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Raymenants, F.; Masson, T.M.; Sanjosé-Orduna, J.; Noël, T.

DOI
10.1002/ange.202308563
10.1002/anie.202308563

Publication date
2023

Document Version
Final published version

Published in
Angewandte Chemie

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Citation for published version (APA):
Raymenants, F., Masson, T. M., Sanjosé-Orduna, J., & Noël, T. (2023). Efficient C(sp^3)−H Carbonylation of Light and Heavy Hydrocarbons with Carbon Monoxide via Hydrogen Atom Transfer Photocatalysis in Flow. *Angewandte Chemie*, *135*(36), Article e202308563. https://doi.org/10.1002/ange.202308563, https://doi.org/10.1002/anie.202308563

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Zitierweise: *Angew. Chem. Int. Ed.* **2023**, *62*, e202308563
doi.org/10.1002/anie.202308563

VIP **Flow Chemistry** *Very Important Paper*

Efficient C(sp^3)–H Carbonylation of Light and Heavy Hydrocarbons with Carbon Monoxide via Hydrogen Atom Transfer Photocatalysis in Flow**

*Fabian Raymenants, Tom M. Masson, Jesús Sanjosé-Orduna, and Timothy Noël**

Abstract: Despite their abundance in organic molecules, considerable limitations still exist in synthetic methods that target the direct C–H functionalization at sp^3-hybridized carbon atoms. This is even more the case for light alkanes, which bear some of the strongest C–H bonds known in Nature, requiring extreme activation conditions that are not tolerant to most organic molecules. To bypass these issues, synthetic chemists rely on prefunctionalized alkyl halides or organometallic coupling partners. However, new synthetic methods that target regioselectively C–H bonds in a variety of different organic scaffolds would be of great added value, not only for the late-stage functionalization of biologically active molecules but also for the catalytic upgrading of cheap and abundant hydrocarbon feedstocks. Here, we describe a general, mild and scalable protocol which enables the direct C(sp^3)–H carbonylation of saturated hydrocarbons, including natural products and light alkanes, using photocatalytic hydrogen atom transfer (HAT) and gaseous carbon monoxide (CO). Flow technology was deemed crucial to enable high gas-liquid mass transfer rates and fast reaction kinetics, needed to outpace deleterious reaction pathways, but also to leverage a scalable and safe process.

The selective and controlled C–H functionalization of sp^3-hybridized carbons is arguably one of the most challenging goals in contemporary synthetic organic chemistry.[1] Despite decades of research, the current state of the art in C–H activation still struggles to achieve selective C–H functionalization of saturated hydrocarbons.[2] This is due to several factors, including the low reactivity of C–H bonds, the difficulty in achieving selective reactions in the absence of directing groups,[3] and the presence of more reactive functional groups that can interfere with the reaction. These difficulties become even more pronounced when gaseous components are involved,[4] either as the starting material or as the reactant, exacerbating the challenges already present due to limitations in gas-liquid mass transfer. Furthermore, the selective conversion of gaseous alkanes, such as methane, ethane, propane and butane, to more useful chemical products remains a largely unsolved issue as these components are considered to be the least reactive.[5,6] Indeed, the direct conversion of light hydrocarbons often requires even more extreme reaction conditions,[7] which reduces their value as precursors for the preparation of complex organic molecules.

Due to their inertness, saturated hydrocarbons are not directly involved in chemical reactions. To utilize them in synthetic chemistry, they must first be converted into more reactive agents (Figure 1A). The first strategy involves steam reforming, in which alkanes are transformed into syngas (a mixture of CO and H_2) at high temperatures (700–1000 °C) and pressures (up to 15–40 bar).[8] This syngas can then be utilized to produce a range of commodity chemicals. The second strategy for using saturated hydrocarbons in synthetic chemistry is to halogenate them, which creates a polarized and reactive site for further chemical reactions.[9] However, this radical halogenation process is low-yielding and unselective, requiring extensive and energy-intensive purification and recycling efforts.[10] Although both processes are not environmentally sustainable in the long run, they remain being performed on a large scale to produce bulk chemicals crucial for the manufacture of pharmaceuticals, agrochemicals, materials, and other industrial chemicals. Thus, a direct and widely applicable C–H functionalization strategy would bring significant benefits, not only by avoiding the energy-intensive and low-yielding reforming and halogenation processes, but also by enabling the late-stage functionalization of complex organic molecules.[11]

Notably, hydrogen atom transfer (HAT) photocatalysis has emerged as a mild strategy for C–H functionalization.[12,13] Irradiation with light excites the HAT photocatalyst which causes scission of the C–H bond at room temperature, producing open-shell reactive intermediates that can participate in useful chemical reactions. Our group[14] and Zuo et al.[15] have independently developed a

[*] F. Raymenants, T. M. Masson, Dr. J. Sanjosé-Orduna, Prof. Dr. T. Noël
Flow Chemistry Group, Van't Hoff Institute for Molecular Sciences (HIMS), University of Amsterdam
Science Park 904, 1098 XH Amsterdam (The Netherlands)
E-mail: T.Noel@uva.nl
Homepage: https://www.NoelResearchGroup.com

[**] A previous version of this manuscript has been deposited on a preprint server (https://doi.org/https://doi.org/10.26434/chemrxiv-2023-jbjh2).

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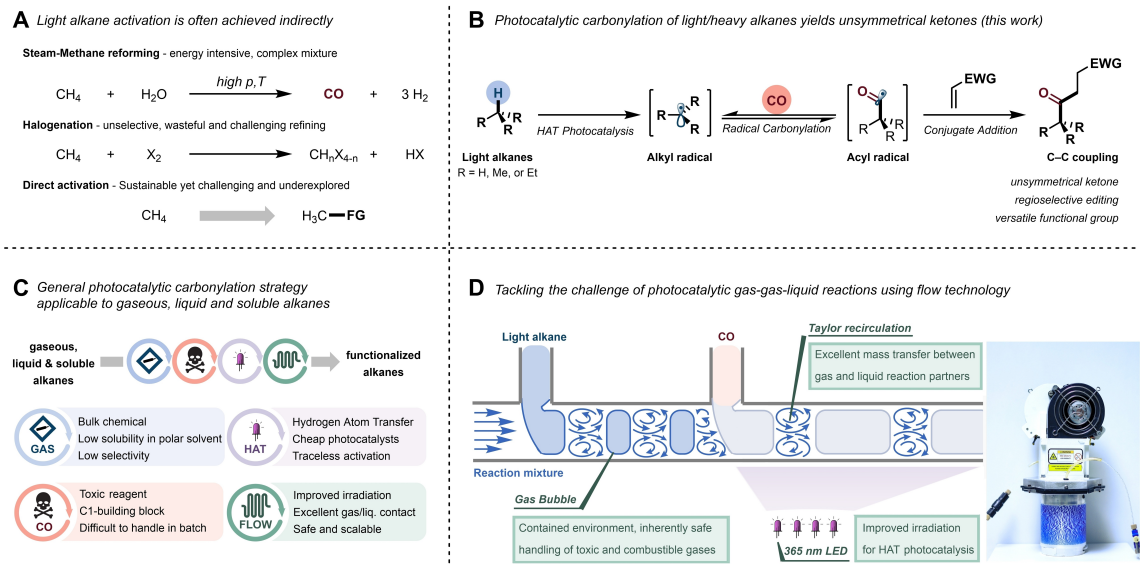

Figure 1. C(sp^3)–H carbonylation of gaseous, liquid and soluble alkanes with carbon monoxide via HAT photocatalysis in flow. (A) Steam reforming and halogenation are mostly used to activate the high inert bonds of light alkanes as direct activation and use is a major challenge. (B) Photocatalytic carbonylation of alkanes would give rise to unsymmetrical ketones. (C) The photocatalytic carbonylation of saturated hydrocarbons requires the merger of HAT photocatalysis, the use of gases, the safe handling of carbon monoxide and flow chemistry. (D) The use of flow chemistry is crucial to develop a safe, practical and scalable process for the photocatalytic carbonylation of alkanes.

protocol for using HAT photocatalysis to activate light alkanes and forge carbon-carbon bonds through capture of the generated carbon-centered radicals by Michael acceptors. Unfortunately, progress in this field has been slow,[16] and the utilization of light hydrocarbons as reactants in synthetic chemistry remains limited to only a few examples, which are often plagued with narrow scope, insufficient scalability, and limited practicality.

Our aim was to identify an efficient C–H functionalization process for regioselective installation of a versatile functional group in both light and heavy hydrocarbon scaffolds (Figure 1B). We believed that installing a carbonyl group would bring significant value due to its abundant associated chemistry.[17,18] We further identified that the most cost-effective strategy for carbonyl installation would utilize readily available, inexpensive carbon monoxide from the hydrocarbon reforming industry (Figure 1C).[19] However, while safety hazards associated with carbon monoxide in combination with flammable alkanes would pose substantial risks in conventional batch reactors, safe processing can be ensured in flow due to the limited amount of chemicals in the microreactor.[20–22] Additionally, the short length scales in micro flow reactors result in a uniform irradiation of the reaction mixture, reducing reaction times and providing opportunities for scaling up (Figure 1D).[23]

We began our investigation into the proposed C(sp^3)–H carbonylation by merging a solution of cyclohexane and di-*n*-butyl maleate in the presence of tetrabutylammonium decatungstate (TBADT) in acetonitrile (0.1 M) with a carbon monoxide gaseous stream. The combined segmented flow was subsequently introduced into a continuous-flow microreactor (PFA tubing, ID = 0.8 mm, 5 mL volume) irradiated with six high-intensity UV-A light sources (Chip-on-Board LED, $\lambda = 365$ nm, 144 W optical power).[24] Further, a back-pressure regulator (BPR) was installed at the reactor outlet to maintain a constant reaction pressure (See Supporting Information for technical details). After screening various reaction parameters (see Figure 2 and Supporting Information), we found that the targeted carbonylated product (**d**) could be obtained in quantitative yield in only 30 minutes residence time. Pressure was found to significantly impact selectivity, with the Giese adduct (**e**) as the main product at atmospheric pressure. Elevated pressure, with 34 bar as the optimal condition, reversed the selectivity towards the carbonylated product (Figure 2A). The residence time positively affected conversion, reaching 82 % after two minutes and being complete at 15 minutes with 4 mol% catalyst loading (Figure 2B). With maximum light intensity (144 W optical power), the photocatalyst loading can be reduced from 4 mol% to 0.25 mol% without significant loss in yield or selectivity (Figure 2C). However, at this low photocatalyst loading (0.25 mol%), the transformation becomes photon limited with decreased light intensity, resulting in only 59 % conversion at 24 W output power (Figure 2D). Control experiments confirmed the photocatalytic nature of the transformation, as no reaction occurred without catalyst or light.

Having optimized the reaction conditions, we next investigated the scope of the photocatalytic carbonylation transformation (Scheme 1). First, cyclohexane was combined with CO and a variety of olefins. These olefins serve as terminal radical traps for the acyl radicals,[25] initially formed through combination of the photocatalytically generated carbon-centered radicals with carbon monoxide. Using di-*n*-butyl maleate and dimethyl maleate as coupling partners resulted in the formation of the targeted unsymmetrical

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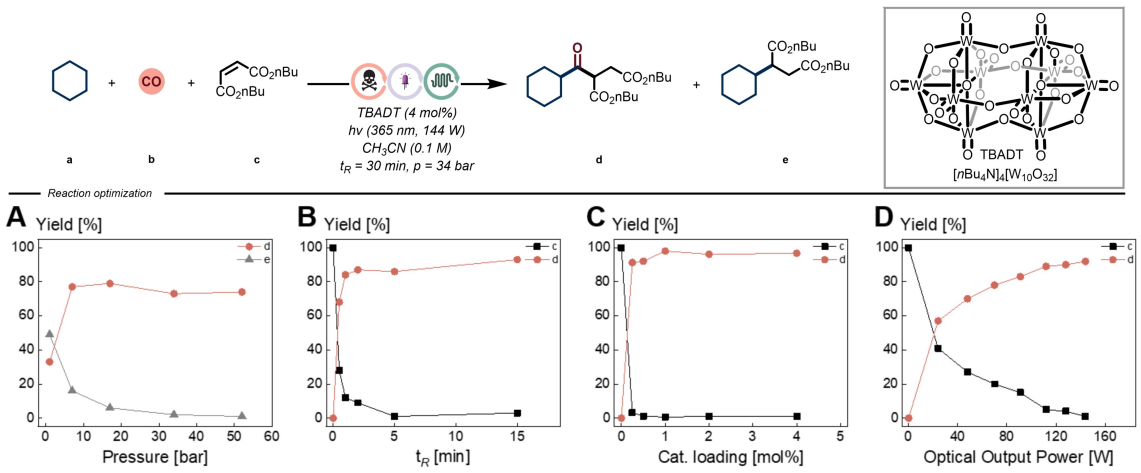

Figure 2. Parametric optimization of reaction pressure, residence time, photocatalyst loading and optical power. Unless otherwise noted, standard reactions are performed with 0.1 M of alkene as limiting reagent, 10 equivalents of alkane, 35 equivalents of CO and with 4 mol% of TBADT loading, under irradiation of UV-A LED light (365 nm, 144 W optical output power). Reported yields reflect those obtained with ^{1}H NMR. (A) Influence of the reaction pressure at two minutes residence time. (B) Influence of the residence time for reactions carried out at 34 bar. (C) Influence of photo catalyst loading for reactions carried out at 30 minutes residence time and at 34 bar. (D) Conversion of di-*n*-butyl maleate in function of the optical output power for reactions carried out with 0.25 mol% catalyst loading and 30 minutes residence time.

ketones in good isolated yields (**1**–**2**, 71–92 %). Notably, compound **2** could be easily scaled to gram quantities without reoptimizing the reaction conditions, simply by pumping stock solution for a longer period of time and thus increasing the amount of starting material pushed through the photochemical flow reactor.[26,27] Moreover, mono-substituted olefins, such as methyl acrylate, 2,2,2-trifluoroethyl acrylate, and 1,1,1,3,3,3-hexafluoropropyl acrylate, can be engaged in the protocol as well, yielding the targeted ketones in synthetically useful yields (**3**–**5**, 27–55 % yield). Similarly, a diverse set of conjugated enones, including cyclohexanone, 3-methylene-norbornanone, and carvone, were successful as radical traps for the generated acyl radicals (**6**–**8**, 33–40 % yield). Importantly, the optimized reaction conditions tolerated various functional groups, such as nitriles, sulfones, phosphonates, ketones, and protected alcohols, yielding the target ketones in acceptable to good isolated yields (**9**–**14**, 28–82 % yield).

Scheme 1 also illustrates how various soluble C–H donors can be utilized in this protocol. The carbonylation of cycloalkanes with ring sizes ranging from five to eight carbons yielded good to excellent results (**15**–**18**, 57–93 %). Similarly, linear alkanes can be successfully modified with an exclusive modification preference for secondary positions (**19**, 75 %), despite the low difference in Bond Dissociation Energy (BDE) between secondary and primary hydrogens (BDE = 99 versus 101 kcal/mol).[12] Notably, electron-withdrawing functional groups, such as ketones, can deactivate the alpha C–H bond in organic molecules due to a polarity mismatch with the electrophilic decatungstate photocatalyst.[28] As a result, we can achieve excellent yield and selectivity (**20**, 85 %) in the functionalization of the distal position of cyclopentanone. Diverse bridged bicyclic alkanes afforded the corresponding ketones with perfect exo selectivity (**21**–**23**, 38–78 %). Importantly, this mild carbonylation method is also applicable to bio-active molecules, as demonstrated by the successful reactions with eucalyptol and sclareolide, which gave satisfactory results (**24**–**25**, 55–67 %).

To further demonstrate the versatility of our developed process, we next evaluated its application for the carbonylation of the light alkane homologous series (C1–C4), which represents the most challenging task for our flow protocol.[29] Indeed, carbonylation of gaseous alkanes requires the cleavage of some of the strongest C(sp^3)–H bonds and, in addition, the subsequent coupling of two gaseous components are required for this transformation. As we have demonstrated, alkyl radical capture with CO can occur rapidly for soluble alkanes. However, the challenge of the carbonylation of light alkanes lies in the fact that two gaseous molecules must simultaneously diffuse into the liquid phase and be present in sufficient amounts to ensure fast kinetics that outpace the competing Giese reaction.[14] This presents an even greater challenge for volatile alkanes, which are sparingly soluble in acetonitrile. Furthermore, to prevent CO extrusion, the acyl radical formed during the reaction must be rapidly captured by a suitable olefin trap. To date, this reversibility has impeded radical carbonylation of volatile alkanes in any practical synthetic context.[30] Given the challenges associated with the radical carbonylation of volatile alkanes, we anticipated that flow photoreactors could potentially overcome these limitations. Specifically, the use of back pressure regulators in combination with high light intensity can seamlessly increase the pressure and boost kinetics ($k \sim I$, in which k is the reaction rate, and I the light intensity).[31] As a result, and due to continuous nature of the technology, we were hopeful to realize for the first time a practical carbonylation of light alkanes at scales which were sufficient to isolate the target compounds.[32,33]

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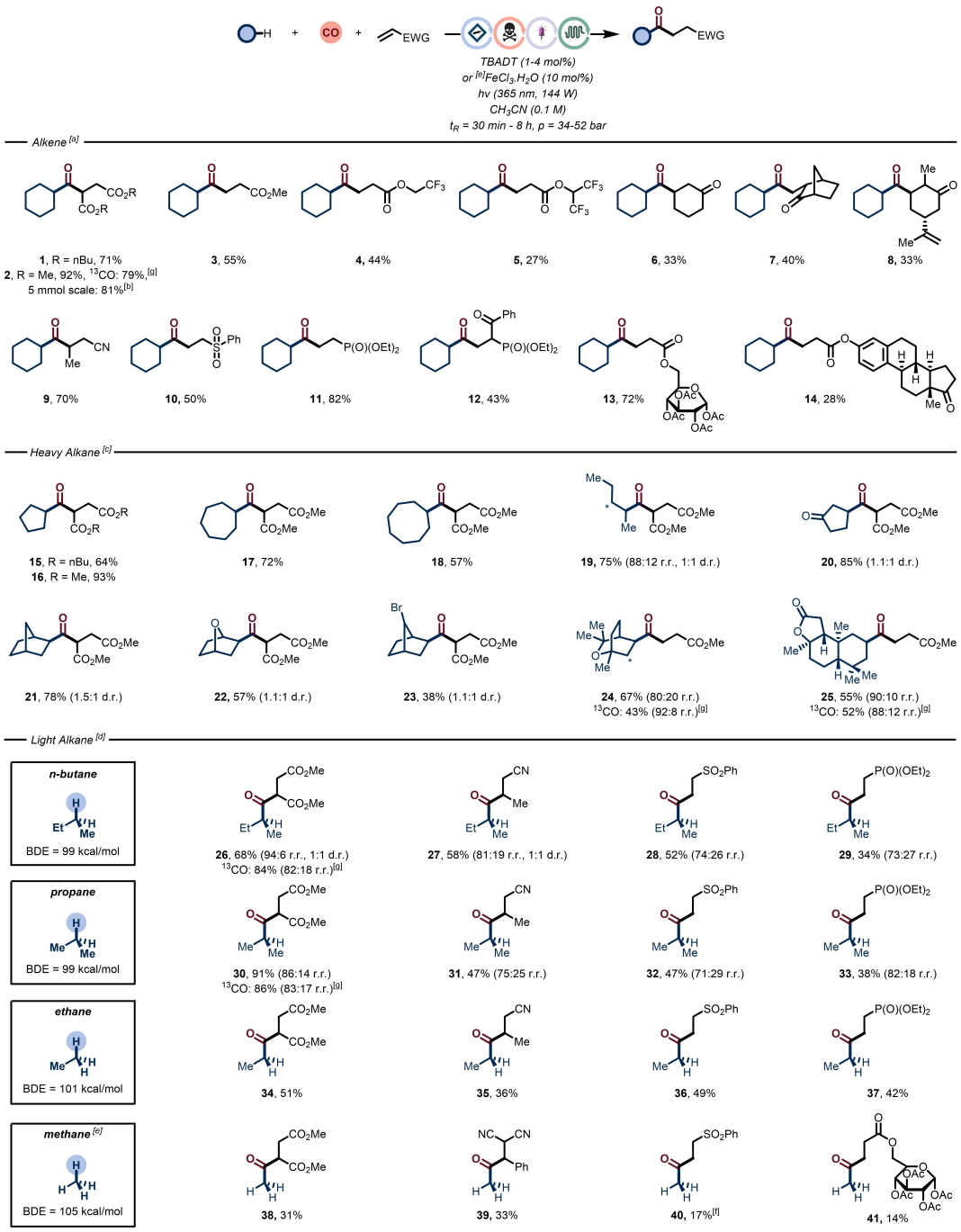

Scheme 1. Scope of the photocatalytic carbonylation of alkanes with carbon monoxide and alkenes yielding unsymmetrical ketones. Reactions are performed in flow at 0.1 M alkene concentration, with 10 equiv. of alkane and 35 equiv. of carbon monoxide gas and 1–4 mol% of TBADT photocatalyst, under irradiation of UV-A light (365 nm, 144 W optical output power) and a pressure of 34 bar. All yields are those of isolated products.[a] For the alkene scope, a residence time of 30 minutes and a catalyst loading of 1 mol% are maintained to ensure full conversion across the entire set of substrates.[b] Scale-up performed with 5 equiv. of CO, at 12 bar reaction pressure and 10 minutes residence time, reacting 5 mmol of stock solution in 3 h processing time.[c] For the alkane scope, a residence time of 1 hour and a catalyst loading of 2 mol% are maintained to ensure full conversion across the entire set of substrates.[d] For the light alkane scope, a reaction pressure of 52 bar and a catalyst loading of 4 mol% are maintained, with a residence time of 2 h, 4 h and 6 h for n-butane, propane and ethane respectively.[e] Methane reactions are performed with 10 mol% of $FeCl_3.6H_2O$ as HAT photocatalyst, with a residence time of 8 h.[f] 20 mol% of catalyst loading applied for benzyl vinyl sulfone.[g] Reactions with ^{13}CO were performed with 5 equiv. of ^{13}CO under otherwise unchanged reaction conditions.

Interestingly, the reaction conditions developed for soluble hydrocarbons were successfully applied to *n*-butane with only a single modification: an extended residence time of 2 hours instead of 1 hour (Scheme 1). Using this protocol, *n*-butane was carbonylated and successfully coupled with a number of electron-deficient alkenes, including dimethyl

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maleate, crotonitrile, phenyl vinyl sulfone and vinyl phosphonate, in good isolated yields (**26**–**29**, 34–68 %). With propane, similar yields were realized for the same set of Michael acceptors (**30**–**33**, 38–91 %), reaching an impressive 91 % for the reaction with dimethyl maleate, in a 3 h reaction time. It should be further noted that secondary C–H bonds are activated preferentially over primary ones, mainly due to the lower BDE and the formation of a more stabilized radical species,[12] in this specific case leading to a regioisomeric ratio of 86:14 secondary versus primary $C(sp^3)$–H bonds. In addition, these results are in good alignment with our previous work on the activation of volatile alkanes.[14] The cleavage of stronger primary C–H bonds in ethane required a longer 4-hour residence time, but still yielded satisfactory results (**34**–**37**, 36–51 %).

After the successful carbonylation of light C2-4 alkanes, we turned our attention to the activation of methane, one of the most abundantly available carbon-based feedstocks.[34] Due to its non-polarized C–H bonds and high BDE's (i.e., 105 kcal/mol),[35] methane is exceptionally challenging to activate at room temperature.[36] Unfortunately, when applying our optimized reaction conditions to methane, only vague traces of methane activation could be observed. In contrast, we did observe competitive HAT activation of the reaction solvent CH_3CN. While effective for the Giese-type hydromethylation, reaction modifications, such as lowering the substrate concentration and use of CD_3CN as solvent, led only to small and synthetically unuseful quantitities of product. Given recent successes of halogen radical-mediated HAT transformations,[37] we decided to change the HAT photocatalyst to cheap and abundantly available $FeCl_3.6H_2O$, functioning as a source of $Cl^{\bullet}$ which can serve as a powerful H-abstractor.[38] To our delight, significantly higher product formation was observed using this photocatalyst, confirming that the carbonylation of methane was within reach. After some minimal reoptimization (See Supporting Information), we isolated dimethyl 2-methylsuccinate **38** in 31 % yield. Importantly, the reaction could be performed in non-deuterated CH_3CN at a synthetically useful concentration (0.05 M). The transformation was subsequently applied to benzylidene malononitrile (**39**, 33 %), benzyl vinyl sulfone (**40**, 17 %) and the acrylate of an acetyl protected sugar (**41**, 14 %). The latter example is a testimony of the impressive selectivity that can be observed for photocatalytic methane activation in presence of more accessible H-atoms in the sugar scaffold. It should be further noted that our methane carbonylation, enables the coupling of two common C1 fragments, i.e. methane and CO, and are effectively combined into an acetyl radical C2 building block. It is further important to realize that while $FeCl_3$ was effective to enable photocatalytic activation of methane, the decatungstate anion remains the HAT photocatalyst of choice for other alkanes. This is due to the significantly reduced selectivity and slow reaction kinetics of $FeCl_3$ (see Supporting Information).

Finally, we sought to incorporate an isotopic label using ^{13}CO gas, which is particularly useful for studying reaction mechanisms and tracing the fate of reactants in complex mixtures.[39] To achieve this, we leveraged the advantages of flow technology, including the high gas-liquid interfacial area and precise stoichiometric control over the gaseous component using mass flow controllers. Therefore, the use of flow technology allows for the precise control of the amount of ^{13}CO gas required, which can be challenging to achieve in conventional batch reactors due to gas accumulation in the headspace. By applying our optimized carbonylation protocol with a lower amount of ^{13}CO gas (5 equivalents), we successfully converted several representative C–H donors to their corresponding carbonylation products in yields comparable to those obtained with ^{12}CO (**1**, **24**–**26**, **30**). This result demonstrates a practical application of our methodology for isotopic labeling of organic molecules.

Our photocatalytic carbonylation reaction provides a powerful method for direct $C(sp^3)$–H activation of diverse alkanes. This process enables regioselective installation of carbonyl moieties in simple and complex organic scaffolds, expanding the toolkit for organic synthesis. Importantly, our method represents a promising pathway for upgrading light hydrocarbons at ambient temperature, opening the door to the use of these readily available feedstocks as coupling partners in the synthesis of complex organic molecules.

Supporting Information

The authors have cited additional references within the Supporting Information.[14,24,28,33,37,40–62]

Acknowledgements

This research was made possible with the generous financial support of the European Union: ERC CoG (FlowHAT, No. 101044355, T.N.), FETopen (FLIX, No. 862179, F.R. and T.N.), RIA-NMBP (FlowPhotoChem, No. 862453, T.M and T.N.), and MSCA Individual Fellowship program (SELECTFLOW, No. 101061835, J.S.O.).

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: CH Activation · Hydrogen Atom Transfer · Light Alkane · Photocatalysis · Flow Chemistry

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Manuscript received: June 17, 2023
Accepted manuscript online: July 17, 2023
Version of record online: July 27, 2023

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