Communication

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Intermolecular Reductive C–N Cross Coupling of Nitroarenes and Boronic Acids by P^{III}/P^{V}=O Catalysis

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Supporting Information Placeholder

ABSTRACT: A main group-catalyzed method for the synthesis of aryl- and heteroarylamines by intermolecular C–N coupling is reported. The method employs a small-ring organophosphorus-based catalyst (1,2,2,3,4,4-hexamethylphosphetane) and a terminal hydrosilane reductant (phenylsilane) to drive reductive intermolecular coupling of nitro(hetero)arenes with boronic acids. Applications to the construction of both C_{sp2}–N (from arylboronic acids) and C_{sp3}–N bonds (from alkylboronic acids) are demonstrated; the reaction is stereospecific with respect to C_{sp3}–N bond formation. The method constitutes a new route from readily available building blocks to valuable nitrogen-containing products with complementarity in both scope and chemoselectivity to existing catalytic C–N coupling methods.

Aryl- and heteroarylamines comprise a diverse class of organic compounds with significant value as pharmaceuticals, agrochemicals, fine chemicals, and optoelectronic materials. The prevailing strategy for the preparation of these useful compounds—*N*-arylation of the parent aniline through carbon-nitrogen (C–N) coupling (Figure 1A)—is currently shaped by transition metal catalyzed methods (*e.g.* Buchwald-Hartwig, Ullmann, Chan-Lam couplings).[1,2] Herein, we describe an alternative main group approach to catalytic intermolecular C–N bond construction that does not rely on transition metals, enabling a complementary route from readily accessible components to (hetero)arylamines. Specifically, we show that a redox active organophosphorus-based catalyst operating in the P^{III}/P^{V}=O manifold drives reductive coupling of nitroarenes and boronic acids with C–N bond formation to give (hetero)arylamine products (Figure 1B) in a manner functionally distinct from current catalytic practice.

Nitroarenes are common intermediates in synthesis (most typically as aniline precursors), but are relatively underutilized for direct catalytic C–N bond forming reactions.[3] Notable exceptions include the work of Nicholas[4] and Baran,[5] who have reported iron-catalyzed reductive C–N bond construction by reaction of nitroarenes with alkynes and alkenes, respectively. Hu has reported a related iron-catalyzed reductive C–N bond formation by reaction of nitroarenes with alkyl[6] and acyl[7] electrophiles. Stoichiometric main group metal approaches have also been described; Knochel,[8] Kürti,[9] and Niggemann[10] have demonstrated reductive conversion of nitroarenes to *N*-arylanilines.

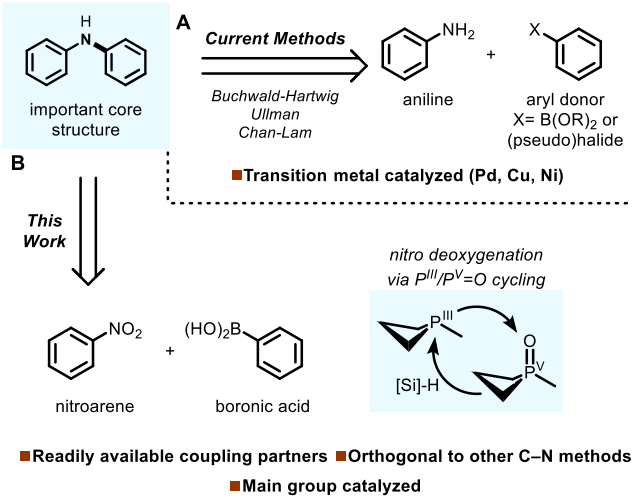


Figure 1. A) Established methods for intermolecular C–N coupling. B) This work: P^{III}/P^{V}=O-catalyzed reductive C–N coupling of nitroarenes and boronic acids.

Our entry into nitroarene functionalization has centered on the use of a redox-active small-ring phosphorus-based compound. We have previously reported that a simple trialkylphosphine catalyst containing a core four-membered ring, in combination with phenylsilane as a terminal reductant, constitutes a competent system for the catalytic transformation of nitroaromatic substrates into azaheterocycles through intramolecular C–N bond forming Cadogan cyclization.[11,12] In this chemistry, the phosphacyclic catalyst promotes reductive *O*-atom transfer from the nitroarene substrates by cycling in the P^{III}/P^{V}=O catalytic couple.[13-16] We considered whether introduction of a suitable exogenous coupling partner to the P^{III}/P^{V}=O catalytic conditions might enable the construction of C–N bonds in an intermolecular manner.

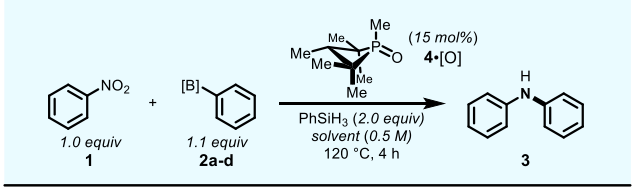
The reaction of nitrobenzene (**1**) and phenylboronic acid (**2a**) to give diphenylamine (**3**) was chosen for discovery and optimization studies (Table 1). An initial attempt at reductive coupling using conditions previously reported for Cadogan cyclization proved promising, providing diphenylamine in an unoptimized 59% yield (Fig. S1). Using the Design of Experiments approach to evaluate the impact of temperature, concentration, and reagent

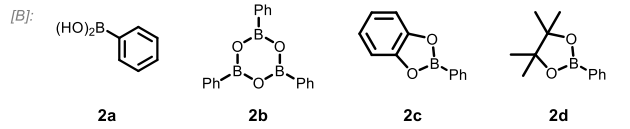
equivalencies on the reaction outcome (Fig. S2), optimization studies converged on the conditions outlined in Table 1 (entry 1, 1.1 equiv of **2a,** 15 mol % of **4**•[O], 0.5 M in *m*-xylene, 120 °C). Under these conditions, the organophosphorus-catalyzed reductive coupling of nitrobenzene and phenylboronic acid gave diphenylamine in 86% GC yield, and 80% isolated yield on a one millimole scale. A comparable performance is observed if the corresponding tricoordinate phosphacycle **4** is employed as catalyst (entry 2), consistent with the interconversion of P^{III} and P^{V}=O oxidation states by catalytic cycling. Relatedly, a stoichiometric implementation of the reductive coupling of **1** and **2a** employing 3 equivalents of phosphetane **4** is successful (89% yield) (Table S2).[17] Control experiments omitting either the phosphorus catalyst (entry 3) or the terminal silane reductant (entry 4) do not give the desired product. The reaction performed well in a variety of nonpolar solvents (entries 1,5,6), but was less efficient in a solvent of high donicity (entry 7). The identity of the boron reagent was found to play a significant role in the success of the reaction (Table 1); both phenylboronic acid (**2a**) and phenylboroxine (**2b**, entry 8) were successfully aminated by nitrobenzene to give diphenylamine **3** under standard catalytic conditions. However, other common phenylboronic esters are either less productive (catecholatoboronate **2c** – entry 9) or unproductive (pinacolatoboronate **2d** – entry 10) when employed as the aryl donor in the catalytic C–N coupling reaction, suggesting the possibility of chemoselective differentiation of boryl moieties (*vide infra*).

A qualitative assessment of the electronic demand of the reaction was undertaken (Figure 2A). For a series of differentially *para*-substituted nitroarenes, an empirical electronic trend is observed where increasingly electron-withdrawing *para* substituents lead to faster qualitative rates and higher yields of C–N coupling (cf. **5**-**8**). Complementarily, the inverse empirical trend with respect to electron demand of the arylboronic acid moiety is observed, where increasingly electron-donating *para* substituents result in higher yields of C–N coupling (cf. **9**-**12**). The consequence of these two differing trends is that the organophosphorus-catalyzed C–N coupling reaction is most productive for union of electron deficient nitroarenes with electron rich arylboronic acids, as illustrated in the synthesis of **15** in 88% by the coupling of electron-deficient nitroarene **13** with electronic-rich boronic acid **14** (Figure 2A). This observed electronic preference serves as a point of distinction with respect to palladium-catalyzed C–N coupling, where the arylation of electron-deficient arylamine substrates are among the most persistently challenging.[18] The current organophosphorus-catalyzed method may therefore provide a route to construction of otherwise electronically deactivated C–N bonds.

Additional synthetic examples illustrating the reaction scope are collected in Figure 2B. The main group-catalyzed conditions for the C–N coupling method show good functional group compatibility and provide complementary chemoselectivities with respect to established transition metal coupling. Since phosphines do not readily undergo oxidative addition to C_{sp2}–X bonds, halogen substitution is well-tolerated on both the nitroarene component (**7**, **19**, **20**) and the boronic acid (**11**, **23**, **24**) component. Even very electrophilic 2-chloro and 2-bromopyridyl substrates (**26**, **27**), which are known to be excellent electrophiles for both S_NAr and transition metal-catalyzed substitution, are carried through the phosphine-catalyzed reductive C–N coupling without undesired cleavage. Protic functional groups such as anilines (**18**, **24**) and phenols (**25**) are orthogonal in reactivity to the nitro group and are therefore tolerated in the coupling chemistry without explicit protection. Even multiple distinct nitro or boryl moieties within a single reaction pair can be differentiated in select circumstances. Due to the aforementioned electronic trends in C–N coupling (Figure 2A), 1,4-dinitrobenzene becomes electronically

Table 1. Discovery and optimization of the organophosphorus-catalyzed reductive C–N coupling reaction.[a]





Entry	[B]	Solvent	R_3P=O	Yield (%)
1	**2a**	*m*-xylene	**4**•[O]	86% (80%)
2	**2a**	*m*-xylene	**4**	82%
3	**2a**	*m*-xylene	none	0%
4	**2a**	*m*-xylene	**4**•[O]; no silane	0%
5	**2a**	dibutyl ether	**4**•[O]	86%
6	**2a**	toluene	**4**•[O]	80%
7	**2a**	DMF	**4**•[O]	17%
8[b]	**2b**	*m*-xylene	**4**•[O]	74%
9	**2c**	*m*-xylene	**4**•[O]	54%
10	**2d**	*m*-xylene	**4**•[O]	2%

[a]Yields were determined through analysis by gas chromatography (GC) with the aid of an internal standard. Yield in parenthesis (entry 1) is for isolated material from a 1.0 mmol reaction scale. [b]0.37 mmol of **2b** was used. See SI for additional optimization experiments.

deactivated following an initial reductive C–N coupling event, such that selective mono-coupling product **28** may be isolated in good yield. And notably, only selective C–N cross coupling product **29** is observed in the reaction of 4-pinacolatoborylnitrobenzene and phenylboronic acid; the Bpin moiety is inert to the main group-catalyzed conditions, allowing for further functionalization by known transition metal-catalyzed chemistry if so desired.

The reaction is not limited to C_{sp2}–N bond formation; indeed, the amination of nitrobenzene with C_{sp3} boronic acid reagents including methyl (**30**), primary alkyl (**31**), secondary alkyl (**32**), and strained cycloalkyl (**33**) provide serviceable yields of the desired C_{sp3}–N cross coupling products. As a further illustration of the synthetic utility of the transformation, a number of heteroarylamine structures displaying varied substitution on both the nitro and boronic acid components were synthesized. Carboxyesters on either the nitroarene or boronic acid reaction component were well tolerated (**34, 35**), and both π-deficient (**37**) and π-excessive (**39**) heterocycles are readily employed. As a general point, since the organophosphorus catalyst is only weakly Lewis acidic, substrates and products with Lewis basic functionalities (amines, pyridines, sulfides) are not inherently inhibitory under these main group coupling conditions.

To demonstrate the potential synthetic utility of this methodology in the context of pharmaceutical chemistry, mefenamic acid (**40)** and tolfenamic acid (**41**) (Figure 3A)—members of the fenamate group of nonsteroidal anti-inflammatory drugs (NSAIDs) marketed under the tradenames Ponstel and Clotam, respectively—were synthesized with 67% and 73% yields on 1 millimole scale in one-pot by organophosphorus-catalyzed reductive C–N cross coupling of 2-nitrobenzonitrile and either 2,3-dimethylphenylboronic acid or 3-chloro-2-methylphenylboronic

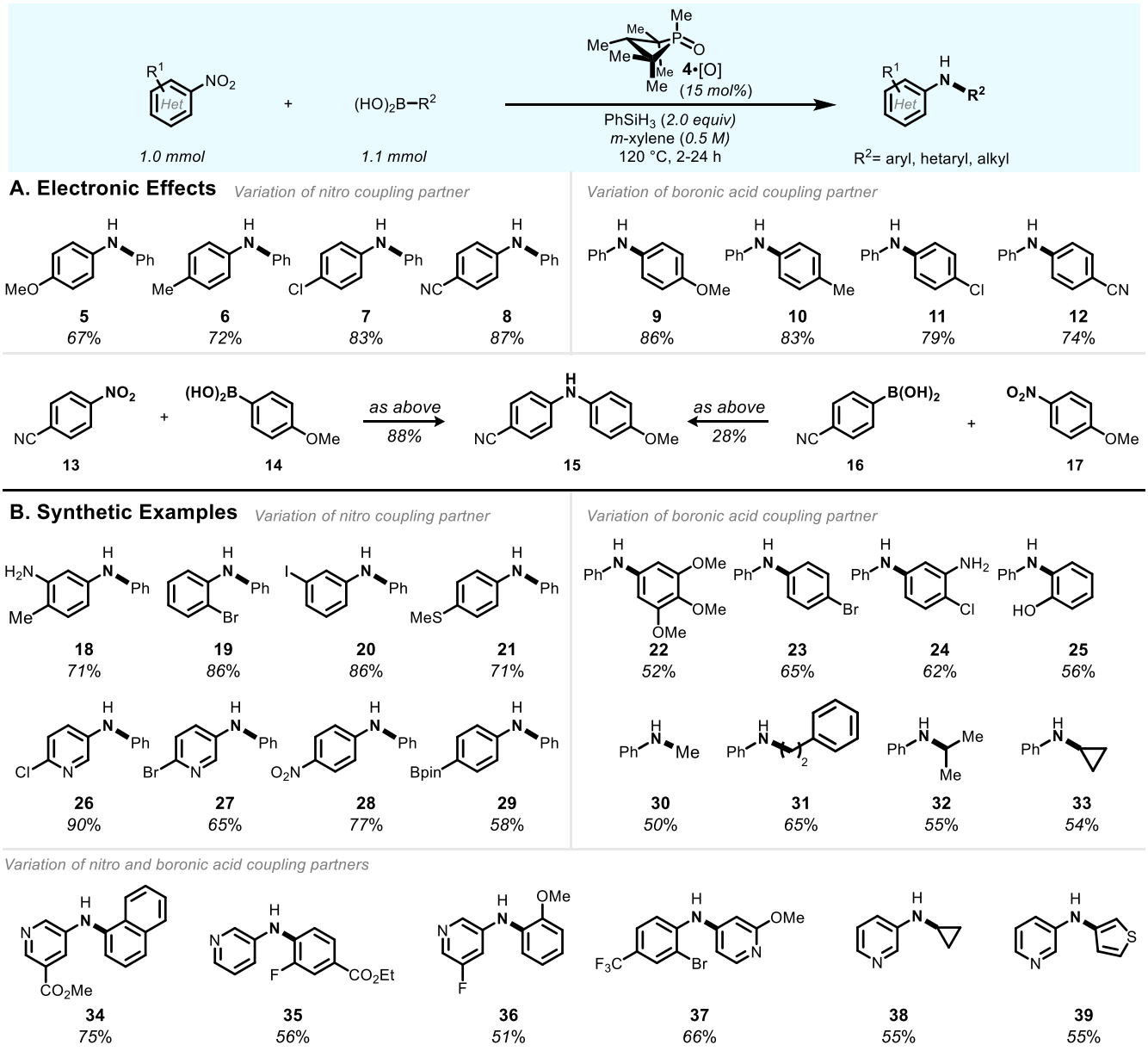


Figure 2. Examples of catalytic reductive C–N coupling. (A) Electronic effects on C–N coupling. (B) Synthetic examples of C–N coupling. See SI for full experimental details and conditions. Yields are reported for isolated material following purification on a 1 mmol scale, except as noted. Compounds **5-12** were prepared on 2 mmol scale; compound **26** was prepared on a 3 mmol scale; and compounds **34-39** were prepared on 1 gram scale. Preparation of **22** used 1.3 equivalents of boronic acid. Compound **36** was isolated as its hydrochloride salt.

acid, followed by alkaline nitrile hydrolysis according to a known procedure.[19]

The stereospecificity of the catalytic C–N coupling reaction was evaluated by amination of stereochemical probe molecules (Fig. 3B). Reductive coupling of *anti*-phenylcyclopropylboronic acid (*anti*-**42**) with nitrobenzene under standard main group-catalyzed conditions gave the *N*-phenyl tranylcypromine derivative *anti*-**43** in 71% NMR yield with retention of configuration. Relatedly, reductive coupling of the *syn*-cyclopropane epimer (*syn*-**42**) with nitrobenzene furnished *syn*-**43**, in 61% NMR yield with stereochemical retention. Consistent with related protocols for amination of boron derivatives,[20] the reductive C–N coupling reaction is stereospecific with respect to the boronic acid component, permitting its potential implementation in stereoselective synthesis.

The complementarity of the current main group method for C–N coupling with respect to existing transition metal strategies is exemplified by the diversification of 1,3,5-trisubstituted arene **44** (Figure 3C). Whereas C–N coupling under existing Cu-mediated (Chan-Lam) or Pd-catalyzed (Buchwald-Hartwig) methods permits chemoselective functionalization at the anilide (site b, **46**) or arylbromide (site c, **47**) positions, respectively, catalytic arylamination by the newly developed organophosphorus-catalyzed coupling approach results in selective functionalization at the nitro moiety (site a, **45**) in 81% yield. These results suggest a strategic orthogonality between the bond constructions possible with the various C–N coupling methods. Viewed in this light, we envision that the main group method will augment technical capacity by providing new freedom to synthesize valuable arylamine products from diverse and readily available building blocks.

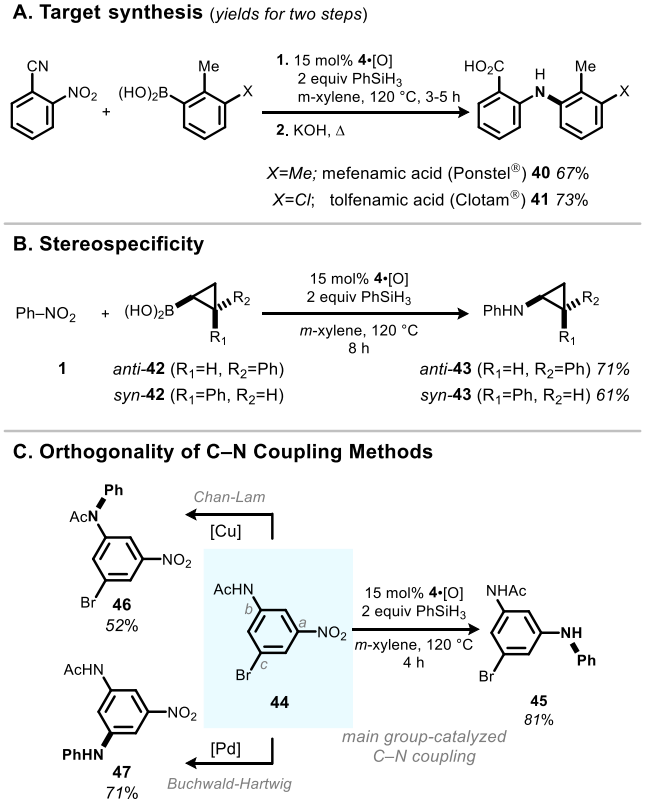


Figure 3. Synthetic applications of the catalytic reductive C–N coupling reaction. (A) Synthesis of mefenamic acid and tolfenamic acid. (B) Demonstration of the stereospecificity of C–N coupling. Yields determined by NMR spectroscopy. (C) Selectivity and complementarity in the functionalization of **44** by C–N coupling methods. See SI for full experimental details and conditions.

The foregoing results constitute a practical, scalable, and operationally robust organophosphorus-catalyzed protocol for intermolecular C–N coupling of nitroarenes and boronic acid partners. These findings expand the biphilic reactivity of phosphetanes as platforms for catalytic reductive O-atom transfer operating in the P^{III}/P^{V}=O redox couple, providing further precedent for the catalytic potential of main group compounds in reaction classes heretofore dominated by transition metal catalysis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Additional optimization results and synthetic procedures (.pdf)
^{1}H, ^{13}C, and ^{31}P NMR spectra (.pdf)

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Notes

The authors declare no competing financial interests.

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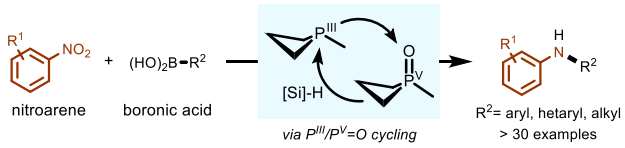
TOC graphic



■Readily available coupling partners ■Orthogonal to other C–N coupling methods

■Main group catalyzed