HHS Public Access

Author manuscript

J Am Chem Soc. Author manuscript; available in PMC 2024 January 11.

Published in final edited form as:

J Am Chem Soc. 2023 January 11; 145(1): 41–46. doi:10.1021/jacs.2c12450.

Tandem C/N-Difunctionalization of Nitroarenes: Reductive Amination and Annulation by a Ring Expansion/Contraction Sequence

Gen Li,

Marissa N. Lavagnino,

Siraj Z. Ali,

Shicheng Hu,

Alexander T. Radosevich*

Department of Chemistry, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, MA 02139, United States

Abstract

A synthetic method for the reductive transformation of nitroarenes into *ortho*-aminated and -annulated products is reported. The method operates via the exhaustive deoxygenation of nitroarenes by an organophosphorus catalyst and a mild terminal reductant to access aryl nitrenes, which after ring expansion are trapped by amine nucleophiles to give dearomatized 2-amino-3H-azepines. Treatment of these ring-expanded intermediates with acyl electrophiles triggers 6π electrocyclization to extrude the nitrogen atom and restore aromaticity of the phenyl ring, delivering via C–H activation 2-aminoanilide and benzimidazole products—important scaffolds in industrially relevant and bioactive molecules.

Graphical Abstract

*Corresponding Author: radosevich@mit.edu.

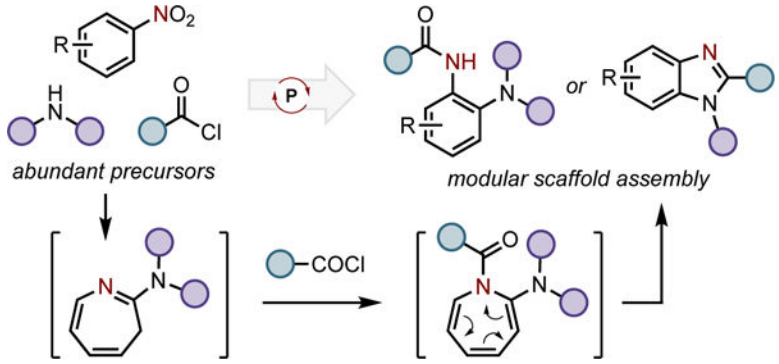
ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website at http://pubs.acs.org.

General methods and synthetic procedures (.pdf).

^{1}H, ^{13}C, ^{19}F and ^{31}P NMR spectra (.pdf).

The authors declare no competing financial interest



Nitroarenes are readily-accessed and versatile starting materials for synthesis.[1] The nitro moiety itself can be transformed through direct reductive transformation[2–3,4] or *ipso* substitution[5] to provide routes to a range of synthetically useful benzenoid intermediates (Figure 1A, a). Alternatively, the nitro moiety can be used to facilitate C–H functionalization reactions[6] that decorate the aryl periphery with retention of the nitro group.[7] Such methods include vicarious nucleophilic substitution (S_NAr^H, Mąkosza reaction), oxidative nucleophilic substitution of hydrogen (ONSH) reactions,[8,9] and directed transition metal-catalyzed C–H functionalization (Figure 1A, b).[10,11] A valuable subclass of nitroarene functionalization reactions accomplishes both nitro group reduction and proximal C–H functionalization simultaneously, permitting annulation as exemplified in the Bartoli indole synthesis[12] and catalytic indole-forming methods (Figure 1A, c).[13] To move beyond indole synthesis, a complementary annulative approach to nitroarene C/N-difunctionalization would ideally provide a synthetically modular method for the synthesis of heterocyclic ring systems, providing the synthetic chemist with control over the functionality incorporated into annulated products (Figure 1A, d).

Towards this goal, a one-pot, three-component coupling protocol utilizing commercially available components was conceived, which relies on the potential of transient nitrogen intermediates—formed under mild conditions from abundant nitroarenes—to participate both as direct sites of bond formation and as indirect activators of proximal sites (Figure 1B). On the basis of prior work,[14] we expected that a redox-active organophosphorus catalyst could drive exhaustive deoxygenation of a nitroarene substrate by P(III)/P(V) cycling[15] to yield a high-energy arylnitrene intermediate (Figure 2). Commonly generated by direct photolytic decomposition of phenylazide,[16]

Phenylnitrene[17] (**I**) is well-known to isomerize to benzazirine[18] (**II**) and dehydroazepine[19] (**III**) valence tautomers, which are susceptible to interception by nucleophilic trapping agents such as amines to give 2-amino-3H-azepines (**V**) by ring expansion.[20–21,22] Subsequent isomerization of **V** was envisioned on the conjecture[23] that an azepine-to-azanorcaradiene 6π electrocyclization[24] (**VI**→**VII**) would be favored by *N*-acylation, and that decomposition of the fused bicyclic aminal **VII** could evolve with rearomatization of the arene core.[25] The resulting 2-aminoanilide product **VIII** is then poised to undergo thermal cyclization under established conditions to arrive at the desired benzimidazole product.

Overall, this synthetic approach would result in a reductive amination of the substrate nitroarene, in which both nitro group reduction and C(sp^2)–H amination are accomplished through a transient ring expansion of the original aromatic system. The method presents a complement to recent work by Burns,[26] which leverages the intermediacy of the azepine ring to perform a nitrogen-for-carbon switch to yield 2-aminopyridines upon ring contraction. Here, we report the development of a one-pot synthetic method for the reductive C/N-difunctionalization of nitroarenes via the intermediacy of high-energy arylnitrenes.[27] This ability to generate arylnitrenes from nitroarenes under thermal catalytic conditions enables an expedient entry to 2-aminoanilide and benzimidazole products scaffold useful in pharmaceutical discovery.[28,29]

In prior work from our group, we established that reductive functionalization of nitroarenes with primary and secondary amine nucleophiles under conditions of P(III)/P(V)=O redox cycling proceeds by direct N-functionalization, culminating in N–N bond formation to yield unsymmetrical hydrazine products.[4f] However, as exemplified by the reaction of 4-trifluoromethylnitrobenzene (**2**) and diethylamine (**3**), we find that related conditions (15 mol % of 1,2,2,3,4,4-hexamethylphosphetane P-oxide **1**·[O][30] as catalyst, 2.0 equivalents of phenylsilane as terminal reductant) but with omission of an explicit Brønsted acid[31] lead instead to 2-diethylamino-5-trifluoromethyl-3H-azepine (**4**) in 78% yield. Presumably, under these conditions, the nitroarene **2** is iteratively deoxygenated by the P(III)/P(V)=O redox catalyst to generate the corresponding arylnitrene,[4b] which then evolves along the sequence indicated in Figure 2A to the 2-amino-3H-azepine. These thermal P(III)/P(V)=O catalytic conditions can be applied broadly for formation of 2-substituted-3H-azepines; a synthetic scope for this conversion is included in the SI (Figures S1 and S2).

Importantly, as shown in Figure 2C, the conditions optimized for the formation of azepine **4** could be extended to a two-part synthetic expansion/contraction synthetic sequence, achieved in a single reaction vessel. Specifically, reaction of nitroarene **2** and diethylamine (**3**) with 15 mol% of 1,2,2,3,4,4-hexamethyl phosphetane P-oxide (**1**·[O]) and 2.0 equiv of phenylsilane in *t*-BuOAc for 12 h, followed by a solvent swap to PhMe and addition of 2.0 equiy each of acyl chloride **5** and DABCO lead directly to isolation of *ortho*-aminoanilide **6** in 78% yield (0.5 mmol scale). As a synthetic transformation, this manipulation brings together readily available nitroarene substrates like **2** with exogenous amines and acyl electrophiles to assemble highly decorated products in a modular fashion by tandem C/N-difunctionalization of the nitroarene substrate.

The scope and potential utility of this method are exemplified in Figures 3–5. 2-Aminoanilide products are reliably accessed by assembly from a range of nitroarenes, secondary amines, and acyl electrophiles (Figure 3). With respect to the amine component, beyond the use of diethylamine (**7**, **8**) as a trapping amine nucleophile, several of the most prevalent secondary amine heterocycles found in pharmaceuticals including piperidine (**9, 10, 14**), piperazine (**11**), and morpholine (**15–17**) derivatives are also readily accessed. Arylalkylamine (**13**) derivatives are similarly incorporated, but less nucleophilic diarylamines are insufficiently reactive to trap the benazirine/dihydroazepine intermediate. In terms of electrophilic reaction partners, substituted benzoyl (**7–9**, **11–12**,

14–15) and related heteroaryl derivatives (**16**) are viable partners, as are alkanoyl (**10**) and fluoroalkanoyl (**13**) compounds, providing (fluoro)acylated products in good yields.

In terms of regiochemistry, nitroarenes bearing a symmetrical substitution patterns only generate one isomer following the ring expansion/contraction reaction sequence (for instance, **7**-**13**, **16**). However, for nitroarene substrates with substitution lacking mirror symmetry, two possible regioisomeric products are in principle possible. To a first approximation, the position of apparent C-H amination is dictated by steric considerations. For instance, product **14** is formed in as a single regioisomer, as a result of the insertion of arylnitrene to the sterically less encumbered position distal from the methyl substituent. Nevertheless, in the absence of a large steric bias, electronic effects dominate the regioselectivity, as exemplified by the product **15**, in which arylnitrene prefers the insertion at the more electronically rich position. Consistent with electronic arguments, the quinolyl substrate (**17**) exhibits regioselectivity with apparent C-H amination proximal to the ring fusion. The unobserved regioisomer of the C/N-difunctionalization would need to arise from a benzazirine intermediate that enforces quinoidal structure on the heterocyclic system, whereas as the benzazirine leading to the observed C/N-difunctionalization product does not require disruption of heteroaromatic stabilization of the pyridyl subunit. Taken together, the C/N-difunctionalization method proceeds with predictable regiochemical preference if both steric and electronic factors are adequately considered.

Reactions with primary amines similarly enable the formation of corresponding 2-aminoanilide products, provided that the acyl electrophile employed is sterically encumbered (for instance, 2,6-chlorobenzoyl as in **12**). However, when a primary amine nucleophile (e.g. benzylamine) is employed in conjunction with a sterically unencumbered acyl moiety (e.g. trifluoroacyl) then a subsequent cyclodehydration reaction spontaneously ensues under the reaction conditions to furnish a benzimidazole (**18**, Figure 4). A brief optimization revealed that the azepine contraction and subsequent aromatization/annulation could be achieved in a simple one-pot procedure (Table S2). This strategy could be applied to form benzimidazoles directly from nitroarenes, secondary amines, and acyl electrophiles (Figure 4); benzimidazole derivatives with N-benzyl (**18**-**20**, **23**-**24**), N-aryl (**21**), and N-alkyl (**22**) substitution could be prepared with the same reductive selectivity for the nitro moiety compared to other reducible (ester **19**, amide **24**) functionality. With 3-nitroanisole as substrate, the reductive C/N-difunctionalization proceeds with excellent regioselectivity to give 1,2,6-trisubstituted benzimidazoles (**25**, **26**) as the major product. Variation of the acyl electrophile allows control over substitution at the 2-position of the benzimidazole.

The modularity and regiochemical predictability of the reductive C/N-difunctionalization allows the benzimidazole to be viewed as a retron accessible by an annulative C/N-difunctionalization transform from simple nitroarenes possessing accessible *ortho* C-H positions. Practically, this feature may have use for the preparation of benzimidazoles with challenging substitution patterns, for instance where direct N-functionalization of the parent N–H benzimidazole would be unselective or unfavorable due to steric considerations affecting the pseudosymmetry of the N1 and N3 positions.[32] In this vein, Figure 5 collects examples of various benzimidazole derivatives synthesized by this protocol with sterically encumbered N-alkyl substituents in the presence of 2-and 7-substitution. Annulated systems

with N-substitution next to primary (**27**, **28**, **31**, **32**) and secondary (**29, 30**) carbon sites could be synthesized in synthetically useful yields. Collectively, this modular one-pot procedure could be used to access a variety of 2-aminoanilides and benzimidazoles from a range of nitroarenes, primary and secondary amines, and acyl electrophiles.

In summary, the results described above constitute a novel strategy for reductive C–H amination of nitroarenes that leverages tandem C- and N-functionalization to construct valuable 2-aminoanilide and benzimidazole products from readily accessible reaction partners. Integral to the success of this method is the efficient thermal generation of reactive arylnitrenes from nitroarenes, and the ability to achieve ring contraction and aromatization of 3H-azepine intermediates. Taken together, these developments enable new expedient routes to 2-aminoanilides and benzimidazoles via a novel synthetic sequence for C–H functionalization and annulation. In connection with our efforts to explore the biphilic catalytic reactivity of phosphetanes for reductive *O*-atom transfer processes via the P(III)/P(V)=O redox cycling, this study portends future developments in tandem C/N-difunctionalization of nitroarenes and homologues to access a wide range of elaborated products.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

Financial support was provided by the National Institutes of Health under Award Number GM114547. G.L. thanks Bristol Myers Squibb for a graduate fellowship. M.N.L. thanks the National Institute of General Medical Sciences of the National Institutes of Health for support under Award Number F32 GM147996. We are grateful to Drs. P. Müller and M. Drance (MIT) for assistance with crystallographic data collection and refinement.

REFERENCES

1. Ono N The Nitro Group in Organic Synthesis; Wiley, New York, 2001.
2. Stoichiometric main group metal approaches, see: (a) Sapountzis I; Knochel P A New General Preparation of Polyfunctional Diarylamines by the Addition of Functionalized Arylmagnesium Compounds to Nitroarenes. J. Am. Chem. Soc 2002, 124, 9390. [PubMed: 12167031] b Doyle W; Staubitz A; Knochel P Mild Synthesis of Polyfunctional Benzimidazoles and Indoles by the Reduction of Functionalized Nitroarenes with Phenylmagnesium Chloride. Chem. Eur. J 2003, 9, 5323. [PubMed: 14613142] c Kopp F; Sapountzis I; Knochel P Preparation of Polyfunctionalized Amines by the Addition of Functionalized Organomagnesium Reagents to Nitrosoarenes. Synlett, 2003, 885.d Sapountzis I; Knochel P A New Method for the Selective Amination of 1,3- and 1,4-Dinitrobenzenes and Protected Nitroanilines Leading to Polyfunctional 1,3- and 1,4- Disubstituted Anilines. Synlett 2004, 955.e Dhayalan V; Saemann C; Knochel P Synthesis of polyfunctional secondary amines by the addition of functionalized zinc reagents to nitrosoarenes. Chem. Commun 2015, 51, 3239.f Gao H; Xu Q-L; Ess DH; Kürti L Transition-Metal-Free, Low-Temperature Intramolecular Amination of Aromatic C-H Bonds: Rapid Synthesis of Fused Heterocycles." Angew. Chem. Int. Ed 2014, 53, 2701.g Rauser M; Ascheberg C; Niggemann M Electrophilic Amination with Nitroarenes. Angew. Chem., Int. Ed 2017, 56, 11570.h Rauser M; Ascheberg C; Niggemann M Direct Reductive N-Functionalization of Aliphatic Nitro Compounds. Chem. Eur. J 2018, 24, 3970. [PubMed: 29378085] i Rauser M; Warzecha DP; Niggemann M O_2-Mediated Oxidation of Aminoboranes through 1,2-N Migration. Angew. Chem., Int. Ed 2018, 57, 5903.j Rauser M; Eckert R; Gerbershagen M; Niggemann M Catalyst-Free Reductive Coupling of

Aromatic and Aliphatic Nitro Compounds with Organohalides. Angew. Chem., Int. Ed 2019, 58, 6713.

3. Catalytic transition metal approaches, see: (a) Gui J; Pan C-M; Jin Y; Qin T; Lo JC; Lee BJ; Spergel SH; Mertzman ME; Pitts WJ; La Cruz TE; Schmidt MA; Darvatkar N; Natarajan SR; Baran PS Practical olefin hydroamination with nitroarenes. Science 2015, 348, 886–891. [PubMed: 25999503] b Cheung CW; Hu X Amine synthesis via iron-catalysed reductive coupling of nitroarenes with alkyl halides. Nat. Commun 2016, 7, 12494. [PubMed: 27515391] c Cheung CW; Ploeger ML; Hu X Nickel-Catalyzed Reductive Transamidation of Secondary Amides with Nitroarenes. ACS Catal 2017, 7, 7092–7096.d Xiao J; He Y; Ye F; Zhu S Remote Sp^3 C–H Amination of Alkenes with Nitroarenes. Chem 2018, 4, 1645–1657.e Suárez-Pantiga S; Hernández-Ruiz R; Virumbrales C; Pedrosa MR; Sanz R Reductive Molybdenum-Catalyzed Direct Amination of Boronic Acids with Nitro Compounds. Angew. Chem. Int. Ed 2019, 58, 2129–2133.
4. (a)Nykaza TV; Cooper JC; Li G; Mahieu N; Ramirez A; Luzung MR; adosevich AT Intermolecular Reductive C−N Cross Coupling of Nitroarenes and Boronic Acids by P^{III}/P^{V}=O Catalysis. J. Am. Chem. Soc 2018, 140, 15200–15205. [PubMed: 30372615] b Li G; Nykaza TV; Cooper JC; Ramirez A; Luzung MR; Radosevich AT An Improved P^{III}/P^{V}=O-Catalyzed Reductive C−N Coupling of Nitroaromatics and Boronic Acids by Mechanistic Differentiation of Rate- and Product-Determining Steps. J. Am. Chem. Soc 2020, 142, 6786–6799. [PubMed: 32178514] c Nykaza TV; Li G; Yang J; Luzung MR; Radosevich AT P^{III}/P^{V}=O-Catalyzed Cascade Synthesis of N-Functionalized Azaheterocycles. Angew. Chem. Int. Ed 2020, 59, 4505–4510.d Li G; Qin Z; Radosevich AT P(III)/P(V)-Catalyzed Methylamination of Arylboronic Acids and Esters: Reductive C−N Coupling with Nitromethane as a Methylamine Surrogate. J. Am. Chem. Soc 2020, 142, 16205–16210. [PubMed: 32886500] e Li G; te Grotenhuis C; Radosevich AT Reductive Csp^2−N Coupling by P^{III}/P^{V}=O−Catalysis. Trends Chem 2021, 3, 72–73. [PubMed: 33681749] f Li G; Miller SP; Radosevich AT P^{III}/P^{V}=O-Catalyzed Intermolecular N–N Bond Formation: Cross-Selective Reductive Coupling of Nitroarenes and Anilines J. Am. Chem. Soc 2021, 143, 14464–14469. [PubMed: 34473484] g Li G; Kanda Y; Hong SY; Radosevich AT Enabling Reductive C-N Cross-Coupling of Nitroalkanes and Boronic Acids by Steric Design of P(III)/P(V)=O Catalysts. J. Am. Chem. Soc 2022, 144, 8242–8248. [PubMed: 35499970]
5. (a)Kashihara M; Nakao Y Cross-Coupling Reactions of Nitroarenes. Acc. Chem. Res 2021, 54, 2928–2935; [PubMed: 34232634] b Muto K; Oshita T; Yamaguchi J Transition-Metal-Catalyzed Denitrative Coupling of Nitroarenes. ACS Catal 2020, 10, 9856–9871
6. Sinha SK; Guin S; Maiti S; Biswas JP; Porey S; Maiti D Toolbox for Distal C-H Bond Functionalizations in Organic Molecules. Chem Rev 2022, 122, 5682. [PubMed: 34662117]
7. Terrier F Modern Nucleophilic Aromatic Substitution, Wiley-VCH, Weinheim, 2013.
8. (a)Mąkosza M; Krzysztof W Nucleophilic Substitution of Hydrogen in Heterocyclic Chemistry. Chem. Rev 2004, 104, 2631; [PubMed: 15137803] b Mąkosza M; Winiarski J Acc. Chem. Res 1987, 20, 282.
9. For amination by $SNAr^{H}$, see:(a)Katritzky AR; Laurenzo KS Alkylaminonitrobenzenes by Vicarious Nucleophilic Amination with 4-(Alkylamino)-1,2,4,-triazoles. J. Org. Chem 1988, 53, 3978.b Pagoria PF; Mitchell AR; Schmidth RD 1,1,1-Trimethylhydrazinium Iodide: A Novel, Highly Reactive Reagent for Aromatic Amination *via* Vicarious Nucleophilic Substitution of Hydrogen. J. Org. Chem 1996, 61, 2934–2935. [PubMed: 11667149] c Seko S; Kawamura N Copper-Catalyzed Direct Amination of Nitrobenzenes with O-Alkylhydroxylamines. J. Org. Chem 1996, 61, 442–443. [PubMed: 11666957] d Seko S; Miyake K; Kawamura N A Convenient Copper-Catalyzed Direct Amination of Nitroarenes with *O*-alkylhydroxylamines. J. Chem. Soc., Perkin Trans 1 1999, 1437.
10. Senguptam S; Das P C-H Activation Reactions of Nitroarenes: Current Status and Outlook. Org. Biomol. Chem 2021, 19, 8409. [PubMed: 34554174]
11. (a)Caron L; Campeau L-C; Fagnou K Palladium-Catalyzed Direct Arylation of Nitro-Substituted Aromatics with Aryl Halides. Org. Lett 2008, 10, 4533; [PubMed: 18811176] b Tan E; Montesinos-Margraner M,; Garcia-Morales G; Mayans JG; Echavarren AM Rhodium-catalysed *Ortho*-alkynylation of Nitroarenes. Chem. Sci 2021, 12, 14731. [PubMed: 34820088]
12. (a)Bartoli G; Dalpozzo R; Nardi M Applications of Bartoli Indole Synthesis. Chem. Soc. Rev 2014, 43, 4728. [PubMed: 24718836] b Bartoli G; Palmieri G; Bosco M; Dalpozzo R The

Reaction of Vinyl Grignard Reagents with 2-Substituted Nitroarenes: A New Approach to the Synthesis of 7-Substituted Indoles 1989, 30, 2129.

13. (a)Penoni A; Nicholas KM A Novel and Direct Synthesis of Indoles *via* Catalytic Reductive Annulation of Nitroaromatics with Alkynes. Chem. Commun 2002, 484;b Özkaya B; Bub CL; Patureau FW Step and redox efficient nitroarene to indole synthesis. Chem. Commun 2020, 56, 13185–13188.
14. (a)Cadogan JIG; Cameron-Wood M; Mackie RK; Searle RJG The reactivity of organophosphorus compounds. Part XIX. Reduction of nitro-compounds by triethyl phosphite: a convenient new route to carbazoles, indoles, indazoles, triazoles, and related compounds. J. Chem. Soc 1965, 4831–4837.b Cadogan JIG Phosphite-Reduction of Aromatic Nitro-Compounds as a Route to Heterocycles. Synthesis 1969, 1969, 11–17.c Cadogan JIG; Todd MJ Reduction of nitro- and nitroso-compounds by tervalent phosphorus reagents. Part IV. Mechanistic aspects of the reduction of 2,4,6-trimethyl-2′-nitrobiphenyl, 2-nitrobiphenyl, and nitrobenzeneJ. Chem. Soc. C 1969, 2808–2813.d Sundberg RJ Deoxygenation of Nitro Groups by Trivalent Phosphorus. Indoles from o-Nitrostyrenes. J. Org. Chem 1965, 30, 3604–3610.e Nykaza TV; Ramirez A,; Harrison TS; Luzung MR; Radosevich AT Biphilic Organophosphorus-Catalyzed Intramolecular Csp2-H Amination: Evidence for a Nitrenoid in Catalytic Cadogan Cyclizations. J. Am. Chem. Soc 2018, 140, 3103–3113. [PubMed: 29389114]
15. (a)Lao Z; Toy PH Catalytic Wittig and aza-Wittig Reactions. *Beilstein* J. Org. Chem 2016, 12, 2577–2587.b Guo H; Fan YC; Sun Z; Wu Y; Kwon O Phosphine Organocatalysis. Chem. Rev 2018, 118, 10049–10293. [PubMed: 30260217] c Lipshultz JM; Li G; Radosevich AT Main Group Redox Catalysis of Organopnictogens: Vertical Periodic Trends and Emerging Opportunities in Group 15. J. Am. Chem. Soc 2021, 143, 1699–1721. [PubMed: 33464903] d Xie C; Smaligo AJ; Song XR; Kwon O Phosphorus Based Catalysis. ACS Cent. Sci 2021, 7, 536–558. [PubMed: 34056085]
16. Levya E; Platz MS; Moctezuma E Investigation of phenyl azide photochemistry by conventional and time-resolved spectroscopy. Elucidation of intermediates and reaction mechanisms. J. Photochem. Photobiol 2022, 11, 100126.
17. (a)Borden WT; Gritsan NP; Hadad CM; Karney WL; Kemnitz CR; Platz MS The Interplay of Theory and Experiment in the Study of Phenylnitrene. Acc. Chem. Res 2000, 33, 765–771. [PubMed: 11087313] b Karney WL; Borden WT Ab Initio Study of the Ring Expansion of Phenylnitrene and Comparison with the Ring Expansion of Phenylcarbene. J. Am. Chem. Soc 1997, 119, 1378.c Gritsan NP; Likhotvorik I; Tsao ML; Çelebi N; Platz MS; Karney WL; Kemnitz CR; Borden WT Ring-Expansion Reaction of Cyano-Substituted Singlet Phenyl Nitrenes: Theoretical Predictions and Kinetic Results from Laser Flash Photolysis and Chemical Trapping Experiments. J. Am. Chem. Soc 2001, 123, 1425.
18. Inui H; Sawada K: Oishi S; Ushida K; McMahon RJ J. Am. Chem. Soc 2013, 135, 10246 [PubMed: 23795602]
19. Chapman OL; Le Roux JP 1-Aza-1,2,4,6-cycloheptatetraene. J. Am. Chem. Soc 1978, 100, 282–285
20. (a)Huisgen R; Vossius D; Appl M Die Thermolyse des Phenylazids in primären Aminen; die Konstitution des Dibenzamils. Chem. Ber 1958, 91, 1–12.b Doering W; Odum RA Ring Enlargement in the Photolysis of Phenyl Azide. Tetrahedron 1966, 22, 81–93
21. Iddon B; Meth-Cohn O; Scriven EFV; Suschitzky H; Gallagher PT Developments in Arylnitrene Chemistry: Syntheses and Mechanisms. Angew. Chem. Int. Ed 1979, 18, 900–917.
22. Previous reports of trivalent phosphorous reagents-mediated 3H-azepine formation from nitroarene, see (a) Streef W, J.; van der Plas C, H. Chemical Evidence for a Didehydroazepine in Reactions of Halogenoazepines with a Strong Base. Heterocycles 1985, 23, 2715.b Ulfa SM; Okamoto H; Satake K Unprecedented Temperature-Dependent Formation of 3- and 7-Methyl-3H-Azepine Derivatives by the Reaction of o-Nitrotoluene with Tributylphosphine in Nucleophilic Media. Chem. Lett 2012, 41, 400–402.
23. (a)Paquette LA; Kuhla DE; Barrett JH Unsaturated heterocyclic systems. LIII. Thermochemical reactions of 1H-azepine derivatives. 2. Aromatization and sigmatropic migrations involving nitrogen. J. Org. Chem 1969, 34, 2879–2884.b Storer W-D; Hoffmann R Effect of Protonation on Aziridine and Oxirane Bond Strengths. Angew. Chem. Int. Ed 1972, 11¸825–826.c Atherton

FR; Lambert RW Nitrenes Generated from Nitro-compounds by Various Phosphorus Reagents in Heterocyclic Synthesis. A Convenient Route to Substituted 3*H*-Azepines. J Chem Soc Perkin Trans, 1973, 1079–1084.d Anderson DJ; Hassner A; Tang DY Reactions of 3*H*-Azepines Derived from Cyclopentadienones and 1-Azirines. J. Org. Chem 1974, 39, 3076–3080.e Smalley RK; Strachan WA; Suschitzky H Thermolysis of Aryl Azides in Benzoyl Chloride. Tetrahedron Lett 1974, 10, 825–828.

24. (a)Jansen H;Slootweg JC;Lammertsma K Valence isomerization of cyclohepta-1,3,5-triene and its heteroelement analogues. Beilstein J. Org. Chem 2011, 7, 1713–1721. [PubMed: 22238550] b Mandal N; Das A; Hajra C; Datta A Stereoelectronic and Dynamical Effects Dictate Nitrogen Inversion During Valence Isomerization in Benzene Imine. Chem. Sci 2022, 13, 704. [PubMed: 35173935]
25. (a)Paquette LA In Nonbenzenoid Aromatics, Snyder JP, Ed.; Academic Press, New York; Vol. 1, p. 293.b Paquette LA Valence Isomerism in Selected Heterocyclic Systems. Angew. Chem. Int. Ed 1970, 10, 11–20.
26. Patel SC; Burns NZ Conversion of Aryl Azides to Aminopyridines. J. Am. Chem. Soc 2022, 144, 17797–17802. [PubMed: 36135802]
27. Gritsan NP; Platz MS Kinetics, Spectroscopy, and Computational Chemistry of Arylnitrenes. Chem. Rev 2006, 106, 3844–3867 [PubMed: 16967923]
28. Selected examples of the pharmaceutical importance of 2-amino anilidines: (a) Bailey BL; Nguyen W; Ngo A; Goodman CD; Gancheva MR; Favuzza P; Sanz LM; Gamo FJ; Lowes KN; McFadden GI; et al. Optimisation of 2-(N-Phenyl Carboxamide) Triazolopyrimidine Antimalarials with Moderate to Slow Acting Erythrocytic Stage Activity. Bioorg. Chem 2021, 115, 105244; [PubMed: 34452759] b Getlik M; Smil D; Zepeda-Velázquez C; Bolshan Y; Poda G; Wu H; Dong A; Kuznetsova E; Marcellus R; Senisterra G; Dombrovski L Hajian T; Kiyota T; Schapira M; Arrowsmith CH; Brown PJ; Vedadi M; Al-awar R Structure-Based Optimization of a Small Molecule Antagonist of the Interaction between WD Repeat-Containing Protein 5 (WDR5) and Mixed-Lineage Leukemia 1 (MLL1). J. Med. Chem 2016, 59, 2478–2496; [PubMed: 26958703] c Siqueira RP; Barros M. V. de A.; Barbosa É. de A. A.; Onofre TS; Gonçalves VHS; Pereira HS; Silva Júnior A; de Oliveira LL; Almeida MR; Fietto JLR; et al. Trifluoromethyl Arylamides with Antileukemia Effect and Intracellular Inhibitory Activity over Serine/Arginine-Rich Protein Kinases (SRPKs). Eur. J. Med. Chem 2017, 134, 97. [PubMed: 28407594]
29. Vitaku E; Smith DT; Njadarson JT Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. J. Med. Chem 2014, 57, 10257 [PubMed: 25255204]
30. Nykaza TV; Cooper JC; Radosevich AT "Preparation of anti-1,2,2,3,4,4-Hexamethylphosphetane 1-Oxide and Its Application in P^{III}/P^{V}=O Redox Catalysis." Org. Synth 2019, 96, 418–435. [PubMed: 31902967]
31. The effect of Brønsted acid in the organophosphorus-catalyzed reductive N–N coupling (ref 4f) is to promote the condensation between nitrosoarene intermediates and amine nucleophiles. When omitting the Brønsted acid additive, the phosphetane-catalyzed deoxygenation of nitrosoarene to nitrene intermediate dominates, leading to 3H-azepine products.
32. Ziegler DT; Choi J; Muñoz-Molina JM; Bissember AC; Peters JC; Fu GC A Versatile Approach to Ullmann C-N Couplings at Room Temperature: New Families of Nucleophiles and Electrophiles for Photoinduced, Copper-Catalyzed Processes. J. Am. Chem. Soc 2013, 135, 13107–13112. [PubMed: 23968565]

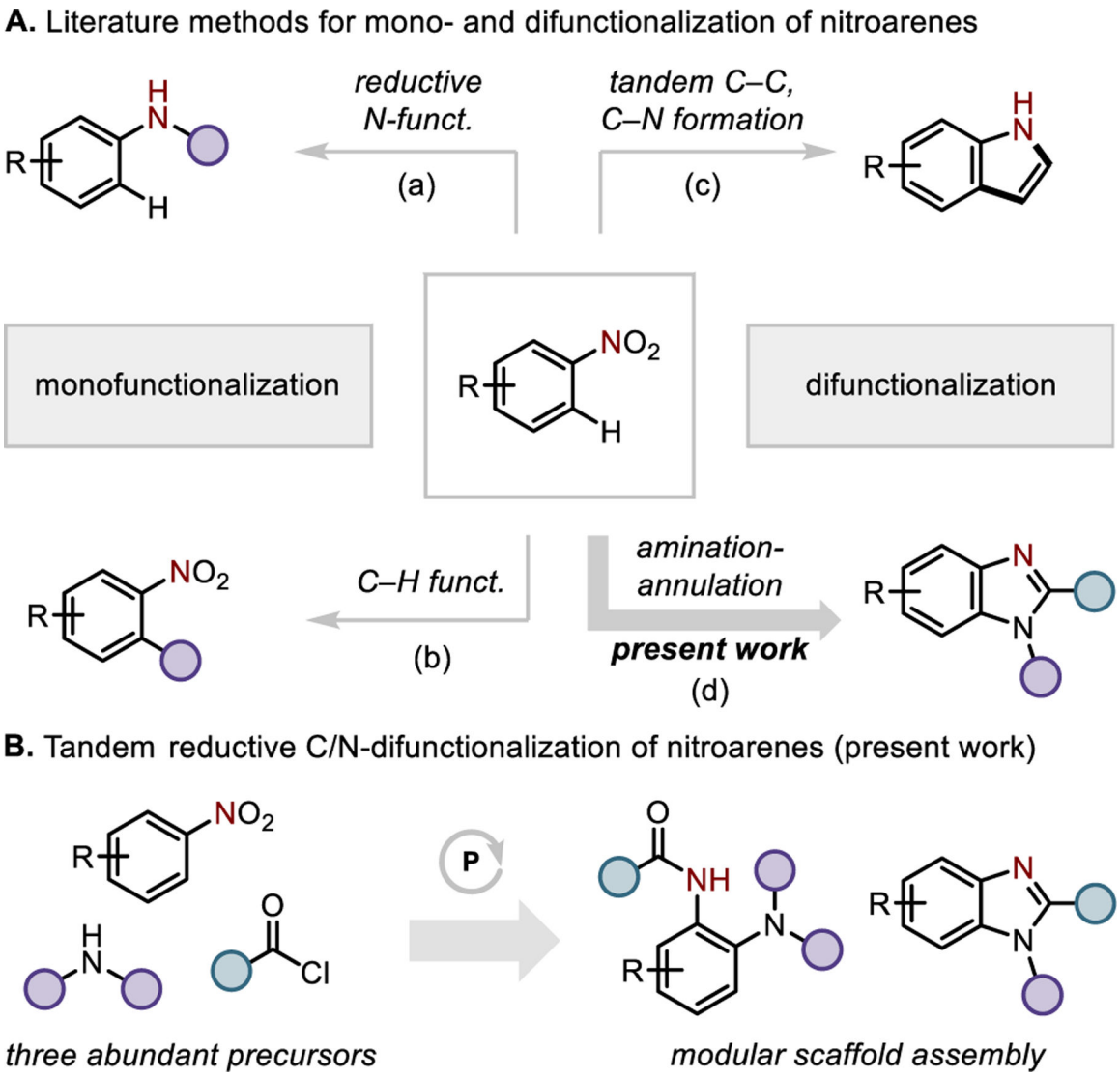


Figure 1.

(A) Mono- and difunctionalization of nitroarenes. (B) Reductive C/N-difunctionalization of nitroarenes as modular entry to 2-aminoanillides and benzimidazoles.

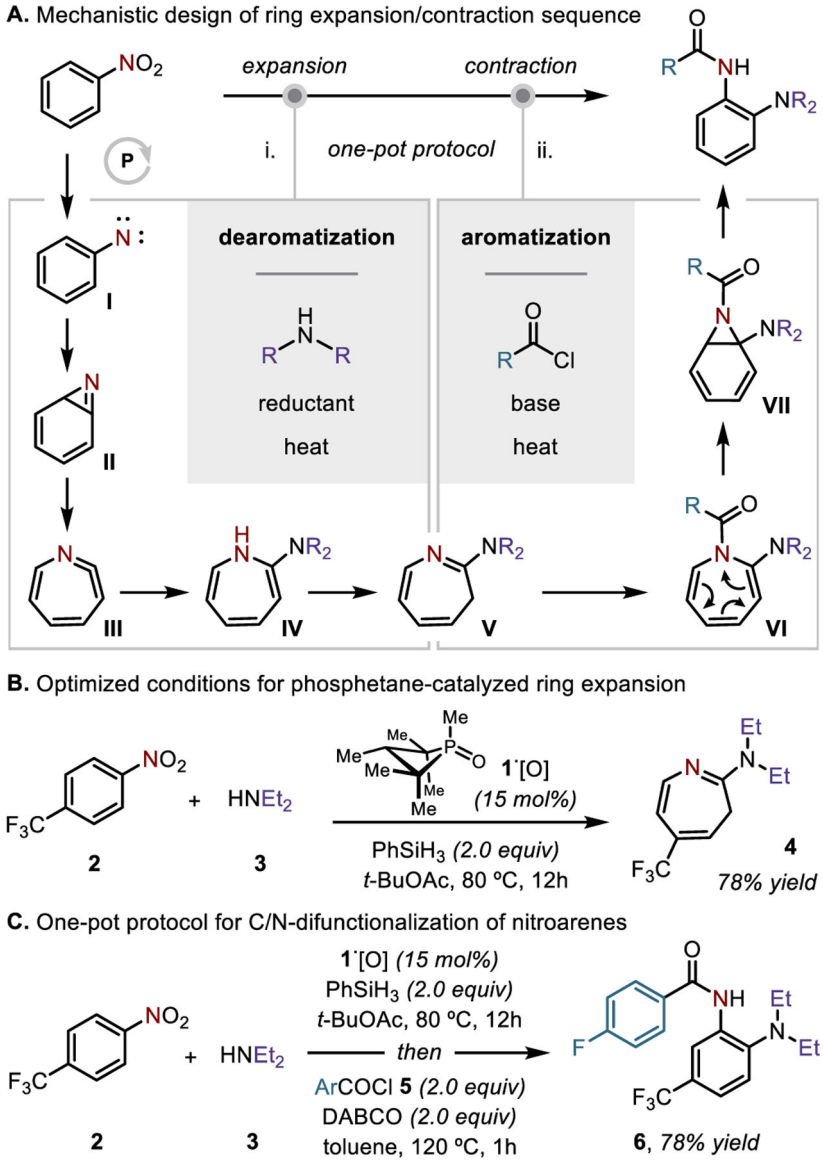


Figure 2.

(A) Mechanistic outline for the reported C/N-difunctionalization of nitroarenes. (B) Conditions for the reductive ring expansion of nitroarenes via arylnitrenes. (C) Synthetic conditions for the one-pot C/N-difunctionalization of nitroarenes.

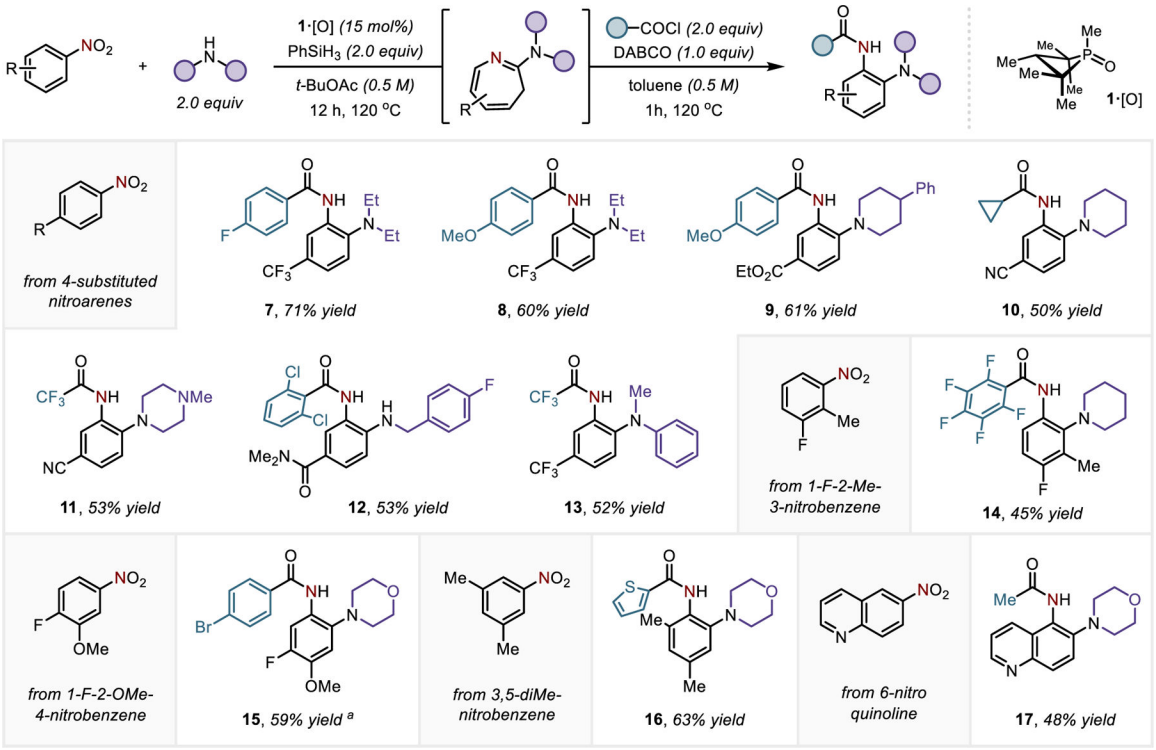


Figure 3.

Synthesis of 2-aminoanilides by reductive C/N-difunctionalization of nitroarenes. [a] 8:1 regioisomeric ratio. See SI for full experimental details.

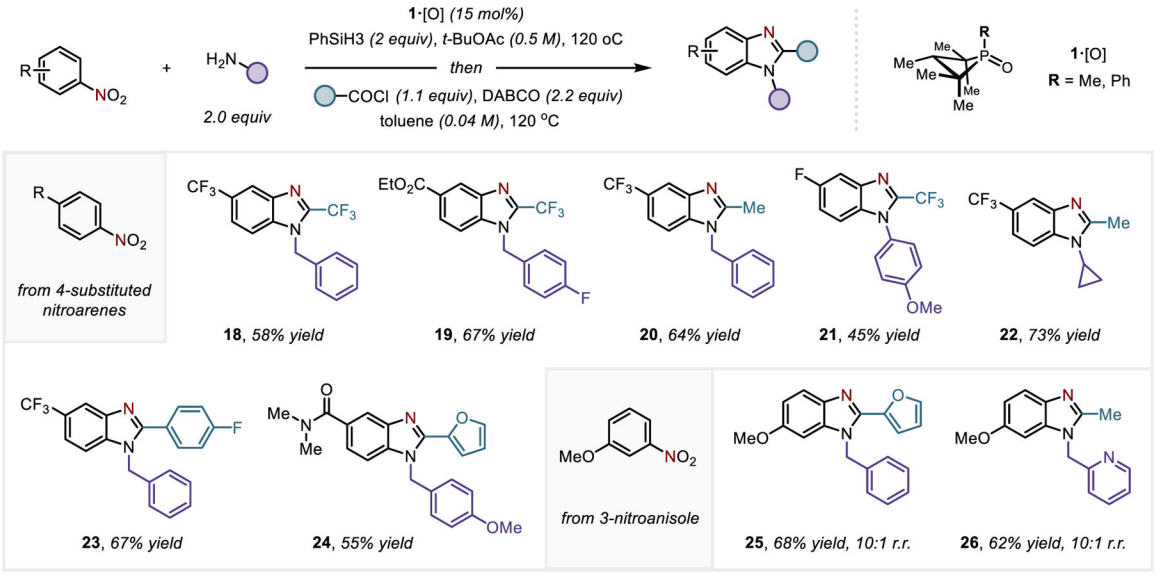


Figure 4.

Synthesis of benzimidazoles by reductive C/N-difunctionalization of nitroarenes. See SI for full experimental details.

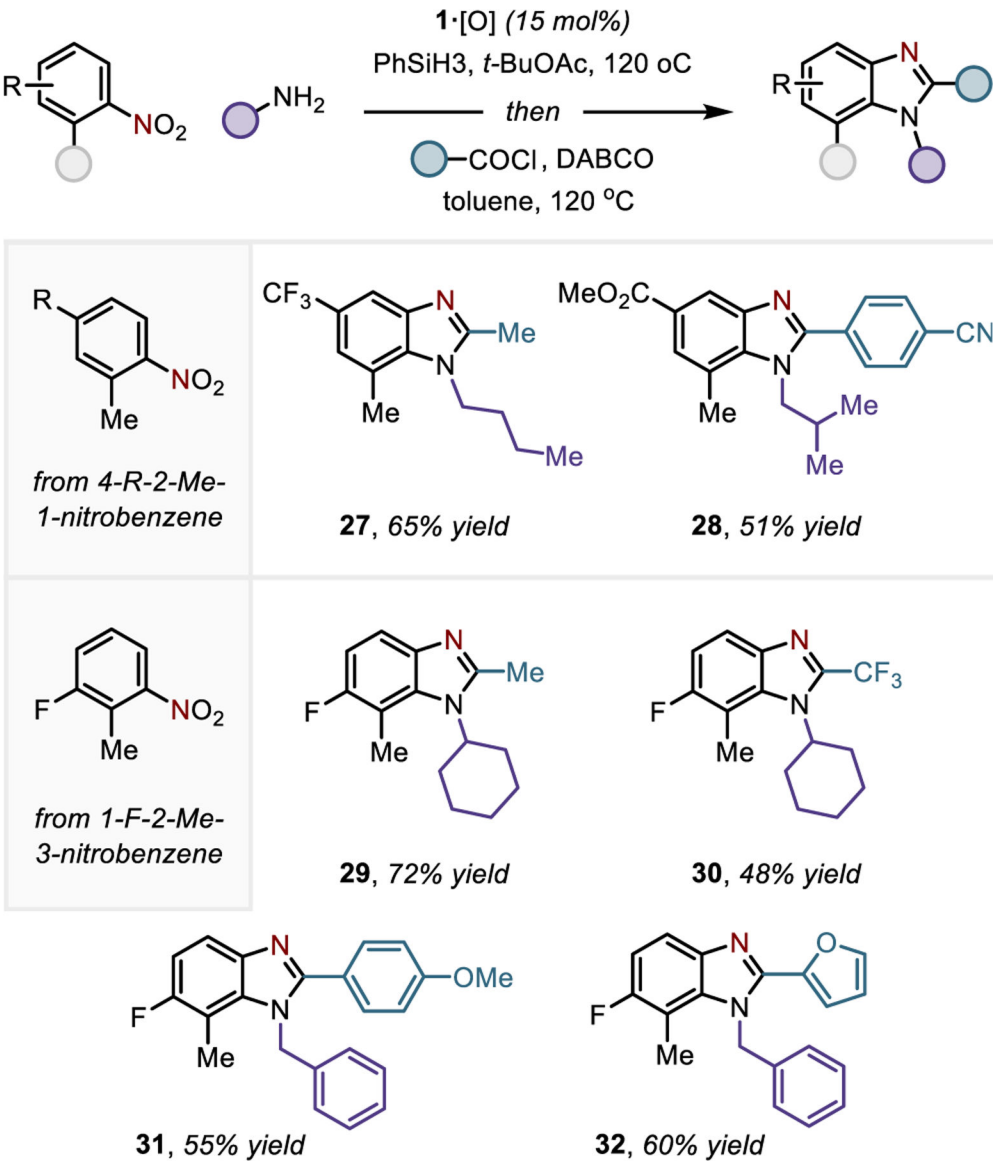


Figure 5.
Regiospecific preparation of 1,2,7-benzimidazoles. See SI for full experimental details.