Communication

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P(III)/P(V)-Catalyzed Methylamination of Arylboronic Acids and Esters: Reductive C–N Coupling with Nitromethane as a Methylamine Surrogate

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Supporting Information Placeholder

ABSTRACT: The direct reductive *N*-arylation of nitromethane by organophosphorus-catalyzed reductive C–N coupling with arylboronic acid derivatives is reported. This method operates by the action of a small ring organophosphorus-based catalyst (1,2,2,3,4,4-hexamethylphosphetane *P*-oxide) together with a mild terminal reductant hydrosilane to drive the selective installation of the methylamino group to (hetero)aromatic boronic acids and esters. This method also provides for a unified synthetic approach to isotopically-labeled *N*-methylanilines from various stable isotopologues of nitromethane (i.e. CD_3NO_2, $CH_3{}^{15}NO_2$ and $^{13}CH_3NO_2$), revealing this easy-to-handle compound as a versatile precursor for the direct installation of the methylamino group.

Nitromethane ($H_3C–NO_2$) is an industrially important commodity chemical, primarily used as a solvent, stabilizer, and fuel additive.[1] Also, $H_3C–NO_2$ is a common and useful carbon pronucleophile in synthesis (Figure 1A, left),[2-5] but it is comparatively less developed as an amination reagent. Recently, Jiao and coworkers reported $H_3C–NO_2$ as a precursor to "$H_2N–X$" equivalents by reductive Nef-like decomposition,[6] but an alternative reductive N-functionalization of $H_3C–NO_2$ that retains the "$H_3C–N$" substructure would trace a role for this inexpensive and easily-handled liquid as a potential surrogate for methylamine—a gaseous List 1 controlled precursor[7]—especially in catalytic coupling chemistry (Figure 1A, right).[8-11] At present, reductive *N*-functionalization of $H_3C–NO_2$ is limited to two isolated examples: Niggemann has reported reductive *N*-benzylation of nitromethane mediated by stoichiometric B_2pin_2 in the presence of excess BnZnBr,[12] and Suarez-Pantiga and Sanz have reported a triphenylphosphine-mediated reductive *N*-phenylation of nitromethane catalyzed by an oxomolybdenum(VI) compound under microwave irradiation.[13] We report here a general catalytic method for the methylamination of arylboronic acids and esters with $H_3C–NO_2$ by reductive C–N coupling driven by P^{III}/P^{V}=O redox cycling (Figure 1B). These results expand the scope of reductive C–N coupling, generalize the use of $H_3C–NO_2$ as a methylamine surrogate in reductive cross coupling, and provide a unique pathway for introducing stable isotopes (^{15}N, ^{13}C, ^{2}H) widely-used for metabolic tracing.[14]

Prior work has established P^{III}/P^{V}=O catalysis[15-17] as a viable approach to reductive *N*-functionalization of nitroarene (Ar–NO_2) substrates,[18-20] but the translation of this technique to reductive *N*-functionalization of $H_3C–NO_2$ requires that the desired C–N coupling sequence (Figure 1B) outcompete numerous unproductive but well-known decomposition pathways, both for $H_3C–NO_2$ (e.g. Nef reaction) and potential deoxygenation intermediates (e.g. tautomerization of $H_3C–NO \rightarrow H_2C=NOH$ and $H_3C–N: \rightarrow H_2C=NH$, inter alia). In principle, the base-free

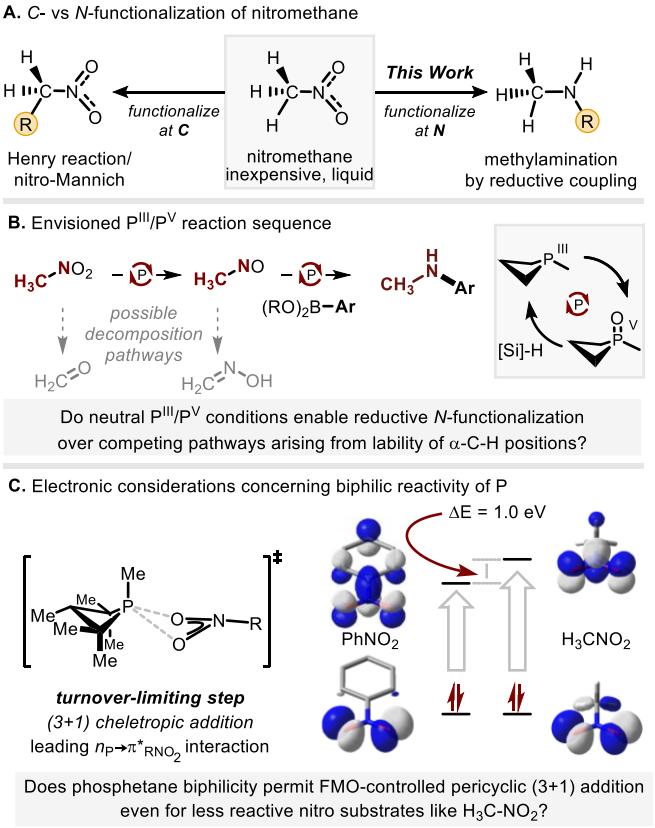


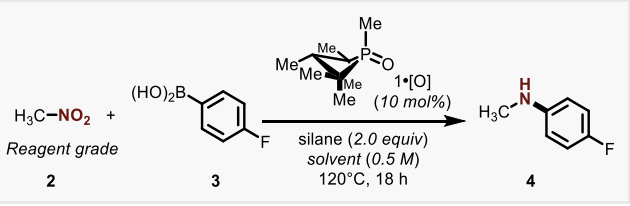
Figure 1. A) Uses of nitromethane in organic synthesis. B) Reaction sequence leading to formation of *N*-methylanilines via P^{III}/P^{V}=O-catalyzed reductive C–N coupling of nitromethane with boronic acids (esters); C) Electronic challenge presented by high frontier orbital gap of $H_3C–NO_2$. FMO=frontier molecular orbital.

conditions of the P^{III}/P^{V}=O catalyzed nitro functionalization, which depends on a rate-limiting (3+1) cheletropic addition of phosphine and nitro substrate, might suppress these processes. However, the nitro moiety of $H_3C–NO_2$ is inherently less reactive than Ar–NO_2 as cycloaddition partner due to a larger local frontier orbital energy gap ($\Delta\Delta E$= 1.0 eV, Figure 1C),[21] resulting in less favorable pairwise orbital interactions that therefore impose a stringent demand of the biphilic character of the phosphetane catalyst.

Investigation of the reductive *N*-functionalization of $H_3C–NO_2$ was initiated with these considerations in mind. Empirical

observations (Table 1) indicate that a catalytic system comprising the organophosphorus O-atom transfer catalyst **1**•[O] [22] and a terminal hydrosilane reductant indeed successfully achieve a methylamination of arylboronic acids by P^{III}/P^{V}=O-

Table 1. Discovery and Control Experiments for Organophosphorus-Catalyzed *N*-methylaniline Synthesis.[a]



Entry	silane	R_3P=O	Yield (%)[b]
1[c]	$PhSiH_3$	**1**•[O]	35
2	$PhSiH_3$	**1**•[O]	95 (90)[d]
3	$PhSiH_3$	**1**	94
4	$PhSiH_3$	None	0
5	None	**1**•[O]	0
6[e]	PMHS	**1**•[O]	85

[a] Unless otherwise noted, reactions were carried out with **1**•[O] (10 mol %), phenylsilane (0.5 mmol, 2.0 equiv), 4-fluorophenylboronic acid (0.25 mmol) and nitromethane (0.75 mmol, 3.0 equiv) in CPME (0.5 mL) at 120 °C for 18 h. [b] Yields were determined by ^{19}F NMR integration with the aid of an internal standard. [c] 1.0 equiv of **2** was used. [d] Isolated yield. [e] 24 h reaction time.

catalyzed intermolecular C–N coupling. With 4-fluorophenylboronic acid (**3**) as a representative substrate, the reductive functionalization of 1.0 equiv of commercial reagent grade $H_3C–NO_2$ (**2**) by 10 mol% of **1**•[O] and 2 equiv of $PhSiH_3$ gave a promising 35% yield of *N*-methyl-4-fluoroaniline (**4**) (Table 1, entry 1), but simply increasing equivalencies of inexpensive $H_3C–NO_2$ (3.0 equiv, entry 2) resulted in excellent yield of **4** (95% NMR yield, 90% isolated yield). A high yield was similarly obtained with phosphetane **1** as a precatalyst (entry 3)—consistent with P^{III}/P^{V}=O redox cycling—but omission of either the precatalyst **1**•[O] or phenylsilane failed to provide methylamination product **4** (entries 4-5). Inexpensive and bench-stable polymethylhydrosiloxane (PMHS) is also a viable terminal reductant for the reaction, albeit with somewhat lower efficiency (85%, entry 6). *In situ* spectral monitoring of the reductive C–N coupling showed that isotopically enriched nitromethane-d_3 (δ 4.32 ppm) is cleanly converted to the product *N*-(methyl-d_3)-4-bromoaniline (δ 2.79 ppm), and no side products or long-lived intermediates were observed (Figure S2). The relatively high concentration of the P^{III} catalyst resting state **1** presumably drives the methylamination forward along the productive reaction pathway in preference to possible side pathways, including the favorable isomerization of nitrosomethane to formaldoxime.[23,24]

As depicted in Figure 2A, the P^{III}/P^{V}=O-catalyzed methylamination method shows excellent functional group tolerance, several facets of which provide for chemoselectivities that complement transition-metal catalyzed C–N coupling methods. For example, halogen substituents are well-tolerated (**5a**, **8**-**10**, **16**) in the P^{III}/P^{V}=O-catalyzed methylamination and intermolecular C–N coupling occurs exclusively at the boronic acid position. Also, the orthogonal reactivity to the nitro group with respect to other nitrogen-containing functional groups permits selective aryl methylamination even in the presence of free -NH_2 groups (**16**) without explicit protection. Carbonyl functionalities such esters (**13**) and ketones (**17**, **19**) that might be susceptible to acylation or condensation reaction with $H_3C–NH_2$

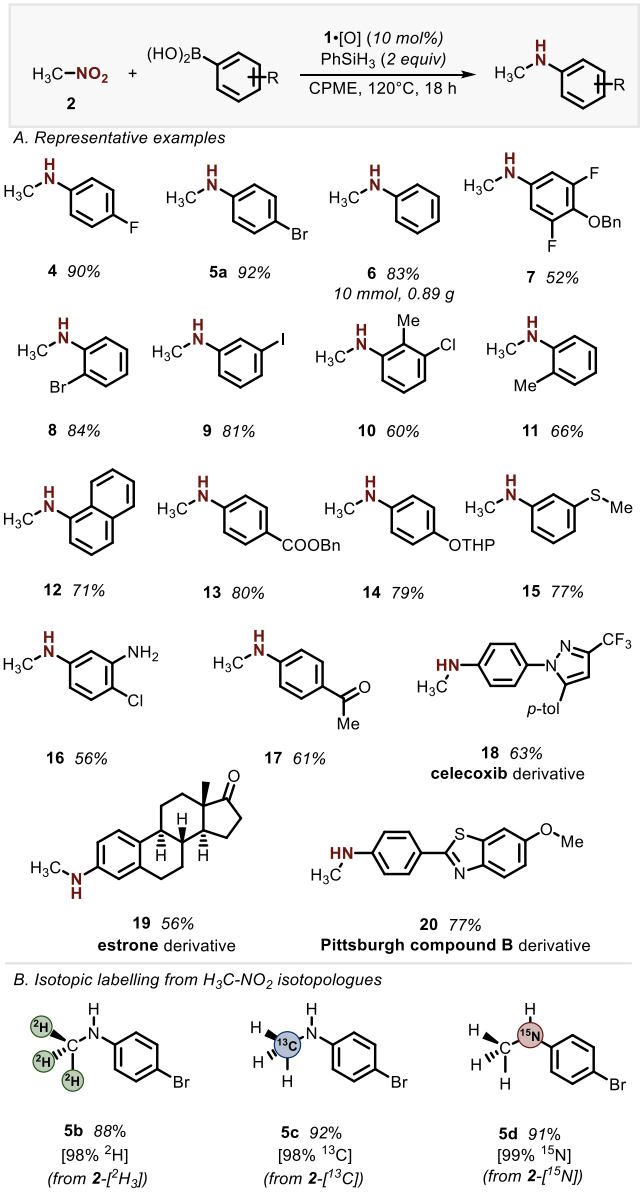


Figure 2. Synthetic scope of P^{III}/P^{V}=O-catalyzed C–N coupling of nitromethane and arylboronic acids. See SI for full experimental details and conditions. Yields are reported for material obtained following purification and isolation.

are retained when $H_3C–NO_2$ is used as a surrogate. Furthermore, substrates with other functional groups including benzyloxy (**7**), tetrahydropyranyl ether (**14**), thiomethyl (**15**), and trifluoromethyl (**18**) groups all yielded the corresponding *N*-methylaniline products in good yields. The method is also applicable to compounds with known bioactive core structures, such as derivatives of celecoxib (**18**), estrone (**19**), and Pittsburgh compound B[25] (**20**).

The ability to use of $H_3C–NO_2$ as a simple synthetic precursor for the MeHN– group presents the opportunity for the preparation of diverse stable-isotope labeled products—useful tools in both laboratory[26] and pharmaceutical[27] research—through a unified synthetic strategy. As illustrated in Figure 2B, a suite of isotopically labeled *N*-methylaniline products **5b**-**5d** are acces-

sible with programmed labeling as dictated by the initial isotopic composition of the nitromethane isotopologue (viz. $^{2}H_3C–NO_2$ (**2b**), $H_3{}^{13}C–NO_2$ (**2c**), $H_3C–{}^{15}NO_2$ (**2d**)). The relative ease with which the isotopologues of nitromethane are accessed make this an attractive approach to potentially valuable stable isotope labeled compounds.

Initial attempts to directly transfer the foregoing P^{III}/P^{V}=O-catalyzed conditions to methylamination of 3-quinolylboronic acid resulted in a disappointing 19% yield of the target compound **21** (Figure 3A, yield in parenthesis). Studies showed that protodeboronation of the heteroarylboronic acid was a primary pathway limiting the productive C–N coupling in this case.[28] Correspondingly, P^{III}/P^{V}=O-catalyzed methylamination of 3-quinolylboronic acid 1,3-propanediolate ester showed a significant improvement in C–N coupling yield (93%), in line with the relative stability of boronic esters to protodeboronation as compared to their parent boronic acids.[28] This phenomenon is general; *B*-heteroaryl-1,3,2-dioxaborinanes including a variety of five- and six-membered heterocyclic derivatives, such as isoquinoline (**22**), indazole (**23**) pyridine (**24**, **27**), thiophene (**25**) and pyrimidine (**26**), were successfully transformed to the corresponding *N*-methylamine derivatives with improved yields relative to their arylboronic acid congeners. *B*-Aryl-1,3,2-dioxaborinanes containing electron-donating

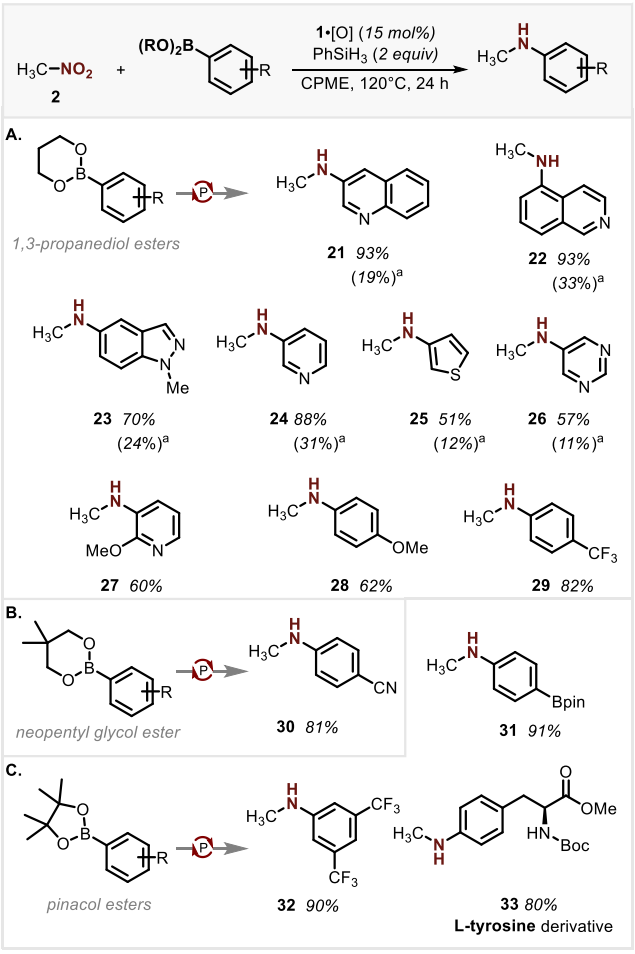


Figure 3. Synthetic scope of P^{III}/P^{V}=O-catalyzed C–N coupling of nitromethane and (hetero)arylboronic esters. See SI for full experimental details and conditions. Yields are reported for material obtained following purification and isolation. [a] Yields for reactions with boronic acids were determined by ^{1}H NMR with dibromomethane as the internal standard.

(**28**) or electron-withdrawing group (**29**) transform smoothly to the desired products, showing the generality of utilizing boronate esters for methylamination reactions. Other common boronate ester residues such as a neopentyl glycol ester (e.g. Ar-Bnep **30**, Figure 3B) and pinacol esters (e.g. Ar-Bpin **31**-**33,** Figure 3C) gave similar efficiency in this methylamination process. Notably, subjection of benzene-1,4-diboronic acid bispinacol ester to the standard reaction conditions afforded single methylamination product **31** with excellent yield; evidently the second (pinacolato)boryl moiety becomes electronically deactivated for amination following an initial reductive C–N coupling.

Competition experiments evidence a differential reactivity of $H_3C–NO_2$ as compared to $Ar–NO_2$ substrates in P^{III}/P^{V}=O-catalyzed reductive C–N coupling. As illustrated in Figure 4A, an equimolar mixture of four componenets—namely $H_3C–NO_2$ (**2**), 4-NC-C_6H_4–NO_2 (**34**), 3,5-$(F_3C)_2$-C_6H_3–Bpin (**35**) and 4-H_3CO-C_6H_4–$B(OH)_2$ (**36**)—was subjected to standard reductive C–N coupling conditions catalyzed by **1**•[O] in a one pot manner. In the event, only two of the possible four products—specifically methylaniline **29** and diarylamine **37**—were observed in greater than 5% yield. Consistent with the FMO rationale in Figure 1,[15i] this observation implies that nitroarene **34** reacts more quickly than nitromethane **2** via (3+1) cheletropic addition with **1**, and goes on to couple selectively with the more reactive boronic acid partner **36**. In a subsequent event, $H_3C–NO_2$ then reacts to give **29** by methylamination of the more inert boronic ester **35,** proceeding without diminished yield for these reaction partners.[29] This kinetically-controlled chemoselectivity was further demonstrated by the modular synthesis of *N,N'*-difunctionalized phenylenediamine (Figure 4B, **42**). The three-component coupling of $H_3C–NO_2$, Ph–$B(OH)_2$ (**40**), and 4-nitrophenylboronic ester (**41**) produced **42** via sequential amination reactions with almost complete suppression of undesired methylaminated product (**6**).

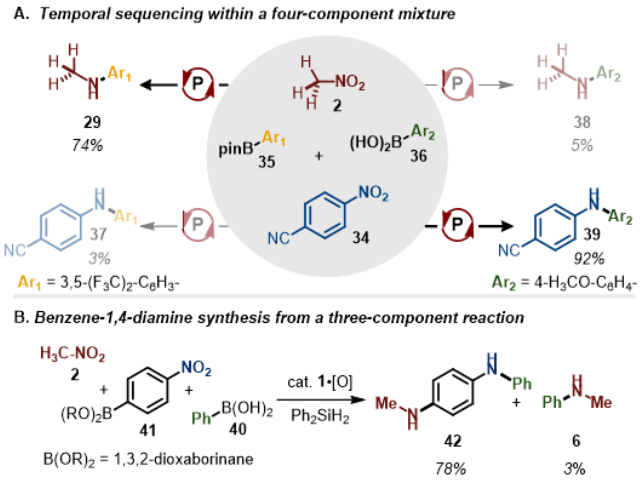


Figure 4. A) Reaction of a four component mixture illustrating differential reactivity of H_3CNO_2 vs $ArNO_2$ and $ArB(OH)_2$ vs $ArB(OR)_2$. (B) Selective three-component coupling via sequential C–N coupling reactions.

A synthesis of the anxiolytic triflubazam[30] (**45**, Figure 5) contextualizes the reductive C–N coupling of nitromethane within the growing portfolio of P^{III}/P^{V}-catalyzed methods promoted by phosphetane catalyst **1**•[O]. Specifically, P^{III}/P^{V}-catalyzed reductive C–N coupling of phenylboronic acid and 4,4,5,5-tetramethyl-2-(2-nitro-5-(trifluoromethyl)phenyl)-1,3,2-diox-

aborolane (**43**), followed in situ by P^{III}/P^{V}-catalyzed amidation[15h,31] with mono-ethyl malonate gives diarylamide **44** in a one-pot sequence. Subsequent P^{III}/P^{V}-catalyzed methylamination by C–N coupling with $H_3C–NO_2$ installs the MeHN– moiety and induces intramolecular cyclization to close the diazepinedione ring, furnishing the medicinal target **45** in an overall 51% yield for the two-pot, three-step, all-P^{III}/P^{V}-catalyzed sequence.

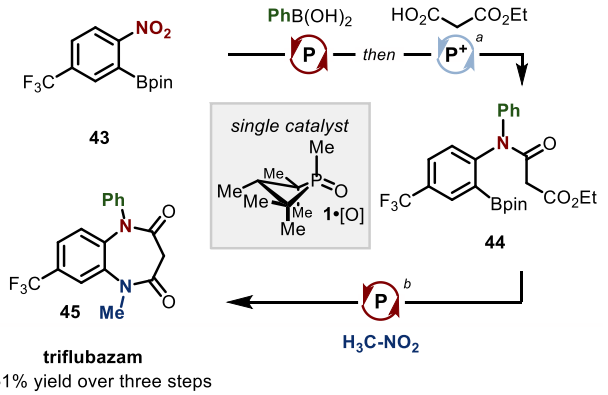


Figure 5. Two-pot, three step synthesis of triflubazam by an all-P^{III}/P^{V}-catalyzed sequence. Reaction conditions: (a) **43** (1.0 equiv), $PhB(OH)_2$ (1.1 equiv), Ph_2SiH_2 (4.0 equiv), **1**•[O] (30 mol%), CPME, 120 °C ; then add monoethyl malonate (1.2 equiv), diethylbromomalonate (1.5 equiv), 40 °C; (b) **44** (1.0 equiv), $H_3C–NO_2$ (3.0 equiv), Ph_2SiH_2 (3.0 equiv), **1**•[O] (15 mol%), CPME, 120 °C.

In summary, we have demonstrated that nitromethane is an inexpensive and easy-to-handle synthetic equivalent for installation of the MeHN– fragment via P^{III}/P^{V}=O catalysis. Readily-available boronic acids and esters are selectively methylaminated in the presence of various functional groups and heteroaromatics. The method serves as a robust complementary tactic to transition metal catalyzed C–N coupling techniques relying on the use of $MeNH_2$ or related surrogates. With respect to our efforts to develop P^{III}/P^{V}=O-catalyzed reductive C–N coupling reactions as modular approach to complex amine synthesis, this study represents our first success with nitroalkane substrates and portends future developments in the deoxygenative *N*-functionalization of higher nitroalkane homologues to access more elaborate *N*-alkyl products

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
General methods and synthetic procedures (.pdf)
^{1}H, ^{2}H, ^{13}C, ^{15}N, ^{19}F and ^{31}P NMR spectra (.pdf).

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Notes

The authors declare no competing financial interests.

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