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A Catalytic Strategy for Regioselective Arylethylamine Synthesis

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Supporting Information Placeholder

ABSTRACT: A mild, modular, and practical catalytic system for 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 accomplish a wide range of important functions (a small sampling of which are 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 ability to access this structural array with modular flexibility remains limited. Specifically, catalytic methods for direct arylethylamine synthesis from readily available synthons where 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*-arylamines,[5] and sulfonamides.[6,7] As a complement to these technologies, we became interested in developing a process for hydroarylation of vinylamine derivatives, where flexible substitution of nitrogen would be possible. The utility of this method would be partially driven by its ability to deliver the desired products with complete anti-Markovnikov selectivity and good functional group compatibility, while employing widely available precursors. We envisioned that a mechanism for 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, 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

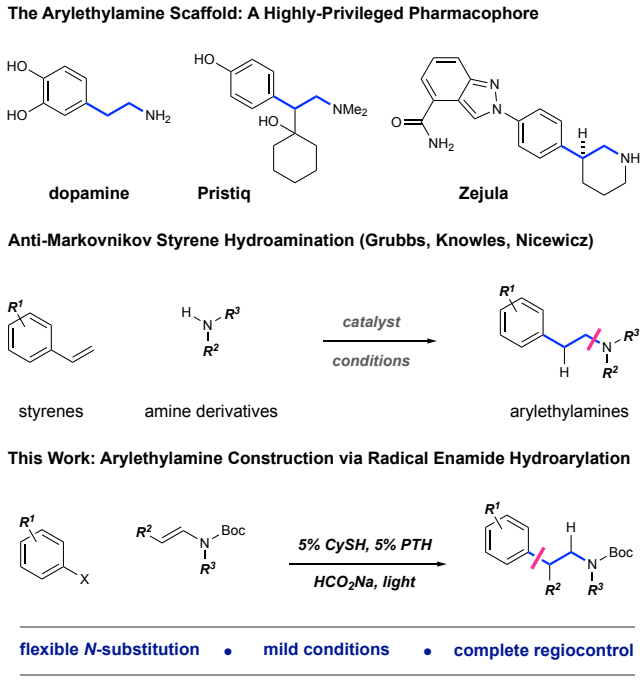


Figure 1. Modular Catalytic Strategies for Arylethylamine Synthesis

pyridyl radicals (accessed via pyridyl halide reduction) undergo chemoselective intermolecular coupling with either electron-defficient[22,23] or electron-rich olefins,[24,25] and Weaver has reported a number of processes involving azolyl or 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), 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 cyclohexanethiols (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

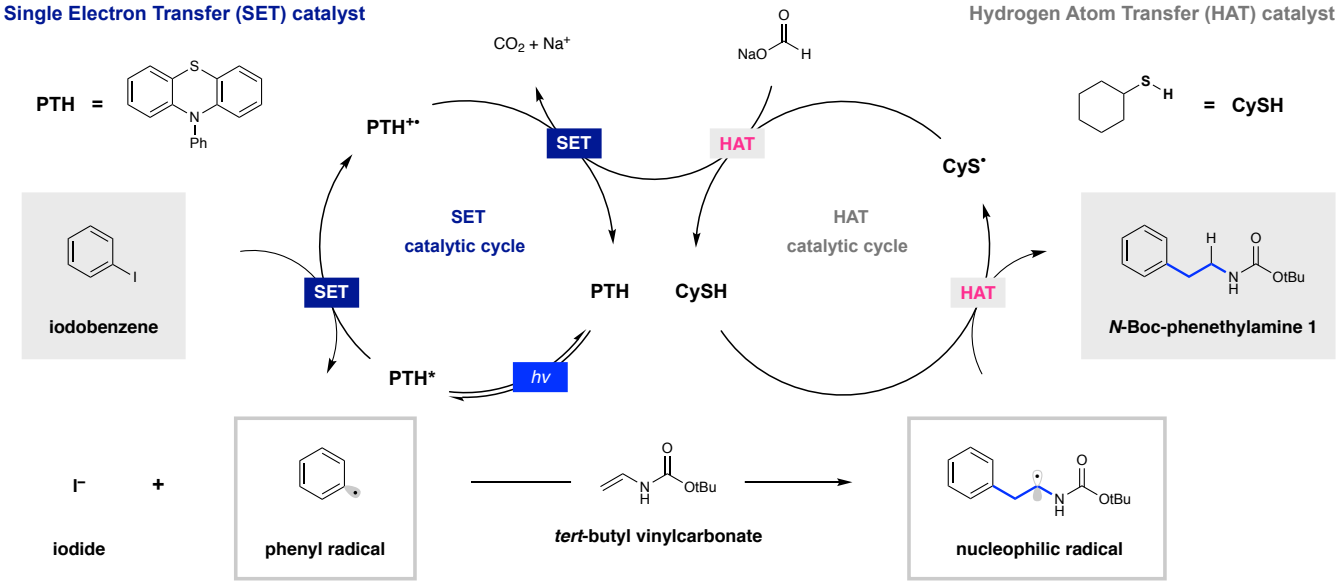


Figure 2. Proposed Dual-Catalytic Mechanism for Intermolecular Radical Hydroarylation.

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 the desired product **1** and the thiyl species CyS•. Finally, regeneration of both catalysts (via HAT and SET events) would liberate the innocuous byproducts CO_2 and NaI.

In practice, we found that iodobenzene effectively reacts with *tert*-butylvinylcarbamate (2.5 equivalents) in the presence of 5 mol% of each catalyst and 3 equivalents of sodium formate under irradiation with blue light in 5% H_2O/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 SI). To more accurately interrogate the potential contributions of short radical chains to 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.

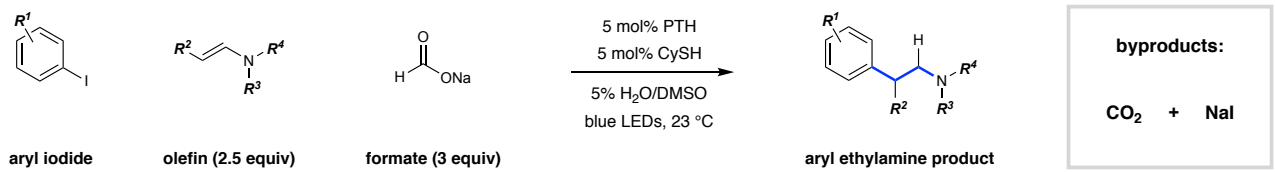
Further evaluation revealed that the aryl iodide scope of this transformation is broad. As shown in Table 1, iodobenzene and derivatives that contained chloride or triflate substituents reacted smoothly with complete retention of the electrophilic cross coupling handles (**1**–**3**, 70–88% yield). Electron-poor arenes were excellent substrates here, and the para-trifluoromethyl and -carboxymethyl groups were not affected (**4** and **5**, 85% and 73% yield, respectively). Electron-releasing substituents (methoxy, carbamate, 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 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 reaction efficiency.

Also demonstrated in Table 1 is the ability of this mechanistic blueprint to tolerate 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 moderate yield 42%, delivering **13** as a mixture of diastereomers (1:1 dr). Further, this strategy is useful for synthesis of complex saturated nitrogen heterocycles, through transformation of endocyclic enecarbamate 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-arylpyridine 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.

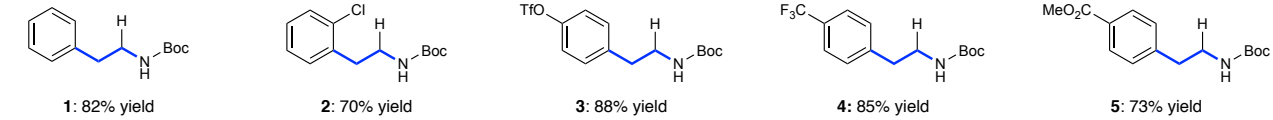
Given our experience with the complications associated with intermolecular heteroaryl radical coupling, we were pleased to find that halogenated heteroaromatics were good substrates under these conditions. Intermolecular coupling of 3-iodopyridine with the same vinylamine derivatives afforded pyridylethylamines **16**–**20** in comparable yields (43–90% yield). Moreover, these conditions generally activate a range of other halogenated pyridines, where regiospecific radical formation enables alkylation of 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. Incorporation of other nitrogen-containing heterocyclic units was seamless, where reduction of halogenated pyrimidine (**24** and **25**), quinoline (**29**), or pyrazine (**30**) substrates resulted in acceptable amounts of alkylated products.

The outlined dual catalytic process employs inexpensive organic compounds as catalysts and reagents. Moreover, it is

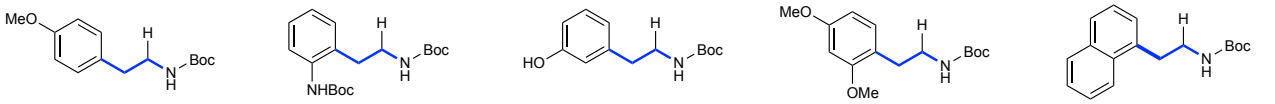
Table 1. Photocatalytic Radical Hydroarylation of Vinyl Amine Derivatives: Substrate Scope[a]



aryl iodide scope

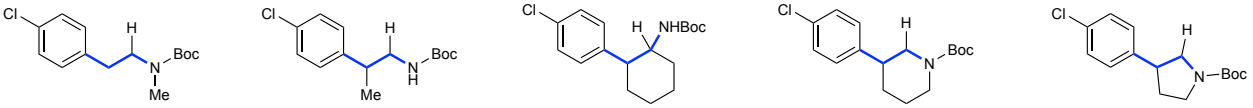


1: 82% yield; **2**: 70% yield; **3**: 88% yield; **4**: 85% yield; **5**: 73% yield

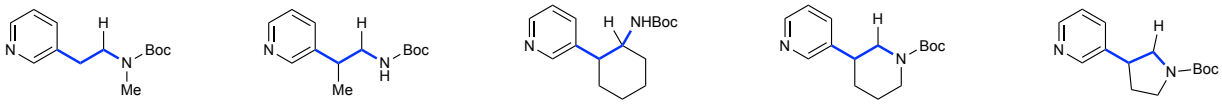


6: 61% yield; **7**: 61% yield; **8**: 72% yield; **9**: 60% yield; **10**: 74% yield

olefin scope

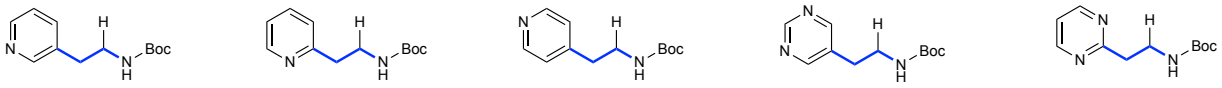


11: 62% yield; **12**: 60% yield; **13**: 42% yield (1:1 dr); **14**: 42% yield[b]; **15**: 53% yield[c]

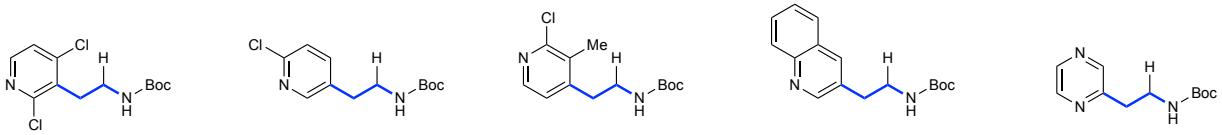


16: 70% yield; **17**: 66% yield; **18**: 43% yield (1:1 dr); **19**: 47% yield; **20**: 67% yield[c,d]

heteroaryl iodide/bromide scope



21: 91% yield; **22**: 69% yield[e]; **23**: 89% yield[e]; **24**: 70% yield[e]; **25**: 64% yield[e]

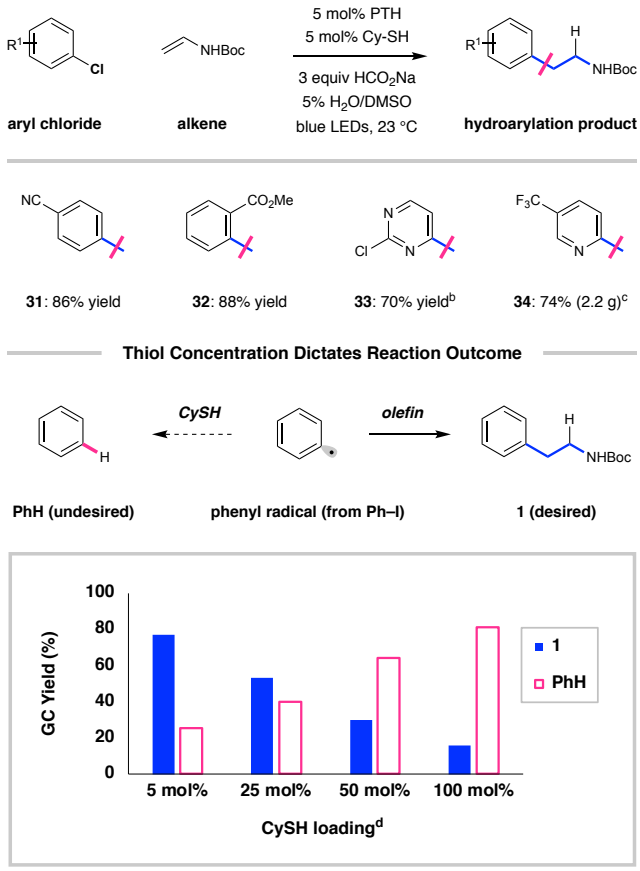


26: 66% yield; **27**: 78% yield; **28**: 75% yield; **29**: 72% yield[b]; **30**: 68% yield

[a]Reaction conditions: Iodoarene (1.0 mmol), olefin (2.5 mmol), PTH (5 mol%), CySH (5 mol%), sodium formate (3.0 mmol), 5% (v/v) H_2O/DMSO (10.0 mL), blue light, 16 h; isolated yields given. [b]Reaction was conducted on 0.5 mmol scale (1-chloro-4-iodobenzene). [c]*N*-1-Naphthylphenothiazine (5 mol%) was used in place of PTH. [d]Olefin (1.0 mmol) was used as limiting reagent with 5.0 mmol 3-iodopyridine. [e]Corresponding heteroaryl bromide was used as aryl substrate.

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

Scheme 1. Hydroarylation Reactions of Aryl Chlorides and Basis for Intermolecular Reactivity[a]



[a]Reactions conducted as in Table 1 using the indicated aryl chloride. [b]Reaction performed on 0.5 mmol scale. [c]Reaction performed on 10 mmol scale. [d]Product ratios were determined using GC with an internal standard.

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 arylethylamines (**31** and **32**: 86% and 88% yield, 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 comprised of unreacted chlorobenzene.

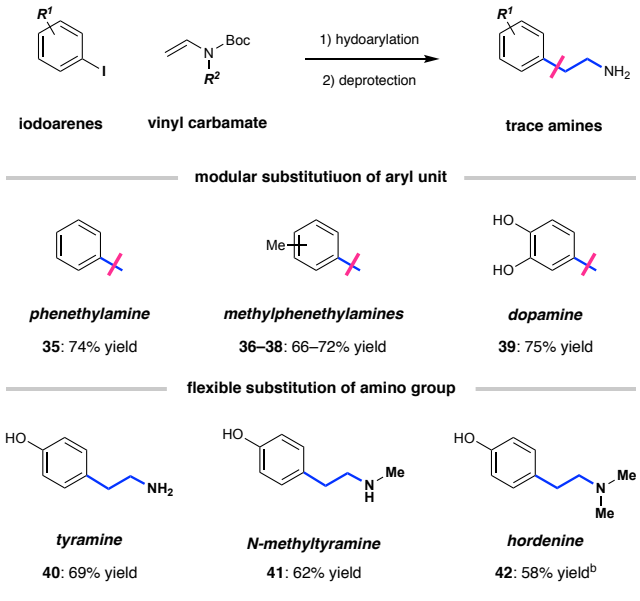
Alkylation of 2,4-dichloropyrimidine occurred exclusively at the 4-position, giving **33** in 70% yield. The selectivity here parallels those which were observed in S_NAr or Pd-catalyzed cross coupling processes. Retention of chloride substituents (in products **16**–**20**, **31**–**33**, and **38**) is possible presumably because installation of the alkyl substituent via hydroarylation would effectively increase reduction potential, thereby protecting the product from subsequent activation. Without alteration of the standard conditions, this catalytic protocol functioned on 10 mmol scale from the chloropyridine, affording 2.15 g of the trifluoromethylpyridine product **34** (74% yield), further illustrating the utility of this protocol (Scheme 1). Importantly, *tert*-butylvinylcarbamate can be accessed on large scale (100 mmol) in a single pot from inexpensive reagents.

This design enables remarkably effective intermolecular reactivity of aryl radial species by employing a combination of thiol HAT catalyst and 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 thiol loading, and yields of the desired product were highest using aliphatic thiol catalysts (see SI for details). Increasing thiol loading was accompanied by a clear increase in arene reduction through HAT. Optimal conditions (with 5 mol% CySH, Ph–I as radical precursor) delivered hydroarylation product **1** in 78% yield. In contrast, when of 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 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, -bromo, and -chlorobenzoate), where the same thiol-dependent product ratios were observed throughout.

The arylethylamine scaffold is conserved across a wide range of natural and synthetic neuromodulators. To demonstrate practical utility, we applied this protocol to the synthesis of the endogenous neurotransmitter dopamine, as well as the trace amine associated receptor (TAAR) agonists[32] 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 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.

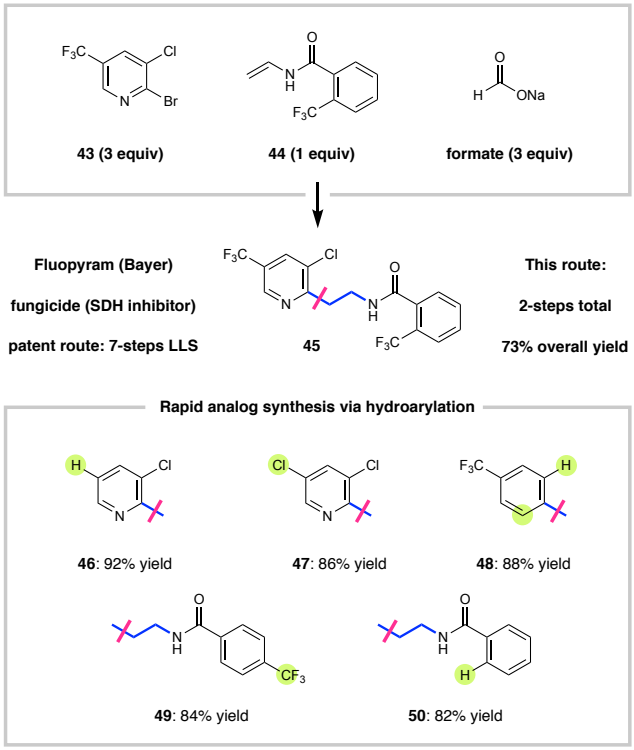
To illustrate the potential of this process in the early-stage development of medicines or agrochemicals, we reacted 2-bromopyridine **43** with *N*-vinylbenzamide **44** to directly afford

Scheme 2. Flexible Synthesis of Neuromodulators[a]



[a]Hydroarylation was accomplished as in Table 2, Boc-deprotection was performed with acid. [a]Hordenine synthesis by reduction with $LiAlH_4$.

Scheme 3. Rapid Synthesis of Fluopyram/Analogs[a]



[a]Reaction conditions: Haloarene (3.0 mmol), olefin (1.0 mmol), PTH (5 mol%), CySH (5 mol%), sodium formate (3.0 mmol), 5% (v/v) H_2O/DMSO (10.0 mL), blue light, 16 h; isolated yields given.

the fungicide Fluopyram (**45**),[33,34] 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 (7-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 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 transfer of electrons and hydrogen atoms, respectively. This system directly affords valuable arylethylamine 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 stoichiometric reductant, will enable a range of mild aryl radical-based transformations.

SUPPORTING INFORMATION

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

Experimental procedures and spectral data (PDF)

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Notes

The authors declare no competing financial interests.

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REFERENCES

(1) Utsunomiya, M.; Kuwano, R.; Kawatsura, M.; Hartwig, J. F. Rhodium-Catalyzed Anti-Markovnikov Hydroamination of Vinylarenes. *J. Am. Chem. Soc.* **2003**, *125*, 5608–5609.

(2) Utsunomiya, M.; Hartwig, J. F. Ruthenium-Catalyzed Anti-Markovnikov Hydroamination of Vinylarenes. *J. Am. Chem. Soc.* **2004**, *126*, 2702–2703.

(3) Basalov, I. V.; Roşca, S. C.; Lyubov, D. M.; Selikhov, A. N.; Fukin, G. K.; Sarazin, Y.; Carpentier, J. F.; Trifonov, A. A. Divalent Heteroleptic Ytterbium Complexes - Effective Catalysts for Intermolecular Styrene Hydrophosphination and Hydroamination. *Inorg. Chem.* **2014**, *53*, 1654–1661.

(4) Musacchio, A. J.; Lainhart, B. C.; Zhang, X.; Naguib, S. G.; Sherwood, T. C.; Knowles, R. R. Catalytic Intermolecular Hydroaminations of Unactivated Olefins with Secondary Alkyl Amines. *Science* **2017**, *355*, 727–730.

(5) Bronner, S. M.; Grubbs, R. H. Formal Anti-Markovnikov Hydroamination of Terminal Olefins. *Chem. Sci.* **2014**, *5*, 101–106.

(6) Nguyen, T. M.; Manohar, N.; Nicewicz, D. A. Anti-Markovnikov Hydroamination of Alkenes Catalyzed by a Two-Component Organic Photoredox System: Direct Access to Phenethylamine Derivatives. *Angew. Chem. Int. Ed.* **2014**, *53*, 6198–6201.

(7) Monos, T. M.; Mcatee, R. C.; Stephenson, C. R. J. Arylsulfonylacetamides as Bifunctional Reagents for Alkene Aminoarylation. *Science.* **2018**, *361*, 1369–1373.

(8) Heinrich, M. R. Intermolecular Olefin Functionalisation Involving Aryl Radicals Generated from Arenediazonium Salts. *Chem. Eur. J.* **2009**, *15*, 820–833.

(9) Kindt, S.; Heinrich, M. R. Recent Advances in Meerwein Arylation Chemistry. *Synthesis* **2016**, *48*, 1597–1606.

(10) Romero, N. A.; Nicewicz, D. A. Organic Photoredox Catalysis. *Chem. Rev.* **2016**, *116*, 10075–10166.

(11) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chem. Rev.* **2013**, *113*, 5322–5363.

(12) Nguyen, J. D.; D'Amato, E. M.; Narayanam, J. M. R.; Stephenson, C. R. J. Engaging Unactivated Alkyl, Alkenyl and Aryl Iodides in Visible-Light-Mediated Free Radical Reactions. *Nat. Chem.* **2012**, *4*, 854–859.

(13) Kim, H.; Lee, C. Visible-Light-Induced Photocatalytic Reductive

Transformations of Organohalides. *Angew. Chem. Int. Ed.* **2012**, *51*, 12303–12306.

(14) Discekici, E. H.; Treat, N. J.; Poelma, S. O.; Mattson, K. M.; Hudson, Z. M.; Luo, Y.; Hawker, C. J.; de Alaniz, J. R. A Highly Reducing Metal-Free Photoredox Catalyst: Design and Application in Radical Dehalogenations. *Chem. Commun.* **2015**, *51*, 11705–11708.

(15) Poelma, S. O.; Burnett, G. L.; Discekici, E. H.; Mattson, K. M.; Treat, N. J.; Luo, Y.; Hudson, Z. M.; Shankel, S. L.; Clark, P. G.; Kramer, J. W.; et al. Chemoselective Radical Dehalogenation and C-C Bond Formation on Aryl Halide Substrates Using Organic Photoredox Catalysts. *J. Org. Chem.* **2016**, *81*, 7155–7160.

(16) Arora, A.; Weaver, J. D. Visible Light Photocatalysis for the Generation and Use of Reactive Azolyl and Polyfluoroaryl Intermediates. *Acc. Chem. Res.* **2016**, *49*, 2273–2283.

(17) Ghosh, I.; Marzo, L.; Das, A.; Shaikh, R.; Konig, B. Visible Light Mediated Photoredox Catalytic Arylation Reactions. *Acc. Chem. Res.* **2016**, *49*, 1566–1577.

(18) Naumann, R.; Kerzig, C.; Goez, M. Laboratory-Scale Photoredox Catalysis Using Hydrated Electrons Sustainably Generated with a Single Green Laser. *Chem. Sci.* **2017**, *8*, 7510–7520.

(19) Matsubara, R.; Yabuta, T.; Idros, U.; Hayashi, M.; Ema, F.; Kobori, Y.; Sakata, K. UVA- and Visible-Light-Mediated Generation of Carbon Radicals from Organochlorides Using Nonmetal Photocatalyst. *J. Org. Chem.* **2018**, *83*, 9381–9390.

(20) Ghosh, T.; Ghosh, J.; Bardagi, I.; König, B. Reduction of Aryl Halides by Consecutive Visible Light -Induced Electron Transfer Processes. *Science.* **2014**, *346*, 725–728.

(21) Bardagi, J. I.; Ghosh, I.; Schmalzbauer, M.; Ghosh, T.; König, B. Anthraquinones as Photoredox Catalysts for the Reductive Activation of Aryl Halides. *European J. Org. Chem.* **2018**, 34–40.

(22) Aycock, R. A.; Wang, H.; Jui, N. T. A Mild Catalytic System for Radical Conjugate Addition of Nitrogen Heterocycles. *Chem. Sci.* **2017**, *8*, 3121–3125.

(23) Aycock, R. A.; Vogt, D.; Jui, N. A Practical and Scalable System for Heteroaryl Amino Acid Synthesis. *Chem. Sci.* **2017**, *8*, 7998–8003.

(24) Boyington, A. J.; Riu, M. L. Y.; Jui, N. T. Anti-Markovnikov Hydroarylation of Unactivated Olefins via Pyridyl Radical Intermediates. *J. Am. Chem. Soc.* **2017**, *139*, 6582–6585.

(25) Seath, C. P.; Vogt, D. B.; Xu, Z.; Boyington, A. J.; Jui, N. T. Radical Hydroarylation of Functionalized Olefins and Mechanistic Investigation of Photocatalytic Pyridyl Radical Reactions. *J. Am. Chem. Soc.* **2018**, *140*, 15525–15534.

(26) Roberts, B. P. Polarity-Reversal Catalysis of Hydrogen-Atom Abstraction Reactions : Concepts and Applications in Organic Chemistry. *Chem. Soc. Rev.* **1999**, *28*, 25–35.

(27) Cismesia, M. A.; Yoon, T. P. Characterizing Chain Processes in Visible Light Photoredox Catalysis. *Chem. Sci.* **2015**, *6*, 5426–5434.

(28) Garden, S. J.; Avila, D. V; Beckwit, A. L. J.; Bowry, V. W.; Ingold, K. U.; Lusztyk, J. Absolute Rate Constant for the Reaction of Aryl Radicals with Tri-N-Butyltin Hydride. *J. Org. Chem.* **1996**, *61*, 805–809.

(29) Jones, P.; Wilcoxen, K.; Rowley, M.; Toniatti, C. Niraparib: A Poly(ADP-Ribose) Polymerase (PARP) Inhibitor for the Treatment of Tumors with Defective Homologous Recombination. *J. Med. Chem.* **2015**, *58*, 3302–3314.

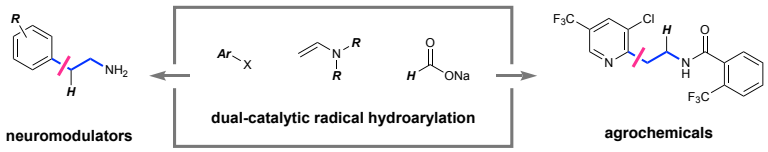
(30) Chung, C. K.; Bulger, P. G.; Kosjek, B.; Belyk, K. M.; Rivera, N.; Scott, M. E.; Humphrey, G. R.; Limanto, J.; Bachert, D. C.; Emerson, K. M. Process Development of C − N Cross-Coupling and Enantioselective Biocatalytic Reactions for the Asymmetric Synthesis of Niraparib. *Org. Process Res. Dev.* **2014**, *18*, 215–227.

(31) Enemærke, R. J.; Christensen, T. B.; Jensen, H.; Daasbjerg, K. Application of a New Kinetic Method in the Investigation of Cleavage Reactions of Haloaromatic Radical Anions. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1620–1630.

(32) Gainetdinov, R. R.; Hoener, M. C.; Berry, M. D. Trace Amines and Their Receptors. *Phramacol. Rev.* **2018**, *70*, 549–620.

(33) Lhermitte, F.; Coqueron, P.-Y.; Desbordes, P.; Himmlet, T.; WO2006/067103, June 29, 2006.

(34) Moradi, W. A.; Schnatterer, A.; Bielefeldt, D.; Gertzmann, R.; Havekest, D.; WO2018/114484, June 28, 2018.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