P III /P V =0 Catalyzed Cascade Synthesis of N#Functionalized Azaheterocycles

As Published: 10.1002/ANIE.201914851

Publisher: Wiley

Persistent URL: https://hdl.handle.net/1721.1/136626

Version: Author's final manuscript: final author's manuscript post peer review, without publisher's formatting or copy editing

HHS Public Access

Author manuscript

Angew Chem Int Ed Engl. Author manuscript; available in PMC 2021 March 09.

Published in final edited form as:

Angew Chem Int Ed Engl. 2020 March 09; 59(11): 4505–4510. doi:10.1002/anie.201914851.

P^{III}/P^{V}=O-Catalyzed Cascade Synthesis of *N*-Functionalized Azaheterocycles

Trevor V. Nykaza[a,c], **Gen Li**[a,c], **Junyu Yang**[a], **Michael R. Luzung**[*,b], **Alexander T. Radosevich**[*,a]

[a]Department of Chemistry, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, MA, 02139 (USA)

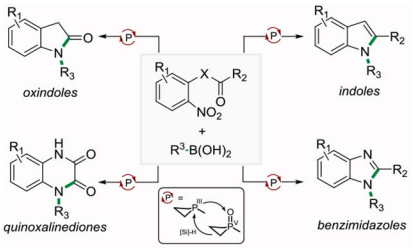
[b]Kallyope Inc., 430 E. 29th St., Suite 1050, New York, NY 10016 (USA)

[c]Authors contributed equally.

Abstract

A main group-catalyzed method for the modular synthesis of diverse *N*-aryl and *N*-alkyl azaheterocycles (i.e. indoles, oxindoles, benzimidazoles, and quinoxalinediones) is reported. The method employs a small ring organophosphorus-based catalyst (1,2,2,3,4,4-hexamethylphosphetane *P*-oxide) and a hydrosilane reductant to drive the conversion of *ortho*-functionalized nitroarenes to azaheterocycles via sequential intermolecular reductive C–N cross coupling with boronic acids, followed by intramolecular cyclization. This method provides for the rapid construction of azaheterocycles from readily available building blocks, including a regiospecific approach to *N*-substituted benzimidazoles and quinoxalinediones.

Graphical Abstract



A main group-catalyzed method for the modular synthesis of diverse *N*-aryl and *N*-alkyl azaheterocycles (i.e. indoles, oxindoles, benzimidazoles, and quinoxalinediones) from readily available building blocks, including a regiospecific approach to *N*-substituted benzimidazoles and quinoxalinediones.

Keywords

Organocatalysis; Cross-coupling; Phosphorus; Nitrogen heterocycles; Cyclization

* radosevich@mit.edu, mike@kallyope.com.

Dedicated to Dr. Guy R. Humphrey (Merck & Co.) on the occasion of his 60th birthday.

Introduction

N-Functionalized azaheterocycles are important constituents of the modern pharmacopeia (see Figure 1A),[1] and synthetic methods that provide rapid and modular entry to this varied group of compounds contribute to the discovery of new drugs. Nitroarenes are attractive substrates for such heterocycle synthesis since—beyond the many nitroaromatic building blocks that are commercially available—the nitro functional group is easily and reliably introduced to arenes, where it exerts a powerful inductive effect that enables proximate transformations.[2] The nitro moiety has many applications in well-known heterocyclization methods, [3,4] but less commonly as a strategic site for consecutive C–N bond formation at nitrogen.[5] We report here a unified cascade approach to multiple classes of useful *N*-functionalized azaheterocycles by the conversion of readily available *ortho*-derivatized nitroarenes in a single main group-catalyzed operation.

The recognition that nitroarenes may serve as masked precursors of reactive nitrogen intermediates for direct azafunctionalization[6,7] informed the view that a one-pot reaction sequence involving: (1) organophosphorus-catalyzed intermolecular reductive C–N cross coupling, [8] and (2) in situ intramolecular acyl substitution or carbonyl condensation would constitute an integrated approach to multiple heterocyclic classes from *o*-functionalized nitroarenes (Figure 1B). As compared to conceptually-related transition metal-catalyzed cyclative coupling of *o*-functionalized haloarenes, [9–12] the envisioned organophosphorus-catalyzed strategy would offer a cohesive synthesis of several distinct azaheterocycles that: (1) proceeds directly from readily-accessible substituted nitroarene precursors with diversifiable *ortho*-functionality, (2) leverages the increasingly vast store of bench stable aryl- and alkylboronic acids now available, and (3) exhibits unique chemoselectivities and functional group tolerance inherent to the all-main-group conditions of the P^{III}/P^{V}=O catalyzed coupling method.[13–14] The versatility of this main group-catalyzed strategy is exemplifed by the regiospecific preparation of multiple classes of useful heterocycles in a single operation with modular and precise control over positional substitution about the heterocyclic periphery.

Results and Discussion

As an initial validation of the target tandem C–N coupling/cyclization reaction sequence, *N*-arylative cyclization of methyl 2-nitrophenylacetate (**1**) with phenylboronic acid (**2**) yielded oxindole product **3** in 85% NMR yield (80% isolated yield) on a 0.5 mmol scale within 4 h using 1,2,2,3,4,4-hexamethylphosphetane oxide [15] (**4**•[O]) as the catalyst and diphenylsilane as the terminal reductant (Table 1, entry 1). Control experiments (entries 2-4) are consistent with a reaction system that is operating via a P^{III}/P^{V}=O redox cycling process and is under catalyst control; specifically, the use of P^{III} compound **4** instead of P^{V} compound **4**•[O] as catalyst is comparably efficient (entry 2, 88%), and omission of either catalyst **4**•[O] (entry 3) or hydrosilane (entry 4) give no product **3**. Among a brief survey of alternate organophosphorus compounds (See Table S2), commercially-available phosphine oxide **4**•[O][16] was found to be most active. A variety of common hydrosilane reducing reagents (phenylsilane, entry 5; poly(methylhydro)siloxane, entry 6) can all similarly be employed.[17] Practically, the method is not bounded by stringent operational constraints; the catalytic

reaction is robust to a variety of solvents (entries 6-8) as well as the presence of both aerobic (entry 9) and aqueous (entry 10) contaminants.

Although no long-lived intermediates en route from **1** to **3** are observed under optimized conditions, the use of *tert*-butyl 2-nitrophenylacetate (**1a**) as substrate (eq. 1) leads primarily to the C–N coupling intermediate **1b** after 4 h (64%), which proceeds further to oxindole **3** only with prolonged heating (68% after 60 h). The initial C–N coupling does not proceed via the free aniline **1c**, for which the optimized conditions did not result in the formation of oxindole **3**; instead, only the parent N-H oxindole **3a** was formed (eq. 2). Moreover, N-H oxindole **3a** itself is not converted to **3** by the main-group catalyzed reaction conditions (eq. 3) but is recovered without N-arylation. Collectively, these probe experiments confirm a two-stage cascade sequence for the *N*-arylative cyclization of **1** involving initial reductive C–N coupling to form **1e** followed by intramolecular cyclization to give **3** (Scheme 1, bottom).

Synthetic examples illustrating the scope of the organophosphorus-catalyzed heterocycle synthesis are collected in Table 2. With respect to oxindole synthesis (Table 2A),[18] complete chemoselectivity for the desired tandem C–N bond constructions in preference to functionalization of aryl halides is observed; halogenation on either the nitroaryl substrate (**5**, **6**) or the arylboronic acid partner (**6**, **8**) result in halogenated oxindole products in good yield. Electronically diverse reaction partners are all incorporated in good yield within the developed scheme; electron-deficient nitroarenes can be paired with electron-rich boronic acids partners as in oxindole **7**, or alternatively electron-rich nitroarenes can likewise be merged with electron-deficient boronic acids as in oxindole product **8**. It was also found that alkylboronic acids can serve as a good partner in the tandem reaction sequence, for instance providing *N*-cyclopropyl substituted oxindole product (**9**) in 61% yield.

N-Arylative cyclization starting from α-(2-nitroaryl)ketones as substrates provides entry to substituted indole [19,20] products through an intramolecular carbonyl condensation of a first-formed reductive C–N coupled intermediate onto the pendant ketone moiety (Table 2B). Notably, many diverse 1,2-disubsituted indoles can be obtained via the developed method. It was found that 1-alkyl-2-aryl (**10**), 1-aryl-2-alkyl (**11, 12**), and 1-aryl-2-aryl (**13-14**) substituted indole products can all be synthesized by selection of the appropriate nitroarene and boronic acid reaction partners. The complementarity of the developed P^{III}/P^{V}=O-catalyzed *N*-arylative cyclization with respect to transition metal approaches is amply demonstrated within this indole series of examples. Sulfur-containing containing products (i.e. *N*-thianthrenyl indole **13**), potential poisons for late metal catalysis, are unproblematic under these main group conditions. Moreover, C–F, C–Cl, C–Br (**13**) and C–I (**14**) substituents are all tolerated without issue and carried through the tandem coupling and cyclization events. The retention of the reactive aryl halides thus permits their use as synthetic handles for the further diversification of the indole core via downstream coupling chemistry.

A family of 6-membered ring containing quinoxalinedione[21] products are similarly accessible starting from oxalate amides of *o*-nitroaniline substrates (Table 2C). A useful feature for this class of molecules is that the products are insoluble in *m*-xylene and can be

isolated by filtration following the reaction. Various *N*-functionality can be introduced from alkyl (i.e. cyclopropyl, **15**), aryl (**16, 18-19**), and heteroaryl (**17**) boronic acids through the tandem sequence, in which intermolecular C–N bond formation leads to intramolecular addition to the pendant ester and regiospecific formation of the quinoxalinedione core. Similarly, not only are different nitroarene functionalities tolerated without issue (**17-19**), but also the method can be applied in the synthesis of the fused heterocyclic pyrido[2,3-*b*]pyrazinedione (**16**).*N*-acylated 2-nitroanilines of diverse substitution undergo P^{III}/P^{V}=O catalyzed *N*-arylative cyclization process to provide *N*-functionalized benzimidazole[22] products (Table 2D). In terms of C2-substitution originating from the amide fragment, (fluoro)alkyl (**20-24**) and heteroaryl substituents (**25**) could be successfully incorporated. Additionally, aryl (**20-23**), heteroaryl (**24**) and alkyl (i.e. cyclobutyl, **25**) boronic acids could all be used as coupling partners in order to introduce a variety of *N*-substitution. Withrespect to functional group tolerance, it was found that esters (**21**), ethers (**22**), halogens (**20-25**), and thienyl units (**24-25**) could all be carried through the tandem reaction sequence without issue.

The P^{III}/P^{V}=O catalyzed *N*-arylative cyclization method provides a regiospecific synthesis of *N*-aryl benzimidazoles in cases direct C–N coupling of the pseudosymmetric *N*-H precursor would be unselective.[23] The full suite of regioisomeric fluorinated *N*-aryl benzimidazole products **26a-26d** (Figure 2A) are accessible with programmed regiochemistry as dictated by the initial position of fluorination on the trifluoroacetyl-2-nitroanilide starting material. As a further practical point of utility, a modular and concise one-pot synthesis of benzimidazole product **28** via in situ acylation and N-arylative cyclization directly from 4-methyl-2-nitroaniline (**27**) is illustrated (Figure 2B). These results present the opportunity for this modular method to be applied in the synthesis of diverse benzimidazole compound libraries through a unified tandem reaction sequence directly from functionalized nitroanilines, boronic acids, and a suitable acylating reagent.

As a further demonstration of the synthetic versatility of the transformation and to demonstrate the potential application of this methodology in the context of medicinal chemistry, the KCNQ K^+ ion channel blocker linopiridine (**30**) [24, 25] was synthesizing from methyl 2-nitrophenylacetate (**1**) using the developed sequential C–N coupling and cyclization approach, followed by in situ alkylation with 4-(bromomethyl)pyridine with 76% yield in one pot (Figure 2C).

Conclusion

The foregoing results constitute a practical, scalable, and operationally robust organophosphorus-catalyzed protocol for the modular (regiospecific) synthesis of azaheterocycles via a tandem intermolecular C–N coupling of nitroarenes and boronic acid partners, followed by intramolecular addition of the intermediary species by either carbonyl condensation (for benzimidazoles and indoles) or acyl substitution (for quinoxalinediones and oxindoles) moieties. The chemoselectivities and functional group tolerance enabled by the all-main-group conditions of the P^{III}/P^{V}=O catalyzed coupling method establish this approach as a useful complement to existing methods to *N*-aryl heterocycles including those based on transition metal C–N coupling.[26] In view of the prevalence of these types of

nitrogen heterocycles in pharmaceuticals,[1] bioactive natural metabolites,[27] and organic materials[28] among other applications, many possible implementations of this method can be envisioned.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Financial support was provided by NIH (GM114547), MIT, and Kallyope Inc.

References

1. a)Catarzi D, Colotta V, Varano F, Med. Res. Rev 2006, 2, 239;b)Kaushik NK, Kaushik N, Attri P, Kumar N, Kim CH, Verma AK, Choi EH, Molecules. 2013, 18, 6620; [PubMed: 23743888] c)Keri RS, Hiremathad A, Budagumpi S, Nagaraja BM, Chem. Biol. Drug Des 2015, 86, 19; [PubMed: 25352112] d)Taylor AP, Robinson RP, Fobian YM, Blakemore DC, Jones LH, Fadeyi O, Org. Biomol. Chem 2016, 14, 6611; [PubMed: 27282396] e)Nautiyal OH, OMCIJ 2018, 5, 555671;f)Pallesen J, Møllerud S, Frydenvang K, Pickering DS, Bornholdt J, Nielsen B, Pasini D, Han L, Marconi L, Kastrup JS, Johansen TN. ACS Chem. Neurosci 2019, 10, 1841. [PubMed: 30620174]
2. Ono N, The Nitro Group in Organic Synthesis. Wiley, New York, 2001.
3. a)Cadogan JIG, Cameron-Wood M, Mackie RK, Searle RJG, J. Chem. Soc 1965, 4831;b)Sundberg RJ, J. Org. Chem 1965, 30, 3604;c)Cadogan JIG, Q. Rev., Chem. Soc 1968, 22, 222;d)Cadogan JIG, Synthesis 1969, 11;e)Cadogan JIG, Todd MJ, J. Chem. Soc. C 1969, 2808.
4. a)Bartoli G, Palmieri G, Bosco M, Dalpozzo R, Tetrahedron Lett. 1989, 30, 2129;b)Bartoli G, Bosco M, Dalpozzo R, Palmieri G, Marcantoni E, J. Chem. Soc., Perkin Trans. 1. 1991, 11, 2757;c)Dobbs AP, Voyle M, Whitall N, Synlett 1999, 10, 1594;d)Bartoli G, Dalpozzo R, Nardi M, Chem. Soc. Rev 2014, 43, 4728. [PubMed: 24718836]
5. a)Výprachtický D, Kmínek I, Pokorná V, Cimrová V, Tetrahedron 2012, 68, 5075;b)Kadam HK, Tilve SG, Eur. J. Org. Chem 2013, 4280.c)Ames DE, Hansen KJ, Griffiths ND. J. Chem. Soc, Perkin Trans 1, 1973, 2818;d)Tanaka A, Yakushijin K, Yoshina S. J. Heterocyclic Chem, 1979, 16, 785;e)Jesudoss K, Srinivasan PC, Synth. Commun 1994, 24, 1701.
6. a)Sapountzis I, Knochel P, J. Am. Chem. Soc 2002, 124, 9390; [PubMed: 12167031] b)Doyle W, Staubitz A, Knochel P, Chem. Eur. J 2003, 9, 5323; [PubMed: 14613142] c)Kopp F, Sapountzis I, Knochel P, Synlett 2003, 885;(d)Sapountzis I, Knochel P, Synlett 2004, 955;e)Srivastava RS, Nicholas KM, Organometallics 2005, 24, 1563;f)Fang X, Jackstell R, Beller M, Angew. Chem. Int. Ed 2013, 52, 14089;Angew. Chem 2013, 125, 14339;g)Gao H, Xu Q-L, Ess DH, Kürti L, Angew. Chem. Int. Ed 2014, 53, 2701;Angew. Chem 2014, 126, 2739;h)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, Science 2015, 348, 886; [PubMed: 25999503] i)Dhayalan V, Saemann C, Knochel P, Chem. Commun 2015, 51, 3239;j)Cheung CW, Hu X, Nat. Commun 2016, 7, 12494; [PubMed: 27515391] k)Cheung CW, Hu X, ACS Catal. 2017, 7, 7092;l)Cheung CW, Ploeger ML, Hu X, Nat. Commun 2017, 8, 14878; [PubMed: 28345585] m)Zhou F, Wang D-S, Guan X, Driver TG, Angew. Chem. Int. Ed 2017, 56, 4530;Angew. Chem 2017, 129, 4601;n)Rauser M, Ascheberg C, Niggemann M, Angew. Chem. Int. Ed. 2017, 56, 11570;Angew. Chem 2017, 129, 11728;o)Rauser M, Ascheberg C, Niggemann M, Chem. - A Eur. J 2018, 24, 3970;p)Cheung CW, Ploeger ML, Hu X, Chem. Sci 2018, 9, 655; [PubMed: 29629132] q)Xiao J, He Y, Ye F, Zhu S, Chem. 2018, 4, 1645.r)Suarez-Pantiga S, Hernandez-Ruiz R, Virumbrales C, Pedrosa MR, Sanz R, Angew. Chem. Int. Ed 2019, 58, 2129;Angew. Chem 2019, 131, 2151;s)Roscales S, Csáky AG, Adv. Synth. Catal 2019, DOI 10.1002/adsc.201901009.

7. For C-N bond formation between nitrosoarenes and boronic acids.a)Yu Y, Srogl J, Liebeskind LS, Org. Lett 2004, 6, 2631; [PubMed: 15255708] b)Roscales S, Csáky AG, Org. Lett 2018, 20, 1667; [PubMed: 29493243] c)Roscales S, Csákÿ AG, ACS Omega 2019, 4, 13943. [PubMed: 31497712]
8. Nykaza TV, Cooper JC, Li G, Mahieu N, Ramirez A, Luzung MR, Radosevich AT, J. Am. Chem. Soc 2018, 140, 15200. [PubMed: 30372615]
9. a)Zheng N, Anderson KW, Huang X, Nguyen HN, Buchwald SL, Angew. Chem. Int. Ed 2007, 46, 7509;Angew. Chem 2007, 119, 7653;b)Zheng N, Buchwald SL, Org. Lett 2007, 9, 4749. [PubMed: 17949007] c)Jui NT, Buchwald SL, Angew. Chem. Int. Ed 2013, 52, 11624;Angew. Chem 2013, 125, 11838.
10. Zou B, Yuan Q, Ma D, Angew. Chem. Int. Ed 2007, 46, 2598;Angew. Chem 2007, 119, 2652.
11. a)Brain CT, Brunton SA, Tetrahedron Lett. 2002, 43, 1893;b)Brain CT, Steer JT, J. Org. Chem 2003, 68, 6814. [PubMed: 12919056]
12. a)Saha P, Ramana T, Purkait N, Ali MA, Paul R, Punniyamurthy T, J. Org. Chem 2009, 74, 8719; [PubMed: 19908912] b)Deng X, Mani NS, Eur. J. Org. Chem 2010, 680;c)Saha P, Ali MA, Ghosh P, Punniyamurthy T, Org. Biomol. Chem 2010, 8, 5692; [PubMed: 20963217] d)Alonso J, Halland N, Nazaré M, R'kyek O, Urmann M, Lindenschmidt A, Eur. J. Org. Chem 2011, 234;e)Peng J, Ye M, Zong C, Hu F, Feng L, Wang X, Wang Y, Chen C, J. Org. Chem 2011, 76, 716. [PubMed: 21175149]
13. For a review of P^{III}/P^{V}=O redox cycling, see:a)Marsden SP, Catalytic Variants of Phosphine Oxide-Mediated Organic Transformations in Sustainable Catalysis; Dunn PJ, Hii KK, Krische MJ, Williams MT, Eds.; John Wiley & Sons, Inc.: New York, 2013; pp 339–361;b)Guo H, Fan YC, Sun Z, Wu Y, Kwon O, Chem. Rev 2018, 118, 10049. [PubMed: 30260217]
14. a)O'Brien CJ, Tellez JL, Nixon ZS, Kang LJ, Carter AL, Kunkel SR, Przeworski KC, Chass GA, Angew. Chem. Int. Ed 2009, 48, 6836;Angew Chem, 2009, 121: 6968;b)van Kalkeren HA, Leenders SHAM, Hommersom CRA, Rutjes FPJT, van Delft FL, Chem. Eur. J 2011, 17, 11290; [PubMed: 21882274] c)van Kalkeren HA, Bruins JJ, Rutjes FPJT, van Delft FL, Adv. Synth. Catal 2012, 354, 1417;d)O'Brien CJ, Lavigne F, Coyle EE, Holohan AJ, Doonan BJ, Chem. Eur. J 2013, 19, 5854. [PubMed: 23526683] e)O'Brien CJ, Nixon ZS, Holohan AJ, Kunkel SR, Tellez JL, Doonan BJ, Coyle EE, Lavigne F, Kang LJ, Przeworski KC, Chem. Eur. J 2013, 19, 15281; [PubMed: 24115040] f)Coyle EE, Doonan BJ, Holohan AJ, Walsh KA, Lavigne F, Krenske EH, O'Brien CJ, Angew. Chem. Int. Ed 2014, 53, 12907;Angew. Chem 2014, 126, 13121;g)Reichl KD, Dunn NL, Fastuca NJ, Radosevich AT, J. Am. Chem. Soc 2015, 137, 5292; [PubMed: 25874950] h)Zhao W, Yan PK, Radosevich AT, J. Am. Chem. Soc 2015, 137, 616; [PubMed: 25564133] i)Lee C, Chang T, Yu J, Reddy GM, Hsiao M, Lin W, Org. Lett. 2016, 18, 3758; [PubMed: 27434727] j)Lao Z, Toy PH, Beilstein J. Org. Chem 2016, 12, 2577; [PubMed: 28144327] k)Saleh N, Voituriez A, J. Org. Chem 2016, 81, 4371; [PubMed: 27080174] l)Saleh N, Blanchard F, Voituriez A, Adv. Synth. Catal 2017, 359, 2304;m)Lin Y-C, Hatzakis E, McCarthy SM, Reichl KD, Lai T-Y, Yennawar HP, Radosevich AT, J. Am. Chem. Soc 2017, 139, 6008; [PubMed: 28398750] n)Nykaza TV, Harrison TS, Ghosh A, Putnik RA, Radosevich AT, J. Am. Chem. Soc 2017, 139, 6839; [PubMed: 28489354] o)Nykaza TV, Ramirez A, Harrison TS, Luzung MR, Radosevich AT, J. Am. Chem. Soc 2018, 140, 3103; [PubMed: 29389114] p)Zhang K, Cai L, Yang Z, Houk KN, Kwon O, Chem. Sci 2018, 9, 1867; [PubMed: 29732112] q)Ghosh A, Lecomte M, Kim-Lee S-H, Radosevich AT, Angew. Chem. Int. Ed 2019, 58, 2864;Angew. Chem 2019, 131, 2890;r)Lecomte M, Lipshultz JM, Kim-Lee S-H, Li G, Radosevich AT, J. Am. Chem. Soc 2019 141, 12507; [PubMed: 31345031] s)Cai L, Zhang K, Chen S, Lepage RJ, Houk KN, Krenske EH, Kwon O, J. Am. Chem. Soc 2019, 141, 9537; [PubMed: 31184143] t)Lorton C, Castanheiro T, Voituriez A, J. Am. Chem. Soc 2019, 141, 10142; [PubMed: 31194912] u)Longwitz L, Spannenberg A, Werner T, ACS Catal. 2019, 9, 9237.
15. For a preparation of 4 [O], see:Nykaza TV, Cooper JC, Radosevich AT, Org. Synth 2019, 96, 418. [PubMed: 31902967]
16. Available from Strem Chemicals, item no. 15-8150.
17. When using phenylsilane, product **3** was found to convert to 1-phenyl-1*H*-indole (87%) at prolonged reaction times (24 h).
18. a)Goehring RR, Sachdeva YP, Pisipati JS, Sleevi MC, Wolfe JF, J. Am. Chem. Soc 1985, 107, 435;b)Bowman WR, Heaney H, Jordan BM, Tetrahedron Lett. 1988, 29, 6657;c)Hennessy EJ,

Buchwald SL, J. Am. Chem. Soc 2003, 125, 12084; [PubMed: 14518981] d)Poondra RR, Turner NJ, Org. Lett 2005, 7, 863; [PubMed: 15727460] e)Dalpozzo R, Bartoli G, Bencivenni G, Chem. Soc. Rev 2012, 41, 7247; [PubMed: 22899437] f)Kiser EJ, Magano J, Shine RJ, Chen MH, Org. Process Res. Dev 2012, 16, 255.

19. a)Humphrey GR, Kuethe JT, Chem. Rev 2006, 106, 2875. [PubMed: 16836303] b)Taber DF, Tirunahari PK, Tetrahedron 2011, 67, 7195. [PubMed: 25484459]
20. For reviews see:a)Wexler RR, Greenlee WJ, Irvin JD, Goldberg MR, Prendergast K, Smith RD, Timmermans PBMWM, J. Med. Chem 1996, 39, 625; [PubMed: 8576904] b)Morphy R, Rankovic Z, J. Med. Chem 2005, 48, 6523; [PubMed: 16220969] c)Schnürch M, Flasik R, Khan AF, Spina M, Mihovilovic MD, Stanetty P, Eur. J. Org. Chem 2006, 3283.
21. a)Nikam SS, Cordon JJ, Ortwine DF, Heimbach TH, Blackburn AC, Vartanian MG, Nelson CB, Schwarz RD, Boxer PA, Rafferty MF, J. Med. Chem 1999, 42, 2266; [PubMed: 10377233] b)Fray MJ, Bull DJ, Carr CL, Gautier ECL, Mowbray CE, Stobie A, J. Med. Chem 2001, 44, 1951. [PubMed: 11384240]
22. a)Panda SS, Malik RM, Jain SC, Curr. Org. Chem 2012, 16, 1905;b)Kurhade S, Rossetti A, Dömling A, Synthesis 2016, 48, 3713.
23. Carvalho LCR, Fernandes E, Marques MMB, Chem. Eur. J 2011, 17, 12544. [PubMed: 21989969]
24. a)Schnee ME, Brown BS, J. Pharmacol. Exp. Ther 1998, 286, 709. [PubMed: 9694925] b)Robbins J, Pharmacol. Ther 2001, 90, 1. [PubMed: 11448722]
25. A three step synthesis from diphenylamine (57% overall yield) is reported.Earl RA, Meyers MJ, Nickolson VJ (DuPont Merck Pharmaceutical Co), US 5173489(A), 1992.
26. For literature concerning N-H functionalization see:a)Lam PYS, Clark CG, Saubern S, Adams J, Winters MP, Chan DMT, Combs A, Tetrahedron Lett. 1998, 39, 2941;b)Lam PYS, Deudon S, Averill KM, Li R, He MY, DeShong P, Clark CG, J. Am. Chem. Soc 2000, 122, 7600;c)Old DW, Harris MC, Buchwald SL, Org. Lett 2000, 2, 1403; [PubMed: 10814458] d)Klapars A, Antilla JC, Huang X, Buchwald SL, J. Am. Chem. Soc 2001, 123, 7727; [PubMed: 11481007] e)Antilla JC, Klapars A, Buchwald SL, J. Am. Chem. Soc 2002, 124, 11684; [PubMed: 12296734] f)Choudary BM, Sridhar C, Kantam ML, Venkanna GT, Sreedhar B, J. Am. Chem. Soc 2005, 127, 9948; [PubMed: 16011328] g)Altman RA, Buchwald SL, Org. Lett 2006, 8, 2779; [PubMed: 16774255] h)Altman RA, Koval ED, Buchwald SL, J. Org. Chem 2007, 72, 6190; [PubMed: 17625886] i)Correa A, Bolm C, Angew. Chem. Int. Ed 2007, 46, 8862;Angew. Chem 2007, 119, 9018–9021;j)Zhu L, Guo P, Li G, Lan J, Xie R, You J, J. Org. Chem 2007, 72, 8535; [PubMed: 17902694] k)Altman RA, Hyde AM, Huang X, Buchwald SL, J. Am. Chem. Soc 2008, 130, 9613; [PubMed: 18588302] l)Zhu L, Li G, Luo L, Guo P, Lan J, You J, J. Org. Chem 2009, 74, 2200; [PubMed: 19196026] m)Ganesh Babu S, Karvembu R, Ind. Eng. Chem. Res 2011, 50, 9594;n)Karchava AV, Melkonyan FS, Yurovskaya MA, Chem. Heterocycl. Comp 2012, 48, 391;o)Ueda S, Su M, Buchwald SL, J. Am. Chem. Soc 2012, 134, 700; [PubMed: 22126442] p)Davis OA, Hughes M, Bull JA, J. Org. Chem 2013, 78, 3470; [PubMed: 23464665] q)Dar'in D, Krasavin M, J. Org. Chem 2016, 81, 12514; [PubMed: 27978721] r)Jung S-H, Sung D-B, Park C-H, Kim W-S, J. Org. Chem 2016, 81, 7717; [PubMed: 27484240] s)Miao B, Li S, Li G, Ma S, Org. Lett 2016, 18, 2556; [PubMed: 27214662] t)Ye Y, Kim S-T, Jeong J, Baik M-H, Buchwald SL, J. Am. Chem. Soc 2019, 141, 3901. [PubMed: 30696242]
27. a)Gul W, Hamann MT, Life Sci. 2005, 78, 442; [PubMed: 16236327] b)Millemaggi A, Taylor RJK, Eur. J. Org. Chem 2010, 4527;c)Corsello MA, Kim J, Garg NK, Chem. Sci 2017, 8, 5836. [PubMed: 28970940]
28. a)Asensio JA, Sánchez EM, Gómez-Romero P, Chem. Soc. Rev 2010, 39, 3210; [PubMed: 20577662] b)Molina P, Tárraga A, Otón F, Org. Biomol. Chem 2012, 10, 1711; [PubMed: 22281703] c)Rabbani MG, El-Kaderi HM, Chem. Mater 2012, 24, 1511;d)Wu J, Chen J, Huang H, Li S, Wu H, Hu C, Tang J, Zhang Q, Macromolecules 2016, 49, 2145;e) Demmer CS, Rombach D, Liu N, Nielsen B, Pickering DS, Bunch L, ACS Chem. Neurosci 2017, 8, 2477; [PubMed: 28872835] f)Wang P, Arza CR, Zhang B, Polym. Chem 2018, 9, 4706;(g)Roke D, Sen M, Danowski W, Wezenberg SJ, Feringa BL, J. Am. Chem. Soc 2019, 141, 7622. [PubMed: 31017421]

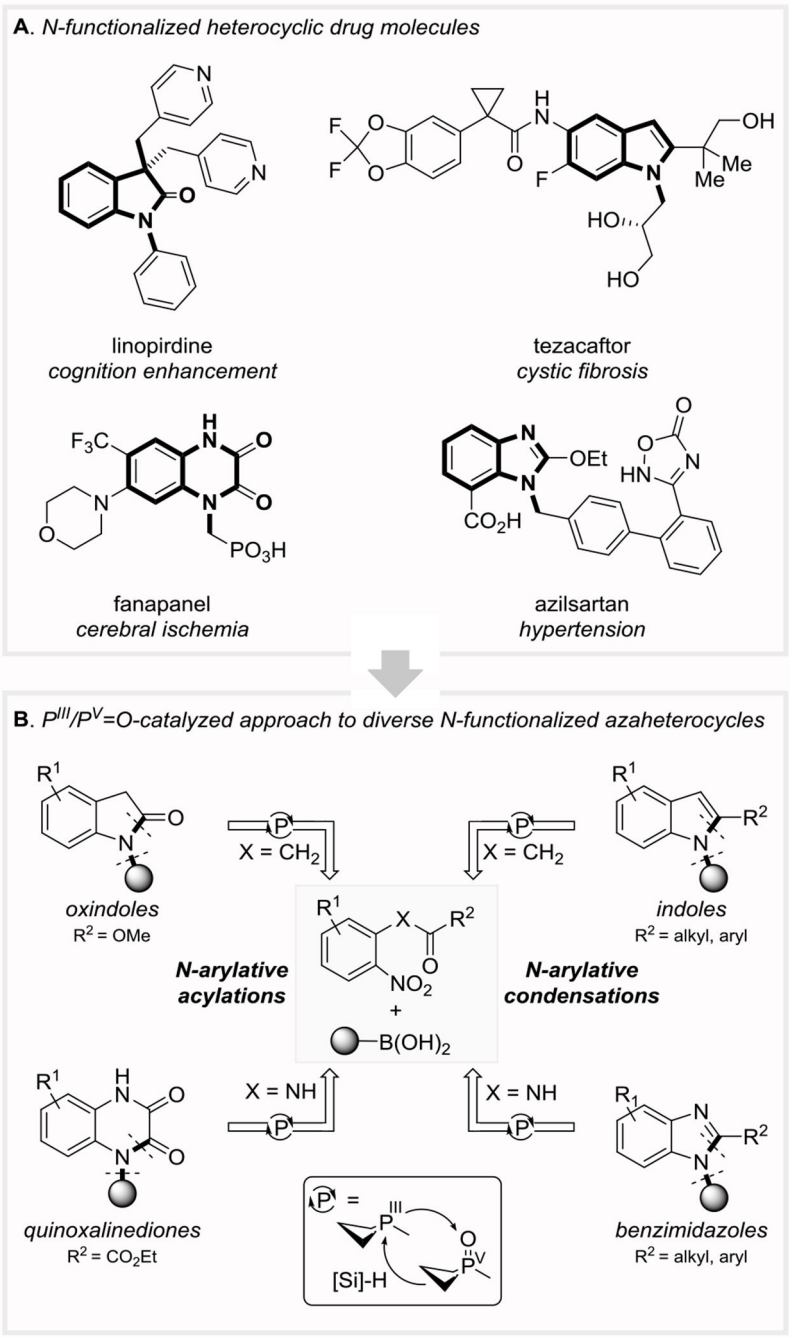


Figure 1.

(A) Selected examples of investigational and FDA-approved N-functionalized azaheterocyclic drugs. (B) Present work: A unified P^{III}/P^{V}=O-catalyzed cyclative coupling approach for the modular synthesis of oxindoles, indoles, quinoxalinediones, and benzimidazoles directly from *o*-functionalized nitroarene precursors.

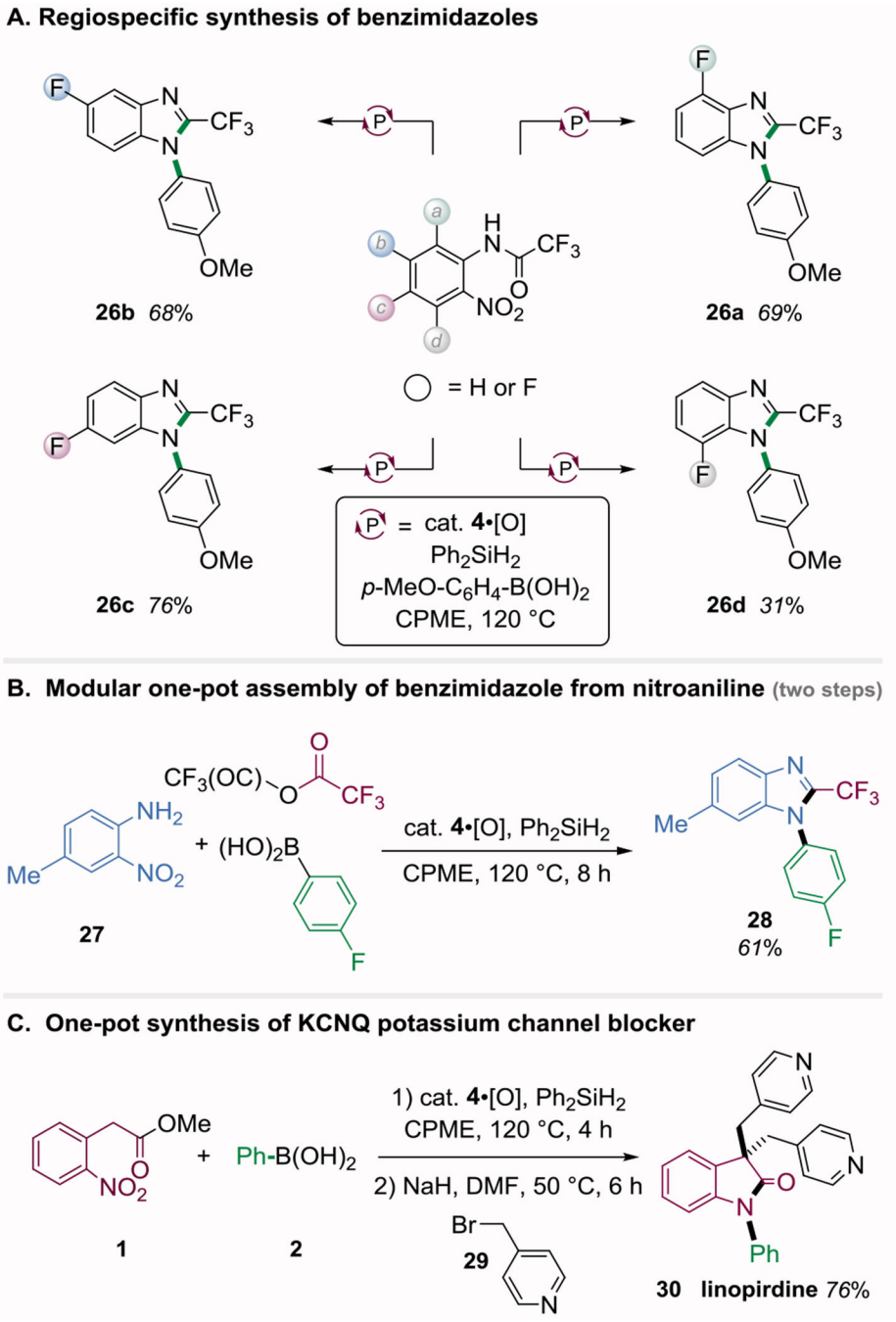
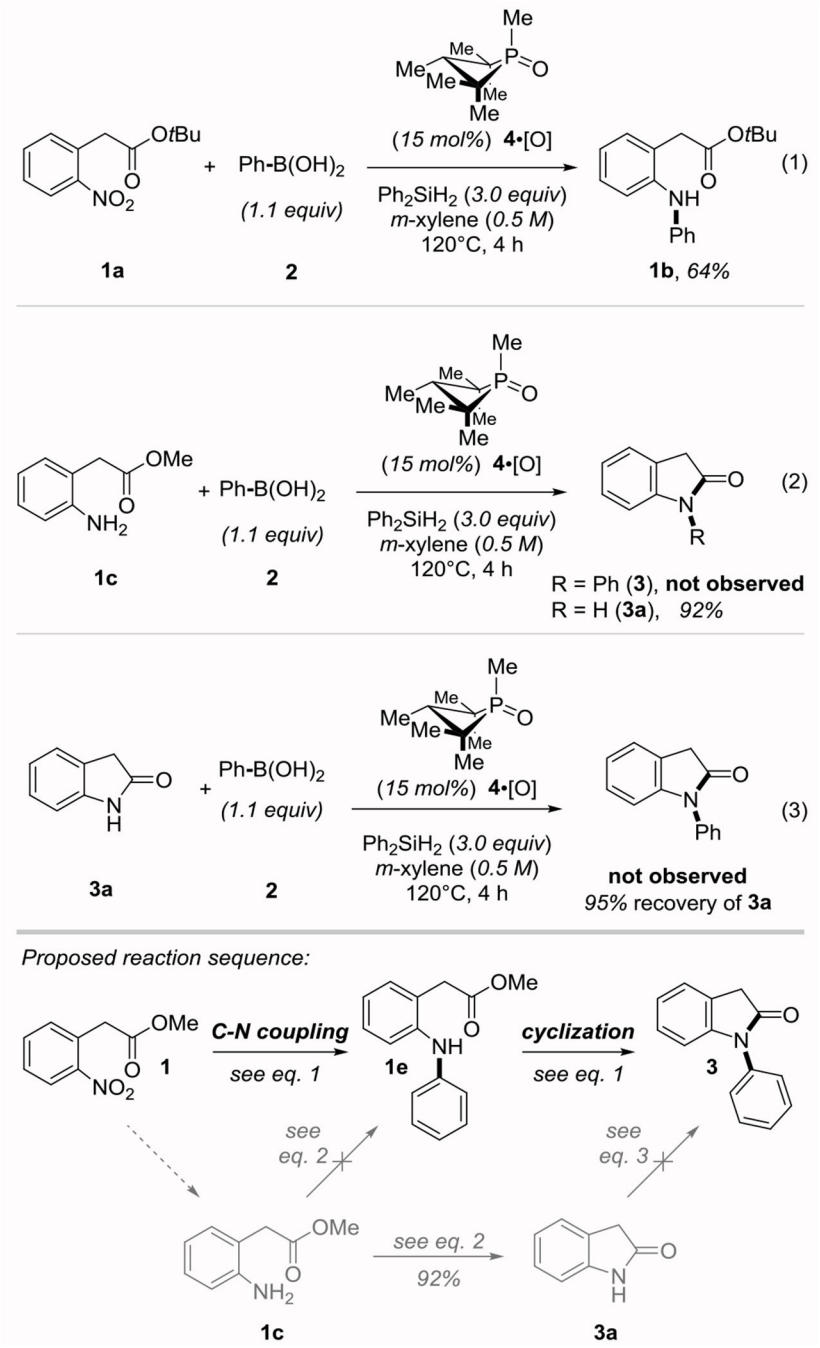


Figure 2.

Examples of catalytic reductive *N*-arylative cyclization. (A) Regiospecific benzimidazole synthesis. (B) Modular one pot amidation/reductive *N*-arylative cyclization. (C) Synthesis of linopiridine. See SI for full experimental details and conditions.

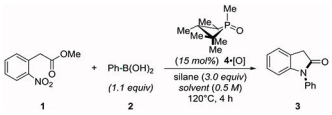


Scheme 1.

Probe experiments and proposal for the reaction sequence leading to formation of oxindole **3**.

Table 1.

Discovery and Optimization of Tandem Organophosphorus-Catalyzed Oxindole Synthesis.[a]



Entry	Solvent	Silane	$R_3P=O$	Yield (%)[a]
1	*m*-xylene	Ph_2SiH_2	**4**•[O]	85
2	*m*-xylene	Ph_2SiH_2	**4**	88
3	*m*-xylene	Ph_2SiH_2	none	0
4	*m*-xylene	none	**4**•[O]	0
5	*m*-xylene	$PhSiH_3$	**4**•[O]	83
6[b]	*m*-xylene	PMHS	**4**•[O]	87
7	CPME	Ph_2SiH_2	**4**•[O]	84
8[b]	PhCN	Ph_2SiH_2	**4**•[O]	70
9[c]	*m*-xylene	Ph_2SiH_2	**4**•[O]	79
10[d]	*m*-xylene	Ph_2SiH_2	**4**•[O]	85

[a] ^{1}H NMR yields compared to internal standard.

[b] 12 h reaction time.

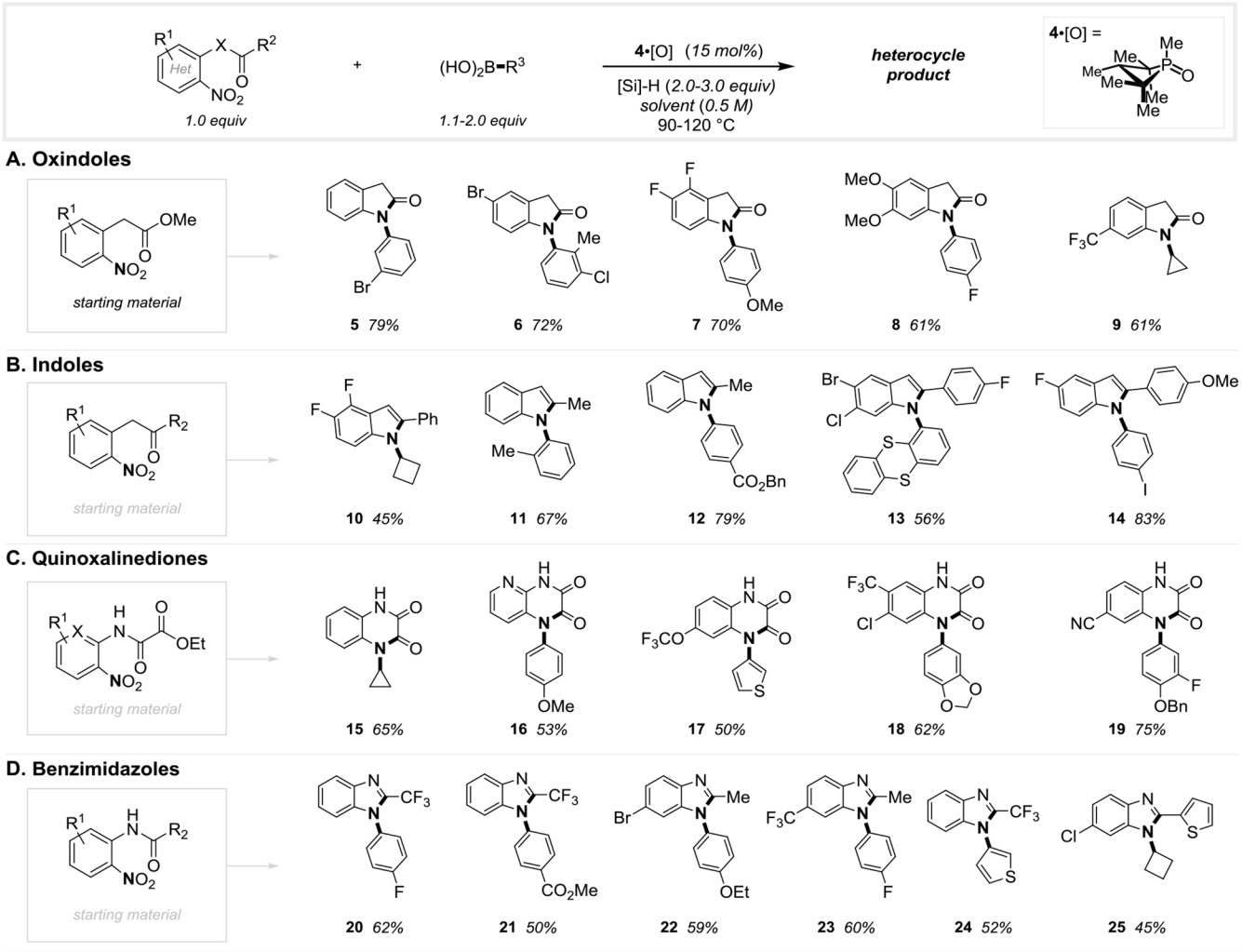
[c] Reaction run under air.

[d] 2 equiv. of H_2O added.

CPME = cyclopentyl methyl ether. See Supporting Information for full synthetic details.

Table 2.

Synthetic scope of P^{III}/P^{V}=O-catalyzed cyclative coupling method.



Representative examples of (A) oxindole, (B) indole, (C) quinoxalinedione, and (D) benzimidazole synthesis via P^{III}/P^{V}=O catalyzed tandem C–N coupling/cyclization. See SI for full experimental details and conditions. Yields are reported for pure isolated material following chromatography or recrystallization.