ORGANIC CHEMISTRY C(sp³)–H functionalizations of light hydrocarbons using decatungstate photocatalysis in flow

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Direct activation of gaseous hydrocarbons remains a major challenge for the chemistry community. Because of the intrinsic inertness of these compounds, harsh reaction conditions are typically required to enable $C(sp^3)$ -H bond cleavage, barring potential applications in synthetic organic chemistry. Here, we report a general and mild strategy to activate $C(sp^3)$ -H bonds in methane, ethane, propane, and isobutane through hydrogen atom transfer using inexpensive decatungstate as photocatalyst at room temperature. The corresponding carbon-centered radicals can be effectively trapped by a variety of Michael acceptors, leading to the corresponding hydroalkylated adducts in good isolated yields and high selectivity (38 examples).

ne of the most challenging reactions in organic synthesis is the selective functionalization of C(sp³)-H bonds that lack activation by proximal functional groups (1). The conversion of light alkanes to high-value added chemicals has especially been a key objective for the synthetic community in the past decades, yet with limited success so far (2-4). Up to now, strategies to introduce such alkyl fragments into organic scaffolds necessitate prefunctionalization of the hydrocarbons to increase their reactivity (Fig. 1A). Volatile alkanes are typically converted into alkyl electrophiles through halogenation by using chlorine or bromine gas at elevated temperatures (>500°C) or by using light activation (5, 6). These radical chain processes result in low-yielding and unselective transformations, with demands for subsequent energy-intensive and elaborate purification and recycling processes [for the effluent guidelines in the chlorine and chlorinated hydrocarbon manufacturing industry, see (7)]. Despite the apparent drawbacks, these classical halogenation strategies are being carried out on a multi-metric ton scale to prepare a variety of halogenated compounds that are key for the production of most pharmaceuticals, agrochemicals, materials, and other industrial chemicals (8). In synthetic organic chemistry, alkyl halides are widely used as electrophiles in nucleophilic substitution reactions or serve as substrates for elimination reactions to install double bonds regioselectively. Furthermore, alkyl halides

*These authors contributed equally to this work. **†Corresponding author. Email: t.noel@tue.nl** can be easily converted into organometallic reagents, which can be engaged as nucleophiles in a variety of transition metal-catalyzed C-C bond forming reactions (9).

A general synthetic strategy that enables the selective and direct activation of a diverse set of light hydrocarbons under mild reaction conditions remains a challenge, suffering from at least one drawback with regard to substrate scope (10-13), practicality, and selectivity (14). The development of such a transformation would be particularly useful, given the broad availability and the inexpensive nature of these starting materials. Furthermore, the reduction in synthetic steps would allow for streamlined reaction sequences and decreased waste generation. However, we reasoned that two fundamental problems needed to be addressed to succeed: First, a suitable transformation would require the selective cleavage of very strong aliphatic C-H bonds [bond dissociation energy (BDE) = 96.5 to 105 kcal/mol] (Fig. 1B), and second, the handling of these gaseous alkanes presents several technological challenges to bring them into close proximity with a suitable catalyst and reaction partner.

Seeking to address these challenges, we wondered if a photoexcited decatungstate anion (*[$W_{10}O_{32}$]^{4–}) could sunder effectively the strong and nonactivated C-H bonds of light alkanes (Fig. 1A). $W_{10}O_{32}^{4-}$ is a versatile and inexpensive polyoxometalate-based hydrogen atom transfer (HAT) photocatalyst that can abstract hydrogen atoms from C(sp³)-H fragments upon activation by near-ultraviolet (UV) light irradiation (~365 nm) (15-18). The resulting carbon-centered radicals are nucleophilic and might be readily engaged in C-C bond forming reactions, thereby effectively bypassing the requirement for more-elaborate reaction strategies while expanding the synthetic toolbox of available alkyl reagents. To date, $W_{10}O_{32}^{4-}$ photocatalysis has enabled a number of synthetically useful C(sp³)-H functionalizations, including oxidations (19, 20), fluorinations (21), arylations (22), and other C-C bond formations (23). However, because of the gaseous nature and the low solubility of light alkanes in organic solvents, we reasoned that the use of flow technology is indispensable to facilitate the gas-liquid decatungstatemediated processes (Fig. 1C) (24). The short length scales in microflow reactors (typically <1-mm optical path) provide a homogeneous irradiation of the entire reaction medium. allowing for the efficient generation of alkyl radicals (25). Furthermore, by increasing the pressure in the reactor through use of operationally simple back-pressure regulators, the gaseous alkanes can be forced into the liquid phase, increasing the odds of C(sp³)-H bond activation through decatungstate photocatalysis (26). Finally, flow processing of these combustible gases can be done safely in microreactors, and the conditions can be readily scaled (27, 28).

Among all volatile alkanes, methane is the hardest one to activate because of high BDE of these C-H bonds (BDE = 105 kcal/mol) (Fig. 1B) (29). However, if we can successfully split methane bonds with decatungstate HAT photocatalysis, cleaving the C-H bond in ethane (BDE = 101 kcal/mol) and other volatile aliphatic feedstock materials, such as propane (BDE = 99 kcal/mol) and isobutane (BDE = 96.5 kcal/ mol), should be within reach. Indeed, we carried out trapping experiments with TEMPO (tetramethylpiperidine-1-oxyl), a stable aminoxyl radical, and the trapped adducts of methane, ethane, propane, and isobutane gave credence to the feasibility of our approach (Fig. 1D). Notably, because of the stability of the generated radical and the lower BDE of the C-H bond, high selectivity was observed for the formation of secondary and tertiary C(sp³)-O bonds from propane and isobutane, which is in contrast to a recently reported HAT approach using alkoxy radicals (14).

We began our investigation into the proposed C(sp³)-H functionalization of light hydrocarbons by exposing isobutane and benzylidenemalononitrile in the presence of tetrabutylammonium decatungstate (TBADT) in acetonitrile:H₂O (7:1), which provides both good solubility and good reactivity of the photocatalyst, to UV-A light [365-nm light-emitting diodes (LEDs), 60 W]. For a number of substrates, limited solubility was observed upon addition of water. However, this could be circumvented by carrving out the reactions in neat acetonitrile. Furthermore, acetonitrile, despite the relatively low BDE (96 to 97 kcal/mol) of its C-H bonds (30), is also inert under the given HAT reaction conditions. This can be attributed to a polarity mismatch between decatungstate and the $C(sp^3)$ -H bonds in acetonitrile. All the experiments were carried out in a standardized, commercially available Vapourtec UV-150 photochemical flow reactor, which should enable reproducibility of the results. After careful

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Fig. 1. Decatungstate enables the direct C(sp³)–H activation of light hydrocarbons. (A) Photocatalytic scission of strong C(sp³)–H bonds of volatile alkanes allows us to generate nucleophilic alkyl radicals and to bypass the use of halogenated alkanes or organometallic reagents. (B) BDE of some common gaseous alkanes (35). (C) Conversion of gaseous alkanes into functionalized alkanes by blending TBADT photocatalysis, the use of gases, and flow chemistry. liq., liquid. (D) TEMPO trapping experiments showing the feasibility of the outlined strategy of HAT activation of aliphatic substrates (results obtained with GC-MS). Me, methyl.

optimization of the reaction conditions (supplementary materials), we observed that the targeted compound 1 could be obtained in an excellent isolated yield of 91% by using 1 mol % of TBADT as a HAT photocatalyst (Fig. 2). Critical to the success of the reaction was the increase of the reaction pressure up to 10 bar, which results in a complete liquefaction of the gas and thus avoids gas-to-liquid mass transfer limitations. Moreover, 4.3 equivalents of isobutane were used to obtain optimal yields, whereas larger amounts did not lead to a further yield improvement (supplementary materials). Furthermore, classical conjugate addition strategies require transition metal catalysts and prefunctionalized nucleophilic organometallic reagents (31). The stepwise and lengthy procedure to prepare such nucleophilic reagents stands in marked contrast to the single-step HAT activation of gaseous alkanes as shown herein.

With optimized reaction conditions in hand, we next explored the scope of the transformation (Fig. 2). A variety of electronically distinct benzylidenemalononitriles (**1** to **7**) could serve as highly efficient radical traps for the photocatalytically generated carbon-centered radicals, yielding the targeted hydroalkylated compounds in excellent isolated yields (82 to 93%) and very good selectivity for the installment of a tertiary butyl group [tBu versus isobutyl (iBu): ~96:4]. Halogenated benzylidene malononitrile substrates (3 to 5) can be engaged in the transformation as well, providing requisite handles to be converted into diverse organic molecules by using classical cross-coupling strategies. Methyl trans-α-cyanocinnamate is another efficient substrate for scavenging tertiary butyl radicals, yielding the targeted compound 8 in 85% isolated yield. Whereas for isobutyl radicals both diastereomers were formed in equal amounts, the trapping of the more sterically demanding tertiary butyl radical resulted in a relatively high diastereomeric ratio (d.r. = 3.1:1). Other traps, such as triethyl ethylenetricarboxylate, N-phenylmaleimide, and 3-methylene-2-norbornanone, resulted in the formation of synthetically useful building blocks (9 to 11) in good to excellent isolated vields (71 to 90%) and excellent selectivity in favor of the tertiary butyl-appended molecules. Complete endoselectivity was observed for compound 11, which is consistent with a hydrogen back-donation from the reduced photocatalyst from the less hindered side of the norbornane moiety (Fig. 3A). We did not observe any significant amount of by-products as detected by gas chromatography-mass spectrometry (GC-MS) analysis (<2%) for a variety of reasons. C-H abstraction from the starting Michael acceptors is not a competitive process, because in most cases, no labile hydrogens are present. Furthermore, C-H cleavage in the alkylated products did not lead to another C-H activation event, in part because of a polarity mismatch (15). TBADT* has a marked preference for the abstraction of nucleophilic hydrogens and avoids dissociating electrophilic C-H bonds such as those present in α -position to the electron-withdrawing functional groups. Moreover, despite the presence of labile benzylic hydrogens in some of the products, no byproducts are generated, because of a combination of the voluminous size of TBADT and the steric hindrance at those benzylic positions (15). Finally, the presence of an excess of gaseous alkanes prevents hydrogen abstraction from any other organic compound in the reaction mixture.

This protocol was also found to enable the efficient activation of propane, a key constituent



Fig. 2. Scope of the decatungstate C(sp³)–H functionalizations of light hydrocarbons. All yields are those of isolated products (average of two runs). The reported selectivities are determined with GC-MS. [*]Standard conditions for the decatungstate C(sp³)–H functionalizations 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-hour reaction time, room temperature. Reported selectivity reflects the *tBuriBu* 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-hour reaction time, room temperature. Reported selectivity reflects the *i*Pr:*n*Pr 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-hour 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-hour reaction time, room temperature. [¶]C_(Michael acceptor) = 0.05 M. [#]Solvent: neat CH₃CN. [**]Solvent: neat CD₃CN. Et, ethyl.

Α

В Proposed mechanistic rationale Kinetic experiment - influence of light source intensity and catalyst loading 100 Stop flow 2 mol% TBADT (36 W) • Flow 0.5 mol% TBADT (60 W) Flow 1 mol% TBADT (60 W) Flow 2 mol% TBADT (60 W) ٠ 80 W10032 2 hydroge GC Yield (%) 60 back-donation W₁₀O H⁺[W₁₀O₃₂]⁵ 40 coniugate hydrogen addition om transfer ١R R 20 vO trapped by TEMPC

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Fig. 3. Proposed mechanism of the decatungstate C(sp³)–H functionalizations of light hydrocarbons. (A) Proposed mechanistic rationale based on our observations. **(B)** Importance of photon flux and catalyst loading for the effectiveness of the decatungstate C(sp³)–H functionalization of propane.

of liquid petroleum gas. Propyl radicals could be scavenged by a variety of Michael acceptors (12 to 22), affording the targeted hydroalkylated compounds in good to excellent isolated yields (73 to 92%). A high selectivity was obtained for the isopropyl derivative (*i*Pr), with selectivities similar to those obtained in the TEMPO trapping experiments [iPr versus *n*-propyl (*n*Pr): ~85:15] (Fig. 1D). The high selectivity in the C-H cleavage is notable despite the low difference in BDE between secondary and primary hydrogens (99 versus 101 kcal/mol) and despite the unfavorable relative abundance (six primary hydrogens versus two secondary ones). With methyl trans- α -cyanocinnamate as the substrate, a significant diastereomeric induction was observed for the trapping of the isopropyl radical (d.r. = 2.7:1 versus d.r. = 1:1 for n-propyl), showcasing the significance of sterical hindrance in the observed selectivity.

Light Alkanes

(with R = H or CH₃)

Another notable gaseous hydrocarbon is ethane, which is isolated from natural gas or obtained as a petrochemical by-product of petroleum refining. It is mainly used as a feedstock for ethylene production, required for the fabrication of polyethylene, which accounts for 34% of the total plastics market. Similar to isobutane and propane, ethane could be engaged in the developed $C(sp^3)$ –H activation protocol using 2 mol % of TBADT and 25 bar of pressure to liquefy the gaseous hydrocarbon. Good isolated yields (62 to 87%) were obtained for a diverse set of hydroethylated compounds (**23** to **33**).

Finally, we turned our attention to the activation of methane, one of the most abundantly available carbon-based feedstocks, using this decatungstate-enabled HAT protocol. Al-

though such a strategy would require cleaving the strongest $C(sp^3)$ -H bond (BDE = 105 kcal/ mol), small changes in the reaction protocol (45-bar pressure and 5.0 mol % TBADT) allowed us to obtain synthetically useful amounts of the corresponding adducts (34 to 38, 38 to 48%) in only 6 hours of residence time. Because of the substantially weaker C-H bond of acetonitrile (BDE = 93 kcal/mol) compared with that of methane, the innate selectivity of decatungstate, imparted by the electrophilic nature of its excited state, could be overruled, and substantial amounts of product derived from CH₃CN activation were observed as well (supplementary materials). This problem could, however, effectively be overcome by using d3acetonitrile as a solvent. Investigations to replace this rather exotic solvent with a cheaper and greener alternative are currently ongoing in our laboratory.

A plausible mechanism for the decatungstate C(sp³)-H functionalizations of light hydrocarbons is outlined in Fig. 3A. Upon absorption of UV-A light, decatungstate reaches a singlet excited state, which rapidly relaxes to the actual reactive state, wO (18). The reactivity of wO originates from the formation of highly electrophilic oxygen centers, which can abstract hydrogen atoms yielding the desired carbon-centered radicals. The power of the light source in combination with a suitable catalyst loading is extremely relevant in photochemical processes (32), and this is especially true for the challenging transformation reported herein. As can be seen from Fig. 3B, the activation of propane is particularly slow when a strip of 32-W UV-A LEDs was used. However, the reaction can be boosted by using 60-W UV-A LEDs, requiring only 4 hours to reach full conversion. For more-challenging transformations, such as the activation of methane, an even stronger light source of 150 W was required to coax the $C(sp^3)$ -H functionalization process. The nucleophilic carbon-centered radicals subsequently undergo a conjugate addition onto a suitable Michael acceptor. The carbon-centered radicals could be trapped with TEMPO, providing isomeric ratios for propane and isobutane similar to those observed in the final products (Fig. 1D). The catalytic cycle is finally closed by hydrogen back-donation, which affords the targeted hydroalkylated product.

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3

Time (h)

Given the straightforward preparation (33) of the photocatalyst and the starting materials and the mild reaction conditions, we believe that the corresponding processes outlined herein can be considered ideal from the vantage point of feedstock upgrading. The ability to directly engage gaseous hydrocarbons as coupling partners in C-C coupling reactions removes the requirement of prefunctionalization and increases the atom efficiency of this important class of transformations. Whereas the throughput of a single microreactor is negligible from a production standpoint, the use of intensified reactors, such as a photo-spinning disk reactor, should enable higher production capacities (34).

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SUPPLEMENTARY MATERIALS

science.sciencemag.org/content/369/6499/92/suppl/DC1 Materials and Methods Figs. S1 to S13 Tables S1 to S10 NMR Data References (36-49)

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Using hydrocarbons as reagents

Adding small alkyl groups to complex molecules usually relies on alkyl halide reagents. Laudadio *et al.* now report a convenient method to add ethane and propane directly across conjugated olefins with no prefunctionalization or byproducts (see the Perspective by Oksdath-Mansilla). The C–H bond scission in this hydroalkylation is accomplished by a decatungstate photocatalyst that also acts as a hydrogen atom transfer agent to complete the process. The reaction, optimized under flow conditions, works with methane as well, albeit with lower efficiency. *Science*, this issue p. 92; see also p. 34

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