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Direct oxidation of C_{sp}^3-H bonds using *in-situ* generated trifluoromethylated dioxirane in flow

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Abstract: A fast, scalable and safer C_{sp}^3-H oxidation of activated and un-activated aliphatic chain can be enabled by methyl(trifluoromethyl)dioxirane (TFDO). The continuous flow platform allows the *in situ* generation of TFDO gas and its rapid reactivity toward tertiary and benzylic C_{sp}^3-H bonds. The process exhibits a broad scope and good functional group compatibility (28 examples, 8 - 99 %). The scalability of this methodology is demonstrated on 2.5 g scale oxidation of adamantane.

The development of new and powerful synthetic methodology for direct C_{sp}^3-H oxidation of un-activated methylene and methine systems is of considerable importance.[1] More specifically, the site-specific C_{sp}^3-H hydroxylation of valuable scaffolds bearing further functional groups is of major current interest for both academia and industry.[2] Over the past decade, direct C_{sp}^3-H oxidation has been investigated using transition metal complexes (Ru, Fe, V, Co, Mn or Ir)[3] and some organocatalysts[4]. Unfortunately, specific challenges including cost of the catalyst, complex synthetic design of the ligand, use of directing group, harsh reaction conditions, functional group incompatibility and site selectivity remain as major drawbacks to the field (Figure 1).[5] Nowadays, new chemical methods such as chemo-catalytic approaches,[6] electrochemical oxidation[7] or photochemical C_{sp}^3-H hydroxylation in pure oxygen[8] or using hydrogen peroxide[9] offer alternative approaches (Figure 1). Nevertheless, regio-selective and stereo-selective oxidation of an un-activated C_{sp}^3-H bond remains a challenging task.

Among existing C_{sp}^3-H oxidation strategies, the use of strong oxidants such as dimethyldioxirane (DMDO, **1**)[10] and methyl(trifluoromethyl)dioxirane (TFDO, **2**)[11], have a long history of success on complex systems without the need for a directing group. Regrettably, their use has been limited due to a long list of disadvantages such as instability, volatility, laborious preparation, safety requirements and scale limitations.[12] Moreover, the use of dioxirane for the direct C_{sp}^3-H oxidation requires precise control of the temperature below 10 °C, a large excess of reagent and long reaction times.[13] For all these reasons, dioxiranes have only been deployed on batch mode and limited to small scale application. Recently, Hilinski published a catalytic batch method for the *in situ* formation of a less volatile but expensive reactive dioxirane (3-butyl-3-(trifluoropentyl)dioxirane, **3**). Specifically, limitations of this method include low temperature (4 °C), long reaction time (72 hours), the use of HFIP (hexafluoro-2-propanol) as co-solvent and iterative addition of reagents to achieve satisfactory yield.[14]

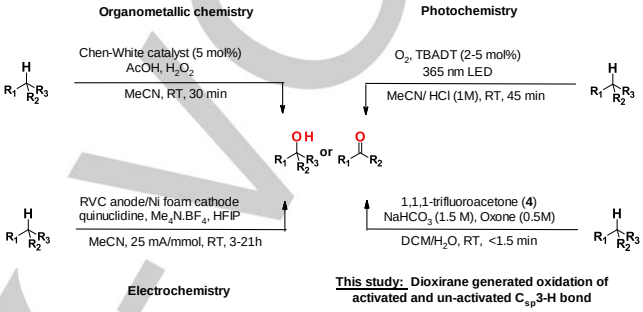

Figure 1. Methods for the direct C_{sp}^3-H oxidation.

In recent years, continuous flow technologies have been recognized as a powerful tool to generate *in situ* hazardous reagents or unstable intermediates with an efficient mass and heat transfer.[15] Additionally, it offers other advantages in making procedures more reproducible and scalable. With an interest in further developing methods for C_{sp}^3-H oxidation, we sought to develop an alternative direct C_{sp}^3-H oxidation using TFDO in a rapid and safer continuous flow process.

A flow set up was investigated using adamantane (**5a**) as a model substrate for the C_{sp}^3-H oxidation (Table 1). A solution of adamantane (0.05 M) in dichloromethane containing 1,1,1-trifluoroacetone (**4**, 1.0 M) was mixed with an aqueous solution of $NaHCO_3$ (1.5 M) and Oxone (0.5 M) in a sequential manner in order to generate *in situ* the TFDO. The desired 1-adamantanol (**6a**) can be efficiently obtained with a conversion of 93 % (Table 1, Entry 1) in an optimal residence time of 80 seconds. A better mass transfer of the reaction mixture was observed with the use of a coil reactor packed with glass beads (425 - 600 µm diameter) compared to the conventional reactor (Table 1, Entry 2 *vs.* Entry 1). Decreasing the amount of the 1,1,1-trifluoroacetone (**4**, 0.5 M) or increasing the quantity of adamantane (**5a**, 0.1 M) have, respectively, an negative effect on the conversion (60 %, Table 1, Entry 3 *vs.* Entry 1) and (62 %, Table 1, Entry 4 *vs.* Entry 1). An excess of $NaHCO_3$ (1.5 M) compared to Oxone (0.5 M) is required to reach higher conversion (Table 1, Entry 5 *vs.* Entry 1), whereas decreasing their flow rates showed inferior results (Table 1, Entry 6 *vs.* Entry 1). Moreover, the reactions proceeded at room temperature, and under pressure, rendering the reaction conditions simple and more reliable than in batch mode[12d] (Table 1, Entry 7 *vs.* Entry 1). Reducing the residence time to 32 seconds, led to a lower conversion (79 %) (Table 1, Entry 8 *vs.* Entry 1).

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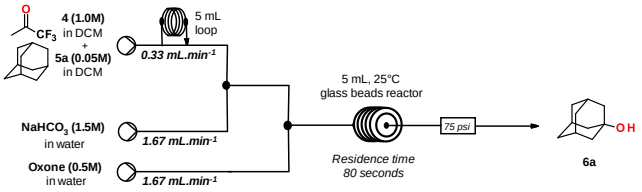
Finally, the use of the less volatile 1,1,1-trifluorobutanone (**7**) did not provide a substantial improvement on the reaction outcome (Table 1, Entry 9 *vs.* Entry 1) and no reaction was observed with acetone as a source of dioxirane due to the formation of a precipitate (Table 1, Entry 10 *vs*. Entry 1).

Table 1. Optimization for the C_{sp}^3-H oxidation of adamantane (**5a**).



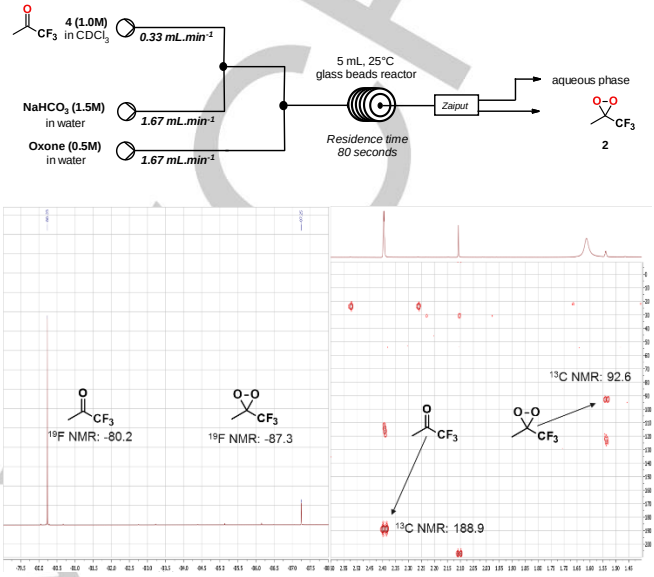
Entry[a]	Deviation from above	Conv (%)[b]
1	/	93
2	No glass beads reactor	87
3	1,1,1-trifluoromethylketone (**4**, 0.5 M)	60
4	Adamantane (**5a**, 0.1 M)	62
5	$NaHCO_3$ (0.5 M)	43
6	Flow rate $NaHCO_3$ and Oxone at 0.333 mL.min^{-1}	58
7	5°C	58
8	Reactor volume = 2 mL	79
9	1,1,1-trifluorobutanone (**7,** 0.5 M)	67
10	acetone	<5

[a] Reaction condition: 0.25 mmol scale reaction. Reaction carried out at 0.05 M concentration of **5a** and 1.0 M of **4** in DCM, 1.5 M concentration of $NaHCO_3$ in water and 0.5 M concentration of Oxone in water, 5 mL glass beads reactor, residence time: 80 seconds, 25 °C. [b] Conversion determined by ^{1}H NMR, average of two reactions.

To confirm the *in situ* formation of TFDO (**2**) in the reaction, a solution of $CDCl_3$ containing 1,1,1-trifluoroacetone (1.0 M) was mixed with an aqueous solution of $NaHCO_3$ (1.5 M) and Oxone (0.5 M) using the flow set up depicted in Scheme 1. After a continuous phase separation, using the Zaiput unit, and collection of the organic phase, ^{19}F and HMBC ^{1}H/^{13}C NMR spectroscopy revealed the formation of TFDO (**2**) (^{19}F NMR = -87.3 ppm).[16] Furthermore, titration of the organic phase, revealed a molarity of TFDO (**2**) around 0.05 M (5 % yield)[17,18] This results emphasise the benefit of the flow procedure to achieve a safe, faster and higher TFDO concentration than reported in batch mode (2 % yield).[12d]

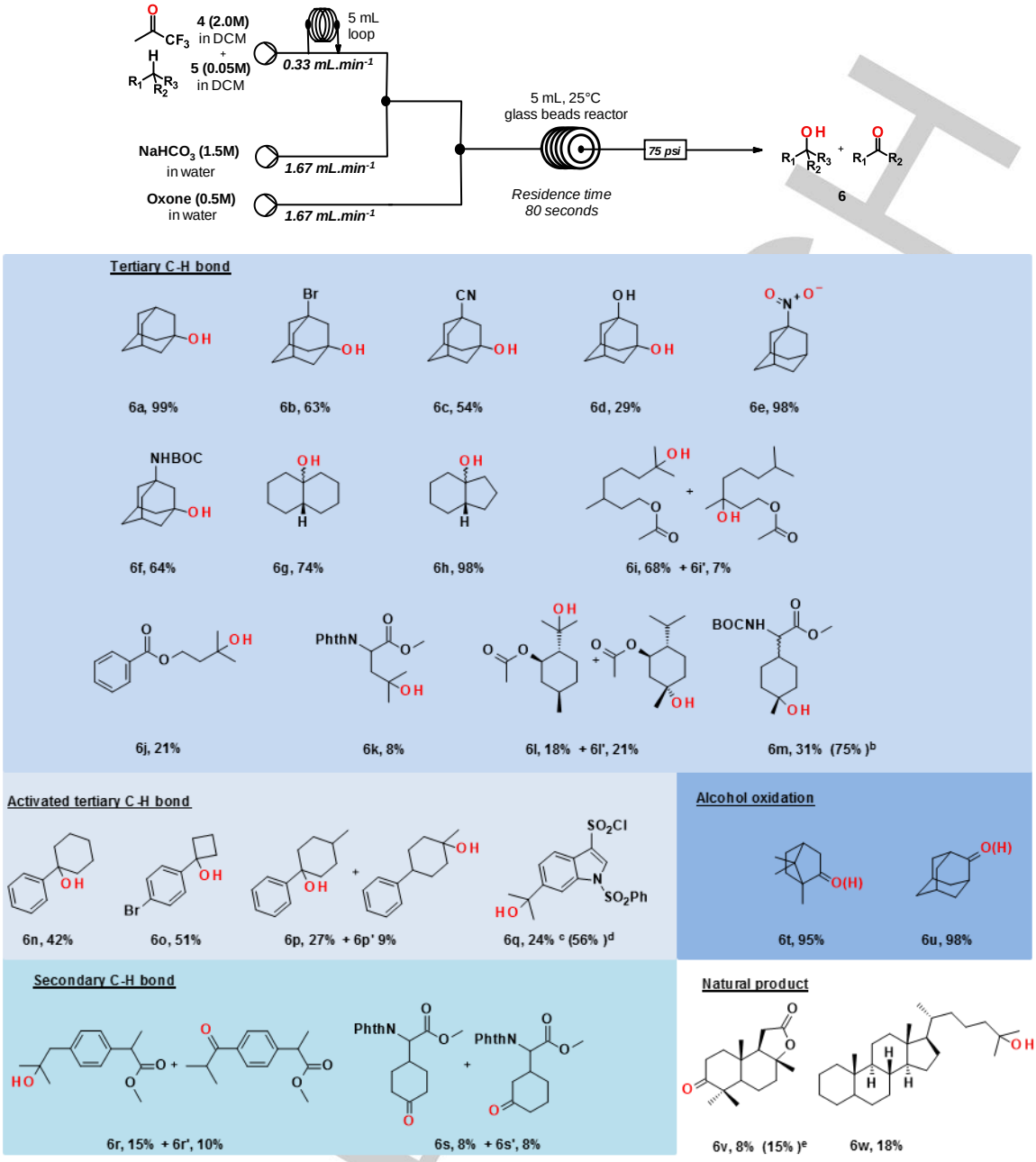
With the optimized conditions in hand, the scope for this transformation was explored as shown in Scheme 2. As expected, investigations of the substrate scope of this new flow method revealed a strong preference for hydroxylation of tertiary centers.

First of all, a panel of adamantane derivatives bearing various substituents such as -H (**5a**), -Br (**5b**), -CN (**5c**), -OH (**5d**) and -NHBOC (**5f**) was investigated. The C_{sp}^3-H oxidation was achieved exclusively at the more sterically hindered C_{sp}^3-H site in moderate to excellent yields (**6d**, 29 %), (**6c**, 54 %), (**6b**, 63 %), (**6f**, 64 %) and (**6a**, 99 %).



Scheme 1. Production of TFDO in flow.

In the same way, trans-decaline (**5g**) and trans-hydrindane (**5h**) afforded the C_{sp}^3-H oxidation products **6g** and **6h** at the tertiary position with an isolated yield of 74 % and 98 %, respectively. Interestingly, product of tertiary hydroxylation remote position are strongly preferred over proximal oxidable position. For example, C_{sp}^3-H oxidation products of **5i** can be obtained with an isolated yield of 68 % (**6i**) and 7 % (**6i'**) with a ratio of (91:9) toward the remote C_{sp}^3-H bond. Lower yields were obtained for substrates (**5j**) and (**5k**) bearing only one hindered proximal tertiary carbon (**6j**, 21 % and **6k**, 8 %). Importantly, the retention of configuration was achieved on the L-menthyl-acetate scaffold (**5l**). As previously described, the C_{sp}^3-H oxidation occurred, preferentially, at the two tertiary remote positions with an isolated yield of 18 % (**6l**) and 21 % (**6l'**), without racemization, suggesting no deviation from the current mechanistic understanding of dioxirane hydroxylation.[18] Product **6m** can be selectively oxidized on the tertiary position with an isolated yield of 31 %. Notably, increasing the residence time and the concentration of 1,1,1-trifluoroacetone (**4**) by a factor of 2 showed higher isolated yield in the desired product (75 %). Activated methylenes, such as benzylic C_{sp}^3-H bonds bearing cyclohexyl (**5n**) and cyclobutyl (**5o**) ring can be oxidized, at the tertiary carbon, with an isolated yield of 42 % and 51 %, respectively. Regio-selectivity was investigated with substrate (4-methylcyclohexyl)benzene (**5p**) bearing an activated benzylic position and an un-activated C_{sp}^3-H bond.



Scheme 2. Substrate scope for the direct Csp^3-H oxidation using TFDO.[a] [a] Reaction conditions: 0.25 mmol scale reaction. Reaction carried out at 0.05 M concentration of **5** and 2.0 M of **4** in DCM, 1.5 M concentration of $NaHCO_3$ in water and 0.5 M concentration of Oxone in water, 5 mL glass beads reactor, residence time: 80 seconds, 25 °C. Isolated yield after chromatography, average of two reactions. [b] Reaction carried out at 0.05 M concentration of **5** and 4.0 M of **4** in DCM, 1.5 M concentration of $NaHCO_3$ in water and 0.5 M concentration of Oxone in water, 20 mL helicoidal static-mixer coil reactor, residence time: 160 seconds, 25 °C. [c] 0.125 mmol scale reaction. Reaction carried out at 0.025 M concentration of **5** and 2.0 M of **4** in DCM. [d] 1.25 mmol scale reaction. Reaction carried out at 0.025 M concentration of **5** and 4.0 M of **4** in DCM. [e] 5.0 M of **4** in DCM.

The benzylic position was preferentially oxidized with an isolated yield of 27 % toward the un-activated methine position (**6p'**, 9 %) with a ratio of (**6p:6p'** = 3:1). Interestingly, indole derivative bearing a sulfonyl chloride functionality (**5q**) can be tolerated. Hydroxylation reaction occurred on the benzylic position with an isolated yield of 24 %. The reaction was also achieved on a 1.25 mmol scale reaching an isolated yield of 56 % with an increase of the 1,1,1-trifluoroacetone (**4**) by a factor of 2.

Secondary C_{sp}^3-H bond oxidation was evaluated using few substrates bearing un-activated and activated positions. The reaction on ibuprofen methyl ester (**5r**) led to oxidation on both benzylic and tertiary C_{sp}^3-H in a 3:2 ratio favouring the tertiary position. In the case of protected phthalimide-methyl ester scaffold bearing a cyclohexyl ring (**5s**), a mixture (1/1) of two regio-isomer ketone **6s** and **6s'** was obtained in low yield 8 % in both cases. The excellent potential of TFDO to oxidize secondary

alcohols was also demonstrated with camphor (95 %, **6t**) and on 1-adamantanone (98 %, **6u**). In general, a variety of functionalities are well tolerated under the reaction conditions. For example, ester, nitrile, carbamate, phthalimide, ketone and sulfonyl chloride remain intact during the reaction, except for non-protected primary amine (**6e**) which are oxidized to the nitro derivative, quantitatively which is an interesting reaction in its own right. Natural products such as sclareolide (**5v**) and cholestane (**5w**) bearing multiple oxidative sites were studied. In the case of the sclareolide, the C_{sp}^3-H oxidation was selectively observed at the secondary carbon position C2 whereas for cholestane the transformation occurred preferentially at the terminal tertiary position.

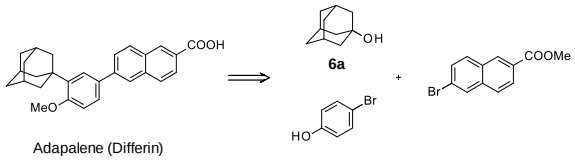
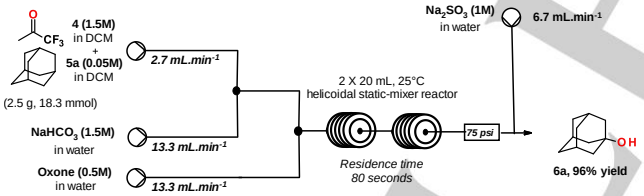


Figure 2. Retrosynthetic step for the synthesis of Adapalene[18]

The scalability of this flow procedure has been demonstrated on 2.7 g synthesis of the alcohol (**6a**), a common starting material for the preparation of Adapalene, a retinoid drug (Figure 2).[20] The initial flow set-up has been scale out by increasing the size of the reactor from 5 mL to 40 mL to accommodate the critical mixing requirement at high flow rate with the use of two "helicoidal static-mixer coil". A 2.3 hours run at steady state in standard conditions provided the desired product **6a** with similar yield (96 %) to the smaller scale reaction with this particular reactor design (Scheme 3).



Scheme 3. The 2.5 grams scale C_{sp}^3-H oxidation of adamantane (**5a**).

In summary, the development of a new general trifluoromethylated dioxirane-mediated C_{sp}^3-H oxidation method has been enabled in a fast, efficient and simple fashion through a continuous flow process. This practical method employs inexpensive reagents and can be applied to a wide panel of substrates bearing a large range of functionalities. The flow conditions provide a scalable and safer solution for transforming simple aliphatic compounds to complex materials.

Acknowledgements

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Keywords: oxidation • Flow • TFDO • dioxirane • Oxone

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Layout 1:

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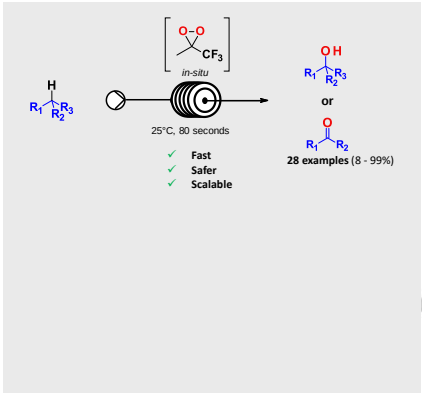

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