Phosphine/Photoredox Catalyzed anti-Markovnikov Hydroamination of Olefins with Primary Sulfonamides via α-Scission from Phosphoranyl Radicals

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Supporting Information Placeholder

ABSTRACT: New strategies to access radicals from common feedstock chemicals hold the potential to broadly impact synthetic chemistry. We report a dual phosphine and photoredox catalytic system that enables direct formation of sulfonamidyl radicals from primary sulfonamides. The method is proposed to proceed via α-scission of the sulfonamidyl radical from a phosphoranyl radical intermediate, generated upon sulfonamide nucleophilic addition to a phosphine radical cation. As compared to the recently well-explored β-scission chemistry of phosphoranyl radicals, this strategy is applicable to activation of *N*-based nucleophiles and is catalytic in phosphine. We highlight application of this activation strategy to an intermolecular anti-Markovnikov hydroamination of unactivated olefins with primary sulfonamides. A range of structurally diverse secondary sulfonamides can be prepared in good to excellent yields under mild conditions.

Photoredox catalysis and electrochemistry have enabled the development of a wide variety of valuable synthetic methods by offering mild, selective, and practical mechanisms for electron transfer.[1,2] While many common functional groups can be easily oxidized or reduced to afford reactive radical intermediates, many others remain inaccessible or present chemoselectivity challenges due to prohibitively high oxidation/reduction potentials.[3] A classic strategy to circumvent these challenges is to append a sacrificial redox auxiliary to the functional group in order to alter its redox potential, albeit this strategy introduces additional synthetic manipulations as well as accompanying waste and scope limitations.[4] Recently, alternative approaches, such as *in situ* activation,[5] proton-coupled electron transfer (PCET),[6] molecular electrocatalysis,[2,7] electro-photochemistry,[8] and multi-photon excitation have been explored to enable the generation of valuable radical classes otherwise challenging to access directly from feedstock chemicals via electron transfer.[9]

In this context, our group and others were drawn to the chemistry of phosphoranyl radicals as a mechanism to effect homolytic cleavage of otherwise redox inaccessible X–Y bonds via photoredox catalysis.[10,11] Seminal publications from Bentrude and Roberts demonstrated that these intermediates fragment to produce new radical species through either β-scission, which results in a net P(III) to P(V) oxidation, or α-scission, wherein a substituent is lost through homolytic cleavage to generate a new P(III) species. (Figure 1A).[12] Historically, phosphoranyl radicals were accessed by direct radical addition to a P(III) species and the harsh conditions required for radical generation limited widespread synthetic applications.[13] More recently, photoredox catalysis has provided a platform to generate phosphoranyl radicals under mild conditions either via radical addition to the P(III) species or single-electron oxidation of the P(III) species followed by nucleophilic addition (Figure 1B).[14] Thus, this activation strategy has seen recent widespread application for deoxygenation and desulfurization reactions of various common organic functional groups.[15] As an example, our group recently described the direct deoxygenation of benzylic alcohols and carboxylic acids and the hydroacylation of olefins with carboxylic acids using a phosphine in conjunction with visible light

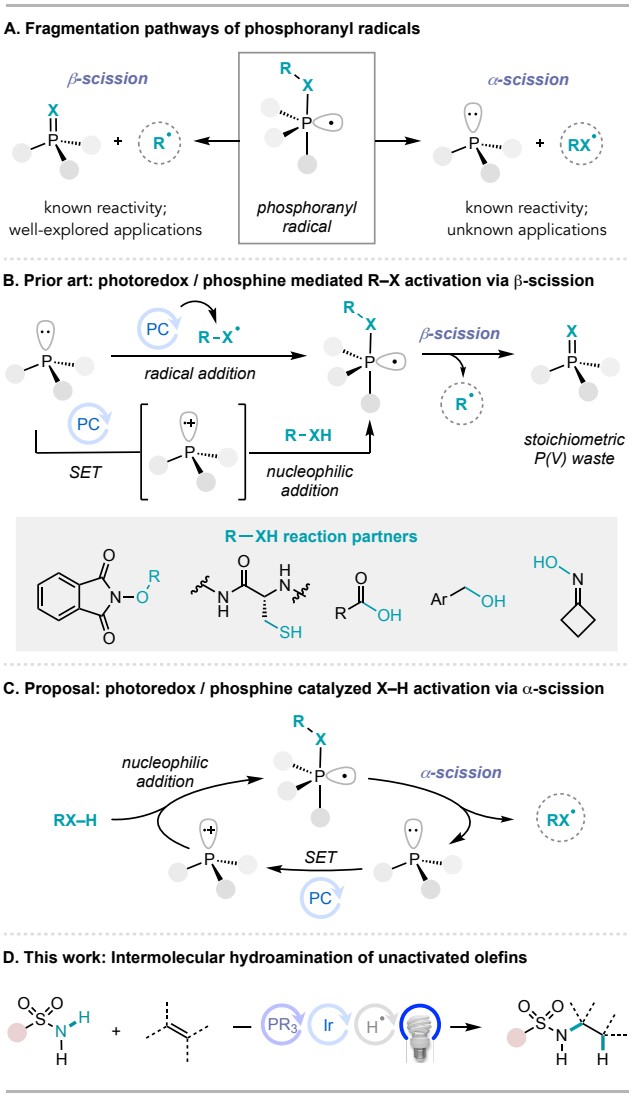


Figure 1. Synthesis and reactivity of phosphoranyl radicals.

photoredox catalysis.[10]

While β-scission methods have proven to be effective in overcoming voltage-gated restrictions, the process is thermodynamically driven by formation of the stoichiometric phosphine oxide byproduct, which has largely limited its utility to oxygen-based nucleophiles. We questioned whether taking advantage of the synthetically unexplored α-scission fragmentation pathway, wherein scission is instead kinetically favored due to an unpaired electron occupying a P–X antibonding orbital, could lead to new opportunities for synthesis and facilitate a process catalytic in phosphine (Fig 1C). Prior studies have shown that α-scission occurs site-selectively from the apical position of a phosphoranyl radical, and that electronegative functional groups have an increased preference for the apical site, suggesting that electronegative ligands could selectively undergo α-scission.[12d, 12e, 16] As such, we envisioned a process wherein a trapped nucleophile would preferentially undergo α-scission, without displacing any P(III) substituents already present, enabling the generation of radical species with only catalytic amounts of phosphine. While the generation of P=O/S bonds via β-scission could potentially compete with α-scission for many O- and S-nucleophiles, we hypothesized that a catalytic α-scission strategy could be applied to N-based nucleophiles, for which no examples of β-scission have been reported. With these criteria in mind, we were drawn to study N–H bond activation of primary sulfonamides, which possess both high N–H bond strength and oxidation potential (BDFE ~ 105 kcal/mol, $E_{1/2}$= +2.6 V versus SCE in MeCN). Here we demonstrate realization of this goal in the context of an anti-Markovnikov olefin hydroamination with primary sulfonamides catalyzed by both tricyclohexylphosphine (PCy_3) and a visible light photoredox catalyst (Figure 1D).

Intermolecular hydroamination reactions between primary sulfonamides and olefins are an attractive method for the direct and atom-economical synthesis of secondary sulfonamides, a prevalent structural feature in bioactive molecules.[17] Whereas Markovnikov-selective approaches have significant precedent,[18] only recently have methods accessing anti-Markovnikov selectivity been described. In particular, Nicewicz and co-workers pioneered a strategy wherein an excited photocatalyst oxidizes electron rich alkenes to the corresponding electrophilic radical cation.[19] Subsequent nucleophilic addition of the sulfonamide and HAT from thiophenol results in the desired anti-Markovnikov product. Whereas this strategy is applicable to trisubstituted aliphatic alkenes and substituted styrenes, Knowles and co-workers showed that anti-Markovnikov hydroamination of unactivated olefins was possible via PCET activation of the N–H bonds to produce a sulfonamidyl radical.[20] While highly enabling, the intermolecular reaction has not been extensively demonstrated beyond electron-rich *p*-methoxybenzenesulfonamide. Thus, identification of new catalytic strategies for N–H bond activation could offer synthetic advances in catalytic olefin hydroamination.[21, 22] In particular, we anticipated that the modularity of P(III) catalysis and the P–N bond weakening in phosphoranyl radicals could afford a general approach to intermolecular anti-Markovnikov hydroamination with sulfonamides.

We envisioned a catalytic cycle beginning with excitation of the photocatalyst, followed by single electron oxidation of a phosphine catalyst **A** to the corresponding radical cation **B** (Figure 2A). Nucleophilic trapping of **B** with sulfonamide **D** would form phosphoranyl radical intermediate **C**. α-Scission of the P–N bond in **C** would liberate an *N*-centered radical **E** and regenerate the phosphine catalyst **A**. Reaction of the *N*-centered radical with the olefin partner would form intermediate **F**, which upon hydrogen atom transfer (HAT) with catalytic thiol **H**, should generate the desired product **G.** Single electron transfer (SET) between the thiyl radical **I** and the reduced photocatalyst, followed by proton transfer (PT), would regenerate the photocatalyst as well as the HAT catalyst, completing the cycle.

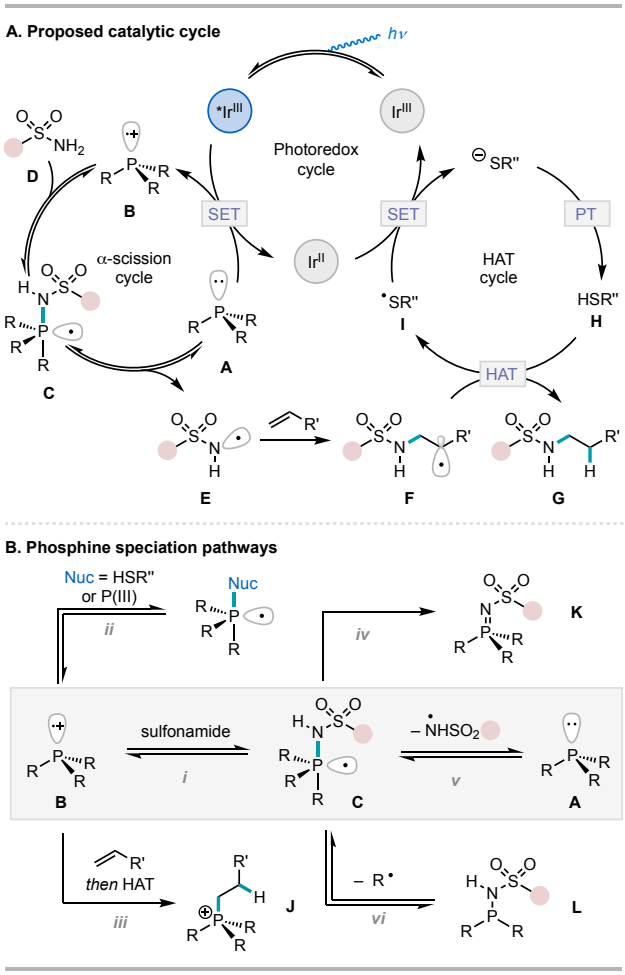


Figure 2. Proposed catalytic cycle and alternative speciation pathways.

Notably, success in the proposed scheme would require that reaction conditions are carefully tuned to accommodate the promiscuous reactivity of phosphine radical cation **B** and phosphoranyl radical **C** (Figure 2B). While nucleophilic trapping of a sulfonamide by **B** would progress the reaction (*i*), the presence of other nucleophilic species, such as excess P(III) **A** and thiol **H**, could lead to unproductive phosphoranyl radical formation (*ii*) and subsequent degradation.[23] Phosphine radical cations have also been shown to react with olefins which could then form the corresponding phosphonium species upon HAT (*iii*).[24] From the phosphoranyl radical **C**, undesired decomposition such as over-oxidation to form imidophosphorane **K** is possible (*iv*).[25] Moreover, while sulfonamide α-scission should be kinetically preferred (*v*), undesired P–R bond α-scission (*vi*) could give rise to aminophosphorane **L**. These pathways are likely to dominate if P–N bond α-scission is inefficient or if the *N*-centered radical is not rapidly trapped by the olefin, leading to reformation of the phosphoranyl radical.

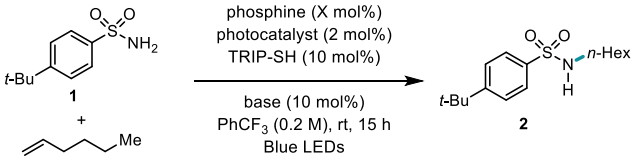
With these considerations in mind, we embarked on initial reaction discovery efforts using the hydroamination of electronically unactivated 1-hexene with *p-tert*-butylbenzene sulfonamide **1** as a model system (Table 1). On the basis of our prior work,[10a] we elected to evaluate [Ir(dF(Me)ppy)$_2$dtbbpy]-PF$_6$ (**3**) [dF(Me)ppy = 2-(2,4-difluorophenyl)-5-methylpyridine; dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine] as a photocatalyst and lutidine as a base to facilitate proton transfer. Sterically hindered 2,4,6-tri*iso*propylbenzenethiol (TRIP-SH) was selected as an HAT catalyst to sterically disfavor nucleophilic addition of the thiol to the phosphine radical cation. To our delight, we found that triphenylphosphine catalyzed the hydroamination in PhCF$_3$ as solvent, albeit in low yield (12%, entry 1). Electron-rich P(*p*-MeOC$_6$H$_4$)$_3$ showed no improvement in yield (12%) and electron-deficient P(*p*-CF$_3$C$_6$H$_4$)$_3$ afforded no product (entries 2 & 3). We were excited to observe that trialkylphosphines exhibited improved levels of reactivity (entries 4–7): PCy$_3$, which is commercially available and relatively inexpensive, provided the highest yield at 46%.[26]

Next, we evaluated other reaction dimensions using PCy$_3$ as catalyst. Hydroamination proceeded in the absence of lutidine (entry 8), likely because PCy$_3$ itself has comparable basicity (pK$_a$ ~ 15 in MeCN) and can facilitate proton transfer with TRIP thiol.[27] Inclusion of a stronger base, such as the monophosphate base employed by Knowles and co-workers in their PCET hydroamination, led to decreased reaction yield, potentially due to promotion of undesired nucleophilic addition into the phosphine radical cation (*ii* in Figure 2B). Further experimentation revealed that the phosphine catalyst loading has a significant impact on reactivity, with lower loadings of phosphine showing an increase in yield (entries 8, 10, and 11). We attribute this observation to the fact that higher concentrations of phosphine could favor addition of the *N*-centered radical to PCy$_3$ to reform the phosphoranyl radical according to LeChatelier's principle (Figure 2B, reverse of *vi*), which could ultimately favor catalyst decomposition according to pathways *iv* and *vi*. We hypothesized that an increase in olefin stoichiometry could kinetically trap the *N*-centered radical, potentially outcompeting the decomposition pathways. Gratifyingly, reactions performed with two equivalents of olefin delivered product **2** in 87% yield (entry 12).[28] Interestingly, despite the use of excess olefin, only monofunctionalized sulfonamide was observed, likely because the product is too sterically hindered to undergo nucleophilic addition to the phosphine radical cation. Upon evaluating a selection of Ir photocatalysts, we found that those with excited state oxidation potentials below that of PCy$_3$ were completely ineffective (entry 13). Catalysts with higher oxidation potentials also led to decreased yields, likely due to over oxidation of the phosphoranyl radical to form the imidophosphorane **K** (entries 14 & 15, *vida infra* for full discussion of the catalytic relevance of **K**). Finally, reactions run on 0.5 mmol scale were conducted using Kessil lamps (34 W) rather than blue LEDs (12 W), resulting in a notable increase in yield (entry 16). Control experiments revealed that each component was required in order to achieve high levels of reactivity (entries 17–20).

Although our observations during reaction optimization were consistent with a phosphoranyl radical mechanism, alternative reaction pathways could lead to product formation. Direct oxidation/deprotonation could instead generate a sulfonamidyl radical, or a multisite PCET pathway (Figure 3A), as demonstrated by Knowles and co-workers, could be operative. Alternatively, it is possible that C–N bond formation occurs through a reductive elimination mechanism from a P(V) intermediate analogous to work from McNally and co-workers in C–C, C–O, and C–N bond formation (Figure 3B).[35] Such a species could arise from either nucleophilic addition of a sulfonamide to phosphonium **J**, or a two-step olefin addition/HAT process with a phosphoranyl radical.

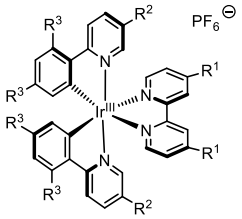
The high redox potential and pK$_a$ of sulfonamides (E$_{1/2}$= +2.6 V versus SCE in MeCN, pK$_a$ ~ 27 in MeCN)[20] eliminates the possibility of a direct oxidation/deprotonation mechanism. Instead, if multisite PCET were operative, the basic phosphine and photocatalyst would work in concert to perform a net HAT (Figure 3A).[29] We reasoned that Stern-Volmer quenching studies would be effective in discriminating between this pathway

Table 1. Optimization studies



entry[a]	phosphine (mol%)	base	photocatalyst	yield (%)[b]
1	PPh_3 (10 mol%)	Lutidine	**3**	12
2	P(4-$MeOC_6H_4$)$_3$ (10 mol%)	Lutidine	**3**	12
3	P(4-$CF_3C_6H_4$)$_3$ (10 mol%)	Lutidine	**3**	0
4	PMe_3 (10 mol%)	Lutidine	**3**	34
5	PEt_3 (10 mol%)	Lutidine	**3**	41
6	P(*t*-Bu)$_3$ (10 mol%)	Lutidine	**3**	37
7	PCy_3 (10 mol%)	Lutidine	**3**	46
8	PCy_3 (10 mol%)	none	**3**	46
9	PCy_3 (10 mol%)	$NBu_4OP(O)(OBu)_2$	**3**	32
10	PCy_3 (5 mol%)	none	**3**	60
11	PCy_3 (2.5 mol%)	none	**3**	63
12[c]	PCy_3 (2.5 mol%)	none	**3**	87
13	PCy_3 (2.5 mol%)	none	**4**	0
14	PCy_3 (2.5 mol%)	none	**5**	49
15	PCy_3 (2.5 mol%)	none	**6**	10
16[d]	**PCy_3 (2.5 mol%)**	**none**	**3**	**79**

entry[a,c]	deviation from best conditions (entry 10)	yield (%)[b]
17	no Phosphine	0
18	no Photocatalyst	0
19	no TRIP-SH	3
20	no Light	0



3: R^1 = *t*-Bu, R^2 = Me, R^3 = F
$Ir^{II}/*Ir^{III}$ = +0.97 V vs SCE
4: R^1 = *t*-Bu, R^2 = H, R^3 = H
$Ir^{II}/*Ir^{III}$ = +0.66 V vs SCE
5: R^1 = *t*-Bu, R^2 = CF_3, R^3 = F
$Ir^{II}/*Ir^{III}$ = +1.21 V vs SCE
6: R^1 = CF_3, R^2 = CF_3, R^3 = F
$Ir^{II}/*Ir^{III}$ = +1.65 V vs SCE

[a] Reactions were performed on 0.1 mmol scale with 1.0 equiv. of sulfonamide **1** and 1.0 equiv of 1-hexene using blue LEDs as a light source. [b] Yield determined by ^{1}H NMR by comparison to 1,4-Bis(trimethylsilyl)benzene as an internal standard and are reported as an average of two runs. [c] Reaction was run with 2.0 equiv of olefin. [d] Reaction was conducted on 0.5 mmol scale using a Kessil 150-H lamp for 24 h.

and a phosphoranyl radical mechanism.[30] If a PCET pathway is operative, then a combination of sulfonamide and phosphine would be more effective at quenching an excited photocatalyst than either component on its own. Instead, we found that PCy_3 was more effective at quenching the excited photocatalyst (Figure 3C, red line, K_{SV} = 1617) than the combination of the phosphine and sulfonamide, which produced a smaller slope (green line, K_{SV} = 1486) (Figure 3C, left). Studies conducted wherein sulfonamide concentration was increased in the presence of constant phosphine showed a slightly negative slope (K_{SV} = -0.02) (Figure 3C, right). These experiments are inconsistent with a PCET mechanism, and suggest instead that hydrogen bonding between the phosphine and sulfonamide removes electron density from the phosphine, making it a less effective quenching species.[31] We also assessed the effective BDFE of the oxidant/base pair, as demonstrated by Mayer and co-workers.[32] A value of approximately 90 kcal/mol is found for PCy_3 and $[Ir(dF(Me)ppy)_2(dtbbpy)]PF_6$ whereas the calculated BDFE of a primary sulfonamide is approximately 105 kcal/mol, making a PCET mechanism thermodynamically unlikely.[20,33] Instead, the rapid oxidation of phosphine in these studies indicates that a phosphine radical cation is readily formed in the reaction mixture, which should facilitate phosphoranyl radical formation.

Although preliminary efforts to directly observe the phosphoranyl radical intermediate were unsuccessful, we were able to detect via ^{31}P NMR aminophosphine **L-1** and imidophosphorane **K-1**, which likely arise *via* the pathways outlined in Figure 2B (Figure 3D) (See SI Section 4.1 for full details).[34] While these species provide indirect evidence for the intermediacy of a phosphoranyl radical intermediate, we also recognized that they could conceivably be catalytically relevant as either catalysts themselves or as bases in multisite PCET. However, subjecting independently synthesized samples of **L-1** and **K-1** to the reaction conditions in the absence of PCy_3 revealed that neither species was catalytically viable (Figure 3D).

While multiple examples of C–C bond formation via P(V) reductive elimination have been reported,[36] no examples exist for C(sp^3)–N bond formation. Nevertheless, we sought to experimentally evaluate the feasibility of the reductive C–N bond formation pathway in Figure 3B. First, we subjected independently prepared phosphonium **J-1** to the catalytic reaction conditions in the absence of PCy_3 (Fig 3D). Hydroamination was not observed, suggesting that the nucleophilic addition pathway to generate the P(V) intermediate is not viable, although counterion effects may influence reactivity. While the olefin addition/HAT pathway is still possible, to the best of our knowledge, there are no reports wherein phosphoranyl radicals have been trapped by olefins, making this pathway unlikely. To investigate the proposed P(V) mechanism further, triethylphosphine was used as the catalyst under standard reaction conditions (Figure 3E). This catalyst would afford P(V) intermediate **8**, from which a mixture of ethylated and *n*-hexylated secondary sulfonamides (**7** and **2**) would be expected since there should be little to no difference in reductive elimination among these two primary alkyl substituents. However, formation of desired product **2** occurred in 50% yield while the ethylated product **7** was not observed by ^1H NMR nor HRMS (See SI Section 4.5 for full details). Together these studies provide strong evidence that the proposed α-scission mechanism is more likely than either a PCET or P(V) reductive elimination, and that PCy_3 is likely the active form of the catalyst.

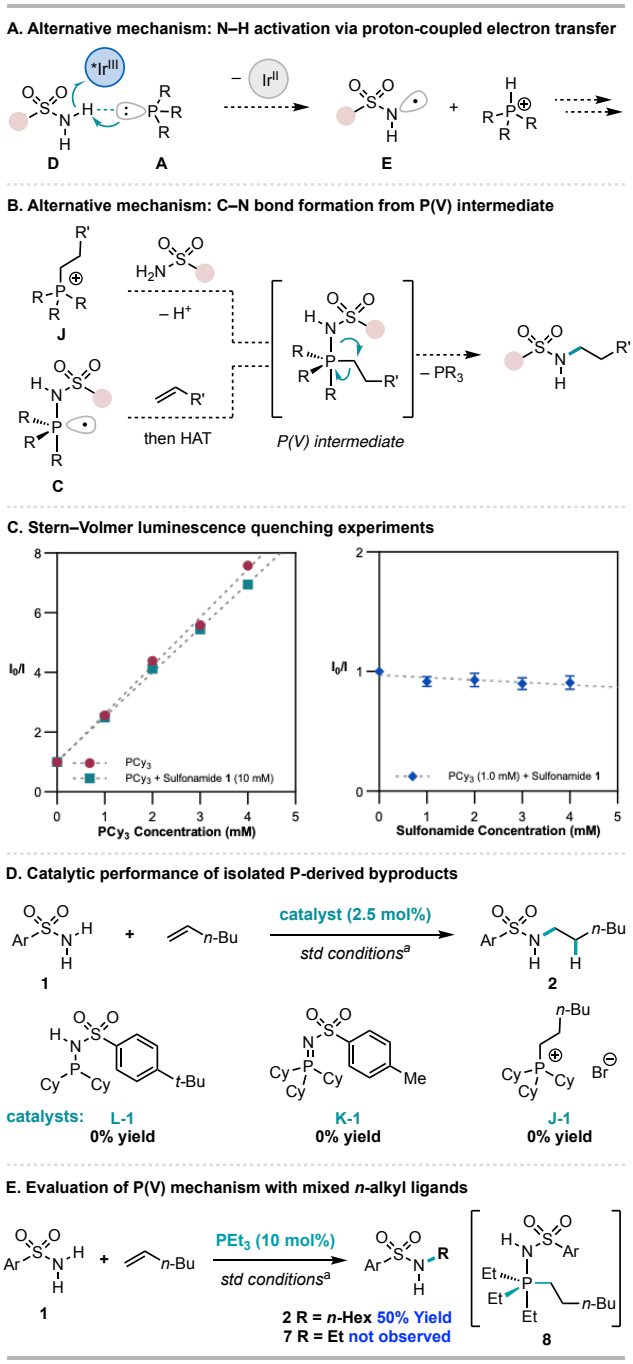


Figure 3. Mechanistic studies. [a]Std conditions: as in entry 16, Table 1 without PCy_3.

We next examined a variety of olefins under our optimized reaction conditions. Acyclic, cyclic and bicyclic olefins underwent hydroamination to afford the desired products in high yield (Figure 4). Terminal monosubstituted, 1,1-disubstituted, and 1,2-disubstituted olefins were also competent reaction partners (**2, 9-13**). In the case of *cis*- and *trans*-4-octene, we found that alkene configuration does not affect reactivity (**14-15**). Trisubstituted and tetrasubstituted olefins were also competent substrates (**16-17**), albeit hydroamination proceeded in lower yields, likely because sulfonamidyl radical trapping is not as efficient with these more hindered olefins, leading to reformation of the phosphoranyl radical and subsequent decomposition pathways (Figure 2B). In general, the electrophilic sulfonamidyl radical undergoes hydroamination in good yield with

electron-rich olefins, such as an enol ether (**18**) and vinylpyrrolidinone (**19**).[37] Only modest reactivity is observed with styrene (**20**) and allyl benzene (**21**).

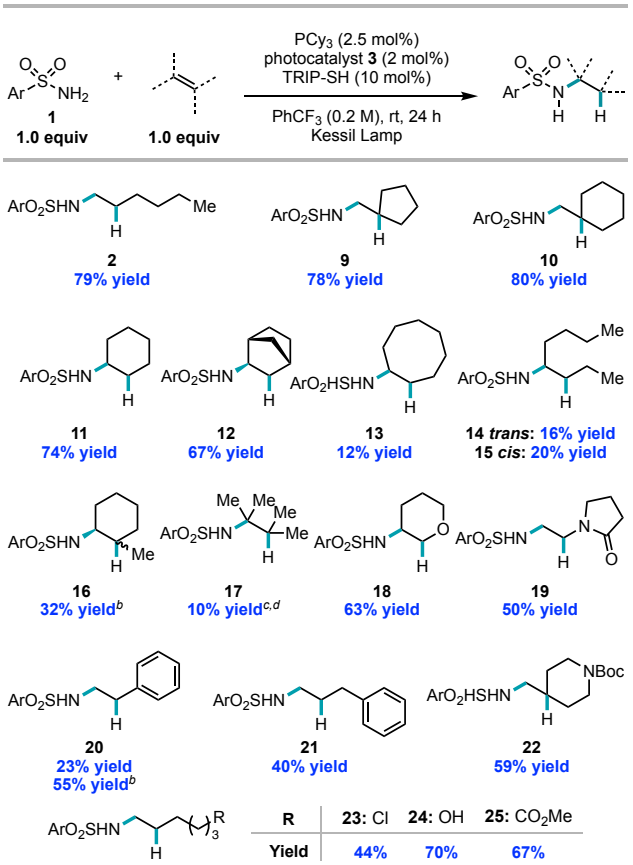


Figure 4. Olefin scope. [a]Reactions performed on 0.5 mmol scale with 1.0 equiv. of sulfonamide **1** (Ar = *p*-*t*-butylbenzene) and 1.0 equiv of olefin. Isolated yield, reported as an average of two runs. [b]1:2 *cis/trans* mixture of diastereomers. [c]Reaction was conducted with 3.0 equiv. of olefin. [d] ^{1}H NMR yield determined by comparison to an internal standard.

Gratifyingly, the standard reaction conditions tolerate a wide range of functional groups, including carbamates (**22**), primary alkyl chlorides (**23**), unprotected primary alcohols (**24**), and methyl esters (**25**). The success of **24**, is particularly encouraging as no competitive β-scission was detected despite the presence of a nucleophilic alcohol.

Turning to the sulfonamide scope, we found that hydroamination of cyclohexene with benzenesulfonamide under the standard reaction conditions delivered only 54% of the desired product **26** (Figure 5). We hypothesized that electron-neutral and deficient arylsulfonamides and alkyl sulfonamides might undergo α-scission less efficiently due to the relative instability of the resulting *N*-centered radical. As such, we reasoned that reactivity could be improved by employing an excess of olefin to rapidly trap the sulfonamidyl radical, and prevent decomposition of the catalyst. Since we previously observed that the method is selective for monoalkylation, we anticipated that over-alkylation would not be an issue. While employment of an excess of olefin is not ideal, sulfonamides are often considered the more valuable component in drug discovery.[17c, 17d, 38]

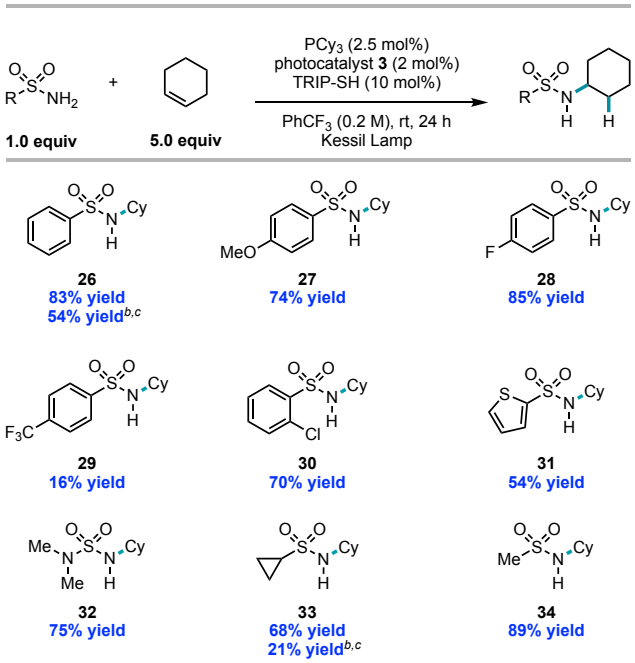


Figure 5. Sulfonamide scope. [a]Reactions were performed on 0.5 mmol scale. Isolated yield, reported as an average of two runs. [b] ^{1}H NMR yield determined by comparison to 1,4-Bis(trimethylsilyl)benzene as an internal standard and reported as an average of two runs. [c]Reaction was conducted with 1.0 equiv. of olefin.

Gratifyingly, upon employing 5.0 equivalents of cyclohexene, we were able to isolate the secondary sulfonamides derived from electron-rich and neutral substrates (**11**, **26–28)** in 74–85% yield. However, an electron-deficient aryl sulfonamide delivered low yield (**29**), likely resulting from poor nucleophilicity of the substrate which limits its ability to trap the phosphine radical cation. Using these conditions, we were pleased to see a variety of medicinally relevant motifs undergo hydroamination. For example, *ortho*-chlorobenzenesulfonamide (**30**), a structure prevalent in 12 approved drugs,[39] proved to be a competent coupling partner (70% yield). Additionally, thiophene-2-sulfonamide, a scaffold in the approved drugs dorzolamide and brinzolamide, and *N,N*-dimethylsulfamoyl amine, present in the approved drug beclabuvir, gave products **31** and **32**, respectively. The catalytic reaction can be extended to aliphatic sulfonamides as well. Cyclopropyl and methyl sulfonamide underwent olefin hydroamination to afford **33** and **34** in 68 and 89% yield, respectively.

In summary, we have developed a catalytic strategy for N–H activation of sulfonamides via phosphine and photoredox catalysis. This strategy was explored in an intermolecular anti-Markovnikov hydroamination of unactivated olefins with sulfonamides. Mechanistic studies suggest that sulfonamidyl radical generation proceeds *via* α-scission from a phosphoranyl radical intermediate in a polar-radical crossover pathway. We anticipate that with improved understanding of the reactivity and selectivity of phosphoranyl radicals it will be possible to further expand the diversity of nucleophiles and reaction classes capable of interfacing with phosphine/photoredox catalysis and apply this strategy in new synthetic contexts.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge at XXXX.

Experimental procedures, experimental data, and

characterization and spectral data for new compounds (PDF).

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Notes

The authors declare no competing financial interest.

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