Heteroarene Phosphinylalkylation via a Catalytic, Polarity-Reversing Radical Cascade

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Supporting Information Placeholder

ABSTRACT: A polarity-reversing radical cascade strategy for alkene di-functionalization by vicinal C-C and C-P bond-formation has been developed. This new approach for concurrently adding phosphorous and a heteroarene across an olefin is enabled by photocatalytic generation of electrophilic P-centered radicals. Upon chemoselective addition to an olefin, the resulting nucleophilic C-centered radical selectively combines with electrophilic heteroarenes, such as pyridines. This multi-component coupling scheme for phosphinylalkylation complements classic two-component methods for hydrophosphinylation of alkenes and C-H phosphinylation of arenes. Included competition and photo-quenching experiments provide insight into the selectivity and mechanism of this polarity-reversal pathway.

Alkene di-functionalization is among the most useful instruments in the synthetic toolbox.[1] Notably, radical-mediated approaches offer complementarity to two-electron strategies, with respect to both reactivity and selectivity.[2,3] For example, electrophilic P-centered radicals[4] add to alkenes to afford hydrophosphinylation with anti-Markovnikov selectivity (Figure 1a).[5,6] Alternatively, P• may also directly add to arenes in a net C-H phosphonation.[7] Yet, in contrast to these couplings with π-nucleophiles, P• combination with electron-deficient heteroarenes is less favored.[8] Given the medicinal importance of both motifs,[9] we sought to develop a method for adding biologically relevant phosphines and heteroarenes to alkenes in a single transformation. Since Minisci's pioneering work, nucleophilic radicals have been employed to construct C-C bonds directly onto heteroarenes.[10,11] Recently, Herzon and Baran have shown that H• addition to an alkene affords alkyl radicals that may also engage in the Minisci heteroarylation mechanism.[12] Given the requirement of nucleophilicity for the alkyl radicals to combine with electrophilic, protonated heteroarenes by this mechanism, we postulated that a three-component coupling reaction could be designed wherein polarity effects would dictate chemo- and regio- selectivity (Figure 1b).

In our design, a polarity-reversal radical cascade strategy could selectively convert phosphine oxides to electrophilic P-centered radicals. Subsequent addition to an olefin (rather than to electron-deficient heteroarenes) would render the resulting open-shell intermediate nucleophilic. This C-centered radical may then chemoselectively combine with heteroarenes to afford a three-component coupling adduct. To our knowledge, only Minisci, Barriault, Liu, and Hong have reported examples of heteroaryl difunctionalization

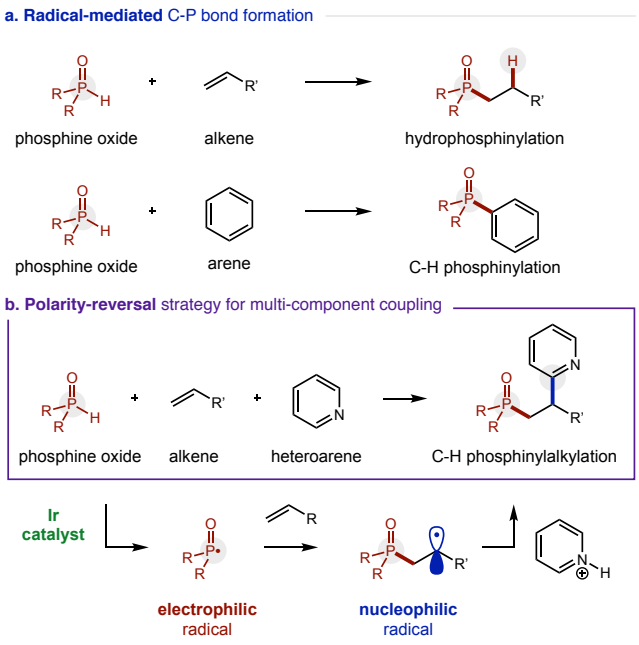


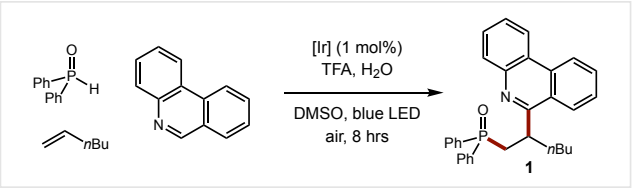
Figure 1. Polarity-reversal strategy for radical C-P couplings.

of alkenes, albeit initiated by alkyl or azide radicals.[13] Despite this inspiration, we were cognizant that hydrophosphinylation via the Pudovik reaction may be a competing pathway.[5] A second side-product pathway might include direct two-electron addition to pyridines, as recently developed by McNally.[14] Moreover, the selective, radical combination of alkenes and heteroarenes remains quite rare, with limited examples of alkene hydroarylation that include Herzon and Baran's stoichiometric protocols[12] and Jui's inverted approach entailing addition of pyridyl radicals.[15] Despite these challenges, we surmised catalytic generation of P• at low concentrations relative to the alkene and heteroarene components may enable a chemoselective cascade.

To test the viability of this radical cascade strategy for multi-component C-P and C-C coupling, diphenyl phosphine oxide, 1-hexene, and phenanthridine were combined in the presence of an acid, photocatalyst, and blue LED irradiation (Figure 2). To our delight, the heteroarene phosphinylalkylation was promoted quite efficiently in the presence of 1 mol% $Ir(ppy)_2(dtbbpy)PF_6$ photocatalyst (entry 1). Interestingly, we noted that some protonated quinolines (e.g. phenanthridine) may autocatalyze this transformation.

However, we observed lower and inconsistent yields (entry 2) in the absence of 1 mol% catalyst (and limited scope), and thus retained the photocatalyst for further optimization. The addition of an acid (1.2 equiv TFA) and water (5.5 equiv) were also found to be crucial components for reaction efficiency – in order to protonate and solubilize the terminal heteroarene electrophile (entries 3-4). Although, this reaction is amenable to varying solvents, concentrations, and non-aerobic conditions, most are inferior, frequently affording Pudovik adducts rather than phosphinylalkylation (entries 5-10). Furthermore, the multi-component coupling does not proceed well in the absence of LED irradiation (entry 11).

Figure 2. Development of a cascade heteroarene phosphinylalkylation.



entry	conditions	conversion	yield **1**
1	standard	**100%**	**77%**
2	w/o photocatalyst	60-95%	55-70%
3	w/o H_2O	73%	61%
4	w/o TFA	27%	12%
5	N_2 instead of air	45%	21%
6	CH_2Cl_2 instead of DMSO	36%	19%
7	MeCN instead of DMSO	68%	29%
8	PhCl instead of DMSO	68%	39%
9	0.05 M DMSO	50%	42%
10	0.2 M DMSO	94%	60%
11	w/o light	10%	0%

Conditions: phenanthridine (0.1 mmol), $Ph_2P(O)H$ (2 equiv), $Ir(ppy)_2(dtbbpy)PF_6$ (1 mol%), DMSO (1 mL), trifluoroacetic acid (1.2 equiv), H_2O (5.5 equiv), and 1-hexene (2 equiv), blue LED, 25°C. ^1H NMR yields vs standard.

Having developed an efficient, photocatalytic method to enable the phosphinylalkylation of heteroarenes, we next investigated the generality of this polarity-reversal radical cascade. As shown in Figure 3, the scope of alkenes that can be employed in this transformation is surprisingly wide – tolerating a broad range of functional groups, including esters, ketones, alcohols, halides, and ethers (**2-6**). Notably, these simple, unbiased alkenes can be employed as suitable P-radical traps. Alternatively, more electron-rich enol ethers are also 1,2-phosphinyl-arylated (**7**) – with even greater efficiency, as the intermediary α-oxy alkyl radical has higher nucleophilicity to promote heteroarene addition.

In order to probe the generality of heteroarenes in this Minisci radical addition mechanism,[10] we then subjected a series of quinolines (**8-11**) and isoquinolines (**12-18**) to this reaction. Notably, a wide range of steric and electronic substituents were tolerated, including halides, esters, and amides. And while, less efficient than the enol ether component, non-activated alkene (e.g. hexene) may also be employed (**9**, **13**).

Given the biological significance of phosphorous,[9] we also investigated variation of the phosphine component and were pleased to find that a range of electronically diverse aryl and heteroaryl phophine oxides may be employed (**19-22**). Interestingly, even an electron-rich, bis-OMe aryl phosphine oxide can undergo polarity-reversal via its electron-poor P-radical (**19-20**). Additionally, dialkyl phosphine oxides, phosphonate esters, and phosphine sulfides are suitable radical precursors (**23-25**).

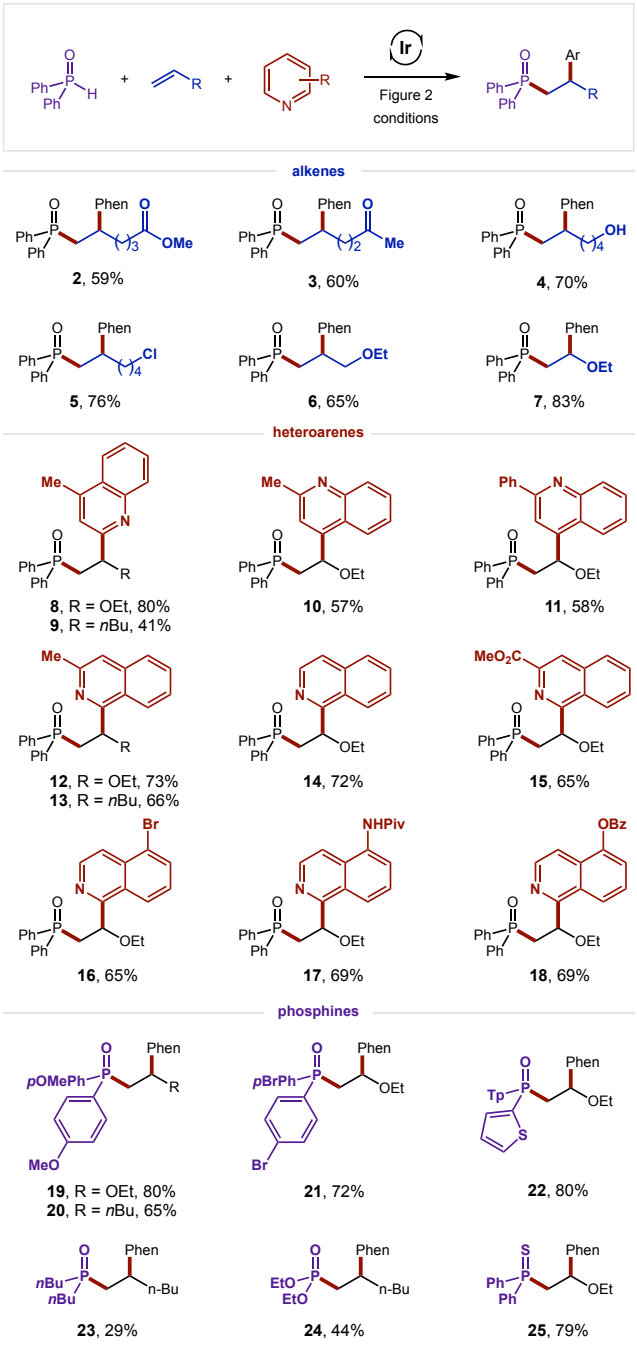
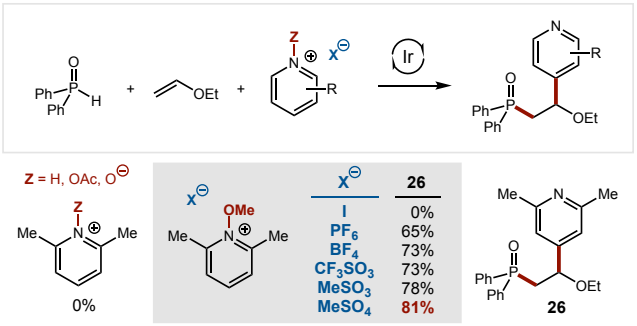


Figure 3. Heteroarene phosphinylalkylation: Reaction scope.

We next turned our attention to the heteroarene component with a specific focus on extending this methodology to simple pyridines (Figure 4). Even with an electron-rich enol ether as the nucleophilic radical precursor, and a basic lutidine, which should provide a strongly electrophilic lutidinium as the terminal trap, we did not

observe any desired three-component coupling adduct. Similarly, the N-oxide, although frequently employed as a radical coupling partner,[16] was incompatible with this cascade (with either Brønsted or Lewis acids). Ultimately, we were pleased to find that N-OMe pyridiniums[17] are suitable heteroarene partners for providing phosphinylalkylation of 2,6-lutidine (**26**). Interestingly, we noted a strong counterion effect on this radical cascade,[18] wherein the oxidizable iodide affords no product, while PF_6, BF_4, CF_3SO_3, and $MeSO_3$ yield **26** with varying efficiency (65-78%). Fortunately, $MeSO_4$, which was the best anion among those we investigated (81%), is also the easiest to access synthetically by directly combining N-oxide with dimethyl sulfate.

Figure 4. Development of a pyridine phosphinylalkylation.



Conditions: pyridinium (0.1 mmol), $Ph_2P(O)H$ (2 equiv), $Ir(ppy)_2(dtbbpy)PF_6$ (1 mol%), DMSO (1 mL), H_2O (5.5 equiv), and alkene (2 equiv), blue LED, 25˚C. ^1H NMR yields vs standard.

With this second-generation strategy in hand for direct C-H phosphinylalkylation of pyridines, the synthetic generality of the radical cascade was further investigated (Figure 5). Noting the high electrophilicity of these N-OMe pyridinium partners, we questioned if they may allow similarly broad scope with respect to the phosphine oxide component. Thus, we were pleased to see that more acidic and nucleophilic variants, including dibutyl phosphine oxide, pinacol phosphonate, and bis-aryl phosphine oxides were suitable partners (**27-30**). However, non-ethereal alkenes are not suitable nucleophiles for this reaction mechanism.

In probing the pyridine component, we noted that an unsubstituted pyridine is regioselectively functionalized at the 4-position in a 3:1 r.r. (**31**). This selectivity likely results from steric repulsion by the N-OMe group, which blocks radical addition at the 2-positions. However, if a 2-Cl substituent is employed to increase the electrophilicity, then regioselectively is decreased to 2:1 (**32**). On the other hand, stabilization of the radical addition by a 2-Ph group affords 6:1 r.r. (**33**). Finally, a 2-Me group sufficiently repels the N-OMe to afford >20:1 regioselectively (**34**). Of note, if the 4-position is blocked by substituents of varying electronics (Me, OMe, CN), then reactivity at the 2-position is observed (**35-37**).

Having developed protocols for the phosphinylalkylation of pyridines at either their 2 or 4 C–H bonds, we questioned if this strategy could also promote functionalization of the electron-rich 3-position. This regioselectivity is not typically favored in Minisci additions due to a mismatch in polarity (both the alkyl radical and C3 are electron-rich). Nonetheless, with this goal in mind, we prepared the 2-alkoxy quinoline (**38**) and subjected it to the initial TFA conditions. We were pleased to find the intermediary 6-exo-trig radical cyclization does in fact occur – affording a fused, 2*H*-pyrano[2,3-*b*]quinoline (**39**) core found in glutamate receptor antagonists, potassium-channel activators, and employed as ligands in Pd-catalyzed C-H functionalization.[19]

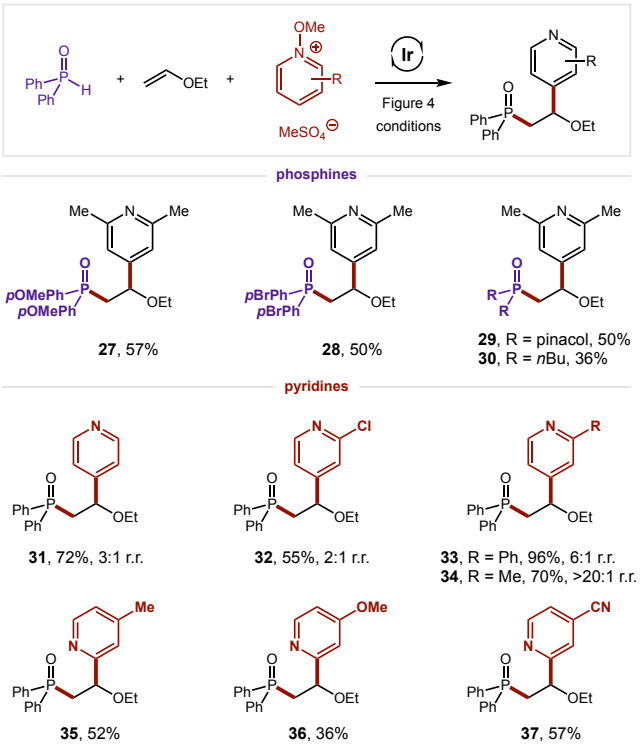


Figure 5. Heteroarene phosphinylalkylation: Pyridine scope.

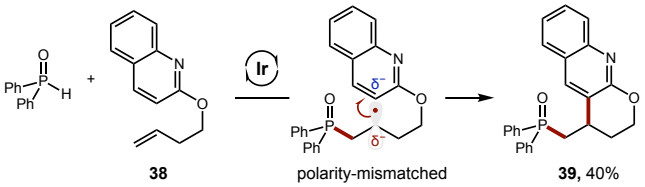


Figure 6. Intramolecular cyclization favors the polarity-disfavored C3-regioisomer.

With two complementary conditions in hand, we were curious how they compared to one another. Thus, we performed a competition experiment in which the protonated phenanthridine and N-OMe lutidinium were combined and reacted in a 1:1 ratio. As shown in Figure 7a, the phenanthridinium partner reacts nearly four times faster. Moreover, both partners individually outcompete the Pudovik reaction[5] handily (Figure 7b) – affording a 7:1 ratio of three-component coupling to two-component hydrophosphinylation in the case of phenanthridine (**1**), or 6:1 for pyridine (**26**).

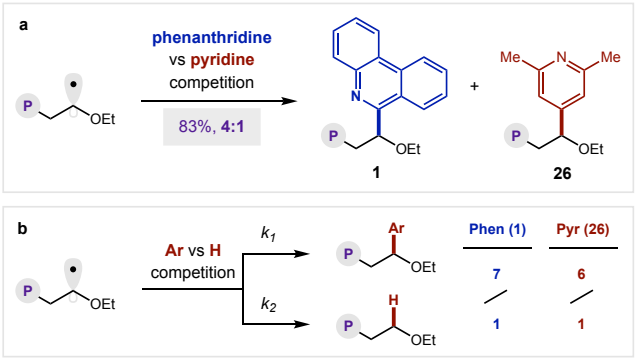


Figure 7. Competition experiments: (a) pyridine vs phenanthridine acceptors, and (b) three-component coupling vs two-component hydrophosphinylation.

As a further probe of the mechanism, we performed Stern-Volmer quenching experiments for the excited Ir photocatalyst in the presence of each reaction component, including the alkene, phosphine oxide, and heteroarene. Interestingly, only the charged heteroarenes provide quenching (K_{SV} 4-55). Surprisingly, even in the presence of various bases (e.g. Na_2CO_3), diphenyl phosphine oxide is not a quencher (nor is PPh_3), suggesting a reductive quenching mechanism is unlikely.[20] On the other hand, O_2 is a strong quencher (K_{SV} >600), which suggests oxidative quenching is more likely operative.[21]

Our proposed mechanism for the multi-component coupling of phosphine oxide **A**, alkene **B**, and heteroarenes **C** is shown in Figure 8. To start, the Ir(III) photocatalyst is excited by visible light and quenched by O_2 to form superoxide ($O_2^{\bullet-}$) along with Ir(IV).[22] This strong oxidant (+1.2 V vs SCE)[23] is capable of removing an electron from neutral phosphine oxide **A** (+1.0 V vs SCE), or its tautomer **D**,[24] to form radical cation **E**, while regenerating the ground state Ir(III) catalyst. This highly electrophilic phosphinium radical cation **E** may then selectively combine with alkenes **B** (of varying nucleophilicity) to afford alkyl radical **F**. Upon Minisci-type addition of this C-centered radical to heteroarene **C**, two divergent mechanistic pathways are then possible, depending on the identity of the heteroarene activating group, Z.

Path A illustrates radical addition into an N-OMe pyridinium, which affords **G** (Z = OMe). This electron-deficient intermediate may be reduced by either excited Ir(III) catalyst or superoxide to form the neutral radical adduct **H**. Rearomatization by loss of methanol then affords the phosphinylalkylated pyridine **I** in a net redox-neutral reaction. Alternatively, Path B shows a mechanism for direct radical addition into a Brønsted acid-protonated hetero-arene to provide **G** (Z = H). Given the acidity of the α-amino C-H (pK_a < 8),[25] its deprotonation would afford neutral α-amino radical **J**. Next, formal loss of H• may occur by aerobic oxidation followed by deprotonative aromatization to yield phosphinylalkylated **K** in a net oxidative reaction, wherein air is the terminal oxidant.

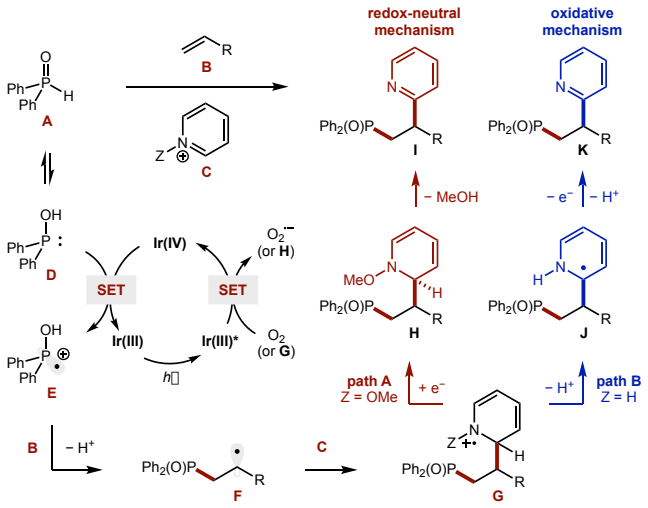


Figure 8. Proposed mechanism for both classes of heteroarenes.

In summary, a polarity-reversal radical cascade strategy has enabled a multi-component coupling of alkenes, heteroarenes, and phosphines. This photocatalytic strategy represents a novel approach to concurrently add a phosphorous and heteroarene across an olefin. We expect the methods and mechanistic insights presented herein will serve as a foundation for developing more multi-component couplings based on radical polarity-reversal.

ASSOCIATED CONTENT

Supporting Information.
The Supporting Information is available free of charge on the ACS Publications website at DOI:
Experimental procedures and characterization for all new compounds (PDF)
^{1}H and ^{13}C NMR spectral data (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We thank the National Institutes of Health (NIH R35 GM119812), National Science Foundation (NSF CAREER 1654656), and the United States Air Force (J.Q.B.) for financial support.

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