C−H Functionalization

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Selective C(sp^3)−H Aerobic Oxidation Enabled by Decatungstate Photocatalysis in Flow

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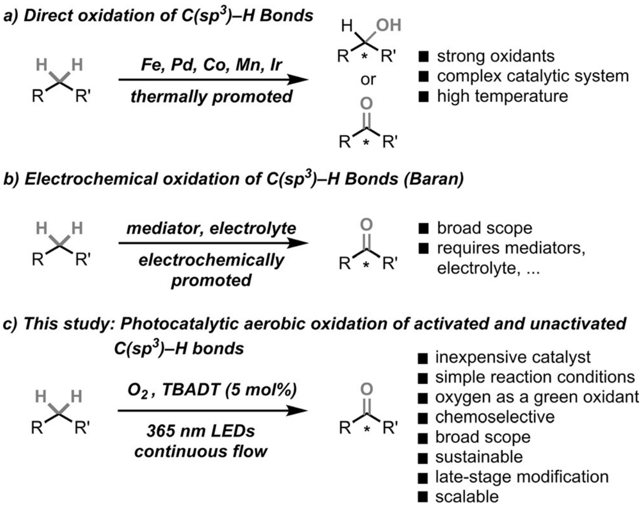
Abstract: *A mild and selective C(sp^3)−H aerobic oxidation enabled by decatungstate photocatalysis has been developed. The reaction can be significantly improved in a microflow reactor enabling the safe use of oxygen and enhanced irradiation of the reaction mixture. Our method allows for the oxidation of both activated and unactivated C−H bonds (30 examples). The ability to selectively oxidize natural scaffolds, such as (−)-ambroxide, pregnenolone acetate, (+)-sclareolide, and artemisinin, exemplifies the utility of this new method.*

An essential part of modern synthetic chemistry is the development of catalytic methods for C−H bond functionalization only at specific sites within a molecule. In recent years, the field has witnessed great progress with regard to metal-catalyzed distal carbon–carbon bond-forming reactions.[1] Typically, directing groups are used to navigate the metal to the appropriate position to facilitate C−H bond cleavage.[2]

In contrast, analogous C−H oxidation processes appear to be far more complicated and are only available to a limited extent, making it a challenging field in which further improvements are highly desired.[3] Promising results have been obtained using catalytic systems based on iron,[4] palladium,[5] cobalt,[6] manganese,[7] or iridium (Scheme 1 a).[8] Also, biocatalytic approaches have been reported that enable C−H oxidation processes with high substrate specificity and chemoselectivity.[9] Unfortunately, most—if not all—of these strategies suffer from scope limitations, the use of high loadings of expensive and complex catalysts, and the need for tailored strong oxidants, for example, methyl(trifluoromethyl)dioxirane (TFDO).[10] Furthermore, in order to enhance the selectivity of these procedures, directing groups are generally needed to steer the metal to the desired locus of action.



Scheme 1. a) Transition-metal-catalyzed C(sp^3)−H oxidation strategies. b) Electrochemical C(sp^3)−H oxidation. c) Our strategy for selective C(sp^3)−H aerobic oxidation enabled by decatungstate photocatalysis in flow.

Another approach to enable C−H bond oxidation is through hydrogen-atom transfer (HAT), which can be promoted either thermally,[11] photochemically,[12] or electrochemically (Scheme 1 b).[3d,13] Following this strategy, hydrogen atoms can be abstracted to produce highly reactive radical species, which are subsequently trapped in a wide variety of synthetically useful transformations. This synthetic pathway can be considered appealing, since the transformation is promoted by the use of photons or electrons as traceless reagents, thus simplifying the catalytic systems involved and reducing the environmental impact of the transformation itself.[12,13b]

Among the different reported photocatalysts, decatungstate (DT) has proved to be a versatile and inexpensive HAT catalyst which can readily perform hydrogen abstraction on C(sp^3)−H fragments upon activation by irradiation with near-ultraviolet light.[14] This strategy allowed for the construction of numerous C−C,[15] C−Si,[16] C−N,[17] and C−F[18] bonds.[15a,19] Intrigued by these seminal reports, we wondered if DT

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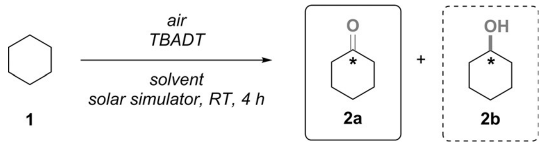
catalysis could be used to effect selective C(sp^3)−H aerobic oxidation. Even though the DT-catalyzed direct oxidation of aliphatic compounds has been explored in the past from a theoretical point of view,[14c,20,21] no synthetically useful methodology was developed so far. We recognized that oxygen as a green oxidant would be needed to highlight the sustainable nature of our methodology. However, direct use of the simple, green, and effective oxidant molecular oxygen is discouraged because of its associated safety hazards and limited solubility in organic solvents, which often leads to mass-transfer limitations. In the past few years, continuous-flow microreactor technology has been hailed as an enabling technology to overcome such limitations, as well as providing means to scale operationally complex transformations, for example, multiphase reactions,[22] hazardous processes,[23] and photochemical transformations,[24] among others.[25] As described below, we present a simple, selective, and synthetically useful decatungstate-photocatalytic aerobic oxidation of C(sp^3)−H bonds using continuous-flow technology to overcome mass- and photon-transfer limitations and safety hazards (Scheme 1 c).

As a model system, we selected cyclohexane as a substrate containing unactivated C(sp^3)−H bonds and used tetrabutylammonium decatungstate (TBADT) as the HAT photocatalyst and oxygen as the oxidant (Table 1). Initial reaction optimization was carried out in a cylindrical batch reactor, which allows maximization of the gas–liquid interfacial area and irradiation surface in batch.[20a] The reaction mixture was subjected to irradiation generated by a solar simulator. A mixture of cyclohexanone and cyclohexanol was obtained in 37% overall yield when the reaction was carried out in acetonitrile (Table 1, entry 1). Other solvent systems proved less effective, partially because of the limited solubility of TBADT (Table 1, entry 2; see Table S4 in the Supporting Information). By adding an acid to the reaction mixture, the reaction rate could be significantly enhanced, and the selectivity towards cyclohexanone was increased (Table 1, entries 3–5).[26] A survey of different acids (see Tables S2 and S3) revealed that hydrochloric acid was optimal for the desired transformation. In contrast, the addition of a base completely inhibited the oxidation process, most likely owing to the instability of the decatungstate ion under basic conditions.[26] The use of 2 mol% of TBADT appeared to be optimal in terms of catalyst loading (Table 1, entries 4, 6, and 7). No reaction occurred in the absence of TBADT (Table 1, entry 8), thus confirming the photocatalytic nature of our transformation. Finally, increasing the reaction time from 4 to 6 h improved the reaction conversion (Table 1, entry 9).

Table 1: Reaction optimization of the C(sp^3)−H oxidation enabled by decatungstate photocatalysis in batch.[a]

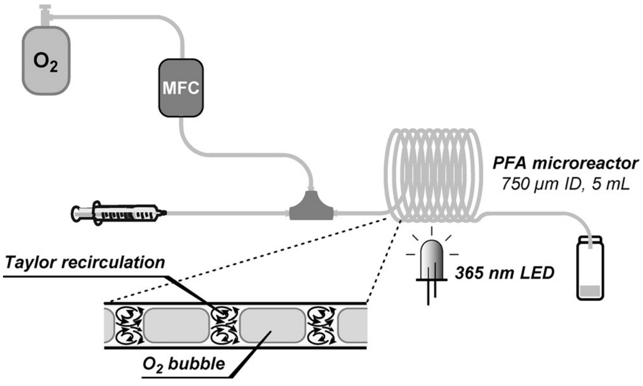


Entry	TBADT (mol%)	Solvent	Yield [%][b] 2a	Yield [%][b] 2b
1	2	CH_3CN	23	14
2	2	acetone/H_2O (4:1)	13	9
3	2	CH_3CN/1 M HCl (1:1)	42	11
4	2	CH_3CN/1 M HCl (2.5:1)	53	6
5	2	CH_3CN/1 M H_2SO_4 (2.5:1)	42	11
6	0.5	CH_3CN/1 M HCl (2.5:1)	36	6
7	5	CH_3CN/1 M HCl (2.5:1)	47	4
8	0	CH_3CN/1 M HCl (2.5:1	0	0
9[c]	**2**	**CH_3CN/1 M HCl (2.5:1)**	**61**	**7**

[a] Reaction conditions: 1.0 mmol of cyclohexane, 7 mL of solvent, 4 h. [b] The yield was determined by GC–MS with an internal standard. [c] Reaction time: 6 h.

Despite the promising results obtained in batch, full conversion could not be reached. We surmised that the hampered diffusion of oxygen into the liquid reaction mixture and the limited light penetration were causing the lower efficiency of the batch reactor.[27] Furthermore, the scaling photochemical reaction conditions is known to be very challenging in batch. Hence, we constructed a continuous-flow photomicroreactor consisting of a 750 μm inner-diameter PFA capillary and LED irradiation.[28] The liquid reagents were infused using a syringe pump and merged with an oxygen stream delivered by a mass flow controller (MFC). This setup resulted in the formation of a segmented flow regime, in which ideal mixing occurs through Taylor recirculation patterns (see Table 2).[29] The choice of the appropriate light source is crucial (Table 2, entries 1–3), as optimal results were obtained with 365 nm LEDs, which matched the absorption characteristics of TBADT. Interestingly, higher

Table 2: Reaction optimization of the C(sp^3)−H oxidation enabled by decatungstate photocatalysis in flow.



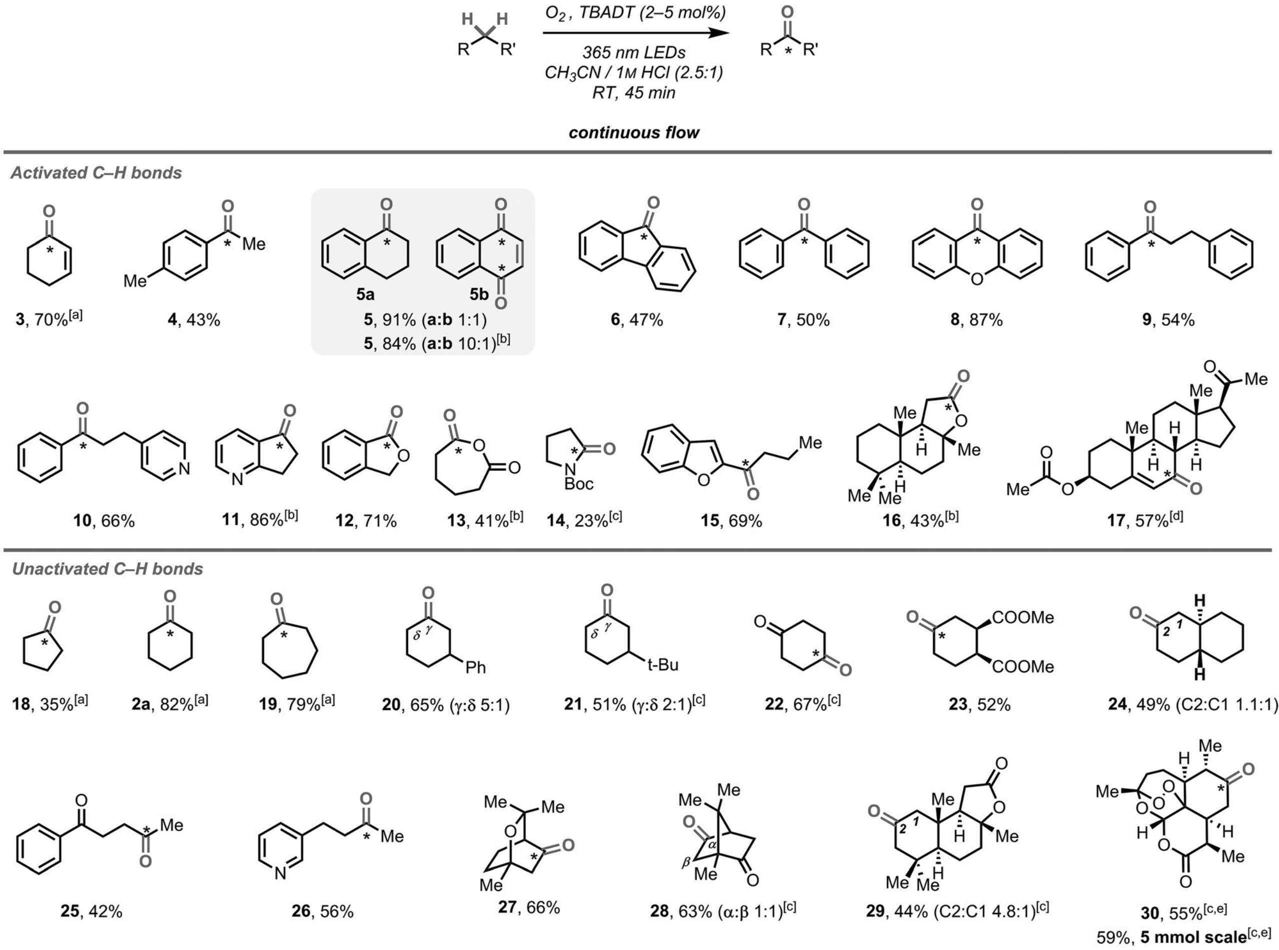
Entry[a]	t_r [min]	V_r [mL]	Yield [%][b] 2a	Yield [%][b] 2b
1[c]	15	3	0	0
2[d]	15	3	31	5
3	15	3	49	9
4[e]	15	3	44	10
5	35	3	67	3
6	45	5	73	7
7[f]	**45**	**5**	**81**	**9**

[a] Reaction conditions: 1.0 mmol of cyclohexane, 2 mol% of TBADT, 365 nm LEDs as the light source, CH_3CN/1 M HCl (2.5 :1, 7 mL). [b] The yield was determined by GC–MS with hexafluorobenzene as an internal standard. [c] 450 nm LEDs were used as the light source. [d] 400 nm LEDs were used as the light source. [e] A back-pressure regulator (5.2 bar) was used. [f] The reaction was carried out with 5 mol% of TBADT.

oxygen pressures did not lead to an increase in performance, thus suggesting an optimal oxygen concentration in the liquid phase at atmospheric pressure (Table 2, entry 4; see also Table S8). Longer residence times up to 45 min resulted in excellent yields (Table 2, entries 5 and 6). A further improvement was observed when the catalyst loading was increased to 5 mol %, with the formation of the target product in 90 % combined yield (Table 2, entry 7).

Having established optimal flow conditions, we next set out to evaluate the scope of the photocatalytic C(sp^3)−H oxidation for the conversion of substrates containing activated sp^3-hybridized carbon atoms into the corresponding ketones (Scheme 2). Our method enabled the selective oxidation of allylic positions in good yield (product **3**, 70 %), as well as benzylic positions (products **4**–**11**). Interestingly, tolyl C−H bonds were left untouched in the presence of longer aliphatic chains (product **4**), thus highlighting the mild nature of this oxidation method.[30] Tetrahydronaphthalene could be oxidized, yielding the targeted product 1-tetralone (**5a**) along with the overoxidized product naphthoquinone (**5b**; 91 % yield, 1:1 selectivity). A higher selectivity for 1-tetralone (**5a**) could be obtained in the absence of hydrochloric acid, as the rate of overoxidation is reduced. Another interesting selective oxidation was observed at benzylic positions in the presence of pyridine moieties (products **10** and **11**).[15b] Such distal oxidation patterns can be explained by the electron-poor nature of pyridines.[15b] Also, α-alkoxy C−H bonds were oxidized effectively (products **12** and **13**). When Boc-protected pyrrolidine was subjected to our reaction conditions, selective oxidation occurred at the α-C−H bond (Shono-type oxidation) in moderate yield (product **14**, 23 %). Other heterocycles were tolerated as well, such as alkyl-substituted benzofuran derivatives (product **15**, 69 %). The capacity of this method to selectively modify natural scaffolds was demonstrated by the selective oxidation of (−)-ambroxide and pregnenolone acetate in synthetically useful yields (products **16** and **17**).

Having established a broadly applicable oxidation protocol for activated carbon atoms, we turned our attention to applying this method to the selective oxidation of unactivated C(sp^3)−H bonds. Smaller cycloalkanes, such as cyclopentane, could be oxidized in low yields (product **18**, 35 %), whereas larger cycloalkanes were converted into the corresponding ketones in excellent yield (products **2a**, 82 % and **19**, 79 %). In



Scheme 2. Scope of the C(sp^3)−H oxidation enabled by decatungstate photocatalysis in flow. The oxidation site is indicated in gray and with an asterisk, unless otherwise noted. [a] The yield was determined by GC. [b] The reaction was carried out in the absence of 1 M HCl. [c] The reaction was carried out with CH_3CN/dichloromethane (2.5:1) as the solvent. [d] The reaction was carried out with a residence time of 1.5 h. Boc = *tert*-butoxycarbonyl.

substituted cyclohexanes, both distal positions γ and δ were successfully oxidized, with a preference for the γ position (products **20** and **21**). Ester and ketone functional groups on the cyclohexane ring were well tolerated (products **22** and **23**). Interestingly, the only observed oxidation product for cyclohexanone was 1,4-cyclohexanedione (**22**, 67 %) resulting from oxidation at the δ position.[24] In the case of *trans*-decalin, both the 2- and the 1-position were oxidized in a 1.1:1 ratio (product **24**, 49 %). Distal C−H bonds were selectively oxidized when the benzylic position was either unavailable (product **25**, 42 %) or deactivated (product **26**, 56 %). Biologically active compounds, such as eucalyptol (product **27**, 66 %) and (1*R*)-(+)-camphor (product **28**, 63 %) were also successfully oxidized. In the case of eucalyptol, the less sterically hindered position was selectively targeted, which can probably be attributed to the large size of the tungstate cluster.[31] Another proof of this steric-hindrance-driven selectivity was observed in the oxidation of (+)-sclareolide, in which the oxidation occurred preferentially at the C2 position (product **29**, 44 %).[3d,32] Finally, the utility of our oxidation protocol was convincingly demonstrated by the scalable oxidation of another complex compound, artemisinin, to its natural derivative artemisitone-9 (**30**) in good yield (59 %, 5 mmol scale).

In conclusion, a photochemical C(sp^3)−H oxidation method was successfully developed. The method relies on the use of molecular oxygen as a green and sustainable oxidant and inexpensive and commercially available TBADT as the photocatalyst. In order to accelerate the reaction, an operationally simple continuous-flow setup was designed, making this transformation safe and readily scalable. The method enabled the C−H oxidation of both activated and unactivated aliphatic bonds (30 examples). These examples include natural scaffolds, such as (−)-ambroxide, pregnenolone acetate, (+)-sclareolide, and artemisinin, thus exemplifying the efficacy of this method.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: aerobic oxidation · C(sp^3)−H functionalization · decatungstate · flow chemistry · photocatalysis

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[1] a) J. He, M. Wasa, K. S. L. Chan, Q. Shao, J. Q. Yu, *Chem. Rev.* **2017**, *117*, 8754–8786; b) F. Roudesly, J. Oble, G. Poli, *J. Mol. Catal. A* **2017**, *426*, 275–296; c) T. Gensch, M. N. Hopkinson, F. Glorius, J. Wencel-Delord, *Chem. Soc. Rev.* **2016**, *45*, 2900–2936; d) J. F. Hartwig, *J. Am. Chem. Soc.* **2016**, *138*, 2–24; e) A. Dey, S. Agasti, D. Maiti, *Org. Biomol. Chem.* **2016**, *14*, 5440–5453; f) T. Newhouse, P. S. Baran, *Angew. Chem. Int. Ed.* **2011**, *50*, 3362–3374; *Angew. Chem.* **2011**, *123*, 3422–3435; g) T. Lyons, M. Sanford, *Chem. Rev.* **2010**, *110*, 1147–1169.

[2] a) S. Bag, R. Jayarajan, R. Mondal, D. Maiti, *Angew. Chem. Int. Ed.* **2017**, *56*, 3182–3186; *Angew. Chem.* **2017**, *129*, 3230–3234; b) U. Dutta, A. Modak, B. Bhaskararao, M. Bera, S. Bag, A. Mondal, D. W. Lupton, R. B. Sunoj, D. Maiti, *ACS Catal.* **2017**, *7*, 3162–3168; c) Z. Zhang, K. Tanaka, J. Q. Yu, *Nature* **2017**, *543*, 538–542; d) N. Hofmann, L. Ackermann, *J. Am. Chem. Soc.* **2013**, *135*, 5877–5884; e) R. J. Phipps, M. J. Gaunt, *Science* **2009**, *323*, 1593–1598.

[3] a) M. L. Condakes, K. Hung, S. J. Harwood, T. J. Maimone, *J. Am. Chem. Soc.* **2017**, *139*, 17783–17786; b) V. Dantignana, M. Milan, O. Cussó, A. Company, M. Bietti, M. Costas, *ACS Cent. Sci.* **2017**, *3*, 1350–1358; c) R. R. Karimov, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2017**, https://doi.org/10.1002/anie.201710330; *Angew. Chem.* **2017**, https://doi.org/10.1002/ange.201710330; d) Y. Kawamata, M. Yan, Z. Liu, D. H. Bao, J. Chen, J. T. Starr, P. S. Baran, *J. Am. Chem. Soc.* **2017**, *139*, 7448–7451; e) M. C. White, *Science* **2012**, *335*, 807–809.

[4] a) T. Nanjo, E. C. De Lucca, M. C. White, *J. Am. Chem. Soc.* **2017**, *139*, 14586–14591; b) B. Chandra, K. K. Singh, S. Sen Gupta, *Chem. Sci.* **2017**, *8*, 7545–7551; c) S. E. Ammann, W. Liu, M. C. White, *Angew. Chem. Int. Ed.* **2016**, *55*, 9571–9575; *Angew. Chem.* **2016**, *128*, 9723–9727; d) P. E. Gormisky, M. C. White, *J. Am. Chem. Soc.* **2013**, *135*, 14052–14055; e) M. S. Chen, M. C. White, *Science* **2007**, *318*, 783–787.

[5] a) J. N. Jaworski, S. D. McCann, I. A. Guzei, S. S. Stahl, *Angew. Chem. Int. Ed.* **2017**, *56*, 3605–3610; *Angew. Chem.* **2017**, *129*, 3659–3664; b) L. V. Desai, K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2004**, *126*, 9542–9543.

[6] a) D. P. Hruszkewycz, K. C. Miles, O. R. Thiel, S. S. Stahl, *Chem. Sci.* **2017**, *8*, 1282–1287; b) N. Sauermann, T. Meyer, C. Tian, L. Ackermann, *J. Am. Chem. Soc.* **2017**, *139*, 18452–18455.

[7] G. Olivo, G. Farinelli, A. Barbieri, O. Lanzalunga, S. Di Stefano, M. Costas, *Angew. Chem. Int. Ed.* **2017**, *56*, 16347–16351; *Angew. Chem.* **2017**, *129*, 16565–16569.

[8] E. M. Simmons, J. F. Hartwig, *Nature* **2012**, *483*, 70–73.

[9] a) W. Zhang, B. O. Burek, E. Fernández-Fueyo, M. Alcalde, J. Z. Bloh, F. Hollmann, *Angew. Chem. Int. Ed.* **2017**, *56*, 15451–15455; *Angew. Chem.* **2017**, *129*, 15654–15658; b) D. Holtmann, M. W. Fraaije, I. W. C. E. Arends, D. J. Opperman, F. Hollmann, *Chem. Commun.* **2014**, *50*, 13180–13200; c) E. Churakova, M. Kluge, R. Ullrich, I. Arends, M. Hofrichter, F. Hollmann, *Angew. Chem. Int. Ed.* **2011**, *50*, 10716–10719; *Angew. Chem.* **2011**, *123*, 10904–10907.

[10] R. Mello, M. Fiorentino, C. Fusco, R. Curci, *J. Am. Chem. Soc.* **1989**, *111*, 6749–6757.

[11] N. Dietl, M. Schlangen, H. Schwarz, *Angew. Chem. Int. Ed.* **2012**, *51*, 5544–5555; *Angew. Chem.* **2012**, *124*, 5638–5650.

[12] L. Capaldo, D. Ravelli, *Eur. J. Org. Chem.* **2017**, 2056–2071.

[13] a) T. Li, T. Kasahara, J. He, K. E. Dettelbach, G. M. Sammis, C. P. Berlinguette, *Nat. Commun.* **2017**, *8*, 390; b) M. Yan, Y. Kawamata, P. S. Baran, *Chem. Rev.* **2017**, *117*, 13230–13319; c) E. J. Horn, B. R. Rosen, Y. Chen, J. Tang, K. Chen, M. D. Eastgate, P. S. Baran, *Nature* **2016**, *533*, 77–81; d) D. H. R. Barton, E. Csuhai, N. Ozbalik, *Tetrahedron* **1990**, *46*, 3743–3752.

[14] a) D. Ravelli, M. Fagnoni, T. Fukuyama, T. Nishikawa, I. Ryu, *ACS Catal.* **2018**, *8*, 701–713; b) S. S. Wang, G. Y. Yang, *Chem. Rev.* **2015**, *115*, 4893–4962; c) C. Tanielian, *Coord. Chem. Rev.* **1998**, *178–180*, 1165–1181; d) D. C. Duncan, T. L. Netzel, C. L. Hill, *Inorg. Chem.* **1995**, *34*, 4640–4646.

[15] a) S. Lazzaroni, D. Ravelli, S. Protti, M. Fagnoni, A. Albini, *C. R. Chim.* **2017**, *20*, 261–271; b) T. Fukuyama, T. Nishikawa, K. Yamada, D. Ravelli, M. Fagnoni, I. Ryu, *Org. Lett.* **2017**, *19*,

6436 – 6439; c) J. J. Murphy, D. Bastida, S. Paria, M. Fagnoni, P. Melchiorre, *Nature* **2016**, *532*, 218 – 222; d) D. Shi, C. He, W. Sun, Z. Ming, C. Meng, C. Duan, *Chem. Commun.* **2016**, *52*, 4714 – 4717.

[16] H. Qrareya, D. Dondi, D. Ravelli, M. Fagnoni, *ChemCatChem* **2015**, *7*, 3350 – 3357.

[17] I. Ryu, A. Tani, T. Fukuyama, D. Ravelli, S. Montanaro, M. Fagnoni, *Org. Lett.* **2013**, *15*, 2554 – 2557.

[18] a) M. B. Nodwell, H. Yang, M. Čolović, Z. Yuan, H. Merkens, R. E. Martin, F. Bénard, P. Schaffer, R. Britton, *J. Am. Chem. Soc.* **2017**, *139*, 3595 – 3598; b) S. D. Halperin, D. Kwon, M. Holmes, E. L. Regalado, L. C. Campeau, D. A. Di Rocco, R. Britton, *Org. Lett.* **2015**, *17*, 5200 – 5203; c) M. B. Nodwell, A. Bagai, S. D. Halperin, R. E. Martin, H. Knust, R. Britton, *Chem. Commun.* **2015**, *51*, 11783 – 11786; d) S. D. Halperin, H. Fan, S. Chang, R. E. Martin, R. Britton, *Angew. Chem. Int. Ed.* **2014**, *53*, 4690 – 4693; *Angew. Chem.* **2014**, *126*, 4778 – 4781.

[19] M. D. Tzirakis, I. N. Lykakis, M. Orfanopoulos, *Chem. Soc. Rev.* **2009**, *38*, 2609.

[20] a) D. Ravelli, S. Protti, M. Fagnoni, *Acc. Chem. Res.* **2016**, *49*, 2232 – 2242; b) W. Wu, Z. Fu, S. Tang, S. Zou, X. Wen, Y. Meng, S. Sun, J. Deng, Y. Liu, D. Yin, *Appl. Catal. B* **2015**, *164*, 113 – 119; c) A. Maldotti, R. Amadelli, V. Carassiti, A. Molinari, *Inorg. Chim. Acta* **1997**, *256*, 309 – 312; d) A. Maldotti, A. Molinari, P. Bergamini, R. Amadelli, P. Battioni, D. Mansuy, *J. Mol. Catal. A* **1996**, *113*, 147 – 157.

[21] Recently, a synthetically useful decatungstate-enabled oxidation method was developed to oxidize remote C–H bonds of aliphatic amines: D. M. Schultz, F. Lévesque, D. A. Di Rocco, M. Reibarkh, Y. Ji, L. A. Joyce, J. F. Dropinski, H. Sheng, B. D. Sherry, I. W. Davies, *Angew. Chem. Int. Ed.* **2017**, *56*, 15274 – 15278; *Angew. Chem.* **2017**, *129*, 15476 – 15480.

[22] H. P. L. Gemoets, Y. Su, M. Shang, V. Hessel, R. Luque, T. Noël, *Chem. Soc. Rev.* **2016**, *45*, 83 – 117.

[23] a) N. Kockmann, P. Thenée, C. Fleischer-Trebes, G. Laudadio, T. Noël, *React. Chem. Eng.* **2017**, *2*, 258 – 280; b) M. Movsisyan, E. I. P. Delbeke, J. K. E. T. Berton, C. Battilocchio, S. V. Ley, C. V. Stevens, *Chem. Soc. Rev.* **2016**, *45*, 4892 – 4928; c) B. Gutmann, D. Cantillo, C. O. Kappe, *Angew. Chem. Int. Ed.* **2015**, *54*, 6688 – 6728; *Angew. Chem.* **2015**, *127*, 6788 – 6832.

[24] a) T. Noël, *Photochemical Processes in Continuous-Flow Reactors*, World Scientific, Singapore, **2017**; b) D. Cambié, C. Bottecchia, N. J. W. Straathof, V. Hessel, T. Noël, *Chem. Rev.* **2016**, *116*, 10276 – 10341.

[25] M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem. Rev.* **2017**, *117*, 11796 – 11893.

[26] I. Texier, J. A. Delaire, C. Giannotti, *Phys. Chem. Chem. Phys.* **2000**, *2*, 1205.

[27] T. Noël, *J. Flow Chem.* **2017**, *7*, 87 – 93.

[28] N. J. W. Straathof, Y. Su, V. Hessel, T. Noël, *Nat. Protoc.* **2016**, *11*, 10 – 21.

[29] T. Noël, Y. Su, V. Hessel, *Top. Organomet. Chem.* **2016**, *57*, 1 – 41.

[30] I. N. Lykakis, M. Orfanopoulos, *Tetrahedron Lett.* **2004**, *45*, 7645 – 7649.

[31] K. Yamada, T. Fukuyama, S. Fujii, D. Ravelli, M. Fagnoni, I. Ryu, *Chem. Eur. J.* **2017**, *23*, 8615 – 8618.

[32] I. Prat, L. Gómez, M. Canta, X. Ribas, M. Costas, *Chem. Eur. J.* **2013**, *19*, 1908 – 1913.

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