Published in final edited form as:

J Am Chem Soc. 2018 November 14; 140(45): 15525–15534. doi:10.1021/jacs.8b10238.

Radical Hydroarylation of Functionalized Olefins and Mechanistic Investigation of Photocatalytic Pyridyl Radical Reactions

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Abstract

We report the photoredox alkylation of halopyridines using functionalized alkene and alkyne building blocks. Selective single-electron reduction of the halogenated pyridines provides the corresponding heteroaryl radicals, which undergo anti-Markovnikov addition to the alkene substrates. The system is shown to be mild and tolerant of a variety of alkene and alkyne subtypes. A combination of computational and experimental studies support a mechanism involving proton-coupled electron transfer followed by medium-dependent alkene addition and rapid hydrogen atom transfer mediated by a polarity-reversal catalyst.

Graphical Abstract

INTRODUCTION

Functionalized pyridines are ubiquitous structural elements in bioactive small molecules that span a wide range of applications.¹ Accordingly, a number of powerful synthetic strategies have been developed to effectively access this heterocyclic family.² In addition to classical methods for pyridine construction using acyclic precursors,³ diversification of pyridine units using transition-metal-based cross-coupling⁴ and C–H functionalization⁵ strategies plays key roles in modern drug discovery, as do nucleophilic aromatic substitution reactions.⁶ In part because of the orthogonal reactivity of radical intermediates to acidic (i.e., X–H) or Lewis

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The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b10238.

Experimental procedures and spectral data (PDF)

basic functional groups,⁷ Minisci radical addition to pyridines remains a tremendously impactful retrosynthetic tool in complex pyridine synthesis.⁸ However, the typical requirement for strong oxidants and the pronounced substrate-dependent regiocontrol limit the applicability of this strategy in many cases.⁹

Among others, we have utilized an alternative approach to complex (hetero)arene synthesis that operates through single-electron reduction of halogenated aryl units to give rise to aryl radicals in a regiospecific manner.^{10,11} In contrast to arenediazonium salts, this approach draws from a vast collection of stable, often commercially available substrates as radical precursors.¹² While arene activation in this manner requires the action of strong reductants, the introduction of photoredox catalysis has enabled the formation of highly reactive aryl radicals under mild conditions.¹³ Our studies in this area have centered on the intermolecular reaction of pyridyl radicals with an array of olefin subtypes. Interestingly, we have developed conditions that enforce divergent reactivity profiles of these typically ambiphilic radicals based solely on the reaction solvent (Figure 1). For example, in aqueous dimethyl sulfoxide (DMSO), pyridyl radicals selectively engage electron-poor alkenes through a radical conjugate addition (RCA) mechanism.^{10a} However, the use of 2,2,2-trifluoroethanol (TFE) as the solvent enables highly selective hydroarylation with simple electron-neutral olefins.¹¹ Importantly, this protocol delivers the desired pyridyl products with complete regiocontrol with respect to both the heterocyclic and olefinic subunits (anti-Markovnikov addition) as a complement to recent radical hydroarylation systems reported by Herzon¹⁴ and Shenvi¹⁵ (Markovnikov addition). Here we describe the development of a system based on this mechanistic blueprint that allows for radical hydroarylation of a diverse collection of olefinic substrate classes. Many of these are shown for the first time as substrates under this synthetic disconnection, giving rise to densely functionalized alkylpyridines. In addition, we offer a mechanistic evaluation of these complementary pathways.

RESULTS AND DISCUSSION

Radical Hydroarylation of Olefinic Substrates

At the outset of this investigation, we treated the feedstock reagent vinyl acetate with 4-bromopyridine (**1**) under conditions that we recently described for anti-Markovnikov hydroarylation of aliphatic olefins.¹¹ More specifically, we employed the commercial iridium-based photoredox catalyst [Ir(ppy)₂ dtbbpy]PF₆ (1 mol %) and Hantzsch ester (HEH) (1.3 equiv) as a stoichiometric reductant using TFE as the reaction solvent. We found that irradiation of this mixture for 16 h with blue light furnished the desired product 2-(4-pyridyl)ethyl acetate (**2**) in low yield (17%) and that the use of TFE was crucial for product formation. However, significant amounts of oligomeric byproducts where pyridyl units coupled with multiple vinyl acetate equivalents (pyridine:olefin ratios of 1:2, 1:3, etc.) were formed. We reasoned that increasing the rate of hydrogen atom transfer (HAT) to the nucleophilic α -oxy radical intermediate—resulting from radical addition to vinyl acetate—would preclude further olefin incorporation.¹⁶ Therefore, we surveyed a number of electrophilic polarity-reversal catalysts (Scheme 1).

While the use of the nitroxyl-based HAT catalysts NHPI¹⁷ and HOBt¹⁸ did not significantly alter the reaction outcome, employing cyclohexanethiol (5 mol % loading) resulted in significantly improved production of **2** (63% yield).¹⁹ Here a much cleaner reaction profile was observed, with pyridine production (via radical hydrodehalogenation) being the major alternative pathway. The beneficial effect of the thiol catalyst was also observed using the isomeric pyridyl radical precursor **3** as the limiting reagent, thus delivering the desired adduct **4** in 65% yield. A range of thiol HAT catalysts were surveyed, although no clear trend was observed between thiol electronics and reaction efficiency. Control reactions revealed that both the photo-catalyst and light were necessary for effective conversion, and in line with our previous results, acidic additives such as AcOH or NH₄Cl increased the yield (see the Supporting Information (SI) for details).

We then applied our optimized conditions to a variety of functionalized alkenes (containing heteroatom substitution) that were absent from the current hydroarylation literature as well as common polymer feedstocks (Table 1).²⁰ Halogenated alkenes were particularly appealing because of the broad utility of the products for further functionalization. Vinyl bromide was an effective coupling partner under the reaction conditions, affording alkyl bromide **6** in 78% yield with no further reduction to the corresponding ethylpyridine. Exposure of the crude mixture to silica gel resulted in rapid quantitative conversion to the corresponding vinylpyridine, a product typically accessed through Stille cross-coupling with vinylstannane.²¹ 2-Chloropropene was similarly effective, providing secondary alkyl chloride **7** in 70% yield, again without undesired reduction of the resulting chloroalkane, and elimination during purification was not observed in this case. The reaction conditions were also tolerant of alkenyl fluorides, producing alkyl fluoride **8** in good yield. Robust methods for the synthesis of alkyl fluorides are highly prized, particularly where S_N2-type approaches are competitive with elimination byproducts.²²

In a process complementary to the recently described work of Aggarwal,²³ alkenylboronic esters also underwent the reaction smoothly under the reaction conditions. Homobenzylic alkylboronic ester **9** was effectively synthesized through this method (58%) without any undesired protodeboronation or oxidation. Alkenes substituted with main-group elements were also readily incorporated, despite relatively scarce examples of the hydroarylation of these moieties and a dearth of knowledge concerning the reactivity of the resulting α -heteroatomic radicals.² Alkenes substituted with Si, P, and S were all tolerated, delivering **10**, **11**, and **12**, respectively, in good yields (41–68%). We envision this method to be applicable to the synthesis of novel bidentate P,N or S,N ligands that are nontrivial to access through other methods.²⁵

The polymer feedstocks vinyl acetate and ethyl vinyl ether both combined with bromopyridine **5** in good yields (57% and 62% yield, respectively), where the remainder of the mass balance was hydrodehalogenated **5** and not higher-order oligomers. Alkyl enol ethers smoothly participated in the reaction to give **14** and **16**, both in 72% isolated yield. In addition to heteroatom-substituted alkenes, a number of alkynes were smoothly converted by this system to provide the corresponding vinylpyridines **17–19** as 1:1 mixtures of geometrical isomers (66%–83% yield). In particular, these transformations were unaffected by unprotected alcohols and primary alkyl chlorides. This method provides an alternative to

classical Mizoroki–Heck chemistry, which is typically intolerant of such sensitive functionality.²⁶

We next explored the scope of the halopyridine component using isopropenyl acetate as the olefinic coupling partner (as indicated in Table 2). The conditions were tolerant of alkyl substituents on the radical precursor (**20**, **24–25**) in addition to other electron-donating groups, including alkoxy (**23**) and carbamate (**27**) functions, with only minor deviations in yield (42–57%). Alkyne-containing pyridine **30** could also be synthesized under the reaction conditions (26%), providing exclusive chemoselectivity for alkene addition, leaving a useful functional handle for further manipulation. Fused heterocycles were likewise tolerated, with pyrrolopyrimidine **26** and azaindole **31** being formed in moderate yields (38–55%). Moreover, 3,4-dibromopyridine underwent chemoselective reaction at the more electron-poor 4-position to provide alkylated bromopyridine **28** without subsequent reductive dehalogenation (38%). Here, radical anion fragmentation occurs selectively through cleavage of the weaker C–Br bond (at the 4-position), and 3-bromopyridine (formed via hydro-debromination) constituted the mass balance. To further illustrate the generality of the process for all pyridine regioisomers, representative members of the alkene scope were coupled to 3- and 4-halopyridines (Table 2, **32–43**). To further demonstrate the scope of the alkene-coupling partner, the antidiabetic pioglitazone²⁷ was prepared in a short synthetic sequence (Table 2, **44**, 64%) that utilized an aryl vinyl ether as olefinic partner. The unique disconnection afforded by this hydroarylation protocol allows for a highly modular synthesis that would be appealing for early-stage discovery programs.²⁸

This photoredox process was amenable to gram-scale synthesis without erosion of the isolated yield (71 vs 76%). Compound **20** was synthesized on a 10 mmol scale without any specialized equipment using only 0.1 mol % Ir catalyst (Figure 2). It has been well-demonstrated that scale-up of photocatalytic processes can be limited by light penetration;²⁹ a common solution to this issue is the use of continuous flow methods,³⁰ which have facilitated the large-scale production of active pharmaceutical ingredients.³¹ To demonstrate that our method is amenable to such scale-up procedures, we performed the reaction in a custom-built flow reactor. By the use of a plug-flow regime with a residence time of 20 min, the alkylated product was formed in 75% yield, corresponding to a continuous flow production of 4.5 mmol/h. Further optimization of the flow reactor setup is ongoing within our laboratory.

Mechanistic Investigation—Having established the utility of pyridyl radical intermediates in the hydroarylation of functionalized olefins, we were interested in gaining a deeper mechanistic understanding of this system. Of particular interest were the following two elements: (i) reductive activation of halopyridine substrates is efficient even in cases where single electron transfer (SET) would appear to be endergonic (as indicated by thermodynamic reduction potentials), and (ii) pyridyl radical species display remarkable chemoselectivity for different olefin types depending on the reaction solvent.

Shown in Figure 3 is a proposed mechanistic scenario for the dual-catalytic hydroarylation process introduced above. Specifically, reductive quenching of the photoexcited iridium catalyst (*[Ir]^{III}) would give rise to the reducing [Ir]^{II} species ($E_{1/2}^{\circ} = -1.51$ V vs SCE).

This mechanism would likely be initiated by oxidation of a sacrificial amount of HEH, as supported by Stern–Volmer quenching studies, in agreement with previous studies by Knowles.³² Reduction of bromopyridine substrate **3** via proton-coupled electron transfer (PCET) (involving TFE as the proton source) followed by rapid mesolytic cleavage would provide protonated pyridine radical **44** and an equivalent of bromide. Regioselective radical addition to the terminal carbon of vinyl acetate (like other nucleophilic olefins) would furnish radical species **45**, which would undergo polarity-matched HAT from the thiol catalyst, concurrently producing the hydroarylation product and thiyl species. Regeneration of the HAT catalyst with HEH would deliver the corresponding dihydropyridine radical (HEH $\cdot$), a mild reductant that would close the photoredox catalytic cycle, delivering the corresponding pyridinium (HP).

Key to this electrophilic radical reactivity is the notorious H-bond-donating (but poorly H-bond-accepting) solvent TFE.³³ Indeed, when the diene compound vinyl crotonate (**46**) was reacted in trifluoroethanol, the pyridyl radical derived from bromopyridine **5** engaged the nucleophilic alkene, giving rise to hydroarylation product **47** as a single regioisomer (72% yield). In contrast, activation of the same radical precursor with the same catalyst in aqueous DMSO as the solvent (25% v/v H₂O/DMSO) resulted in exclusive radical conjugate addition to the Michael acceptor, affording **48** as a single regioisomer (56% yield). Regiochemical analysis in these experiments was conducted by GC and, in both cases, <1% yield of the alternate regioisomer was observed. Here, picoline production was the major alternative pathway. These results, which are completely consistent with a previously reported set of competition experiments, indicate that pyridyl radical addition to olefins operates through different reactive intermediates, as dictated by the solvent.¹¹ Further evaluation of these scenarios is presented in the following sections.

Proton-Coupled Electron Transfer—As indicated above, we propose that pyridyl radical formation occurs primarily through a reductive quenching pathway of the iridium photocatalyst. However, analysis of the salient reduction potentials in this system is complicated. Accurate measurement of the reduction potentials of halogenated pyridines remains a challenge because fragmentation of the resulting radical anions is rapid and pyridyl radicals readily undergo reduction to the corresponding anions. However, the reduction potential of 2-bromopyridine has been reported to be between -1.80^{34} and -2.29 V vs SCE,³⁵ which is significantly beyond the reducing ability of the Ir catalyst ($E_{1/2}^{\circ} = -1.51$ V vs SCE). Although protonation of the halopyridine substrate would significantly decrease the reduction potential ($E_{1/2}^{\circ} = -1.10$ V vs SCE), a cursory analysis of the pK_a values of TFE ($pK_a = 12$ in DMSO) and 2-bromopyridinium ($pK_a = 0.5$ in DMSO) does not support the formation of a discrete pyridinium salt. Thus, we reason that reductive activation of pyridine substrates in TFE occurs through a PCET mechanism.³⁶

The effect of pyridine protonation on the energetics of electron transfer has been well-studied, particularly within the context of CO₂ reduction.³⁷ However, reports detailing the exact impact of protonation on the pyridine reduction potential remain disparate. Because the complications associated with halopyridine reduction potential measurements (vide supra) are compounded by the fact that TFE has a narrow usable electrochemical window,

we turned to density functional theory (DFT) calculations to further interrogate this step (Scheme 2A). At the uB3LYP level of theory, the reduction potential of 2-bromopyridine was calculated to be -2.61 V vs SCE,³⁸ and the potentials of H-bonded substrate **49** ($E_{1/2}^{\circ} = -2.29$ V vs SCE; N–H–O bond length = 2 Å) and fully protonated substrate **50** ($E_{1/2}^{\circ} = -1.1$ V vs SCE; bond length = 1.1 Å) were also computed. Indeed, the measured reduction potential of the $[\text{Ir}]^{\text{II}}$ catalytic species ($E_{1/2}^{\circ} = -1.51$ V vs SCE) lies squarely between these values.¹³ As shown in Scheme 2B, protonation of the neutral species with TFE is endergonic by 27 kcal/mol but is thermoneutral after reduction. Similarly, reduction of bromopyridine at 2 Å is endergonic by 18.1 kcal/mol but exergonic by 9.4 kcal/mol after protonation. The lowest energetic barrier (where the two curves intersect) was calculated to be 13 kcal/mol at a N–H bond length of 1.55 Å, a reasonable energetic barrier for the proposed PCET event. An endergonic electron transfer of this type is feasible from a ground-state reductant because of the highly exergonic heterolytic cleavage event that occurs immediately after reduction (i.e., the Curtin–Hammett principle). While this principle could account for a decoupled protonation/electron transfer sequence, we posit that a concerted mechanism is operative.

Chemoselective C—C Bond Formation—Among the most interesting features of this pyridyl-radical-based strategy is the highly pronounced chemoselectivity that is imparted by the chosen reaction solvent. Shown in Scheme 3 are two electronically diverse olefins along with the optimal reaction solvents for their intermolecular couplings with pyridyl radicals. Because high chemoselectivity for either electron-rich or -poor olefins has been observed (vide supra), we hypothesize that these complementary systems differ in the identity of the pertinent pyridyl radical species. More specifically, we propose that protonated, electrophilic radical species (e.g., **44**) are active in TFE, while proton dissociation in polar, H-bond-accepting solvents favors neutral, nucleophilic aryl radicals (e.g., **51**).³⁹

As an excellent H-bond donor and a weak H-bond acceptor, TFE has the ability to form strong H-bonding networks that effectively stabilize anions or protonate very weak bases.³³ As a result, the use of TFE as the reaction solvent has led to divergent selectivity profiles in other systems that are reminiscent of our findings.³³ To investigate the relevance of this solvent property in our systems, we attempted to overturn the observed pyridyl radical chemoselectivity through a series of competition experiments. As indicated in Scheme 3, treatment of **5** with both electron-rich isopropenyl acetate and electron-poor dimethylethylidene malonate (3 equiv each) under standard conditions in TFE led to the exclusive production of **20**. However, addition of various amounts of water was accompanied by increasingly significant formation of the radical conjugate addition product **52**. With 150 equiv of H_2O , the two products were formed in nearly equal amounts, presumably resulting from increased dissociation of the proton from the pyridyl radical species by the H-bond acceptor H_2O .⁴⁰ Addition of acids to the same mixtures in DMSO did not have an impact on the chemoselectivity, which is also consistent with the suggestion that protons are highly dissociated from the pyridyl radical species in polar (aqueous) solvents.

An alternative set of reactive intermediates that could potentially account for the observed solvent-based complementary selectivity of this method could arise from differential rates of

radical anion fragmentation depending on the solvent. In this scenario, an α -bromo, α -amino radical (resulting directly from PCET) would undergo C–C bond formation prior to bromide dissociation, presumably as an intermediate in radical conjugate addition (i.e., aqueous DMSO). Indeed, Weaver has proposed that the rate of radical anion fragmentation is responsible for altered selectivity in reductive photoredox processes of 2-haloazoles (where differential reactivity resulted from different halogens).⁴¹ Along the same lines, it has been shown that the rate of 2-halopyridine (2-X-pyr) radical anion fragmentation decreases significantly in the series $X = I > Br > Cl \gg F$.^{35a} While the fluoropyridine-based radical anion persists long enough to observe reversible redox by CV, bromopyridine radical anion fragmentation is exceedingly rapid, as measured by Savéant and co-workers.⁴² Solvent polarity has also been shown to alter the fragmentation rate to a lesser extent, but unimolecular fragmentation rates remain significantly higher than the relevant bimolecular addition rates for aryl radical addition to olefins.⁴³

Radical Termination after Alkene Addition—During our investigations of the addition of pyridyl radicals to olefins, we have observed different radical termination mechanisms that are highly dependent on the employed alkene subtype. While different reaction modes often lead to identical outcomes (e.g., Giese termination via HAT⁴⁴ or a reduction/enolate protonation sequence⁴⁵), they could be expected to have discrete implications for photocatalyst turnover or, more importantly, the structural nature of the product. Using combinations of deuterium-labeled HEH and solvents, we have shown that dehydroalanine-derived **53** undergoes essentially exclusive reduction and enolate protonation to give the desired amino acid products.^{10b} In contrast, radicals **54** and **55** receive α -protons or deuterons primarily from HEH, indicating HAT as the primary termination events (>80% incorporation of the label from HEH rather than the solvent).^{10a,11} When coupling to more nucleophilic vinyl heteroatoms is considered, both oxidation and HAT processes of the intermediate radical (e.g., **56** derived from vinyl acetate) are relevant, as they would likely be product-determining. For example, in a method described by Buchwald, a similar α -oxy radical generated by Meerwein addition to an enol acetate is efficiently oxidized by ferrocenium to provide an aldehyde product.⁴⁶ However, the conditions that are introduced here appear to enforce termination via HAT, even though single-electron oxidation of **56** would be facile ($E_{1/2}^{\circ} = 0.21$ V vs SCE).

Evidence for product formation via terminal HAT is offered in Figure 4, where the two potentially competing pathways involving radical intermediate **57** are illustrated. Work by Moeller⁴⁷ and Horner and Newcomb⁴⁸ indicates that oxidation to the corresponding cation would be followed by exceedingly rapid cyclization to form dioxolane **58**. However, hydroarylation product **19** was delivered in 72% yield without any indication of **58** by NMR or GC–MS analysis. Furthermore, isotopic labeling experiments involving deuterated HEH and/or solvent were consistent with this proposal (see the SI for details). The discrepancy between these results and the system reported by Buchwald⁴⁶ arises from effective concentration of the putative oxidant: 10 mol % Cp_2Fe^+ (generated through highly exergonic reduction of arenediazonium salts) versus the minute concentration of photooxidant.

Alternative Redox Pathways—Although the mechanistic analyses that we have presented are consistent with experimental data, the observed results likely arise from an ensemble of related mechanistic pathways. For example, the proposed role of the stoichiometric reductant (HEH) is highly consistent with previous reports, facilitating product formation through sequential HAT and SET steps. However, the order of these events is experimentally ambiguous, as HEH consumption via the same steps in reverse order (SET then HAT) would reasonably lead to the same experimental results.

To further evaluate the validity of the proposed photoredox pathway, we conducted a series of temporal studies. Under these conditions, hydroarylation of isopropenyl acetate (to give **20**) exhibited zeroth-order kinetics with respect to the starting materials and catalyst in a manner that was highly dependent on the light source,⁴⁹ as shown in Figure 5. In conjunction with the finding that the benchmark reaction reached completion within 10 min, these results led us to question the degree of radical chain character of this process.⁵⁰ However, the relatively low quantum yield of this process ($\Phi = 0.31$) indicates that photosensitized processes are dominant. Control experiments showed that formation of **20** can occur in the absence of the iridium catalyst, but the reaction rate is considerably lower (~10% yield after 16 h vs 72% yield after 10 min; see the SI for details). We suggest that the catalyst-free reaction arises from reduction of the halopyridine by the HEH excited state.⁵¹ Charge transfer complexes between HEH and bromopyridine were not observed in either the ground state via ¹H NMR analysis or the excited state via UV/vis spectroscopy (see the SI for further details). Moreover, alteration of the catalyst properties had a noticeable impact on the overall reaction efficiency (see the SI for full details).⁵⁰ Taken in aggregate, these findings implicate the outlined catalytic manifold as the major contributor to product formation in this system.⁵⁰

CONCLUSIONS

A general and efficient method for the hydroarylation of electron-rich olefins has been developed. Addition of a thiol polarity-reversal catalyst promotes a rapid intermolecular HAT step that prevents side reactions such as olefin polymerization and single-electron oxidation to provide the anti-Markovnikov products exclusively. Investigation of the reaction mechanism revealed a solvent-dependent mechanistic divergence. Use of the highly coordinating solvent TFE leads to a protonated, electrophilic pyridyl radical that is polarity-matched for alkene addition with electron-rich olefins. Use of a H-bond-accepting medium such as aqueous DMSO leads to a dissociated, neutral pyridyl radical that is polarity-matched for electron-poor olefins. We believe that these data will provide a greater rationale for chemistries utilizing heteroaryl radicals and expand the scope and understanding of related radical–olefin couplings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

This project was supported by funds from the National Institutes of Health (R01 GM129495) and NMR spectra were obtained under the support of the National Science Foundation (CHE-1531620). Z. Xu acknowledges financial support by the U.S. Department of Energy, Solar Photochemistry Program (DE-FG02-07ER-15906). The authors thank Savannah Post (Emory University) for preliminary experiments, Professors R. Brian Dyer and Tianquan Lian (Emory University) for generous access to instrumentation, and Professor Zachary Wickens (University of Wisconsin) for helpful discussions.

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Previous work: Intermolecular reactions of pyridyl radical species via photoredox catalysis

Figure 1.

Catalytic intermolecular reactions of pyridyl radical intermediates.

Figure 2.
Enol acetate hydroarylation on a gram scale.

Figure 3.
Mechanistic proposal: the solvent dictates the nature of the pyridyl radical, imparting divergent chemoselectivity.

Figure 4.
Mechanisms of radical termination.

Figure 5.
Temporal evaluation of the reaction profile.

Scheme 1. Anti-Markovnikov Vinyl Acetate Hydroarylation Using HAT Catalysts^a

^aPerformed with [Ir(ppy)₂(dtbbpy)]PF₆ (1 mol %), Hantzsch ester (1.3 equiv), halopyridine (1 equiv), vinyl acetate (3 equiv) in 2,2,2-trifluoroethanol (0.1 M) at 23 °C for 16 h. Yields were determined by ¹H NMR analysis. ^b4-Bromopyridine hydrochloride was used as the substrate.

(B) Energetic consequences of bromopyridine (3) / TFE interaction

Scheme 2. Proposed Mechanism of Reduction: PCET^a

^aDFT calculations were performed at the uB3LYP/6-311+G(d,p)/CPCM=DMSO level of theory.

Scheme 3. Proposal for the Observed Solvent-Dependent Chemoselectivity of Pyridyl Radicals^a

^aThe competition experiments were performed with [Ir(ppy)₂(dtbbpy)]PF₆ (1 mol %), Hantzsch ester (1.3 equiv), 2-bromo-6-methylpyridine (1 equiv), dimethylethylidene malonate (3 equiv), and isopropenyl acetate (3 equiv) in 2,2,2-trifluoroethanol (0.1 M) at 23 °C for 16 h.

Table 1.

Anti-Markovnikov Hydroarylation with Pyridyl Radicals: Scope of the Functionalized Olefins^a

hydroarylation product		
olefin	product	compound #: yield	olefin	product	compound #: yield
6: 78%			13: 57%
7: 70%			14: 72%
8: 65% ^b			15: 62%
9: 58% ^c			16: 72%
10: 68%			17: 75%, 1:1 (E:Z)
11: 41% ^b			18: 83%, 1:1 (E:Z)
12: 52%			19: 66%, 1:1 (E:Z)

^aPerformed with [Ir(ppy)₂dtbbpy]PF₆ (1 mol %), Hantzsch ester (1.3 mmol), 2-bromo-6-methylpyridine (1 mmol), alkene (3 mmol), and CySH (5 mol %) in 2,2,2-trifluoroethanol (0.1 M) at 23 °C for 16 h. Isolated yields are shown.

^bThe reaction was performed on a 0.1 mmol scale.

^cThe reaction was performed on a 0.25 mmol scale.

Table 2.

Scope of the Halogenated Pyridinea

HetAr-X	alkene/alkyne	hydroarylation product
 20 (X = Br): 71%	 21 (X = Br): 70% ^b	 22 (X = Br): 64%
 23 (X = Br): 42%	 24 (X = Br): 50%	 25 (X = Br): 47%
 26 (X = Br): 55% ^c	 27 (X = Br): 57%	 28 (X = Br): 38%
 29 (X = Br): 50%	 30 (X = Br): 26%	 31 (X = Br): 38%
 32 (X = I): 49%	 33 (X = I): 65% ^d	 34 (X = I): 56% ^e
 35 (X = Br): 72% ^b	 36 (X = Br): 74% ^{b,f}	 37 (X = Br): 60% ^{b,e}
 38 (X = I): 43% ^g	 39 (X = I): 56%	 40 (X = I): 65%
 41 (X = Br): 76% ^b	 2 (X = Br): 62% ^b	 43 (X = Br): 45% ^b
 44 (X = Br): 64%		

^aThe reactions were conducted as in Table 1. Isolated yields are shown.

^b4-Bromopyridine·HCl was used as the starting material.

^cThe reaction was performed on a 0.5 mmol scale.

^dFormed as a 1.7:1 mixture of olefin isomers.

^eThe reaction was performed on a 0.25 mmol scale.

^fFormed as a 3:1 mixture of olefin isomers.

^gIsolated as a 1.2:1 mixture of regioisomers. The gray asterisk indicates the connectivity of the minor regioisomer.