P III /P V #0-Catalyzed Intermolecular N–N Bond Formation: Cross-Selective Reductive Coupling of Nitroarenes and Anilines

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P^{III}/P^{V}=O-Catalyzed Intermolecular N–N Bond Formation: Cross-Selective Reductive Coupling of Nitroarenes and Anilines

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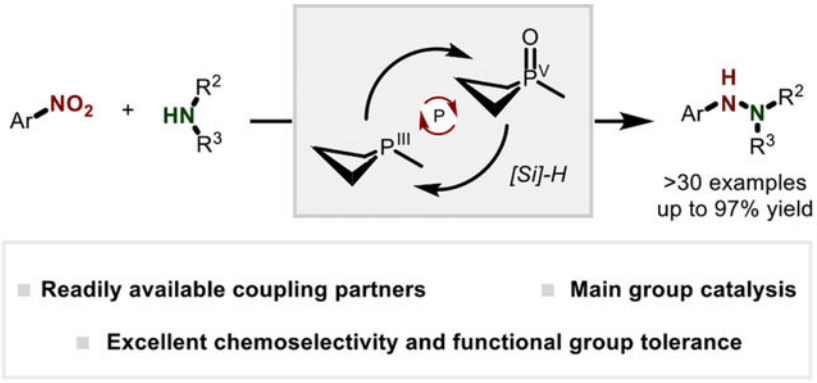
Abstract

An organophosphorus-catalyzed method for the synthesis of unsymmetrical hydrazines by cross-selective intermolecular N–N reductive coupling is reported. This method employs a small ring phosphacycle (phosphetane) catalyst together with hydrosilane as the terminal reductant to drive reductive coupling of nitroarenes and anilines with good chemoselectivity and functional-group tolerance. Mechanistic investigations support an auto-tandem catalytic reaction cascade in which the organophosphorus catalyst drives two sequential and mechanistically-distinct reduction events via P^{III}/P^{V}=O cycling in order to furnish the target N–N bond.

Graphical Abstract



Hydrazines and related N–N containing derivatives have significant value in organic chemistry,[1,2] including as natural products[3] and pharmaceuticals (Figure 1A).[4,5] Although the NN bond presents a potential strategic site for synthesis—especially within medical

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

General methods and synthetic procedures (.pdf)

^{1}H, ^{13}C, ^{19}F and ^{31}P NMR spectra (.pdf).

The authors declare no competing financial interests.

chemistry—it is only infrequently targeted for retrosynthetic disconnection. In part, this state of play reflects certain constraints in the methods for N–N bond formation, particularly in an intermolecular sense.[6,7] Stoichiometric methods employ prefunctionalized *N*-based reagents whose stability and structural variation are intrinsically bracketed by the high electronegativity of the nitrogen atom.[8–14] Complementarily, several notable advances have recently been achieved in catalytic intermolecular N–N bond formation,[15–18] despite the inherent challenges associated with synthesis of such a weak and nonpolar bond.[19,20] Transition metal-catalyzed nitrene transfer has successfully been applied to the imination of tertiary amines[15–17] and the N–H insertion of acylnitrene equivalents to N-alkylanilines,[18] specifically by decomposition of bespoke nitrene donors such as iminoiodinanes and 1,4,2-dioxazol-5-ones (Figure 1B). Among unfunctionalized precursors, simple diarylamine/carbazole substrates have been subject to intermolecular oxidative N–N coupling under aerobic Cu-catalyzed[21–23], Fe-catalyzed[24] or anodic electrochemical conditions,[25] although the realization of cross selectivity remains substrate dependent.

With the goal of advancing the perception of N–N bonds as strategic sites in synthesis, we aimed to develop an approach to N–N bond formation that would leverage simple precursor substrates for precise and selective intermolecular coupling. Nitroarenes are readily-accessed compounds with increasing use as direct amination reagents.[26–28] In this vein, prior work has established the viability of organophosphorus-catalyzed reductive *N*-functionalization of nitroarenes by P^{III}/P^{V}=O cycling.[29–36] We considered whether this reactive manifold might enable new cross-selective intermolecular N–N bond forming reactivity by the introduction of an exogenous aniline partner. Herein, we describe the realization of method for the synthesis of unsymmetrical hydrazines by reductive N–N coupling of readily-available nitroarene and aniline substrates (Figure 1C). These results provide a modular and cross-selective N–N coupling strategy enabled by the versatility of the P^{III}/P^{V}=O redox couple[37–40] to manage diverse reductive transformations en route to the target N–N bond.

The reaction of 4-nitrobenzonitrile (**2**) and 4-fluoroaniline (**3**) to generate hydrazine **4** was selected to evaluate the possibility of reductive intermolecular N–N coupling via P^{III}/P^{V}=O catalysis. Using 1,2,2,3,4,4-hexamethylphosphetane P-oxide **1**·[O][41] as catalyst, diphenylsilane as terminal reductant and 2,4,6-trimethylbenzoic acid as an additive, the desired hydrazine **4** was indeed obtained with complete cross selectivity in 86 % yield after 24 h (Table 1, entry 1). Further experiments show that utilization of phosphetane **1** in the place of phosphetane oxide **1**·[O] also smoothly provided hydrazine **4**, in line with the notion of P^{III}/P^{V}=O redox cycling (entry 2). Lower catalyst loading (entry 3) showed similar reaction efficiency, albeit with longer reaction time. No hydrazine is formed in the absence of either phosphetane oxide **1**·[O] or hydrosilane (entries 4,5). The carboxylic acid additive proves to be essential to the N–N bond formation process; only trace product is observed when this additive was omitted (entry 6). Despite the reducing conditions, this catalytic reaction could be conducted with similar yield under ambient air (entry 7). Reactions at either higher temperature (entry 8) or higher dilution (entry 9) resulted in erosion of yield. To probe the reaction sensitivity with respect to the interplay of the reaction components and conditions, a five-factor, half-fractional factorial design of

experiments (DoE) containing four center point replicates was subsequently performed (see SI). Reaction concentration was identified as a statistically significant factor affecting reaction performance, along with secondary interactions between silane-loading/temperature and silane-loading/2,4,6-trimethylbenzoic acid-loading. The DoE experiments support the prescribed optimal conditions in Table 1 and provide a picture of relative robustness with respect to variables.

The optimized N–N reductive coupling protocol provides direct and cross-selective access to hydrazine products from the coupling of widely-available nitroarene starting materials with anilines (Figure 2). A variety of anilines yielded the corresponding hydrazine with high levels of efficiency (**4**–**7**). Notably, both electron-poor and electron-rich anilines are transformed smoothly into the desired products with good efficiency (**5** and **7**, 77% and 90% yields, respectively). Similarly, *N*-alkylaniline (**8**), *N*-alkyl-heterocyclic amines (**9**, **29**) and *N*-allyl-aniline (**10**) are all incorporated into corresponding hydrazine products successfully. Moreover, as exemplified by indoline (**19**, **21**), 1,2,3,4-tetrahydroquinoline (**20**, **31**), 2,3,4,5-tetrahydrobenzoazepine (**22**), 1,4-benzoxazine (**23**) and 2,3-dihydroquinolin-4-one (**24**), a variety of arylamines bearing *ortho*-fused aliphatic rings are all transformed smoothly into the corresponding hydrazine products.

The organophosphorus-catalyzed reaction exhibits chemoselectivity for the nitro group as a coupling partner, with the preservation of a range of easily-reduced functional groups such as carbonyls (**11**, **20**, **29**), esters (**12, 31**), amides (**13, 32**), sulfonamides (**14**) and sulfones (**22**). Notably, mono-functionalization of 1,4-dinitrobenzene could be achieved with excellent yields, as the second nitro group becomes electronically deactivated after an initial reductive N–N coupling event. Moreover, this method is also applicable to nitroarenes bearing an unsaturated carbon-carbon triple bond (**28**, 83% yield). Halogen atoms are all maintained (**17**, **21**, **23–27**, 51%–90% yields), providing handles for further functionalization by transition-metal catalysis. Other functional groups such as methoxy (**23**, **26**), trifluoromethyl (**18**–**19**) and cyano (**24**) can also be preserved via this approach. Nitropyridines (**15**, **28**) were also amenable to the formation of hydrazine due to the inherently low Lewis acidity of the catalytic components. Compounds with bioactive core structures—as exemplified by flavone (**30**), novocaine (**31**), and flutamide (**32**) derivatives—are similarly applicable.

As a further demonstration of the synthetic utility of this transformation within the context of medicinal chemistry, indazolone **35**—an investigational TPRV1 receptor antagonist[42]—was synthesized in 69% yield in a one pot sequence involving organophosphorus-catalyzed cross-selective N–N coupling of ethyl 2-aminobenzoate (**33**) and 4-nitrobenzotrifluoride (**34**), followed by intramolecular cyclization onto the pendent ester group (Figure 3). The modularity of this entry to the indazole core suggests numerous additional opportunities within medicinal chemistry campaigns.

Concerning the catalytic mechanism, *in situ* ^{19}F NMR spectroscopy of the model reaction of 4-cyanonitrobenzene (**2**) with 4-fluoroaniline (**3**) revealed that **3** (δ −128.2 ppm) was converted to the desired hydrazine product **4** (δ −125.3 ppm) with the observation of an additional minor species (δ −107.5 ppm), identified as the corresponding azoarene **36** (see

SI, Figure S2). Curiously, subjection of independently-prepared azoarene **36** to the nominal catalytic conditions resulted in poor conversion and yield of hydrazine **4** (47% conversion, 23% yield, Figure 4A, eq 1). However, the deliberate addition of H_2O as an additive to the initial catalytic conditions significantly improved the conversion from azoarene **36** to the hydrazine **4** (>99% conversion, 96% yield, Figure 4A, eq 2), pointing to an important role for adventitious water in the azoarene reduction.[43] A similarly efficient reduction of azoarene **36** is achieved under stoichiometric conditions starting from P^{III} phosphetane **1**, illustrating the importance of the P^{III} oxidation state for this transformation (Figure 4A, eq 3). Additionally, a crossover experiment in which azoarene **36** is added to an intermolecular reductive coupling of 4-nitrobenzotrifluoride (**34**) and 4-chloroaniline (**37**) under catalytic conditions provided **4** (70%) along with the intermolecular N-N coupling product **38** (53%) without scrambling (Figure 4B).

Taken together with literature precedent, these experimental findings are best accommodated by an auto-tandem catalytic reaction mechanism for the intermolecular N–N reductive coupling involving two sequential and mechanistically-distinct reduction events, as illustrated in Figure 5.[44] In a first catalytic stage, the nitroarene substrate is deoxygenated by P^{III} phosphetane **1**, giving nitrosoarene intermediate (**Int-2**) by a [3+1]/retro-[2+2] sequence via **Int-1** as previously described.[29,34] Once formed, nitrosoarene **Int-2** advances off-cycle to azoarene **Int-3** by dehydrative condensation.[45 – 47] The equivalent of water thus released proves critical for the second catalyzed reduction event; azoarene **Int-3** is reduced by **1** in the presence of carboxylic acid via hydrazinylphosphonium **Int-4**,[48–50] whose hydrolytic decomposition depends on adventitious water for release of the desired hydrazine product and phosphetane oxide **1**·[O].[51] A common feature uniting both catalytic cycles is the hydrosilane-mediated reductive turnover of the P^{V}=O catalyst **1**·[O] to regenerate the reactive P^{III} state (**1**), a mechanistic step which is kinetically facilitated by the presence of the small-ring in the organophosphorus catalyst.

In summary, the results described above constitute a new and robust organophosphorus-catalyzed protocol for cross-selective intermolecular N–N coupling via P^{III}/P^{V}=O redox cycling that makes use of readily accessible coupling partners in the construction of valuable hydrazine products. Despite the potential lability of the N-N bond under reducing conditions, the high chemoselectivity of the catalytic system reductive allows the synthesis of the target bond with excellent functional group tolerance even among other reductively sensitive functionalities. Critical to the success of this method is the versatility of the P^{III}/P^{V}=O redox couple to manage diverse reductive transformations, which is manifest in the two-stage, auto-tandem catalytic reaction process. Given the ready-accessibility of nitroarene and aniline partners, we envision that these results might enable a fragment coupling approach to the preparation of highly functionalized hydrazines and related N–N containing derivatives with potential utility in medicinal chemistry and other applications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

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43. *In situ* NMR studies with 4-nitrobenzotrifluoride and *N*-methylaniline were also conducted but with no long-lived intermediate observed (Figures S4–5), presumably due to fast reduction of the corresponding diazenium to hydrazine product.
44. The intervention of nitrene or nitrenoid intermediates in this N–N bond construction is not supported by experimental data. Arylnitrenes are known to be trapped with amines to give 2-aminoazepines by ring expansion (Huisgen, R.; Vossius, D.; Appl, M. Die Thermolyse des Phenylazids in primären Aminen; die Konstitution des Dibenzamils. *Chem. Ber.* **1958**, *91*, 1–12). No such 2-aminoazepine product was observed under organophosphorus-catalyzed conditions. For comparison, see Ref. 32.
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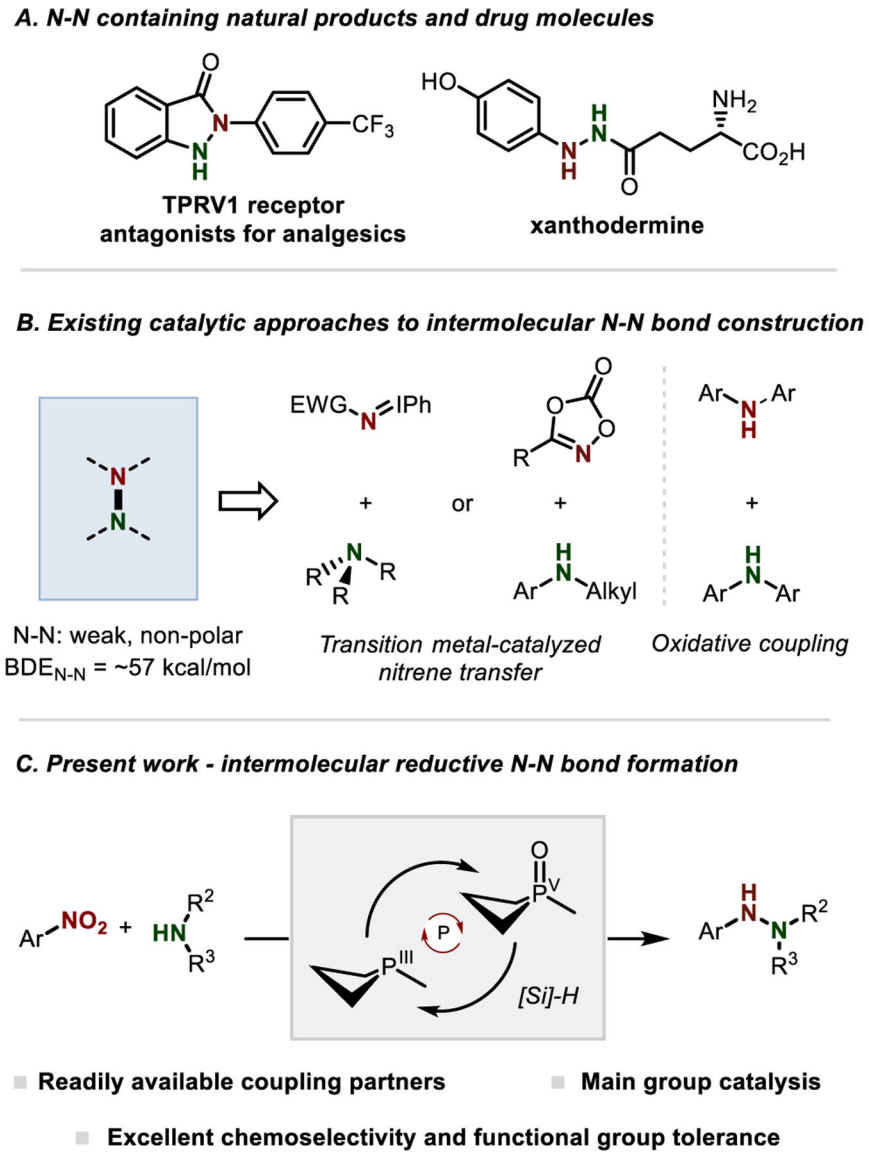


Figure 1.

A) N–N containing natural products and drug molecules; B) Current strategies for N–N bond construction; C) Present work: P^{III}/P^{V}=O-catalyzed reductive N–N coupling of nitroarenes and anilines.

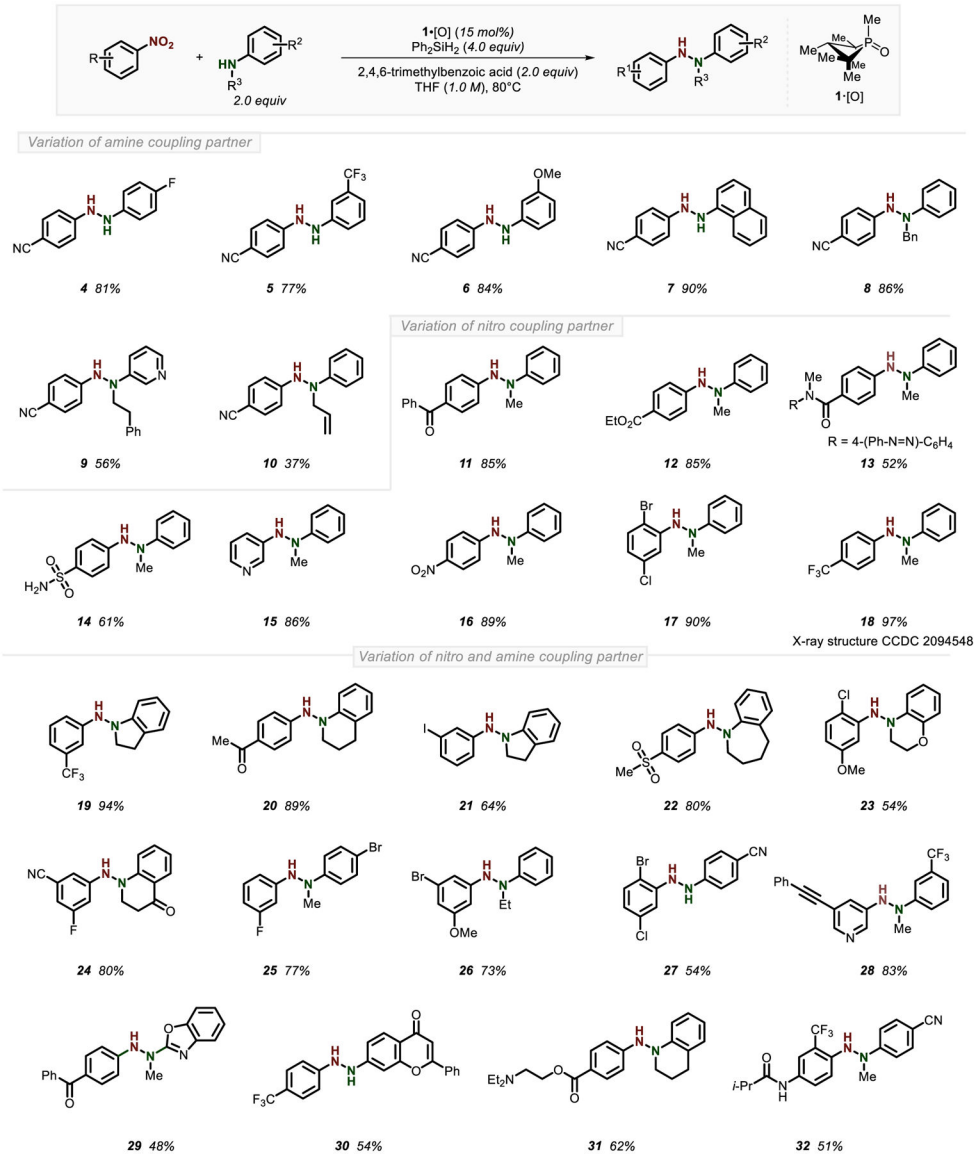


Figure 2.

Synthetic scope and representative examples of hydrazine via P^{III}/P^{V}=O catalyzed N–N coupling. See SI for full experimental details and conditions.

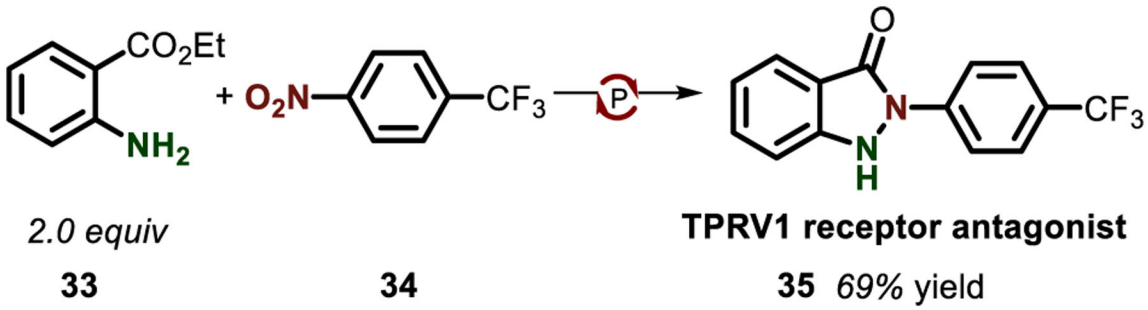


Figure 3.

One pot synthesis of TPRV1 receptor antagonists for analgesics. Reaction conditions: **33** (2.0 equiv), **34** (1.0 equiv), Ph_2SiH_2 (4.0 equiv), **1**·[O] (15 mol %), THF (1 M), 80 °C; then NaHMDS, rt.

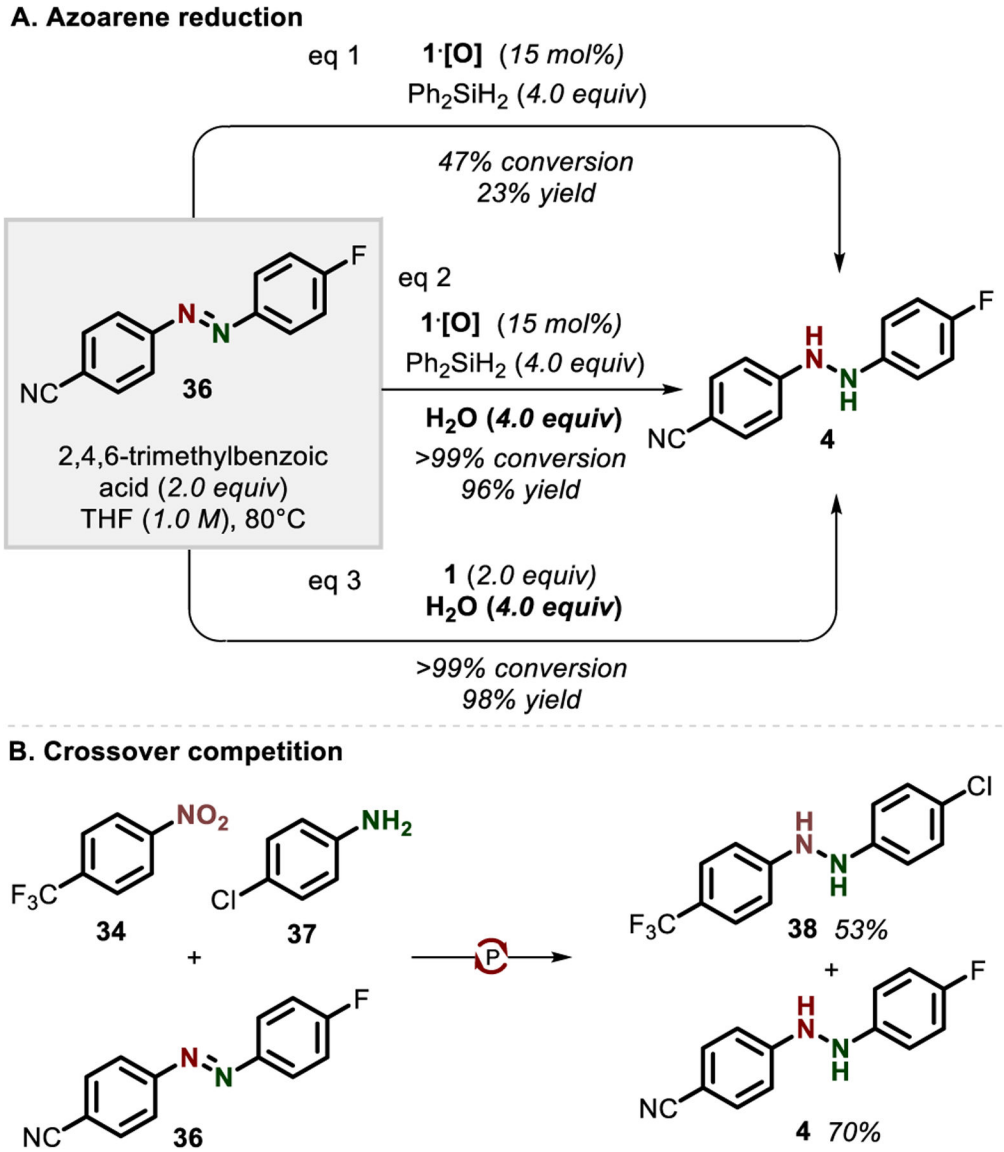


Figure 4.

Mechanistic studies of catalytic reductive N–N coupling. (A) Azoarene reduction investigation (B) Crossover competition.

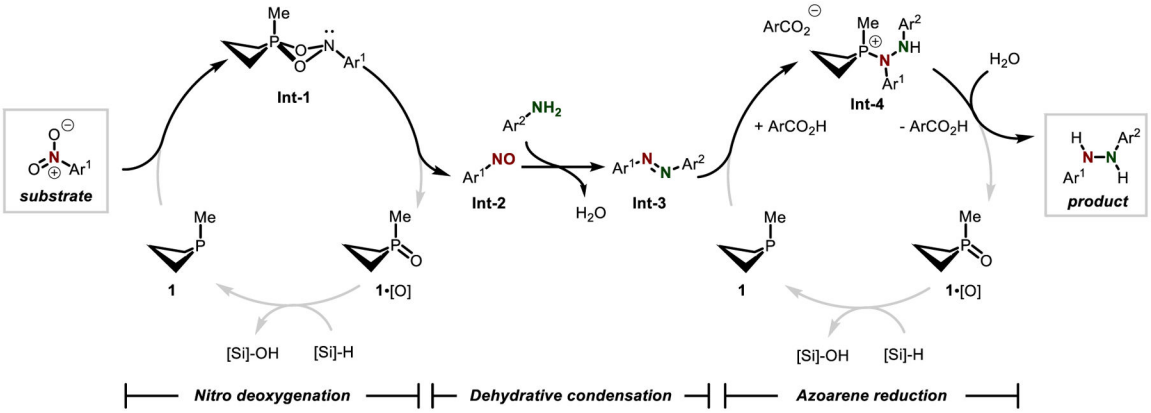
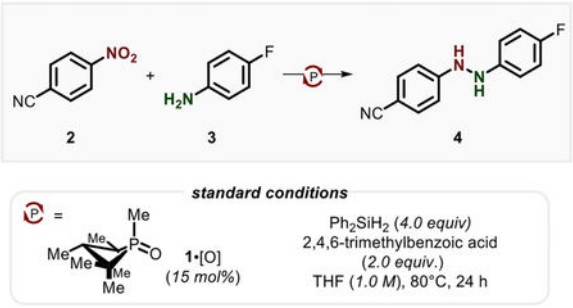


Figure 5.

Proposed reaction mechanism for the organophosphorus-catalyzed cross-selective reductive N–N coupling. Methyl groups on catalyst omitted for clarity.

Table 1.

Discovery and Optimization of Organophosphorus-Catalyzed N–N cross coupling.[a]



Entry	Change from "standard conditions"	Yield (%)[a]
1	none	86 (81)
2	**1** (1.5 *mol%*)	86
3	**1**·[O] (*5 mol%*)	84[b]
4	no catalyst **1**·[O]	0
5	no silane	0
6	no 2,4,6-trimethylbenzoic acid	trace
7	under ambient air	82
8	100 °C	79
9	THF (*0.5 M*)	41

[a]Yields were determined through ^{19}F NMR with 4-fluorotoluene as an internal standard.

[b]72 h reaction time. See Supporting Information for full synthetic details.