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

Gen Li, Trevor V. Nykaza, Julian C. Cooper, Antonio Ramirez, Michael R. Luzung, and Alexander T. Radosevich*

1. INTRODUCTION

Aryl- and heteroarylamines are common in pharmaceuticals, natural products, agrochemicals, and functional materials. Consequently, the efficient construction of C–N bonds has been the target of considerable innovation. In particular, developments in transition-metal-catalyzed C–N coupling chemistry have shaped the dominant approach to arylamine synthesis. Chief among these methods is the Buchwald–Hartwig reaction (Figure 1A), which enables the net redox-neutral nucleophilic substitution of aryl (pseudo)halide with N-nucleophiles via Pd(0)/Pd(II) activation of the electrophilic partner through oxidative addition. A growing mastery over this important reaction has been enabled by increasingly detailed mechanistic understanding, with progressive optimizations of reaction conditions, ligands, and catalyst precursors resulting in ever-improving scope and efficiency. In an alternative approach, intermolecular C–N cross coupling can be achieved in an oxidative manner by the reaction of N-nucleophiles with arylboron reagents under aerobic copper catalysis (i.e., Chan–Lam reaction, Figure 1B). In addition to the synthetic complementarity, this approach is supported in a practical sense by the impressive catalog of arylboron derivatives now available both commercially and by synthesis. And as with the Buchwald–Hartwig reaction, considerable experimental effort has helped to decrypt significant aspects of the Chan–Lam mechanism, providing the basis for an increasingly reliable and predictive model of reactivity with this method.
As part of an ongoing program aimed at developing designer main-group compounds as biphilic organocatalysts in organic synthesis, we reported recently a reductive method for intermolecular C–N cross coupling. This method relies on an all-main-group system composed of an organophosphorus P(III)/P(V) redox catalyst and hydroxilane terminal reductant to transform nitroarenes and boronic acids into N-arylamines through intermolecular C–N bond formation (Figure 1C).

The chief attributes of this method include (1) the use of precursors (i.e., nitroarenes) that are distinct from—but no less accessible than—those used in established C–N cross coupling methods, and (2) unique chemoselectivities and functional group tolerance inherent to the all-main-group conditions of the P(III)/P(V) catalytic manifold.

To better understand the reductive P(III)/P(V)–O-catalyzed C–N bond-forming process and facilitate its further synthetic development, we were animated by several unresolved questions, including the following: (1) What is the nature of the turnover-limiting step in the catalytic C–N coupling reaction, and what is the role of the organophosphorus catalyst in this step? (2) What is the relationship of the catalytic C–N coupling reaction to related methods involving P(III)/P(V)–O-catalyzed nitroarene deoxygenation, and to what extent do the reactive intermediates coincide? (3) Can further improvements in reaction scope be attained, especially as informed through hypothesis-based experimentation within a mechanistic rationale?

In this Article, we provide an integrated experimental, spectroscopic, and computational description of the biphilic organophosphorus-catalyzed reductive C–N coupling strategy that systematically delineates the nature of deoxygenative events of nitroaromatics, especially in the context of the C–N bond formation. Among the key findings, we present herein: (1) a qualitative description of reaction parameters, culminating in a generally improved set of reaction conditions that enable heretofore challenging coupling reactions of azaheterocyclic nitroarene and boronic acids partners; (2) competition experiments that differentiate the intermolecular C–N cross coupling reaction from previous P(III)/P(V)–O-catalyzed C–N bond-forming methods, and weigh against the intermediacy of veritable arylnitrene intermediates along the C–N coupling pathway; (3) experimental spectroscopic and kinetic evidence that establish a P(III) resting state of the phosphetane catalyst and imply a rapid P(V)→O→P(III) turnover step for this small-ring phosphacycle; (4) a computational description of the overall energy landscape for the C–N coupling reaction pathway with an explicit description of the importance of organophosphorus biphilicity through energy decomposition analysis of the turnover-limiting transition state. Through these results, we establish the P(III)/P(V)–O-catalyzed intermolecular reductive C–N cross coupling of nitroarenes and aryloboronic acids as an operationally robust and mechanistically well-defined main-group complement to the established transition-metal-based methods for catalytic intermolecular C–N coupling.

2. RESULTS

2.1. Impact of Reaction Condition Variables. An evaluation of experimental variables for the organophosphorus-catalyzed reductive C–N coupling of nitroarenes and boronic acids was undertaken in order to provide a qualitative description of the parameter space that controls reaction yield and efficiency.

2.1.1. Solvent Dielectric Influences Yield. Prior optimization efforts had identified the high-boiling hydrocarbon m-xylene (ε = 2.6) as a suitable solvent for reductive intermolecular C–N coupling. Specifically, coupling of nitrobenzene (2) and phenylboronic acid (3) in m-xylene proceeds with full conversion of starting material and an 86% yield of product diphenylamine 4 over the course of 4 h at 120 °C. The ethereal solvent di-n-butyl ether (ε = 3.1) performed similarly (Figure 2). However, with increasing solvent polarity a significant and non-monotonic effect of solvent on the reaction outcome was observed. Solvents of moderate polarity, such as cyclopentyl methyl ether (CPME, ε = 4.8) and 1,2-dichlorobenzene (ε = 9.9) lead to improved yields (Table 1, entries 3 and 4), but further increases in solvent polarity (i.e., benzonitrile (PhCN, ε = 26.0), N-methyl-2-pyrrolidone (NMP, ε = 32.0), and dimethyl sulfoxide (DMSO, ε = 46.7) were shown to erode both the conversion and the yield. On the basis of the foregoing experiments, CPME—which exhibits favorable process characteristics—was selected as the solvent of choice for the further study.

2.1.2. Performance Is Maintained at Low Catalyst Loading and Temperature. The robustness of the phosphetane catalyst 1-[O] under conditions of catalysis allow for significant decreases in its loading. For instance, decrease in loading of 1-[O] to 5 mol% (Table 1, entry 2) or 2 mol% (Table 1, entry 3) permits high conversion and yield, with the provision of a compensatory elongation of the reaction time to 10 and 36 h, respectively. Relatedly, the catalytic transformation is retained with high yield even at temperatures down to 60 °C (Table 1, entries 4 and 5), emphasizing the high reactivity of the phosphetane catalyst.

2.1.3. Numerous Common Hydroxilane Reductants Are Viable. Our “first-generation” conditions for P(III)/P(V)–O-catalyzed reductive C–N coupling called for the use of 2.0...
The reaction does not strictly require PhSiH₃ as the hydrosilane terminal reductant, but instead a wide range of common silicon-based reducing reagents are able to be interfaced with the PIII/PV=O-catalyzed reductive C–N coupling. Along with Ph₂SiH₂ (Table 1, entry 9), a variety of siloxane-based reductants including 1,1,3,3-tetramethyldisiloxane (TMDS, Table 1, entry 10), 2,4,6,8-tetramethylcyclotetrasiloxane (TMCTS, Table 1, entry 11), and poly(methylhydro)siloxane (PMHS, Table 1, entry 12) are viable. Of these, PMHS is particularly attractive due to its ease of handling and low cost, recommending it for further method development.

As previously observed, the aryl C–N coupling reaction is most effective when aryloboronic acid coupling partners are employed. Even under optimal reaction conditions, the use of phenylboronic acid pinacol ester (Ph–Bpin) in place of phenylboronic acid (3) results in only trace formation of coupling product 4 (Table 1, entry 13). The lower overall observed conversion (49%) is connected to substantial catalyst decomposition when the less-efficient boronate partner is employed.

2.1.4. Modified Conditions Enable Coupling of Previously Challenging Partners. With an eye toward an expanded scope for the PIII/PV=O-catalyzed reductive C–N coupling method, we sought to determine if the versatility of the reaction conditions observed in the foregoing sections would provide an opportunity to approach previously problematic classes of coupling partners. The reaction of 1-methyl-5-nitroindole (5) with 4-fluorophenylboronic acid (6) is an illustrative example (Table 2). When applying typical first-generation reaction conditions (Table 2, entry 1), only 13% yield was obtained of the desired reductive coupling product 7. However, consistent with the solvent effect reported in section 2.1.1, a solvent

Table 1. Effect of Hydrosilane Loading and Identity on the Organophosphorus-Catalyzed Reductive C–N Coupling Reaction

| entry | change from *standard conditions* | conv (yield) (%) | entry | change from *standard conditions* | conv (yield) (%) |
|-------|----------------------------------|-----------------|-------|----------------------------------|-----------------|
| 1     | none                             | 99 (96)         | 2     | 5 mol% of 1-[O], 10 h            | 99 (95)         |
| 2     | 2 mol% of 1-[O], 36 h            | 99 (93)         | 3     | 80 °C, 20 h                      | 99 (95)         |
| 4     | 60 °C, 96 h                      | 99 (95)         | 5     | 0.77 equiv of PhSiH₃             | 98 (94)         |
| 6     | 0.66 equiv of PhSiH₃             | 85 (79)         | 7     | 0.33 equiv of PhSiH₃             | 49 (46)         |
| 8     | 3.0 equiv of Ph₂SiH₂             | 98 (88)         | 9     | 3.0 equiv of TMDS               | 93 (85)         |
| 10    | 1.5 equiv of TMCTS               | 99 (83)         | 11    | 4.0 equiv of PMHS               | 99 (96)         |
| 12    | Ph-Bpin instead of Ph(OH)₂       | 49 (trace)      | 13    |                                 |                 |

*Yields were determined through analysis by gas chromatography with the use of dodecane as an internal standard. ²Solvents: CPME, cyclopentyl methyl ether; DCB, 1,2-dichlorobenzene; PhCN, benzonitrile; NMP, N-methyl-2-pyrrolidone; DMSO, dimethyl sulfoxide. ³ε is the dielectric constant.

Figure 2. Solvent effect evaluation on the organophosphorus-catalyzed reductive C–N coupling reaction. *Yields were determined through analysis by gas chromatography with the use of dodecane as an internal standard.

Table 2. Impact of Reaction Variables on Reductive C–N Coupling of Heterocyclic Nitroarenes

| entry | SiH (equiv) | solvent       | yield (%) | entry | SiH (equiv) | solvent       | yield (%) |
|-------|-------------|---------------|-----------|-------|-------------|---------------|-----------|
| 1     | PhSiH₃ (2)  | m-xylene (0.25 M) | 13        | 2     | PhSiH₃ (2)  | CPME (0.25 M) | 27        |
| 3     | PMHS (6)    | m-xylene (0.25 M) | 47        | 4     | PMHS (6)    | CPME (0.25 M) | 68 (66)b |

*Yields were determined through analysis by ¹⁹F NMR with the aid of 4-fluorotoluene as an internal standard. bIsolated yield in parentheses.
change to CPME resulted in a somewhat improved yield (27%, entry 2). Even more significantly, though, use of the hydroysilane reductant PMHS in m-xylene resulted in significantly improved yields (47%, Table 2, entry 3). The beneficial solvent and hydrosilane effects are synergistic in this case, such that the reaction of 5 and 6 conducted with PMHS in CPME provides coupling product 7 in a preparatively useful yield (68%, Table 2, entry 4).

These “second-generation” conditions (i.e., catalyst, 15 mol % 1,2,2,3,4,4-hexamethyldiphosphate oxide (H:D); reductant, poly(methylhydro)siloxane; solvent, CPME) have been found to provide a general improvement in yield for all C−N coupling reactions we have assayed to date, and especially so for a variety of five- and six-membered heterocyclic nitroarenes that had previously been challenging to the intermolecular reductive P(III)/P(V)=O-catalyzed C−N coupling method (Table 3). In addition to indole 7, a range of heteroarylnitro substrates are converted with reductive C−N coupling into the corresponding heteroarylamines as exemplified by pyrazole 8, 2H-indazole 9, pyrimidine 10, and aminobenzothiazole 11. Furthermore, reactions involving the incorporation of heteroaryl boronic acid coupling partners are similarly advantaged by the modified “second-generation” conditions; for instance, 1H-indazolyl (12), pyrazolyl (13), pyrimidinyl (14), and pyridinyl (15) boronic acids are successfully coupled with (hetero)aryl nitro partners. In all cases, though, the modified “second-generation conditions” afford marked improvements over the previously reported “first-generation conditions” and allow preparatively useful yields of functionally dense heteroarylamines. In instances where the heteroaryl boronic acid is found to be thermally unstable with respect to protodeboronation, a further modification to decrease the reaction temperature (80−100 °C) is found to be permissible (12−14).

### Table 3. Examples of Reductive C−N Coupling of Heterocyclic Nitroarenes and/or Boronic Acids

| Entry | R1 | R2 | Yield | See Supporting Information for full experimental details |
|-------|----|----|-------|----------------------------------------------------------|
| 7     | Me | Me | 13%   | 66%                                                     |
| 8     | Me | Me | 22%   | 67%                                                     |
| 9     | Me | Me | 72%   | 78%                                                     |
| 10    | Me | Me | 49%   | 84%                                                     |
| 11    | Me | Me | 34%   | 65%                                                     |
| 12    | Me | Me | 41%   | 66%                                                     |
| 13    | Me | Me | 55%   | 86%                                                     |
| 14    | Me | Me | 27%   | 65%                                                     |
| 15    | Me | Me | 28%   | 70%                                                     |
| 16    | Me | Me | 32%   | 56%                                                     |

*Yields reported for isolated products. Reaction was conducted at 100 °C. Reaction was conducted at 80 °C. See Supporting Information for full experimental details.*

#### 2.2. Competition Studies: Intermolecular C−N Coupling vs Arylnitrene Reactivity

In an effort to delineate the relationship between the reductive C−N coupling reaction from previously reported P(III)/P(V)=O-catalyzed reactions of nitroarenes, we designed a set of competition experiments as described in Tables 4 and S. As a point of reference, subjection of 2-nitrobiphenyl (17) to first-generation catalytic conditions with omission of the phenylboronic acid coupling partner resulted in formation of carbazole (19) by intramolecular cyclization (Table 4, entry 1). As previously reported, this C=N−H amination reaction proceeds by two-fold sequential deoxygenation to give an arylnitrene that undergoes insertion into the proximal C−H position. We postulated that if similar arylnitrene intermediates were involved in the C−N cross coupling reaction with boronic acids, then a competition between intramolecular carbazole cyclization and intermolecular arylnitrene amination with 2-nitrobiphenyl as a probe substrate would favor the former on kinetic grounds. In the event, reaction of 2-nitrobiphenyl (17) in the presence of phenylboronic acid 3 under otherwise identical reaction conditions led preferentially to the intermolecular reductive C−N cross coupling as the dominant reaction product (Table 4, entry 2). Notably, the use of CPME as the solvent (Table 4, entry 3) accentuates the bias in favor of the C−N cross coupling.

In a related fashion, intermolecular competition experiments are similarly inconsistent with formation of arylnitrenes on the pathway to C−N cross coupling. Deoxygenation of 4-nitrobenzonitrile (20) under conditions of P(III)/P(V)=O catalysis proves competent for arylnitrene generation, as inferred from in situ trapping with diethylamine to give azepine 22 as the major product (Table S, entry 1). However, when phenylboronic acid is admitted under otherwise identical reaction conditions, the reaction is shunted away from formation of azepine 22, instead providing the diarylamine 21 by C−N coupling in good yield (Table S, entry 2). As before, CPME as the solvent (Table S, entry 3) further favors formation of the C−N cross coupling product 21 relative to azepine 22.

The implications of these results are two-fold. First, the C−N cross coupling reaction evidently does not result from amination of the arylboronic acids by a free arylnitrene, but rather the mechanistic branching point along the pathway leading to cyclization or coupling must precede arylnitrene formation. Second, the impact of CPME on the product ratio suggests that the qualitative solvent effect observed in section 2.1.1 may arise through the relative suppression of the nitrene-forming pathway, which is nonproductive with respect to intermolecular C−N bond formation.

#### 2.3. In Situ Spectroscopic Studies

2.3.1. Catalyst Speciation in Reductive C−N Coupling. In order to evaluate the catalyst speciation, in situ 31P NMR spectra (161.9 MHz, 100 °C) were recorded under conditions of catalysis for the coupling reaction of nitrobenzene and phenylboronic acid (1.0
equiv of 2, 1.1 equiv of 3, 15 mol% of 1·[O], 2 equiv of phenylsilane, 0.2 M in toluene-d8). These spectra showed that phosphetane oxide 1·[O] (δ 55.9 ppm) is rapidly converted (t1/2 ≈ 5 min) to the corresponding tricoordinate phosphetane epimers anti-1 and syn-1 (δ 32.9 and δ 19.2 ppm, respectively)21 (Figure 3). Over the ensuing reaction time during which 2 is converted to 4, the tricoordinate epimers of 1 remain the only observable phosphorus-containing compounds in solution. Evidently, reduction of the phosphetane oxide 1·[O] is quite swift and the reduced tricoordinate phosphetane 1 represents the resting state with respect to the catalytic phosphorus component. These observations run counter to prevailing notions about the kinetic inertness of phosphine oxides and provide evidence for the exceptional reactivity of phosphetane oxide 1·[O] as a biphilic O-atom transfer catalyst.

2.3.2. Reactant Speciation in Reductive C–N Coupling. 1H NMR spectra (400 MHz, 100 °C) of a catalytic reaction show consumption of nitrobenzene over ca. 3 h with concomitant appearance of diphenylamine 4 as the major product (Figure 4). 15N NMR spectra (40.5 MHz, 100 °C) collected under identical conditions indicate that isotopically enriched 15N-nitrobenzene (δ 369.4 ppm) is cleanly converted into the product diphenylamine (δ 86.0 ppm), and no long-lived intermediates are observed in the range 950 ppm > δ > −50 ppm (Figure S1).

2.4. Catalytic Kinetics Experiments. The kinetic progress of the catalytic coupling of nitrobenzene 2 and phenylboronic acid 3 was monitored via ex situ HPLC analysis.
of reaction aliquots drawn at intervals over the course of 7 h. Nitrobenzene 2 is converted to diphenylamine 4 in >95% efficiency with no discernible intermediates (chromatograms in Figure S4), consistent with the observations from NMR spectroscopy. The decrease in concentration of starting material 2 as a function of time fits a first-order kinetic model (Figure S5A), where the initial rates vary linearly with 

\[ \nu = k_{\text{exp}}[1\cdot[O]]^{2}[2]^{3}[\text{PhSiH}_{3}]^{0} \]

2.5. Computational Studies. 2.5.1. Initial Deoxygenation and Rate-Determining Step. Density functional theory calculations, conducted with the M06-2X/6-311++G(d,p) level with a polarizable continuum model (PCM) for solvation in m-xylene (ε = 2.3478), provide an atomistic-level proposal of mechanism that agrees with spectroscopic and kinetic studies. In accordance with our previous calculations on nitroarene-phosphine reactivity, DFT predicts a stepwise pathway for reductive C–N coupling initiated by a (3+1) chelotropic addition of nitrobenzene 2 with phosphetane 1 to form pentacoordinate spiro-bicyclic dioxazaphosphetane Int-1 (Figure 6A). The transition state for the concerted (3+1) addition step can be viewed as a Woodward–Hoffmann allowed \([\sigma_{e}+\omega]_{1}\) cycloaddition (TS-1, Figure 6B) with a computed barrier of \(\Delta G^2_{\text{el}} = +31.0 \text{ kcal/mol}\). By virtue of this relatively high barrier, passage through TS-1 represents the slowest step in the computed pathway, kinetically gating all downstream events and providing a rationale for the failure to spectroscopically detect any reaction intermediates. Dioxazaphosphetane Int-1 evolves by a retro-(2+2) fragmentation with a low kinetic barrier via TS-2 (Figure 6B, \(\Delta G^2_{\text{el}} = +10.8 \text{ kcal/mol}\)) to give phosphine oxide 1-[O] and nitrosobenzene (Int-2) (\(\Delta G^2_{\text{el}} = −31.9 \text{ kcal/mol}\)). The lower activation barrier calculated for the collapse of the spirobicyclic Int-1 (via TS-2) relative to its formation (via TS-1) stems from the incipient dissociation of P-oxide 1-[O] and release of ring strain during the fragmentation.

EDA-NOCV calculations of the charge flow and pairwise orbital interactions of TS-1 validate the biphilic character of phosphetane 1. Electrostatic (\(\Delta E_{\text{elstat}} = −81.1 \text{ kcal/mol}\)) and orbital interactions (\(\Delta E_{\text{orb}} = −68.2 \text{ kcal/mol}\)) between the phosphetane 1 and nitrobenzene 2 fragments are attractive and comparable in magnitude, accounting for 54.3% and 45.7% of the bonding interactions, respectively. Together, \(\Delta E_{\text{elstat}}\) and \(\Delta E_{\text{orb}}\) offset the Pauli electron pair repulsion term (\(\Delta E_{\text{Pauli}} = 137.8 \text{ kcal/mol}\)) to afford a total binding energy of −11.5 kcal/mol. Analysis of the deformation densities displays both the electron donation from the HOMO of phosphetane 1 to the LUMO of nitrobenzene 2 and the backward electron donation from the HOMO of nitrobenzene 2 to the LUMO of phosphetane 1. The main deformation density (\(\Delta q_{\text{el}} = −1.0592\)) corresponds to a strong σ-donation from the phosphorus lone pair to the nitroarene and contributes to a stabilization of −56.8 kcal/mol (Figure 7A). An additional deformation densities with a smaller contribution (\(\Delta q_{\text{el}} = −0.2823\)) is consistent with π-backdonation from the nitroarene to the P–C σ* antibonding orbitals of the phosphetane and provide a considerable stabilization of −9.0 kcal/mol (Figure 7B).

A second-order perturbation natural bond orbital (NBO) analysis of TS-1 affords additional insight into donor–acceptor interactions. Phosphorus lone pair σ-donation is represented by incipient σ P–O bonds polarized toward the oxygen that display an approximate composition of 38.52% P(sp^2.44) + 62.59% C(sp^4.40), also act as donors delocalized over the O lone pairs. Interestingly, endocyclic σ P–C bonds of the phosphetane, which are polarized toward the carbon and present an approximate composition of 37.41% P(sp^2.44) + 62.59% C(sp^1.61), also act as donors delocalized into the geminal acceptor σ* P–O bonds. In contrast, π-symmetry back-donation from the nitroarene to the P–C σ* antibonding orbitals of the phosphetane provides a considerable stabilization of −7.9 kcal/mol (Figure 7B).
attack of the phosphorus on the oxygen\textsuperscript{27} in agreement with a prevalence of the LUMO coefficient of the N\textsuperscript{O} group at the nitrogen atom.\textsuperscript{28} Electrophilic ring opening of oxazaphosphirane Int-3 with phenylboronic acid via TS-4 (\(\Delta G^\ddagger_{\text{rel}} = +6.2\) kcal/mol) coincides with the favorable formation of phosphonium oxyaminoborate betaine Int-4 (\(\Delta G^\ddagger_{\text{rel}} = -2.1\) kcal/mol), featuring a typical aminoboronate B\textendash{}N bond length and an intramolecular charge-dipole contact between the phosphorus and the OH group of the aminoborate moiety. As a suitable zwitterionic retron for 1,2-metalate rearrangement,\textsuperscript{24,29} Int-4 represents the immediate precursor to C\textendash{}N bond formation, evolving via TS-5 (\(\Delta G^\ddagger_{\text{rel}} = +11.7\) kcal/mol) with departure of phosphine oxide \(1\cdot\text{[O]}\) by antiperiplanar migration of the phenyl group from boron to nitrogen to give phenylboramidic acid (Figure 7D). A DFT analysis of the competition between the Cadogan cyclization and the reductive C\textendash{}N coupling pathways for 2-nitrobiphenyl (17) qualitatively supports the experimental preference for C\textendash{}N coupling discussed in section 2.2 (Tables 4 and 5).\textsuperscript{30} Following a rate-limiting first deoxygenation of the nitro group by phosphetane \(1\cdot\text{[O]}\) (TS-6, \(\Delta G^\ddagger_{\text{rel}} = +29.7\) kcal/mol) to afford 2-nitrosobiphenyl (23) (Figure 8A), reaction of the nitroso group with \(1\) takes place via a significantly lower barrier (TS-8, \(\Delta G^\ddagger_{\text{rel}} = +17.2\) kcal/mol) to give the “branching” intermediate oxazaphosphirane Int-6. In the Cadogan cyclization pathway, Int-6 evolves through loss of phosphetane P\textendash{}oxide \(1\cdot\text{[O]}\) (TS-9, \(\Delta G^\ddagger_{\text{rel}} = +15.0\) kcal/mol) to form the carbazole product (19) via C\textendash{}H insertion of the biphenylnitrene Int-7 (TS-10, \(\Delta G^\ddagger_{\text{rel}} = +8.9\) kcal/mol).\textsuperscript{15c} Alternatively, in the reductive C\textendash{}N coupling pathway, Int-6 reacts with phenylboronic acid (TS-11, \(\Delta G^\ddagger_{\text{rel}} = +9.9\) kcal/mol) to generate phosphonium oxyaminoborate betaine Int-8, which undergoes 1,2-metalate rearrangement and dissociation of phosphine P\textendash{}oxide \(1\cdot\text{[O]}\) (TS-12, \(\Delta G^\ddagger_{\text{rel}} = +12.2\) kcal/mol). Inspection of the nonlimiting steps that intervene in the branching of oxazaphosphirane Int-6 suggests that the experimental preference for reductive C\textendash{}N coupling can be attributed to the circumvention of the biphenylnitrene pathways that mediates the Cadogan cyclization via a higher energy barrier TS-9 (Figure 8B).

\[
\sigma(R_3P \rightarrow O_2N-R) \quad \pi(R_3P \leftarrow O_2N-R)
\]

\[
\Delta q^{d}_{\sigma} = -1.0592 \quad \Delta q^{bd}_{\pi} = -0.2823
\]

\[
\Delta E_{\text{orb}} = -56.8 \text{ kcal mol}^{-1} \quad \Delta E_{\text{orb}} = -9.0 \text{ kcal mol}^{-1}
\]
3. DISCUSSION

As a complement to established net redox neutral (Buchwald−Hartwig and related) and net oxidative (Chan−Lam) transition-metal-catalyzed C−N coupling methods, the current method brings together nitroarene and arylboronic acid coupling partners through net reductive catalysis enabled by the P(III)/P(V) redox couple. Nitroarenes are attractive coupling partners because they are readily accessible and easily transformed in synthesis; the nitro functional group is both easily installed and strategically useful due to its powerful inductive effect.31 And while nitroarenes are common precursors to aryl amine and aryl halide substrates for known transition-metal-catalyzed couplings, they are less commonly used as substrates themselves for direct catalytic C−N bond-forming reactions. Precedent within this vein includes the work of Nicholas, who established iron-catalyzed reductive C−N bond construction by reaction of nitroarenes with alkynes;32 Baran, who has discovered an iron-catalyzed synthesis of N-alkylamines by reductive C−N bond formation between nitroarenes with alkynes;33 and Shaver and Thomas, who have described related transformations catalyzed by an iron bis(phenolato)amine catalyst.34 Hu has reported iron- and nickel-catalyzed reductive C−N bond formation by reaction of nitroarenes with alkyl and acyl electrophiles, respectively.35

Apart from these catalytic methods, there exist several reagent-based approaches to direct conversion of nitroarenes to the corresponding N-functionalized anilines. Knochel36 and Kužiti37 have demonstrated the use of excess Grignard reagents to convert nitroarenes to N-arylanilines directly. Niggemann has found that the combination of nitroarenes with organozinc reagents in the presence of stoichiometric B2pin2 results in reductive conversion to N-functionalized anilines.38 Recent works from our group19 and Csáky40 have validated a stoichiometric, phosphine-mediated reductive coupling of nitroarenes and aryloboronic acids. Relatedly, Suárez-Pantiga and Sanz reported that phosphine-mediated reductive coupling of nitroarenes and boronic acids is catalyzed by an oxomolybdenum compound.41 Among these varied approaches, the P(III)/P(V) O-catalyzed method—with its relatively mild conditions, commercial catalyst, and inexpensive reductant—compares rather favorably.

With regard to the mechanism of the P(III)/P(V) O-catalyzed reductive C−N coupling reaction, the combined experimental and computational data point toward a catalytic reaction sequence that evolves in two stages—an initial deoxygenation of the nitroarene substrate to the corresponding nitrosoarene (Figure 9, top hemisphere), and a subsequent second deoxygenation that converts the intermediate nitrosoarene into the observed N-arylated product (Figure 9, bottom hemisphere). The common thread uniting these two sequential reduction events is the action of the small-ring phosphacycle to catalyze O-atom transfer by redox cycling in the P(III)/P(V) couple. Since O'Brien's initial report of an organophosphorus-catalyzed Wittig reaction,42,43 P(III)/P(V) redox catalysis has emerged as an productive area of organophosphorus catalysis,44−46 with work from Woerpel,47 Rutjes and van Delft,48 Werner,49 Mecinovic,48g Kwon,50 and Voituriez,51 among others.52−55 In the context of the current C−N coupling method, the observation that the resting state of the catalyst resides at the P(III) oxidation state (i.e., phosphetane 1) confirms the swift deoxygenation kinetics of small-ring phosphine oxides noted by Marsi56 and Keglevich57 and makes clear that P(V)O−P(III) turnover...
is not a significant impediment to method development in the P(III)/P(V) couple with these catalytic structures.

The initial nitroarene-to-nitrosarene deoxygenation event is gated by a (3+1) chelotropic addition of nitrobenzene 2 with phosphetane 1. Consistent with experimental spectroscopy and kinetics, DFT modeling confirms that this step is turnover limiting and highest in energy of any transition state in the entire reductive C–N coupling sequence. Analysis of the transition structure within both the EDA-NOCV and NBO theoretical frameworks validates the notion of pairwise orbital interactions allowing for electron flow both to and from the phosphorus site, in accord with the concept of “biphlic” (i.e., synergistic single-site donor/acceptor) reactivity of the phosphetane. The relative magnitudes of the donor and acceptor interactions suggest that the former predominates, which is consistent with Hammett studies (see SI) indicating a net transfer of electron density to the nitroarene in the transition state. Once formed, Int-1 evolves via retro-(2+2) fragmentation to liberate phosphate oxide 1·[O] and nitrosobenzene (Int-2), an obligatory albeit unobserved intermediate under catalytic conditions. The phosphate oxide 1·[O] is itself subject to rapid deoxygenation by hydrosilane to return to the P(III) resting state (1) and close the first catalytic deoxygenation cycle.

The second deoxygenation stage commences with capture of nitrosobenzene (Int-2) by P(III) phosphetane 1 through an asynchronous (2+1) addition to provide an oxazaphosphirane Int-3. On the basis of product distributions obtained from competition studies between intermolecular C–N coupling vs arylnitrene reactivity, we posit that this oxazaphosphirane Int-3 serves as the pivotal “branching” intermediate whose fate is a key determinant of product distribution. Whereas unimolecular loss of phosphate oxide 1·[O] from Int-3 liberates an arylnitrene reactive intermediate that results in azepine ring expansion or Cadogan cyclization (cf. TS-9), DFT predicts a low-energy bimolecular reaction of oxazaphosphirane Int 3 with arylboronic acid leads to heterolytic ring-opening (cf. TS-4) and formation of betaine Int-4. We surmise that the apparent solvent influence in the competition experiments (section 2.1) operates by stabilization of partial charge buildup in the transition states leading to and from dipolar structure Int-4 (i.e., TS-4 and TS-5), relative to dissociative loss of phosphetane oxide 1·[O]. In analogy to numerous related electrophilic amination reactions of organoboror reagents, an ensuing 1,2-metalate rearrangement of betaine Int-4 results in the formation of the desired C–N bond, which either upon hydrolysis with adventitious water or upon workup gives the target amine. A final hydrosilane-mediated reduction of phosphate oxide 1·[O] returns the catalyst to the P(III) resting state (1) and closes the second catalytic deoxygenation cycle.

4. CONCLUSION

P(III)/P(V) = O-catalyzed intermolecular reductive C–N cross-coupling of nitroarenes and arylboronic acids is emerging as an operationally robust and mechanistically well-defined main-group complement to the established transition-metal-based methods for catalytic intermolecular C–N coupling. Combined experimental, spectroscopic, and computational experiments provide a description of the biphlic organophosphorus-catalyzed method by systematically differentiating the nature of deoxygenative events of nitroaromatics especially in the context of the C–N bond formation. Namely, the rate-determining step is a (3+1) addition. The product-determining step involves the ring-opening of an oxazaphosphirane. Combined, these findings enrich the fundamental understanding of the biphlic reactivity of phosphetanes as generalized platforms for catalytic reductive O-atom transfer operating in the P(III)/P(V) redox manifold and provide an experimentally based mechanistic framework to guide iterative catalyst design and method development.

5. EXPERIMENTAL SECTION

![Catalyst Design](image-url)
spectra (ppm is relative to 85% H₃PO₄ external standard) were collected at 15, 60, 180, and 360 min.

5.3. Kinetics Experiments. For a kinetic run corresponding to a single rate constant, a solution of nitrobenzene (2) and phosphinite P-oxide [1]O in m-xylene was prepared under nitrogen in an oven-dried, three-neck round-bottom flask fitted with a silicon-tipped IR probe and a magnetic stir bar. The solution temperature was stabilized to be reproducible within experimental error (±10%). The solution was diluted at room temperature into acetonitrile (80%), as determined by the disappearance of nitrobenzene (2) and growth of diphenylamine (4) relative to a standard calibration curve, and the initial rates (Δ[A]/Δt) were calculated by multiplying the pseudo-first-order reaction rate constants (exponential slopes) by the corresponding concentrations of nitrobenzene (2). Rates were shown to be reproducible within experimental error (±10%).

5.4. Computational Methods. Geometries were optimized in Gaussian 09 using the M06-2X[4] density functional with the 6-311+G(d,p) basis set. The calculated energies (∆G, 298.15 K, 1.0 atm) result from the sum of electronic and thermal free energies as obtained from the frequency analysis at the same level of theory. Open-shell singlet energies were spin-projected.67 Frequency calculations for all stationary points were carried out to describe them either as minima (i = 0) or as first-order transition states (i = 1). For all transition structures, visualization of the imaginary frequencies corresponded to the expected normal mode for the elementary step under investigation. Intrinsic reaction coordinate calculations were performed from the transition states in forward and reverse directions to confirm the lowest energy reaction pathways that connect the corresponding minima. See Supporting Information for further details.

ASSOCIATED CONTENT

1 Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c01666.

General methods, additional optimization, synthetic procedures; [H, 13C, 15N, and 31P NMR spectra; kinetics data; spectroscopy data; computational details; and Cartesian coordinates, including Figures S1–S12 and Tables S1–S8 (PDF)

AUTHOR INFORMATION

Corresponding Author
Alexander T. Radosevich — Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States; orcid.org/0000-0002-5373-7343; Email: radosevich@mit.edu

Authors
Gen Li — Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States; orcid.org/0000-0001-6857-0235
Trevor V. Nykaza — Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States; orcid.org/0000-0002-7683-2984
Julian C. Cooper — Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States; orcid.org/0000-0001-8231-2654
Antonio Ramirez — Chemical and Synthetic Development, Bristol-Myers Squibb Company, New Brunswick, New Jersey 08903, United States; orcid.org/0000-0003-2636-6855

Michael R. Luzung — Chemical and Synthetic Development, Bristol-Myers Squibb Company, New Brunswick, New Jersey 08903, United States; orcid.org/0000-0001-9729-2211

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.0c01666

Notes
The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Funding was provided by NIH NIGMS (GM114547), MIT, and Bristol-Myers Squibb.

REFERENCES

(1) (a) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals. J. Med. Chem. 2014, 57, 10257. (b) Knölker, H.-J., Ed. The Alkaloids: Chemistry and Biology; Elsevier: San Diego, 2011; Vol. 70. (c) Cirić-Markanović, G. Recent advances in polyaniline research: polymerization mechanisms, structural aspects, properties and applications. Synth. Met. 2013, 177, 1.

(2) (a) Hartwig, J. F. Carbon-Heteroatom Bond Formation Catalysed by Organometallic Complexes. Nature 2008, 455, 314. (b) Barwil, J.; Van der Eycken, E. C–N Bond Forming Cross-coupling Reactions: an overview. Chem. Soc. Rev. 2013, 42, 9283.

(3) (a) Jiang, L.; Buchwald, S. L. Palladium-Catalysed Aromatic Carbon-Nitrogen Bond Formation. In Metal-Catalysed Cross-Coupling Reactions, 2nd ed.; De Meijere, A., Diderich, F., Eds.; Wiley-Blackwell: Hoboken, NJ, 2008; pp 699–760. (c) Dorel, R.; Grugel, C. P.; HaydL, A. M. The Buchwald–Hartwig Amination After 25 Years. Angew. Chem., Int. Ed. 2019, 58, 17118.

(4) For Ni-catalyzed reactions, see: (a) Marín, M.; Rama, R. J.; Nicasio, M. C. Ni-Catalyzed Amination Reactions: An Overview. Chem. Rev. 2016, 116, 1819. (b) Corcoran, E. B.; Pirnot, M. T.; Lin, S.; Dreher, S. D.; DiRocco, D. A.; Davies, I. W.; Buchwald, S. L.; MacMillan, D. W. C. Amino Amination using Ligand-free Ni(II) Salts and Photoredox Catalysis. Science 2016, 353, 279. (c) Oderinde, M. S.; Jones, N. H.; Juneau, A.; Frenette, M.; Aquila, B.; Tentarelli, S.; Robbins, D. W.; Johannes, J. W. Highly Chemoselective Iridium Photoredox and Nickel Catalysis for the Cross-Coupling of Primary Aryl Amines with Aryl Halides. Angew. Chem. Int. Ed. 2016, 55, 13219. (d) Lin, C. H.; Kudisch, M.; Liu, B.; Miyake, G. M. C–N Cross-Coupling via Photoexcitation of Nickel-Amine Complexes. J. Am. Chem. Soc. 2018, 140, 7667.

(5) For Cu-catalyzed reactions, see: (a) Beletskaya, I. P.; Cheprakov, A. V. The Complementary Competitors: Palladium and Copper in C–N Cross-Coupling Reactions. Organometallics 2012, 31, 7753. (b) Sambiagio, C.; Marsden, S. P.; Blacker, A. J.; McGowan, P. C. Copper Catalysed Ullmann Type Chemistry: From Mechanistic Aspects to Modern Development. Chem. Soc. Rev. 2014, 43, 3525.

(6) (a) Hartwig, J. F. Transition Metal Catalyzed Synthesis of Arylamines and Aryl Ethers from Aryl Halides and Triflates: Scope and Mechanism. Angew. Chem., Int. Ed. 1998, 37, 2046. (b) Bruese, A. T.; Hartwig, J. F. Palladium-Catalyzed Arylation of Fluoroalkylamines. J. Am. Chem. Soc. 2015, 137, 8460. (c) Peacock, D. M.; Roos, C. B.; Hartwig, J. F. Palladium-Catalyzed Cross Coupling of Secondary and Tertiary Alkyl Bromides with a Nitrogen Nucleophile. ACS Cent. Sci. 2015, 1, 677. (d) Peacock, D. M.; Jiang, Q.; Hanley, P. S.; Cundari, T. R.; Hartwig, J. F. Reductive Elimination from Phosphine-Ligated Alkylpalladium(II) Amido Complexes to Form Sp3 Carbon-Nitrogen Bonds. J. Am. Chem. Soc. 2018, 140, 4893.

(7) (a) Dennis, J. M.; White, N. A.; Liu, R. Y.; Buchwald, S. L. Breaking the Base Barrier: An Electron-Deficient Palladium Catalyst
Enables the Use of a Common Soluble Base in C-N Coupling. J. Am. Chem. Soc. 2018, 140, 4721. (b) Dennis, J. M.; White, N. A.; Liu, R. Y.; Buchwald, S. L. Pd-Catalyzed C-N Coupling Reactions Facilitated by Organic Bases: Mechanistic Investigation Leads to Enhanced Reactivity in the Arylation of Weakly Binding Amines. ACS Catal. 2019, 9, 3822.

(8) (a) Park, N. H.; Vinogradova, E. V.; Surry, D. S.; Buchwald, S. L. Design of New Ligands for the Palladium-Catalyzed Arylation of α-Branchied Secondary Amines. Angew. Chem., Int. Ed. 2015, 54, 8259. (b) Ruiz-Castillo, P.; Blackmond, D. G.; Buchwald, S. L. Rational Ligand Design for the Arylation of Hindered Primary Amines Guided by Reaction Progress Kinetic Analysis. J. Am. Chem. Soc. 2015, 137, 3085. (c) Olsen, E. P. K.; Arrechea, P. L.; Buchwald, S. L. Mechanistic Insight Leads to a Ligand Which Facilitates the Palladium-Catalyzed Formation of 2-(Hetero)arylaminooxazoles and 4-(Hetero)-arylaminothiazoles. Angew. Chem., Int. Ed. 2017, 56, 10569.

(9) Ingoglia, B. T.; Buchwald, S. L. Oxidative Addition Complexes as Precatalysts for Cross-Coupling Reactions Requiring Extremely Bulky Dialkylphosphine Ligands. Org. Lett. 2017, 19, 2853. (b) Uehling, M. R.; King, R. P.; Ksivka, S. W.; Cernak, T.; Buchwald, S. L. Pharmaceutical diversification via palladium oxidative addition couples. Science 2019, 363, 405. (c) Ruiz-Castillo, P.; Buchwald, S. L. Applications of Palladium-Catalyzed C-N Cross-Coupling Reactions. Chem. Rev. 2016, 116, 12564.

(11) (a) Hall, D. G.; Wiley-VCH: Weinheim, 2005. (b) Fyfe, J. W. B.; Watson, A. J. B. Recent Developments in Organoboron and Carboxylic Acids by Sequential C−C Bond-Forming Cadogan Heterocyclization via P III/PV Chemical Valence Scheme (ETS-NOCV). J. Org. Chem. 2009, 74, 4769. (12) (a) King, A. E.; Brunold, T. C.; Stahl, S. S. Mechanistic Study of Copper-Catalyzed Aerobic Oxidative Coupling of Arylboronic Esters and Methanol: Insights into an Organometallic Oxidative Reaction. J. Am. Chem. Soc. 2009, 131, 5044. (b) King, A. E.; Ryland, B. L.; Brunold, T. C.; Stahl, S. S. Kinetic and Spectroscopic Studies of Aerobic Copper(I)-Catalyzed Methoxylation of Arylboronic Esters and Insights into Aryl Transmetalation to Copper(II). Organometallics 2012, 31, 7498. (c) Vantourout, J. C.; Law, R. P.; Isido-Llobet, A.; Atkinson, S. J.; Watson, A. J. B. Chan-Evans-Lam Amination of Boronic Acid Pinacol (BPin) Esters: Overcoming the Aryl Amine Problem. J. Org. Chem. 2016, 81, 3942. (d) Vantourout, J. C.; Miras, H. N.; Isido-Llobet, A.; Sproules, S.; Watson, A. J. B. Spectroscopic Studies of the Chan−Lam Amination: A Mechanism-Inspired Solution to Boronic Ester Reactivity. J. Am. Chem. Soc. 2017, 139, 4769.

(13) West, M. J.; Fyfe, J. W. B.; Vantourout, J. C.; Watson, A. J. B. Mechanistic Development and Recent Applications of the Chan−Lam Amination. Chem. Rev. 2019, 119, 12491.

(14) Kirby, A. J.; Warren, S. G. The Organic Chemistry of Phosphorus; Elsevier: Amsterdam, 1967; p 20.

(15) (a) Zhao, W.; Yan, P. K.; Radoshevich, A. T. A Phosphetane Catalyzes Deoxygenative Condensation of α-Keto Esters and Carboxylic Acids via $^{31}$P−$^{31}$P=O Redox Cycling. J. Am. Chem. Soc. 2015, 137, 616. (b) Nykaza, T. V.; Harrison, T. S.; Ghosh, A.; Putnik, R. A.; Radoshevich, A. T. A Biphilic Phosphetane Catalyzes N−N Bond-Forming Cadogan Heterocyclization via $^{31}$P−$^{31}$P=O Redox Cycling. J. Am. Chem. Soc. 2017, 139, 6839. (c) Nykaza, T. V.; Ramirez, A.; Harrison, T. S.; Luzung, M. R.; Radoshevich, A. T. Biphilic Organophosphorus-Catalyzed Intramolecular Csp$^{2}$−H Amination: Evidence for a Nitrenoid in Catalytic Cadogan Cyclizations. J. Am. Chem. Soc. 2018, 140, 3103. (d) Nykaza, T. A. V.; Li, G.; Yang, J.; Luzung, M. R.; Radoshevich, A. T. Angew. Chem., Int. Ed. 2020, 59, 4505. (e) Ghosh, A.; Lecomte, M.; Kim-Lee, S.-H.; Radoshevich, A. T. Organophosphorus-Catalyzed Deoxygenation of Sulfonyl Chlorides: Electrophilic (Fluoroalkyl)Sulfonylation by $^{31}$P=O$^{31}$P=O Redox Cycling. Angew. Chem., Int. Ed. 2019, 58, 2864. (f) Lecomte, M.; Lipshults, J. M.; Kim-Lee, S.-H.; Li, G.; Radoshevich, A. T. Driving Recursive Dehydration by $^{31}$P−$^{31}$P Catalysis: Annulation of Amines and Carboxylic Acids by Sequential C−N and C−C Bond Formation. J. Am. Chem. Soc. 2019, 141, 12507.
(47) Harris, J. R.; Haynes, M. T.; Ji, Thomas, A. M.; Woerpel, K. A. Phosphine-catalyzed reductions of alkyl silyl peroxides by titanium hydride reducing agents: Development of the method and mechanistic investigations. J. Org. Chem. 2010, 75, 5083.

(48) (a) van Kalkeren, H. A.; van Delft, F. L.; Rutjes, F. P. J. T. Organophosphorus catalysis to bypass phosphine oxide waste. ChemSusChem 2013, 6, 1615. (b) van Kalkeren, H. A.; Blom, A. L.; Rutjes, F. P. J. T.; Huijbregts, M. A. J. On the usefulness of life cycle assessment in early chemical methodology development: The case of organophosphorus-catalyzed Appel and Wittig reactions. Green Chem. 2013, 15, 1255. (c) van Kalkeren, H. A.; Leenders, S. H.; Hommersom, C. R.; Rutjes, F. P. J. van Delft, F. L. In situ phosphine oxide reduction: A catalytic Appel reaction. Chem. - Eur. J. 2011, 17, 11290. (d) van Kalkeren, H. A.; van Delft, F. L.; Rutjes, F. P. J. T. Catalytic Appel reactions. Pure Appl. Chem. 2012, 85, 817. (e) van Kalkeren, H. A.; Bruins, J. J.; Rutjes, F. P. J. T.; van Delft, F. L. Organophosphorus-catalysed Staudinger reaction. Adv. Synth. Catal. 2012, 354, 1417. (f) van Kalkeren, H. A.; te Grotenhuis, C.; Haasjes, F. S.; Hommersom, C. R. A.; Rutjes, F. P. J. T.; van Delft, F. L. Catalytic Staudinger/aza-Wittig sequence by in situ phosphane oxide. J. Org. Chem. 2012, 70, 3541.

(49) (a) Zhang, K.; Cai, L.; Yang, Z.; Houk, K. N.; Kwon, O. Catalytic asymmetric Staudinger-Aza-Wittig reaction. Chem. - Eur. J. 2011, 17, 11290. (b) Cai, L.; Zhang, K.; Chen, S.; Lepage, R. J.; Houk, K. N.; Krenske, E. H.; Kwon, O. Catalytic Asymmetric Staudinger-Aza-Wittig reaction. Adv. Synth. Catal. 2011, 354, 1417. (c) van Kalkeren, H. A.; de Grothenhuis, C.; Haasjes, F. S.; Hommersom, C. R. A.; Rutjes, F. P. J. T.; van Delft, F. L. Organophosphorus-catalysed Appel reaction. Chem. - Eur. J. 2011, 17, 11290. (d) van Kalkeren, H. A.; Leenders, S. H.; Hommersom, C. R.; Rutjes, F. P. J. van Delft, F. L. In situ phosphine oxide reduction: A catalytic Appel reaction. Chem. - Eur. J. 2011, 17, 11290. (e) van Kalkeren, H. A.; Bruins, J. J.; Rutjes, F. P. J. T.; van Delft, F. L. Organophosphorus-catalysed Staudinger reaction. Adv. Synth. Catal. 2012, 354, 1417. (f) van Kalkeren, H. A.; te Grotenhuis, C.; Haasjes, F. S.; Hommersom, C. R. A.; Rutjes, F. P. J. T.; van Delft, F. L. Catalytic Staudinger/aza-Wittig sequence by in situ phosphane oxide. J. Org. Chem. 2012, 70, 3541.

(50) (a) Zhang, K.; Cai, L.; Yang, Z.; Houk, K. N.; Kwon, O. Catalytic asymmetric Staudinger-Aza-Wittig reaction. Chem. - Eur. J. 2011, 17, 11290. (b) Cai, L.; Zhang, K.; Chen, S.; Lepage, R. J.; Houk, K. N.; Krenske, E. H.; Kwon, O. Catalytic Asymmetric Staudinger-Aza-Wittig reaction. Adv. Synth. Catal. 2011, 354, 1417. (c) van Kalkeren, H. A.; de Grothenhuis, C.; Haasjes, F. S.; Hommersom, C. R. A.; Rutjes, F. P. J. T.; van Delft, F. L. Organophosphorus-catalysed Appel reaction. Chem. - Eur. J. 2011, 17, 11290. (d) van Kalkeren, H. A.; Leenders, S. H.; Hommersom, C. R.; Rutjes, F. P. J. van Delft, F. L. In situ phosphine oxide reduction: A catalytic Appel reaction. Chem. - Eur. J. 2011, 17, 11290. (e) van Kalkeren, H. A.; Bruins, J. J.; Rutjes, F. P. J. T.; van Delft, F. L. Organophosphorus-catalysed Staudinger reaction. Adv. Synth. Catal. 2012, 354, 1417. (f) van Kalkeren, H. A.; te Grotenhuis, C.; Haasjes, F. S.; Hommersom, C. R. A.; Rutjes, F. P. J. T.; van Delft, F. L. Catalytic Staudinger/aza-Wittig sequence by in situ phosphane oxide. J. Org. Chem. 2012, 70, 3541.
(62) Starkov, P.; Jamison, T. F.; Marek, I. Electrophilic Amination: The case of Nitrenoids. *Chem. - Eur. J.* 2015, 21, 5278.

(63) Lower oxygenates of nitrogen or alternative nitrogen reagents are more common in C–N bond formation with boronic acids. Nitrosoarenes: (a) Yu, Y.; Srogl, J.; Liebeskind, L. S. Cu(I)-Mediated Reductive Amination of Boronic Acids with Nitroso Aromatics. *Org. Lett.* 2004, 6, 2631. (b) Roscales, S.; Csáky, A. G. Synthesis of Di(hetero)arylamines from Nitrosoarenes and Boronic Acids: A General, Mild, and Transition-Metal-Free Coupling. *Org. Lett.* 2018, 20, 1667. N-Alkyl hydroxylamines: (c) Sarma, M. J.; Phukan, P. Metal-Free Synthesis of Secondary Amines by the Reaction of Tosyl Triazene and Aryl Boronic Acid. *Synth. Commun.* 2018, 48, 656.

(64) Accurate reaction sampling and dilution was performed using a probe-based Mettler-Toledo EasySampler 1210 system, see: Zawatzky, K.; Grosser, S.; Welch, C. J. Facile Kinetic Profiling of Chemical Reactions Using MISER Chromatographic Analysis. *Tetrahedron* 2017, 73, 5048.

(65) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, revision B.01; Gaussian, Inc.: Wallingford, CT, 2009.

(66) (a) Zhao, Y.; Truhlar, D. G. The M06 Suite of Density Functionals for Main Group Thermochemistry, Thermochemical Kinetics, Noncovalent Interactions, Excited States, and Transition Elements: two New Functionals and Systematic Testing of four M06-class Functionals and 12 Other Functionals. *Theor. Chem. Acc.* 2008, 120, 215. (b) Zhao, Y.; Truhlar, D. G. Density Functionals with Broad Applicability in Chemistry. *Acc. Chem. Res.* 2008, 41, 157.

(67) Yamaguchi, K.; Takahara, Y.; Fueno, T.; Houk, K. N. Extended Hartree-Fock (EHF) Theory of Chemical Reactions - III. Projected Møller-Plesset (PMP) Perturbation Wavefunctions for Transition Structures of Organic Reactions. *Theor. Chim. Acta* 1988, 73, 337.