

Optimization of a Decatungstate-Catalyzed C(sp³)-H Alkylation Using a Continuous Oscillatory Millistructured Photoreactor

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ABSTRACT: Tetrabutylammonium decatungstate (TBADT) has emerged as an efficient and versatile photocatalyst for hydrogen atom transfer (HAT) processes that enables the cleavage of both activated and unactivated aliphatic C–H bonds. Using a recently developed oscillatory millistructured continuous-flow photoreactor, investigations of a decatungstate-catalyzed C(sp³)-H alkylation protocol were carried out, and the results are presented here. The performance of the reactor was evaluated in correlation to several chemical and process parameters, including residence time, light intensity, catalyst loading, and substrate/reagent concentration. In comparison with previously reported batch and flow protocols, conditions were found that led to considerably higher productivity, achieving a throughput up to 36.7 mmol/h with a residence time of only 7.5 min.

KEYWORDS: hydrogen atom transfer, C–H functionalization, photocatalysis, decatungstate, flow photochemistry, process intensification

INTRODUCTION

Over the past decade, photocatalysis has emerged as a powerful methodology to enhance the greenness and sustainability of many chemical transformations.¹ Among the various photocatalytic methods, hydrogen atom transfer (HAT) processes are particularly useful for the functionalization of substrates containing unreactive C–H bonds without recurring to metal catalysis or strong oxidants.² Light-induced HAT catalysis can proceed via three different pathways: direct HAT,³ indirect HAT,⁴ and proton-coupled electron transfer (PCET) processes.⁵ Among these, direct HAT processes are the most reagent-economical, as the other two approaches require the addition of additives to the reaction. Only a limited number of catalysts are able to promote direct HAT upon absorption of light, including aromatic ketones,⁶ eosin Y,^{3b} uranyl salts,^{3c} and polyoxometalates, the latter mainly represented by tetrabutylammonium decatungstate ([*n*Bu₄N]₄(W₁₀O₃₂)], TBADT).⁷ The decatungstate anion has been proven to be a robust and versatile catalyst for the functionalization of unactivated aliphatic C–H bonds upon irradiation with near-UV light (Scheme 1).^{7a} Notable examples are alkylation,^{3a,8} arylation,⁹ fluorination,¹⁰ trifluoromethylation,¹¹ and oxygenation.¹²

Although the synthetic utility of photochemical methods has been amply demonstrated, their applications in industry are still limited.¹³ Indeed, photochemistry suffers from light-attenuation effects due to the Beer–Lambert law, which makes traditional scale-up (enlarging reactor dimensions) strenuous. When reactor vessels are scaled out beyond the laboratory (mL) scale, a photon gradient becomes apparent between the wall and the center of the reactor. To compensate for the “dark zone” generated in the vessel, photochemical processes are often run at prolonged reaction times, resulting in local overirradiation, which in turn leads to the potential erosion of yield and selectivity. To counteract such nonideal reaction

conditions, ensuring a homogeneous irradiation profile in the reactors is most crucial in order to obtain the ideal photochemical reaction conditions.¹⁴ Continuous-flow (micro)reactors are often considered as a “go-to technology” in order to address these issues. In flow photochemistry, the reaction occurs in narrow transparent channels or thin fluid beds, ensuring quasi-homogeneous irradiation and consequently a higher selectivity and shorter reaction time due to the increase in photon input per unit volume. Considerable advances have been reported in this field in terms of both reaction methodology and reactor design.^{14,15}

Several large-scale photoreactions in flow have been described in the past few years, mostly based on specific reactor designs.¹⁶ Recently, the HANU reactor, a multipurpose continuous-flow photoreactor developed by Creaflow,¹⁷ was utilized for the multigram-scale synthesis of an *N*-arylpiperidine derivative via a heterogeneous Ni/photoredox dual-catalyzed C–N coupling.¹⁸ This milli-structured photoreactor combines an oscillatory flow regime and static mixing elements along a narrow channel, ensuring good irradiation and mixing properties (Scheme 1).¹⁹ In addition, the HANU reactor comes in different sizes (reactor volumes of up to 150 mL) and features narrow residence time distributions (RTDs), thus holding considerable potential for scaling up photochemical processes.

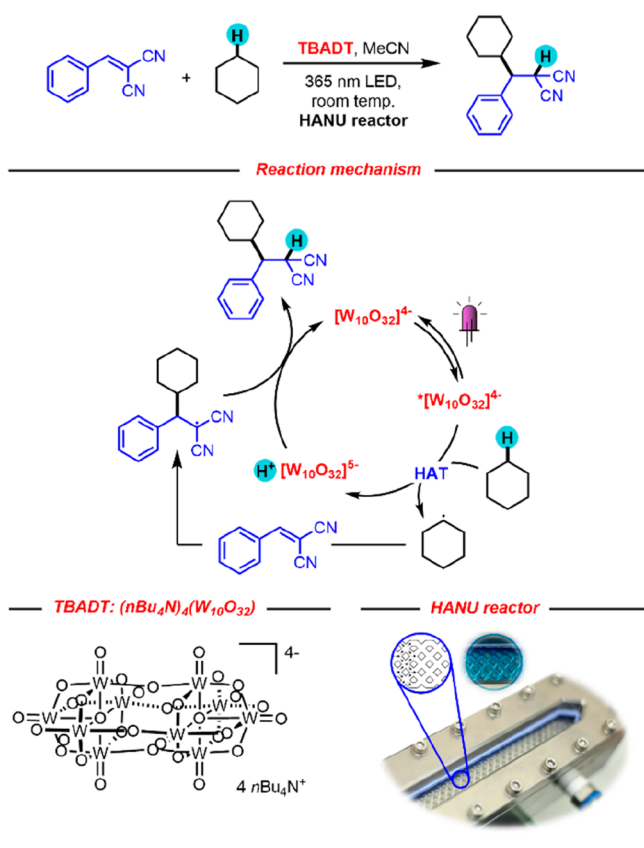
Following our interest in flow photochemistry^{14,16c,e,20} and C–H functionalization^{8c,12,21} as enabling methods in organic

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Scheme 1. TBADT-Catalyzed C(sp³)-H Alkylation Studied in This Work

synthesis, herein we present the optimization of a TBADT-catalyzed C(sp³)-H alkylation process using the HANU reactor. The radical addition of cyclohexane to the electron-poor olefin 2-benzylidenemalononitrile, which occurs via the mechanism shown in Scheme 1, was selected as a model reaction.²² This conceptually simple transformation represents an appealing and atom-economical protocol for C-C bond formation.

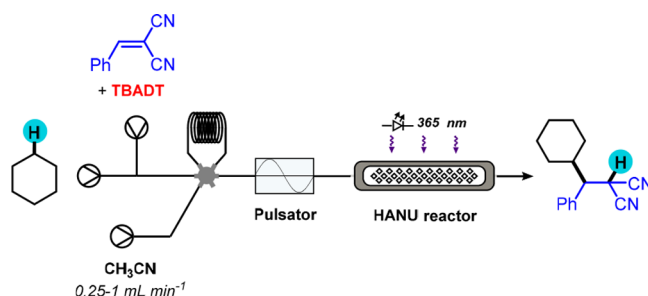
EXPERIMENTAL SECTION

General Information. Commercially available chemicals were purchased from Sigma-Aldrich and TCI and used as received, unless otherwise noted. Solvents were purchased from Biosolve. TBADT²³ and 2-benzylidenemalononitrile²⁴ were prepared according to literature procedures. All capillary tubing and microfluidic fittings were bought from IDEX Health & Science. BD Discardit II plastic syringes were purchased from VWR Scientific. The photoreactor employed was a HANU reactor (model HANU HX 15-316L-CUB), with a reactor size of 540 mm × 60 mm × 60 mm, channel dimensions of 480 mm × 20 mm × 2 mm, and a series of cubic static mixing elements (2 mm × 2 mm × 2 mm) along its length. The volume of the channel in the reactor is 15 mL, but only half of the reactor was irradiated (see the Supporting Information), so the volume considered was 7.5 mL. The light source employed for the photochemical process (FireEdge FE400 240 × 10AC 365-4W; input power of 240 W; optical output power of 96 W) was purchased from Phoseon Technology. Product purification was performed automatically by a Biotage Isolera Four system with Biotage SNAP KP-Sil 10 or 25 g flash chromatography cartridges. TLC analysis was

performed using silica on aluminum TLC plates (F254, Supelco Sigma-Aldrich) with visualization under UV light (254 and 365 nm). ¹H and ¹³C NMR spectra were recorded with a Bruker Avance 400 spectrometer at 400 and 100 MHz, respectively, and referenced to the internal deuterated solvent (CDCl₃) at 7.26 ppm (¹H) and 77.2 ppm (¹³C). GC analyses were performed on a GC-FID system (Shimadzu GC-2010) with biphenyl as an internal standard.

Experimental Setup. As shown in Scheme 2, two syringe pumps (Fusion 200 Touch, Chemyx Inc.) were used to inject

Scheme 2. Experimental Setup for Decatungstate Photocatalysis in Flow



the two feeds. Feed 1: substrate solution (0.1–0.8 M) + biphenyl (0.1 M) + TBADT (2–7 mol %), flow rate = 1 mL/min. Feed 2: cyclohexane (5–15 equiv), flow rate = 0.11–0.86 mL/min according to the equivalents of cyclohexane. The two feeds were mixed in a T-mixer and pumped into a feeding loop (PFA tubing, 0.75 mm i.d., 10 mL volume, IDEX). Once the reaction mixture was loaded into the loop (slug flow between the two different phases), the resulting mixture was pumped through the HANU reactor with acetonitrile via a six-way valve.

Experimental parameters such as the flow rate (0.25–1 mL/min) and light intensity were evaluated and optimized. At the reactor outlet, the samples were collected in GC vials, diluted with acetonitrile, and analyzed by GC-FID (for the detailed GC method, see the Supporting Information). In order to obtain the isolated products, the solvent (acetonitrile) was removed in vacuo, and the dry crude material was purified via flash chromatography (cyclohexane/EtOAc 95:5).

RESULTS AND DISCUSSION

Effect of Residence Time. For comparison purposes, we first performed the reaction in a homemade capillary reactor (PFA tubing, 0.75 mm i.d.), irradiated with a 36 W 365 nm LED strip. With this setup, 74% conversion over a residence time of 30 min was obtained (see the Supporting Information). The reaction was then transferred to the HANU reactor with a dedicated irradiation source. A screening of residence times from 2.5 to 30 min revealed that full conversion was reached after 7.5 min, corresponding to an 82% GC yield. Only a slightly higher yield (88%) was obtained even at double the residence time (see Figure S5). Because of the biphasic nature of the reaction (the liquid phases of cyclohexane and acetonitrile are immiscible), we envisaged that the use of a pulsator might improve the mixing efficiency and film refreshment at the window, possibly leading to improved reaction rates and hence shortened residence times. Moreover, a certain degree of pulsation was shown to be fundamental in minimizing the RTD inside the HANU reactor, leading to plug

flow behavior. On the basis of these studies,^{18,25} we performed experiments at different residence times with a pulsation amplitude corresponding to 5% of the maximum and a frequency of 3 Hz.²⁶ With this addition, higher conversions and yields were obtained at residence times of ≤ 5 min in comparison with the nonpulsated reaction (Figure 1, see also

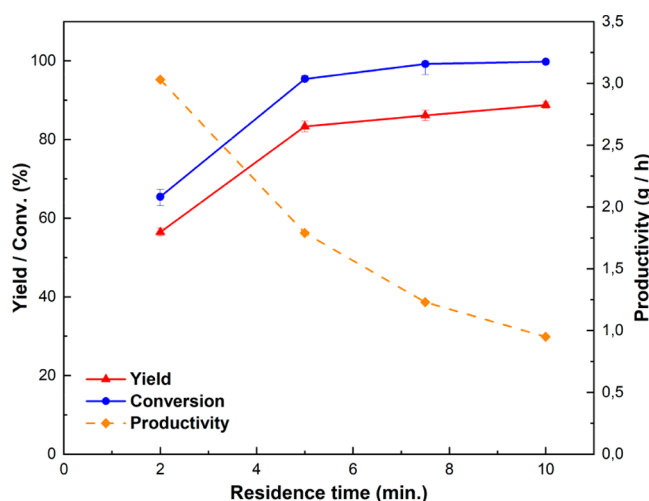


Figure 1. Effect of residence time on conversion, yield, and productivity. Reaction conditions: 0.1 M alkene substrate, 2 mol % TBADT, 10 equiv of cyclohexane, 5% pulsation, 96 W 365 nm light.

Figure S5). However, full conversion was reached only at 7.5 min, which was thus chosen for further experiments. Although no pulsation effect was observed at this residence time, 5% pulsation was maintained to ensure a narrow RTD and improved mixing, which is independent of the net flow rate used.

Effect of Light Intensity. The effect of different light intensities was then investigated in order to evaluate potential light-limiting conditions. From the data reported in Figure 2, it is clear that the photochemical process becomes light-limited for optical output below 48 W (50% light intensity). At maximum optical output (96 W), a sufficient number of

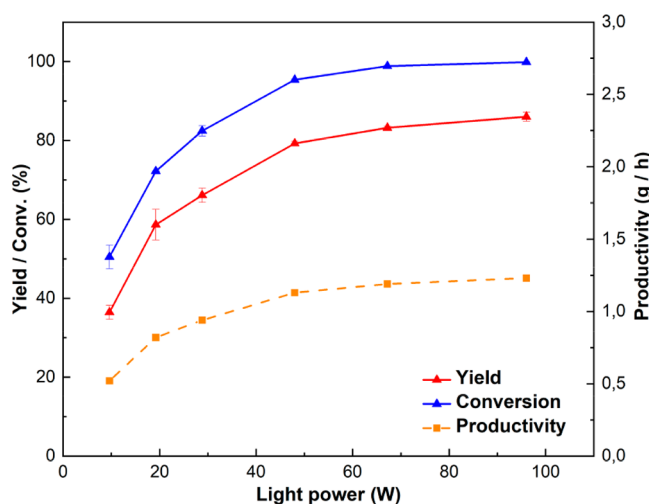


Figure 2. Effect of light intensity on substrate conversion, yield, and productivity. Reaction conditions: 0.1 M substrate, 2 mol % TBADT, 10 equiv of cyclohexane, 5% pulsation, 7.5 min.

photons have been absorbed to allow full conversion, and thus, this was chosen as optimal.

Effect of the Amount of Cyclohexane. We next evaluated the effect of the cyclohexane stoichiometry on the reaction (Figure 3). It is apparent that 10 equiv of cyclohexane

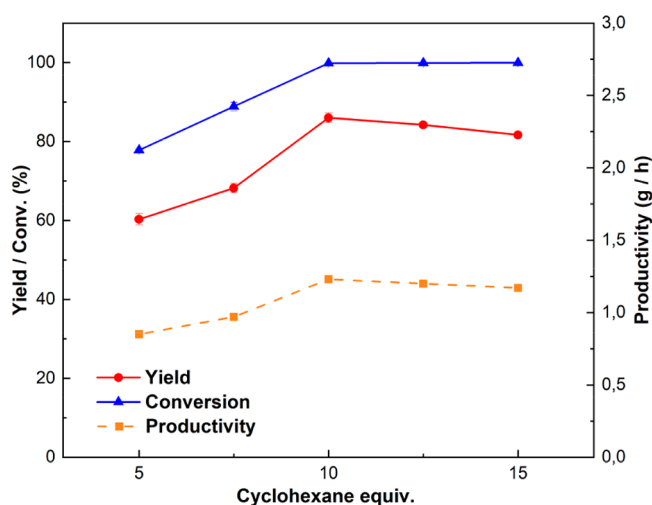


Figure 3. Effect of cyclohexane excess on conversion, yield, and productivity. Reaction conditions: 0.1 M substrate, 2 mol % TBADT, 96 W 365 nm light, 5% pulsation, 7.5 min.

gave the optimal result. While a lower excess of cyclohexane was insufficient to reach full conversion within a residence time of 7.5 min, at higher excesses the reaction resulted in lower selectivity due to the formation of larger amounts of side products. Additionally, higher amounts of cyclohexane also translated to a larger amount of immiscible phase, potentially contributing to the lower yield under these conditions.

Effects of Substrate Concentration and Catalyst Loading. With the aim of increasing the reaction throughput, the effect the substrate concentration was studied in combination with different catalyst loadings (Table 1). When the concentration of the substrate was doubled to 0.2 M, incomplete conversion and lower yields were obtained (entries 1 and 2). Doubling the catalyst loading to 4 mol % resulted in

Table 1. Optimization of Substrate Concentration and TBADT Loading^a

entry	conc. (M)	TBADT (mol %)	conv. (%) ^b	yield (%) ^b	productivity (g/h)	productivity (mmol/h)
1	0.1	2	100	86	1.2	5.0
2	0.2	2	91	81	2.3	9.9
3	0.2	4	100	91	2.6	11.1
4	0.3	4	96	84	3.7	15.7
5	0.4	5	97	85	4.8	20.3
6	0.4	6	100	90	5.5	23.3
7	0.5	7	100	91	6.5	27.2
8	0.6	5	100	82	6.9	29.1
9	0.6	7	99	92	7.9	33.1
10	0.7	5	100	82	8.2	34.3
11	0.7	7	100	88	8.7	36.7
12	0.8	7	100	80	9.1	38.4

^aReaction conditions: 10 equiv of cyclohexane, 96 W 365 nm light, 5% pulsation, 7.5 min. ^bDetermined by GC-FID with biphenyl as an internal standard.

Table 2. Literature Comparison of the Productivity of the C–H Functionalization of 2-Benzylidenemalononitrile to 2-(Cyclohexyl(phenyl)methyl)malononitrile

reactor type	catalyst	irradiation source (power input)	reaction time/temperature	productivity (mmol/h)	STY [mmol/(L/h)]
batch ^{3b}	eosin Y (2 mol %)	white LED (18 W)	24 h/60 °C	0.003	3
batch ^{3c}	[UO ₂](NO ₃) ₂ ·6H ₂ O (8 mol %)	456 nm LED (40 W)	24 h/r.t.	0.04	40
stopped-flow microtubing reactor ²⁸	Mes-Acr ⁺ ClO ₄ ⁻ (2 mol %)/HCl (5 mol %)	blue LED (81 W)	24 h/50 °C	0.112	4.1
capillary flow reactor ²⁸	Mes-Acr ⁺ ClO ₄ ⁻ (2 mol %)/HCl (5 mol %)	blue LED (54 W)	6 h/50 °C	0.113	13.9
homemade capillary (this work)	TBADT (2 mol %)	365 nm LED (36 W)	30 min/r.t.	0.74	148
HANU reactor (this work)	TBADT (7 mol %)	365 nm LED (240 W)	7.5 min/r.t.	36.7	2447

full conversion and a 91% yield, which translates to a productivity of 11.1 mmol/h (entry 3). Further increasing both the substrate concentration and catalyst loading up to 0.7 M and 7 mol %, respectively, resulted in full conversion in 88% yield and a throughput of 36.7 mmol/h (entry 11). Both the use of 0.6–0.7 M concentrations in combination with a lower catalyst loading (entries 8 and 10) and a further increase in concentration to 0.8 M (entry 12) resulted in a significant drop in yield. Loadings of TBADT higher than 7% were considered not practical because of solubility limitations.

Comparison of Different Photoreactors and Scale-Up. In order to compare the results obtained with the HANU reactor to previously reported photochemical setups, we have listed the published productivities for the same product in Table 2. Although a direct comparison between the different methods is challenging because of a lack of experimental details, this table helps to put into perspective the potential of this protocol. It can be seen that this protocol by far outperforms other reactors/conditions reported in the literature in terms of both productivity and space-time yield (STY).²⁷ Furthermore, the design concept of the HANU reactor allows linear scalability by broadening the reactor channel, since all of the critical process properties (e.g., channel dimensions, mass-, heat-, and light-transfer capabilities, and RTD)^{17,18} are retained. Larger versions of the HANU reactor (e.g., the HANU HX-150 with an internal volume of 150 mL) can enable further scale-up of this procedure.

CONCLUSION

We have illustrated the utility of a continuous oscillatory millistructured photoreactor for the optimization of a photochemical decatungstate-catalyzed C(sp³)–H alkylation. The conversion, yield, and productivity of the reaction were evaluated by changing various parameters, including residence time, light intensity, reactant concentrations, and catalyst loading. Following the optimization study, conditions leading to a productivity of 36.7 mmol/h were found, and full conversion was obtained after a residence time of only 7.5 min. This investigation further demonstrated the efficiency of the HANU reactor and its potential use for the scale-up of photocatalytic transformations.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.oprd.0c00235>.

Experimental and analytical procedures, reactor photographs, supplementary graphs, compound characterization data, and NMR spectra (PDF)

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Notes

The authors declare the following competing financial interest(s): K.V.A. and H.P.L.G. are employees of CreaFlow, the company that developed and commercialized the HANU reactor used in this study.

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