Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

REVIEW

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Cite this: *Org. Biomol. Chem.*, 2021, **19**, 8409

C–H activation reactions of nitroarenes: current status and outlook

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Ring substitution reactions of nitroarenes remain an under-developed area of organic synthesis, confined to the narrow domains of S_NAr and S_NArH reactions. While searching for alternative methodologies, we took stock of the C–H activation reactions of nitroarenes which unearthed a variety of examples of nitro directed regioselective C–H functionalization reactions such as *ortho*-arylation, -benzylation/alkylation, and -allylation, oxidative Heck and C–H arylation reactions on (hetero)aromatic rings. A collective account of these reactions is presented in this review to showcase the existing landscape of C–H activation reactions of nitroarenes, to create interest in this field for further development and propagate this strategy as a superior alternative for ring substitution reactions of nitroarenes. The prospect of merging the C–H activation of nitroarenes with C–NO_2 activation, thereby harnessing NO_2 as a transformable multitasking directing group, is also illustrated.

Received 26th July 2021,
Accepted 31st August 2021

DOI: 10.1039/d1ob01455b

rsc.li/obc

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1. Introduction

Nitroarenes are useful starting materials in aromatic synthesis due to their low cost, commercial abundance and ready access *via* nitration of petroleum derived aromatic hydrocarbons.[1,2] Nitroarenes have a profound impact on the chemical industry. While nitrobenzene is the primary source of various commercial aromatics through functional group manipulations (*e.g.* 95% of industrial nitrobenzene is utilized for aniline production), nitroarenes are the key starting materials in the process development of nearly 65% of active pharmaceutical ingredients (APIs). Nitrobenzene is also a high boiling dehydrogenating solvent which has found use in heterocycle synthesis (Skraup quinoline synthesis), the aromatization of Diels–Alder adducts and the metal catalyzed dehydrogenation of ethylbenzene (to styrene) with concomitant reduction to aniline.[3] Nitrated aromatic compounds are toxic to animals, a property which has been judiciously exploited in drug discovery, especially against tropical diseases, leading to commercialization of several nitroarene based anti-parasitic, anti-kinetoplastid (HAT, Chagas, leishmania), and anti-TB drugs (*e.g.* **1–4**, Fig. 1)[4] and their redox-active prodrug appendages.[5] Recently, nitazoxanide (**1**) has attracted worldwide interest due to its potent *in vitro* activity against SARS-CoV-2 virus (EC_{50} 2–3 μM).[4e] The nitro group is a powerful electron withdrawing group which strongly perturbs the electronic and photophysical properties of the attached aromatic rings. Rational modulation of these effects has led to the development of various nitroarene based high energy,[2d,6] redox-active organic materials[7] (*e.g.* **5–8**) and a number of functional molecular devices.

The chemistry of nitroarenes has been the subject of a great many studies but they are largely centered on the reactions of the nitro group.[2] Thus, the nitro group can be transformed into amine, nitroso, hydroxylamine, azoxy, hydroxy, formyl, isocyanate, amide, *etc*. or directly used for heterocycle construction as in the Cadogan indole and carbazole syntheses.[8] Recently, Pd-catalyzed denitrative coupling of nitroarenes has emerged which holds much promise in aromatic synthesis.[9] On the other hand, ring substitution of nitroarenes has limited application since electrophilic substitution is precluded on the highly electron deficient ring, unless carried out under forcing conditions.[10] Hence, ring substitution of nitroarenes is carried out *via* nucleophilic substitution reactions which, however, are restricted to less than a handful of methods, *viz*. *ipso*-substitution,[11] S_NAr reactions on halo-substituted nitroarenes and vicarious S_NArH based reactions (Makosza reaction[12] and Bartoli indole synthesis[13]) (Fig. 2). In addition, few dearomative cycloaddition reactions have been reported for elaboration of nitro-heterocycles, in particular 3-nitro indoles.[2d,e,14] With the growing importance of nitroarenes as industrial chemicals, drug discovery scaffolds and functional materials, the ring substitution of nitroarenes deserves to be expanded beyond the narrow domains of nucleophilic substitution reactions through conceptually new approaches. Towards this goal, main group organometallic approaches *e.g.* preparation of nitroaryl Grignard reagents or nitro-directed *ortho*-lithiation reactions, met with limited success due to unwanted electron transfer from hard organometallic reagents to the nitro group.[15] Transition metal organometallic approaches, *e.g.* Pd-catalyzed reactions (Heck, Suzuki, Hartwig–Buchwald and Sonogashira couplings) of nitro-substituted aryl halides and pseudo-halides, are far more rewarding which, till date, are the most effective methods for ring substitution of nitroarenes but require additional, often non-trivial, steps for pre-functionalization of substrates. In this context, transition metal mediated C–H functionalization of nitroarenes is undoubtedly an auspicious strategy which, backed by high atom- and step-economy of the C–H activation

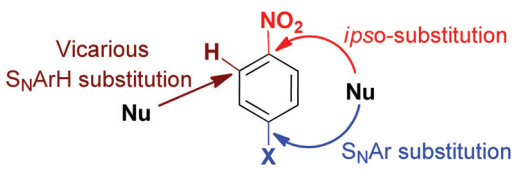


Fig. 2 Current options for ring substitution reactions of nitroarenes.

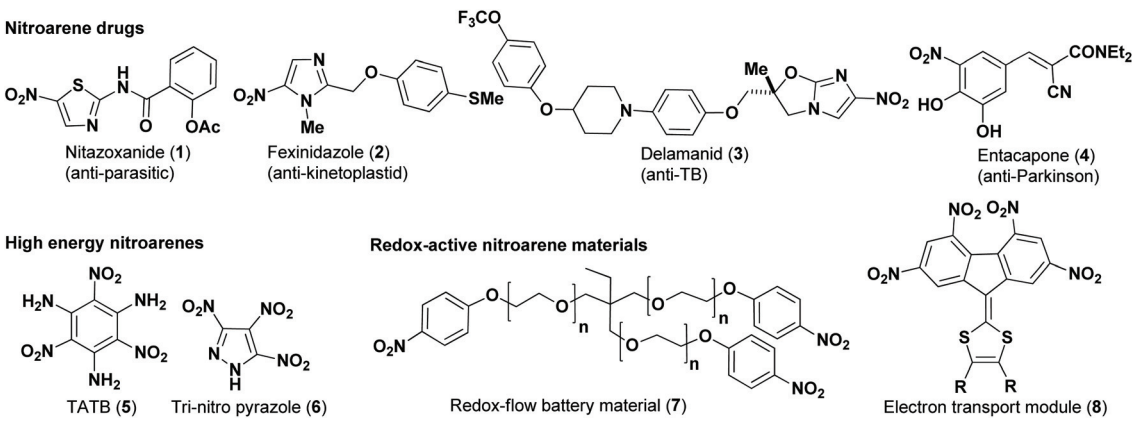


Fig. 1 Examples of nitroarene drugs (**1–4**) and high value organic materials (**5–8**).

strategy, promises broader synthetic ramifications. However, among the wide range of functional groups that have been developed as directing groups for aromatic C–H activation reactions,[16] the nitro group has received limited attention. The purpose of this review is to present the current status of nitro-directed aromatic C–H activation reactions and bring into focus this conceptually new strategy for direct, yet regioselective, ring substitution of nitroarenes through new carbon–carbon and carbon–heteroatom bond formations and at the same time, to propagate this strategy to an underdeveloped area of C–H activation. The review is divided into two major sections: C–H activation reactions of benzenoid nitroarenes (section 2.2) and those of heterocyclic nitroarenes (section 2.3), each section dealing with C–H arylation and -alkenylation reactions among others. Heterocyclic nitroarenes, which have found more applications, are further subdivided into azines (section 2.3.1) and azoles (section 2.3.2). For comparison, non-directed C–H functionalizations of nitroarenes are also discussed at appropriate intersections. An outlook for C–H activation reactions in nitroarenes, especially the potential utility of NO_2 as a multi-tasking directing group, is presented in the Conclusion. In the accompanying schemes, new bonds created *via* NO_2 directed C–H activation are shown in red whereas subsequent transformations of the NO_2 group, where applicable, are shown in blue.

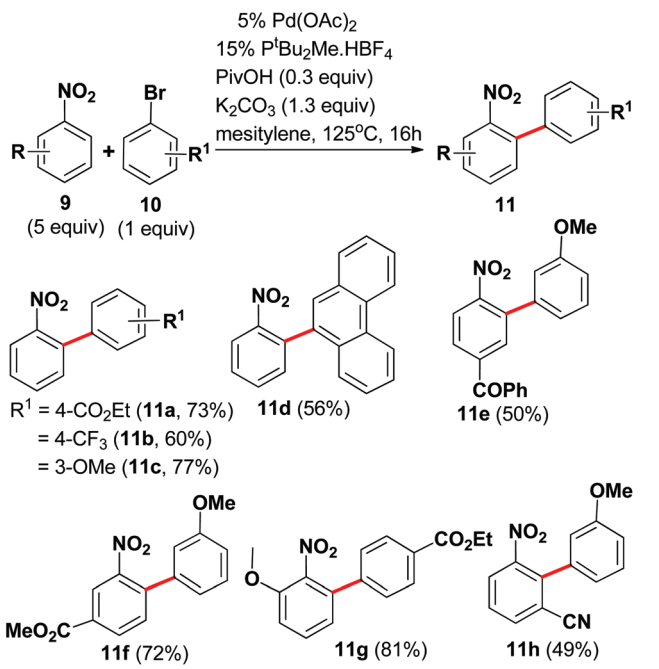
2. Nitro group directed C–H activation reactions

2.1. Pros and cons

A priori, nitro directed C–H activation held much promise, firstly because nitro is iso-electronic with carboxylate which is a proven *ortho*-directing group and secondly, the nitro group imparts high acidity to *ortho*-C–H bonds, thereby enhancing the prospect of *ortho*-metalation *via* the concerted metalation–deprotonation (CMD) mechanism.[17] The feasibility of prior co-ordination of the nitro group to transition metals has received support from the literature reports of nitroarenes acting as ligands in transition metal complexes, including cyclometallated Pt, Rh and Ir complexes.[18] 8-Nitroquinoline has recently been used as a bidentate ligand for the Pd-catalyzed *meta*-C–H activation reaction where the intermediate *meta*-palladated complex is stabilized by dual co-ordination from quinoline nitrogen and the 8-nitro group.[18d] Nevertheless, it is the strength of the nitro group as an *ortho*-directing group which remains the major point of contention. Nitro-substituted aromatic substrates are often used in *ortho*-C–H activation reactions as a mark of functional group tolerance. In no such cases, evidence of side products arising out of nitro-directed C–H activation has been reported so far.[19a–i] Hickman and Sanford have even used nitrobenzene as a solvent for Pd(II)-catalyzed C–H arylation of naphthalene with diaryl iodonium salts.[19j] Hence, it appears that nitro is a weak directing group *vis-à-vis* other *ortho*-directing functional groups. A further point of concern is diminished yields, even complete shut-down of C–H activation reactions, often observed with nitro-substituted substrates, perhaps due to redox interference by the nitro group.[18,20] It thus transpires that nitro directed aromatic C–H activation reactions may face a number of synthetic challenges.

2.2. C–H activation of benzenoid nitroarenes

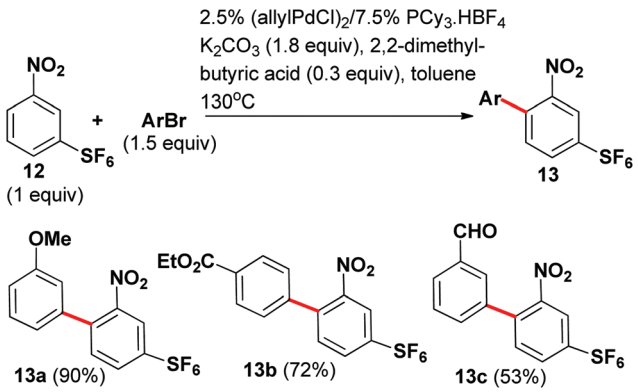
2.2.1. Arylation reactions. Seminal examples of nitro directed Pd-catalyzed C–H activation reactions were reported by Fagnou and co-workers in 2008 (Scheme 1).[21] Carried out with 3–10 equivalents of nitroarene **9**, aryl bromide **10** or tosylate[22] (but not aryl iodides) and $Pd(OAc)_2$/$PtBu_2Me{\cdot}HBF_4$ as the catalyst, the success of these reactions was heavily dependent on additives/bases (0.3 equiv. of PivOH and 1.3 equiv. of K_2CO_3 but not KOPiv or CsOPiv) and the solvent (a nonpolar solvent like mesitylene is highly preferred) in order to achieve good yields of *ortho*-arylated nitroarenes **10** with high regioselectivity [$o:(m+p)$ >34 : 1]. Intriguingly, the use of PivOH in a sub-stoichiometric amount (and not a full equivalent) was essential for the observed high regioselectivity. Polar solvents *e.g.* DMA severely compromised the regioselectivity but not the yield.[23] Intermolecular competition experiments were carried out with anisole and methyl benzoate which clearly demonstrated the preference for nitrobenzene as the C–H activation substrate. In the case of substituted nitroarenes, the regioselectivity of C–H arylation was primarily driven by steric factors (**11f,g**), except for 3-cyano nitrobenzene which showed a co-operative effect in directing the reaction at C-2 (**11h**). This unusual regioselectivity was later confirmed by Ihanainen



Scheme 1 Nitro directed *ortho*-C–H arylation reactions with aryl bromides.

et al. during their investigation on cyano directed C–H arylation reactions.[24]

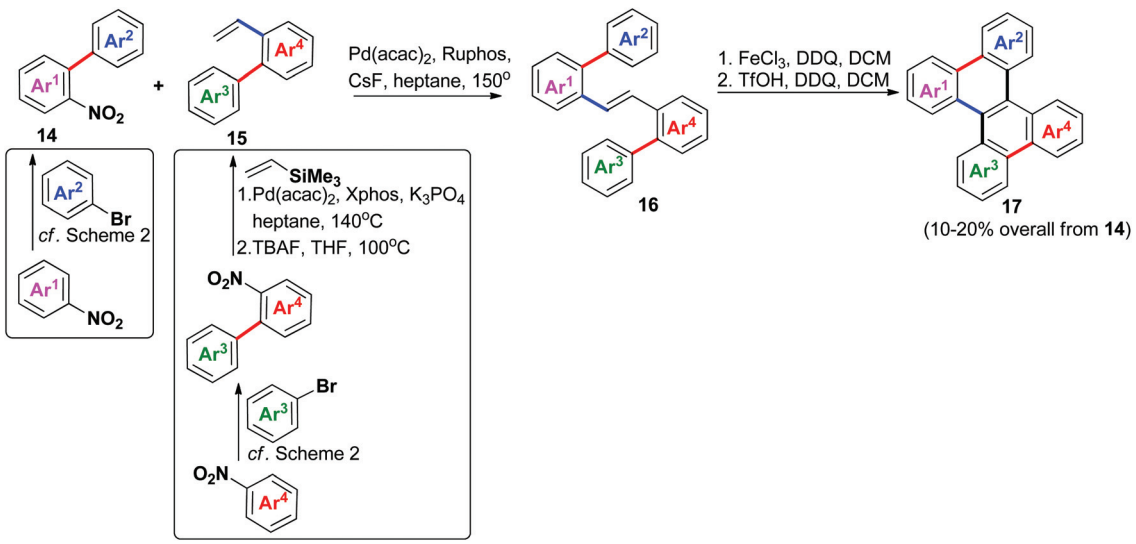
In 2013, Zhang and co-workers published a major improvement in reaction conditions [(allylPdCl)$_2$-PCy$_3$.HBF$_4$, K$_2$CO$_3$ (1.8 equiv.), 2,2-dimethylbutyric acid (0.3 equiv.), toluene, 130 °C] under which nitroarene, specifically *m*-SF$_6$ nitrobenzene (**12**), could be used in stoichiometric amounts for C–H arylation reactions (Scheme 2).[25] PivOH was replaced with more bulky 2,2-dimetylbutyric acid but, again, used in a sub-stoichiometric amount, whereas a nonpolar solvent like toluene was retained. Good yields of *ortho*-arylated products (**13**) were obtained by this procedure with <5% contamination from *meta*-arylated isomers. With *p*-SF$_6$ nitrobenzene, 2,6-diarylated products were obtained when 2.5 equivalents of aryl bromides were employed. Intermolecular competition experiment between **12** and 2-*d*-**12** showed a KIE of 1.91 which, however, could not provide a clear-cut indication that C–H bond breaking is rate-limiting.



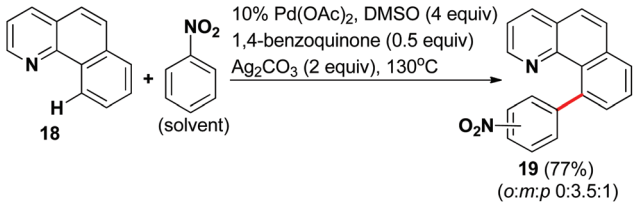
Scheme 2 Nitro directed regioselective C–H arylation reactions of *m*-SF$_6$ nitrobenzene.

Recently, Zhou *et al.* have elegantly exploited the Pd-catalyzed nitro directed C–H arylation and denitrative Heck reaction, in an iterative fashion, for a facile convergent assembly of a series of carbohelicenes **17** in a few steps (Scheme 3).[26] On one hand, nitro directed C–H arylation under Zhang's conditions (*cf.* Scheme 2) was used to synthesize nitro-biaryl building block **14**. On the other hand, sequential nitro directed C–H arylation followed by a denitrative Heck reaction (with vinyltrimethylsilane) afforded the styryl building block **15**, clearly demonstrating the orthogonal relationship between C–H activation and C–NO$_2$ activation in nitroarenes. A denitrative Heck reaction of **14** with **15** then led to the intriguing (biaryl)ethylenes **16** which were readily cyclized under oxidative acidic conditions to helicenes **17** in good overall yields. Merging of C–H activation and C–NO$_2$ activation shown in this work promises a new chemical strategy in aromatic synthesis, especially towards the synthesis of complex polyaryls (also see section 3).

At this point, it is contextual to discuss other methods reported for C–H arylation of nitroarenes, especially in terms of their observed regioselectivities. Recently, transition metal catalyzed cross dehydrogenative coupling (CDC) has been intensely studied by several groups as a direct approach towards unsymmetrical biaryl synthesis.[27] However, CDC reactions involving nitrobenzene as one of the partners are rarely found in the literature due to the electron deficient nature of nitroarenes. One such example was reported by Hull and Sanford where Pd-catalyzed coupling of benzo[*h*]quinoline (**18**) with nitrobenzene (as the solvent) was carried out leading to the formation of *m*-substituted biaryl **19** as the major product, with no trace of *o*-substituted isomer (Scheme 4).[28] The regiochemical outcome, which is in sharp contrast to *ortho*-C–H arylations with aryl bromides, was explained in terms of steric clash between the bulky cyclopalladated intermediate arising out of **18** and the nitro group. Electronic control of regioselectivity was ruled out since 1,3-dimethyl anisole and 1,3-



Scheme 3 Convergent assembly of carbohelicenes (**17**) *via* tandem *ortho*-C–H arylation and denitrative vinylation of nitroarenes.



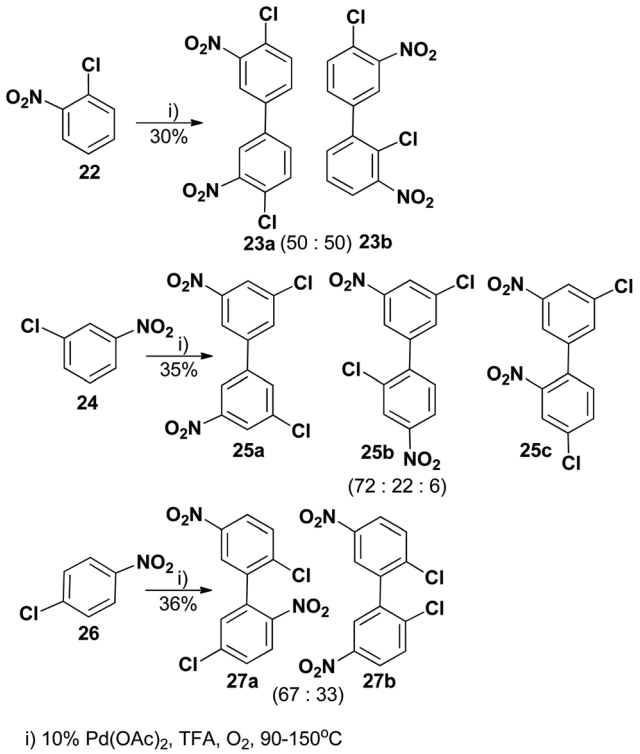
Scheme 4 Regioselective oxidative arylation of benzo[*h*]quinoline (**18**) with nitrobenzene.

dimethyl nitrobenzene both gave nearly identical yields of the respective *p*-substituted products. Similar *meta*-oriented product formation was also observed during Pd-catalyzed cross dehydrogenative arylation of 7-azaindole and azole-4-carboxylate esters, *e.g.* **20** with nitrobenzene (Scheme 5).[29]

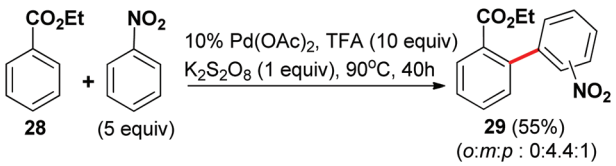
Recently, Zhou and Lu revisited the homocoupling reaction of nitrobenzene, first described by Fujiwara *et al.* in 1970 using the ethylene–$PdCl_2$ complex and $AgNO_3$ (1 : 1 ratio) to provide 3.3′-dinitro biphenyl (60%),[30a] employing cat. $Pd(OAc)_2$ in the presence of TFA under an O_2 atmosphere and used a variety of substituted nitroarenes as substrates.[30b] A statistical mixture of homocoupled products was obtained in these reactions, but in all cases, *meta*-coupling (with respect to the NO_2 group) was favoured (S_ER mechanism) as shown in Scheme 6 with three chloronitro benzene isomers **22**, **24** & **26**. Only in the case of *p*-Cl nitrobenzene (**26**), one could observe an *ortho*-preference as evident in the major product **27a**.

Zhou and Lu also carried out cross dehydrogenative biaryl coupling between ethyl benzoate (**28**) and nitrobenzene under carefully optimized conditions, especially in the amount of TFA, in order to avoid homocoupling products.[30b] The resulting unsymmetrical biaryl **29** (55%) again showed a preference for *meta*-orientation with respect to the NO_2 group (Scheme 7). Interestingly, complete *ortho*-selectivity was achieved with respect to the ester group.

In summary, high *ortho*-selectivity obtained in Pd-catalyzed C–H arylation of nitroarenes with aryl bromides is not reflected in their cross dehydrogenative C–H arylation reactions. Apparently, in the latter case, steric and/or electronic effects prevail, either *via* the CMD or S_ER mechanism, leading to preferential formation of *meta*-substituted (with respect to the NO_2 group) products.

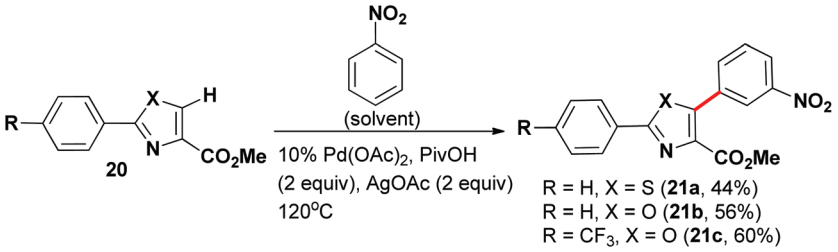


Scheme 6 Pd-Catalyzed homocoupling of chloronitrobenzene isomers.

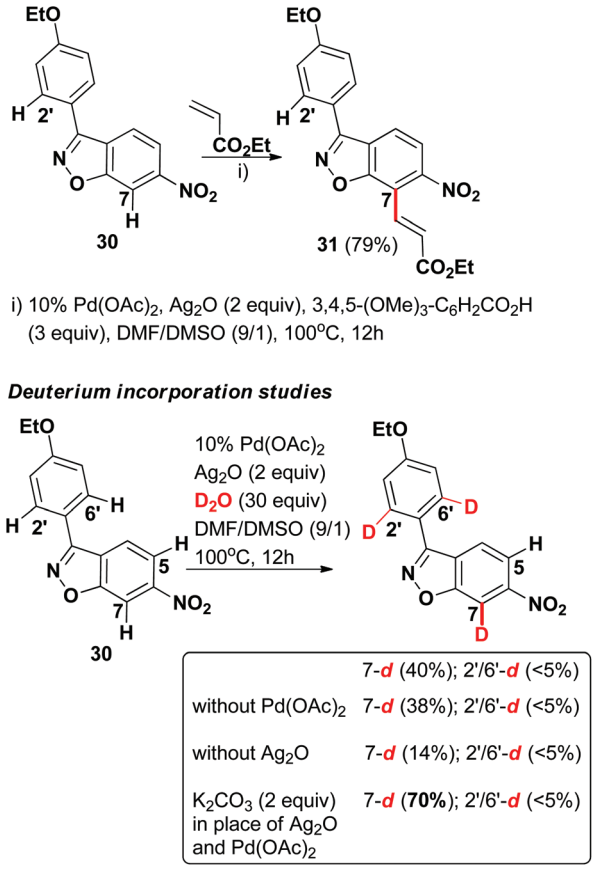


Scheme 7 Pd-Catalyzed cross dehydrogenative coupling between ethyl benzoate and nitrobenzene.

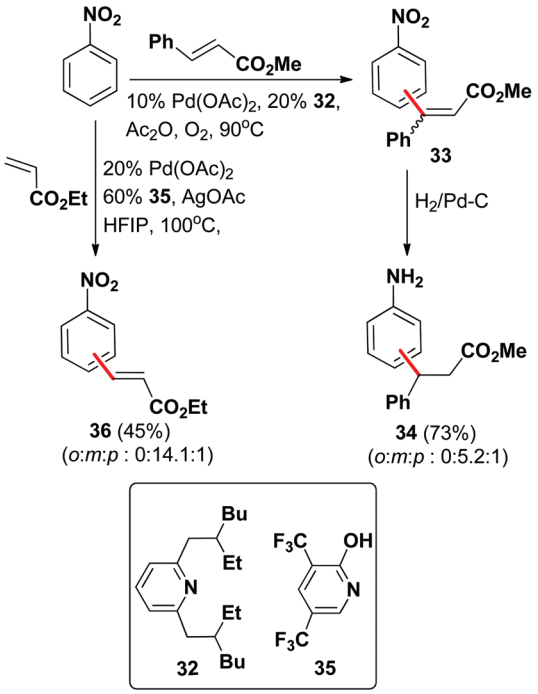
2.2.2. Alkenylation reactions. There is only one example of nitro directed *ortho*-C–H alkenylation of nitrobenzene derivatives (for examples on the heterocyclic series, see section 2.3.2), despite its promise as a superior alternative to vicarious *ortho*-vinylation reactions of nitroarenes employing hard Grignard reagents for the synthesis of *ortho*-vinyl nitroarenes



Scheme 5 Dehydrogenative arylation of azole-4-carboxylates **20** with nitrobenzene.



Scheme 8 Regioselective oxidative Heck reaction of 6-nitrobenzisoxazole **30** and mechanistic deuterium incorporation studies.



Scheme 9 Ligand driven Pd-catalyzed oxidative Heck reactions of nitrobenzene.

which are valuable intermediates for indole synthesis. In this example, a highly regioselective oxidative Heck reaction of 6-nitro benzisoxazole (**30**) was described together with the evidence in favour of a nitro directed process (Scheme 8).[31] An oxidative Heck reaction of **30** with ethyl acrylate occurred exclusively at C-7 to give **31** in 79% yield, despite the presence of other potentially vulnerable C–H bonds *viz.* C5–H and C2′–H, the latter getting directing assistance from isoxazole nitrogen. Deuterium incorporation studies revealed a clear-cut preference for C-7-deuteriation over C-2′/6′ & C-5 under the reaction conditions. Ag_2O or even better K_2CO_3 alone could induce facile 7-deuteriation which clearly demonstrated the high acidity of C7–H imparted by the adjacent nitro group, thereby facilitating a base assisted C7-palladation with high regioselectivity (Scheme 8).[31]

In comparison, it may be noted that the oxidative Heck reaction of nitrobenzene was first reported by Fujiwara in 1969 using styrene and stoichiometric $Pd(OAc)_2$ to produce *m*-nitrostilbene (60%).[32] A catalytic version had to wait till 2009 when Yu and co-workers reported on the ligand driven oxidative Heck reaction of nitrobenzene with methyl cinnamate using 10 mol% $Pd(OAc)_2$ and a bulky 2,6-disubstituted-pyridine ligand **32** under an O_2 atmosphere (Scheme 9).[33] The initially formed isomeric product mixture **33** was hydrogenated to **34** (73% overall) for the ease of characterization. High *meta*-preference (*m* : *p* 5.2 : 1) was observed in **34** with no trace of *ortho*-isomer which was also the feature of the oxidative C–H arylation reactions of nitrobenzene (*cf.* Schemes 4 and 5).[28,29] A monoligand complex [**32**·$Pd(OAc)_2$] was proposed to be the catalytically active species.[34] Systematic theoretical studies of this reaction by Zhang and co-workers (using 2,6-lutidine instead of **32**) revealed a CMD mechanism for the C–H activation step where transition states for *meta*- and *para*-C–H activation were favoured over those for *ortho*-C–H activation by 2.5 and 1.5 kcal mol^{-1}, respectively, a trend which was shared by other electron withdrawing groups (CO_2Me, COMe) also, except for F.[35] Recently, Yu and co-workers carried out a catalytic oxidative Heck reaction of a wide variety of arenes with ethyl acrylate using **35** as a privileged ligand.[36] Nitrobenzene produced a modest yield (**36**, 45%) but again with high *meta*-selectivity (*o* : *m* : *p* 0 : 14.1 : 1) (Scheme 9). Interestingly, reaction with *p*-nitroanisole occurred adjacent to the OMe group indicating electronic control.

2-Hydroxy-1,10-phenanthroline was used as a ligand for the oxidative Heck reaction of nitrobenzene which again showed a preference for the *meta*-substituted product (*o* : *m* : *p* 1 : 3.8 : 1).[37] 1,10-Phenanthroline was totally ineffective in this regard. An oxidative Heck reaction of nitrobenzene with a 1,1-disubstituted allyl amine has been reported by Lei *et al.*, leading to a *m*-nitro cinnamylamine product in moderate yield but with high *Z*-stereoselectivity.[38]

It thus transpires that for unsubstituted nitrobenzene, the oxidative Heck reaction (and the oxidative arylation reaction)

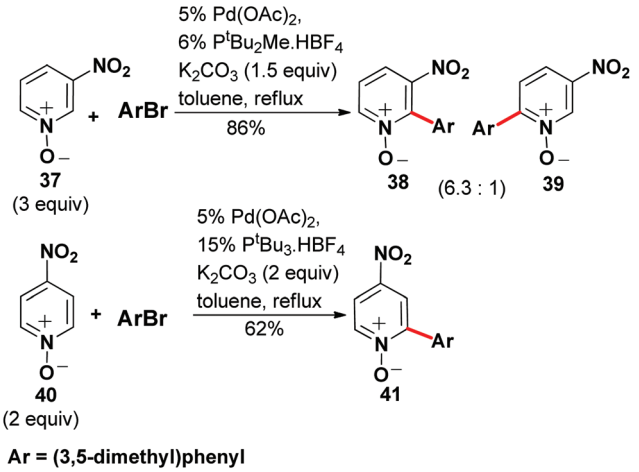
would be guided by preferential *meta*-C–H activation. For more encumbered nitroarenes, the electronic effects and acidity of adjacent C–H bonds could come into play.

2.3. C–H activation of heterocyclic nitroarenes

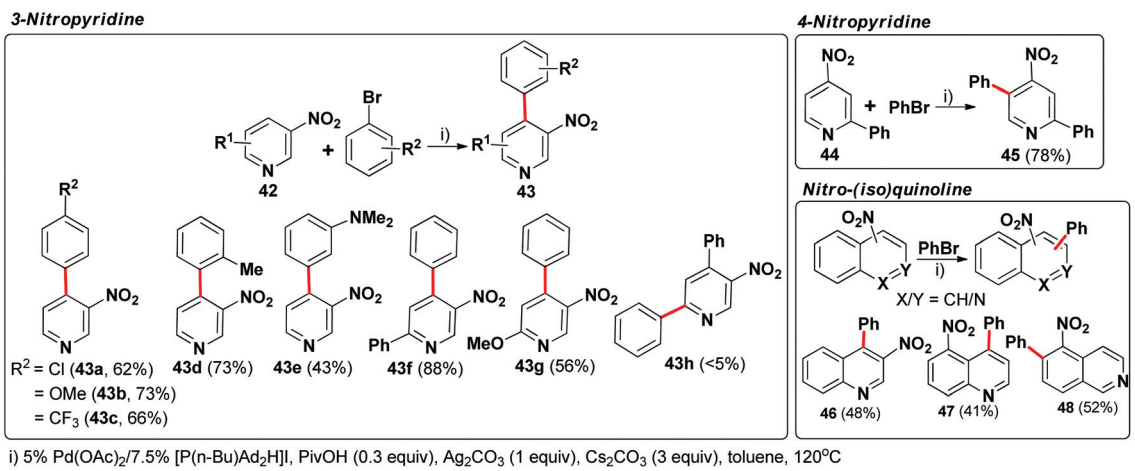
Heterocyclic motifs are widely found in drugs, natural products, biological entities and organic materials. Hence, a synthetic strategy for regioselective ring substitution of heterocycles, irrespective of their inherent electronic properties (electron-rich and electron-deficient), is in great demand. Towards this goal, C–H activation provided a powerful synthetic methodology for regioselective functionalization of various electron-rich and electron-deficient heterocycles without any pre-functionalization requirement.[39,40] From the pK_a considerations alone,[41] the C–H bonds of aromatic heterocycles are potentially more susceptible to the C–metalation reaction with transition metals than the benzenoid C–H bonds. The effect is likely to be further amplified in nitro-substituted heterocycles, enhancing their prospect in C–H activation reactions with high degrees of regioselectivity and overall efficacy.

2.3.1. Azines. While investigating the C–H arylation reactions of heterocyclic *N*-oxides, Fagnou and co-workers found that the C–H arylation of 3-nitropyridine *N*-oxide (**37**) preferentially occurred at the sterically hindered C2-position (*cf.* **38**, Scheme 10),[42a] pointing towards a supplementary directing role of the 3-nitro group. 3-CN and 3-F pyridine *N*-oxides also showed a similar regiochemical preference which is reminiscent of a co-operative effect previously observed with 3-nitro benzonitrile (*cf.* **11h**, Scheme 1).[21,24] 4-Nitropyridine *N*-oxide (**40**) gave 2-arylated product **41** only,[42b,c] demonstrating the superior directing ability of *N*-oxide. Suresh *et al.* carried out Pd-catalyzed decarboxylative heteroarylation of 3-nitropyridine *N*-oxide with 5-phenylthiophene-2-carboxylic acid which, again, led to a selective C2-arylated product.[42d] Subsequent deoxygenation of the *N*-oxide function in these products would lead to C2-aryl 3-nitropyridines, a regiochemical outcome that is complementary to the nitro directed C–H arylation of 3-nitropyridines (*cf.* Scheme 11).

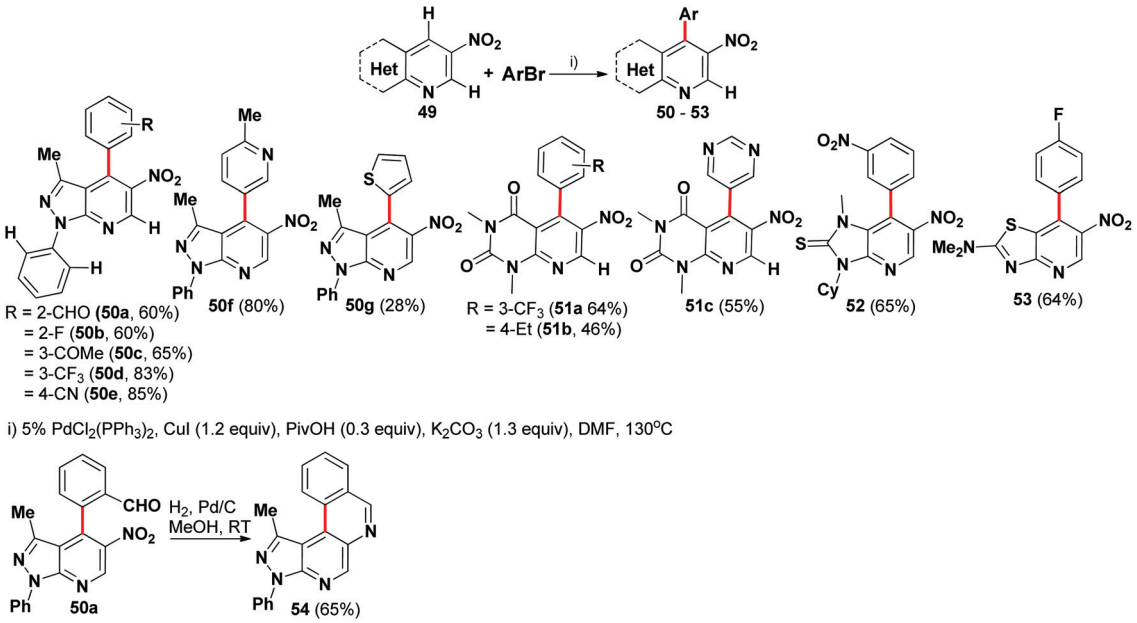
Soon after Fagnou's disclosures, the Sames group published a highly regioselective strategy for C–H arylation of pyridines and quinolines using nitro as the directing group (Scheme 11).[43] It was envisioned that in nitropyridines, C–metalation by the Pd-carboxylate catalyst should occur away from the ring nitrogen (electronic repulsion) at positions flanking the nitro group (high acidity), thereby ensuring high regioselectivity. Similar factors also govern the regioselectivity of the Directed *ortho*-Metalation (DoM) of pyridines.[44] In the event, C–H arylation of 3-nitropyridine (in a stoichiometric amount) with aryl bromides under the optimized reaction conditions ($Pd(OAc)_2$, P(*n*-Bu)Ad_2, PivOH, Ag_2CO_3, Cs_2CO_3, toluene, 120 °C) took place preferentially at C-4 (**42** → **43**) with < 10% of C-2 or C-5 attack.[43] The bulky P(*n*-Bu)Ad_2 ligand was essential for success as was Ag_2CO_3, the latter possibly acting as a Lewis acid for activating the 4-position *via* silver co-ordination with pyridyl nitrogen. Substituents at the C-2- or C-6-posi-



Scheme 10 Regioselective C–H arylations of nitropyridine *N*-oxides.



Scheme 11 Regioselective Pd-catalyzed C–H arylation reactions of nitro-pyridines and -quinolines.



Scheme 12 Regioselective Pd-catalyzed C–H arylation reactions of heterocycle-fused nitropyridines.

tions of pyridine were well tolerated (**43f,g**), whereas substituents at the 4-position, obviously, caused the shutdown of the C–H activation process (**43h**). For 4-nitropyridine, C–H arylation took place adjacent to the nitro group but away from a 2-substituent (**45**). 3(5)-Nitroquinoline and 5-nitroisoquinoline also underwent C–H arylation reactions with high regioselectivity but in moderate yields (**46–48**). Other electron withdrawing groups *e.g.* F, Cl or CN were also examined which, however, lacked the high efficacy shown by the nitro group.

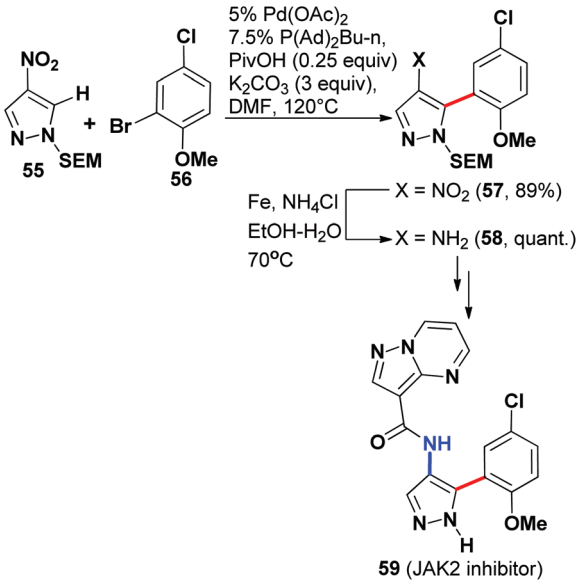
Iaroshenko *et al.* investigated the C–H arylation reaction of a wide variety of heterocycle-fused 3-nitropyridines and found C-4-arylation as the common regiochemical outcome (Scheme 12).[45] 5-Nitro-1-phenyl azaindazole was examined in detail due to the importance of the azaindazole scaffold in drug discovery. Optimization of reaction conditions with bromobenzene revealed a combination of $Pd(PPh_3)_2Cl_2$ as the catalyst, CuI as the Lewis acid additive and polar solvents like DMF to be ideal for carrying out these reactions, leading to C-4 arylated products **50a–g**, with little or no competition from the C-6 or *ortho*′-position of the *N*-phenyl group. $Ni(PPh_3)_2Cl_2$ lowered the yields, whereas Ru, Rh and Ir complexes were totally ineffective. Replacing the nitro group with aryl, CN or ester returned the starting materials only, reiterating the powerful influence of NO_2 as an activating-directing group in these systems. 3-Nitropyridine fused with pyrimidinedione, imidazothione and thiazole moieties also participated in this C–H arylation protocol to furnish the respective C-4 arylated products **51–53**. However, 3-cyano-5-nitro-7-azaindole gave a 50/50 mixture of C-2/C-4 arylated products. Among other nitro-substituted heteroarenes, only 2-nitrothiophene and *N*-methyl-2-cyano-4-nitropyrrole successfully underwent C–H arylation at C-3 and C-5 centers, respectively, whereas nitro derivatives of chromenones, pyrimidines, 7-dimethyamino quinoline, furan, azaindazolone and pyrazolo[1,5-*a*]pyrimidine all failed in this regard. The utility of 4-arylated products was demonstrated with 4-(2′-formyl)phenyl azaindazole (**50a**) which upon catalytic hydrogenation led to one-pot reduction and cyclization to furnish heterocycle fused phenanthridine **54** which promises interesting photophysical properties.

In view of the above, cross dehydrogenative biaryl couplings of 3-nitro-azines and the corresponding *N*-oxides, hitherto unexplored, appear to hold much synthetic promise. Only one example of cross dehydrogenative biaryl coupling between benzothiazole and 4-nitropyridine *N*-oxide is known.[46a] On the other hand, only one example of oxidative Heck reaction of 3-nitro-pyridine, specifically 6-methoxy-3-nitropyridine, leading to the C-2-vinylated product in low yield has been reported.[46b] The oxidative Heck reactions of 3-nitropyridines and in particular, 3-nitropyridine *N*-oxides are also promising prospects.

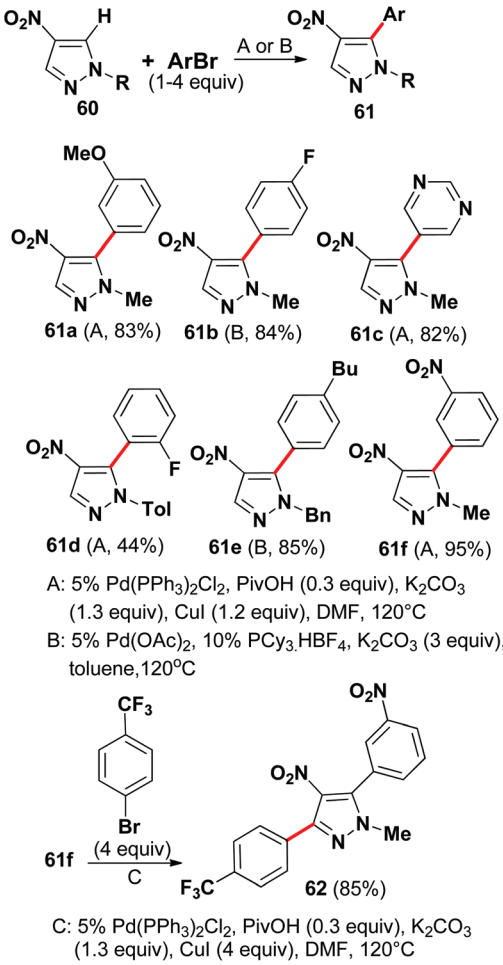
2.3.2. Azoles

2.3.2.1. Pyrazole. Nitro group directed C–H activation of azoles was first described by chemists from Genentech in 2012.[47] In order to prepare 4-amino-5-arylpyrazoles *viz*. **58**, required for the synthesis of the pyrazolo[1,5-*a*]pyrimidine-3-carboxamide class of JAK2 inhibitors **59**, the authors borrowed the Sames pyrazole strategy[48] and carried out Pd-catalyzed C–H arylation of SEM-protected 4-nitropyrazole **55** with bromoarene **56** to obtain 5-aryl-4-nitropyrazole **57** (89%) with high regioselectivity (Scheme 13). The latter was then reduced to the desired 4-aminopyrazole **58** in quantitative yield and coupled with pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid to obtain **59**.

In 2014, the groups of Iaroshenko and Joo, almost simultaneously, published their work on the C–H arylation reactions



Scheme 13 Regioselective C–H arylation of *N*-SEM-4-nitropyrazole (**55**) towards JAK2 inhibitor synthesis.

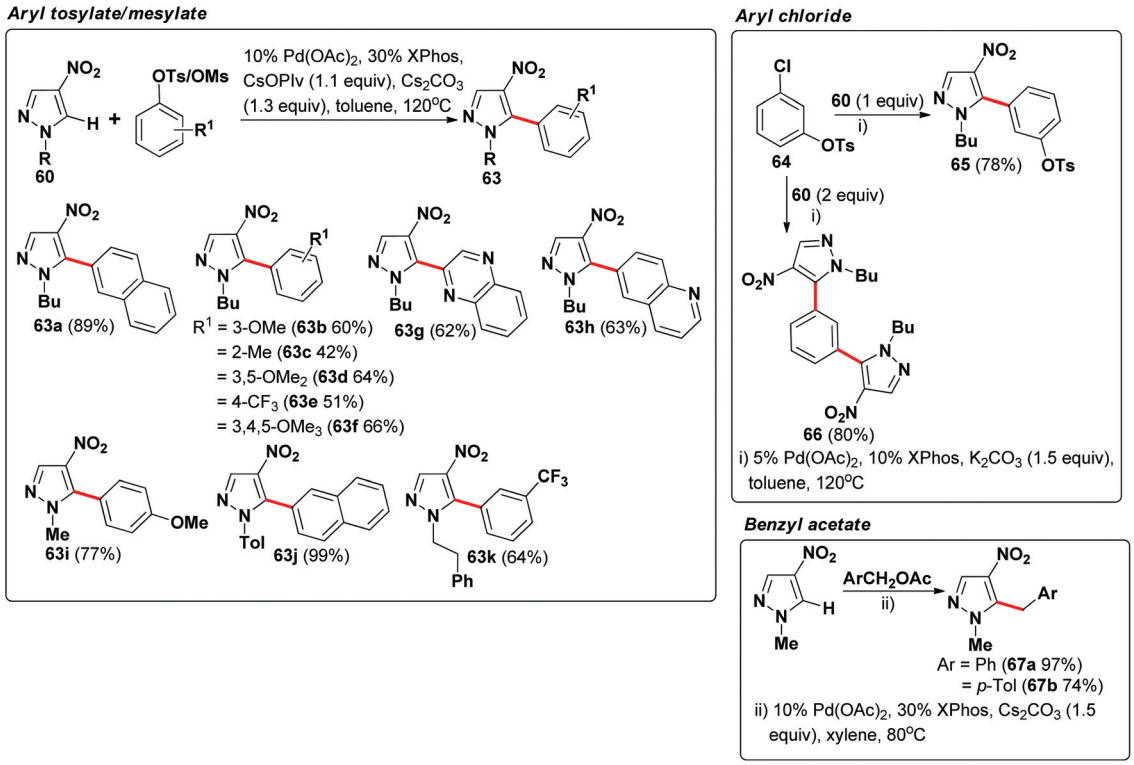


Scheme 14 Regioselective C–H arylations of 4-nitropyrazoles with aryl bromides.

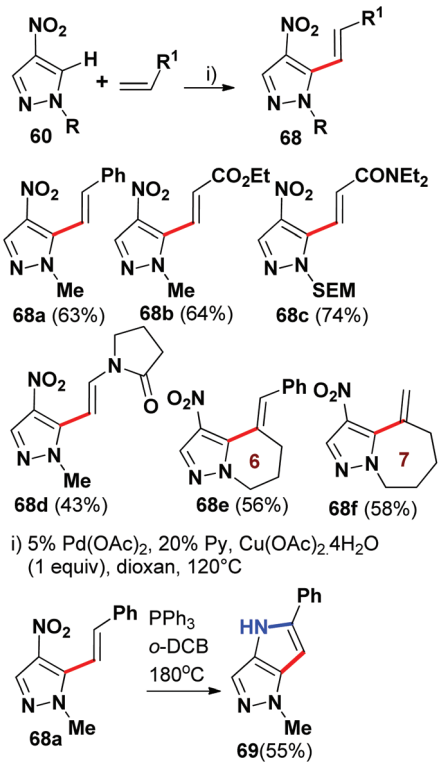
of 4-nitropyrazoles.[49] While Iaroshenko's group employed Pd$(PPh_3)_2Cl_2$ as the catalyst in DMF with stoichiometric CuI as the additive,[49a] Joo's group reported additive free conditions using cat. Pd$(OAc)_2$-PCy_3 in toluene,[49b] both recording good to high yields of products with exclusive C-5 selectivity (**61**, Scheme 14). With *N*-tolyl 4-nitropyrazoles, C–H arylation took place only at C-5 and not on the *N*-tolyl ring (*e.g.* **61c,d**). Ni$(PPh_3)_2Cl_2$, [Ru(p-cymene)Cl_2]$_2$ and [Rh(COD)Cl]$_2$ were also examined as catalysts which were either inferior or totally inactive.[49a] With selected 4-nitro-5-arylpyrazole products *e.g.* **61f**, Iaroshenko's group carried out further C–H activation reactions at C-3 which, however, required an excess of CuI (4 equiv.) as an additive to achieve a good yield of the unsymmetrical 3,5-diaryl pyrazole **62** (Scheme 14).[49a] The latter result may have important bearings on the diversity oriented synthesis of pyrazole scaffolds. C–H arylation of 4-nitropyrazole was later investigated by Kalyani's group by employing XPhos as the ligand (10% Pd$(OAc)_2$, 30% XPhos, Cs_2CO_3/K_2CO_3, toluene, 120 °C) which enabled aryl tosylates, mesylates and even chlorides to be used as coupling partners to obtain uniformly high yields of C-5-arylated products (**63**, **65**, Scheme 15).[22] The yields are comparable to those obtained using aryl bromides (*cf.* Scheme 14).[49] *N*-Methyl pyrazole was found to be inert under these conditions, reiterating the need for the nitro group as the directing-activating group. Aryl chlorides were found to be more reactive than aryl tosylates as shown by intramolecular completion experiment (**64** → **65**). Double C–H arylation of 4-nitropyrazole with 3-chloro-phenyl tosylate (**64**) was also demonstrated leading to bis-(4-nitro)pyrazolyl arene **66** in high yield. The authors also demonstrated regioselective C-5-benzylation of 4-nitropyrazoles with benzyl acetates in good yields (**67**, Scheme 15).[22] Joo and co-workers demonstrated C-5-benzylation and -allylation of 4-nitropyrazole with benzyl chlorides and allyl chlorides/acetates.[50] Again, the nitro group on pyrazole was essential for success since other electron withdrawing groups *viz.* Cl or ester were much inferior *vis-à-vis* the nitro group.

A recent report on the regioselective C-5-alkylation of 4-nitropyrazoles with ethyl chloroacetate, either *via* a vicarious nucleophilic substitution protocol or better, *via* a Pd-catalyzed process, has appeared in the literature to synthesize 4-nitropyrazole-5-acetic acid esters.[51]

The oxidative Heck reaction of 4-nitropyrazoles was reported by Joo and co-workers with interesting synthetic ramifications (Scheme 16).[52] The reactions were best carried out with cat. Pd$(OAc)_2$ in the presence of 10% pyridine as an additive and Cu$(OAc)_2$ as a stoichiometric oxidant to furnish C-5-vinylated products **68** in good yields. However, other substituents, *viz.* Br, Cl, Ac, ester, Me, and Ph, present at the 4-poisition of pyrazole, worked equally well, perhaps reflecting on the Sames C–H activation strategy on pyrazoles[48] and the relative ease of oxidative Heck reactions on this activated heterocycle. Intramolecular oxidative Heck reactions of 4-nitropyrazoles bearing *N*-tethered olefins were also feasible which may



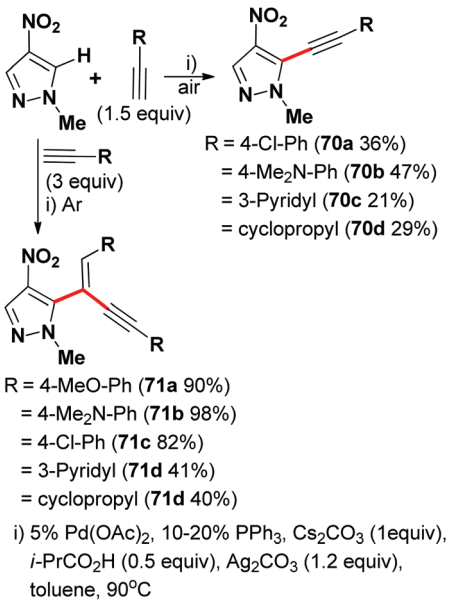
Scheme 15 Regioselective C–H arylation and benzylation of 4-nitropyrazoles with aryl/benzyl tosylates/mesylates, chlorides and acetates.



Scheme 16 Regioselective inter- and intra-molecular oxidative Heck reactions of 4-nitropyrazoles.

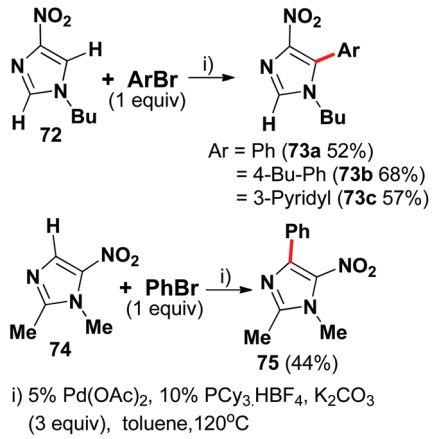
provide a novel synthetic access to annulated pyrazoles, *viz.* **68e,f**. The Sundberg-type nitrene cyclization of the Heck product **68** was also demonstrated to furnish pyrrolo[3,2-*c*]pyrazole **69** in 55% yield.

Oxidative C–H alkynylation of 4-nitropyrazoles was reported by Joo and co-workers (Scheme 17).[53] With 1.5 equiv. of a term-



Scheme 17 Oxidative C–H alkynylations of 4-nitropyrazoles.

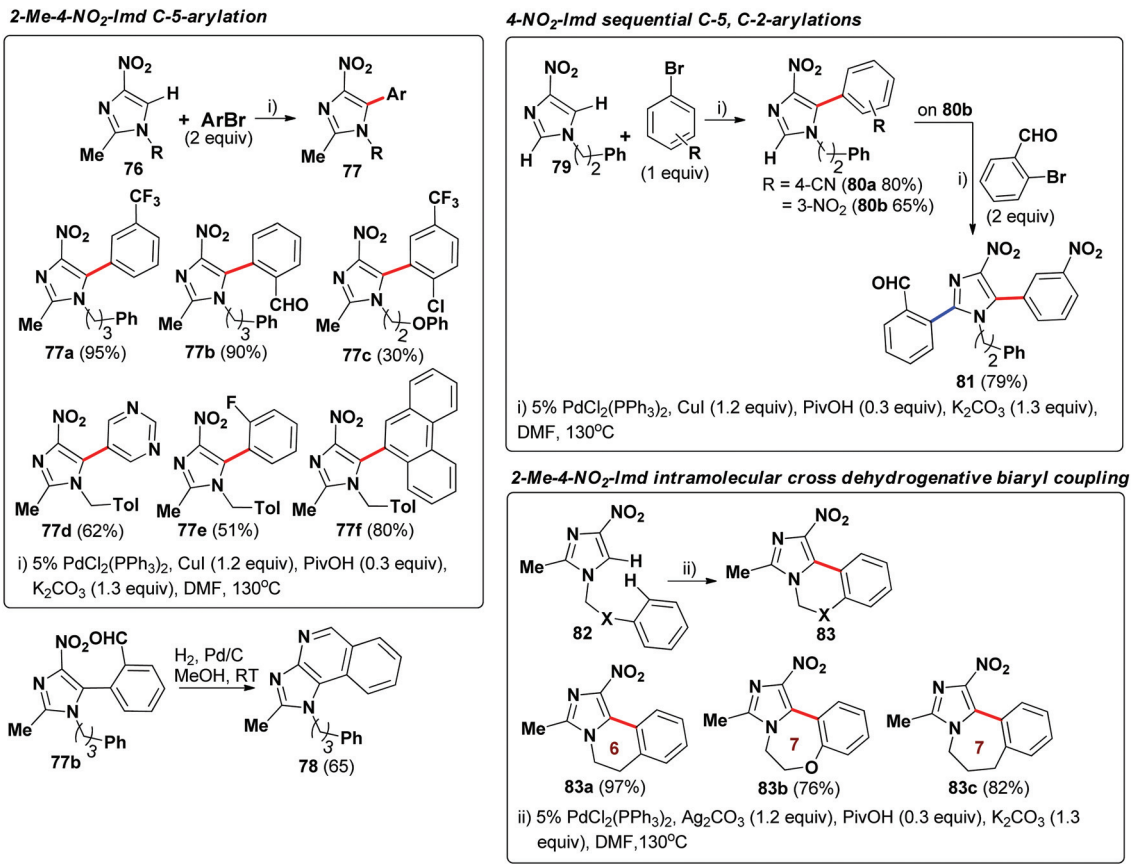
inal alkyne, C-5-alkynyl pyrazoles **70** were produced in moderate yields together with the formation of *ca.* 10–20% of alkyne homocoupling side products. Ag_2CO_3 and isobuytyric acid additive (better than PivOH) were both essential for success. When an excess of alkynes was used, sequential homocoupling to 1,3-diynes followed by stereo- and regioselective arylation of 1,3-diynes with 4-nitropyrazole took place to deliver 4-nitropyrazole substituted *E*-eneynes **71** in high yields. Arylacetylenes were found to work better than alkylacetylenes in these reactions.



Scheme 18 Regioselective C–H arylation of 4-nitroimidazoles with aryl bromides.

2.3.2.2. Imidazole. C–H arylation of 4-nitroimidazoles was first reported by Joo's group in 2014 but with only a handful number of examples.[49b] Synthetically useful yields of C-5-arylated products **73** (50–60%) could be obtained (Scheme 18), although 2,5-diarylated products (10–15%) were also formed. A 5-nitroimidazole substrate **74** also underwent C–H arylation at C-4 (**75**, 44%) but *N*-Bu imidazole failed completely, pointing to the crucial requirement of the nitro substituent for success. Kalyani's group later showed that aryl tosylates and mesylates could also be used for C-5-arylation of 4-nitroimidazoles.[22] A Cu_2O/Pd-Fe_3O_4 nanocomposite was recently used for C-5 arylation of *N*-butyl 4-nitroimidazole with recycling options.[54]

In 2015, Iaroshenko's group published a detailed report of their studies on the C–H arylation of 4-nitroimidazoles.[55] Using conditions earlier employed in their C–H arylation reactions of 4-nitropyrazoles (Method A, Scheme 14) and with 2-Me-4-nitroimidazoles **76** as substrates, the authors reported high yields (up to 95%) of C-5-arylated products **77** with a variety of aryl and heteroaryl bromides (Scheme 19).[55] The use of CuI as a stoichiometric additive was found to be crucial for success. $NiCl_2(PPh_3)_2$ could also be used as a catalyst but gave



Scheme 19 Regioselective C–H arylation and intramolecular cross dehydrogenative biaryl couplings of 4-nitroimidazoles.

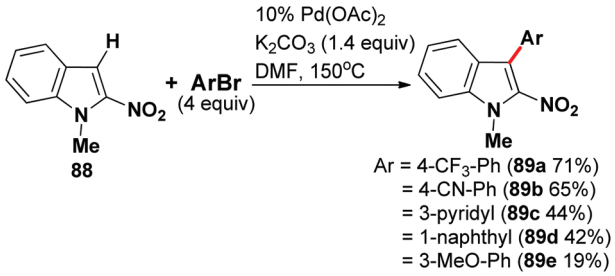
somewhat lower yields. While the nitro group in 5-arylated products **77** could be easily reduced *via* catalytic hydrogenation to NH_2 and NMe_2 (with formalin), the 5-(*o*-formyl)phenyl product **77b** smoothly cyclized to imidazo[4,5-*c*]isoquinoline **78** under these conditions.

Regioselective C–H arylation was then carried out with the unbiased 4-nitropyrazole **79** bearing a competitive C–H bond at C-2, which gratifyingly delivered C-5-arylated products **80a,b** in good yields, clearly displaying the efficacy of the 4-nitro group in directing C–H activation at the C-5 position (Scheme 19).[55] The product **80b** then underwent a second C–H arylation at C-2, to furnish the unsymmetrical 2,5-diaryl-4-nitroimidazole **81**. Using excess aryl bromides with **79**, symmetrical 2,5-diaryl derivatives could be directly obtained. For comparison, the authors also explored the Suzuki couplings of 5-bromo-4-nitroimidazoles which while delivering good yields of 5-aryl-4-nitroimidazoles required additional steps, including isomer separation, for preparation of 5-bromo-4-nitroimidazole.

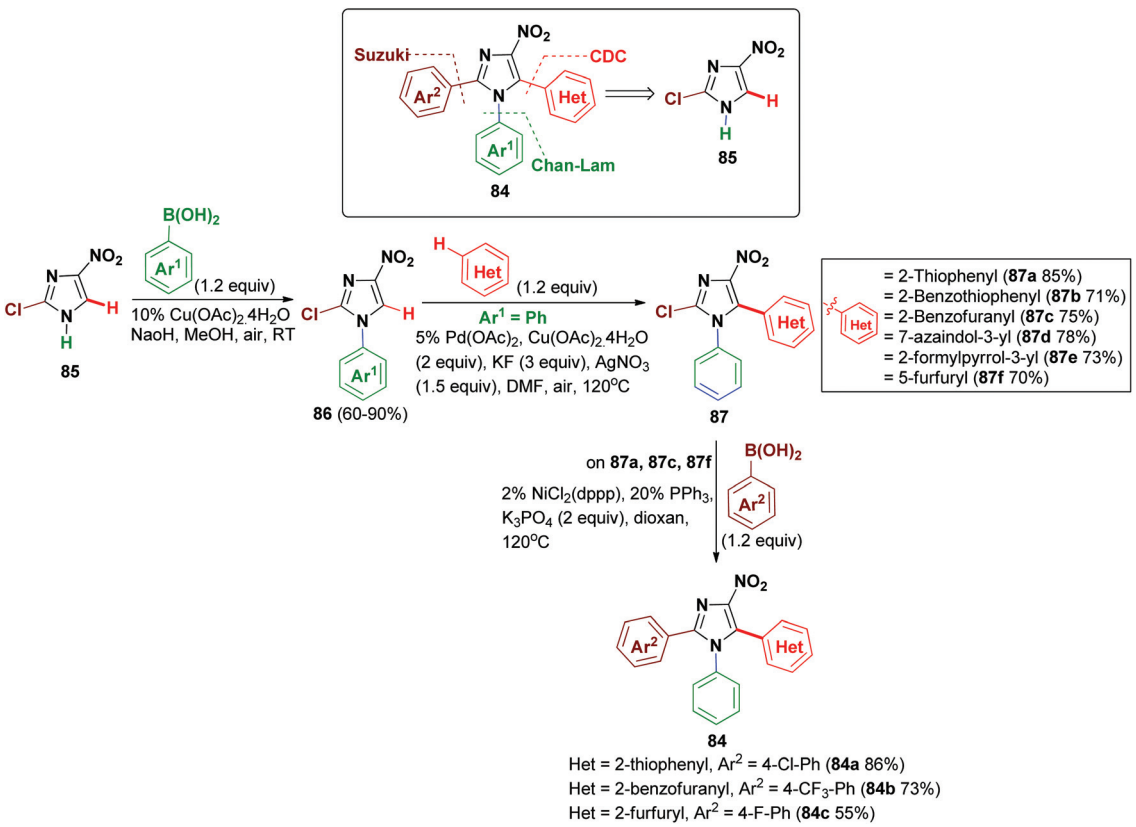
In an interesting development, Iaroshenko *et al.* also reported on intramolecular cross dehydrogenative biaryl coupling with 4-nitroimidazole derivatives **82**, *N*-tethered with pendant phenyl groups, to furnish fused tricyclic nitroimidazoles **83a–c** in good yields (Scheme 19).[55] Ag_2CO_3 (in lieu of CuI) was found to be a crucial additive in these reactions to achieve good yields of the desired products.

It may be noted that regioselective C–H benzylation and acetate coupling of 4-nitroimidazoles (at C-5) were also reported, in parallel, during C–H activation studies on 4-nitropyrazoles.[22,50,51]

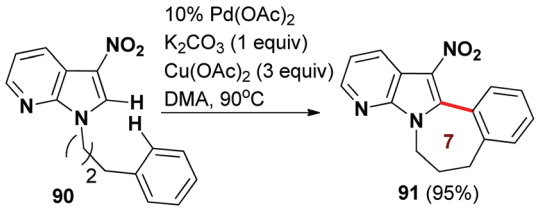
In a broad research objective directed towards the synthesis of polyaryl heterocycles of medicinal and photoelectronic interests,[56] we envisaged a programmed synthesis of polysubstituted imidazoles,[57] specifically 1,2,5-triaryl imidazoles **84**, from readily available 2-Cl-4-NO_2-imidazole scaffold **85** *via* sequential application of three mutually orthogonal arylation protocols *viz*. Chan–Lam coupling (at N-1), nitro directed CDC reaction (at C-5) and Suzuki coupling (at C-2) (Scheme 20).[58] Towards this end, various aryl groups Ar^1 could be easily intro-



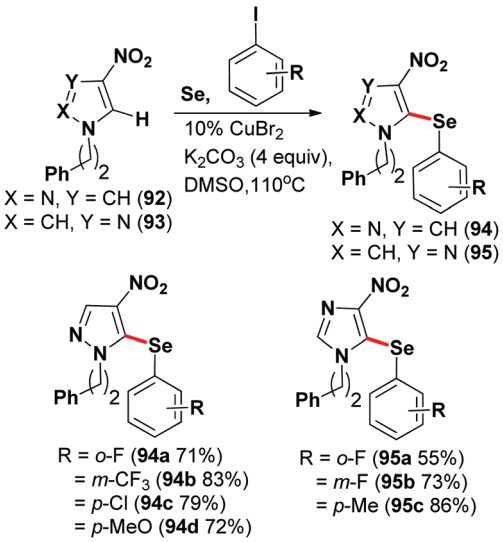
Scheme 21 Regioselective C-3 arylation of 2-nitroindole.



Scheme 20 Programmed synthesis of 1,2,5-triarylimidazoles **84** *via* a nitro directed CDC reaction with heteroarenes.



Scheme 22 Nitro assisted intramolecular oxidative biaryl coupling on the azaindole scaffold.

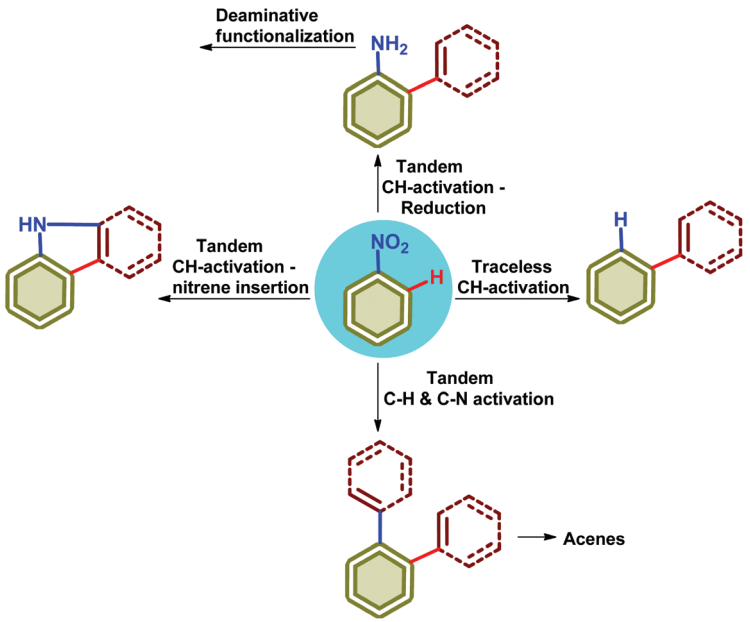


Scheme 23 Regioselective Cu-catalyzed C–H selenoarylation of 4-nitroazoles.

duced on N-1 of **85** *via* Chan–Lam coupling (to give **86** in high yields). The crucial cross dehydrogenative coupling of **86** (at C-5) with heteroarenes was then carried out (5% $Pd(OAc)_2$, Cu $(OAc)_2{\cdot}4H_2O$, KF, $AgNO_3$, DMF, 120 °C) using various heteroarenes, including oxidation prone indole and pyrrole, which underwent highly regioselective nitro directed CDC with **86** (Ar^1 = Ph) at C-5 to provide high yields of N-1, C-5-diaryl imidazole derivatives **87a–f**. Both KF and $AgNO_3$ were required as additives, in addition to $Cu(OAc)_2$ as a stoichiometric oxidant, to obtain high yields in these CDC reactions. Finally, the third aryl group (Ar^2) was introduced at C-2 either *via* Ni- or Pd-catalyzed Suzuki coupling with different $Ar^2B(OH)_2$ delivering 1,2,5-triaryl imidazoles **84a–c**. The programmed nature of this strategy allows introduction of C-5 and C-2 aryl groups as per convenience *i.e.* first C-5 then C-2 or *vice versa* adding versatility towards the diversity oriented synthesis of triaryl imidazole products. After serving its role as a CDC directing group, the nitro in **84** could be potentially utilized in annulation reactions (*via* the Cadogan protocols) or in denitrative couplings, leading to per-substituted or ring annulated imidazoles with potentially interesting photoelectronic properties.

Among benzo-fused azoles, C–H arylation of *N*-Me-2-nitroindole (**88**) with aryl bromides was reported to deliver 3-aryl derivatives **89** in moderate to good yields (Scheme 21).[59a] However, only electron deficient aryl bromides gave synthetically useful yields. Arylation of 2-nitrobenzofuran (at C-3) was also reported.[59b] Pd-Catalyzed coupling of *N*-Bn-3-nitroindole with $ClCH_2CO_2Et$ reportedly gave ethyl *N*-Bn-3-nitroindolyl-2-acetate in 48% yield.[51]

Pintori and Greaney published an interesting nitro directed intramolecular oxidative biaryl construction on a 3-nitro-7-azaindole scaffold **90**, bearing a *N*-tethered terminal phenyl group (Scheme 22).[60] Among other activating groups (CHO &



Scheme 24 Synthetic prospects of the merged C–H activation and NO_2 transformations of nitro(hetero)arenes.

CN), the nitro group proved to be the most effective, furnishing 7-membered ring cyclized product **91** in 95% yield *via* double C–H activation.

All C–H activation reactions described above have so far dealt with new carbon–carbon bond formations on nitroarenes. In comparison, direct carbon–heteroatom bond formation on nitroarenes is confined to only one report on Cu-catalyzed arylselenation of 4-nitro-pyrazoles and -imidazoles.[61] In that work, a $CuBr_2$ catalyzed reaction of nitroazoles with a combination of selenium powder and aryl iodides produced a series of 5-arylseleno azoles **94** & **95** in high yields (Scheme 23).[61] Alternatively, diaryl diselenides could also be used to install the 5-selenoaryl moiety. 1-Phenethylpyrazole or its 4-ester derivative gave poor yields of selenoarylation, showcasing the crucial activating role of the 4-nitro substituent in **92**.

Nitro directed C–H activation reactions of pyrazoles and imidazoles have reaped rich benefits both in terms of efficacy and further transformative manipulations that have enabled facile access to condensed heterocycles. Again, regioselective dehydrogenative biaryl coupling of nitro-azoles, exemplified in Schemes 20 and 22, appears to hold much promise as a concise method for the synthesis of hetero-biaryl motifs without pre-functionalization requirements.

3. Conclusions and outlook

The existing landscape of C–H activation of nitroarenes is presented in this review. Although an under-developed terrain, many examples of nitro assisted *ortho*-arylation, -allylation, -benzylation/alkylation as well as regioselective oxidative Heck and arylation reactions on nitroarenes, in particular nitro-substituted heteroarenes, have been reported in the literature, which strongly support the C–H activation strategy on nitroarenes. Given the fact that nitroarenes are cheap commercial chemicals, C–H activation reactions of nitroarenes promise broad synthetic ramifications. Firstly, this unveils C–H activation as an attractive new strategy for regioselective ring substitution of nitroarenes beyond the existing narrow domains of S_NAR and S_NArH reactions, both in terms of efficacy and functional group tolerance. Secondly, regioselective C–H functionalization of nitro-substituted (hetero)arenes can be effectively programmed for diversity oriented synthesis of multiaryl and condensed heterocycles of medicinal and photophysical interest (*cf.* Schemes 14, 19 and 20). Thirdly and most importantly, post C–H activation, the NO_2 group can be transformed into various functional groups or used in a Cadogan-type heteroannulation or engaged in denitrative Pd-catalyzed coupling,[9] providing unique opportunities to use NO_2 as a transformable multitasking directing group.[62] As illustrated in Scheme 24, tandem nitro assisted C–H activation reactions and subsequent manipulations of the nitro group can potentially achieve otherwise difficult synthetic objectives in aromatic chemistry *viz*. *o*-teraryl synthesis, convergent assembly of (hetero)acenes (*cf.* Scheme 3), synthesis of polycondensed heterocycles, *etc*. Hopefully, this review would entice organic chemists to conduct further explorations in this area and expand the existing repository, especially nitro directed cross dehydrogenative (hetero)biaryl coupling, while addressing existing limitations.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

S. S. thanks IIT Dhanbad for the warm hospitality. P. D. thanks the Science and Engineering Research Board (SERB), New Delhi (EMR/2017/002533) and IIT Dhanbad (FRS(121)/2018-19/AC) for research grants.

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