Photocatalytic Hydroaminoalkylation of Styrenes with Unprotected Primary Alkylamines

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ABSTRACT: Catalytic, intermolecular hydroaminoalkylation (HAA) of styrenes provides a powerful disconnection for pharmacologically relevant γ-arylamines, but current methods cannot utilize unprotected primary alkylamines as feedstocks. Metal-catalyzed HAA protocols are also highly sensitive to α-substitution on the amine partner, and no catalytic solutions exist for α-tertiary γ-arylamine synthesis via this approach. We report a solution to these problems using organophotoredox catalysis, enabling a direct, modular, and sustainable preparation of α-(di)substituted γ-arylamines, including challenging electron-neutral and moderately electron-rich aryl groups. A broad range of functionalities are tolerated, and the reactions can be run on multigram scale in continuous flow. The method is applied to a concise, protecting-group-free synthesis of the blockbuster drug Fingolimod, as well as a phosphonate mimic of its in vivo active form (by iterative α-C−H functionalization of ethanolamine). The reaction can also be sequenced with an intramolecular N-arylation to provide a general and modular access to valuable (spirocyclic) 1,2,3,4-tetrahydroquinolines and 1,2,3,4-tetrahydronaphthyridines. Mechanistic and kinetic studies support an irreversible hydrogen atom transfer activation of the alkylamine by the azidyl radical and some contribution from a radical chain. The reaction is photon-limited and exhibits a zero-order dependence on amine, azide, and photocatalyst, with a first-order dependence on styrene.

INTRODUCTION

Aliphatic amines and (semi)saturated azacycles are privileged motifs in pharmaceuticals, agrochemicals, biological probes, and other functional molecules, and the development of more efficient methods for their synthesis is a research priority. Perhaps the most attractive and atom-economical approach for the construction of α-alkylated amines is the net insertion of an alkene into an amine α-C−H bond, often termed a hydroaminoalkylation (HAA) reaction. For secondary and tertiary amines, the catalytic HAA of non-electrophilic alkenes has been dominated by early transition-metal-based catalysts. These reactions are typically sensitive to the substitution α to nitrogen, with the majority of reports focusing on N-methyl group functionalization, and linear selectivity being a particular challenge. Linear-selective alkene HAAAs with non-electrophilic alkenes are more common for late transition metal catalysis, but there is a need for specially tailored directing groups on the amine nitrogen. A different strategy altogether for alkene HAA deploys nucleophilic α-amino radicals generated via photoredox catalysis, but this approach is typically limited to suitably electrophilic alkenes such as acrylates or vinylpyridines. For example, we recently reported a photoredox-catalyzed formation of γ-lactams from primary alkylamines 1 and acrylates 2, and Rovis, Schoenebeck, and co-workers developed a similar process based on in situ N-protection of the amine with CO2 (Figure 1A). Despite the above successes, the HAA of electronically unbiased styrenes with primary alkylamines lacks a general and practical solution, although styrene HAA reactions have recently been developed with tertiary and (protected) secondary amines. With primary amines, the only reported intermolecular examples have utilized 2-pyridyl directing groups on the amine nitrogen (with Ru or Ir catalysts) or N-silyl protecting groups at high temperature (>140 °C with Ti or Zr catalysts). The use of unprotected primary alkylamines in catalytic HAA with non-electrophilic alkenes is currently limited to simple, unfunctionalized examples in the intramolecular mode (110−145 °C, 5−20 mol% Ti catalyst).
radicals are highly nucleophilic and they engage successfully with electrophilic alkenes such as acrylates and vinyl phosphonates. To determine if non-electrophilic alkenes could be accommodated as reaction partners, we irradiated p-methylstyrene 6a with cyclohexylamine 1a in MeCN at 425 nm, using 4CzIPN as the photocatalyst and tetrabutylammonium azide (Bu4N+N3) 10 as the HAT catalyst (Figure 2).

**RESULTS AND DISCUSSION**

**Reaction Optimization.** The generation of α-amino radicals directly from primary alkylamines 1 by single-electron oxidation followed by deprotonation is complicated by the high oxidation potential of the nitrogen lone pair (E_1/2 = +1.53 V vs SCE in MeCN for cyclohexylamine)[9d], and the possibility for aminium radicals to form N-centered aminyl radicals by N−H cleavage. We recently found that azide ion (N3−) can serve as an effective catalytic mediator in the photoredox-catalyzed formation of α-amino radicals from primary alkylamines.[9d] Chemoselective oxidation of azide ion (E_1/2 = +0.87 V vs SCE in MeCN)[9d] by the excited photocatalyst 2,4,5,6-tetra(9H-carbazol-9-yl)isophthalonitrile (4CzIPN)[18] serves to generate the highly electrophilic azidyl radical (N3·), that can participate in a polarity-matched HAT process with the weak α-C−H bond of a primary alkylamine (BDE = 89−91 ± 2 kcal mol−1). The resultant α-amino

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**Figure 1.** (A) Prior art for catalytic γ-lactam synthesis from unprotected 1° alkylamines. (B) Importance of γ-arylamines. (C) This work.

Given the importance of γ-arylamines and their occurrence in several clinically approved drugs [e.g., Fingolimod 4, Elayta 5 (Figure 1B), Cinacalcet, Fendiline, Pheniramine], a generally applicable catalytic HAA of simple styrenes with unprotected primary alkylamines would constitute a significant advance. We report a solution to this problem using visible-light photoredox catalysis in combination with hydrogen atom transfer (HAT) catalysis.[15] This enables a direct and modular synthesis of pharmacologically relevant γ-arylamines 7, including Fingolimod 4 and analogues thereof. Further application to the expedient synthesis of (spirocyclic) 1,2,3,4-tetrahydroquinolines 8 and 1,2,3,4-tetrahydronaphthyridines 9 is also described (Figure 1C).

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**Figure 2.** Yields measured by 1H NMR against 1,3,5-trimethoxybenzene as an internal standard. Reference for redox potentials of photocatalysts.[23] References for oxidation potentials of HAT catalysts: 10, ref 9d; 11, ref 27; 12, ref 16; 13, ref 25; 14, ref 16; and 15, ref 9i.
that doubling the loading of azide ion to 20 mol% enhanced the yield (entry 4), which may be a consequence of the reduced excited state lifetime of 3DPA2FBN ($k_{p-1} = 4.2$ ns) relative to 4CzIPN ($k_{p-1} = 12.7$ ns) (i.e., competition of bimolecular quenching by $N_3^\text{−}$ with unimolecular fluorescence from $1\text{PC}^\ast$).\textsuperscript{23} After switching the alkene partner to styrene 6b for further optimization, giving a somewhat reduced yield (entry 5), we changed the reaction solvent to dimethylformamide (DMF) from acetonitrile (MeCN) (entry 6). Finally, we surveyed a series of other commonly used HAT catalysts (11–15), to gauge whether or not the use of azide ion conferred unique reactivity. Although tri(isopropyl)silanethiolate 11 (entry 7) did give appreciable turnover (56% NMR yield), it significantly underperformed azide ion 10. Bromide ion 12,\textsuperscript{24} thio benzoate 13,\textsuperscript{25} chloride ion 14,\textsuperscript{26} and quinuclidine 15 all gave negligible reactivity (entries 8–11). Control experiments verified that 3DPA2FBN, visible light, and azide catalyst are all necessary components for successful HAA.

**Amine Scope.** With optimized conditions in hand, we next sought to determine the generality of the HAA reaction with respect to the alkylamine component 1 (Figure 3). 2-Bromostyrene 6c was selected as the representative alkene partner, not because this confers the highest yields (i.e., electron-neutral styrenes 6a or 6b are superior), but because the bromine atom provides a useful synthetic handle for further elaboration (vide infra). The good performance of simple α,α-
dialkylated amines such as cyclohexylamine 1a and isopropylamine 1b highlights a particular strength of this strategy relative to state-of-the-art metal-catalyzed HAA:s the insensitivity of the reaction to steric encumbrance at the α-position of the alkylamine. Indeed, this process is one of the few catalytic transformations on record that gives direct access to unprotected α-tertiary primary amines by C–C bond formation at the α-position.20,21 Pleasingly, the reaction also proved efficient with α-monosubstituted amine 1c, with only 6% of α,α-dialkylation (with respect to 1c). Some other α-monosubstituted amines gave more substantial α,α-dialkylation, but this issue was remedied by employing a 3-fold excess of the alkylamine partner does not in itself pose a chemo- and selectivity issue, despite the fact that such C–H bonds are likely to be responsible for its lower reactivity.22 A variety of heteroaromatic motifs were also engaged in the HAA protocol. Even the complex antiviral drug Oseltamivir (1aa) could be α-C–H alkylated at the unprotected amino group, albeit in low yield.

**Scale Up in Continuous Flow.** To demonstrate the scalability of the HAA process, we next performed a gram-scale reaction between 4-amino-N-Boc-piperidine 1k and 2-bromostyrene 6c in continuous flow.31 Using a Vapourtec R-series flow system equipped with a Uniqsis cold coil tubing module (5 mL) and a PhotoSyn HP LED photoreactor with a water-cooled 420 nm LED array (∼260 W radiant output power), a steady-state space-time yield (STY) of 625 mg h⁻¹ for γ-arylamine 7kc was obtained (Figure 3B). For a run time of 149 min, this delivered 1.55 g of isolated 7kc, though a productivity of 6.25 g h⁻¹ would be possible using the 50 mL reactor coil.

**Styrene Scope.** The generality of the HAA protocol with respect to the styrene partner was next determined (Figure 4). Both styrene itself (6b) and α-methylstyrene (6d) returned γ-
arylamines 7ab and 7ad, respectively, in yields exceeding 90%, although trans-β-methylstyrene (6e) gave incomplete conversion to 7ae (i.e., 24% remaining 6e), which was isolated in 28% yield. A similar issue was encountered with the cis-configured alkene indene (6f), which delivered 7af in 38% yield. Notably, methyl cinnaamate (6g) gave a HAA product derived from radical attack at the α-position of the cinnamate, contrary to the behavior of simple acrylates but congruent with other literature reports.51b,c,32 Remarkably, the electron-rich acceptor p-methoxystyrene (6h) afforded the HAA product 7ah in 59% yield,33 despite the pronounced polarity-mismatch of this reaction. Other electronically diverse para-substituents surveyed on the styrene partner included methyl (6a), fluoro (6i), bromo (6j), (pinacolato)boryl [pinB] (6k), trifluoromethyl (6l), and methyl ester (6m), with acceptable to excellent yields obtained in all cases. An electronic trend is difficult to identify, but it is clear that inclusion of strong +M (e.g., −OMe) or −M groups (e.g., −CF3) on the styrene partner does diminish the isolated yield. It should also be noted that a degree of styrene polymerization was suspected in some cases (i.e., insoluble precipitates formed when running earlier reactions in MeCN), and this may be operative to different extent with various styrenes. Although borylated product 7ak was generated cleanly and quantitatively by1H NMR, difficulties in purification led us to oxidize this compound with H2O2 and isolate the corresponding phenol (in >99% yield over two steps). Doubly halogenated styrenes 6n and 6o also participated, but the latter substrate also produced 22% of a debrominated HAA side-product, significantly compromising the yield of 7ao (13%). This may arise from competitive attack of the electron-rich α-aminol radical intermediate on the C–Br bond (activated by the adjacent chloro substituent) in an X atom transfer (XAT) step.34 Heteroaromatic styrene analogues were also assessed, bearing pyridyl (6p), thiazolyl (6q), and pyrazinyl (6r) motifs in lieu of a benzenoid ring. Although the pyridyl ring was well tolerated, and the thiazolyl ring to a lesser extent, the vinylypyrazine 6r performed poorly, giving 22% of the HAA product 7ar. Competitive telomerization (9% of a 1:2 adduct) and reductive homocoupling of 6r (43% with respect to 6r) were identified as side reactions in the latter case. Finally, the use of 2-bromovinylpyridine (6s) was attempted, to provide a functional handle for further elaboration (vide infra). However, competitive XAT at the C–Br bond was again problematic, and 7as was obtained in 27% yield, alongside its debrominated analogue (~1.5:1 ratio). Thankfully, this problem could be resolved by utilizing the 2-fluoro analogue 6t, which delivered the γ-pyridylidine 7at in 97% yield.

**Synthesis of Fingolimod.** To showcase the utility of our method, we next sought to apply our HAA protocol to the synthesis of a blockbuster drug. Fingolimod (4), developed by Novartis, is a S1P1 receptor agonist used to treat relapsing-remitting multiple sclerosis, with worldwide sales of $3 billion in 2020.35 It has also been recently identified as a promising lead for troponin-directed heart failure therapeutics.56 Several concise synthetic routes to Fingolimod 4 have been developed over the past two decades,57 but we reasoned that a HAA approach could raise the bar in terms of atom- and step-economy. Gratifyingly, the application of our optimized conditions to serinol 16 and 4-octylstyrene 17 (derived in 1 step from the commercial aldehyde) gave Fingolimod 4 in 43% isolated yield (Figure 5A). This is the shortest synthesis of Fingolimod on record, exhibiting 100% atom economy in the key step and with no recourse to any protecting groups. We anticipate that this operationally simple HAA procedure will find use in the synthesis of a diverse range of γ-arylamines as potential S1P1 receptor agonists.38

We were also drawn to the possibility of synthesizing α-tertiary amines by tandem sequential α-C–H alkylation of ethanolamine (1r). Note: [a] 23% of the dialkylation product of 1r with 17 was also isolated. TMS = trimethylsilyl.

Figure 5. (A) Application to a protecting group-free synthesis of Fingolimod (4). (B) One-pot synthesis of a phosphonate mimic (21) of Fingolimod phosphate by tandem sequential α-C–H alkylation of ethanolamine (1r). Note: [a] 23% of the dialkylation product of 1r with 17 was also isolated. TMS = trimethylsilyl.
the synthesis of 1,2,3,4-tetrahydroquinolines (THQs) 

As partially saturated, benzo-fused N-heterocycles, THQs occupy a privileged position as core scaffolds in a host of natural and unnatural bioactives. Of the ∼43,000 known small-molecule THQs featuring alkylation α to nitrogen at C(2), only a third are α,α-dialkylated (almost exclusively α,α-dimethyl), and only ∼1% are spirocyclic at C(2). Given the explosion of interest in spirocycles in medicinal chemistry over the past two decades, the rarity of spirocyclic THQs is somewhat surprising. Thus, a modular strategy to access C(2)-(di)-alkylated (including spirocyclic) THQs that is relatively insensitive to the electronics of the benzenoid component could greatly expand the accessible chemical space in this area. This is of particular relevance to fragment-based drug discovery, given that THQs exhibit multiple synthetically accessible growth vectors in three dimensions, and α-alkylated THQs have already been reported as fragment hits.

Proposed Catalytic Cycle and Mechanistic Analysis.

Our proposed catalytic cycle for the HAA process is outlined in Figure 7A. Initial oxidation of azide ion (E\text{p/2} = +0.87 V vs SCE in MeCN) by the photoexcited 3DPA2FBN [E\text{1/2} (PC*/PC−) = +0.92 V vs SCE] generates the azidyl radical, N3−. This reductive quenching step is supported by Stern−Volmer luminescence quenching experiments (Figure 7B). Subsequent HAT from the relatively weak α-C−H bond of the primary alkylamine (BDE = 89−91 ± 2 kcal mol−1) occurs to give α-amino radical 25, which undergoes addition to the styrene acceptor to give a benzylic radical [E\text{1/2} red = −1.43 V vs SCE for CH2Ph/−CH2Ph in MeCN]. Reduction of this radical to the corresponding carbanion by the [3DPA2FBN]− radical anion [E\text{1/2} (PC/PC−) = −1.92 V vs SCE in MeCN] is presumably followed by proton transfer from HN3 (pK\text{a} = 7.9 in DMSO) to give the γ-arylamine product and regenerate the azide ion. Alternatively, a chain process involving HAT from HN3 to the benzylic radical (BDE = 85.4 ± 1.5 kcal mol−1 for PhCH2Me) can be envisaged. To probe the latter possibility, the reaction quantum yield (Φ\text{prod}) was measured for the reaction of cyclohexylamine with styrene and found to be 0.31 (at 66% conversion to 7ab by NMR). Given that quantum efficiencies for dual catalytic photoredox processes in which a cocatalyst is the quencher are typically very low (Φ\text{prod} < 0.1), a value of 0.31 is suggestive of at least some contribution from an innate chain (with a photonically inefficient initiation step). The operation of a photoredox process in parallel with an innate chain thus cannot be excluded. The reversibility of the HAT step between the 

Figure 6. (A) Modular synthesis of 1,2,3,4-tetrahydroquinolines (THQs). In all cases except for 8an, the remaining mass balance comprised unreacted starting material. Note: [a] Obtained as an inseparable mixture with 8ac (14%), the proto-dechlorinated analogue of 8an. (B) Modular synthesis of 1,2,3,4-tetrahydronaphthyridines (THNs).
alkylamine and N₃ was next investigated. Using enantiopure amine (S)-1e, the reaction with styrene 6b was run to incomplete conversion (i.e., 78% of 1e remaining) and the unreacted 1e was recovered (Figure 7C). The enantiopurity of 1e was found to have suffered no erosion during catalytic turnover (i.e., still >99:1 er), proving that formation of α-amino radical 25 is irreversible under the conditions. To gain further insight into the reaction mechanism, a variable time normalization analysis (VTNA) kinetic study was also conducted. The reaction of isopropylamine 1b with styrene 6b in DMF was run in continuous flow (see Supporting Information), using automated variation of residence times to construct the necessary concentration−time profiles (Figure 7D). The reaction displayed first order kinetics, with a first order dependence on styrene 6b and a zero order dependence on amine 1b, azide ion and photocatalyst (3DPA2FBN). This suggests that α-amino radical 25 addition to styrene 6 or, potentially, the photocatalyst regeneration step (PC* + 26 → PC + 27) is turnover-limiting. A zero-order dependence on photocatalyst is consistent with the reaction operating in a “photon-limited” regime, where the rate is controlled by the light intensity and not by the photocatalyst concentration.

**CONCLUSION**

We have developed a metal-free, photoredox-catalyzed HAA of styrenes with unprotected primary alkylamines that provides direct access to γ-arylamines, including valuable α-tertiary derivatives. The protocol is executed under mild conditions, tolerates a wide variety of functional groups, and can be readily scaled in flow. We further illustrate the utility of this method in the shortest ever synthesis of the blockbuster drug Fingolimod, requiring no protecting groups. An iterative double α-C−H functionalization of the simple feedstock chemical ethanolamine is also showcased, to provide direct, one-pot access to a complex α-tertiary β-hydroxy amine (20) that previously required an eight-step synthesis. The application of this chemistry to the expedient synthesis of functionalized (and spirocyclic) 1,2,3,4-tetrahydroquinolines (THQs) and 1,2,3,4-tetrahydronaphthyridines (THNs) is also demonstrated, affording access to underexplored chemical space for drug discovery. Detailed mechanistic studies, including luminescence quenching and kinetic analyses, support a catalytic mechanism featuring reductive quenching of the organic photocatalyst by azide ion, to generate a highly reactive azidyl radical. This engages with the primary alkylamine in an

![Proposed catalytic cycle](image1)

![Stern−Volmer luminescence quenching](image2)

![Irreversibility of HAT step](image3)

![Variable time normalization (VTNA) kinetic analysis using automated flow chemistry](image4)
irreversible HAT step to generate the key α-amino radical intermediate. The turnover-limiting step of the cycle is either radical addition to the styrene or regeneration of the photocatalyst, and a quantum yield measurement suggests some contribution from a radical chain process. In summary, we believe that the unique disconnection enabled by this new HAA protocol, together with its operational simplicity and sustainability, will help streamline the synthesis of complex alkylamines in both academia and industry.  

**REFERENCES**

(1) Nugent, T. C. Chiral Amine Synthesis: Methods, Developments and Applications; Wiley-VCH, 2010.

(2) Blakemore, D. C.; Calcito, L.; Churcher, J.; Rees, D. C.; Thomas, A. W.; Wilson, D. M.; Wood, A. Organic Synthesis Provides Opportunities to Transform Drug Discovery. Nat. Chem. 2018, 10, 383–394.

(3) (a) Manßen, M.; Schafer, L. L. Early Transition Metal-Catalyzed Hydroaminoalkylation. Trends Chem. 2021, 3, 428–429. (b) Trowbridge, A.; Walton, S. M.; Gaunt, M. J. New Strategies for the Transition-Metal Catalyzed Synthesis of Aliphatic Amines. Chem. Rev. 2020, 120, 2613–2692. (c) Edwards, P. M.; Schafer, L. L. Early transition metal-catalyzed C–H alkylation: hydroaminoalkylation for Csp3–Csp bond-formation in the synthesis of selectively substituted amines. Chem. Commun. 2018, 54, 12453–12460.

(4) (a) Manßen, M.; Deng, D.; Zheng, C. H. M.; DiPuccio, R. C.; Chen, D.; Schafer, L. L. Ureate Titanium Catalysts for Hydroaminoalkylation: Using Ligand Design to Increase Reactivity and Utility. ACS Catal. 2021, 11, 4550–4560. (b) Koperniku, A.; Schafer, L. L. Zirconium Catalyzed Hydroaminoalkylation for the Synthesis of α-Arylated Amines and N-Heterocycles. Chem. - Eur. J. 2021, 27, 6534–6539. (c) Daneshmand, P.; Roșca, S.-C.; Dalhoff, R.; Yin, K.; DiPuccio, R. C.; Ivanovic, R. A.; Polat, D. E.; Beaucemyn, A. M.; Schafer, L. L. Cyclic Ureate Tantalum Catalyst for Preferential Hydroaminoalkylation with Aliphatic Amines: Mechanistic Insights into Substrate Controlled Reactivity. J. Am. Chem. Soc. 2020, 142, 15740–15750. (d) Bielefeld, J.; Doye, S. Fast Titaniam-Catalyzed Hydroaminomethylation of Alkenes and the Formal Conversion of Methylene. Angew. Chem., Int. Ed. 2020, 59, 6138–6143. (e) Warsitz, M.; Doye, S. Linear Hydroaminoalkylation Products from Alkyl-Substituted Alkenes. Chem. - Eur. J. 2020, 26, 15121–15125.

(5) Greik, D.; Rosien, M.; Bielefeld, J.; Schmidtmann, M.; Doye, S. Titanium-Catalyzed Intermolecular Hydroaminoalkylation of Alkenes with Tertiary Amines. Angew. Chem., Int. Ed. 2021, 60, 9936–9940.

(6) We use this term to refer to alkenes that do not readily participate as Michael acceptors in polar reactions with two-electron nucleophiles (e.g., non-conjugated alkenes, styrenes lacking σ-acceptor substituents).

(7) (a) Verma, P.; Richter, J. M.; Chekhin, N.; Qiao, J. X.; Yu, J.-Q. Iridium(1)-Catalyzed α-C(sp3)–H Alkylation of Saturated Azacycles. J. Am. Chem. Soc. 2020, 142, 5117–5125. (b) Tran, A. T.; Yu, J.-Q. Practical Alkoxycarbonyl Auxiliaries for Iridium(I)-Catalyzed C–H Alkylation of Amines: The Benzoaxoazole Mesityl as a Removable Directing Group. Org. Lett. 2014, 16, 4201–4203. (d) Schinkel, M.; Wang, L.; Bielefeld, K.; Ackermann, L. Ruthenium (II)-Catalyzed C(sp3)–H α-Alkylation of Pyrrolidines. Org. Lett. 2014, 16, 1876–1879.

(8) Visible light photocatalysis in organic chemistry; Stephenson, C. R. J., Yoon, T., MacMillan, D. W. C., Eds.; Wiley-VCH: Berlin, 2018.

(9) Selected examples: (a) Zhao, H.; Leonori, D. Minimization of Back-Electron Transfer Enables the Eulusive sp3 C–H Functionalization of Secondary Anilines. Angew. Chem., Int. Ed. 2021, 60, 7669–7674. (b) Grayson, J. D.; Cresswell, A.; Ja, Y.-S. Photocatalytic α-C–H Alkylation of Primary Amines. Tetrahedron 2021, 81, 131896. (c) Leng, L.; Fu, Y.; Liu, P.; Ready, J. M. Regioselective, Photocatalytic α-Functionalization of Amines. J. Am. Chem. Soc. 2020, 142, 11972–11977. (d) Ryder, A. S. H.; Cunningham, W. B.; Ballantyne, G.; Mules, T.; Kinsella, A. G.;
Turner-Dore, J.; Alder, C. M.; Edwards, L. J.; McKay, B. S. J.; Grayson, M. N.; Cresswell, A. J. Photocatalytic β-Aryl†Ternary Amine Synthesis via C–H Alkylation of Unmasked Primary Amines. Angew. Chem., Int. Ed. 2020, 59, 14986−14991. (i) Cao, K.; Tan, S. M.; Lee, R.; Yang, S.; Jia, H.; Zhao, X.; Qiao, B.; Jiang, Z. Catalytic Enantioselective Addition of Prochiral Radicals to Vinylpyridines. J. Am. Chem. Soc. 2019, 141, 5437–5443. (i) Ashley, M. A.; Yamauchi, C.; Chu, J. C. K.; Otsuka, S.; Yorimitsu, H.; Rovis, T. Photoredox-Catalyzed Site-Selective α-Csp3–H Alkylation of Primary Amine Derivatives. Angew. Chem., Int. Ed. 2019, 58, 4002−4006. (g) Rossolini, T.; Leitch, J. A.; Grainger, R.; Dixon, D. J. Photocatalytic Three-Component Umpolung Synthesis of 1,3-Diamines. Org. Lett. 2018, 20, 6794−6798. (h) Trowbridge, A.; Reich, D.; Gaunt, M. J. Multicomponent synthesis of tertiary alkylamines by photocatalytic olefin-hydroaminoalkylation. Nature 2018, 561, 522−527. (i) Ye, J.; Kalvet, L.; Schoenebeck, F.; Rovis, T. Direct α-alkylation of primary aliphatic amines enabled by CO2 and electrostatics. Nat. Chem. 2018, 10, 1037−1041. (j) McManus, J. B.; Onuska, N. P. R.; Nicewicz, D. A. Generation and Alkylation of α-Carbamyl Radicals via Organic Photoredox Catalysis. J. Am. Chem. Soc. 2018, 140, 9056−9060. (k) Lee, K. N.; Lei, Z.; Nagai, M.-Y. β-Seeded Reductive Coupling of Aldehydes with Alkylamines and Imines via Synergistic Lewis Acid/Photoredox Catalysis. J. Am. Chem. Soc. 2017, 139, 5003−5006. (l) Chu, L.; Ohta, C.; Zuo, Z.; MacMillan, D. W. C. Carboxylic Acids as A Traceless Activation Group for Conjugate Additions: A Three-Step Synthesis of (±)-Pregabalin. J. Am. Chem. Soc. 2014, 136, 10886−10889. (m) Miyake, Y.; Nakajima, K.; Nishibayashi, Y. Visible-Light-Mediated Utilization of α-Aminoalkyl Radicals: Addition to Electron-Deficient Amines Using Photoredox Catalysts. J. Am. Chem. Soc. 2012, 134, 3338−3341. (10) The non-catalytic HAA of unprotected primary amines with non-electrophilic amines necessitates a large excess of the amine partner (~13−26 equiv) and forcing reaction conditions (~120 °C, ~10 mol% peroxide) and gives extensive telomerization. See: Urry, W. H.; Juveland, D. O. Free Radical Additions of Amines to Olefins. J. Am. Chem. Soc. 1958, 80, 3322−3328. (11) Non-electrophilic styrenes in photoredox-catalyzed, intramolecular HAA are scarce and limited to tertiary amines or N-Boc α-amino acids: (a) Wu, Z.; Gockel, S.; Hull, K. Anti-Markovnikov Hydro(amin)alkylation of Vinylarenes via Photoredox Catalysis. Research Square Preprint 2021, DOI: 10.21203/rs.3.rs-366556/v1. (b) Larionova, N.; Ondozabal, J. M.; Smith, E. G.; Cambero, X. A. A photocatalytic regioselective hydroaminoalkylation of aryl-substituted aldehydes has been achieved via an SET oxidation mechanism (134, 1178). (b) Pan, S.; Endo, J.; Kaplan, J.; Soltysiak, R.; Przybylski, J.; MacMillan, D. W. C. Photothiolation of α-Aminoalkyl Radicals: Addition to Vinylarenes with Selective C–H alkylation via polarity-match-based cross-coupling. Nat. Chem. 2017, 9, 79−83. (20) Luo, Y.-R. Comprehensive Handbook of Chemical Bond Energies; CRC Press: Boca Raton, FL, 2007. (21) (a) Sim, B. A.; Griller, D.; Wayner, D. D. M. Reduction Potentials for Substituted Benzyl Radicals: pK Values for the Corresponding Toluenes. J. Am. Chem. Soc. 1989, 111, 754−755. (b) Wayner, D. D. M.; McPhee, D. J.; Griller, D. Oxidation and reduction potentials of transient free radicals. J. Am. Chem. Soc. 1988, 110, 132−137. (22) Bortolamei, N.; Isse, A. A.; Gennaro, A. Estimation of standard reduction potentials of alkyl radicals involved in atom-transfer radical polymerization. Electrochem. Acta 2010, 55, 8312−8318. (23) Speckmeier, E.; Fischer, T. G.; Zeiher, K. A Toolbox Approach To Construct Broadly Applicable Metal-Free Catalysts for Photo-redox Chemistry: Delicate Tuning of Redox Potentials and Importance of Halogens in Donor–Acceptor Cyanoraneos. J. Am. Chem. Soc. 2018, 140, 15353−15365. (24) Ji, X.; Liu, Q.; Wang, Z.; Wang, P.; Deng, G.-J.; Huang, H. LiBr-promoted photoredox neutral Minisci hydroxyalkylations of quinolines with aldehydes. Green Chem. 2020, 22, 8233−8237. (25) Ide, T.; Barham, J. P.; Fujita, M.; Kawato, K.; Egami, H.; Hamashima, Y. Regio- and chemoselective Csp3–H arylation of benzylamines by single electron transfer/hydrogen atom transfer synergistic catalysis. J. Chem. Sci. 2018, 9, 8453−8460. (26) Rohe, S.; Morris, A. O.; McCallum, T.; Barriault, L. Hydrogen Atom Transfer Reactions via Photoredox Catalyzed Chlorine Atom Generation. Angew. Chem., Int. Ed. 2018, 57, 15664−15669. (27) Zhou, R.; Goh, Y. Y.; Liu, H.; Tao, H.; Li, L.; Wu, J. Visible-Light-Mediated Metal-Free Hydroxyalkylation of Alkenes through Selective Hydrogen Atom Transfer for Si–H Activation. Angew. Chem., Int. Ed. 2017, 56, 16621−16625. (28) Morisaki, K.; Morimoto, H.; Oshima, T. Recent Progress on Catalytic Addition Reactions to N-Unsubstituted Imines. ACS Catal. 2020, 10, 6924−6951. (b) Nicastro, M. C.; Lehnherr, D.; Lam, Y.-H.; DiRocco, D. A.; Rovis, T. Synthesis of Sterically Hindered Primary Amines by Concurrent Tandem Photoredox Catalysis. J. Am. Chem. Soc. 2020, 142, 987−998. (c) Lehnherr, D.; Lam, Y.-H.; Nicastro, M. C.; Liu, J.; Newman, J. A.; Regalado, E. L.; DiRocco, D. A.; Rovis, T. Electrochemical Synthesis of Hindered Primary and Secondary Amines via Proton-Coupled Electron Transfer. J. Am. Chem. Soc. 2020, 142, 468−478. (d) Ushakov, D. B.; Gilmore, K.; Kopetzki, D.; McCuaide, I. T.; Seeger, P. H. Continuous-Flow Oxidative Cyanation of Primary and Secondary Amines Using Singlet Oxygen. Angew. Chem., Int. Ed. 2014, 53, 557−561. (29) The addition step may be slower than potential side reactions (e.g., benzyl radical dimerization) or be reversible and endogenic, such that catalytic turnover is impeded. However, the photocatalytic α-Csp3–H alkylation of tertiary benzyl amines has been achieved via an SET oxidation–deprotonation approach; see ref 9c. (30) In general, quantification of the HAT site selectivity was possible, but minor unidentified byproducts were visible in the crude
\(^1\)H NMR spectra for some compounds. We previously showed, both experimentally and theoretically, that the selectivity for \(\alpha-C-\)H functionalization of cyclohexylamine versus cyclohexanol with photogenerated azidyl radical is \(>20:1\), with cyclohexanol itself being \(\alpha-C-\)H alkylated with methyl acrylate in only 12% yield in a standalone experiment; see ref 9d.

(31) Cambiè, D.; Bottecchia, C.; Straathof, N. J. W.; Hessel, V.; Noël, T. Applications of Continuous-Flow Photochemistry in Organic Synthesis, Material Science, and Water Treatment. Chem. Rev. 2016, 116, 10376–10341.

(32) Incidentally, compound 7ag was missigned as the other regioisomer in our previous work; see ref 9d. We now have conclusive 2D NMR and single-crystal XRD support for the revised structure of 7ag.

(33) As the closest literature comparison, a recent \(\alpha\)-amino radical addition to 6h (with a tertiary amine) proceeded in only 7% yield; see ref 11b.

(34) Constantin, T.; Zanini, M.; Regni, A.; Sheikh, N. S.; Júlia, F.; Leonori, D. Aminoalkyl radicals as halogen-atom transfer agents for activation of alkyl and alyl halides. Science 2020, 367, 1021–1026.

(35) Sanford, M. Fingolimod: A Review of Its Use in Relapsing-Remitting Multiple Sclerosis. Drugs 2014, 74, 1411–1433.

(36) Parajit, P.; Kondacs, L.; Alexandrovich, A.; Gautel, M.; Cobb, A. J. A.; Kompourakis, T. High Throughput Screen Identifies Small Molecule Effectors That Modulate Thin Filament Activation in Cardiac Muscle. ACS Chem. Biol. 2021, 16, 225–235.

(37) Mulakayala, N. A Comprehensive Review on Synthetic Approach for Fingolimod. Indian J. Adv. Chem. Sci. 2016, 4, 362–379.

(38) Urbano, M.; Guerero, M.; Rosen, H.; Roberts, E. Modulators of the Sphingosine 1-phosphate receptor 1. Bioorg. Med. Chem. Lett. 2013, 23, 6377–6389.

(39) Mandala, S.; Hajdu, R.; Bergstrom, J.; Quackenbush, E.; Xie, J.; Miller, J.; Thornton, R.; Shi, G. J.; Card, D.; Keohane, C. A.; et al. Altered lymphocyte trafficking by sphingosine-1-phosphate receptor agonists. Science 2002, 296, 343–349.

(40) (a) Chen, S.; Yang, L.; Shang, Y.; Mao, J.; Walsh, P. J. Base-Promoted Tandem Synthesis of 2-Azaryl Tetrahydroquinolines. Org. Lett. 2021, 23, 1594–1599. (b) Warsitz, M.; Doye, S. Two-Step Procedure for the Synthesis of 1,2,3,4-Tetrahydroquinolines. Eur. J. Org. Chem. 2020, 2020, 6997–7014.

(41) Muthukrishnan, I.; Sridharan, V.; Menéndez, J. C. Progress in the Chemistry of Tetrahydroquinolines. Chem. Rev. 2019, 119, 5057–5191.

(42) Based on a Scifinder search conducted in April 2021, with the following constraints applied: benzenoid-fused only, 800 MW max, no other ring fusions, only H/C/S attached to N, no isotopes/metals. Following constraints applied: benzenoid-fused only, 800 MW max, no other ring fusions, only H/C/S attached to N, no isotopes/metals.

(43) Hiesinger, K.; Dar’in, D.; Proshak, E.; Krasavin, M. Spiroyclic Scaffolds in Medicinal Chemistry. J. Med. Chem. 2021, 64, 150–183.

(44) St. Denis, J. D.; Hall, R. J.; Murray, C. W.; Heightman, T. D.; Rees, D. C. Fragment-based drug discovery: opportunities for organic synthesis. RSC Med. Chem. 2021, 12, 321–329.

(45) Twigg, D. G.; Kondo, N.; Mitchell, S. L.; Galloway, W. R. D.; Sore, H. F.; Madin, A.; Spring, D. R. Partially Saturated Bicyclic Heteroaromatics as an sp\(^*\)-Enriched Fragment Collection. Angew. Chem., Int. Ed. 2016, 55, 12479–12483.

(46) Law, R. P.; Atkinson, S. J.; Bamborough, P.; Chung, C.-w.; Harris, G. R.; Smith, M. A.; Gaunt, M. J. Modular Photocatalytic Copper Catalysis. Angew. Chem., Int. Ed. 2017, 56, 1599–1608.

(47) Procopiou, P. A.; Anderson, N. A.; Barrett, J.; Barrett, T. N.; Crawford, M. H. J.; Fallon, B. J.; Hancock, A. P.; Le, J.; Lemma, S.; Marshall, R. P.; et al. Discovery of (S)-3-(3-(3,5-Dimethyl-H-pyrazol-1-yl)phenyl)-(R)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-1)-ethyl)pyrrolidin-1-yl)butanoic Acid, a Nonpeptide \(\alpha_\beta\) Integrin Inhibitor for the Inhaled Treatment of Idiopathic Pulmonary Fibrosis. J. Med. Chem. 2018, 61, 8417–8443.