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

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

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 regioselective approach to *N*-substituted benzimidazoles and quinoxalinediones.

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

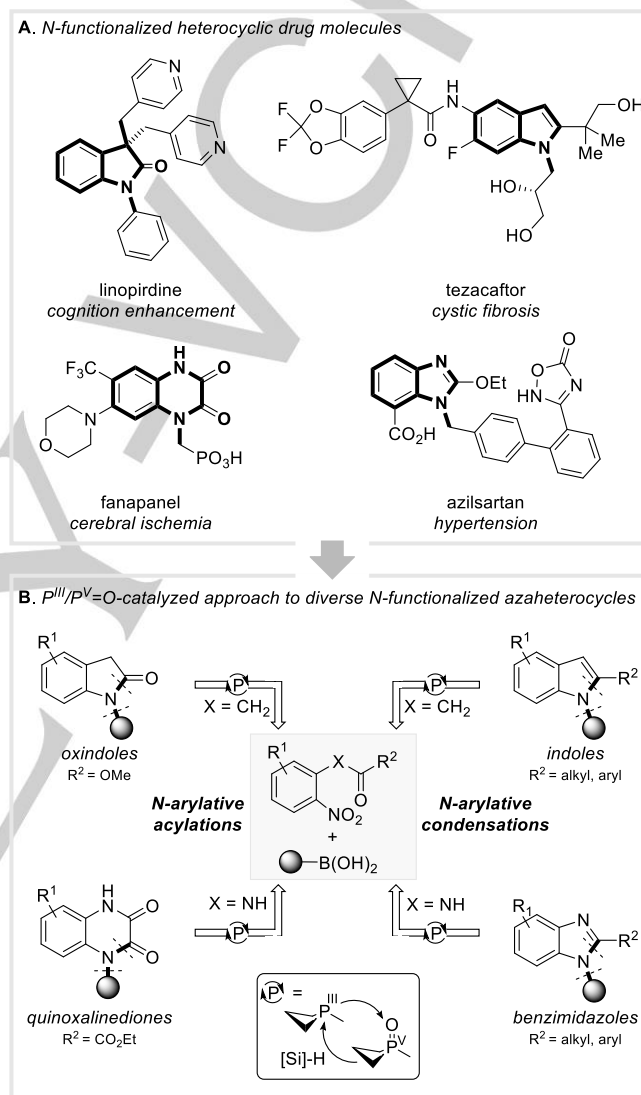


Figure 1. (A) Selected examples of investigational and FDA-approved *N*-functionalized azaheterocyclic drugs. (B) Present work: A unified P^{III}/P^V=O-catalyzed cyclative coupling approach for the modular synthesis of oxindoles, indoles, quinoxalinediones, and benzimidazoles directly from *o*-functionalized nitroarene precursors.

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 exemplified

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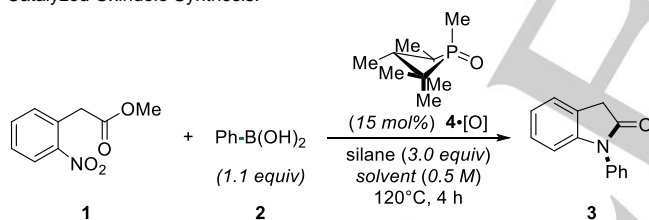
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by the regioselective preparation of multiple classes of useful heterocycles in a single operation with modular and precise control over positional substitution about the heterocyclic periphery.

Results and Discussion

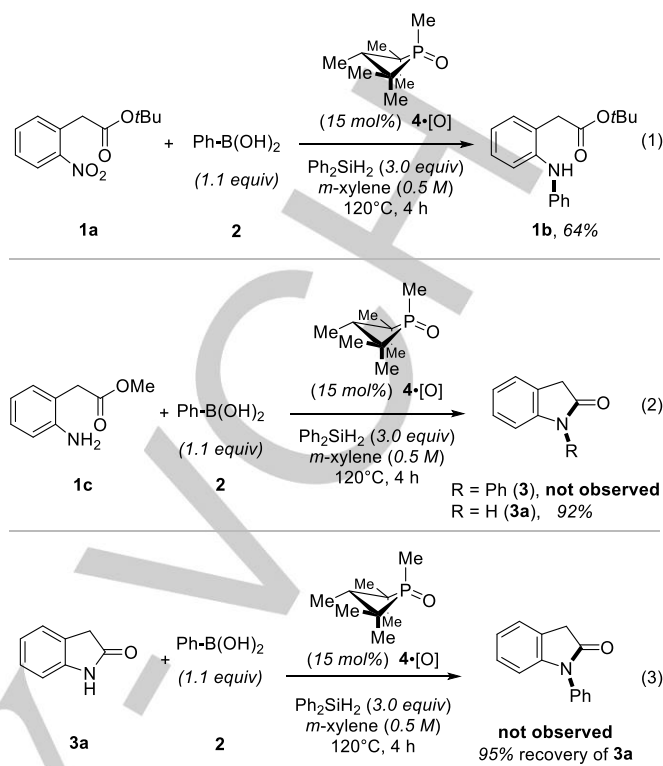
As an initial validation of the target tandem C–N coupling/cyclization reaction sequence, *N*-arylation cyclization of methyl 2-nitrophenylacetate (**1**) with phenylboronic acid (**2**) yielded oxindole product **3** in 85% NMR yield (80% isolated yield) on a 0.5 mmol scale within 4 h using 1,2,2,3,4,4-hexamethylphosphetane oxide¹⁵ (**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.

Table 1. Discovery and Optimization of Tandem Organophosphorus-Catalyzed Oxindole Synthesis.^[a]

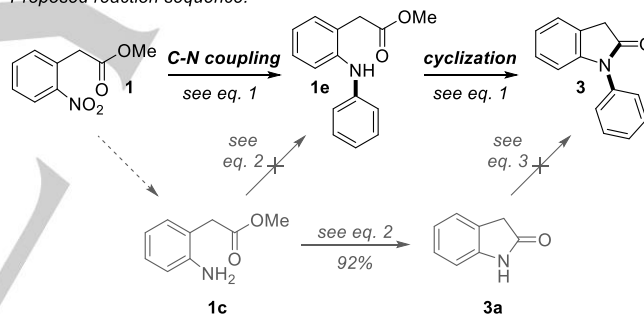


Entry	Solvent	Silane	R ₃ P=O	Yield (%) ^[a]
1	<i>m</i> -xylene	Ph ₂ SiH ₂	4•[O]	85
2	<i>m</i> -xylene	Ph ₂ SiH ₂	4	88
3	<i>m</i> -xylene	Ph ₂ SiH ₂	none	0
4	<i>m</i> -xylene	none	4•[O]	0
5	<i>m</i> -xylene	PhSiH ₃	4•[O]	83
6 ^b	<i>m</i> -xylene	PMHS	4•[O]	87
7	CPME	Ph ₂ SiH ₂	4•[O]	84
8 ^b	PhCN	Ph ₂ SiH ₂	4•[O]	70
9 ^c	<i>m</i> -xylene	Ph ₂ SiH ₂	4•[O]	79
10 ^d	<i>m</i> -xylene	Ph ₂ SiH ₂	4•[O]	85

[a] ¹H NMR yields compared to internal standard. [b] 12 h reaction time. [c] Reaction run under air. [d] 2 equiv. of H₂O added. CPME = cyclopentyl methyl ether. See Supporting Information for full synthetic details.

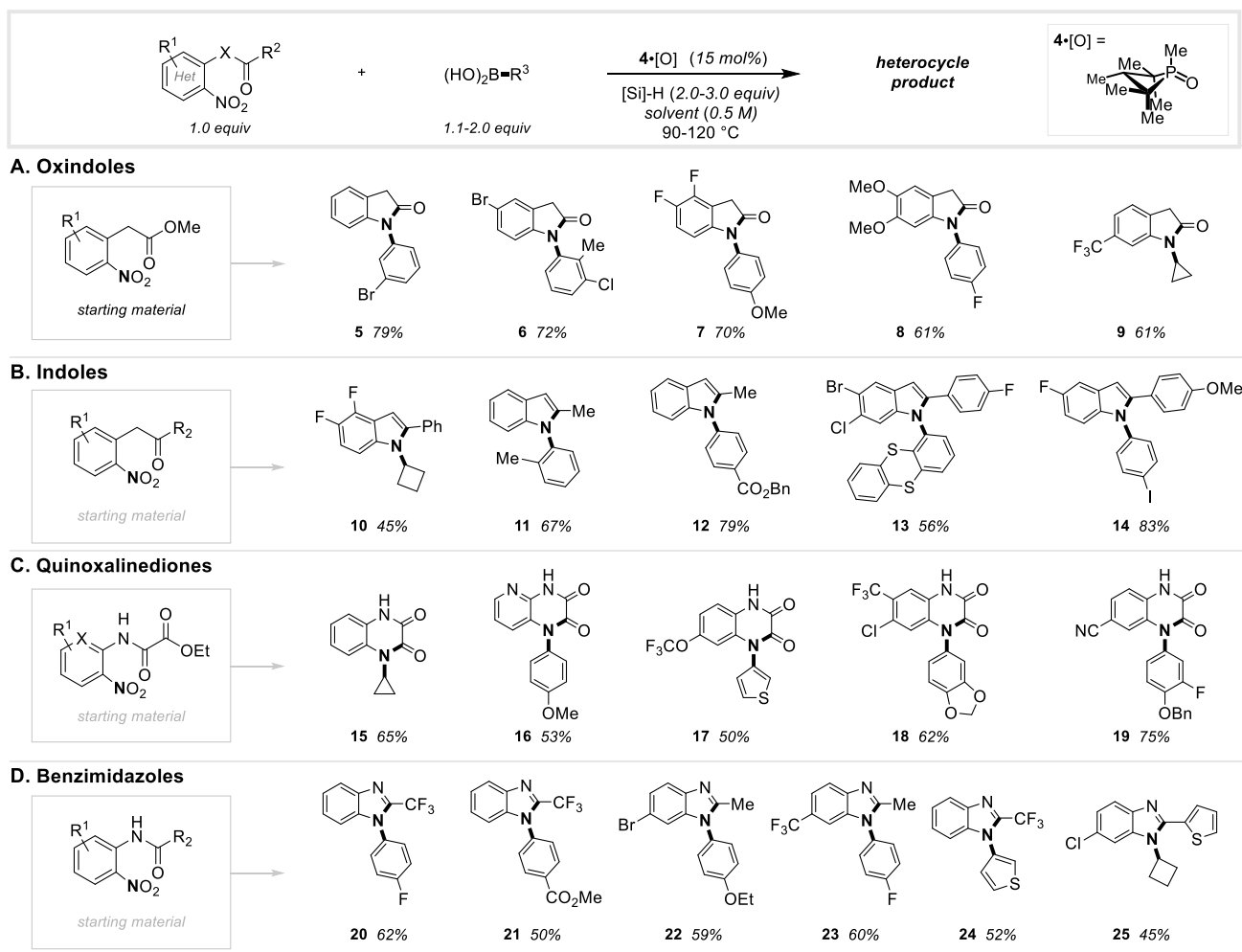


Proposed reaction sequence:



Scheme 1. Probe experiments and proposal for the reaction sequence leading to formation of oxindole **3**.

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*-arylation cyclization of **1** involving initial reductive C–N coupling to form **1e** followed by intramolecular cyclization to give **3** (Scheme 1, bottom).

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.

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-disubstituted 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*-arylation cyclization with respect to transition metal approaches is amply demonstrated within this indole series of examples. Sulfur-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

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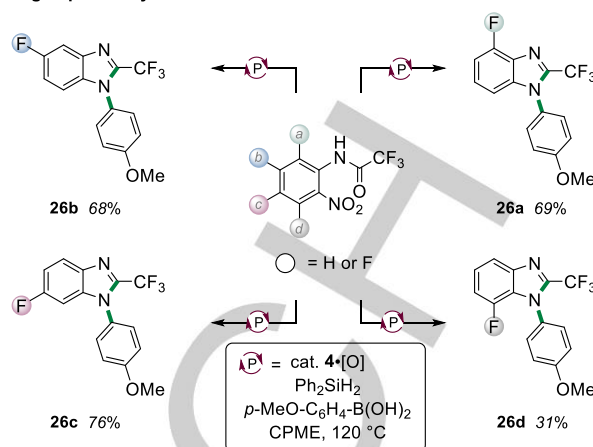
synthetic handles for the further diversification of the indole core via downstream coupling chemistry.

A family of 6-membered ring containing quinoxalinedione²¹ 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 regioselective 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*-arylation cyclization process to provide *N*-functionalized benzimidazole²² 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. With respect 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.

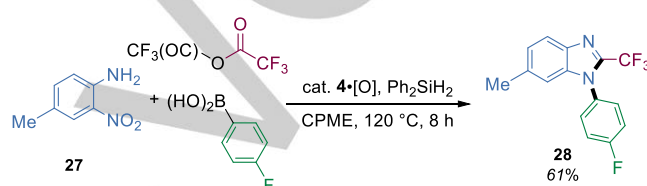
The P^{III}/P^V=O catalyzed *N*-arylation cyclization method provides a regioselective synthesis of *N*-aryl benzimidazoles in cases direct C–N coupling of the pseudosymmetric *N*-H precursor would be unselective.²³ The full suite of regioisomeric fluorinated *N*-aryl benzimidazole products **26a-26d** (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*-arylation 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 synthesized 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).

A. Regiospecific synthesis of benzimidazoles



B. Modular one-pot assembly of benzimidazole from nitroaniline (two steps)



C. One-pot synthesis of KCNQ potassium channel blocker

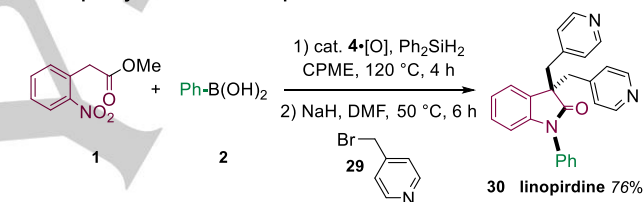


Figure 2. Examples of catalytic reductive *N*-arylation cyclization. (A) Regiospecific benzimidazole synthesis. (B) Modular one pot amidation/reductive *N*-arylation cyclization. (C) Synthesis of linopiridine. See SI for full experimental details and conditions.

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 materials²⁸ among other applications, many possible implementations of this method can be envisioned.

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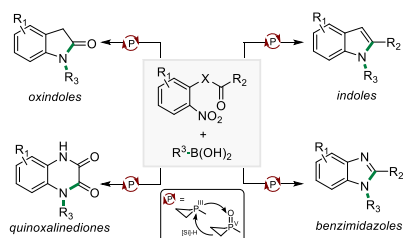
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TOC graphic:



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.