

Continuous-Flow C(sp³)-H Functionalizations of Volatile Alkanes Using Decatungstate Photocatalysis

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C(sp³)-H functionalization of alkanes in the absence of proximal directing groups is considered one of the most challenging and important reactions in contemporary synthetic organic chemistry. In particular, the incorporation of light alkanes, such as methane, ethane, propane and butane, into organic molecules is extremely attractive because it would move the perception of these chemicals essentially as fuel materials to potentially valuable synthetic building blocks.¹

Building on their experience in decatungstate-photocatalyzed C–H oxidations,² the group of Prof. Dr. Timothy Noël at the Eindhoven University of Technology (The Netherlands) focused their attention on this valuable – yet absent in organic synthesis – chemical conversion of gaseous alkanes, which could benefit from continuous-flow microreactor technology. First author of the paper, Dr. Gabriele Laudadio, remarked: “At the onset of the project, we wondered if we could engage these inert and insoluble gasses into synthetically valuable transformations using cheap decatungstate as a photocatalyst. Decatungstate had shown its value for activating larger alkane scaffolds, often with remarkably high selectivity which can be ascribed to the large size of the catalyst and its electronic properties. If successful, this catalyst would show significant scope, allowing for a diverse set of synthetic applications using Hydrogen Atom Transfer (HAT) photocatalysis.” Furthermore, as noted by Prof. Dr. Timothy Noël: “Flow chemistry would be

key in our reaction design: not only to make sure that the reaction medium is well irradiated, but also to bring the gasses into close contact with the photocatalyst³ (Figure 1).”

Preliminary trapping experiments with TEMPO afforded the corresponding TEMPO-propane adducts and gave the group confidence for potentially interesting and useful reactivity. In particular, the authors were intrigued by the excellent selectivity provided by decatungstate for the most substituted carbon of propane (86:14 ratio of secondary vs primary derivative).

Prof. Dr. Noël recalls that he immediately realized the importance of this seminal result, knowing how difficult it is to obtain good selectivity without the presence of directing groups. He said: “I still remember the meeting when this result was presented; I became really excited. We decided to investigate further to see if we could obtain more synthetically useful results.” At that point, Prof. Dr. Noël asked Yuchao Deng, who was a visiting Chinese PhD student in the lab, to join the team.

Yuchao and Gabriele carried out the propane optimization and identified the substrate scope. Gabriele remarked: “The decision to employ a Vapourtec setup was crucial, because we could move from stop flow to continuous flow, accelerating our reaction dramatically (Scheme 1). Importantly, a high-intensity light source was needed to provide much-reduced reaction times.”

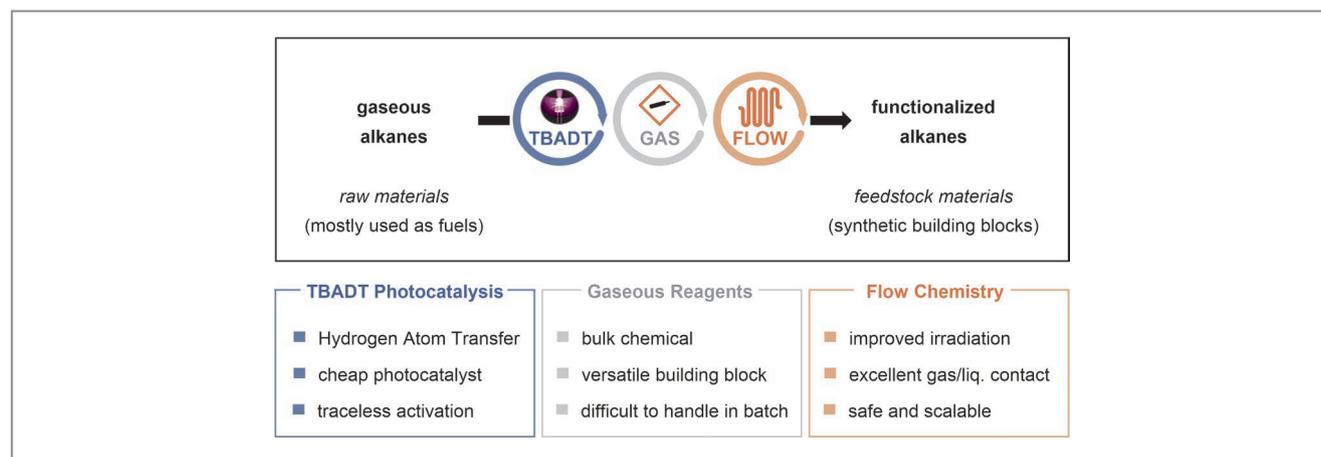
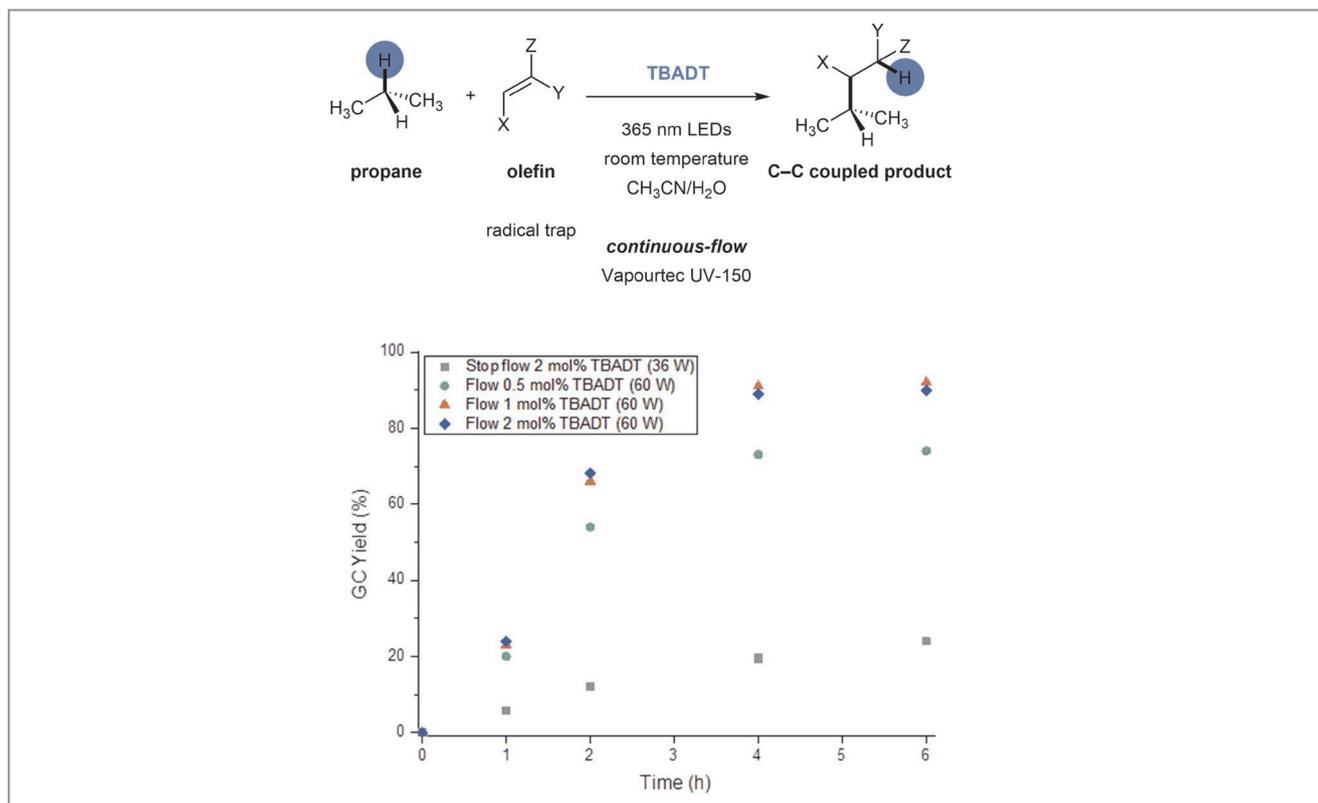


Figure 1 Decatungstate photocatalysis in flow enables the activation of light alkanes



Scheme 1 Importance of photon flux and catalyst loading for the effectiveness of the decatungstate C(sp³)-H functionalization of propane

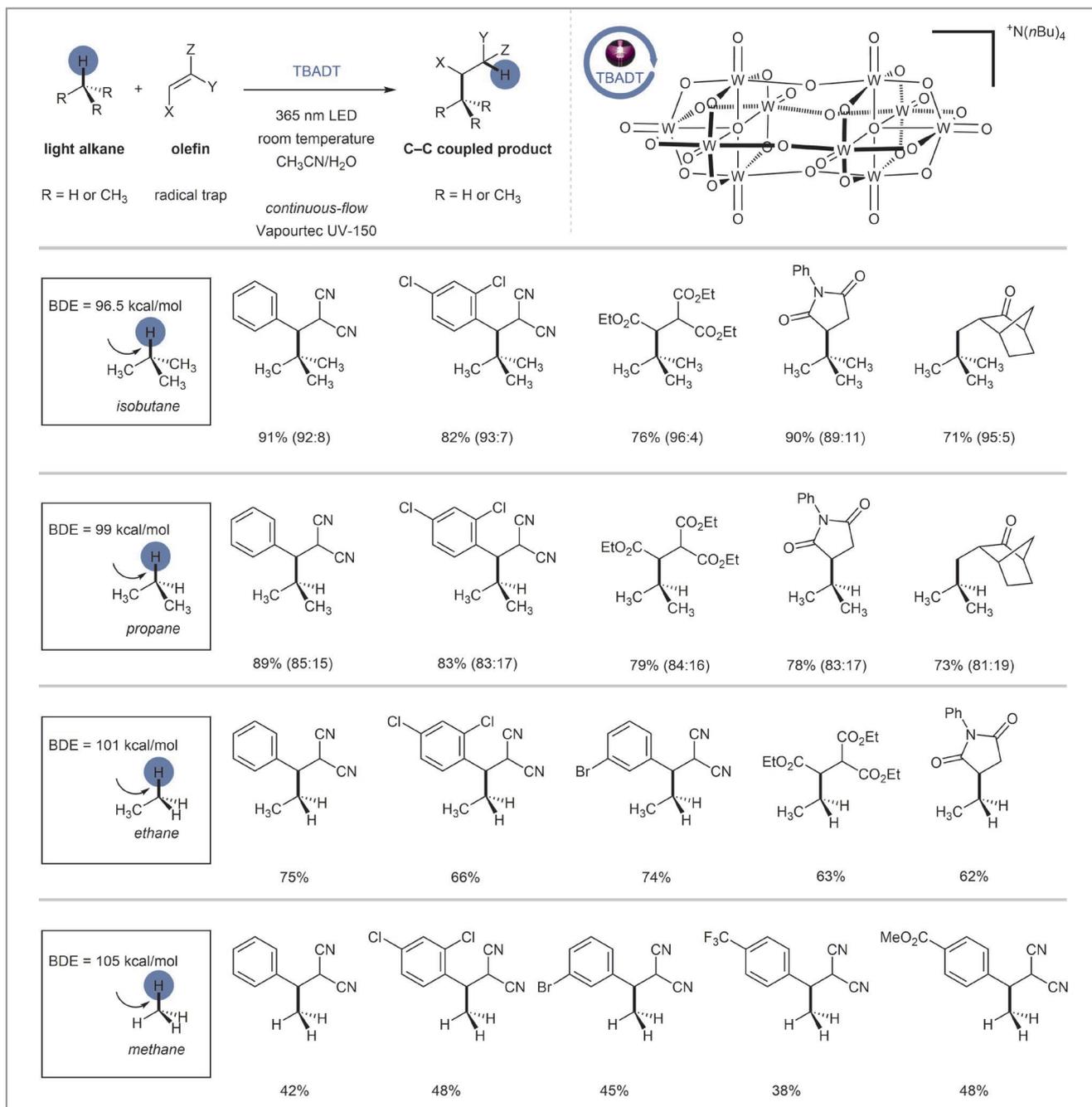
Next, Gabriele and Yuchao set out to explore different gaseous substrates (Scheme 2). Yuchao said: “Activation of isobutane led to a novel methodology to install *tert*-butyl groups in a very easy and scalable way, with high selectivity (96:4 *tert*-butyl versus isobutyl). Also, activation of ethane was successfully achieved just by cranking up the pressure, which was needed to get ethane into solution, and requiring only minor adjustments to the reaction protocol.”

When the ethane transformation was also wrapped up, the group was ready to take on the final challenge of methane. “Methane possesses the strongest C(sp³)-H bonds known in Nature and we were not sure whether decatungstate would be able to cleave those efficiently,” said Prof. Dr. Noël. He continued: “Methane has been a daunting challenge for many decades, occupying many researchers without much success so far. Typically, cleaving methane’s C(sp³)-H bonds requires extremely high temperatures (> 500 °C) and is only industrially done for a few processes. We reckoned that if methane would work, it would be a big deal.” However, in their first attempts, the group realized that HAT on acetonitrile was prominent, with only traces of the desired methylated product observed.

“We did not expect this outcome, because activation of C-H bonds on acetonitrile should be prevented due to a polarity mismatch,” observed Gabriele, continuing: “We realized that this solvent effect could only be observed when the reactivity of tetrabutylammonium decatungstate (TBADT) is pushed to its limits.”

The presence of this byproduct was suppressed simply by using acetonitrile-*d*₃ as solvent. “In this way the corresponding methylated products could be isolated,” confirmed Prof. Dr. Noël, who concluded: “This method represents an important strategy to convert light alkanes into value-added molecules. Via decatungstate photocatalysis, we could break strong C(sp³)-H bonds at room temperature, avoiding harsh reaction conditions. In addition, it is important to notice that similar transformations typically require organometallic reagents to yield these compounds. Hence, decatungstate photocatalysis literally allowed us to take the clutter out of synthesis. Our laboratory is already working on scaling up this process and improving some minor limitations of our method (e.g. deuterated solvents for methane functionalization).”

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Scheme 2 Selection of the scope obtained with the decatungstate C(sp³)-H functionalization of light hydrocarbons. Standard conditions for the decatungstate C(sp³)-H functionalization of isobutane: olefin (1 equiv, 0.1 M), isobutane (4.3 equiv), TBADT (1.0 mol%), CH₃CN/H₂O (7:1), 10 bar pressure, 60 W of 365 nm LEDs, 4 h reaction time, room temperature. Reported selectivity reflects the *tert*-butyl/*isobutyl* ratio. Standard conditions for the decatungstate C(sp³)-H functionalizations of propane: olefin (1 equiv, 0.1 M), propane (4.1 equiv), TBADT (1.0 mol%), CH₃CN/H₂O (7:1), 10 bar pressure, 60 W of 365 nm LEDs, 4 h reaction time, room temperature. Reported selectivity reflects the *isopropyl*/*n*-*propyl* ratio. Standard conditions for the decatungstate C(sp³)-H functionalizations of ethane: olefin (1 equiv, 0.1 M), ethane (8 equiv), TBADT (2.0 mol%), CH₃CN/H₂O (7:1), 25 bar pressure, 60 W of 365 nm LEDs, 8 h reaction time, room temperature. Standard conditions for the decatungstate C(sp³)-H functionalizations of methane: olefin (1 equiv, 0.02 M), methane (20 equiv), TBADT (5.0 mol%), CD₃CN/H₂O (7:1), 45 bar pressure, 150 W of 365 nm LEDs, 6 h reaction time, room temperature.

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About the authors



Dr. G. Laudadio

His research interests focus on novel synthetic methodologies combining continuous-flow microreactor technology with electrochemistry and photochemistry.

Gabriele Laudadio was born in 1991 near Pescara, Italy. In 2016 he received his M.Sc. degree in organic chemistry at the University of Pisa (Italy). His Master's thesis was conducted under the supervision of Professor A. Carpita. He recently obtained his Ph.D. in chemistry with *Cum Laude* at the Eindhoven University of Technology (The Netherlands) in the group of Prof. Dr. Timothy Noël. His research inter-



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most recently the VIDI award (2015), the Thieme Chemistry Journals Award (2016), the DECHEMA prize (2017) and the Hoogewerff Jongerenprijs 2019. He is the editor in chief of *Journal of Flow Chemistry*.

Timothy Noël was recently promoted to Full Professor at the University of Amsterdam (The Netherlands) where he is the Chair of Flow Chemistry. His research interests range from organic chemistry to chemical engineering and encompass more specifically flow chemistry, organic synthesis and synthetic catalytic methodology development. His work has received several awards, including