HHS Public Access

Author manuscript

Synthesis (Stuttg). Author manuscript; available in PMC 2024 July 29.

Published in final edited form as:

Synthesis (Stuttg). 2022 July ; 54(14): 3142–3161. doi:10.1055/a-1792-6579.

Recent Advances to Mediate Reductive Processes of Nitroarenes Using Single-Electron Transfer, Organomagnesium, or Organozinc Reagents

Haoran Zhu[a], **Tom G. Driver**[*,a]

[a]Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois, USA, 60607.

Abstract

Recent advances in the development of reductive reactions of nitroarenes using organomagnesium-, organozinc-, and single electron transfer reagents is discussed within this review. The review is divided into the following sections:

1. Introduction
2. Organomagnesium-mediated reductive reactions
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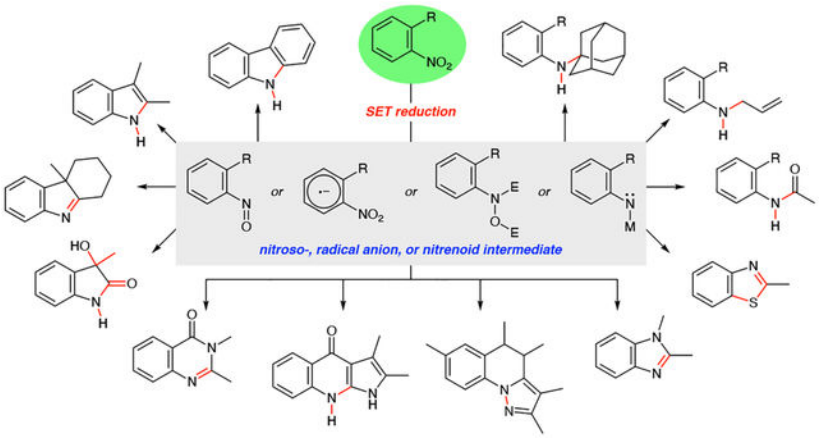
Graphical Abstract

[*]indicates the main/corresponding author. tgd@uic.edu.



Keywords

Nitroarenes; nitrosoarenes; single electron transfer; organomagnesium; organozinc; titanium(III); reduction

Introduction

For over a century, the ubiquity of nitroarenes has inspired the development of reductive processes to form C–NAr bonds via reactive nitrogen intermediates. The appeal of using nitroarenes as substrates stems from their ready availability. They are easily constructed through nitration processes of arenes and heteroarenes,[1,2,3] and functionalized through S_NAr-,[4] cross-coupling-,[5] and radical reactions.[6] The reductive cyclization of nitroarenes to afford carbazoles, indoles, indazoles, and other *N*-heterocycles in boiling triethyl phosphite was reported first by Cadogan and co-workers and explored by Sundberg and co-workers.[7,8] This process was recently rendered catalytic in phosphine by Radosevich and co-workers, who reported evidence that cyclization occurred via nitrosoarene **2** and **3** (Scheme 1).[9] Significant progress has been also been made to catalyze reductive amination reactions of nitroarenes using the combination of a transition metal catalyst and carbon monoxide or a hydride. In 1994, Watanabe and co-workers reported that $Pd(OAc)_2$, phenanthroline, and CO catalyzed the formation of indoles and 2*H*-indazoles from 2-substituted nitroarenes via palladacycle **6**.[10,11] Since these initial reports, advances were made to further develop this reductive amination technology by the Söderberg-,[12] Ragaini-,[13] Cenini-,[14] and Davies groups.[15] Knölker and co-workers showcased the power of Pd-catalyzed reductive amination reactions to facilitate the synthesis of carbazole alkaloids from nitroarenes.[16] A significant advance in metal-catalyzed reductive amination reactions was reported by Baran and co-workers in 2015 who showed that exposure of a nitroarene and an olefin to the combination of 30 mol % of iron acetate produced tertiary *N*-aryl amines.[17] Zhu and co-workers reported that this intermolecular reductive amination reaction could be catalyzed by nickel bipyridyl complexes using $Me(MeO)_2SiH$ as the terminal reductant.[18] The metal hydride catalyst serves multiple roles in the transformation: reduction of nitroarene to nitrosoarene **9** as well as formation of tertiary radical **10** from the olefin.[19] The Driver- and Wang laboratories reported that the combination of iron catalyst and a silane could be used to construct *N*-

heterocycles from 2-substituted nitroarenes.[20] These strategies have significantly advanced the construction of C–NHAr bonds using nitroarenes. Because they have been subject of recent reviews,[21] this current review focuses on recent advances achieving reductive amination processes of nitroarenes using organomagnesium-, organozinc-, and single electron transfer reagents via unique reactive intermediates.[22]

Organomagnesium-mediated reductive reactions of nitroarenes

An organomagnesium-mediated reductive cyclization of 2-substituted nitroarenes was reported by Bartoli and co-workers in 1989 to access 7-substituted indoles (Scheme 2).[23] This is an extraordinarily efficient method because of its modularity where the C2- and C3 carbons of the indole are introduced using the vinyl Grignard reagent. If the 2-substituent was absent from the nitroarene, however, only very low yields of the indole product was obtained.[23a] Careful analysis of the by-products of the reaction, reactivity studies of potential reactive intermediates, and labeling studies led Bartoli and co-workers to propose that the reaction proceeds through a nitrosoarene reactive intermediate.[24] Addition of the organomagnesium to the oxygen-atom of the nitroarene **15**, and a subsequent elimination affords nitrosoarene **16** and magnesium enolate, whose aldehyde could be detected upon acid work up. Addition of a second vinyl magnesium reagent to the oxygen-atom produces **17**, which undergoes a [3,3] sigmatropic rearrangement to afford aldehyde **18**. Cyclization followed by tautomerization forms **19**, which is deprotonated by a third equivalent of the Grignard reagent. Protonation and dehydration were proposed to occur during aqueous quenching of the reaction to afford 7-substituted indole **21**

In 2014, Kürti, Ess, and co-workers reported a significant advance on the Bartoli-indole synthesis to show that carbazoles could be constructed from 2-arylnitroarenes (Scheme 3).[25] The authors' method emerged from their observations into the effect of varying the identity of the 2-substituent of the nitroarene substrate on its reactivity with aryl magnesium reagents to construct 2-amino-2'-hydroxy-1,1'-biaryls.[26] The authors found that when 2-halo-substituent was replaced with a phenyl group that treatment of 2-nitrobiphenyl with PhMgBr afforded a 3.2:1 mixture of carbazole **23a** and *N*-([1,1'-biphenyl]-2-yl)-*N*-phenylhydroxylamine **24a**. The authors' optimization experiments revealed that increasing or decreasing the temperature of the reaction from 0 °C did not improve the ratio of **23a**:**24a**, and that at least 3 equivalents of the Grignard reagent was required to convert all the nitroarene substrate. The scope of their method was found to be broad. In addition to tolerating alkyl substituents, reducible methyl carboxylate- and nitrile groups were allowed. The authors' reaction was regioselective: 2-nitrobiaryl **22f** was converted to only carbazole **23f**. The authors reported that the reaction was sensitive to the steric environment with a diminished yield of carbazole **23g** obtained. The authors showcased the power of their reaction by preparing carbazole alkaloids, clausine V and glycoborine in preparatively useful quantities. The authors also demonstrated that their method could be used to access complex fused *N*-heterocycles **23j** – **23l** as single regioisomers.

Using a combination of DFT calculations and experiments, the authors proposed that carbazole formation occurred via a nitrenoid reactive intermediate (Scheme 3). The authors ruled out a mechanism involving an *N*-biaryl nitrene because they did not observe potential

by-products and eliminated an electrocyclization mechanism because DFT calculations suggested the process was too high in energy. Instead, their calculations identified an alternative pathway for carbazole formation via nitrenoid **27**. This species is formed from nucleophilic addition of the aryl Grignard reagent to the oxygen-atom of nitro-group to afford **25**, which undergoes two consecutive N–O bond fragmentations to produce the nitrenoid. The authors proposed that C–NAr bond formation occurred through an aromatic addition or pseudo-electrocyclization to form **28**, which rearranges to carbazole **23a**.

In 2015, Dhayalan and Knochel reported that secondary amines could be constructed from tertiary nitroalkanes and organomagnesium reagents (Scheme 4). This work built on Knochel's seminal 2002 report,[27] which reported that cross-coupling of Grignard reagents with nitroarenes could access functionalized diarylamines after an iron-mediated reduction of the N–O bond. In contrast, the use of adamantylzinc required electron-rich nitrosoarenes for good yields.[28] Dhayalan and Knochel showed that this limitation could be overcome by using 1-nitroadamantane and an aryl magnesium reagent. The scope of this method is broad with electron-neutral-, electron-deficient-, electron-rich aryl Grignard reagents affording secondary amines in good yields. Remarkably, despite the established reactivity of esters towards organomagnesium reagents, amine **31c** could be constructed using the authors' method. Dhayalan and Knochel also reported that tertiary alkyl magnesium reagents could be used as cross-coupling partners to afford sterically congested secondary amines, such as **31e** or **31f**, in good yields. Further the authors showed that this reactivity was not restricted to 1-nitroadamantane, but that secondary arylamines (e.g. **31g** and **31h**) could be accessed from 2-methyl-2-nitropropane.

To accommodate the requirement of greater than 2 equivalents of the organomagnesium reagent, the authors proposed a mechanism for secondary amine formation that is similar to the Bartoli-indole synthesis.[23] The first equivalent of the organomagnesium reagent adds to the oxygen of the nitro-group of 1-nitroadamantane **29a** to produce 1-nitrosoadamantane **32** and magnesium *tert*-butoxide. The second equivalent of the magnesium reagent then adds to the nitrogen-atom of the nitroso-group to produce **30a**. Reduction of the N–OMgCl bond by the combination of iron(II) chloride and sodium borohydride furnishes the secondary amine.

Organozinc-mediated reductive reactions of nitroarenes

Niggemann and co-workers reported that secondary amines could be accessed from nitroarenes or nitroalkanes using in situ generated organozinc reagents from alkyl halides and B_2pin_2 (Scheme 5). The author's strategy is clever because it couples together two electrophilic reagents—nitroarenes and alkyl halides—and significant because secondary amines are obtained without dimerization or rearrangement of the nitroso intermediate or over alkylation. The authors were able to achieve this advance by developing conditions that leveraged their B_2pin_2-mediated direct reductive *N*-functionalization of nitro-groups with diethyl zinc to produce secondary- or tertiary aryl amines.[29] Critical to the success of the author's strategy was the inclusion of lithium chloride. When it was replaced with trimethylsilyl chloride or triethyl amine, only reduction to aniline was observed. Their method was broad tolerating increased steric environment around the nitro-group and potentially sensitive functional groups, such as phenols, to furnish secondary amines

35b and **35c**. Nitroarenes bearing electron-withdrawing substituents were particularly well-behaved to provide **35d** and **35e** in good yields. The authors reported that a range of alkyl halides could be used as coupling partners to synthesize secondary amines with *N*-allyl-groups and secondary substituents including *N*-Boc protected piperidine. The latter, however, required increased temperature to produce **35i**. Remarkably, the author's method could be extended to nitroalkanes to produce secondary amines, such as **35j**, in good yields.

Because nitroalkanes were tolerated as substrates, the authors proposed a mechanism that did not proceed via a nitroso intermediate. Reduction of the alkyl halide by zinc produces an organozinc species. In contrast to the reactivity observed with organomagnesium reagents, the organozinc reagent does not react with the nitro-group. Instead, it reacts with B_2pin_2 to produce anion **36**. This anion reacts with one of the oxygen atoms of the nitro group to produce the borylated dihydroxylamine **37** and boronic acid ester R^2Bpin, which undergoes transmetalation to afford organozinc reagent ZnR^2X.[30] Dihydroxylamine **37** reacts with another equivalent of B_2pin_2 to produce nitrenoid **38**. This nitrenoid reacts with ZnR^2X to produce anion **39**, which triggers a 1,2-migration to afford aminoborane **34**.[31] Hydrolysis then furnishes the secondary amine product. Analysis of the reaction using time-resolved ^{11}B-{^1H} NMR spectroscopy revealed the formation of boron anions **36** and **39** to provide evidence for the proposed mechanism.

In 1897, Reissert reported that 2-substituted indoles could be obtained from nitroarenes **40** through a zinc-mediated reduction (Scheme 6).[32] The role of zinc in this venerable reaction is to reduce the nitro-group to the aniline presumably via a nitro reactive intermediate, and it can be substituted with other reductants such as iron or H_2.[33,34] The use of hydrogen enables the reaction to be run using a continuous-flow reactor.[35]

Recently, the use of zinc as a terminal reductant was cleverly employed by Hu and co-workers to achieve the Ni-catalyzed amidation of esters (Scheme 7).[36] Following up their Fe-catalyzed cross-coupling of nitroarenes with aryl halides using zinc as the stoichiometric reductant and trimethylsilyl chloride as the oxygen-atom acceptor,[37] the authors leveraged initial reports by the Shi-[38] and Garg and Houk[39] groups who showed that nickel complexes could catalyze the oxidative addition of aryl- or acyl C–O bonds to show that amides **44** could be formed from unactivated esters using nitroarenes as the *N*-aryl nitrogen source. The authors anticipated that inclusion of zinc and trimethylsilyl chloride would achieve reduction of nitroarene to form a reactive *N*-aryl nitrogen species which could react with an in situ generated nickel acyl complex. In addition to mediating the reduction of the nitroarene, zinc would also serve to reduce the nickel(II) pre-catalyst to nickel(0). In line with the author's hypothesis, this combination effectively catalyzed amide formation when phenanthroline was used as the ligand. While $NiCl_2$ or $Ni(cod)_2$ could be used without much attenuation of the yield of amidation, Hu and co-workers found that the optimal catalyst to be $Ni(glyme)Cl_2$. The authors reported that the identity of the reductant was not critical, and that manganese could be used in place of zinc without significant deterioration of the yield. While changing the silane to trimethylsilyl bromide reduced the yield slightly, no amide was produced when the silane was omitted from the reaction mixture. The author's amidation method was broad tolerating a range of acyl esters and nitroarenes. Remarkably, electron-poor- or electron-rich nitroheteroarenes could be employed, although

5-nitroquinoline required the catalyst loading to be increased to 10 mol % to afford **44c**. Saturated- and unsaturated acyl esters were competent substrates, and no isomerization of the olefin in **44e** was reported by the authors. The functional group tolerance of the reaction was ably demonstrated by showing that primary alkyl chlorides and cyclopropenyl groups were tolerated by the reaction conditions to access **44f** and **44g**. The authors also reported that aryl- or heteroaryl esters could be used as substrates irrespective of their electronic nature to give **44h** – **44j**.

On the basis of several experiments, the authors proposed two possible catalytic cycles to account for amide formation. They reported that the steric properties of esters impacted their reactivity with primary alkyl esters reacting faster than aryl esters reacting faster that secondary alkyl esters. Remarkably, they reported that amide **44** was observed using a wide range of *N*-aryl nitrogen precursors including nitrosoarene, *N*-hydroxyaniline, aniline, and even azoxybenzene or azobenzene, although reduced yields were obtained using aniline or *N*-hydroxyaniline. The authors interpreted these results to suggest that ester activation could happen first to form nickel acyl complex **45**, which reacts with azobenzene to form nickel(II) hydrazide **46**. Two molecules of **46** were proposed to react with one another to form azobenzene and nickel amide **47**,[40] which is reduced by zinc to afford zinc amide **48** and produce the nickel(0) catalyst. Alternatively, nickel(0) could react with azobenzene to produce nickel *N*-aryl nitrene **49**,[40c] which reacts with the ester to produce nickel(II) amidate. The amidate is reduced by zinc to form the nickel(0) catalyst.

Recently, Hu and co-workers demonstrated that their Ni-catalyzed amidation of esters technology could be harnessed to achieve a significant advance in nickel-catalyzed transamidation using zinc or manganese as the terminal reductant (Scheme 8).[41] Secondary transamidation has remained a gap in the synthetic repertoire because the thermodynamics of the process afford an equilibrium mixture of starting materials and products. The authors chose to investigate Boc-activated amides, which were first reported by Garg and co-workers as a work around to overcome the inert nature of amides in transamidation processes.[42] Hu and co-workers reported that the combination of 10 mol % of Ni(glyme)Cl_2 and a phenanthroline using 5 equiv of Zn(0) and 1.5 equiv of Me_3SiCl was all that was needed to transform Boc-activated alkyl amides into secondary amides **50**. Despite the inertness of amides, their method was broad with respect to both the Boc-amide and the nitroarene. As long as the starting amide was activated with a Boc-group, R^1 could be a benzyl-, phenethyl-, -CH_2CH_2OMe, trifluoroethyl-, or even contain a cyclopropyl fragment to enable the synthesis of amides **50a** – **50d**. The scope with regards to the nitroarene was also general. Transamidation was readily accomplished with irrespective of the electronic environment of the nitroarene. Nitroheteroarenes were also competent facilitating access to amides **50f** or **50g** with *N*-quinoline or *N*-benzoxazole substituents. The authors showcased the functional group tolerance of their reaction by showing that alkyl amides containing a terminal olefin or primary alkyl chlorides could be transformed into secondary amides **50h** or **50i**, although the latter required the catalyst loading to be increased to 15 mol %.

Switching from alkyl amides to aryl Boc-activated tertiary amides required optimization of the reaction conditions. While the identity of the nickel pre-catalyst remained consistent, employing di-*tert*-butyl-substituted bipyridine as the ligand and using manganese as the

reductant improved the reaction outcome. The authors also found that using Me_3SiI also led to a slightly increased yield. With this combination, the transamidation reaction exhibited a similarly broad scope as their previous reports: the identity of the *N*-alkyl R^1-substituent on the amide substrate could be varied, and a range of nitroarenes were shown to participate in the reaction to give **51a** – **51h**. The authors did report, however, that nitroarenes with a strong electron withdrawing group (e.g. SO_2Me) or increased steric environment around the nitro-group required slightly harsher conditions to access amides **51g** or **51h**.

The authors reported the results of several experiments, which they interpreted to indicate that the reaction proceeded via a nickel nitrene catalytic intermediate (Scheme 8). In contrast to their prior study,[36] they found that transamidation of alkyl Boc-activated amides could only be triggered using nitroarenes or azobenzenes and zinc. Transamidation of aryl Boc-activated amides could be accomplished using nitrosoarenes and manganese, albeit in significantly reduced yield. These results suggested to the authors that nitroarenes were reduced and deoxygenated using the combination of zinc or manganese and the chlorosilane to afford azoarenes. Reaction with nickel(0) produces nickel nitrene **52**, which reacts with the Boc-activated amide substrate to produce anion **53**. The resulting nickel(II) catalytic intermediate is reduced by zinc or manganese to re-generate the active nickel(0) catalyst.

These transamidation reports were followed up by Hu and co-workers with a surprising manganese-mediated reductive amidation of non-activated tertiary amides using nitroarenes as the nitrogen source (Scheme 9).[43] Because neither anilines nor *N*-hydroxyanilines were identified as potential reactive intermediates in their transamidation method of Boc-activated amides,[41] the authors anticipated that using nitroarenes would avoid forming an equilibrium mixture—a limitation of existing methods[44]—and that a method could be developed using non-activated substrates that could overcome this weakness. While the authors found that the combination of (glyme)$NiCl_2$ (10 mol %), terpy (10 mol %), manganese, and iodotrimethylsilane effectively triggered transamidation of non-activated tertiary amides, control experiments established that nickel was not necessary. Optimization revealed that equally high yields could be obtained simply using 10 mol % of phenanthroline, 5 equiv of manganese, and 1 equiv of Me_3SiI. Manganese was found to be unique, no transamidation was observed when zinc was used in its place. The authors' reaction was general. Nitroarenes bearing electron-donating or electron-withdrawing substituents could be employed to access secondary amides such as **55a** – **55d**. The conditions were not restricted to aryl tertiary amide starting materials. The authors demonstrated that alkyl- or cycloalkyl amides could be efficiently converted to **55e** or **55f**. Heteroaryl tertiary amides, irrespective of their electronic nature, were also competent substrates enabling access to furyl **55g** or pyridyl **55h**. Their transamidation also exhibited a broad tolerance to the identity of the *N*-substituents on the tertiary amide starting material. Replacing one of the *N*-phenyl substituents with an alkyl group did not change the reaction outcome enabling access to amides **55i** – **55l**. The authors also reported that tertiary amides derived from *N*-heterocycles such as **54m** or **54n** could be efficiently converted to alkyl amide **55m** or aryl amide **55n**. The identity of the *N*-aryl nitrogen reactive intermediate was interrogated by the author, and they reported that while neither aniline nor *N*-hydroxyaniline could

be converted to amide, both azobenzene and nitrosobenzene could be used as substrates although the latter required 4 equiv of manganese.

Iodine-catalyzed redox cyclization of nitroarenes

A two electron reductive redox cyclization was recently reported by Nguyen, Ermolenko and Al-Mourabit to convert 2-aminosubstituted nitroarenes **56** into 1,2-disubstituted benzimidazoles **58** (Scheme 10).[45] Their method is cunning because both oxidation of the aminomethylene and reduction of the nitro-group occur in one reaction, which the authors achieved using a substoichiometric amount of redox active molecular iodine or hydroiodic acid and formic acid. When a non-redox active acid was used as the catalyst only trace amount of the benzimidazole was observed. The scope of their method is broad tolerating electron donating- or electron withdrawing substituents on the nitroarene moiety. Impressively, substrates containing nitro-, cyano-, or ester groups were converted into 1,2-fused benzimidazoles **58d** – **58f** with the reducible functional groups intact.

The authors proposed that the mechanism for their reductive redox cyclization involved an internal reduction of the nitro-group (Scheme 10). Protonation of the nitro-group in **56** with in situ generated HI produces **59**, which triggers a [1,5] hydride shift to afford **60**. Deprotonation of the resulting amine generates **61**, where the nitro-group and the aminomethylene have been successfully reduced and oxidized. Intramolecular attack of the amine onto the iminium ion forms *N*-heterocycle **62**. Dehydration creates benzimidazole *N*-oxide **57**, which is reduced by formic acid to produce the product and CO_2. Alternatively, reduction could be mediated by iodide anion to afford **58** and IO^-.

Titanium(III)-mediated reductive reactions

Titanium trichloride-mediated reductive cyclization of nitroarylketones is well established to construct *N*-heterocycles by reducing the nitro-group to an amine (Scheme 11). In 1999, Rawal and co-workers reported a general method that converted aryl ketones (e.g. **64**) into 2,3-disubstituted indoles **66**.[46] The power of their method was showcased by Rawal and co-workers in the synthesis of *Aspidosperma* alkaloids. Indole **69**, a key synthetic intermediate, was synthesized from enol silane **67** in two steps where the nitrophenyl group was introduced through an α-arylation using *ortho*-nitrophenylphenyliodonium fluoride followed by a $TiCl_3$-mediated reductive cyclization.[47] Zhu and co-workers showed that even vinyl triflates survived the mild $TiCl_3$-mediated reductive cyclization of aryl ketone **70** to provide 2,3,3-trisubstituted indolenine **71** in their total synthesis of (±)-aspidophylline A.[48]

A significant advance using Ti(III)-mediated reductive cyclization of 2-substituted nitroarenes was reported by Zhu and co-workers (Scheme 12).[49] In 2015, the authors reported that the nitrosoarene intermediate generated by treating nitrostyrene **72** with an aqueous solution of titanium trichloride could be intercepted by the *ortho*-alkenyl substituent to construct indole **74** before reduction of nitrosoarene **73** to the amine. The authors showcased the mildness of their reductive amination reaction by showing that substrates bearing reducible (e.g. CO_2Me, Cl, or Br) or polar functional groups (e.g. NMe_2, CN, or OH) could be efficiently transformed into indoles **74a** – **74g**. Zhu and co-workers showed

that their method was relatively insensitive to the steric environment of the *ortho*-alkenyl substituent to access pinene-derived **74h**. Following the seminal report of Sundberg and co-workers,[7e,f] the authors reported that exposure of β,β-disubstituted nitrostyrenes to reaction conditions triggered a tandem cyclization-migration reaction to selectively produce 2,3-disubstituted indoles **74j** – **74m**. The yield of this reaction was reported by the authors to be sensitive to the electronic nature of the migrating aryl group with higher yields obtained with electron-rich β-substituents.

The authors proposed that indole formation occurred via a nitrosostyrene reactive intermediate (Scheme 12). This species is formed from a $TiCl_3$-mediated deoxygenation of nitrostyrene **72**. A 6π-electron-electrocyclization then occurs to form **75**.[15b,c] When R^{β} is hydrogen, deprotonation occurs to afford *N*-hydroxyindole **76**, which is reduced by $TiCl_3$. Alternatively, when R^{α} is hydrogen, a [1,2] R^{β}-aryl migration is triggered to give **77**. Deprotonation produces *N*-hydroxyindole **78**, which is reduced by $TiCl_3$.

Zhu and co-workers showcased the power of their reductive method of nitrostyrenes in the asymmetric total synthesis of (+)-1,2-dehydroaspidospermidine and (+)-condyfoline (Scheme 13).[50] The biomimetic synthesis of aspidospermidine alkaloids was shown by Harley-Mason and Kaplan to occur through an acid-mediated retro-Mannich, Mannich tandem reaction sequence.[51] Zhu and co-workers wrote that they were curious if a related reactivity pattern could be harnessed using $TiCl_3$ from nitrostylenes because Driver and co-workers had shown that reductive cyclization-1,2-shift could be triggered from trisubstituted nitrostilbenes using the combination of a palladium catalyst and $Mo(CO)_6$.[52] Exposure of nitroarene to dehydration followed by $TiCl_3$-mediated reduction afforded (+)-1,2-dehydroaspidospermidine in 78% yield. This reductive cyclization occurs through a $TiCl_3$-mediated single electron reduction of the nitro-group to furnish nitrosoarene **81**, which engages the *ortho*-alkenyl substituent in an electrocyclization to produce cation **82**.[15b,c] Formation of this cationic intermediate triggers a selective [1,2] alkyl shift of the aminomethine to result in ring-contraction to produce **83**, which is reduced to the monoterpene alkaloid. Similarly, (+)-condyfoline was constructed by the authors by subjecting nitrostylene **84** to aqueous $TiCl_3$: reduction of the nitro-group produced nitrosoarene **85**, which underwent a cyclization-[1,2] migration tandem reaction to produce the monoterpene. As before, the [1,2] shift was selective and only migration of the aminomethine was observed. The authors showed that (+)-condyfoline rearranged to (−)-tubifoline in 93% through an apparent retro-Mannich/Mannich sequence by simply sitting at −18 °C to underscore the difference in reactivity patterns between the nitrosoarene intermediate and the 3*H*-indole.

Sulfur-mediated reductive reactions of nitroarenes

Organic reductants that trigger radical redox processes of nitroarenes are also emerging as efficient methods to construct *N*-heterocycles from nitroarenes. In 2013, Nguyen and co-workers reported that 2-heteroarylbenzothiazoles could be synthesized from 2-chloronitroarenes and methyl-substituted *N*-heterocycles using elemental sulfur (Scheme 14).[53] Their method is experimentally simple, requires no solvent for product formation, and creates three new bonds in one step. The optimal conditions were found by the authors

to use a slight excess of elemental sulfur and a larger excess of the methyl-substituted *N*-heteroarene. Critical to the success of the author's transformation was the use of elemental sulfur activated by the methyl-substituted heterocycle. Complex mixtures were observed when S_8 was replaced with sodium- or ammonium sulfide salts. Positioning of the methyl-substituent on the pyridine was also found to be important. While high yields of **89a** or **89b** were obtained from 4- or 2-methyl-substituted pyridine, no product was obtained if 3-methyl-substituted pyridine was employed. This difference in reactivity was exploited by the authors to access **89c** as a single regioisomer from 3,4-dimethylpyridine. The author's transformation was insensitive to increasing the steric environment around the reaction center: 2,3-dichloronitrobenzene was converted to **89d** in high yield. The authors also reported that the nitroarene could be substituted at the 5-position with an electron-releasing- or electron-withdrawing substituent without inhibiting the reaction. Strikingly, dinitro-substituted substrates could be used, and only the nitro-group adjacent to the chloro-substituent reacted to afford **89g**, albeit in an attenuated yield relative to the other examples. In addition to substituted pyridines, the authors reported that electron-rich methyl-substituted *N*-heterocycles could be used to access 2-benzimidazole- or 2-imidazole-substituted benzothioxazoles **89h** and **89i**. The author's reaction also tolerated 2-methylpyrazine or nitro-substituted pyridine as substrates to furnish **89j** or **89k**.

Based on control experiments, the authors proposed that benzothiazole formation occurred via radical intermediates through a cyclization-reduction mechanism (Scheme 14). Acid-mediated isomerization of 4-picoline to enamine **90** triggers nucleophilic attack of sulfur to produce **91**. Homolysis of the C–S bond produces radical **92**, which could add to the nitrogen-atom of the nitro-group to produce **93**. Dehydration and sulfur-mediated reduction forms **94**, which produces **89a** through a cascade cyclization-reduction reaction.[54] Alternatively, reduction could occur first to produce thioamide **95**.[55] The authors reported, however, that thioamide does not cyclize to produce the *N*-heterocycle.

In 2020, Nguyen and co-workers advanced sulfur-mediated reductive formation of benzothiazoles by showing that they could be accessed from aryl acetic acids and nitroarenes through an aryl C–H bond amination reaction (Scheme 15).[56] As with the 2013 study, the authors reported the presence of an amine base, in this case DABCO, was required to achieve product formation. Using this combination, a range of 5-aminobenzothiazoles could be formed from 3-aminonitroarenes and aryl- or heteroaryl acetic acids. The use of aryl acetic acids as the benzyl radical source enabled a greater range of benzothiazoles to beconstructed with 2-aryl or 2-heteroaryl substituents irrespective of their electronic- or steric environment. For example, benzothiazoles **97a** – **97c** were successfully constructed with methyl-, fluoro-, or methoxy substituents. Increasing the steric environment also did not have a detrimental effect on the reaction accessing **97d** in good yield. Electron rich- or electron deficient heteroaryl acetic acids were also competent substrates to facilitate synthesis of **97e** – **97i**.

A slightly different mechanism was suggested than Nguyen and co-worker's 2013 report (Scheme 15). The authors proposed that benzyl radical **98** is formed from a sulfur-DABCO-mediated decarboxylation.[57] After addition to the nitro group, deoxygenation occurs to form imine **99**, which is attacked by an S_3-radical anion to form **100**. Intramolecular cyclization

produces radical **101**, which is oxidized to form **102**. Deprotonation re-establishes aromaticity and a subsequent oxidation produces the benzothiazole product.

Alkoxide-mediated reductive reactions of nitroarenes

Alkoxides were reported as nitroarene reductants in the 19th century by the Zinin- and Klinger laboratories (Scheme 16).[58] These two groups reported that exposure of nitrobenzene to sodium methoxide in boiling methanol produced azoxybenzene. In 1902, Lachman followed up on these seminal reports to reveal that azoxybenzene was produced from nitrobenzene irrespective of whether the sodium alkoxide was prepared from methanol using sodium(0) or sodium hydroxide,[59] and in 1927, Fry and Cameron rigorously quantified the stoichiometry of the reaction and reported the deleterious effect of water on the amount of reduction, which they interpreted to indicate that H_2 was produced and served as the reductant.[60] This mechanistic assertion was contradicted by a kinetic analysis of the reaction by Ogata and Mibae in 1962.[61] Their investigation revealed that the rate of azoxybenzene formation was $k[PhNO_2][MeONa]^2$. The authors proposed that the second-order dependence on the rate with methoxide could be accounted in the deoxygenation of the nitro-group via six-membered transition state **104**. Further clarity on the mechanism of the reduction emerged when the reaction of *tert*-butoxide with *p*-nitrotoluene was examined using EPR spectroscopy by Russell and Janzen.[62] Exposure of *p*-nitrotoluene to potassium *tert*-butoxide in *tert*-butanol produced a blood-red solution, which exhibited an ESR signal that the authors attributed to the formation of radical anion **105**. This radical anion dimerized to afford *p,p*'-dinitrobibenzyl upon acidification of the solution with excess water. Russell and co-workers reported that a radical anion was also observed using EPR spectroscopy from the reaction of nitrosobenzene and *tert*-butoxide.[63] The nitrosobenzene radical anion's signal decayed rapidly and azoxybenzene was obtained. Together these reports suggested the potential for radical anions to trigger reaction at either the benzyl position or at the nitrogen-atom.

Interest in using *tert*-butoxide as a single electron reductant has resurfaced to trigger transition metal-free cross-coupling reactions (Scheme 17).[64] In 2010, the Shi-, Hayashi-, and Lei laboratories independently reported that *tert*-butoxide mediated the cross-coupling of aryl halides with arenes. Shi and co-workers reported that iodoarenes were readily converted to biaryls such as **108** using the combination of 20 mol % of phenanthroline and 2 equiv of potassium *tert*-butoxide and a large excess of the arene if the reaction mixture was heated to 100 °C.[64a] Aryl bromides could also be employed as the cross-coupling partner, but a higher catalyst loading (40 mol %) and a larger excess of KO*t*-Bu (3 equiv) was required. Hayashi and co-workers reported that either potassium- or sodium *tert*-butoxide (2 equiv) could mediate the cross-coupling of aryl chlorides, aryl bromides, or aryl iodides with an excess of the arene (120 equiv) using 10 mol % of 4,7-diphenylphenanthroline (Ph-phen) at 155 °C to afford 1,1'-biphenyls such as **111**.[64b] The scope of the reaction was explored using NaO*t*-Bu because it afforded a slightly higher yield of the biaryl product. Lei and co-workers reported that DMEDA could be used as the catalyst in place of Ph-phen at only 80 °C using KO*t*-Bu as the alkoxide to afford **111**.[64c] While their conditions are milder, the cross-coupling partner is restricted to aryl iodides. The yield of the transformation was significantly attenuated using aryl bromides. Both Hayashi- and

Lei groups proposed that the cross-coupling reaction occurred through the single electron reduction of the aryl halide to form radical anion intermediate **109**. Hayashi and co-workers proposed that fragmentation of **109** occurred to form aryl radical **110**, which added to the excess arene through a homolytic aromatic substitution reaction.[65] Tuttle, Murphy and co-workers focused on elucidating the role of the phenanthroline catalyst using a combination of computational and experimental techniques.[64f] Their study was motivated by the large and unfavorable ΔG (60 kcal•mol^{-1}) values that they calculated for the direct transfer of an electron from a phenanthroline complex of sodium- or potassium *tert*-butoxide to an aryl iodide. These calculations in combination with Murphy and co-workers' prior work triggering radical formation using super-electron *N*-heterocyclic donors,[66] inspired them to investigate the fate of phenanthroline catalyst. They found that the cross-coupling of 2,6-dimethyl-iodobenzene and benzene could be accomplished in the absence of KO*t*-Bu if the organic electron donor **112** was used. To determine if a related super-organic-electron donor was formed, phenanthroline was exposed to KO*t*-Bu in PhH in an inert atmosphere glove box, and pyrophoric **114** was isolated; oxidation with molecular iodine formed the phenanthroline dimer, which was characterized. Murphy and co-workers' results suggest that *tert*-butoxide initially reacts with the phenanthroline sodium- or phenanthroline potassium *tert*-butoxide complex to form a super electron donor, which can reduce the aryl halide cross-coupling partner much more efficiently than *tert*-butoxide or the phenanthroline *tert*-butoxide complex.

Despite their well-established ability to participate in single electron transfer reactions, the use of nitroarenes in alkoxide-mediated reactions to form *N*-heterocycles has lagged in comparison to the development of cross-coupling reactions. In 2017, Liu, Xu and co-workers reported that pyrrolo[2,3-*b*]-quinolones could be formed from nitrochalcones through *t*-PeONa triggered [3+2] cycloaddition/reductive cyclization tandem reaction sequence (Scheme 18).[67] The authors reported that the optimal conditions for pyrrolo[2,3-*b*]-quinolones was the combination of 2 equiv of isocyanide and 1 equiv of alkoxide. While sodium hydroxide or potassium *tert*-butoxide afforded product, the highest yields were observed using *t*-amylalkoxide (*t*-PeONa) as the base. The scope of the tandem reaction was broad. A range of R^2-aryl or heteroaryl groups on the chalcone were efficiently converted to **119**, and the tandem reaction worked well irrespective of the electronic environment of the nitrochalcone to afford **119f** or **119g**. The authors' reaction was more sensitive to the identity of the isocyanide: while esters, amides, or aryl groups were tolerated as R^3-substituents to afford **119i** – **119j**, tosyl groups were not.

Based on their calculations, the authors proposed that the mechanism for pyrrolo[2,3-*b*]-quinolone formation occurred through a tandem [3+2] cycloaddition followed by reductive cyclization reaction (Scheme 18). Cycloaddition of the isocyanide with the nitrochalcone affords dihydropyrrole **118a**. Deprotonation of **118a** followed by intramolecular cyclization produces spirocycle **120**, which undergoes a Cope-type elimination to afford anion **121**.[68] Elimination of hydroxide forms nitrosoarene **122**, which triggers a cyclization to produce **123**. Hydride shift could produce *N*-hydroxy **124**, but the authors could not locate a transition state in their calculations to account for cleavage of the N–O bond. Instead, they propose that reduction occurs through alkoxide attack to produce **125**. Elimination

of peroxide produces **126**, which tautomerizes to afford pyrrolo[2,3-*b*]-quinolone. Despite the precedence of electron-transfer from alkoxide to the electron-deficient nitrochalcone, a mechanism involving radical anion intermediates was not proposed.

In 2021, Driver, Zadrozny, and co-workers discovered that exposure of 2-nitrostilbenes to *tert*-butoxide produced either *N*-hydroxyindoles or 2-oxindoles depending on the identity of the counterion (Scheme 19).[69] During their study of transition metal-catalyzed reductive cyclizations of nitroarenes,[20a,52,70] the authors discovered a transition metal-free, counter-ion-controlled reaction to afford *N*-hydroxyindole **128** or oxindole **129** depending on whether sodium- or potassium *tert*-butoxide was used. While the highest yields were obtained using *tert*-butoxide, *N*-heterocycle formation was observed using methoxide or ethoxide. In contrast to *tert*-butoxide-mediated cross-coupling reactions, neither elevated reaction temperatures nor an additive (such as phenanthroline or DMEDA) was required. The identity of the counterion was critical for heterocycle formation: neither **128** nor **129** were observed if LiO*t*-Bu or $Mg(O\textit{t}\text{-Bu})_2$ was used. The authors reported that the yield of *N*-hydroxyindole formation was dependent on the electronic-identity of the 2-nitrostilbene with higher yields observed for substrates bearing electron-releasing substituents to give **128a** – **128c**. This trend extended as well to the β-aryl substituent: successful *N*-hydroxyindole formation was obtained only with electron-releasing-, electron-neutral-, or fluorine-substituted β-arenes. In contrast, KO*t*-Bu-mediated oxindole formation exhibited a broader scope: substrates bearing stronger electron-withdrawing groups could be successfully transformed into oxindoles (e.g. **129f** and **129h**). Adding an additional β-aryl substituent changed the reaction outcome: exposure of **127i** to NaO*t*-Bu afforded *N*-hydroxyoxindole **130i**. No *N*-heterocycle formation was observed, however, for substrates with non-aryl β-substituents irrespective of whether NaO*t*-Bu or KO*t*-Bu were used.

To investigate the mechanism of the counterion-controlled *N*-heterocycle formation, the authors reported the results of several experiments (Scheme 19). The deep red colored solution thst resulted from mixing the *tert*-butoxide with 2-nitrostilbene indicated the potential of radical anion formation. Analysis of the reaction using EPR spectroscopy confirmed this suspicion and revealed that the identity of the radical intermediate depended on the counterion. The EPR spectrum obtained using NaO*t*-Bu was consistent with **131** where the spin density was localized only on the nitro-group. In contrast, a complex spectrum was obtained using KO*t*-Bu; simulation of this spectrum produced the best match using a 93:7 composite of **132** and **133**—where the potassium ion is not bound to the nitro-moiety in either. Counterion coordination appears to control the reaction outcome: the addition of 15-crown-5 to the reaction of 2-nitrostilbene and NaO*t*-Bu afforded only oxindole **129a** as the only product. To gain insight into the mechanism of oxygen-atom transfer, the authors examined the reaction outcome when ^{18}O-labeled reagents were used. While no incorporation of the ^{18}O-label into oxindole was observed using K^{18}O*t*-Bu, crossover of the label was observed when a mixture of **127a** and **127j**-^{18}O was exposed to reaction conditions. Analysis of the mass spectrum fragmentation pattern indicated that intermolecular oxygen-atom transfer occurred only to the C2-position of the oxindole.

The authors proposed mechanisms to account for *N*-heterocycle formation that was dependent on the coordination of the counterion to the nitro-group (Scheme 20).[69] For

N-hydroxyindole formation, the authors proposed that electron-transfer occurred from sodium *tert*-butoxide to afford radical anion **131** where sodium is coordinated to both oxygen-atoms. While the authors proposed that coordination of the sodium atom occurred after electron-transfer, it is possible that coordination precedes transfer. The author's observation of acetone in the reaction mixture indicated that the resulting *tert*-butoxy radical underwent β-scission to produce methyl radical. The radical anion **131** was proposed to accept another electron from *tert*-butoxide to produce anion **134**, which eliminates sodium oxide to form nitrosostilbene **135**. Electrocyclization forms **136**, which rearranges to form *N*-hydroxyindole. For the mechanism for oxindole formation, the authors proposed that electron transfer from *tert*-butoxide to nitrostilbene produced radical anion **132**. To account for the crossover experiment result, they proposed that intermolecular radical addition occurred next to produce **137**, which underwent a 3-*exo*-*tet* cyclization to form epoxide **138**. While these cyclizations are rare,[71] this epoxide appears to be a reactive intermediate (or can be converted to a reactive intermediate) because authors reported that exposure of epoxide **138** to reaction conditions resulted in oxindole formation. The authors did not speculate in detail on how the nitrosoarene radical anion by-product was converted into oxindole, and the remaining steps in the mechanism are more speculative. Ring-opening could occur to afford **139**,[72,73] which could be reduced to produce **140**. Fragmentation produces nitrosoarene **141**.[74] H-atom abstraction followed by enolization produces **143**,[75] which can attack the nitroso-group to form *N*-heterocycle **144**. A [1,2] phenyl shift affords *N*-hydroxyoxindole **145**,[76] which is reduced to oxindole **129a**.

4,4'-Bipyridine-mediated reductive reactions of nitroarenes

In 2018, Tsurugi, Mashima and co-workers reported that reductive amination reactions of 2-substituted nitroarenes to afford carbazoles or indoles could be mediated by an organosilicon reductant (Scheme 21).[77] This report built on earlier reports by this group that used *N,N'*-bis(trimethylsilyl)-4,4'-bipyridinylidene (*Si*-DHBP) **147** and related organosilicon reagents to reduce titanocene dichloride, aryl bromides, dihalo compounds, and α-halo carbonyls.[78] The authors reported that exposure of 2-nitrobiaryls or 2-nitrostyrenes to 2.5 equivalents of *Si*-DHBP **147** at room temperature produced *N,O*-bis(trimethylsilyl)hydroxylamine **148**, which upon thermolysis produced the *N*-heterocycle after acidic work-up of the reaction mixture. If a trapping reagent of **148** was present (e.g. dibenzothiophene), reduction of the nitro-group to the amine was competitive with cyclization to the *N*-heterocycle. The scope of the authors transformation was broad tolerating reducible functional groups (e.g. methyl carboxylate, chloride, or thiophene) on the substrate without reduction of the yield of **149a** – **149e**. 3-Nitropyridines were also effective substrates to enable access to **149f** in good yield. While 2-phenylindole could be accessed using the author's technology, the yield of the transformation was attenuated in comparison to carbazole formation.

In 2019, the authors significantly expanded the use of organic reductants by showing that the combination of a diboron reagent (B_2nep_2) and 2 mol % of 4,4'-bipyridine enabled the reduction of nitroarenes to anilines (Scheme 22).[79] While no catalysis was reported for *N*-heterocycle formation, the authors reported that exposure of 2-nitrobiphenyl to 2.2 equivalents of in situ generated *N*-(2-biphenyl)-N,O-bis{(neopentylglycolato)-boryl}−2-

hydroxylamine **153** afforded carbazole in 60% with only 12% of 2-aminobiphenyl. DFT calculations by Qi and Jiao suggested that radical **154** was a key reactive intermediate in the formation of *N,N'*-diboryl-4,4'-bipyridinylidene and reduction of the nitroarene.[80]

Visible light-driven reductive amination reactions

Recently, the development reductive amination processes of nitroarenes that avoid the use of precious-metal catalysts or high pressures of carbon monoxide has been pursued to achieve new environmentally benign processes. Lin and Yang reported the visible light photoredox catalysis of indazolo[2,3-*a*]quinolines from 2-nitrophenyl-tetrahydroquinolines (Scheme 23).[81] The authors reported that exposure of **155a** to 1 mol % of $Ru(bpy)_3Cl_2$ and visible light produced indazole **156a** in 95%. The identity of the photoredox catalyst could be changed to photosensitizer Eosin Y, and indazole **156a** could be obtained with a slightly attenuated yield (80%). Using these conditions, the scope of the reaction was explored and was found to be relatively broad: indazole formation smoothly occurred if an electron-neutral- or electron deficient nitroarene was employed. The scope of the tetrahydroquinoline component was also reported and alkoxy- and fluoro-aryl substituents as well as ethereal, amide-, or carbazole substituents on the saturated portion of the ring were tolerated to give **156d** – **156g**.

The authors proposed that the formation of indazolo[2,3-*a*]quinoline occurred through visible light photoredox catalysis (Scheme 21). Oxidation of quinoline **155a** by photo-excited $[Ru(bpy)_3^{2+}]^*$ produces radical cation **157**, which is deprotonated intramolecularly to form **158**. Radical cyclization produces **159**, which oxidizes $Ru(bpy)_3^{+}$ to $Ru(bpy)_3^{2+}$ and forms indazolo[2,3-*a*]quinoline **156a** and hydrogen peroxide.

Zheng and co-workers recognized that visible-light-induced photochemistry on nitroarenes might be harnessed in the absence of a photoredox catalyst because the *ortho*-nitrobenzyl is widely used in photoimaging and biochemistry.[82] In 2019, they reported a visible-light-mediated thiourea-catalyzed intramolecular reductive cyclization of *ortho*-substituted nitroarenes to produce polycyclic quinazolinones (Scheme 24).[83] Their investigations showed that making changes to the structure of the thiourea catalyst impacted the yield of the transformation. No reaction was observed in the absence of light, and the yield was severely attenuated when silane was omitted or when air was used in place of the N_2 atmosphere. While the best result was obtained using phenylthiourea, 72% of quinazolinone **161a** resulted when 1-methyl-1-phenylthiourea was used to suggest that a two-point binding might not be required to activate the nitroarene towards reduction. Using their optimal conditions, the reaction scope was broad. While the reductive amination reaction was insensitive to the electronic identity of the nitroarene to give **161a** – **161d**, increasing the steric environment around the nitro-group diminished the yield of quinazolinone **161e**. The tetrahydroisoquinoline portion of the substrate could be decorated with halide-, carboxylate-, or hydroxyl substituents without dramatically affecting the reaction outcome to afford **161f** – **161h**. The authors demonstrated that quinazolinone **161a** could be scaled efficiently using a continuous-flow reactor, and that their technology could be used to access tetracyclic imidazoles such as **162a** – **162c**.

Based on control experiments and DFT calculations, the authors proposed that the mechanism occurred via a thiourea-coordinated biradical species (Scheme 24). Irradiation of nitrobenzamide **160a** produces triplet **163**, which triggers a 1,7 H-atom transfer reaction to form *aci*-nitro tautomer **164**. Coordination of this species with the thiourea catalyst forms **165**, which undergoes a single electron transfer reaction to generate biradical **166**. Radical recombination followed by deprotonation forms *N*-oxide **168**, which is reduced by phenyl silane to produce quinazolinone **161a**.

A light-promoted nickel-catalyzed C–N bond cross-coupling reaction between aryl halides and nitroarenes was recently reported by Xue and co-workers (Scheme 25).[84] Interestingly, their cross-coupling reaction requires no photosensitizer or stoichiometric reductant (e.g. $PhSiH_3$, Zn, or Mn) for a successful reaction outcome. The scope of their Ni-catalyzed reaction is broad. A range of electron-releasing- and electron-withdrawing substituents were permitted on the cross-coupling reaction between the nitroarene and methyl 4-bromoacetate to give **170aa** – **170ea**, although 4-chloronitrobenzene required 15 mol % of the Ni(II) catalyst for the highest yield of **170da**. The reaction outcome also did not depend on the steric environment around the nitro-group: 2-methylnitrobenzene was converted to diaryl amine **170fa** in 73%. The scope of the reaction was broader with respect to the aryl bromide component with a larger range of electron-withdrawing substituents compatible to afford **170ga** – **170ka**. Both the nitroarene- and the aryl bromide component could be substituted with heterocycles and still afford diaryl amines **170ma** – **170oa** in good yield. Aryl chlorides could also be used as the nitroarene cross-coupling partner. The yields, however, were attenuated in comparison to using aryl bromides, for example the yield of **170aa** was reduced from 75% to 46% when 4-chloroanisole was used. While the authors did not propose a potential catalytic cycle to account for product formation, they did report control experiments that suggested that the coupling proceeded via radical intermediates, and that a nitrosoarene reactive intermediate might be formed. Further, their study of the light dependence of oxidative addition suggested that it occurred to a photo-generated Ni(I) complex.[85] The authors did not speculate the fate of the two oxygen-atoms on the nitro group.

Electrochemical reductive reactions

Electrochemical reduction of 2-piperidine-nitroarenes **171** was reported by Begonov and co-workers to afford benzimidazoles **172** (Scheme 26).[86] While chemical reduction using tin- or titanium reductants are established, the authors wrote that they were motivated to replace them with electricity to simplify the isolation of the *N*-heterocyclic product and to reduce the waste generated in the process. The authors discovered that the desired transformation could be accomplished best using a lead cathode and a graphite plate anode. Critical to success of the reductive cyclization was inclusion of 8% HCl, which the authors attributed to protonating the nitro-group to ease the reduction. If the amount of HCl was increased, however, reduction to aniline **173** was observed as a by-product. Decreasing the amount of HCl resulted in poor solubility of the nitroarene. The initial scope of the transformation revealed that nearly quantitative amounts of the benzimidazole **172a** – **172f** could be obtained from electron-deficient nitroarenes and heteroarenes. Strikingly,

the authors method tolerated a second nitro-substituent to produce benzimidazole **172a** without additional reductive processes occurring. While several mechanisms are possible to account for benzimidazole formation, the authors interpreted their cyclic voltammetry experiments to suggest that cyclization occurred via nitrosoarene **174** because only the two-electron reduction product was observed; neither the four-electron *N*-hydroxy-amine nor the six-electron aniline products were observed.

In 2021, Lei and co-workers published an electrochemical reductive method to access diaryl amines from aryl boronic acids and nitroarenes (Scheme 27).[87] The authors discovered that the optimal conditions for the reductive cross-coupling reaction employed a platinum plate anode and a carbon cloth cathode in an undivided cell under 10 mA constant current using an 80:1:1 mixture of HFIP, acetonitrile, and formic acid. Using a different cathode (e.g. nickel plate) or a different anode (e.g. carbon cloth) led to diminished yield of diaryl amine **176a**. The pKa of the acid co-solvent also impacted the yield of diaryl amine: lower yields correlated with lower acid pkas. Inclusion of triethyl phosphite was also critical to the reaction outcome. Significantly lower yields were obtained when it was absent or substituted with triphenyl phosphine or triethyl phosphate. While the requirement of phosphite appears similar to the Cadogan reaction conditions,[7a,b] the authors reported that electricity was critical. No diaryl amine was observed when electricity was excluded from the reaction. The scope of the reaction was reported by the authors to tolerate a series of *para*-alkyl- or *para*-halide substituents on the nitroarene component. Increasing the steric environment around the nitro-group was found not to have a detrimental effect on the reaction providing diaryl amine **176b** in good yield. The authors also reported that their reductive electrochemical cross-coupling reaction also tolerated a range of different *para*-substituted aryl boronic acids. In contrast to the nitroarene component, the authors reported that aryl boronic acids bearing electron-donating methoxy substituents could be employed to access to diaryl amines such as **176f**. While the reactivity of *ortho*-tolyl boronic acid was not reported, the authors showed that dibenzo[*b*,*d*]furan-4-ylboronic acid could be used to construct diaryl amine **176j**, albeit in an attenuated yield. Using an electrochemical continuous flow cell, the authors demonstrated that their reaction could be scaled to 5 mmol.

On the basis of cyclic voltammetry experiments and the reactivity of potential reactive intermediates, the authors proposed potential mechanisms to account for diaryl amine formation (Scheme 27). The cyclic voltammetry experiments reported by the authors revealed that acetonitrile, formic acid, and triethyl phosphite facilitated the reduction of nitrobenzene, and that the inclusion of phosphite accelerated the initial reaction rate. The authors also examined the reactivity of other *N*-aryl nitrogen species. They reported that while diaryl amine formation was observed using nitrosobenzene or *N*-hydroxyaniline, no cross-coupling with phenyl boronic acid was obtained using aniline or azobenzene as the *N*-aryl nitrogen source. The authors interpreted this data to indicate that nitrosobenzene **177** is a reactive intermediate, which could be accessed directly from nitrobenzene through a two-electron reduction followed by an acid-mediated dehydration. Alternatively, it could be formed stepwise via **178**, which is formed through nucleophilic attack of the phosphite onto the oxygen-atom of the nitro-group followed by a two-electron reduction acid-mediated dehydration. Coordination of nitrosobenzene with the boronic acid produces

179; subsequent reduction and protonation furnishes *N*-hydroxy-**180**, which undergoes a [1,2] phenyl shift and acid mediated dehydration to produce **181**. In the presence of phosphite, the authors proposed that **181** could be produced via **182**, which is formed from nucleophilic addition of phosphite to the oxygen-atom of nitroso-group. Phenyl migration and elimination of ethanol and diethylphosphite forms **181** from **182**. Diaryl amine results from protonation of **181**. Because oxygen could be detected in the reaction mixture, the authors proposed that water was oxidized at the anode.

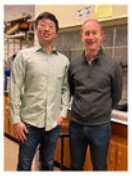
Conclusions

There has been significant progress using nitroarenes as the *N*-aryl nitrogen component in intramolecular and intermolecular reductive amination reactions. These methods have advanced the formation of C–NAr bonds to be more efficient and more environmentally benign by developing conditions to access reactive nitrogen species without requiring precious metal catalysts or carbon monoxide. By avoiding the formation of metal hydride the resulting technology largely evades the formation of aryl amine by-products and expands the functional group tolerance of the reaction. While these methods have resulted in significant advances, the current challenges will be to develop more atom-economic processes by replacing the stoichiometric reductant with sustainable sources and exploit the nitroarene as an oxygen atom source to develop methods that form not only C–NAr bonds but also C–O bonds. The future is bright.

Acknowledgment

We are grateful to National Institutes of Health (NIGMS) R01GM138388 for their generous financial support.

Biography



Haoran Zhu is a PhD candidate in the Driver laboratory at the University of Illinois at Chicago. He received his Bachelor’s degree in from the China Pharmaceutical University in 2018. His research work is focused on transition metal-catalyzed, radical- and electrochemical reactions of nitroarenes for the synthesis of *N*-heterocycles.

Tom G. Driver is a Professor of Chemistry. He obtained his B.S. in Chemistry from Indiana University, Bloomington in 1999, and his Ph.D. from the University of California, Irvine under the mentorship of K. A. Woerpel in 2004. After an NIH-funded postdoctoral position at Caltech under the supervision of John E. Bercaw and Jay A. Labinger, he began his independent academic career at the University of Illinois at Chicago in 2006. His group’s research program is centered on the development of new reactions that exploit electrophilic *N*-aryl nitrogen intermediates for the construction of C–N and C–C bonds and the use of these methods in medicinal chemistry applications.

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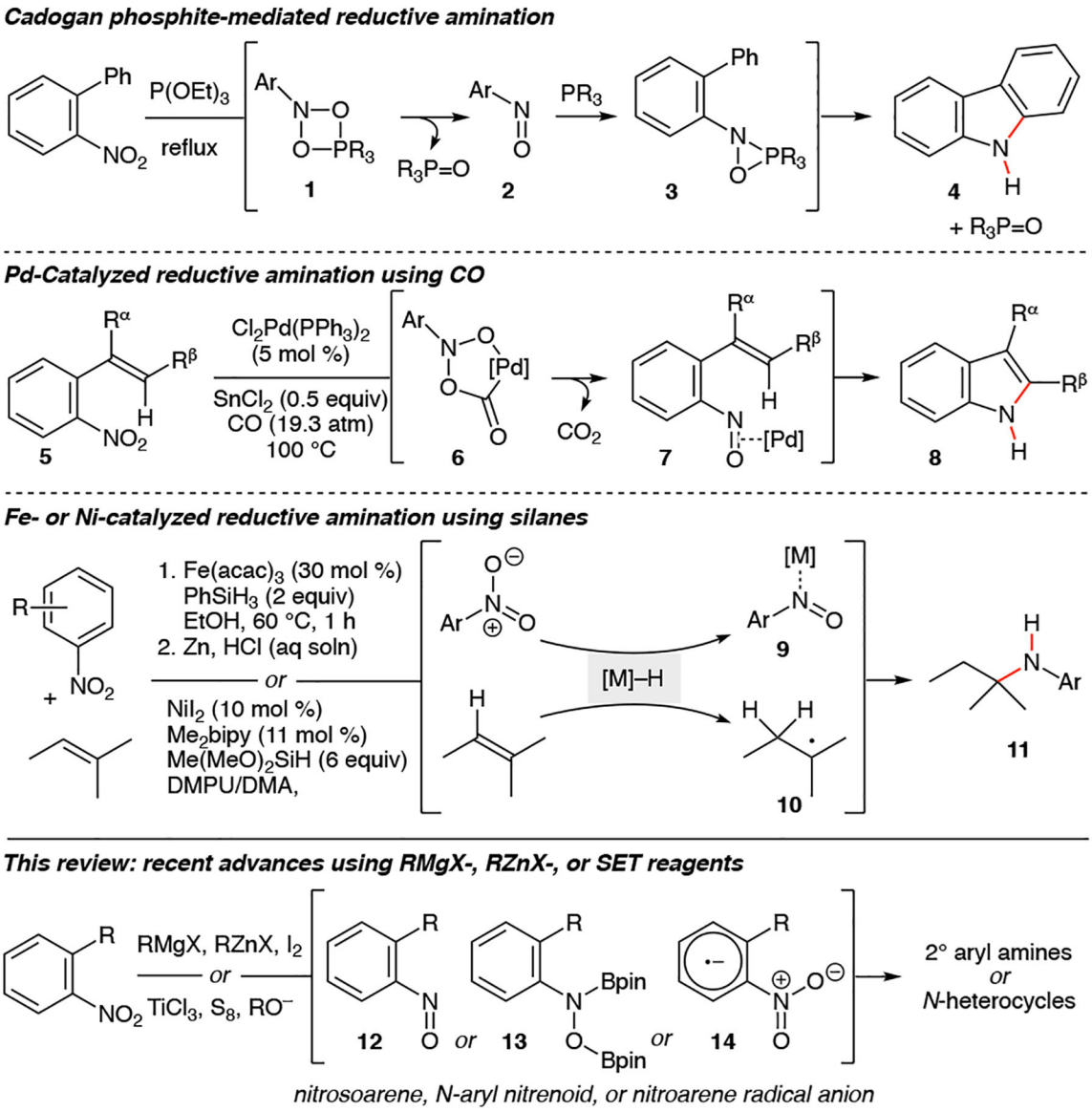
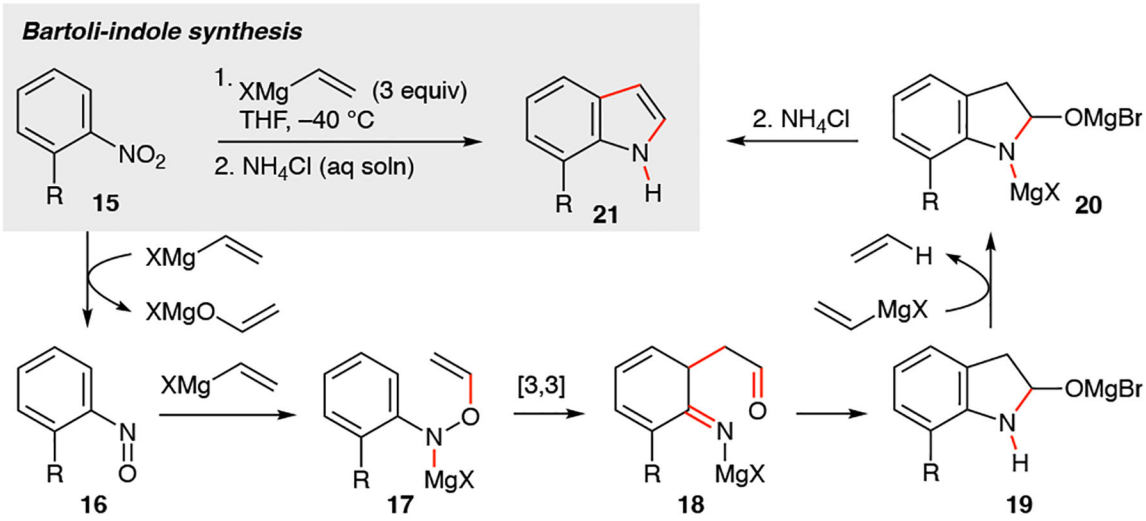
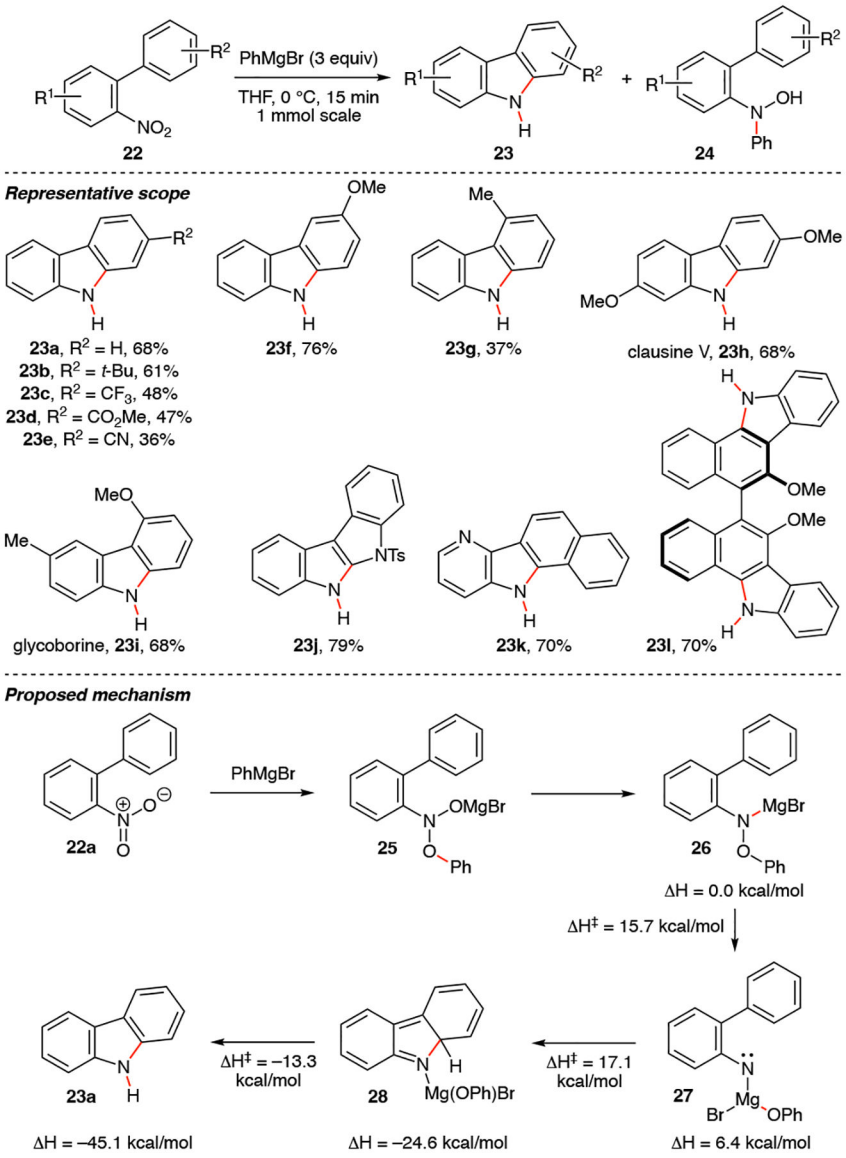


Scheme 1.

Overview of reductive processes of nitroarenes.

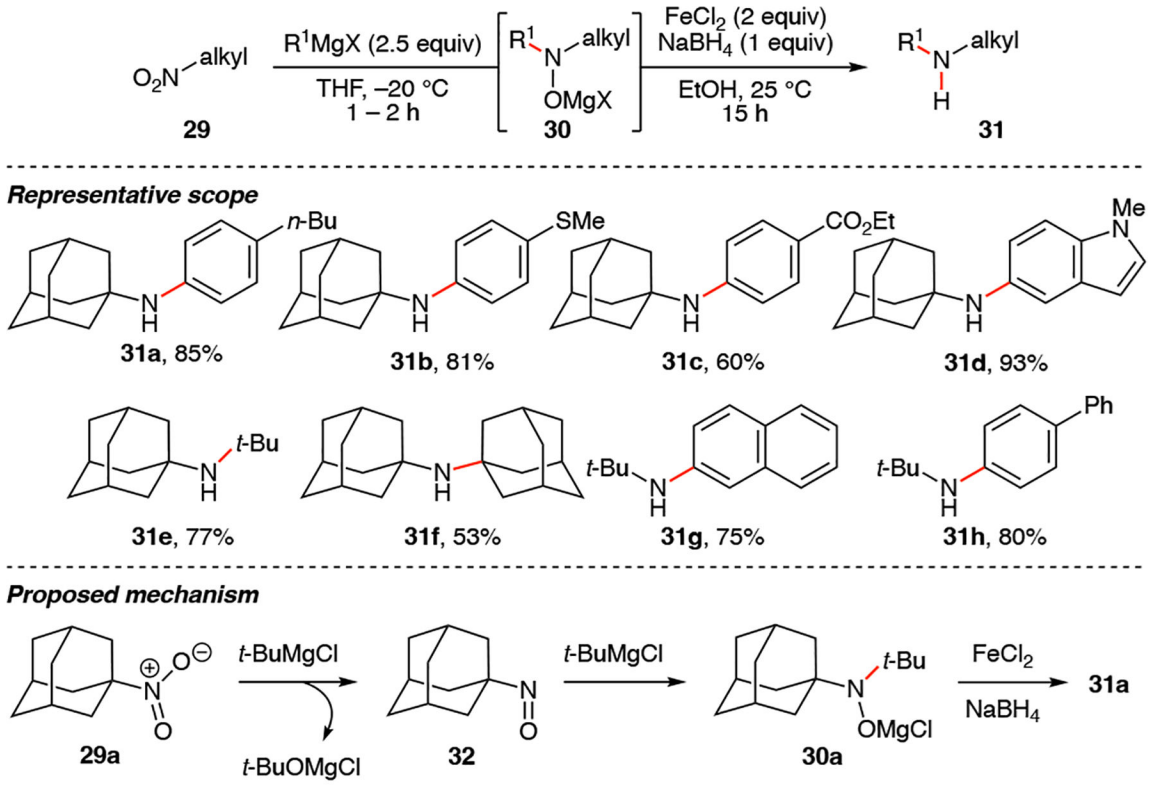


Scheme 2.
Bartoli-indole synthesis organomagnesium reagents.



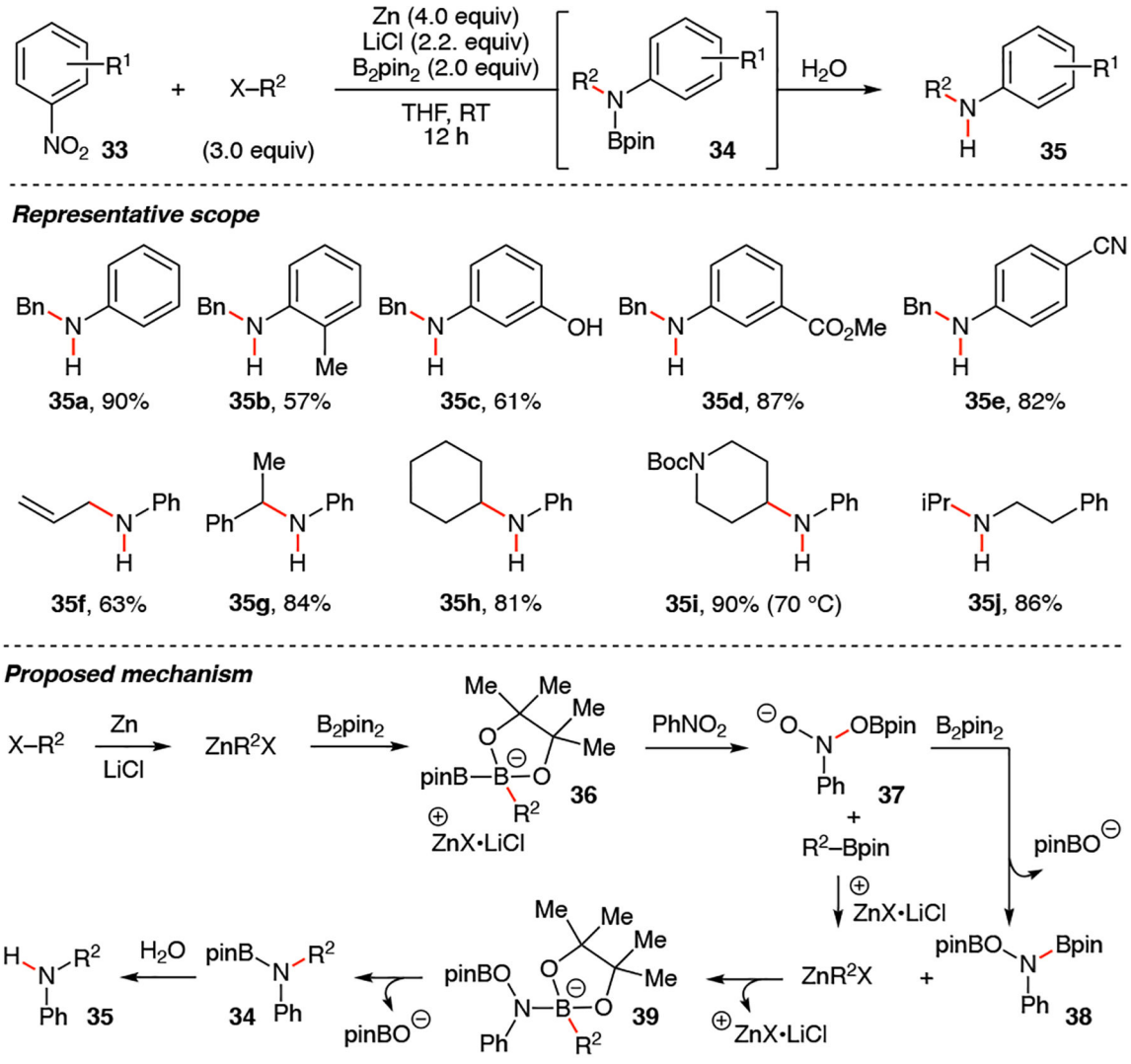
Scheme 3.

Organomagnesium-mediated carbazole formation from 2-arylnitroarenes.



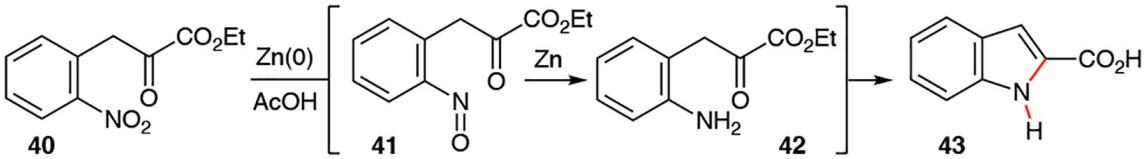
Scheme 4.

Secondary amine construction from nitroalkanes and organomagnesium reagents.

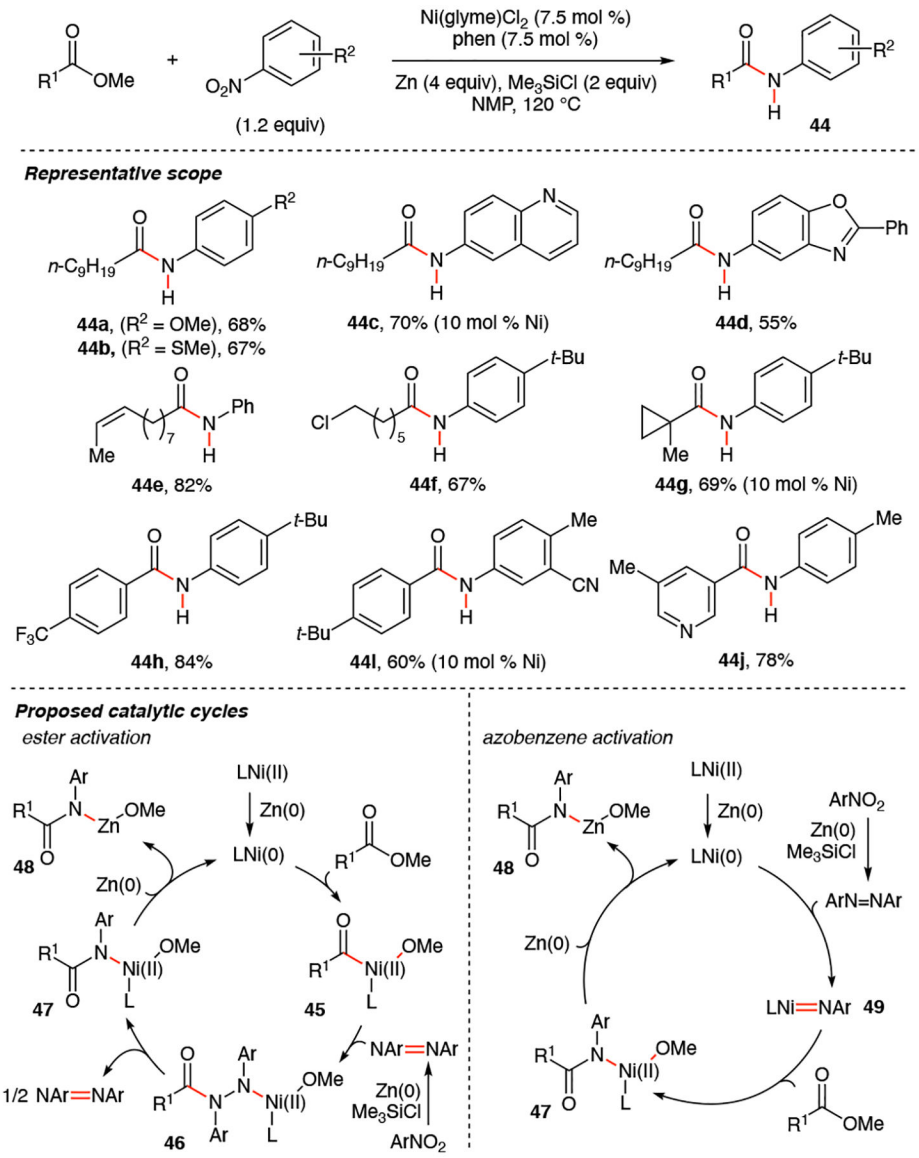


Scheme 5.

Secondary amine construction from nitroarenes or nitroalkanes and alkyl halides.

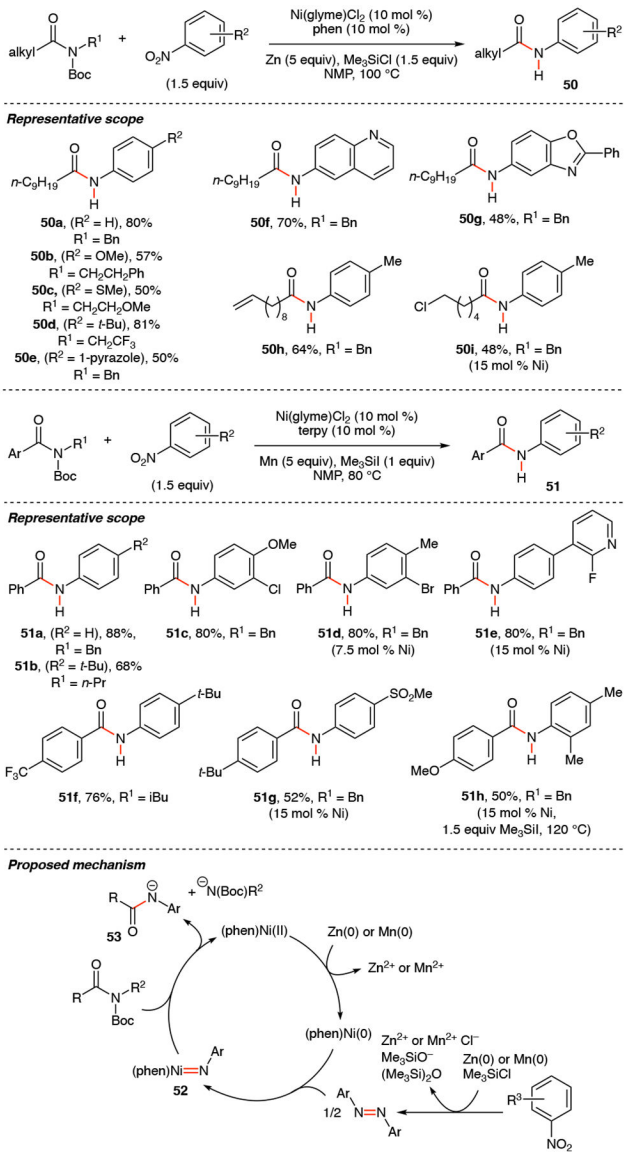


Scheme 6.
Reissert indole synthesis.



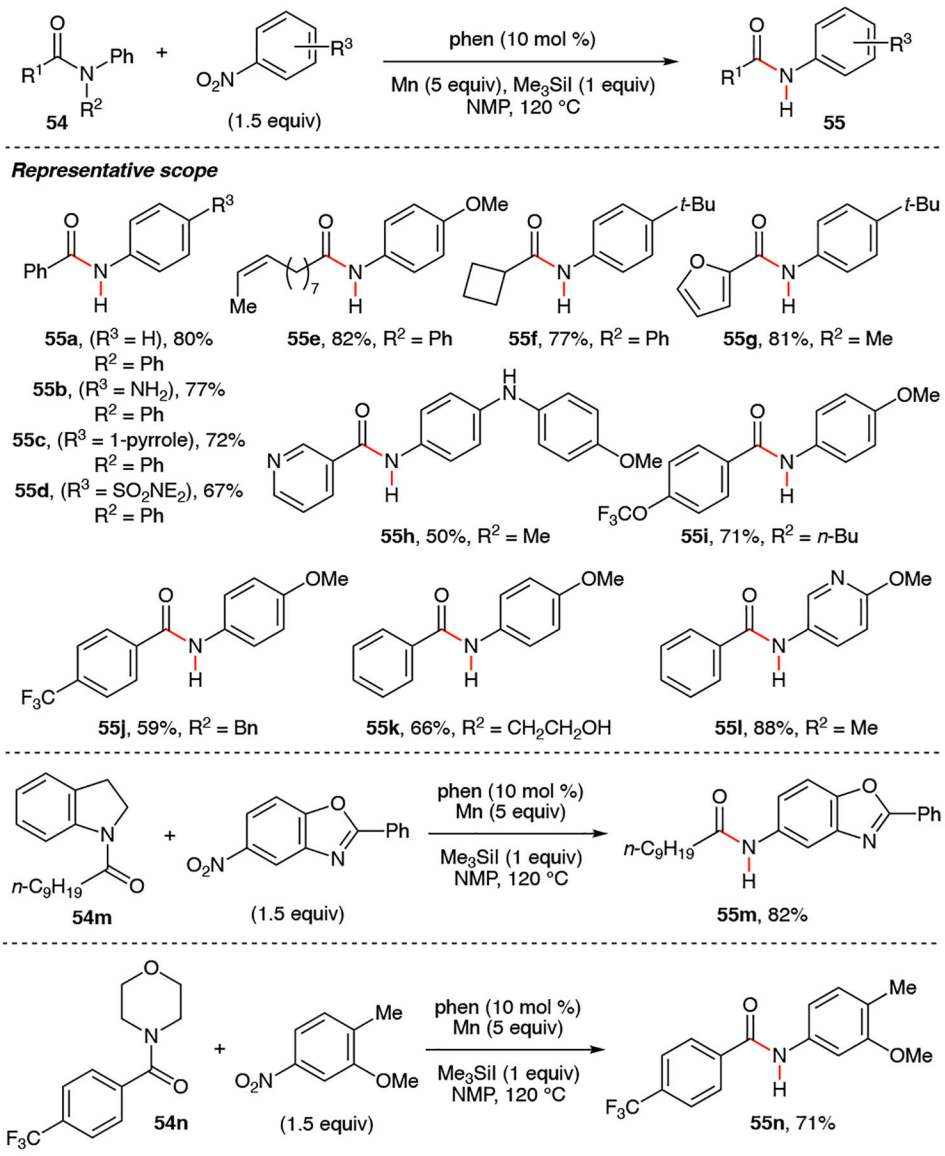
Scheme 7.

Nickel-catalyzed reductive amidation of esters with nitroarenes.



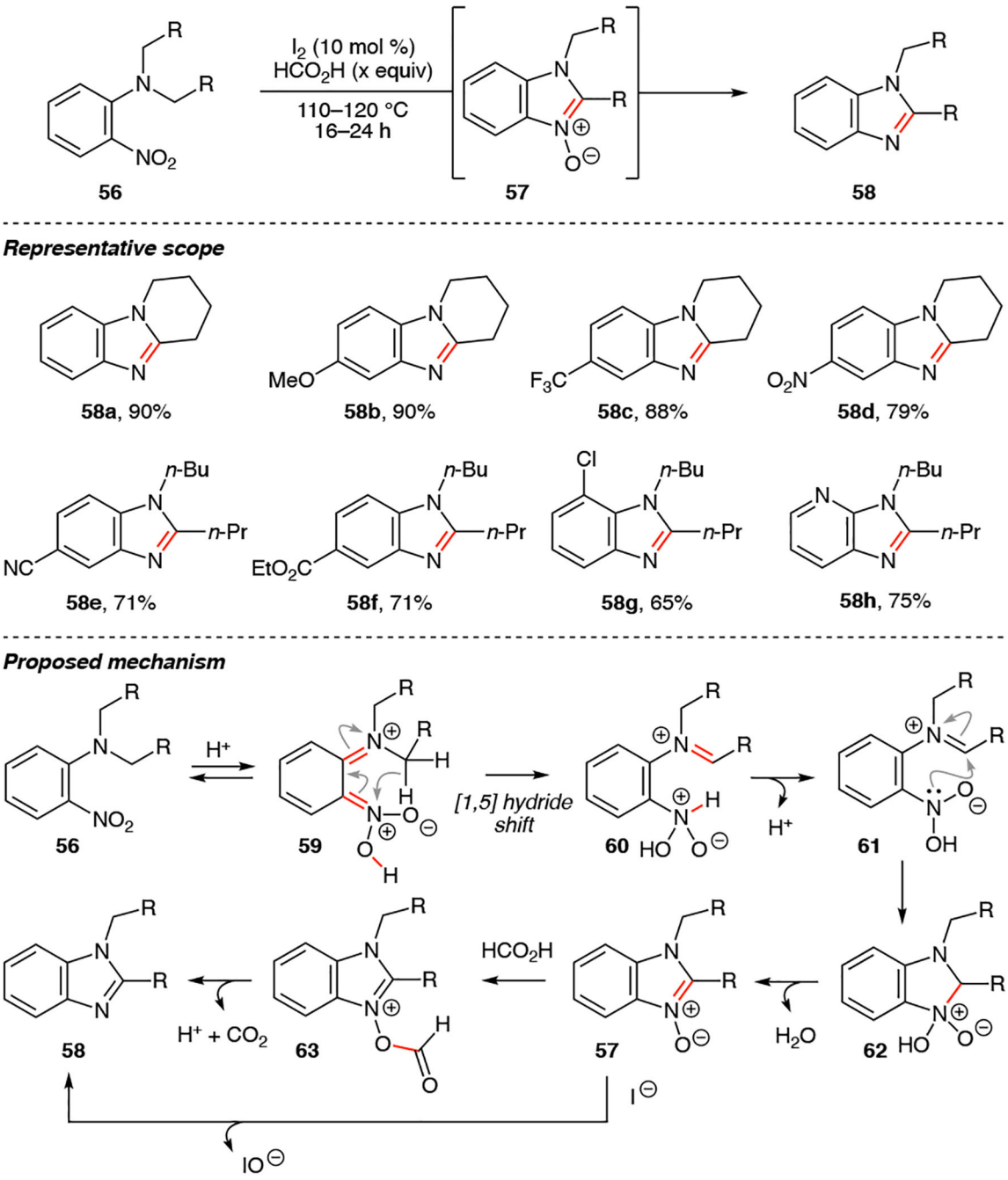
Scheme 8.

Nickel-catalyzed secondary transamidation using nitroarenes.



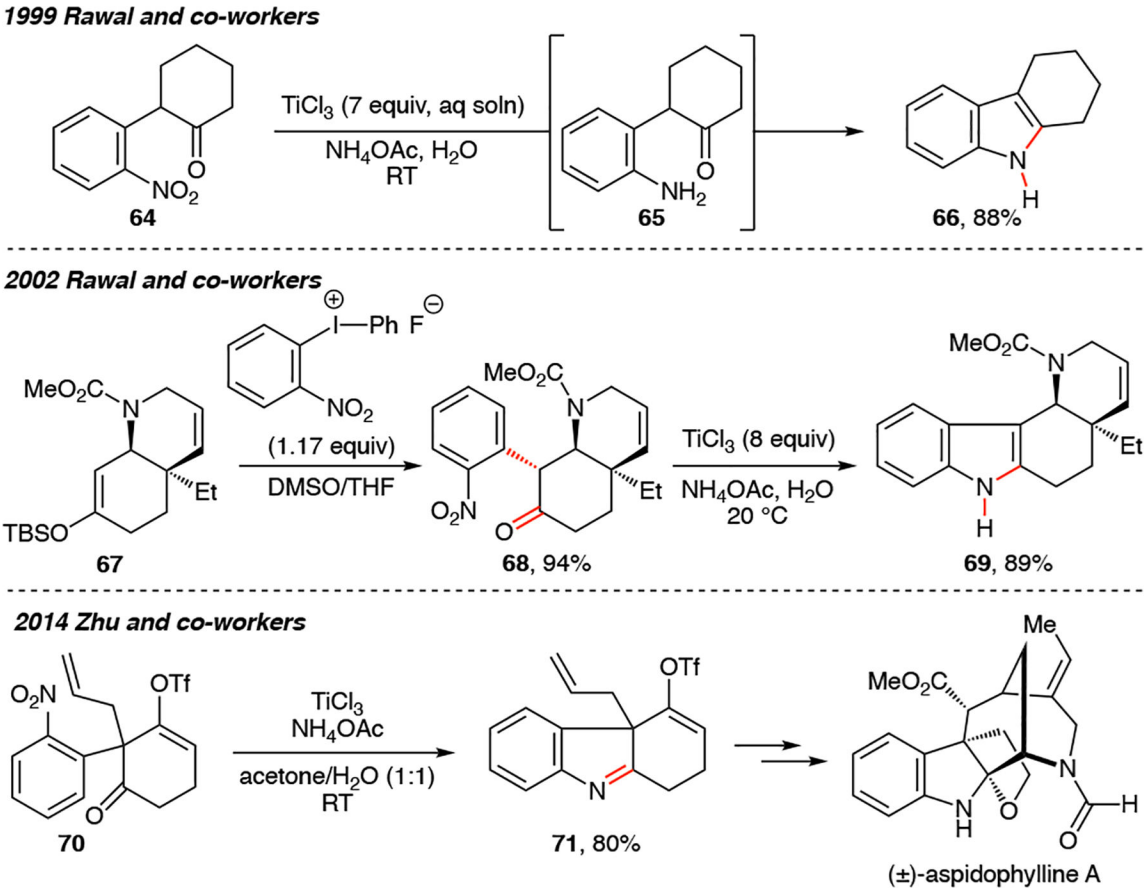
Scheme 9.

Manganese-mediated transamidation of non-activated tertiary amides using nitroarenes as the *N*-aryl nitrogen-source.



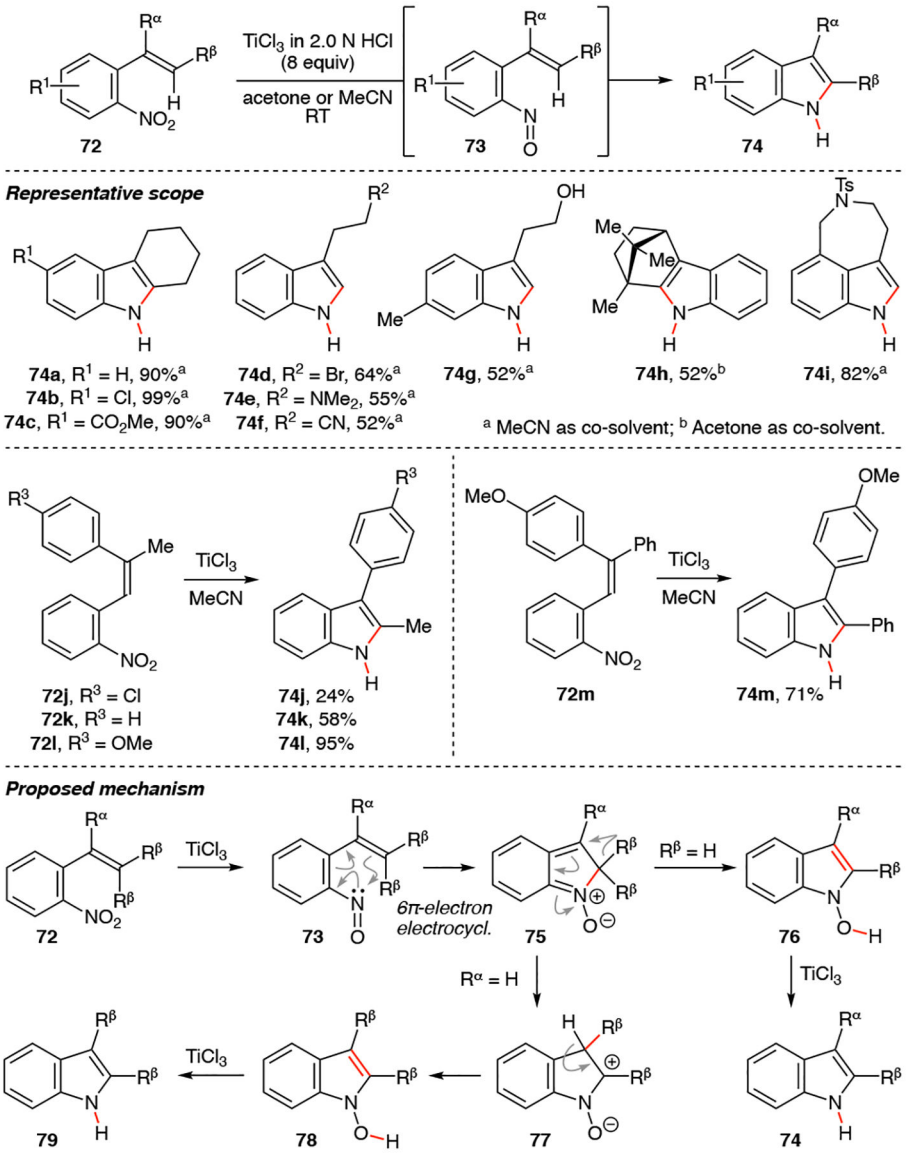
Scheme 10.

Iodine-catalyzed reductive redox cyclization of nitroarenes to produce 1,2-fused benzimidazoles.



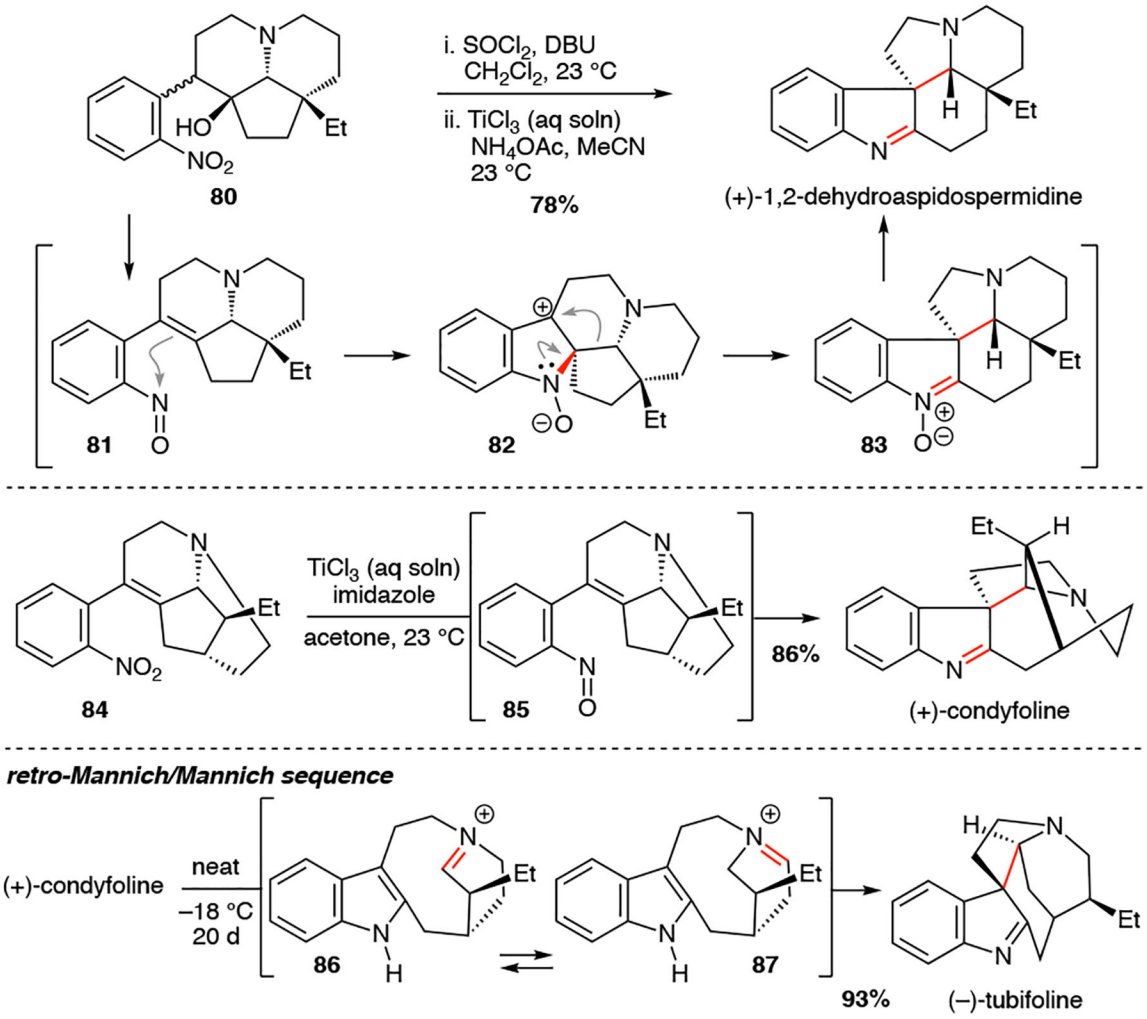
Scheme 11.

Ti(III)-mediated reductive cyclization of nitroarylketones.



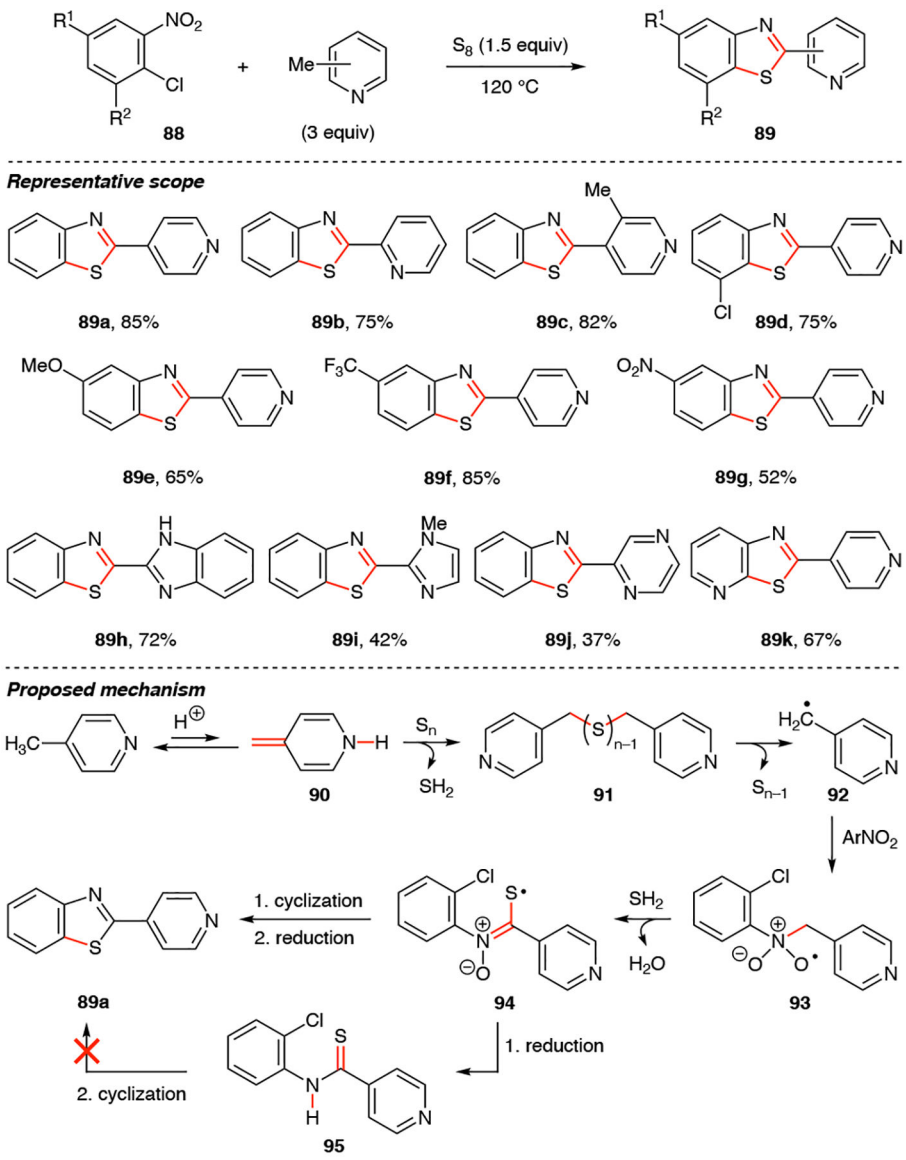
Scheme 12.

Ti(III)-mediated reductive cyclization of nitroarenes.



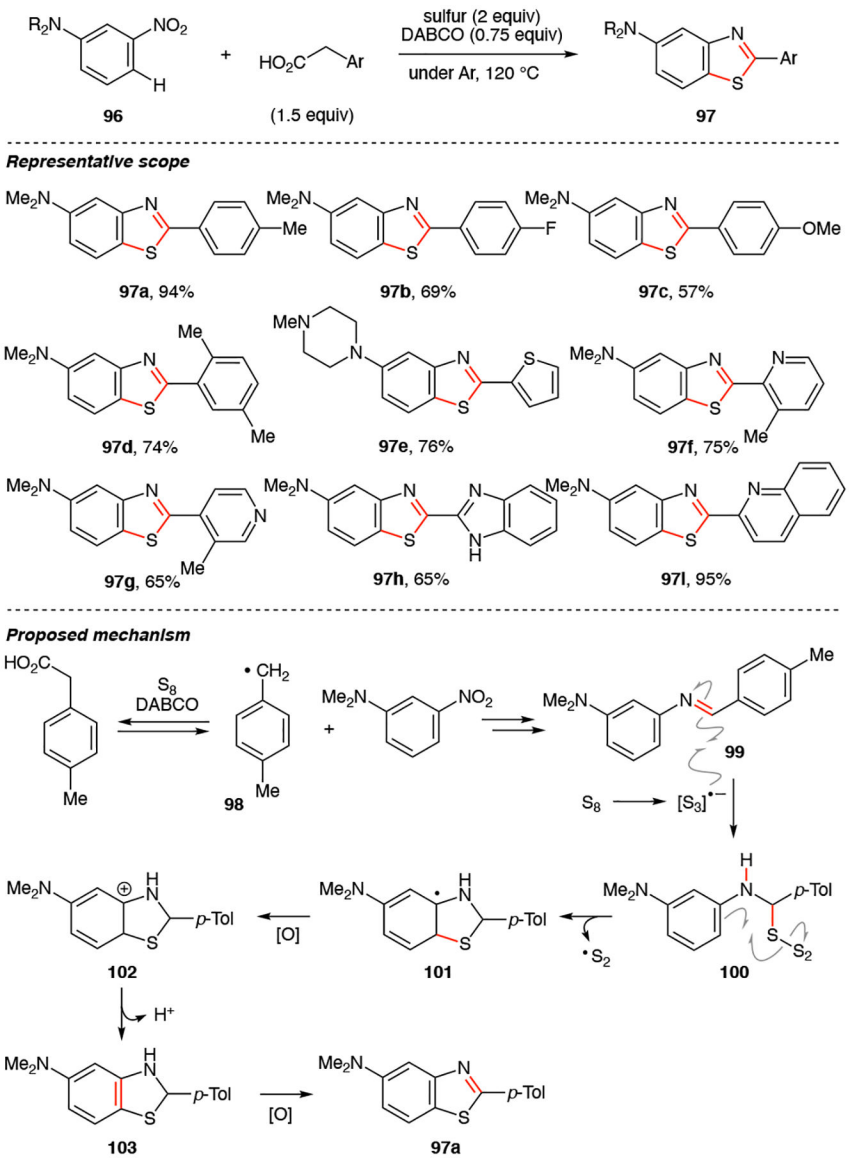
Scheme 13.

Late-stage Ti(III)-mediated reductive cyclization of nitrostyrenes in the asymmetric total synthesis of (+)-1,2-dehydroaspidospermidine and (+)-condyfoline alkaloids.



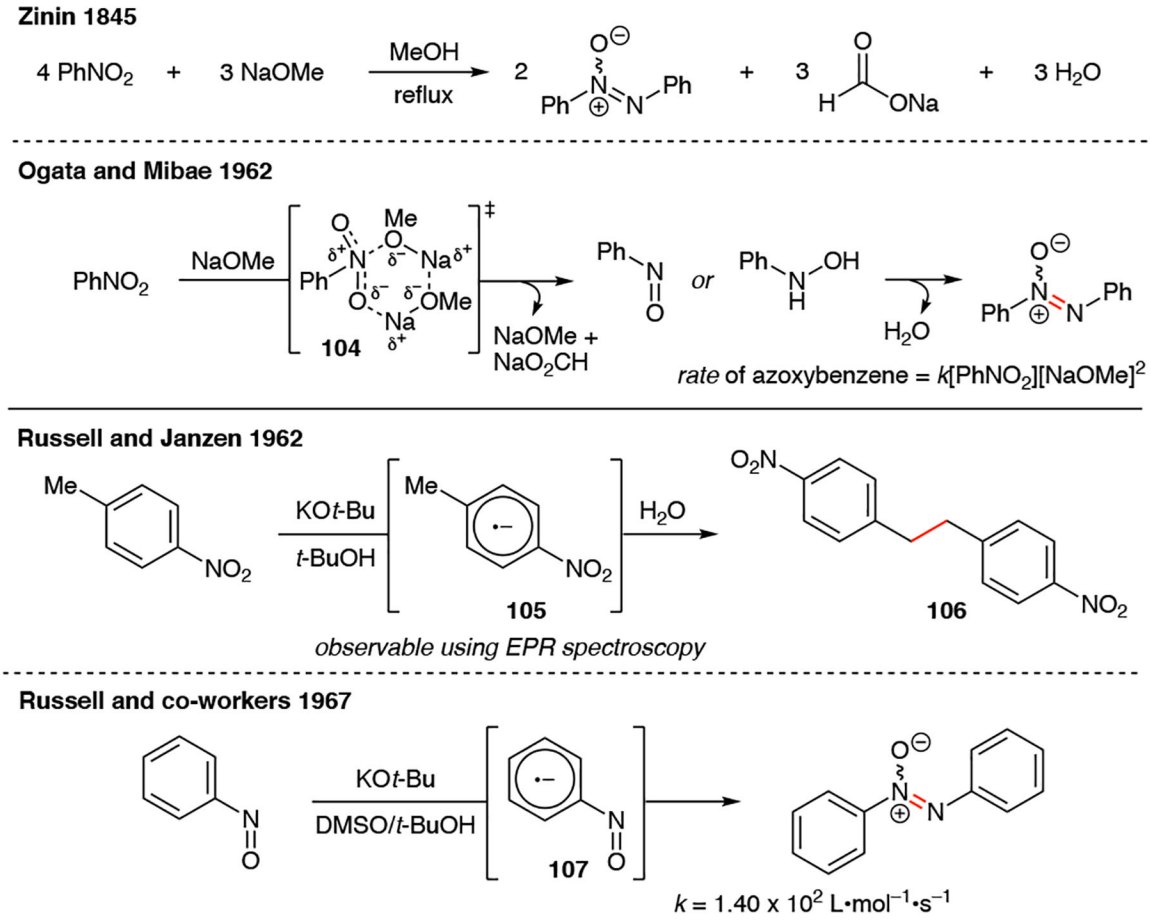
Scheme 14.

Sulfur-mediated reductive amination to produce benzothiazoles from nitroarenes.

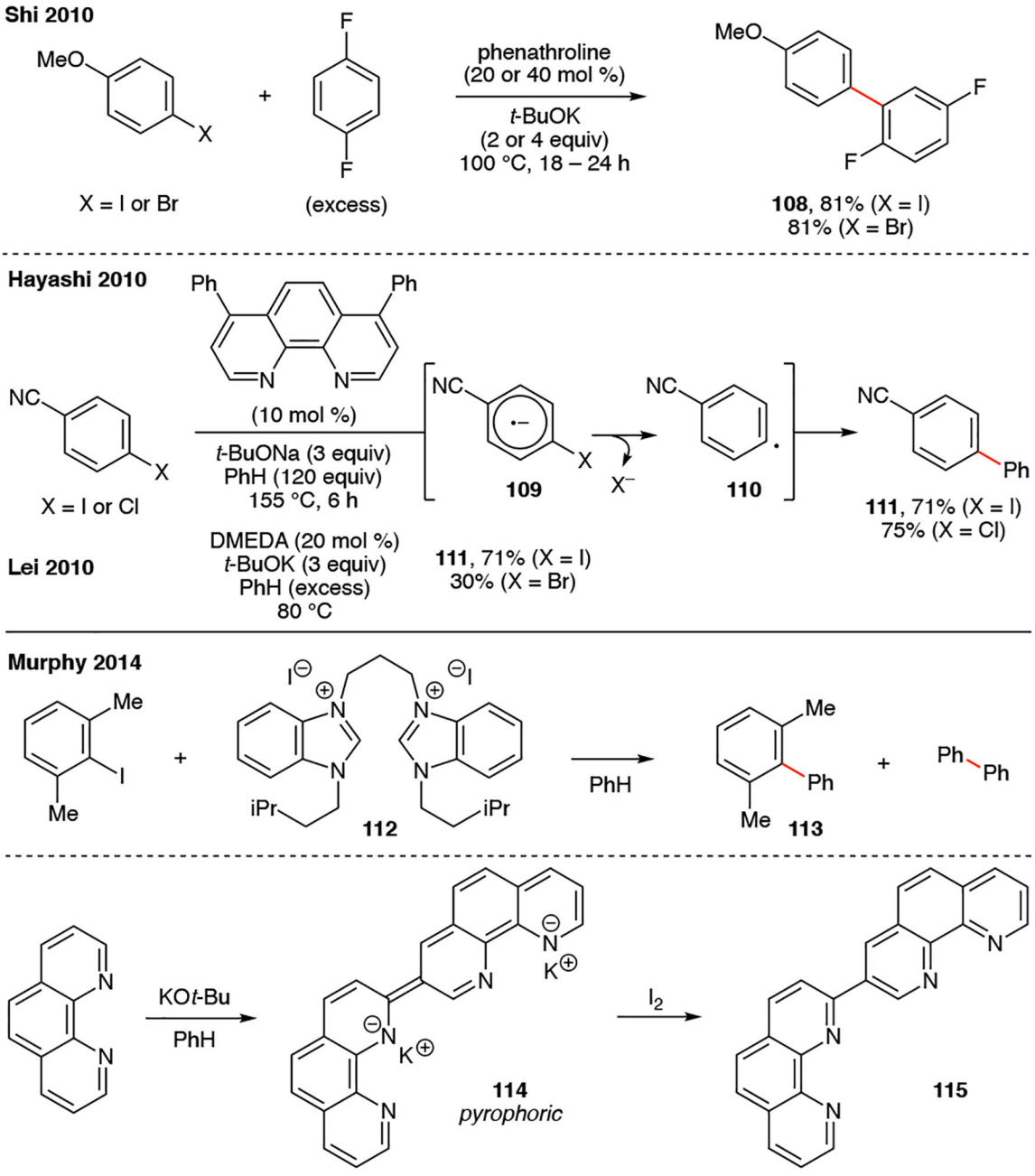


Scheme 15.

Sulfur-mediated reductive amination to produce benzothiazoles from nitroarenes through C–H bond functionalization.

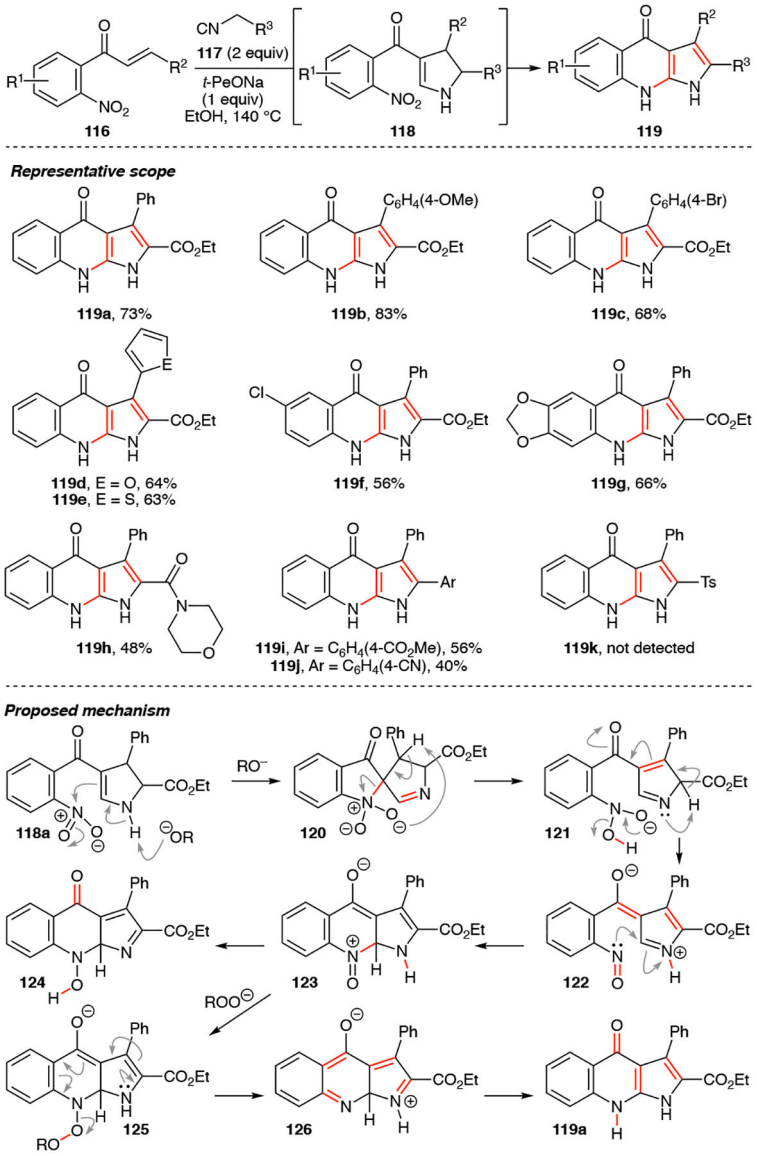


Scheme 16.
Alkoxide-mediated reduction of nitroarenes.



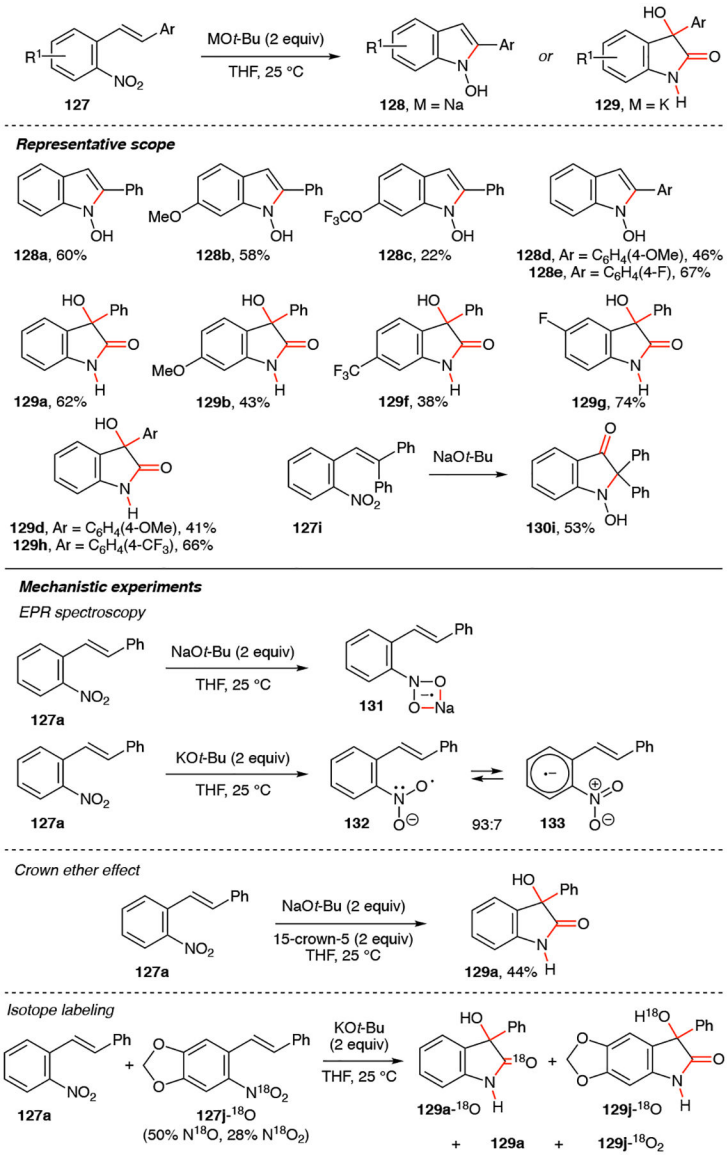
Scheme 17.

Alkoxide-mediated cross-coupling of aryl halides and arenes.



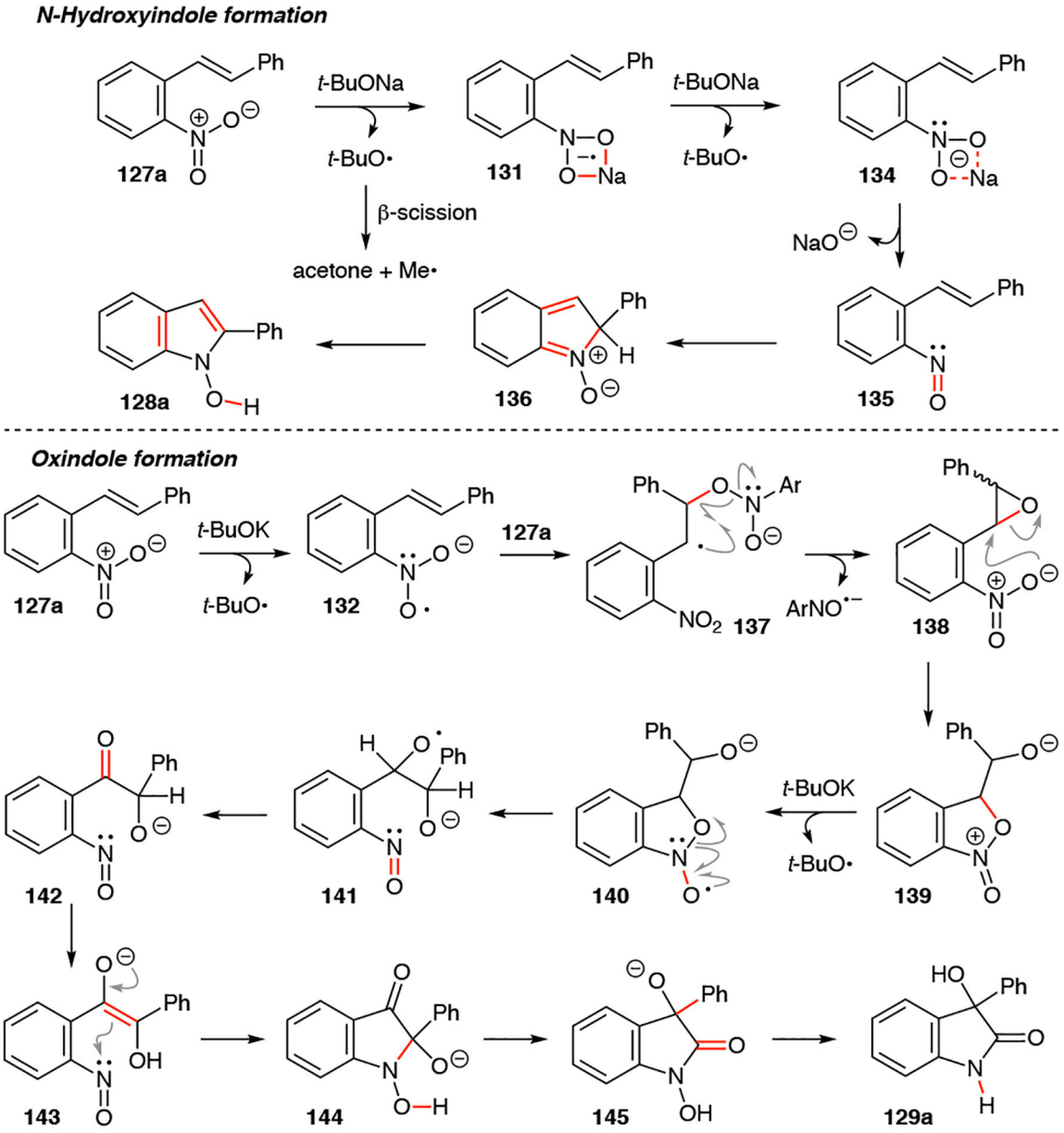
Scheme 18.

t-PeONa-mediated tandem [3+2]/reductive cyclization reaction to construct pyrrolo[2,3-*b*]-quinolones from nitrochalcones.



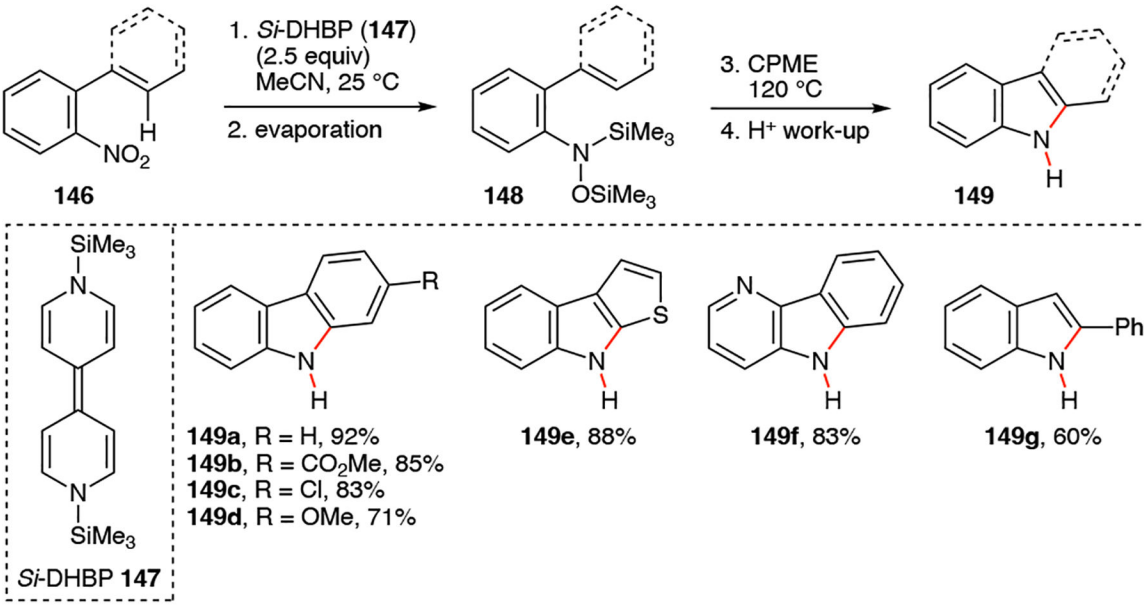
Scheme 19.

Counterion-controlled formation of *N*-hydroxyindole or oxindole from 2-nitrostilbenes using *tert*-butoxide as the single electron reductant.



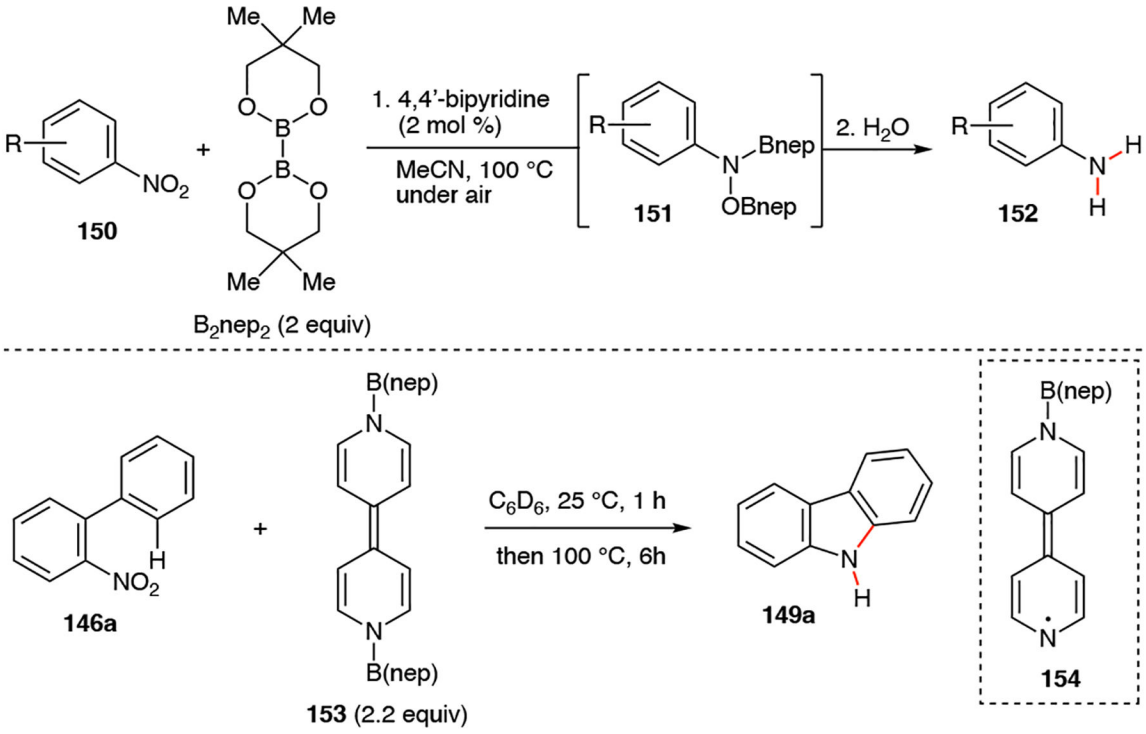
Scheme 20.

Potential mechanisms to account for *N*-hydroxyindole or oxindole formation from 2-nitrostilbenes.



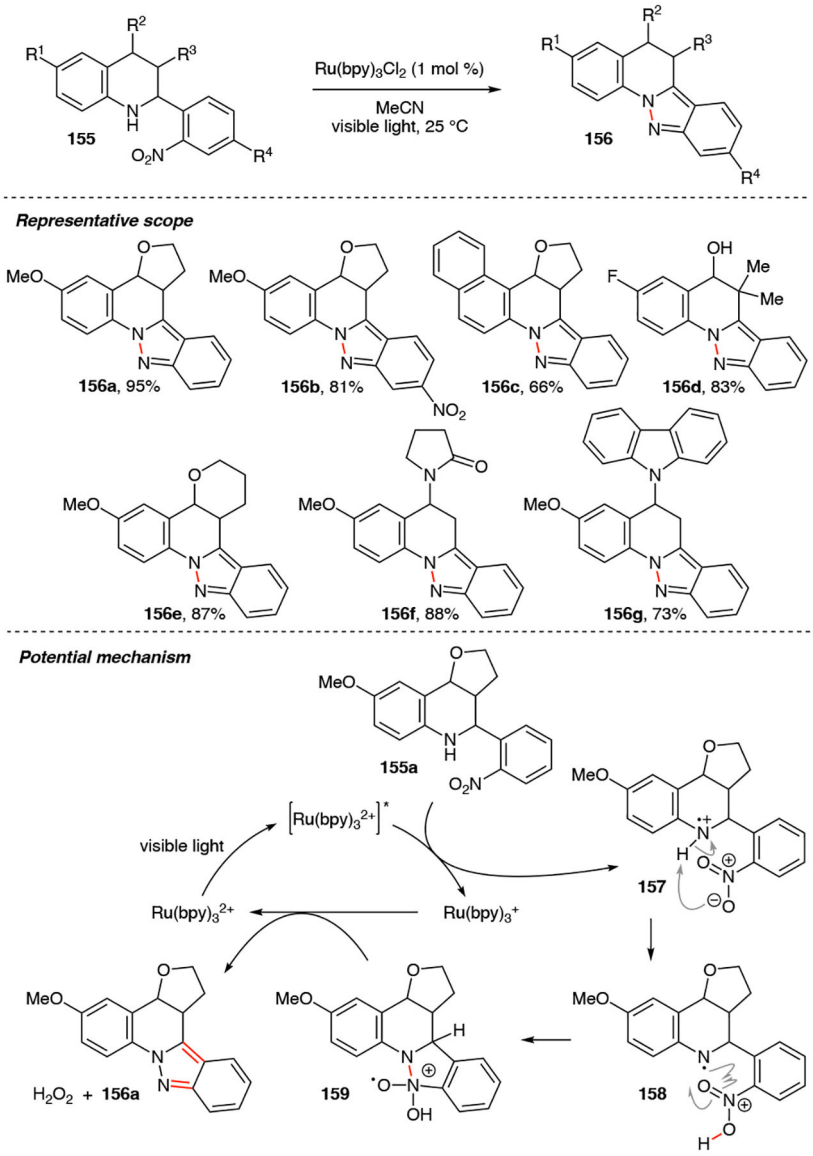
Scheme 21.

Organosilicon-mediated reduction of 2-substituted nitroarenes to produce carbazoles or indoles.



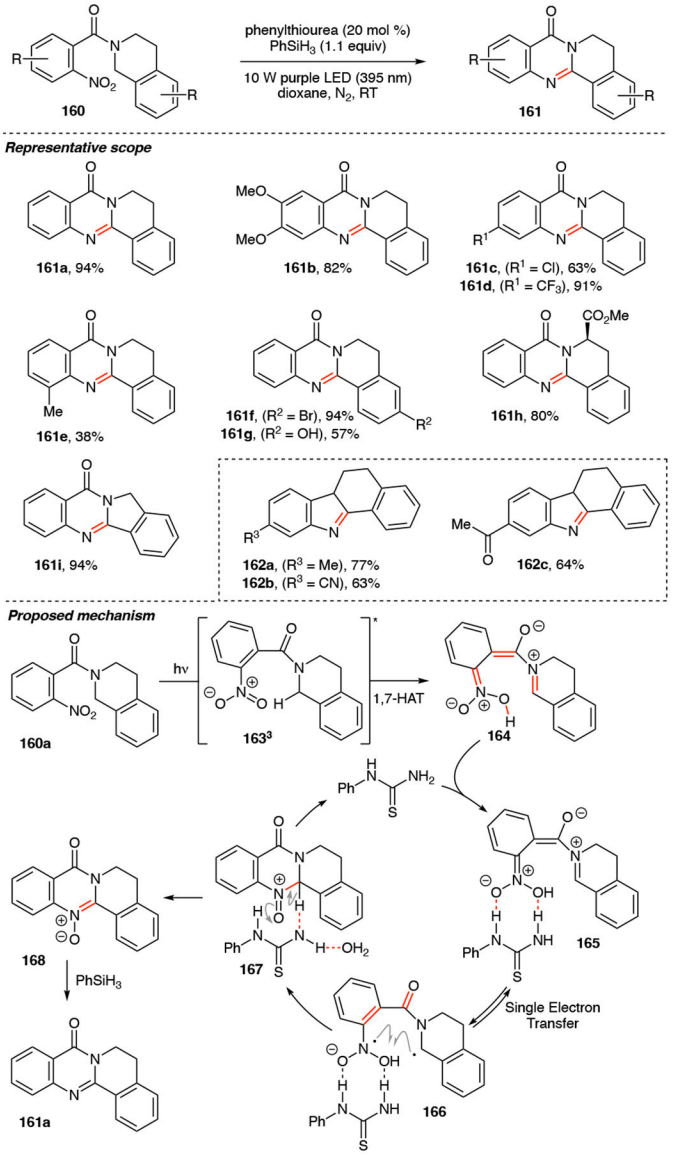
Scheme 22.

4,4'-Bipyridine-catalyzed reduction of nitroarenes using diboron as the stoichiometric reductant.



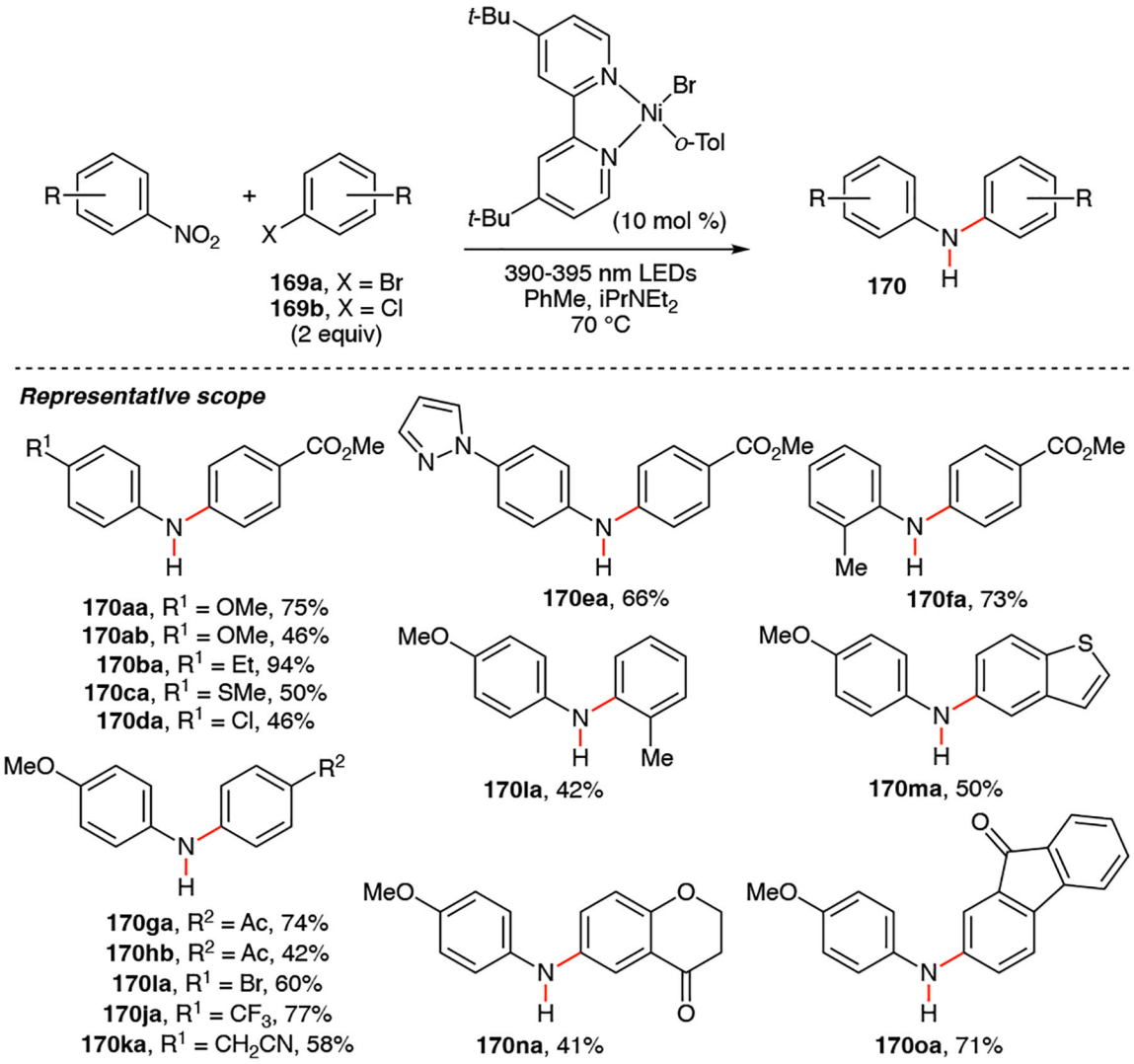
Scheme 23.

Light-driven photoredox catalyzed synthesis of indazoles from nitroarenes.



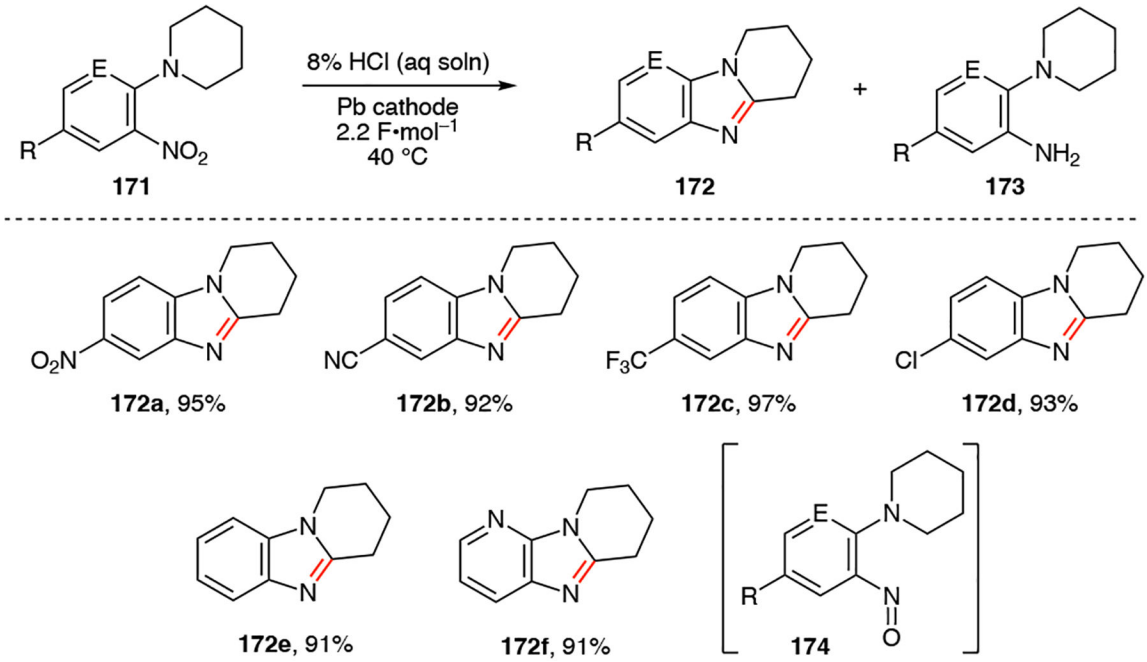
Scheme 24.

Light-driven photoredox catalyst-free formation of quinazolinones or tetracyclic imidazoles from nitroarenes.

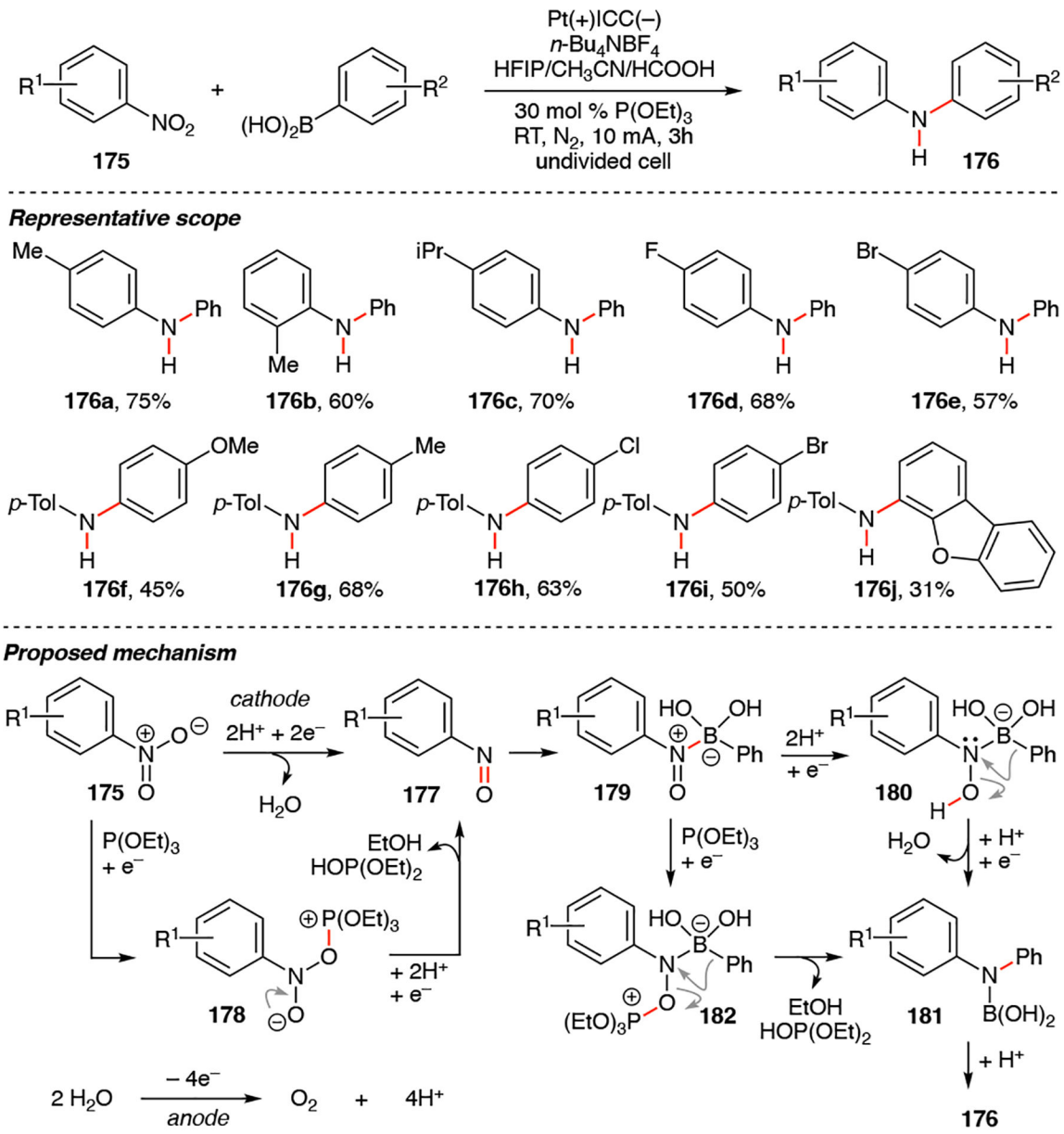


Scheme 25.

Light-mediated, nickel-catalyzed cross-coupling of nitroarenes with aryl halides.



Scheme 26.
Electrochemical formation of benzimidazoles from nitroarenes.



Scheme 27.

Electrochemical-reductive cross-coupling of aryl boronic acids with nitroarenes.