic decomposition of phenylazide, is known to undergo isomerization to benzazirine **II** and dihydroazepine **III** valence tautomers.[54] These intermediates can react with nucleophiles such as amines to form 2-amino-3*H*-azepines **IV** and **V** through ring expansion, a transformation confirmed by isolating **V** in the absence of acyl chloride. The proposed mechanism involves an azepine-to-azanorcaradiene 6π electrocyclization (**VI–VII**), which is promoted by *N*-acylation, followed by decomposition of the fused bicyclic aminal **VII** with rearomatization of the arene core. Consequently, 2-aminoanilide **51** can undergo thermal cyclization under established conditions to yield the target benzimidazole **52**.

More recently, the Leonori group also reported a strategy for *ortho*-phenylenediamine synthesis *via* dearomative-rearomative coupling of nitrobenzenes with amines using bule LED (Fig. 5A).[55] This one-pot procedure involved the initial reaction of nitroarenes **1** and amine **50** with $P(OiPr)_3$

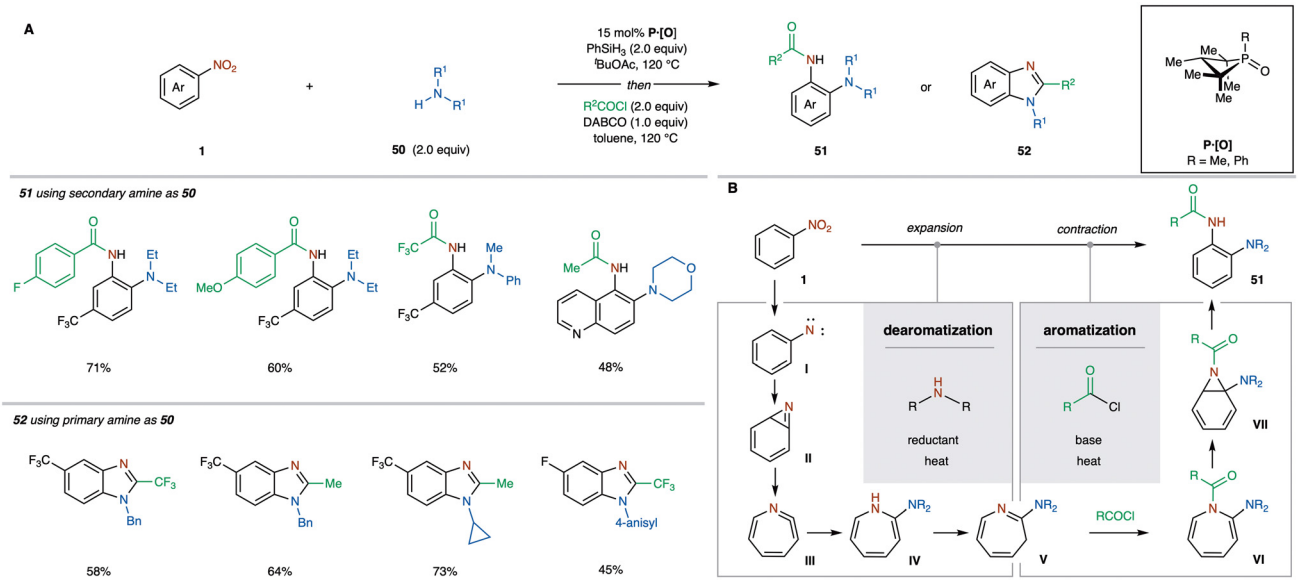


Fig. 4 (A) Reductive C/N-difunctionalization of nitroarenes as a modular approach to synthesize 2-aminoanilides and benzimidazoles. (B) Proposed mechanism illustrating key intermediates in the skeletal editing process (Radosevich group).

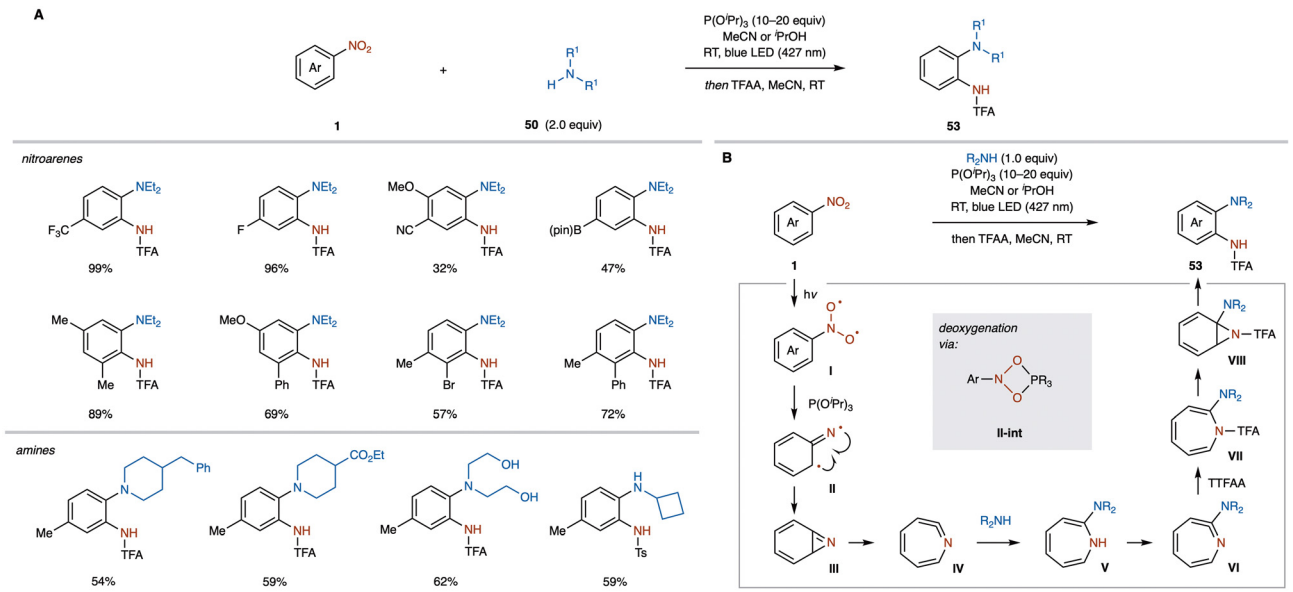


Fig. 5 (A) Synthesis of *ortho*-phenylenediamines *via* dearomative–rearomative coupling of nitroarenes with amines. (B) Proposed mechanistic outline involving triplet nitroarene and key intermediates (Leonori group).

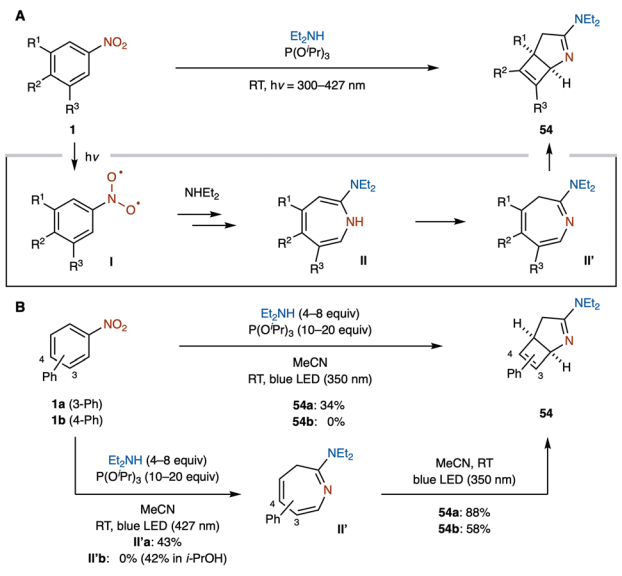
under blue LED irradiation, followed by a dark reaction with trifluoroacetic anhydride (TFAA), affording aniline derivatives **53** in moderate to good yields. The reaction proceeds through the generation of an aryl nitrene intermediate from nitroarenes under mild blue light irradiation at room temperature. This method showed broad substrate compatibility, successfully transforming various nitroarenes bearing electron-donating and electron-withdrawing substituents into the desired phenylenediamines **53**. Additionally, fluoro, boryl, and bromo substituents were well-tolerated. Both primary and secondary amines with diverse structures were also effective as reaction partners.

Based on prior studies, they proposed a mechanism in which blue light irradiation excites nitroarene **1** to its triplet excited state **I** (Fig. 5B).[52,56] The triplet nitroarene, acting as a strong electrophile, undergoes a stepwise radical [3 + 1] cycloaddition with electron-rich phosphite, forming the deoxygenated singlet nitrene **II** *via* intermediate **II-int**. Nitrene **II** then undergoes cyclization to form azirine **III**, which undergoes a 6π electrocyclic ring opening, yielding the seven-membered

ketimine **IV**. In its strained, reactive state, ketimine **IV** is readily intercepted by an amine, forming a second C–N bond to give 1*H*-azepine **V**, which subsequently isomerizes to the more thermodynamically stable 3*H*-isomer **VI**. In the final steps, **VI** reacts with TFAA as an electrophilic trapping agent, producing the heteroaromatic compound **VII** through enolization. This thermodynamic driving force initiates a second 6π electrocyclization in a ring-closing direction, forming N–TFA aziridine **VIII**. The push–pull characteristics of this intermediate facilitate aromatization, affording the *ortho*-aniline **53**. Thus, although the reactivity and mechanism of nitroarenes in these transformations have been known for some time,[56] the use of blue LED light as an energy source has significantly expanded functional group tolerance and substrate generality, making this a prime example of a classic reactivity reintroduced as a novel reaction.

3.2. Bicyclic pyrrolines synthesis

Saturated nitrogen heterocycles are frequently used scaffolds in the discovery of bioactive compounds,[57] with sp^3-rich fragments particularly valued for enhancing the biological activity of lead molecules. Among these, saturated bicyclic amines stand out due to their structural rigidity, which allows for precise three-dimensional (3D) orientation of substituents, making them especially relevant in this context.[58] The Leonori group recently developed an efficient method for synthesizing 2-azabicyclo[3.2.0]heptanes (**54**) from nitroarenes **1** *via* a triplet excited state (Scheme 21A).[59] Although this transformation is based on a known reaction, the use of blue LED irradiation, as in the previous section, enabled a significant expansion of substrate scope, enhancing functional group compatibility.[60] Under blue LED irradiation, nitroarenes **1** reacted with $P(OiPr)_3$ and amines to afford the corresponding 2-azabicyclo



Scheme 21 (A) Proposed mechanistic pathway for the synthesis of 2-azabicyclo[3.2.0]heptanes. (B) Comparative reactivity of 3-Ph and 4-Ph substituted nitroarenes under photochemical conditions.

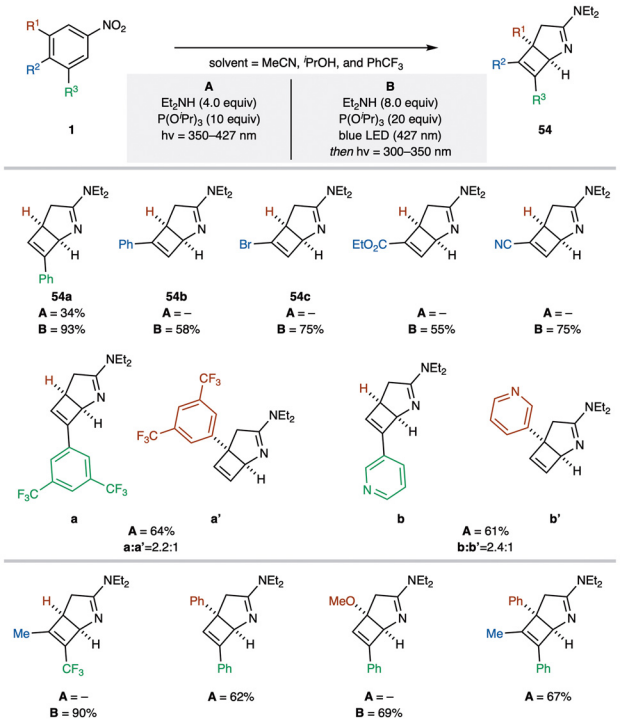
[3.2.0]heptanes **54**. In a mechanism similar to their previously reported *ortho*-diamine synthesis (Fig. 5B), the triplet-excited state of nitroarene **I** undergoes reaction with an amine to produce the 1*H*-azepine **II** *via* dearomatization. Subsequently, **II** isomerizes to the 3*H*-azepine **II′**, which then undergoes a 4π electrocyclization to give the desired 2-azabicyclo[3.2.0] heptane **54**.

This reaction explores a photochemical strategy that leverages the excited-state reactivity of both nitroarene **1** and azepine intermediate **II′**, along with two electrocyclic processes: one thermal and one photochemical (Scheme 21B). The process requires two photoexcitations, which may proceed either in a single step or as two sequential steps, depending on the absorption properties of the intermediates. Using *meta*- and *para*-phenyl-substituted nitroarenes (**1a**[3-Ph] and **1b**[4-Ph]), they found that irradiation of **1a** with 350 nm light afforded the desired product **54a** in moderate yield, whereas similar conditions for **1b** failed to produce trace amounts of the pyrroline isomer **54b**.

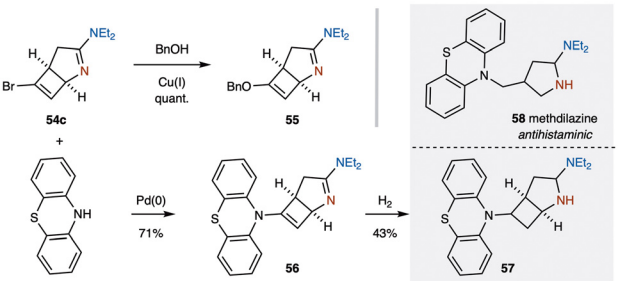
To further investigate the reactivity, they isolated the *N*-insertion and 4π electrocyclization steps. Irradiating **1a** under 427 nm light afforded intermediate **II′a** in 43% yield, while **1b** led to a complex mixture. However, using iPrOH as the solvent enabled the isolation of **II′b** in 42% yield. Subsequent irradiation of **II′a** and **II′b** with 350 nm light produced the desired cyclized products, with **II′a** smoothly converting to **54a** in yields comparable to the direct method. Although the 4π electrocyclization of **II′b** was more challenging, it still afforded **54b** in 58% under diluted conditions. These findings indicate that a stepwise approach, separating azepine formation from electrocyclization, can effectively give the target C6 pyrroline isomer **54b**. Further analysis of the calculated singlet excited-state HOMO–LUMO energy gap of 3*H*-azepine **II′** revealed that **II′a** (3-Ph) is more reactive than **II′b** (4-Ph), providing insights into the reactivity differences observed.

Two synthetic protocols (A or B) for converting nitroarenes **1** into bicyclic pyrrolines **54** have successfully provided C6-functionalized derivatives **54** in good to moderate yields (Scheme 22). This approach is compatible with nitroarenes **1** bearing various aromatic substituents, including halogens and electron-withdrawing groups. The use of *meta*-substituted nitroarenes proceeds smoothly under the direct protocol (A), affording the desired products in moderate yields and often resulting in two isomeric forms. Additionally, this method is applicable to polysubstituted nitroarenes, efficiently converting the corresponding C6-functionalized derivatives **54**.

They further explored derivatization of the C6–Br derivative **54c**, demonstrating its conversion to the desired pyrroline products **55** and **56** in high yields using standard Ullmann and Buchwald–Hartwig cross-coupling methods (Scheme 23). Additionally, coupling product **56** under standard hydrogenolysis conditions afforded amino-substituted heterocycles **57**. Notably, **57** serves as a potential precursor for the synthesis of conformationally constrained analogues of the antihistaminic drug methdilazine **58**. The 3D spatial arrangement of *anti*-5-



Scheme 22 Substrate scope for the conversion of nitroarenes **1** to C6-functionalized bicyclic pyrrolines **54** (Leonori group).



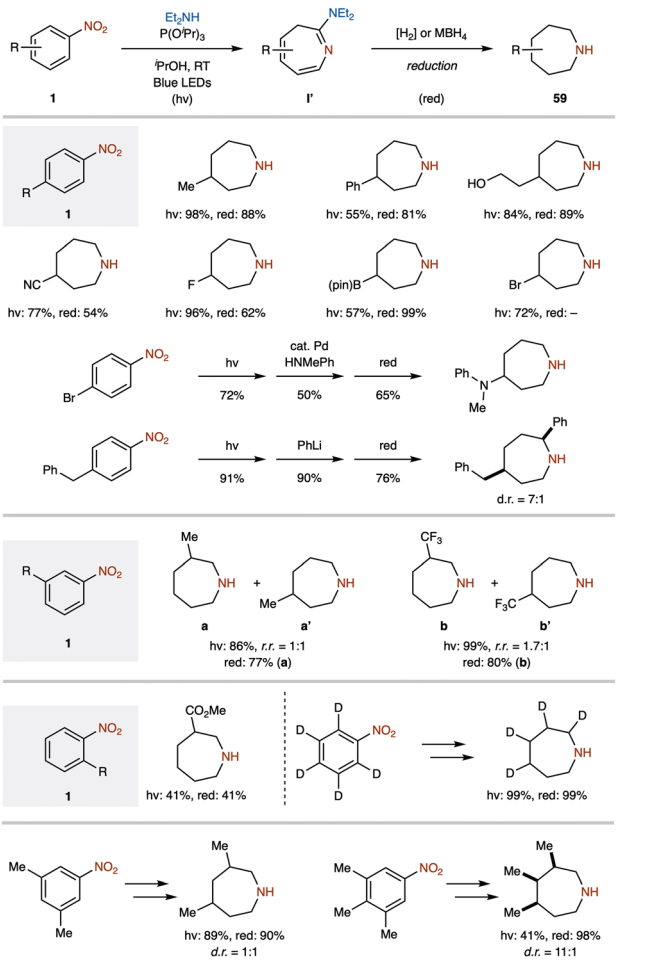
Scheme 23 Derivatizations of pyrroline **54c** by cross-coupling reactions.

substituted-2-azabicyclo[3.2.0]heptanes allows for "cyclobutanation" to access highly strained conformations, with distortion energies exceeding 34 kcal mol^{-1}.

3.3. Synthesis of polysubstituted azepanes

Nitrogen-containing heterocycles are essential building blocks in the discovery and development of bioactive materials.[61] Saturation and ring substitution are critical features in medicinal chemistry, as they produce molecules with globular shapes and multiple vectors for exploring three-dimensional (3D) chemical space. However, the prevalence of certain nitrogen heterocycles in high-value products is often limited by their commercial availability, which depends on ease of synthesis and functionalization. For example, piperidine, a commonly used saturated nitrogen heterocycle, can be converted to pyrrolidine by one-carbon deletion and is readily accessible. In contrast, adding one carbon forms azepane, a far less common structure (<1% of N-heterocycles)[49c] due to the synthetic challenges associated with seven-membered rings compared to more accessible six- and five-membered rings. Existing methods for synthesizing azepanes typically involve multi-step transformations from linear precursors or Beckmann rearrangement of functionalized piperidones, limiting versatility and hindering the preparation of highly substituted derivatives.[62]

Recently, the Leonori group developed a method for converting commercially available nitroarenes **1** into saturated azepane heterocycles **59** (Scheme 24).[63] This process involves generating nitrene intermediates *via* blue light irradiation, followed by a one-atom ring expansion to form an intermediate, which is then subjected to hydrogenolysis. While this method effectively provides azepanes, it primarily involves simple hydrogenation of intermediates like those seen in Fig. 5. Although similar reductions of azepine intermediates to related compounds have been reported in the past,[56] few reports have emerged since then.[64] This strategy enabled the



Scheme 24 Substrate scope for the synthesis of polysubstituted azepanes (Leonori group).

synthesis of several *para*-substituted derivatives, yielding C4-substituted azepanes in good yields. While *para*-bromonitrobenzene underwent efficient ring expansion, subsequent hydrogenolysis presented challenges, as it led to nearly complete dehalogenation under standard conditions. Nevertheless, they achieved successful C4 arylation through Buchwald–Hartwig amination following ring expansion, thus enabling access to previously unattainable aminated derivatives.

Furthermore, a three-step synthetic sequence using *para*-substituted nitroarenes with phenyl lithium nucleophiles enabled the synthesis of disubstituted azepanes in good yields. The reaction also proceeded smoothly with *meta*-substituted nitrobenzenes, producing the desired products along with C4 isomers. Despite difficulties in achieving *N*-insertion with *ortho*-substituted nitrenes, they successfully conducted the reaction with ester-containing derivatives, obtaining C3-functionalized azepanes in useful yields. Additionally, the method proved effective with pentadeuterated nitrobenzene, resulting in a tetradeuterated azepane with near-quantitative yield. Multi-substituted nitroarenes also afforded the corresponding azepanes in good yields.

Skeletal editing *via* nitrene intermediates offers a powerful tool for molecular rearrangement and functionalization. However, controlling the reactivity of high-energy intermediates such as nitrenes remains a challenge, often requiring specific reaction conditions. Future efforts should explore strategies to achieve greater regioselectivity and to extend these transformations to more complex and biologically relevant substrates.

4. The utilization of nitroarenes with N–O bond cleavage as an oxygen source

This chapter discusses recent radical reactions in which nitroarenes serve as the oxygen source, reacting with substrates and subsequently undergoing N–O bond cleavage. It is important to note that this review does not cover reactions where the addition step proceeds through an ionic mechanism (*e.g.*, the reduction of nitro compounds to nitroso compounds followed by addition)[65] or where nitro compounds react *via* a radical mechanism but do not primarily yield products resulting from N–O bond cleavage.[66]

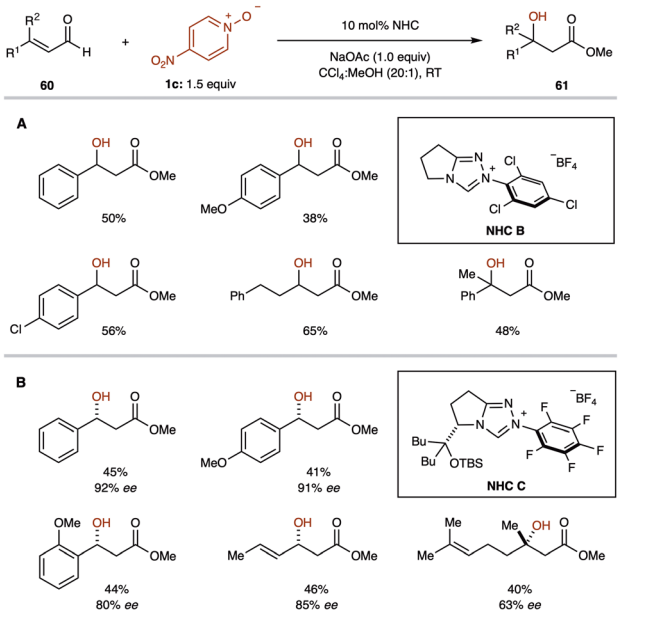
4.1. NHC-catalyzed β-hydroxylation of enals

β-Hydroxyl (α-unsubstituted) esters and their derivatives are valuable building blocks, commonly found as subunits in biologically active compounds and natural products.[67] facilitates acyl anion reactivity, and numerous transformations employing α,β-unsaturated aldehydes as substrates have been developed.[68] However, most of these reactions rely on two-electron mechanisms. In contrast, recent research has investigated single-electron pathways as an alternative. Rovis demonstrated that by using nitropyridine *N*-oxide (**1c**) as a single-electron oxidant, β-hydroxy ester **61** can be synthesized from cinnamaldehyde **60** and NHC catalyst **B** in methanol (Scheme 25A).[69] This approach highlights how selecting single-electron oxidants can expand reaction pathways.

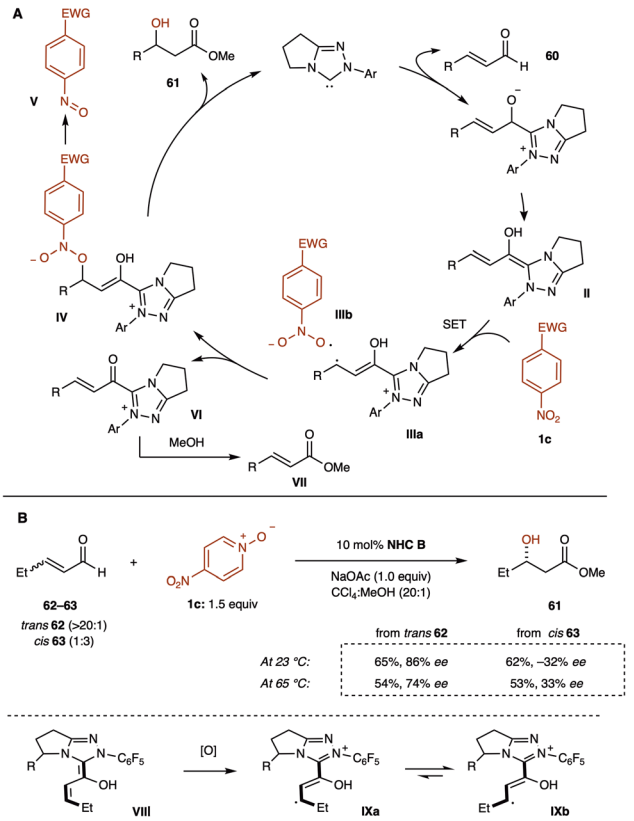
The scope of this reaction is remarkably broad, proceeding efficiently with both aryl and alkyl substitutions at the β-position of the enal **60**. Aliphatic substrates, in particular, yield high quantities of the desired product under these conditions. Additionally, β,β-disubstituted substrates also participate in the reaction, affording tertiary alcohols in moderate yields. Furthermore, using a chiral NHC **C** catalyst enables asymmetric transformations, rendering the reaction applicable to both aryl and aliphatic enals (Scheme 25B).

The Rovis group proposed a reaction mechanism involving Breslow-centered radical cation species **IIIa** (Scheme 26A). The reaction begins with the formation of the Breslow intermediate **II**, which undergoes single-electron oxidation by nitrobenzene **1**, generating a Breslow-centered radical cation **IIIa** and a nitrobenzene-derived radical anion **IIIb**. These radicals then combine, where the homoenolate-centered radical and oxygen-centered radical react to form intermediate **IV**. This intermediate decomposes to release an NHC-bound alkoxide and nitrosobenzene **V**. The NHC-bound alkoxide subsequently reacts with methanol to regenerate the catalyst and produce the β-hydroxy ester **61**. Additionally, α,β-unsaturated methyl ester **VII** may form through deprotonation of intermediate **III**, followed by a second single-electron abstraction, resulting in the formation of α,β-unsaturated acyl azolium **VI**, which is then intercepted by methanol.

To investigate the stereochemical outcome of the reaction, the group tested both *cis*- and *trans*-enals (**62** and **63**). If the reaction proceeds *via* a radical mechanism, with radical recom-



Scheme 25 (A) Substrate scope for the racemic β-hydroxy ester formation. (B) Substrate scope for the asymmetric β-hydroxy ester formation using chiral NHC catalyst (Rovis group).

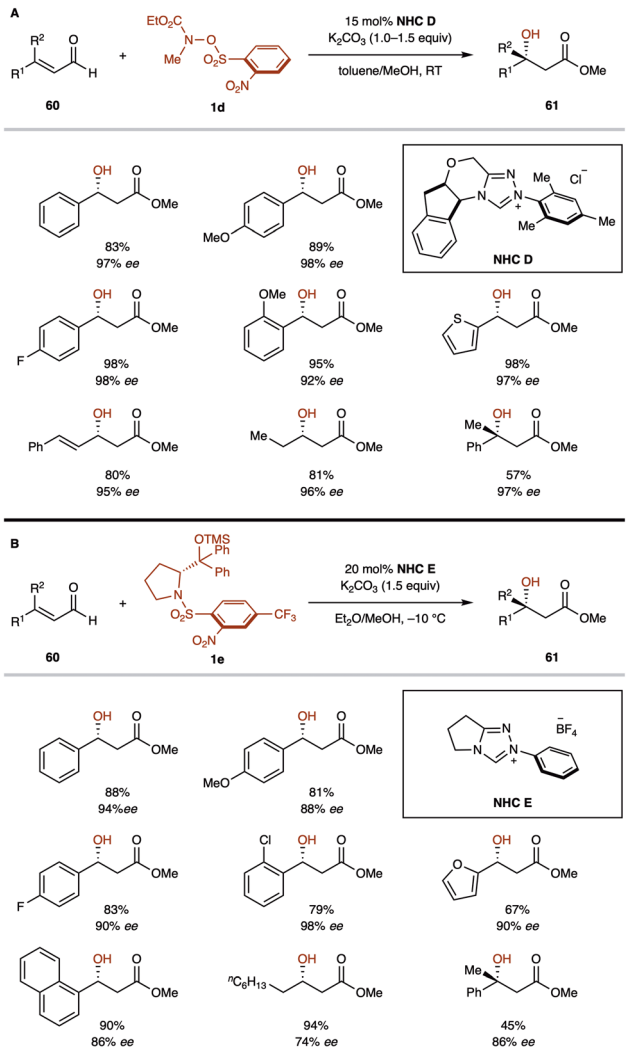


Scheme 26 (A) Proposed mechanism for the β-hydroxylation reaction. (B) Stereochemical investigation using *cis*- and *trans*-enals as probes.

bination slower than bond rotation, the *cis*- and *trans*-enals should produce the same major enantiomer **61′** through interconversion of intermediates **IXa** and **IXb** (Scheme 26B). At room temperature, however, the *cis*- and *trans*-olefin isomers produced opposite major enantiomers. At 65 °C, enantiomeric convergence was observed, supporting the hypothesis of a discrete radical intermediate in the reaction mechanism.

More recently, the Chi group reported an NHC-catalyzed oxidative single-electron transfer (SET) of enals, introducing a hydroxyl group at the β-carbon of enals **60** (Scheme 27A).[70] They found that nitrobenzenesulfonic carbamate (**1d**) served as an effective oxidant when combined with NHC catalyst **D** and K_2CO_3, successfully affording β-hydroxy esters **61** from enals **60**. This catalytic system exhibits broad applicability, accommodating a wide range of enals, including β-(hetero)aryl and β-alkyl enals, and enabling the highly enantioselective synthesis of β-hydroxy esters with valuable applications. Mechanistic studies suggest that the reaction proceeds *via* a radical pathway involving multiple radical intermediates.

Subsequently, Chi and coworkers reported an asymmetric oxidation using a chiral nitroarene as the oxidant (Scheme 27B).[71] When the chiral oxidant **1e** was reacted with enal **60** in the presence of NHC catalyst **E**, the corresponding ester **61** was obtained in high yield and with excellent enantioselectivity. The key to achieving high enantioselectivity was the introduction of the nitro group at the *ortho* position, which brings the reaction site



Scheme 27 (A) Substrate scope for the chiral NHC-catalyzed β-hydroxylation of enals (Chi group). (B) Substrate scope for the NHC-catalyzed β-hydroxylation of enals using a chiral nitoroarene as an oxidant (Chi group).

into close proximity to the chiral environment. Additionally, introducing a trifluoromethyl group at the *para* position further improved both the yield and enantioselectivity. The reaction proceeded efficiently with various cinnamaldehyde derivatives bearing various functional groups. High enantioselectivity was maintained even when the benzene ring was replaced with furan or naphthalene. For alkyl-substituted enals, although enantioselectivity slightly decreased, moderate to high yields of the desired ester **61** were still achieved. Since **1e** acts as the oxidant, it must be used in stoichiometric amounts. However, a significant advantage is that it can be easily prepared by simply mixing the corresponding sulfonyl chloride and amine.

4.2. Fe-Catalyzed anaerobic Mukaiyama-type hydration of alkenes

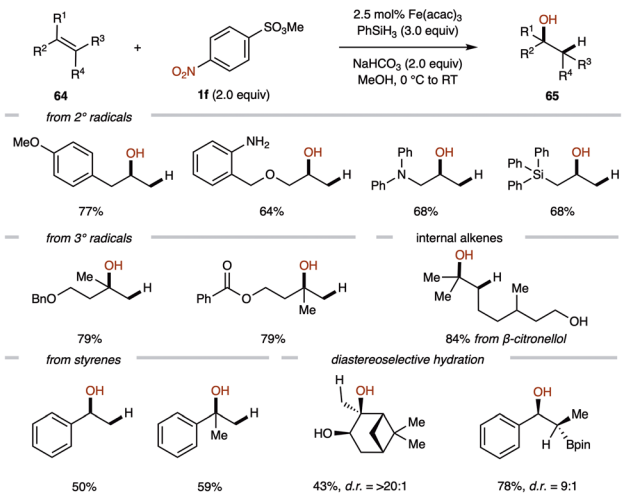
The transformation of alkenes into alcohols is a key process in synthesis, as alcohol functionalities are prevalent in pharma-

ceuticals and natural products. While acid-catalyzed hydration is the simplest approach, it often presents practical challenges, including ether formation and cationic rearrangements. Consequently, Mukaiyama-type radical Markovnikov hydration and *anti*-Markovnikov hydration *via* hydroboration–oxidation are commonly employed at the laboratory scale.[72]

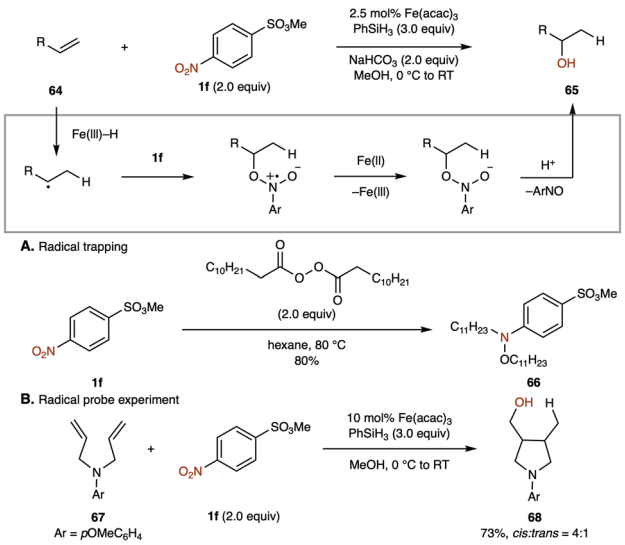
Recently, the Studer group developed an anaerobic Mukaiyama-type alkene hydration reaction using nitroarenes **1f** as non-gaseous oxygen donors under catalytic conditions (Scheme 28).[73] Using an iron catalyst and $PhSiH_3$ as a stoichiometric reductant, they achieved high selectivity and stereoselectivity in converting alkenes **64** into secondary and tertiary alcohols **65**. This method accommodates internal alkenes, including natural products like β-citronellol, and provides benzylic alcohols in moderate to good yields from styrene derivatives. Additionally, the reaction demonstrates excellent diastereoselectivity, producing diastereomerically enriched alcohols.

Mechanistically, the Fe(III)–H species first undergoes hydrogen atom transfer (HAT) with alkene **64**, forming a radical adduct (Scheme 29). This radical is then trapped by nitroarene **1f**, resulting in the formation of a heteroatom-centered radical and an Fe(II) species. The radical intermediate is subsequently reduced by Fe(II), leading to ionic fragmentation and protonation to give **65** while regenerating the Fe(III) species, which is then converted back to Fe(III)–H. Unlike previous studies by the Baran group and by Cheung and Hu, where nitroarenes are reduced early in the reaction and serve as radical amination reagents, here, the nitroarene acts as a trapping agent for alkyl radicals.[74]

To confirm that nitroarenes **1f** can function as alkyl radical acceptors, they thermally decomposed dodecanoyl peroxide in the presence of **1f**, confirming the formation of alkoxyamine **66** (80%) and undecanol (45%) (Scheme 29A). The formation of undecanol suggests that the nitro group in electron-deficient nitroarenes reacts with the C-radical at the oxygen



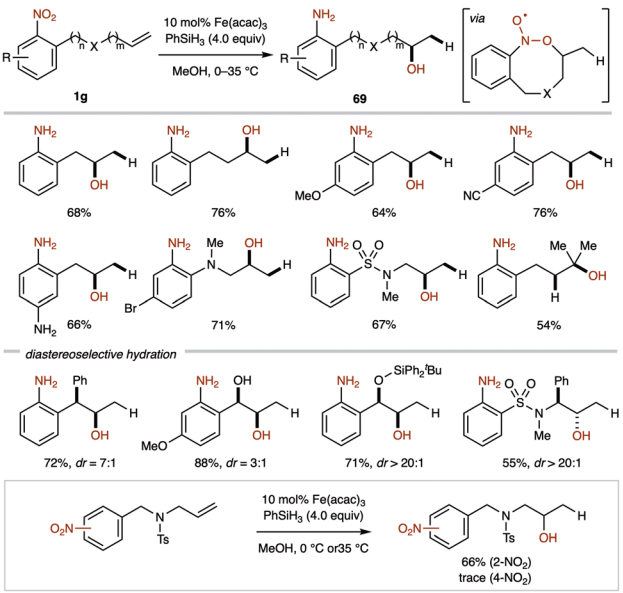
Scheme 28 Fe-Catalyzed Mukaiyama-type hydration of alkenes using nitroarenes as oxygen donors (Studer group).



Scheme 29 Proposed mechanism for Fe-catalyzed Mukaiyama-type hydration of alkenes. (A) Mechanistic pathway involving Fe(III)–H and nitroarene as radical trapping agents. (B) Radical probe experiments supporting the proposed mechanism.

atom, indicating that the alcohol is unlikely to originate from a hydroxylamine or alkoxyamine intermediate under oxidative conditions. To further verify the involvement of radical pathways, they conducted radical probe experiments using 1,6-diene **66** (Scheme 29B). The product **68**, formed *via* radical 5-*exo* cyclization, was obtained in good yield and moderate *cis*/*trans* selectivity, supporting the proposed mechanism.

More recently, Studer group reported an intramolecular variant of the Mukaiyama hydration reaction (Scheme 30).[75] Using substrate **1g**, in which a linker and an olefin are attached *ortho* to the nitro group of a nitroarene, the reaction proceeds in the presence of Fe catalyst and $PhSiH_3$ to afford the hydrated product **69**. Unlike the intermolecular reaction, this transformation does not require an electron-deficient nitroarene. Functional groups such as methoxy or unprotected amino groups are well tolerated, and substrates bearing cyano or bromo substituents also react smoothly, undergoing a 1,6-oxygen shift to give the desired product **69**. Additionally, the reaction proceeds efficiently even when the linker contains nitrogen or sulfonylamide moieties, producing not only secondary alcohols but also tertiary alcohols. When chiral alkenes with stereogenic centers are employed, the reaction proceeds diastereoselectively. For example, phenyl-substituted alkene exhibit a diastereomeric ratio (*dr*) of 7 : 1, while smaller substituents like a hydroxyl group reduce the selectivity (*dr* = 3 : 1). However, using a bulky silyl-protected hydroxyl group restores high diastereoselectivity, enabling efficient oxygen-transfer reactions. The position of the nitro group on the aromatic ring is also critical. While C2 substitution facilitates the reaction, substrates with the nitro group at the C4 position fail to undergo the transformation. This observation suggests that the reaction involves an intramolecular radical oxygen-transfer mechanism rather than an intermolecular process.



Scheme 30 Intramolecular radical oxygen-transfer reactions using nitroarenes (Studer grpup).

4.3. Photoinduced oxygen transfer using nitroarenes for the anaerobic cleavage of alkenes

The oxidative cleavage of alkenes to produce key carbonyl groups is a fundamental transformation in synthetic organic chemistry, essential for natural products and drug candidates.[76] Although ozonolysis is a common method, it poses challenges due to the explosive nature of ozone, specialized equipment requirements, and difficulty in controlling stoichiometry.[77] While other oxidative methods exist, they are limited in scope and produce significant toxic waste.[78] Recently, Parasram and co-workers developed a visible light-induced anaerobic cleavage of alkenes using nitroarenes as oxygen transfer reagents, achieving the synthesis of ketones and overcoming traditional limitations.[79] In a similar reaction reported by Buchi *et al.* in the 1950s using UV light, the ketone yields were notably low.[80] In contrast, the present method employing 390 nm (purple light) irradiation successfully converts various olefins to ketones with significantly improved yields. This reaction enables the efficient formation of acetophenones and benzophenones **71** by reacting alkenes **70** with cyanonitrobenzene in MeCN under 390 nm (purple light) irradiation (Fig. 6Aa). The method also works with less reactive aliphatic alkenes **71**, affording carbonyl compounds effectively.

Mechanistically, the reaction begins with the excitation of nitroarene **1h** upon absorbing 390 nm light, leading to a radical addition to alkenes **70** and the formation of a transient dioxazolidine intermediate **I** (Fig. 6Ab). Subsequent intramolecular radical ring closure affords another intermediate, which decomposes *via* a radical or polar pathway to produce carbonyl compounds **71**. Using *in situ* ^{1}H and ^{19}F photoNMR, they confirmed that the reaction of *cis*-cyclooctene (**72**) with 4-trifluoromethylnitrobenzene gave dioxazolidine **I′** at 25 °C (Fig. 6Ac). Thermolysis of **I′** at 60 °C produced dicarbonyl compound **73**, indicating that its decomposition is not photochemically promoted. Furthermore, hydrogenation of **I′** resulted in a 1 : 1 mixture of *cis*- and *trans*-diols **74**, supporting a non-stereospecific radical ring closure.

To determine if additional intermediates form during the reaction, they monitored the reaction progress of *cis*-styrene (**75**) with nitroarene **1f** in CD_2Cl_2 at −40 °C using photoNMR (Fig. 6Ad). Upon irradiation at 395 nm, two proton resonances (**I″** and **II**) and corresponding ^{19}F signals increased in the initial 2 h, with a modest increase in aldehyde **76**. Intermediates **I″** and **II** are likely due to 1,3-dipolar cycloaddition between **76** and a carbonyl imine, resembling ozonolysis. Increasing the temperature from −40 °C to −20 °C caused rapid decomposition of **I″** and **II**, affording **76** and additional products **77**–**79**.

Almost simultaneously, Leonori reported a similar ketone synthesis from alkenes **80** using nitroarenes **1** under 390 nm purple light irradiation (Fig. 6B).[81] They found that using CH_2Cl_2 with HFIP as an additive was crucial for good reactivity. Since excited-state nitroarenes can abstract hydridic α-C(sp^3)–H bonds, HFIP is thought to suppress this side reaction through hydrogen bonding with the heteroatom, enhancing reactivity with unactivated alkenes. By tuning nitroarene substituents, this method exhibited high functional group compatibility and site selectivity, making it applicable to a broad range of pharmaceutical compounds and natural products.

4.4. Olefin dihydroxylation using nitroarenes

Vicinal diols are frequently found in various bioactive compounds and are essential in high-value products across the pharmaceutical, agrochemical, and fragrance industries.[77b] Numerous methods for olefin dihydroxylation have been developed to synthesize vicinal diols, yet it remains challenging to convert olefins into vicinal diols under mild conditions, especially when working with a broad range of unactivated olefins.

As previously mentioned, Leonori and colleagues reported the synthesis of ketones through oxidative cleavage of alkenes using nitroarenes (Fig. 6B). Building on this work, they have more recently developed a method for synthesizing vicinal diols by applying a similar approach. Specifically, their method involves the formation of a dioxazolidine intermediate from alkenes **81**, followed by reductive cleavage of the N–O bond under light irradiation, using nitroarene **1i** as the oxygen source to give vicinal diols **82** (Scheme 31A).[82] This method successfully converts various alkenes, including terminal, internal, and cyclic alkenes such as cyclooctene and cyclohexene, to their corresponding diols, achieving high yields even with geminally disubstituted alkenes.

In examining stereoselectivity, they found that *syn*-diol **84** was preferentially obtained over *anti*-diol **84′** when using (*E*)-5-decene or (*Z*)-5-decene **83** as substrates (Scheme 31B). This stereoselectivity is attributed to the rapid bond rotation of triplet biradicals **I** and **I′**, which equilibrate to the less sterically

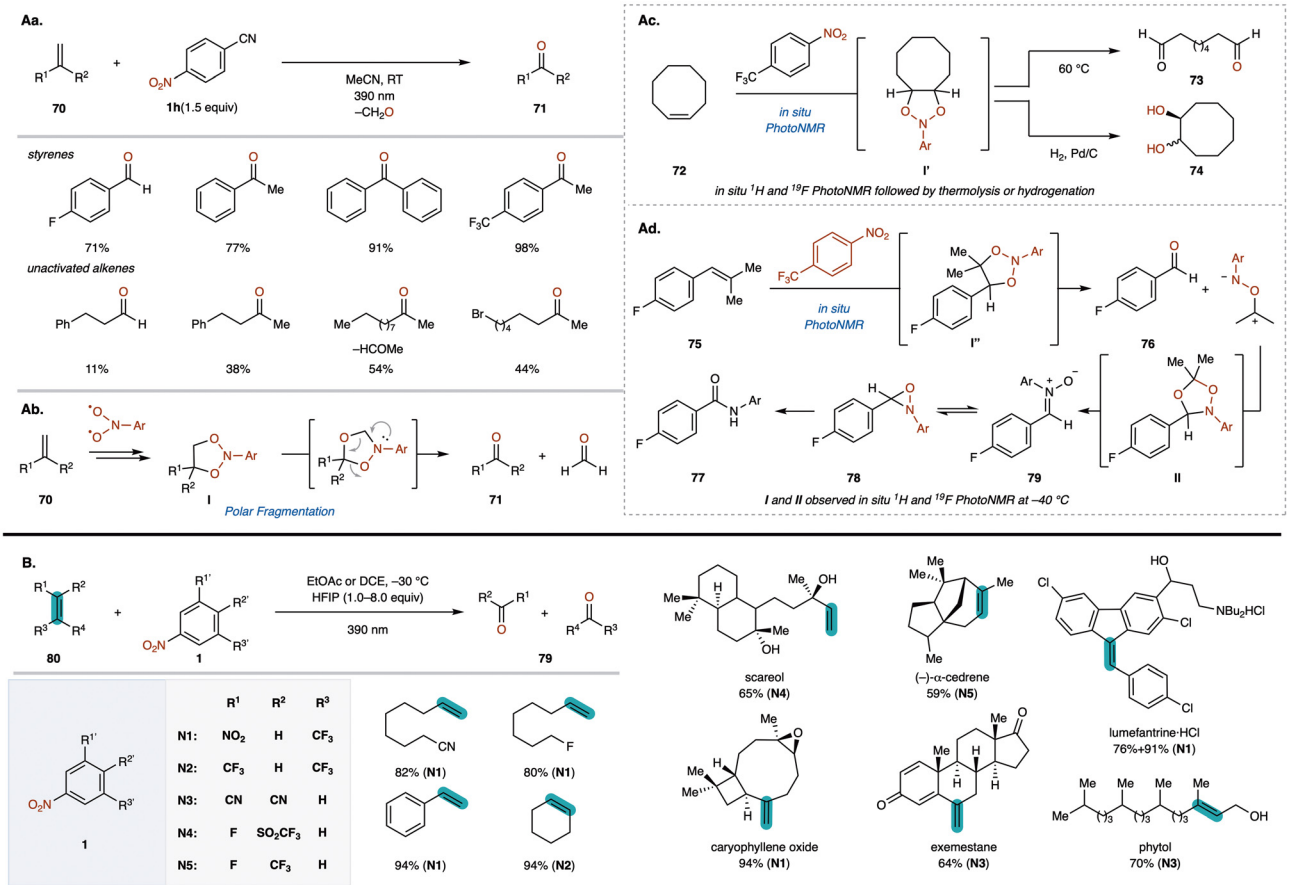
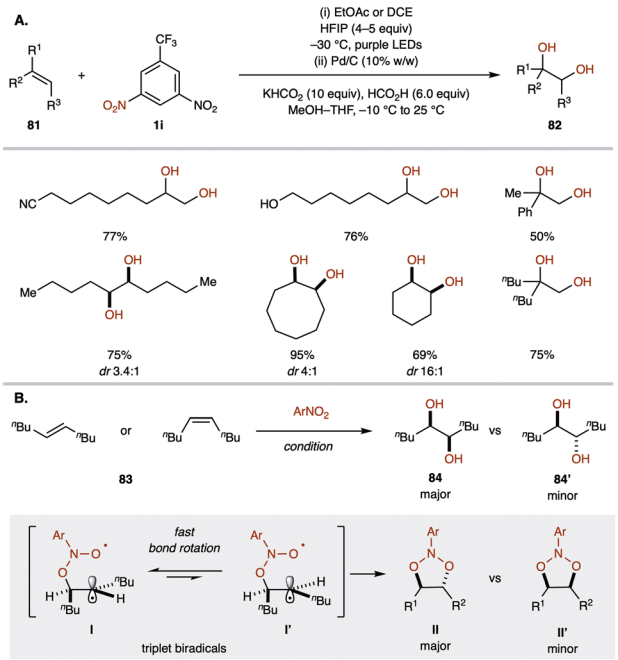


Fig. 6 (A) Visible light-induced anaerobic cleavage of alkenes using nitroarenes as oxygen sources (Parasram group). (B) Anaerobic oxidative cleavage of alkenes with nitroarenes under purple light irradiation (Leonori group).



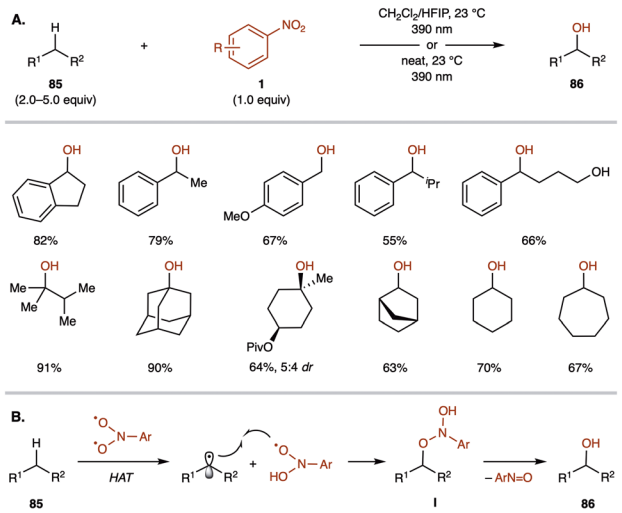
Scheme 31 Olefin dihydroxylation *via* nitroarenes as an oxygen source (Leonori group).

hindered **I**. This intermediate then undergoes cyclization, producing the *syn*-cycloadduct **II** as the major component.

4.5. Anaerobic hydroxylation of C(sp^3)–H bonds

The direct transformation of aliphatic C–H bonds into alcohol groups is a significant challenge in modern organic chemistry.[83] This process requires selective activation of robust C(sp^3)–H bonds, efficient C–O bond formation, and compatibility with oxidation-sensitive functional groups. Various strategies have emerged for incorporating oxygen into aliphatic frameworks, including direct C–H oxidation.[84] However, this approach often necessitates harsh reaction conditions and faces challenges with site-selectivity and preferential alcohol formation. Although transition-metal catalysts and enzyme-based methods have been explored, these methods frequently require directing groups, incur high costs associated with precious metals, and suffer from low efficiency.[85]

In 2023, the Parasram group introduced an anaerobic C–H hydroxylation method for aliphatic systems using photoexcited nitroarenes **1** (Scheme 32A).[86] Although this type of reaction has been reported previously, it traditionally required harsh UV irradiation conditions or was limited to intramolecular reactions under visible light.[87] Under visible light irradiation



Scheme 32 (A) Anaerobic hydroxylation of C(sp^3)–H bonds using nitroarenes (Parasram group). (B) Proposed mechanism for the hydroxylation process.

in CH_2Cl_2/HFIP, nitroarenes **1** facilitate benzylic C–H hydroxylation, producing cyclic benzylic alcohols **86** in various ring sizes, as well as ethylbenzene and toluene derivatives. This method also achieves efficient hydroxylation of tertiary C–H bonds and C–H bonds in cyclic alkanes **85**, yielding alcohols **86** in good to excellent yields.

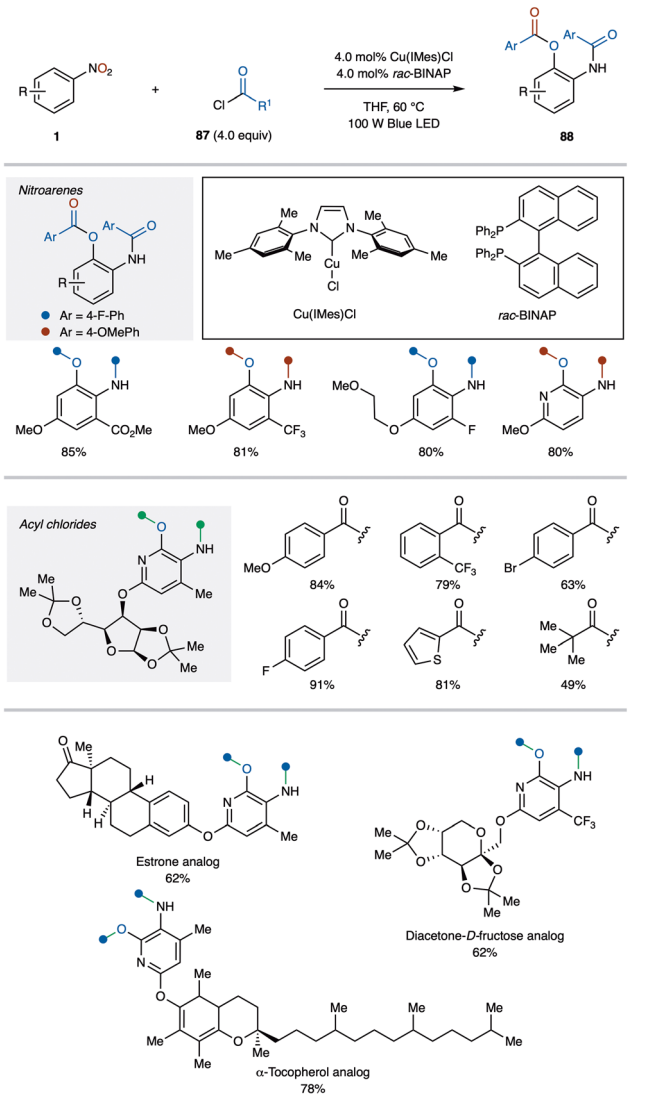
The proposed mechanism involves the direct photoexcitation of the nitroarene to generate a triplet biradical intermediate (Scheme 32B). This intermediate undergoes hydrogen atom transfer (HAT) with the C(sp^3)–H bond of the hydrocarbon, forming an alkyl radical and an oxygen-centered dihydroxyaniline radical. Radical recombination then affords intermediate **I**, which decomposes to produce the oxygen-transfer product **86**. The possibility of alcohol formation through hydrolysis of intermediate **I** is considered low, as demonstrated by the lack of ^{18}O incorporation when $H_2{}^{18}O$ was added to the reaction.

More recently, Miyake and colleagues reported the synthesis of keto-functionalized low-density polyethylene (Keto-LDPE) through the oxidation of C(sp^3)–H bonds in LDPE using nitroarenes as oxidants under LED irradiation.[88] While methods such as carbon monoxide copolymerization and transition metal-catalyzed C–H oxidation are well-established, this approach stands out for its simplicity and its potential to oxidize waste polyolefins, making it a more practical and versatile alternative.

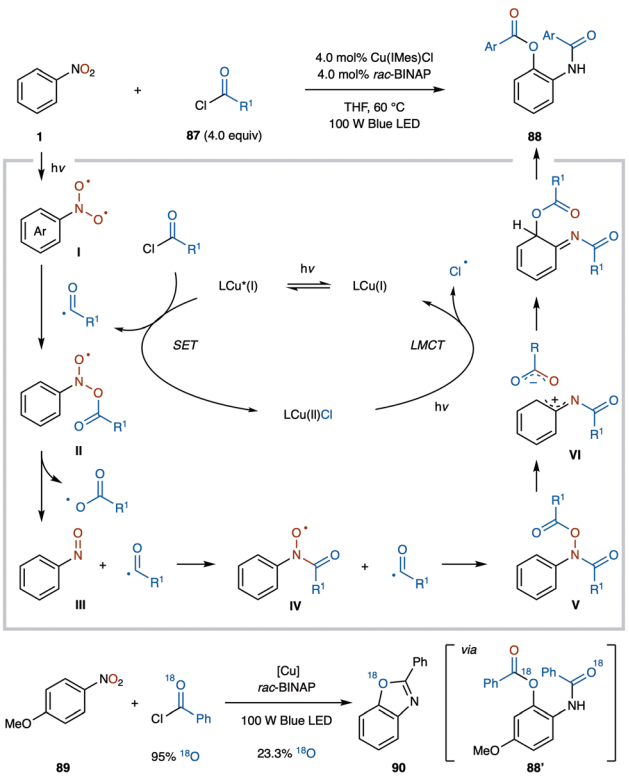
4.6. Access 2-aminophenols *via* excited-state Cu catalysis and nitroarenes

2-Aminophenol derivatives are essential scaffolds in many top-selling pharmaceuticals, and synthesizing them from readily available and inexpensive nitroarenes significantly enhances their practicality. Ngai and colleagues successfully demonstrated the first direct synthesis of 2-aminophenols **88** from nitroarenes **1** using excited-state copper catalysis (Scheme 33).[89] They found that 2-aminophenol derivatives **88** could be obtained by reacting nitroarenes **1** and acyl chlorides **87** with the copper catalyst Cu(IMes)Cl and *rac*-BINAP under visible light irradiation in THF at 60 °C. This mild reaction is compatible with a wide range of substrates, including aromatic nitroarenes with diverse substituents as well as both aromatic and aliphatic acyl chlorides. It also accommodates complex structures, such as derivatives of marketed drugs, natural products, and bio-relevant compounds.

The proposed reaction mechanism involves several key steps (Scheme 34). Photoexcitation of the Cu(I)–BINAP complex forms an excited-state [Cu*(I)–BINAP] complex, which reduces the acyl chloride to generate a Cu(II)Cl–BINAP complex and releases an acyl radical. Simultaneously, the photoexcited nitroarene **1** undergoes intersystem crossing to form a triplet-state radical intermediate **I**, which reacts with the acyl radical



Scheme 33 Excited-state copper-catalyzed synthesis of 2-aminophenols from nitroarenes (Nugai group).



Scheme 34 Proposed reaction mechanism for excited-state copper-catalyzed synthesis of 2-aminophenols.

to produce a short-lived radical intermediate **II**. Intermediate **II** then decomposes to give nitrosobenzene **III** and a carboxyl radical. Nitrosobenzene **III** acts as an effective radical trap, capturing a second acyl radical to form a persistent radical **IV**. Radical **IV** then combines with another acyl radical to generate the bis-acylated intermediate **V**, which undergoes in-cage 1,3-acyl migration and tautomerization to afford the desired 2-aminophenol **88**. Concurrently, the Cu(II)Cl–BINAP complex undergoes ligand-to-metal charge transfer (LMCT) under visible light, releasing a chlorine radical and regenerating the Cu(I)–BINAP catalyst, thereby completing the copper catalytic cycle.

Studies using ^{18}O-labeled benzoyl chloride as the acyl radical source produced an acylated aminophenol **88′**, which, upon debenzoylation, cyclization, and dehydration, yielded a benzoxazole **90** with 23.3% incorporation of ^{18}O from nitroanisole **89**. These findings suggest that acyloxy migration proceeds *via* an in-cage contact ion pair **VI** mechanism.

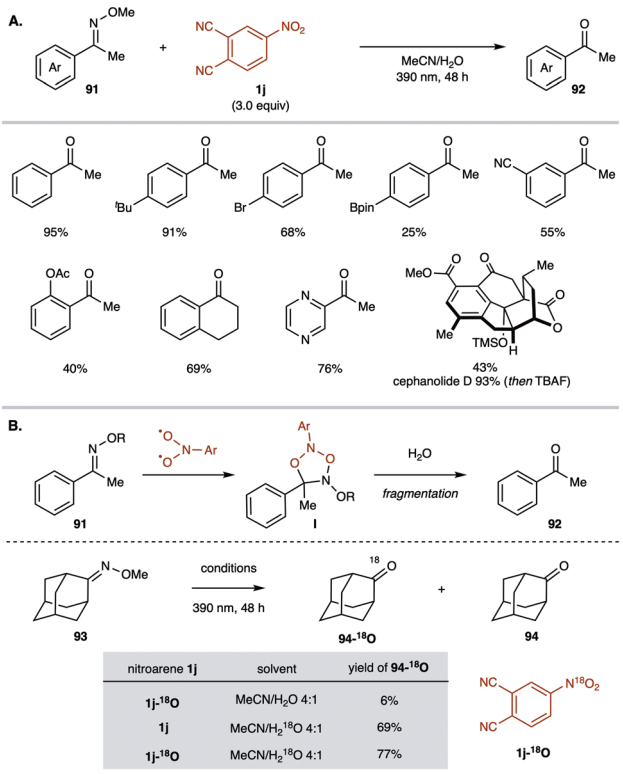
4.7. Oxidative cleavage of ketoximes to ketones using photoexcited nitroarenes

4.7. and 4.8. sections: Although the ultimate oxygen source is water rather than nitroarene, nitroarenes are utilized in these reactions for the conversion of ketoximes to ketones and in the hydration of alkynes.

As part of ongoing research into the total synthesis of natural products, including cephalotane family members, developing methods to convert methoximes to ketones is critically important.[90] Over the past decade, methoximes have gained attention as effective directing groups for C–H functionalization, enabling the formation of value-added products with diverse substituents.[91] However, unlike O–acetyl oximes, methoximes are notoriously difficult to convert back to ketones, often requiring harsh conditions that result in low yields.

In 2023, Sarpong reported a photoirradiation reaction using nitrobenzene **1j** to efficiently cleave benzyl ketoximes **91** and generate the corresponding ketones **92** (Scheme 35A).[92] This reaction demonstrated high efficiency across a range of alkyl ketoximes, including substrates with halogens, boron groups, and cyclic ketones. Notably, the oxime cleavage was applicable to complex substrates, with a cephanolide D derivative affording 43% after deprotection.

The proposed mechanism involves a cycloaddition reaction between photoexcited nitroarene **1j** and oxime **91**, followed by cleavage and subsequent reaction with water to give the ketone **92** (Scheme 35B). To investigate this mechanism, they performed experiments using ^{18}O-labeled nitroarene (**1j-^{18}O**) and $H_2{}^{18}O$. Treating adamantanone methoxime **93** with ^{18}O-labeled nitroarene in a mixture of acetonitrile and ^{18}O-labeled water resulted in 6% ^{18}O incorporation in ketone **94-^{18}O**. Using unlabeled nitroarene with ^{18}O-labeled water led to 69% ^{18}O incorporation, indicating rapid oxygen exchange in the ketone



Scheme 35 (A) Oxidative cleavage of ketoximes to ketones using nitroarenes (Sarpong group). (B) Proposed mechanism for the nitroarene-mediated cleavage reaction.

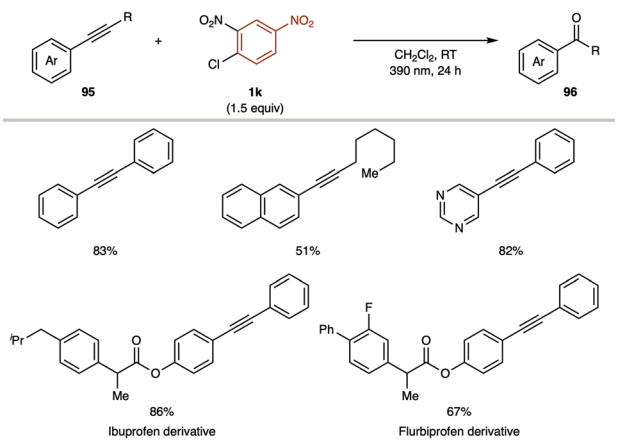
group. When both **1j-^{18}O** and ^{18}O-labeled water were used, the ^{18}O content in the product increased to 77%, suggesting that both the nitroarene and water contribute to the oxygen atom in the ketone.

4.8. Triplet excited nitroarene converts linear alkynes to bent ketones by deleting a carbon atom

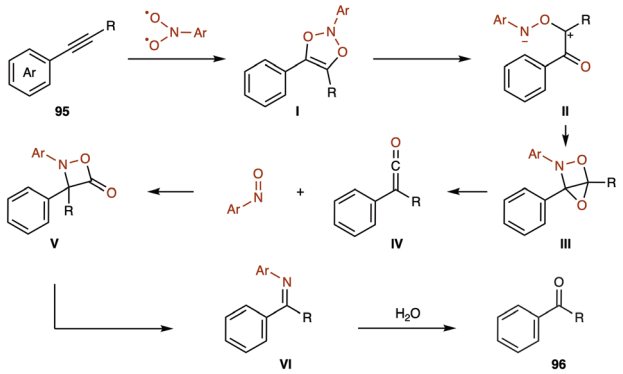
The ozonolysis of alkynes typically produces a mixture of products, with the composition influenced by reaction conditions and substrate electronic characteristics.[93] Traditional methods for alkyne cleavage include using stoichiometric amounts of transition metal oxides, hypervalent iodine, peracids, or pressurized molecular oxygen. Previous studies involving photoexcited nitrobenzene under mercury arc lamp irradiation for three days resulted in complex mixtures, including benzophenone anil, carbon dioxide, nitrosobenzene, dibenzanilide, 2-hydroxyazobenzene, and β-lactam.[94] However, these harsh conditions and product complexity have limited the practicality of such approaches, particularly in fine chemical industries and fields requiring high-throughput techniques.

To address these limitations, Maji and co-workers proposed using triplet-excited nitroarenes **1k** as an alternative to ozone, enabling oxygen atom introduction under mild, visible-light irradiation (Scheme 36).[95] They irradiated alkynes **95** with nitrobenzene **1** as an oxygen atom donor in 1,2-dichloroethane, using purple LEDs (λ_{max} = 390 nm) at 25 °C, producing ketone **96**. This method is effective with both symmetrical diaryl and unsymmetrical aryl–alkyl alkynes. Notably, complex molecules, including derivatives of ibuprofen and flurbiprofen, reacted smoothly, yielding products in 67–86% while preserving a variety of sensitive functional groups.

They propose a reaction mechanism (Scheme 37). The excited state of nitroarene, generated through irradiation with purple light, is expected to participate in a stepwise [3 + 2] cycloaddition with alkyne **95**. This initially forms transient species **I**, which then undergoes cleavage of a weak O–N bond to give zwitterion **II**. Zwitterion **II** rearranges to form strained



Scheme 36 Conversion of linear alkynes to bent ketones *via* triplet-excited nitroarenes (Maji group).



Scheme 37 Proposed reaction mechanism for the conversion of alkynes to ketones using triplet-excited nitroarenes.

intermediate **III**, which decomposes to produce ketene **IV** and nitrosoarene. Control experiments have validated the presence of these intermediates. At this stage, ketene **IV** and nitrosoarene are proposed to undergo a [2 + 2] cycloaddition, generating the four-membered intermediate **V**. A retro [2 + 2] cycloaddition of **V** then releases imine **VI** and CO_2, while subsequent hydrolysis of **VI** produce the final product **96**, which has one less carbon atom than the original alkyne.

The use of nitroarenes as an oxygen source in oxidation reactions has introduced a more sustainable alternative to traditional oxidants. Nonetheless, achieving higher atom economy and expanding the applicability to unactivated alkenes or C–H bonds in a broader range of substrates remain areas requiring further exploration. Innovations in catalyst design or the development of dual catalytic systems could address these limitations and enable more efficient transformations.

5. Conclusions

Over the past decade, remarkable progress has been made in the chemistry of nitroarenes, particularly in transition metal-catalyzed denitrative transformations that enable the formation of diverse bonds, including C–C, C–N, C–H, C–O, C–B, and C–Si. The development of advanced catalytic systems, such as Pd/BrettPhos, has not only expanded the scope of these reactions but also deepened our mechanistic understanding. Moreover, the advent of metal-free denitrative coupling reactions has introduced new possibilities for nitroarene transformations. In parallel, the photoexcitation of nitroarenes to their triplet excited state has enabled unprecedented aromatic ring expansions, facilitating the synthesis of a wide range of aniline derivatives and aliphatic heterocycles. Additionally, the innovative use of nitro groups as an oxygen source has paved the way for anaerobic oxidation protocols, providing sustainable alternatives to traditional methodologies, such as alkene hydration and oxidative cleavage, which often rely on oxygen or ozone. Despite these substantial advancements, the full potential of nitroarenes in large-scale applications remains underexplored. Challenges such as cost-

effectiveness, scalability, and compatibility with sensitive functional groups must be addressed to unlock their broader adoption. Leveraging computational tools for reaction design and exploring tandem or cascade processes involving nitroarenes hold significant promise for future breakthroughs in this field.

As discussed throughout this review, the transformative power of nitroarene chemistry lies in its ability to target entirely different elements—carbon, nitrogen, and oxygen—within the aromatic nitro group. This precise control has been made possible by the development of novel catalysts (*e.g.*, Pd-based systems) and innovative reaction conditions (*e.g.*, blue LED irradiation). While many of these transformations trace their origins to classical reactions, modern technologies have reimagined nitroarenes, transforming them from "classic materials" into a new generation of versatile building blocks. These advancements have profoundly enhanced the utility of nitroarenes, offering sustainable and environmentally friendly methodologies for organic synthesis. The growing body of research underscores the evolving role of nitroarenes, highlighting their potential for continued innovation, broad applications, and their unique ability to bridge historical foundations with cutting-edge technologies.

Data availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Conflicts of interest

There are no conficts to declare.

Acknowledgements

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