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Research Article

Accelerated and Scalable C(sp^3)−H Amination via Decatungstate Photocatalysis Using a Flow Photoreactor Equipped with High-Intensity LEDs

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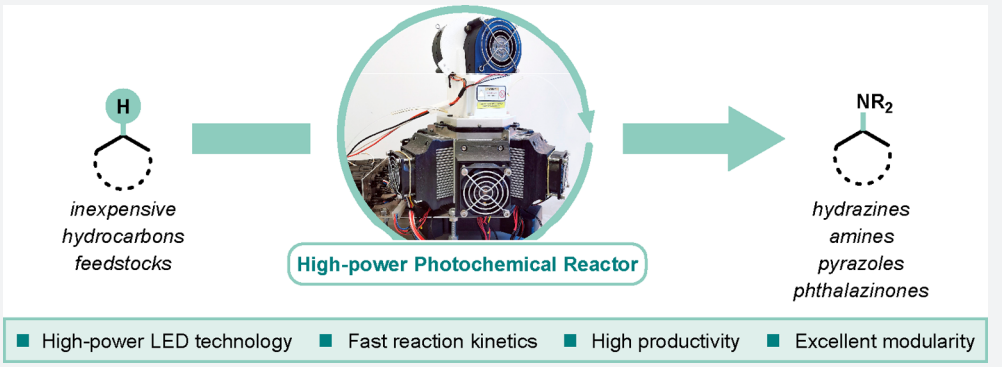

ABSTRACT: Carbon−nitrogen bonds are ubiquitous in biologically active compounds, prompting synthetic chemists to design various methodologies for their preparation. Arguably, the ideal synthetic approach is to be able to directly convert omnipresent C−H bonds in organic molecules, enabling even late-stage functionalization of complex organic scaffolds. While this approach has been thoroughly investigated for C(sp^2)−H bonds, only few examples have been reported for the direct amination of aliphatic C(sp^3)−H bonds. Herein, we report the use of a newly developed flow photoreactor equipped with high intensity chip-on-board LED technology (144 W optical power) to trigger the regioselective and scalable C(sp^3)−H amination via decatungstate photocatalysis. This high-intensity reactor platform enables simultaneously fast results gathering and scalability in a single device, thus bridging the gap between academic discovery (mmol scale) and industrial production (>2 kg/day productivity). The photocatalytic transformation is amenable to the conversion of both activated and nonactivated hydrocarbons, leading to protected hydrazine products by reaction with azodicarboxylates. We further validated the robustness of our manifold by designing telescoped flow approaches for the synthesis of pyrazoles, phthalazinones and free amines.

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INTRODUCTION

Carbon−nitrogen bonds are ubiquitous in natural products, pharmaceuticals, agrochemicals, and materials, stimulating the interest of the synthetic community to develop new amination protocols.[1] Especially C(sp^2)−N bonds can be readily formed by stitching carbon electrophiles (e.g., aryl halides) and various N-based nucleophiles together using transition metal catalysts,[2−5] with one notable example being the Buchwald−Hartwig amination.[6,7]

Currently, small molecules with increased sp^3 hybridization are required to reduce the attrition rate in drug discovery and to explore new chemical space (so-called "escape-from-flatland strategy").[8,9] C(sp^3)−N bonds can be easily forged by rudimentary nucleophilic substitution on alkyl halides. However, the direct C(sp^2)−H to C−N bond conversion has attracted significant amounts of attention as it improves the atom efficiency of the overall process.[10] While thermocatalytic approaches have proved to be the method of choice for the functionalization of C(sp^2)−H bonds, photocatalysis has rapidly emerged as a powerful strategy for the selective activation of C(sp^3)−H bonds.[11] Two seminal approaches to establish these coveted C(sp^3)−N bonds were independently reported by Zuo and co-workers[12−14] and Kokotos et al.[15] The methods exploited, respectively, a cerium salt[16] and phenylglyoxylic acid[17] to generate H atom abstractors. These species are subsequently capable of homolytically cleaving C(sp^3)−H bonds and afford a carbon-centered radical, which is finally

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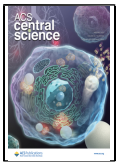

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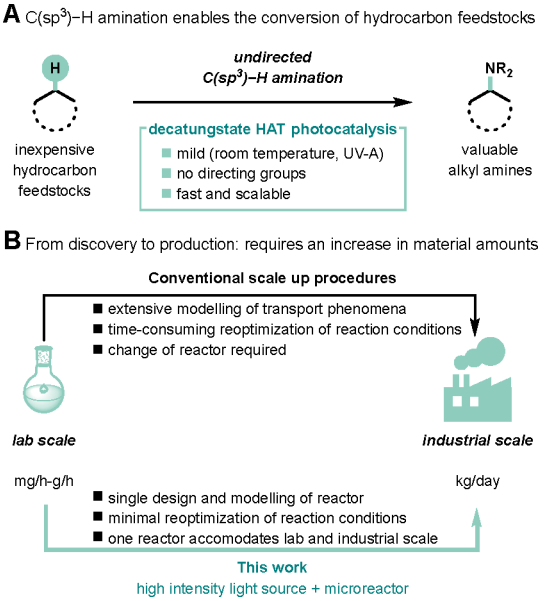
trapped by an azodicarboxylate to afford the targeted C(sp^3)–N bond.

Given the importance of this transformation and in line with our mission to bridge the gap between academic discovery and industrial production through technology,[18] we decided to design a high-productivity platform for photocatalytic C(sp^3)–H amination. To this end, the intended methodology should be (i) robust and reproducible, (ii) easily scalable, and (iii) compatible with other chemistries to design telescoped approaches to access various useful compounds. To realize a widely applicable C(sp^3)–H amination protocol, we selected direct hydrogen atom transfer (d-HAT) as the activation strategy and decatungstate as a suitable photocatalyst (Scheme 1A).[19,20] Decatungstate enables efficient d-HAT under mild reaction conditions (i.e., room temperature and low-energy UV-A light) in both activated and nonactivated organic compounds.[21−26] Moreover, d-HAT typically requires no additives that might interfere with the transformation.[27] As for scalability and compatibility, we purposely designed a flow photoreactor equipped with high intensity and dimmable chip-on-board (COB) LED technology (Figure 1). Since photochemical reaction rates are strongly dependent on the local light intensity,[28] we surmised that the high intensity in combination with microscale flow reactors should enable the high productivities (kg/day/unit) required for scale-up in pharmaceutical settings (Scheme 1B). Hence, this potent photochemical reactor enabled both fast results gathering and scalability in a single device, thus bridging the gap between academic discovery and industrial production (Scheme 1B).

Scheme 1[a]



[a](A) Decatungstate HAT photocatalysis enables undirected C(sp^3)–H amination in both activated and nonactivated hydrocarbons. (B) Challenges associated with the scale-up of photochemical transformations can be alleviated with suitable reactor technology in combination with high intensity light sources.

RESULTS AND DISCUSSION

Aiming to develop a fast and scalable C(sp^3)–H amination protocol, we commenced with the development of a new photochemical reactor which provides large amounts of photonic flux (Signify Eagle Reactor). The reactor consists of a translucent perfluoroalkoxy capillary microreactor (PFA, 750 μm ID, 5 mL volume) and is cooled by a fan and irradiated with six UV-A 365 nm COBs protected by a quartz exit window, providing a maximum of 144 W optical power (Figure 1) (see the Supporting Information (SI)). The light sources are attached to a heat dissipation element containing cooling fins and a fan, to cool the COBs for an optimized irradiation efficiency.

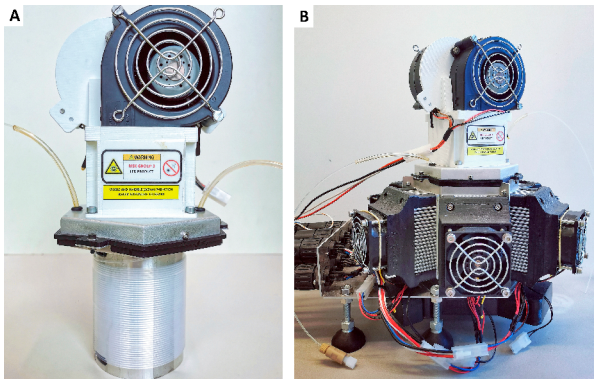
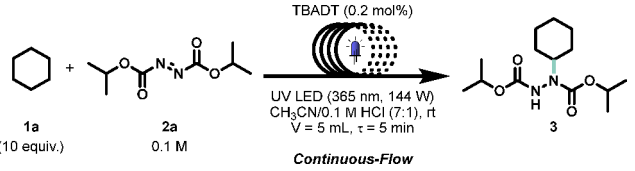


Figure 1. Signify Eagle Reactor. (A) Reactor coil with cooling fan. (B) Entire reactor assembly with six LED COB light source modules; each light module is individually controllable and dimmable to 1%.

Using this powerful photochemical reactor, the C(sp^3)–H amination of cyclohexane (**1a**) with diisopropyl azodicarboxylate (**2a**) in the presence of 2 mol % TBADT (TBADT: tetrabutylammonium decatungstate, $(Bu_4N)_4W_{10}O_{32}$) could be realized in only 5 min residence time in an excellent GC yield of 85% (Table 1, entry 1).[19] Notably, lowering the catalyst loading to 0.2 mol % resulted in a similar yield (Table 1, entry 2), which is beneficial to minimize trace metal impurities and thus reduce the overall cost of the process. Lowering the amount of H-donor (**1a**) from 10 to 5 equiv resulted in a reduction of the yield (Table 1, entry 3). The amination

Table 1. Optimization of Reaction Conditions[a]



entry	variation from conditions	yield (%)[b]
1	TBADT (2 mol %)	85
2	none	87 (73)
3	**1a** (5 equiv)	72
4	solvent: CH_3CN	38
5	solvent: CH_3CN/H_2O 7:1	36
6	solvent: CH_3CN/1 M HCl 7:1	64
7	no TBADT	0
8	no light	0

[a]Reaction conditions (1 mmol scale): **2a** (0.1 M), **1a** (10 equiv), TBADT (0.2 mol %) in CH_3CN/0.1 M HCl 7:1 (10 mL). Irradiation source: λ = 365 nm (144 W), residence time: 5 min (see the SI for additional details). [b]The yield was determined by GC-FID using biphenyl as the internal standard. Isolated yield is reported in parentheses.

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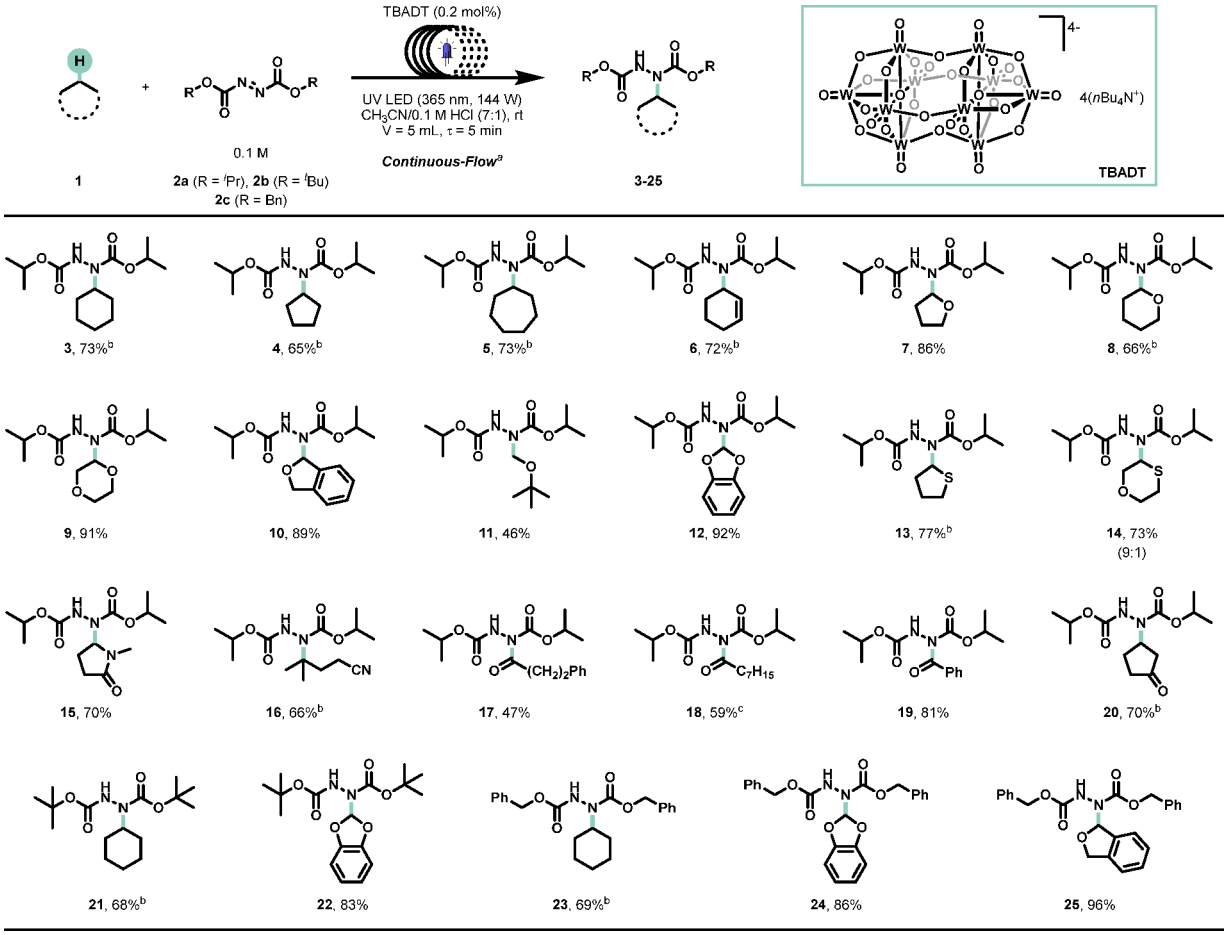
ACS Cent. Sci. 2022, 8, 51−56

Scheme 2. Substrate Scope of the Decatungstate-Photocatalytic C(sp^3)−H Amination in Flow



[a]Reaction conditions (2 mmol scale): **2a−c** (0.1 M), **1** (5 equiv), TBADT (0.2 mol %) in CH_3CN/0.1 M HCl 7:1 (20 mL). Irradiation source: λ = 365 nm (144 W), residence time: 5 min (see the SI for additional details). Isolated yields are given. [b]10 equiv of H-donor. [c]1.4 equiv of H-donor.

protocol works optimally in a CH_3CN/0.1 M HCl (7:1) solvent mixture (Table 1, entry 2 vs entries 5 and 6). Finally, control experiments revealed that the C(sp^3)−N bond formation is photocatalytic in nature as no product was observed in the absence of either photocatalyst or light (Table 1, entries 7 and 8).

With these optimized reaction conditions established, we sought to evaluate the scope of the photocatalytic C(sp^3)−H amination methodology (Scheme 2). Thus, cyclic alkanes with ring sizes from 5 to 7 underwent the C−N bond-forming reaction promptly (**3**−**5**, 65−73%), transforming unactivated alkyl substrates into synthetically valuable hydrazines. It is worth noting that polyfunctionalization of the hydrocarbon backbone was never observed. Activated allylic positions were rapidly converted into the corresponding C−N bond (**6**, 72%). Also, efficient α-to-O C−H amination was observed for a variety of cyclic and noncyclic ethers (**7**−**11**, 46−91%) and an acetal moiety (**12**, 92%). Similarly, α-to-S and α-to-N C−H bond functionalization was achieved (**13**−**15**, 70−77%), with excellent selectivity over competitive activation at the α-to-O position (**14**). Tertiary C(sp^3)−H bonds were selectively activated over weak, yet polarity-mismatched, α-cyano C-(sp^3)−H bonds (**16**, 66%).[29] Notably, aldehydes could be readily activated with decatungstate yielding the corresponding hydrazides in good yields (**17**−**19**, 47−81%).[30,31] A cyclic ketone showed exclusive selectivity for functionalization of the β-position (**20**, 70%).[29] Other dialkyl azodicarboxylates (**2b** and **2c**) were equally effective as acceptors in this C(sp^3)−H amination protocol, delivering the corresponding Boc (*tert*-butoxycarbonyl, **21** and **22**, 68−83%) or Cbz (benzyloxycarbonyl, **23**−**25**, 69−96%) protected hydrazine derivatives.

To demonstrate the utility of the developed methodology for the synthesis of *N*-based heterocycles, we converted the obtained protected hydrazines to pyrazoles via a telescoped Knorr pyrazole synthesis (Scheme 3A).[32]

A diverse set of alkyl-bearing pyrazoles could be obtained in good overall yields (**26**−**33**, 39−75%) simply by merging the reaction stream exiting the photochemical reactor with a flow containing different 1,3-dicarbonyl derivatives (**A**−**C**) in 4 M HCl in dioxane. It should be further noted that this two-step flow protocol enables access to pyrazoles bearing unactivated alkanes, which could not be prepared using our direct decatungstate-mediated C(sp^3)−H azolation.[33] In addition, by adding 2-formylbenzoic acid derivatives (**D**, **E**) instead, the corresponding phthalazinones (**34**−**37**, 55−69%) could be obtained by means of this streamlined flow process (Scheme 3A). Finally, we also demonstrated that the protected hydrazines can be readily converted to the corresponding primary amines via hydrogenation (**38**, 87%) (Scheme 3B).

The scaling of photochemical transformations has long been perceived as an insurmountable challenge, preventing such activation modes from being routinely used in the preparation

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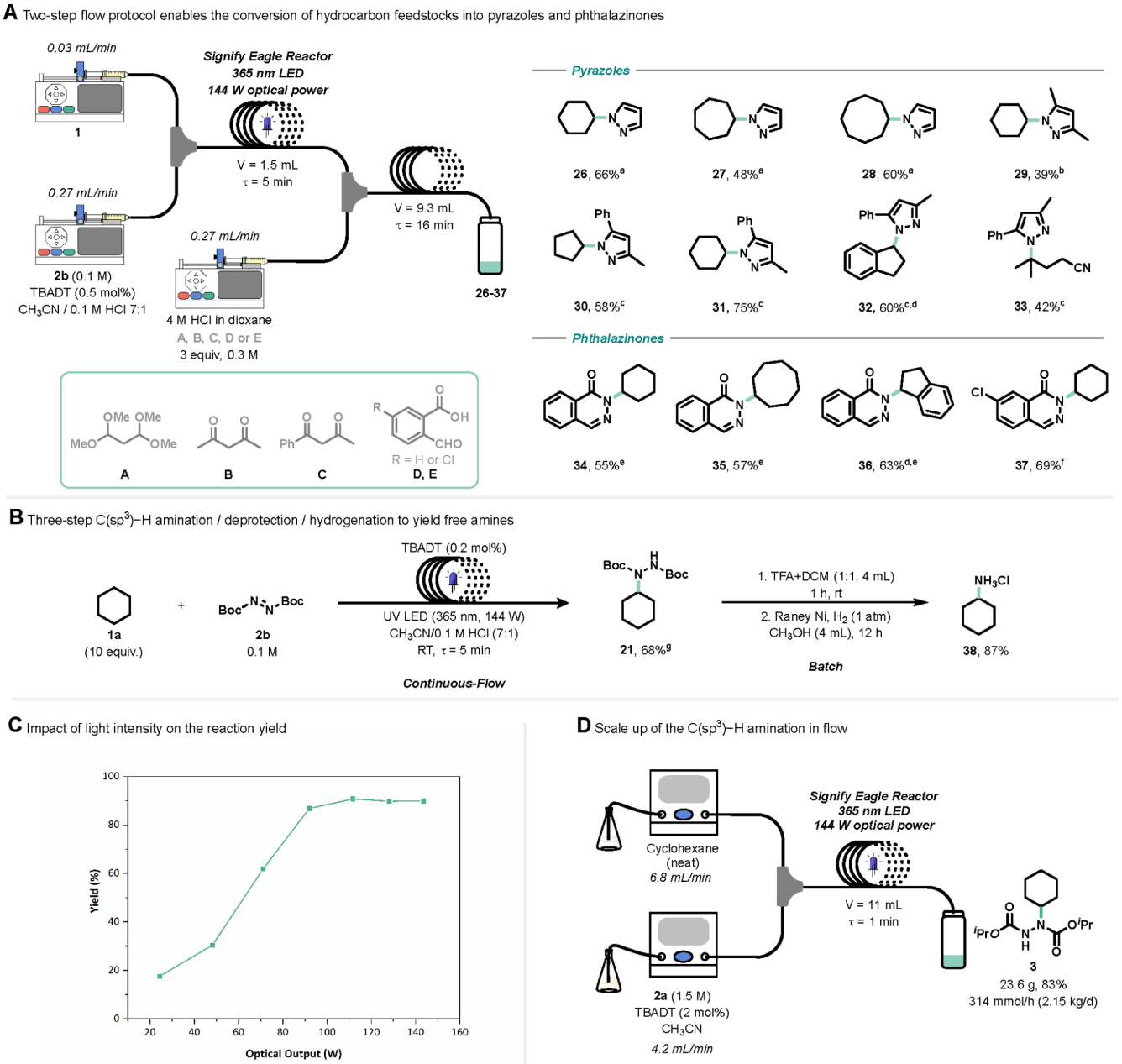
ACS Cent. Sci. 2022, 8, 51−56

Scheme 3. Compatibility, Productivity Screening, and Scale-Up of Our Platform[A]



[A](A) Two-step flow synthesis of pyrazoles and phthalazinones. Reported yields are those over the two steps. [a]Using 1,1,3,3-tetramethoxypropane (**A**, 3 equiv). [b]Using acetylacetone (**B**, 3 equiv). [c]Using 1-phenylbutane-1,3-dione (**C**, 3 equiv). [d]5 equiv of H-donor; only one feed was used for the photochemical reaction (flow rate: 0.3 mL/min). [e]Using 2-formylbenzoic acid (**D**, 3 equiv). [f]Using 5-chloro-2-formylbenzoic acid (**E**, 3 equiv). (B) Access to free amines via a three-step protocol. Reported yields are for individual steps. [g]Compound **21** was purified before further functionalization (see the SI for additional details). Detailed description of the reaction conditions are provided in the SI. (C) Effect of the optical output on the reaction yield. Reaction conditions: **2a** (1.5 M), **1a** (10 equiv), TBADT (2 mol %) in CH_3CN. Irradiation source: λ = 365 nm with different optical output power, residence time: 1 min. See the SI for further information. (D) Sketch of the setup adopted for the scale-up. Reaction conditions (100 mmol scale): **2a** (1.5 M), **1a** (10 equiv), TBADT (2 mol %) in CH_3CN (67 mL). Irradiation source: λ = 365 nm (144 W), residence time: 1 min. See the SI.

of complex molecules, such as pharmaceuticals and agrochemicals.[34−38] Since the kinetics of photochemical transformations are critically dependent on the amount of photons, the choice of the light source is paramount to scale any photon-dependent reaction.[36,39] Indeed, when varying the light intensity, an initial linear increase of the yield was observed with increasing photon flux (Scheme 3C). At high light intensities (>120 W optical power), the photocatalytic C(sp^3)–H amination reaction becomes ultimately independent of the photon flux and thus the reaction mixture is "saturated" with photons. However, the linear regime of the curve can be extended either by increasing the catalyst loading or by increasing the flow rate (and thus reducing the residence/reaction time), which allows to boost the throughput in the flow reactor. Both aspects are crucial in our scale-up strategy where we increased the catalyst loading to

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ACS Cent. Sci. 2022, 8, 51−56

2 mol % and reduced the residence/reaction time to only 1 min (see the Supporting Information for more details). This enabled us to reach 314 mmol/h productivity, amounting to a 2.15 kg/day in a single microreactor of only 11 mL volume (750 μm ID) (Scheme 3D). It should be noted that these are quantities that are sufficient to even meet the material demand required for clinical trials.[40]

CONCLUSIONS

In conclusion, we have developed a fast and scalable decatungstate-catalyzed C(sp^3)−H amination protocol, able to convert both activated and nonactivated hydrogen donors. The modularity of our protocol is exemplified by the possibility to carry out telescoped processes for the synthesis of (protected) hydrazines, pyrazoles, phthalazinones, and amines. Key in the successful scale-up of the transformation is the development of a new photochemical flow reactor with high intensity LED light source modules. Our results show that essentially the same reactor, requiring only a minimal reoptimization of the reaction conditions, is capable of providing the quantities needed on both the laboratory (i.e., ∼2 mmol) and process scale (>2 kg/day). We are optimistic that the results presented herein can inspire others to combine simultaneously synthetic methodology development and chemical engineering principles to rapidly transition from initial discoveries to applications on a process scale.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscentsci.1c01109.

Experimental procedures, characterization data of synthesized compounds, NMR spectra (PDF)

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Author Contributions

[§]T.W. and Z.W. contributed equally to this work. T.W., G.L., L.C., and R.L. performed and analyzed the experiments on a laboratory scale. Z.W. performed the scale up studies with support from T.W. and L.C. T.W., Z.W., G.L., L.C., and T.N. designed the experiments. The photochemical reactor was developed by R.B. and colleagues from Signify. J.A.R., P.G-L., C.M., and M.O.F. provided intellectual contributions via monthly discussions with regard to substrate scope and reaction design. L.C. and T.N. prepared this manuscript with input from all coauthors.

Notes

The authors declare the following competing financial interest(s): Signify holds Intellectual Property for the light sources.

FAIR data (primary NMR FID files) for compounds **3**−**38** can be found at https://doi.org/10.21942/uva.17040392.

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