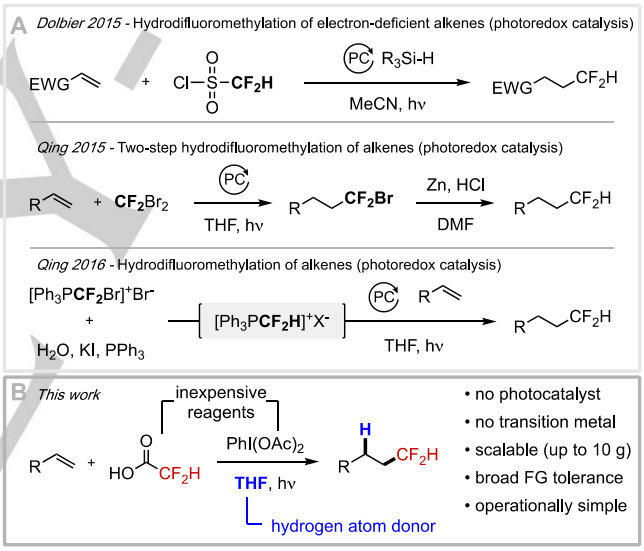
Hydrodifluoromethylation of Alkenes with Difluoroacetic Acid

Claudio F. Meyer,[a,b] Sandrine M. Hell,[a] Antonio Misale,[b] Andrés A. Trabanco,[b] and Véronique Gouverneur*[a]

Abstract: *A facile method for the regioselective hydrodifluoromethylation of alkenes is reported using difluoroacetic acid and phenyliodine(III) diacetate in tetrahydrofuran under visible light activation. This metal-free approach stands out as it uses inexpensive reagents, does not require a photocatalyst, and displays broad functional group tolerance. The procedure is also operationally simple and scalable, and allows access in one step to high value building blocks for application in medicinal chemistry.*

Fluorinated compounds are of high interest in drug discovery due to the unique ability of fluorine to modulate the lipophilicity, polarity, metabolic stability and solubility of potential drug candidates, properties that directly influence bioavailability and adsorption.[1] The difluoromethyl group (CF_2H) stands out as a metabolically stable lipophilic bioisostere of weak hydrogen bond donors such as alcohols, anilines, amines or thiophenols, and as such has been used in a variety of drug molecules.[2] Traditionally, the CF_2H group is generated by deoxyfluorination of an aldehyde with reagents such as *N,N*-dimethylaminosulfur trifluoride (DAST) or bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor®).[3] These reagents react with alcohols, ketones and carboxylic acids with poor selectivity, thereby imposing extensive protecting group chemistry for molecules featuring these functionalities.[4] Furthermore, the exothermic decomposition of these reagents at elevated temperature or in contact with water presents safety concerns, especially for large-scale synthesis.[5] In response to these challenges, late stage difluoromethylation of (hetero)arenes,[6] and new transformations such as the hydrodifluoromethylation of alkene starting materials have been developed. In 2015, Dolbier and co-workers disclosed an elegant photocatalytic hydrodifluoromethylation of electron deficient alkenes.[7] Qing and co-workers reported that hydrodifluoromethylation of a broader range of terminal alkenes is possible applying a two steps sequence consisting of hydrobromodifluoromethylation with ozone-depleting CF_2Br_2 followed by Zn-mediated reductive debromination.[8] The same group subsequently reported a one step process exploiting the reactivity of the difluoromethyl radical generated from bromodifluoromethylphosphonium bromide and water. This method requires three reagents including a phosphonium salt that is not an atom economical source of CF_2, and the photocatalyst *fac*-[Ir(ppy)$_3$]; careful handling in a glovebox is also necessary for this reaction to proceed (Scheme 1A).[9]

Our objective was to develop an operationally simple and scalable process for the hydrodifluoromethylation of alkenes using inexpensive difluoroacetic acid under visible light activation.[10] We were encouraged by studies demonstrating that the photolysis of preformed hypervalent iodine (III) reagents enables direct C-H difluoromethylation of heteroarenes.[11] Hypervalent iodine (III) reagents are also suitable for the hydroaryldifluoromethylation of alkenes under Ir-based photoredox catalysis.[12] These observations led us to consider that visible light irradiation could enable hydrodifluoromethylation of alkenes in the absence of photocatalyst using inexpensive difluoroacetic acid and the oxidant phenyliodine(III) diacetate (PIDA) in a solvent capable of hydrogen atom transfer e.g tetrahydrofuran (THF).[8,9] In this scenario, THF (α-C–H, BDE = 385 kJ/mol)[13] would react with the carbon-centered radical generated upon addition of CF_2H radical onto the alkene. This process would release a THF α-radical that could in turn activate the *in situ* formed difluoromethylation I(III) reagent (Scheme 1B).



Scheme 1. A. Known methods for the hydrodifluoromethylation alkenes. B. Streamlined novel process for the hydrodifluoromethylation of alkenes in the absence of photocatalyst. EWG = electron-withdrawing group. PC = photocatalysis. DMF = dimethylformamide. THF = tetrahydrofuran.

Hex-5-enyl benzoate **1a** was chosen as model substrate to investigate the proposed decarboxylative hydrodifluoro-methylation. Initial efforts focused on combining hypervalent iodine oxidants **3a**-**3c** with difluoroacetic acid **2** as the difluoromethyl source in THF under visible light irradiation (blue LEDs, λ = 450 nm) at 50 ºC. The desired hydrodifluoro-methylated product **4a** was observed with complete regioselectivity, albeit in moderate yields (Table 1, entries 1-3). Phenyliodine(III) diacetate **3a** (PIDA) was the most efficient oxidant affording **4a** in 59%. The yield was not improved when alternative non-protic solvents such as NMP, MTBE, MeCN, DMF or DMA were used (Table 1, entries 4-8).[14] Protic solvents were not suitable (Table 1, entry 9),[15] and the yield of **4a** was not increased in the presence of photocatalyst.[16] Running the reaction at higher concentration did not influence the reaction outcome (Table 1, entry 10). When a second batch of PIDA was added after 6 h, the yield of **4a** was significantly improved (Table 1, entry 11). A control experiment showed that **4a** was obtained

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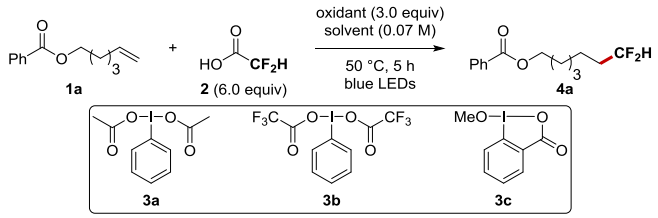
in 21% yield when the reaction was performed in the absence of light (Table 1, entry 12).[17]

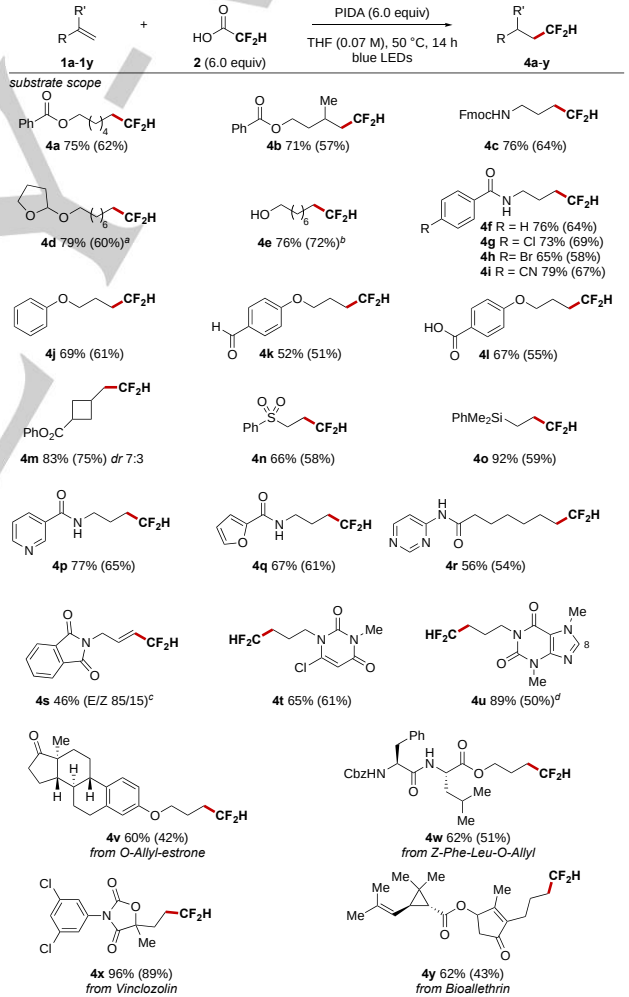
Table 1. Optimization of the reaction conditions.[a]



entry	solvent	oxidant	yield [%]
1	THF	**3a**	59
2	THF	**3b**	4[b]
3	THF	**3c**	27
4	NMP	**3a**	41
5	MTBE	**3a**	41
6	MeCN	**3a**	12
7	DMF	**3a**	51
8	DMA	**3a**	40
9	MeOH	**3a**	2
10[c]	THF	**3a**	60
11[d]	**THF**	**3a**	**77**
12[e]	THF	**3a**	21

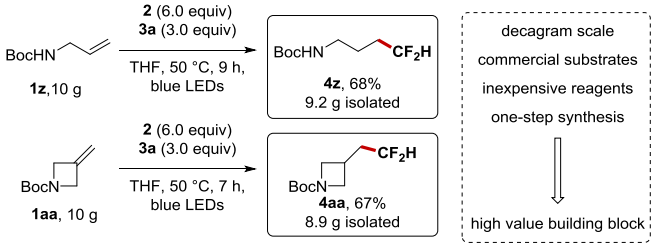
[a] **1a** (0.1 mmol), oxidant (0.3 mmol), **2** (0.6 mmol), solvent (1.5 mL), blue LED irradiation (λ = 450 nm) for 14 h. The yield was determined by ^{19}F NMR spectroscopy using trifluorotoluene as internal standard. [b] Hydrotrifluoromethylation not observed. [c] THF (0.1 M). [d] A second portion of **3a** (0.3 mmol) was added after 6 h. [e] Reaction in the absence of light. THF = tetrahydrofuran. NMP = *N*-methyl-2-pyrrolidone. MTBE = methyl *tert*-butyl ether. DMF = dimethylformamide. DMA = dimethylacetamide.

With the optimized conditions in hand (Table 1, entry 11), the generality of this new protocol for hydrodifluoromethylation was studied. As illustrated in Scheme 2, a broad variety of functional groups, such as esters, amides, alcohols, aldehydes, halides and nitriles were tolerated, and the desired products **4a**-**i** were isolated in moderate to good yields. The hydrodifluoromethylation of alkenes containing a carboxylic acid or aldehyde was successful affording **4l** and **4k** in moderate yields; such functional groups would require protecting group chemistry with deoxyfluorination chemistry. Alkene **1d** with a pending alcohol functionality afforded the tetrahydrofuranyl ether **4d**, so *in situ* deprotection is necessary to isolate the alcohol **4e** in 72% yield. A methylene cyclobutane derivative underwent hydrodifluoromethylation in good yield (**4m**), and electron deficient alkene such as phenylvinylsulfone led to **4n** in 58% yield. The incorporation of difluoromethyl groups onto a vinyl silane was also successful (**4o**). Heteroarenes are well tolerated and did not undergo competitive heteroaryl C-H difluoromethylation under the reaction conditions (**4p**-**r**). Alkynes are suitable substrates as demonstrated with the isolation of **4s**. Alkene-containing biologically relevant molecules were investigated next. Uracil derivative **4t** was obtained in moderate yield. *N*-Allyl caffeine **1u** known to undergo facile difluoromethylation at C8 was selected to study the chemoselectivity of the reaction. Under our standard reaction conditions, the hydrodifluoromethylated product **4u** was formed in 89% yield (^{19}F NMR) with only trace amounts of product resulting from competitive C8-H difluoromethylation. Tetrahydrofuran was critical for this reaction to be successful as **4u** was not formed in $CDCl_3$; this later solvent favored difluoromethylation at the heteroarene albeit with poor conversion (C8, 14%).[16] Hydrodifluoromethylation of O-allyl-estrone and Z-Phe-Leu-O-allyl proceeded in moderate yields (**4v**, 4**w**), with no erosion of diastereomeric ratio observed for **4w**. Vinclozolin (**1x**) and Bioallethrin (**1y**) afforded **4x** and **4y** isolated in 89% and 43%, respectively. In terms of limitations, styrene resulted in a mixture of products, and 1,2-disubstituted alkenes were low yielding.[16]



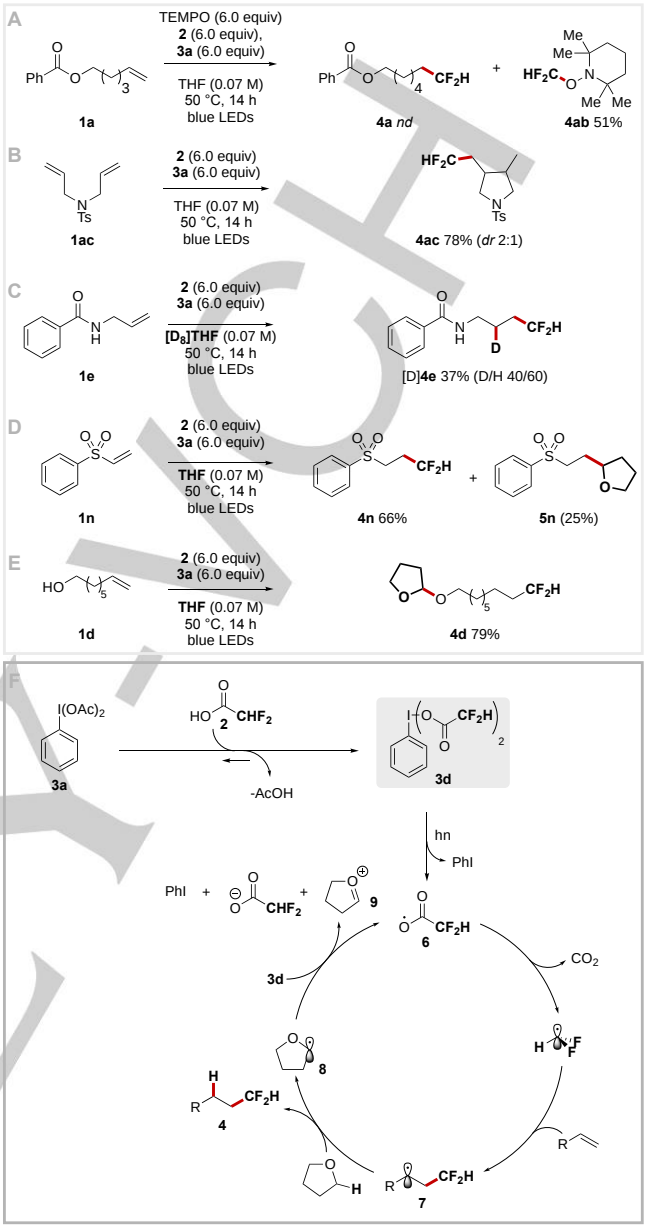
Scheme 2. Substrate scope. Reaction conditions: alkene **1a**-**y** (0.3 mmol), **2** (1.8 mmol), **3a** (0.9 mmol), THF (4.5 mL), blue LED irradiation (λ = 450 nm), 50 °C, 14 h. After 6 h a second portion of **3a** (0.9 mmol) was added. Yields determined by ^{19}F NMR spectroscopy using trifluorotoluene as internal standard, yields of isolated products in brackets. [a] The starting material is 7-octen-1-ol. [b] HCl (conc. 0.5 mL) was added after completion of the reaction. [c] The starting material is *N*-propargylphtalimide (**1s**). [d] In $CDCl_3$, the C8-H difluoromethylated product is obtained in 14% yield.

With the aim of scaling up our reaction from milligram to multigram, we selected alkene starting materials that are converted into valuable difluoromethylated building blocks for application in medicinal chemistry (Scheme 3). 4,4-Difluorobutan-1-amine is a known compound previously prepared in five steps applying deoxyfluorination chemistry.[18] Pleasingly, the hydrodifluoromethylation of *t*-butyl allyl *N*-carbamate **1z** was accomplished in one step on a 10 g scale affording **4z** isolated in 68% yield (9.2 g). For this process, the concentration was increased from 0.07 M to 0.13 M, and three equivalents of PIDA **3a** was sufficient. Similar conditions enabled the multigram synthesis of azetidine **4aa** (8.9 g, 67%).[19]



Scheme 3. Scale-up synthesis of building blocks highly valuable for medicinal chemistry.

A series of experiments were performed to gain more insight into the reaction mechanism. Addition of the radical quencher 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) inhibited the formation of product **4a** affording instead the TEMPO adduct **4ab** in 51% yield (Scheme 4A). Next, when diene **1ac** was submitted to the reaction conditions, the cyclized product **4ac** was obtained in 78% yield (Scheme 4B). Collectively, these data are consistent with the presence of a CF_2H radical intermediate and strongly suggest a radical-based mechanism. The hydrodifluoromethylation of **1e** in [D_8]THF led to the desired product in 37% yield with 40% deuterium incorporation, indicating that THF acts as hydrogen atom donor (Scheme 4C). Moreover, the hydrodifluoromethylation of the electron-deficient alkene **1n** afforded the THF adduct **5n** in addition to the desired product of hydrodifluoromethylation **4n**, a result consistent with the formation of a nucleophilic THF α-radical (Scheme 4D). Reaction of alcohol **1d** under the standard reaction conditions afforded the THF protected ether **4d** in 79% yield; an electrophilic tetrahydrofuran-derived oxonium ion is therefore present that can react with the alcohol group (Scheme 4E). Based on these experiments, a reaction mechanism is proposed in Scheme 4F. The exchange of difluoroacetic acid **2** with the acetate group on **3a** affords **3d**.[20] Photolysis under blue light exposure releases **6** that can undergo decarboxylation to generate $^{\bullet}CF_2H$. This radical would be well-suited to add regioselectively to the alkene substrate. The resultant carbon radical **7** would subsequently react with THF to afford the product of net hydrodifluoromethylation. Hydrogen atom abstraction from tetrahydrofuran releases the THF α-radical **8** that could undergo single electron transfer to **3d** with concomitant release of the oxonium ion **9**, iodobenzene, difluoroacetate, and radical **6** for further alkene functionalization. Hydromethylation was not observed as expected considering the superior stability of $^{\bullet}CF_2H$ with respect to $^{\bullet}CH_3$.[21]



Scheme 4. Mechanistic considerations. Yields were determined by ^{19}F NMR spectroscopy using trifluorotoluene as internal standard. Yields of isolated products are shown in brackets. *dr* = diastereomeric ratio. *nd* = not detected.

In conclusion, we have developed a new streamlined protocol for the hydrodifluoromethylation of alkenes as part of our recent late stage fluorination program aimed at avoiding operationally complex, over-engineered, and costly processes.[22] Difluoroacetic acid was used as an inexpensive difluoromethyl radical source and phenyliodine(III) diacetate as oxidant, both reagents used in excess to maximize yields. These mild conditions tolerate a wide array of functional groups. This novel reaction was applied to the multigram-synthesis of pharmaceutically relevant building blocks providing shorter and safer synthetic routes compared to synthesis relying on classical deoxyfluorination protocols.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: difluoroacetic acid • hydrodifluoromethylation • hypervalent Iodine • photochemistry • radicals

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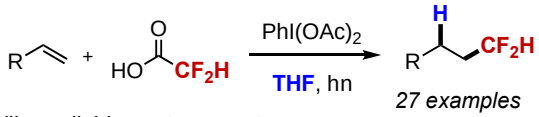

readily available starting materials | inexpensive reagents | *27 examples* high value products

no photocatalyst
no transition metal
scalable (up to 10 g)
broad FG tolerance
operationally simple

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Terminal alkenes undergo net hydrodifluoromethylation in the presence of an excess of difluoroacetic acid and phenyliodine(III) diacetate in tetrahydrofuran applying visible light irradiation (λ = 450 nm). This highly practical protocol telescopes access to biorelevant building blocks that would require multiple synthetic steps applying deoxyfluorination chemistry.

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