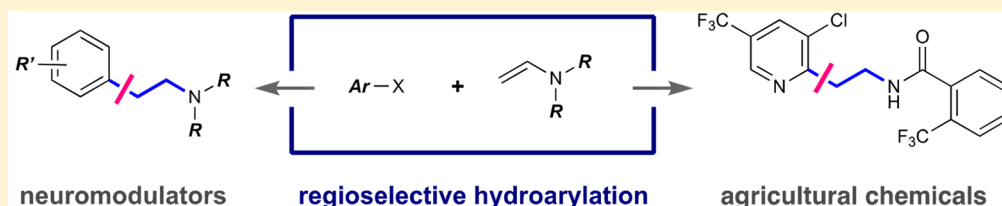


Catalytic Strategy for Regioselective Arylethylamine Synthesis

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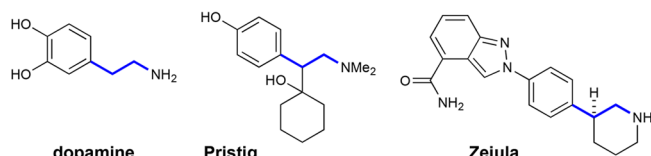
S Supporting Information



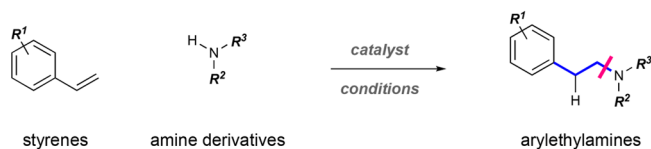
ABSTRACT: A mild, modular, and practical catalytic system for the synthesis of the highly privileged phenethylamine pharmacophore is reported. Using a unique combination of organic catalysts to promote the transfer of electrons and hydrogen atoms, this system performs direct hydroarylation of vinyl amine derivatives with a wide range of aryl halides (including aryl chlorides). This general and highly chemoselective protocol delivers a broad range of arylethylamine products with complete regiocontrol. The utility of this process is highlighted by its scalability and the modular synthesis of an array of bioactive small molecules.

The arylethylamine scaffold is a key pharmacophore in endogenous neurotransmitters, natural products, and pharmaceuticals that accomplishes a wide range of important functions (a small sampling of which is provided in Figure 1). While this molecular scaffold can be produced through a range of classical technologies (e.g., amino acid decarboxylation or reductive amination) that utilize functionalized precursors, the

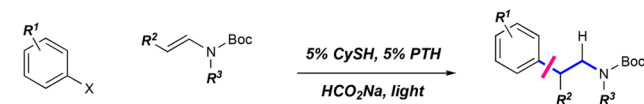
The Arylethylamine Scaffold: A Highly-Privileged Pharmacophore



Anti-Markovnikov Styrene Hydroamination (Grubbs, Knowles, Nicewicz)



This Work: Arylethylamine Construction via Radical Enamide Hydroarylation



flexible *N*-substitution • mild conditions • complete regiocontrol

Figure 1. Modular catalytic strategies for arylethylamine synthesis.

ability to access this structural array with modular flexibility remains limited. Specifically, we consider catalytic methods for direct arylethylamine synthesis from readily available synthons where the alteration of the aryl unit, ethyl skeleton, and nitrogen atom would be particularly powerful if they utilized readily available starting materials. Toward this aim, significant progress has been made in intermolecular anti-Markovnikov styrene hydroamination using *N,N*-dialkylamines,^{1–4} *N*-aryl-amines,⁵ and sulfonamides.^{6,7} As a complement to these technologies, we became interested in developing a process for the hydroarylation of vinylamine derivatives, where the flexible substitution of nitrogen would be possible. The utility of this method would be partially driven by its capacity to deliver the desired products from widely available precursors with complete anti-Markovnikov selectivity and good functional group compatibility. We envisioned that a mechanism for the reductive activation of aryl halides to the corresponding radicals and intermolecular addition could be utilized to accomplish these goals.

Aryl radicals are highly reactive intermediates that readily engage a range of unsaturated systems.^{8,9} As an alternative to arenediazonium salt-based approaches, the single-electron reduction of aryl halides using photoredox catalysts^{10,11} is a powerful method for aryl radical formation from stable starting materials.^{12–19} Building on previous results by Stephenson,¹² Konig,^{20,21} and Read de Alaniz and Hawker, we have shown that pyridyl radicals (accessed via pyridyl halide reduction) undergo chemoselective intermolecular coupling with either electron-deficient^{22,23} or electron-rich olefins,^{24,25} and Weaver has reported a number of processes involving azolyl or

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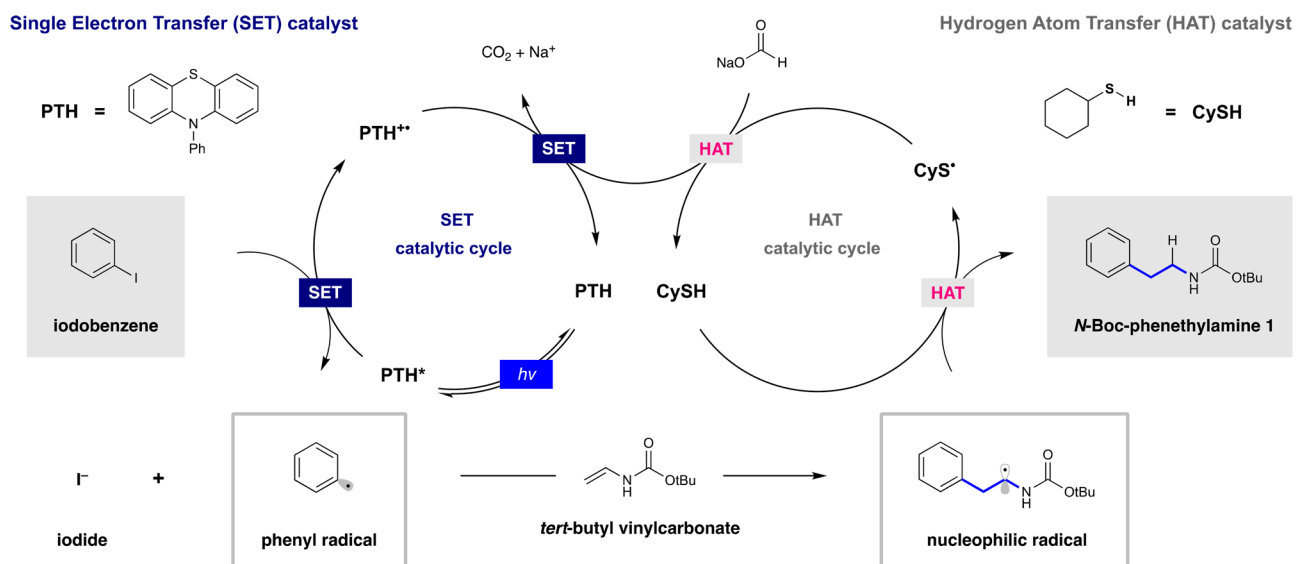


Figure 2. Proposed dual-catalytic mechanism for intermolecular radical hydroarylation.

perfluoroaryl radicals.¹⁶ However, because aryl halide reduction potentials are very negative and the resulting aryl radicals undergo rapid reduction through hydrogen atom transfer (HAT), a general translation of these findings to aryl systems has yet to materialize.

From the outset, we recognized two elements that would be critical to the success of the proposed transformation: a powerful catalytic reductant (capable of aryl halide activation) and a catalytic hydrogen atom source (such that the rate of aryl radical addition to vinylamines would be competitive with reduction pathways involving HAT). Accordingly, we reasoned that the highly reducing *N*-phenylphenothiazine (PTH) and cyclohexanethiol (CySH) could operate in concert through transferring electrons and hydrogen atoms, respectively, as illustrated in Figure 2. Specifically, iodobenzene ($E_{1/2}^0 = -1.51$ to -2.20 V vs SCE)¹² activation via single-electron transfer (SET) from photoexcited PTH ($E_{1/2}^* = -2.10$ V vs SCE)¹⁴ would give rise to the corresponding radical anion. Rapid mesolytic fragmentation would expel iodide, thereby delivering the neutral phenyl radical. Regioselective intermolecular addition to the vinylcarbamate substrate would deliver the nucleophilic α -carbamoyl radical, which would undergo polarity-matched HAT from the electrophilic thiol catalyst.²⁶ This event would concurrently furnish desired product 1 and thiyl species CyS^\bullet . Finally, the regeneration of both catalysts (via HAT and SET events) would liberate innocuous byproducts CO_2 and NaI.

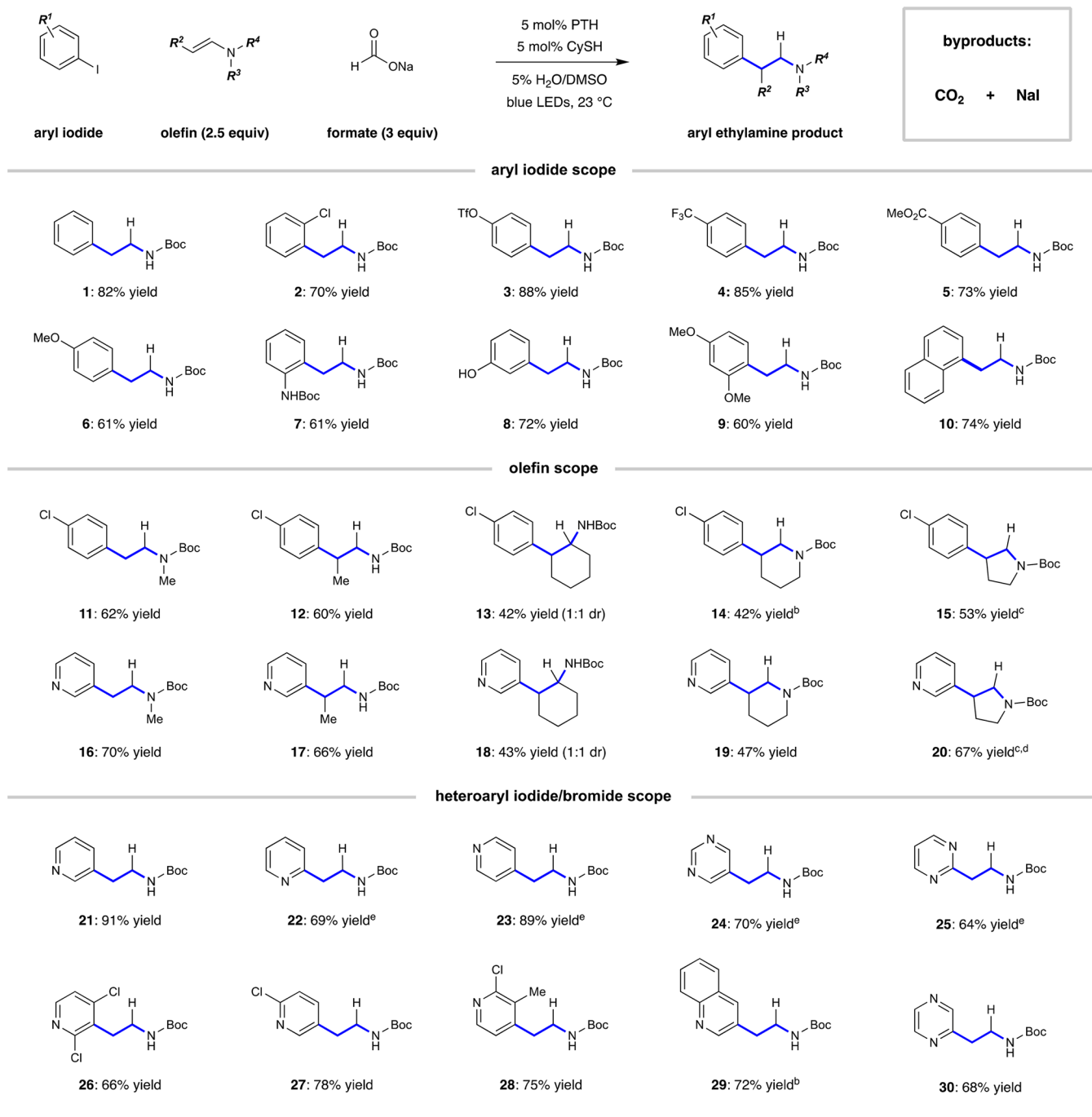
In practice, we found that iodobenzene effectively reacts with *tert*-butylvinylcarbamate (2.5 equiv) in the presence of 5 mol % of each catalyst and 3 equiv of sodium formate under irradiation with blue light in 5% $\text{H}_2\text{O}/\text{DMSO}$, affording the desired adduct as a single regioisomer (82% isolated yield). Control experiments indicated that all of the reaction components are required for effective conversion of the starting materials. This mechanistic proposal is supported by Stern–Volmer experiments and an experiment with alternating light–dark periods. (Optimization and mechanistic experiments are given in the Supporting Information.) To more accurately interrogate the potential contributions of short radical chains in light of the observed results,²⁷ we measured the quantum yield of this process. While $\Phi = 0.29$ is most

consistent with a photosensitized mechanism, radical chains may contribute to product formation.

Further evaluation revealed that the aryl iodide scope of this transformation is broad. As shown in Table 1, iodobenzene and derivatives that contained chloride or triflate substituents reacted smoothly with complete retention of the electrophilic cross-coupling handles (1–3, 70–88% yield). Electron-poor arenes were excellent substrates here, and the *para*-trifluoromethyl and -carboxymethyl groups were not affected (4 and 5, 85 and 73% yields, respectively). Electron-releasing substituents (methoxy, carbamate, and hydroxy) were tolerated, although yields of the desired products were slightly lower (6–9, 60–72%). These results are in line with the assertion that the aryl radical SOMO lies within the plane of the arene such that the presence of electron-donating or -withdrawing substituents does not significantly impact the reactivity.²⁸ We also found that substitution is tolerated at various positions around the aryl ring, and as expected, acidic elements did not negatively impact the reaction efficiency.

Also demonstrated in Table 1 is the ability of this mechanistic blueprint to tolerate the substitution of the olefinic partner on nitrogen (11) and at the β -position (12). Hydroarylation of a cyclic encarbamate, derived from cyclohexanone through vinyl triflate formation and subsequent C–N coupling with *tert*-butylcarbamate, occurred in a moderate yield of 42%, delivering 13 as a mixture of diastereomers (1:1 dr). Furthermore, this strategy is useful for the synthesis of complex saturated nitrogen heterocycles through the transformation of endocyclic encarbamate substrates. Specifically, the 3-arylpiperidine (14) framework was accessible under this paradigm, albeit in diminished yield (42%). This is noteworthy because this particular motif has proven challenging to access directly, where 3-arylpiperidine reduction or a lactam α -arylation and reduction sequence were utilized in the development of Zejula.^{29,30} Likewise, a dihydropyridine derivative underwent hydroarylation to afford 3-phenylpyrrolidine (15) in 53% yield.

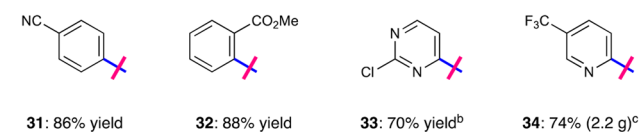
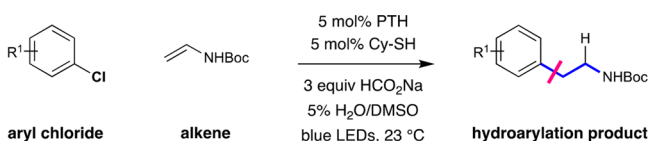
Given our experience with the complications associated with intermolecular heteroaryl radical coupling, we were pleased to find that halogenated heteroaromatics were good substrates under these conditions. Intermolecular coupling of 3-iodopyridine with the same vinylamine derivatives afforded

Table 1. Photocatalytic Radical Hydroarylation of Vinyl Amine Derivatives: Substrate Scope^{a,b,c,d,e}

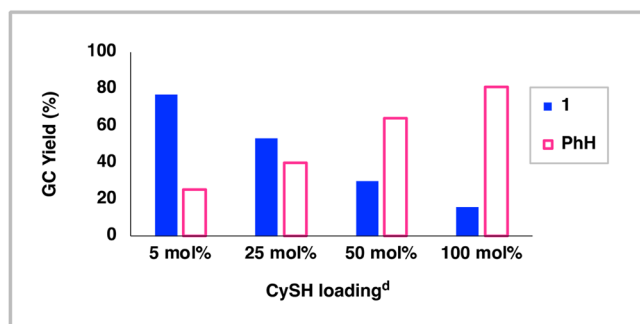
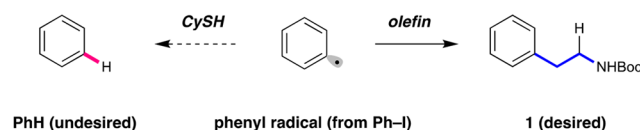
^aReaction conditions: Iodoarene (1.0 mmol), olefin (2.5 mmol), PTH (5 mol %), CySH (5 mol %), sodium formate (3.0 mmol), 5% (v/v) H₂O/DMSO (10.0 mL), blue light, 16 h; isolated yields given. ^bThe reactions to produce **14** and **29** were conducted on a 0.5 mmol scale (1-chloro-4-iodobenzene). ^cIn the reactions to produce **15** and **20**, *N*-1-naphthylphenothiazine (5 mol %) was used in place of PTH. ^dIn the reaction to produce **20**, olefin (1.0 mmol) was used as a limiting reagent with 5.0 mmol of 3-iodopyridine. ^eIn the reactions to produce **22–25**, corresponding heteroaryl bromide was used as the aryl substrate.

pyridylethylamines **16–20** in comparable yields (43–90%). Moreover, these conditions generally activate a range of other halogenated pyridines, where regioselective radical formation enables alkylation at the 2-, 3-, or 4-position in 66–91% yield. As demonstrated before, iodide cleavage occurs with excellent fidelity, even in the presence of chloride substituents. Pyridylethylamines **26–28** were produced in good yield without overreduction products, thus retaining the ability to

perform subsequent cross-coupling or nucleophilic aromatic substitution (S_NAr) reactions. In addition, products **26** and **28** further illustrate the ability of this system to tolerate ortho substitution. The incorporation of other nitrogen-containing heterocyclic units was seamless, where the reduction of halogenated pyrimidine (**24** and **25**), quinoline (**29**), or pyrazine (**30**) substrates resulted in acceptable amounts of alkylated products.

Scheme 1. Hydroarylation Reactions of Aryl Chlorides and the Basis for Intermolecular Reactivity^{a,b,c,d}

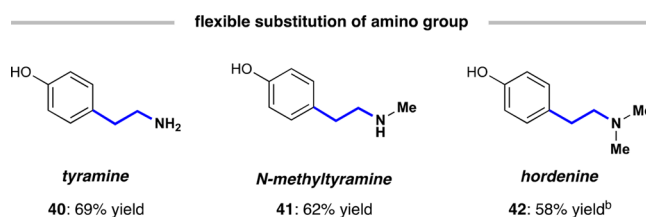
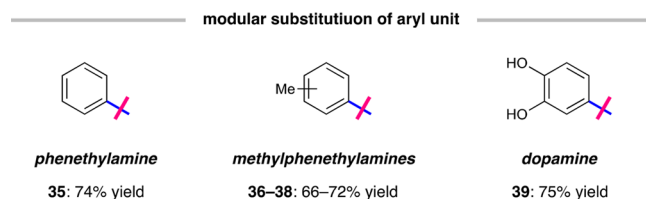
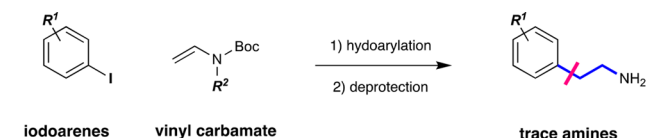
Thiol Concentration Dictates Reaction Outcome



^aReactions were conducted as in Table 1 using the indicated aryl chloride. ^bThe reaction to produce 33 was performed on a 0.5 mmol scale. ^cThe reaction to produce 34 was performed on a 10 mmol scale. ^dIn the bar graph, product ratios were determined using GC with an internal standard.

The outlined dual catalytic process employs inexpensive organic compounds as catalysts and reagents. Moreover, it is highly tolerant of important functional groups and completely selective for the linear hydroarylation regioisomers. However, we recognize that the requirement for aryl iodide substrates as radical precursors is suboptimal because they are relatively expensive in comparison to the corresponding aryl bromides or chlorides. While these substrate classes are cheaper and more accessible, they are more difficult to reduce (with aryl chloride reduction potentials being the most negative throughout this series). However, as demonstrated earlier by Read de Alaniz and Hawker,¹⁴ reductive activation of these classes can be performed using PTH. Indeed, activated chlorobenzene derivatives couple readily with the benchmark vinyl carbamate under standard conditions. As indicated in Scheme 1, 4-chlorobenzonitrile and ethyl-2-chlorobenzoate ($E_{1/2}^0 = -2.00$ to -2.10 V vs SCE)³¹ were effectively converted to the corresponding aryethylamines (31 and 32: 86% and 88 yields, respectively), but chlorobenzene ($E_{1/2}^0 = -2.79$ V vs SCE)³¹ conversion was slower (28% yield after 16 h), where the mass balance was largely composed of unreacted chlorobenzene.

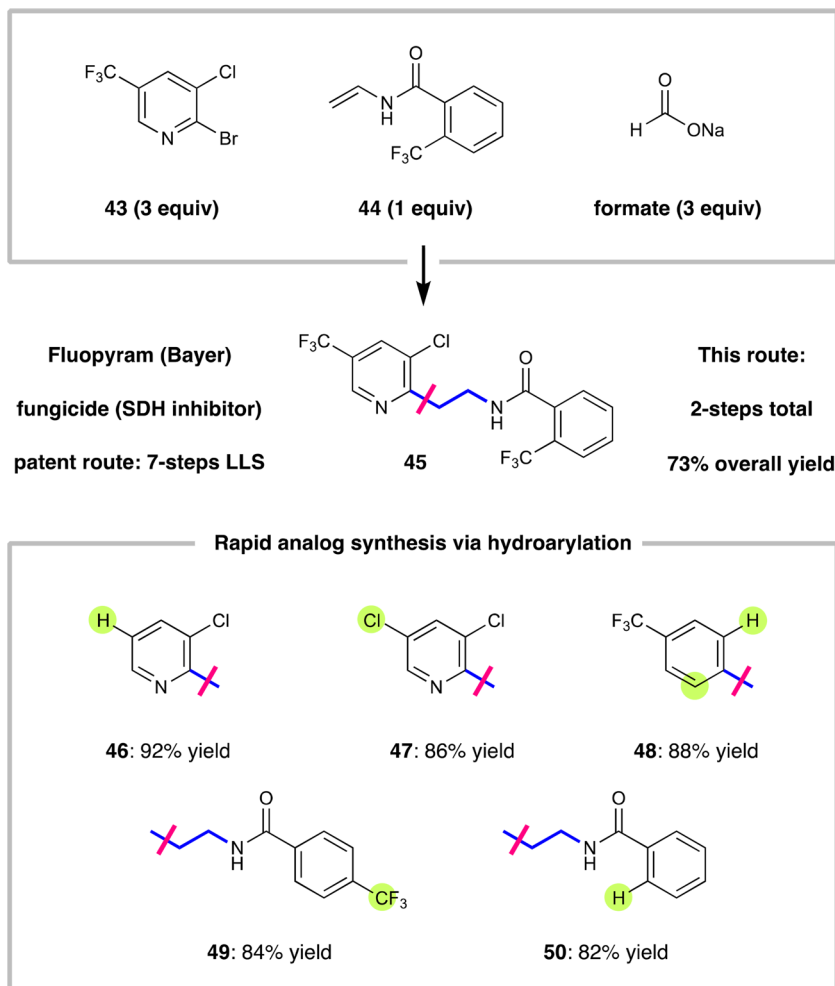
The alkylation of 2,4-dichloropyrimidine occurred exclusively at the 4-position, giving 33 in 70% yield. The selectivity here parallels those which were observed in S_NAr or Pd-

Scheme 2. Flexible Synthesis of Neuromodulators^{a,b}

^aHydroarylation was accomplished as in Table 1, and Boc deprotection was performed with acid. ^bHordenine synthesis was accomplished by reduction with LiAlH₄.

catalyzed cross-coupling processes. The retention of chloride substituents (in products 16–20, 31–33, and 38) is possible presumably because the installation of the alkyl substituent via hydroarylation would effectively increase the reduction potential, thereby protecting the product from subsequent activation. Without an alteration of the standard conditions, this catalytic protocol functioned on a 10 mmol scale from the chloropyridine, affording 2.15 g of trifluoromethylpyridine product 34 (74% yield), further illustrating the utility of this protocol (Scheme 1). Importantly, *tert*-butylvinylcarbamate can be accessed on a large scale (100 mmol) in a single pot from inexpensive reagents.

This design enables the remarkably effective intermolecular reactivity of aryl radical species by employing a combination of a thiol HAT catalyst and a stoichiometric formate reductant. As illustrated in Scheme 1, there are two competing pathways for the aryl radical intermediates that are produced here: intermolecular addition to olefins (desired) and reduction by HAT from the electrophilic thiol (undesired). The relative rates of these pathways can be conveniently manipulated by varying the thiol loading, and the yields of the desired product were highest using aliphatic thiol catalysts. (See the SI for details.) Increasing the thiol loading was accompanied by a clear increase in arene reduction through HAT. Optimal conditions (with 5 mol % CySH, Ph-I as a radical precursor) delivered hydroarylation product 1 in 78% yield. In contrast, when a full equivalent of thiol (100 mol %) was utilized, the selectivity was completely overturned, giving benzene (PhH) as the major product (81% yield). While it is understood that radical anion fragmentation rates vary with the halide substituent, we propose that this system operates uniformly via neutral aryl radicals, regardless of the Ar–X substrate class. This hypothesis is supported by thiol loading experiments across a series of halobenzene substrates (using methyl-4-iodo,

Scheme 3. Rapid Synthesis of Fluopyram/Analog^a

^aReaction conditions: haloarene (3.0 mmol), olefin (1.0 mmol), PTH (5 mol %), CySH (5 mol %), sodium formate (3.0 mmol), 5% (v/v) H₂O/DMSO (10.0 mL), blue light, 16 h; isolated yields are given.

-bromo, and -chlorobenzoate), where the same thiol-dependent product ratios were observed throughout.

The arylolethylamine scaffold is conserved across a wide range of natural and synthetic neuromodulators. To demonstrate its practical utility, we applied this protocol to the synthesis of endogenous neurotransmitter dopamine as well as to the trace amine-associated receptor (TAAR) agonists³² that are shown in Scheme 2. This system allows for modular substitution of the aryl unit, affording phenethylamine (35), all three methylphenethylamine isomers (36–38), and dopamine (39) through a two-step hydroarylation/boc-deprotection sequence (66–75% yield). In addition, this method allows for the flexible substitution of the nitrogen atom, where tyramine (40), *N*-methyltyramine (41), and hordenine (42) were all accessible in two steps from *tert*-butyl (4-iodophenyl) carbonate.

To illustrate the potential of this process in the early-stage development of medicines and agrochemicals, we reacted 2-bromopyridine (43) with *N*-vinylbenzamide (44) to directly afford fungicide Fluopyram (45),^{33,34} as shown in Scheme 3. Optimal conditions for this transformation involved inverted stoichiometry (using 3 equiv of radical precursor 43). This olefinic partner is available in a single step from commercial materials.

This two-step sequence compares favorably to the patent route of this agrochemical (seven steps). The value of this modular hydroarylation strategy is further highlighted by the expedient preparation of Fluopyram analogs 46–50, where systematic substitution on either side of the scaffold could be accomplished with excellent fidelity (82–92% yield for the corresponding hydroarylation processes).

In conclusion, we have developed a protocol for the intermolecular addition of aryl and heteroaryl radicals to enecarbamate substrates. This process operates at ambient temperature, mediated by the concerted action of two different catalytic species (PTH and CySH) that accomplish the transfer of electrons and hydrogen atoms, respectively. This system directly affords valuable arylolethylamine structures with complete regiocontrol with excellent functional group compatibility, and it utilizes stable halogenated arenes as radical precursors. The highly reducing character of the organic photoredox catalyst here allows for effective activation of a wide range of aryl halides, including electron-deficient aryl chlorides. We expect that this protocol, founded on the use of a thiol HAT catalyst in combination with a stoichiometric reductant, will enable a range of mild aryl radical-based transformations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b01077.

Experimental procedures and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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