Difluoromethylation

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Deuteriodifluoromethylation and *gem*-Difluoroalkenylation of Aldehydes Using $ClCF_2H$ in Continuous Flow

*Wai Chung Fu and Timothy F. Jamison**

Abstract: *The deuteriodifluoromethyl group (CF_2D) represents a challenging functional group due to difficult deuterium incorporation and unavailability of precursor reagents. Herein, we report the use of chlorodifluoromethane ($ClCF_2H$) gas in the continuous flow deuteriodifluoromethylation and gem-difluoroalkenylation of aldehydes. Mechanistic studies revealed that the difluorinated oxaphosphetane (OPA) intermediate can proceed via alkaline hydrolysis in the presence of D_2O to provide α-deuteriodifluoromethylated benzyl alcohols or undergo a retro [2+2] cycloaddition under thermal conditions to provide the gem-difluoroalkenylated product.*

Introduction

The incorporation of fluorine or fluorocarbon groups into molecules is an important tactic in medicinal chemistry to enhance biological properties such as the bioavailability, binding selectivity and metabolic stability.[1] In particular, the difluoromethyl group (CF_2H) is a lipophilic hydrogen bond donor that can serve as a metabolically stable bioisostere for thiols, alcohols and amines.[2] Deuteration is also an efficient tool to optimize drug pharmacokinetics,[1a,3] and has widespread applications in organic synthesis,[4] structure determination,[5] mechanistic investigations,[6] and quantitative analyses.[7] Deutetrabenazine (Austedo) is the first deuterated drug to be approved by the U.S. Food and Drug Administration (FDA) in 2017 to treat both tardive dyskinesia and Huntington's disease chorea (Figure 1a).[8] Given the utility of both deuterated and fluorinated molecules, we became interested in the largely underexplored deuteriodifluoromethyl group (CF_2D).

A review of the literature[9,10] revealed there are few methods to access the CF_2D group, and that useful levels of deuterium incorporation to generate this moiety can be a significant challenge. An example of an exception to this, is the work by Colby's research group, in which deuteriodifluoromethyl ketones and sulfones were synthesized with deuterium incorporation levels in the range of 96–99%.[9] As shown in Figure 1b, their approach relied on the release of trifluoroacetate from a highly fluorinated diol. The resulting carbanion was then quenched by D_2O to yield the CF_2D functionalized molecules.

In general, difluoromethylating reagents have limited accessibility and efficiency (Figure 1c).[11,12] Some of these precursors are toxic, expensive, have low atom economies or require multiple synthetic steps to prepare. Chlorodifluoromethane ($ClCF_2H$) is an inexpensive industrial chemical used for the production of fluorinated polymers such as Teflon.[13] It is regulated as an ozone depleting substance under the Montreal Protocol,[14] but exemptions were given for research and development purposes, including its use as a reaction feedstock. We envisioned this fluorinated gas as a potential atom-efficient reagent for difluoromethylation. Although it has been demonstrated as an effective difluorocarbene source,[15] there are many challenges associated with the use of this gaseous compound under batch conditions, namely (1)

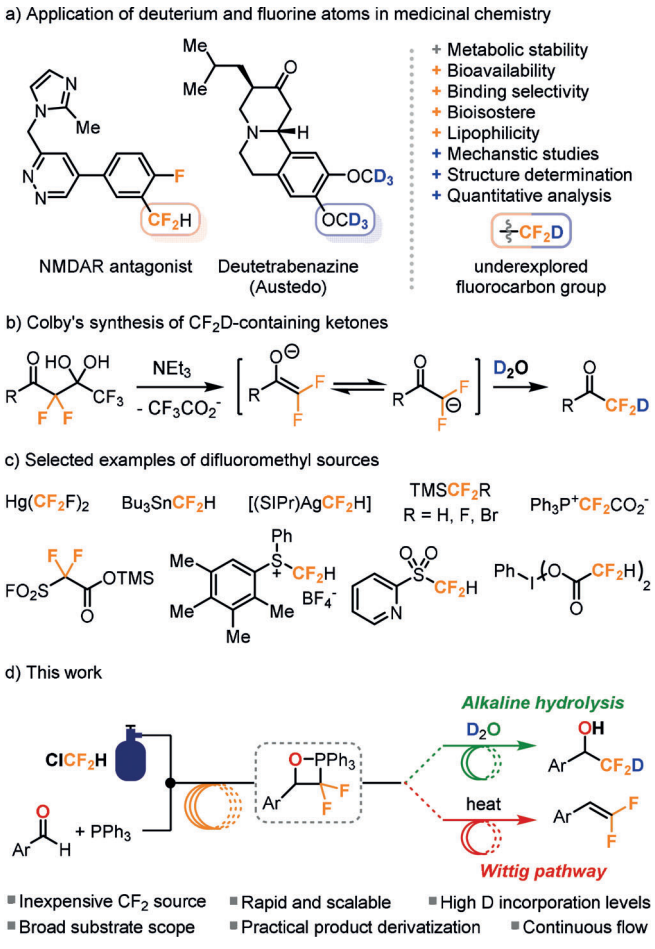

Figure 1. a) Examples of deuterated and fluorinated molecules in medicinal chemistry. b) Colby's work on the synthesis of deuteriodifluoromethyl ketones. c) Difluoromethylating reagents. d) This work: deuteriodifluoromethylation and *gem*-difluoroalkenylation using chlorodifluoromethane gas.

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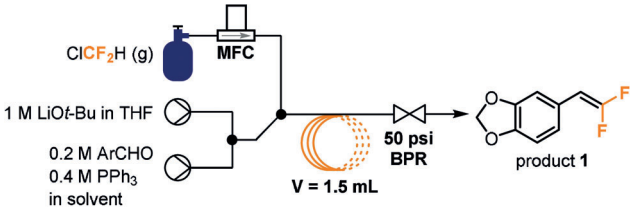
the need for prolonged bubbling into a solvent for saturation; (2) the choice of reaction solvent is limited by the gas solubility; (3) the release of gas into the system headspace during the reaction; (4) the lengthened reaction time caused by insufficient gas-liquid interfacial contact or continuous bubbling into the mixture, and (5) safety concerns and scalability issues. With our continuing interest in flow methodology development,[16] we were intrigued to address these limitations by using mircoflow technology. Flow processing provides many advantages relative to batch techniques[16,17] including the enhanced reactivity through improved heat and mass transfer, steady-state small scale generation with immediate consumption of unstable/hazardous reagents, and facile pressurization for significantly increased gas-liquid interfacial contact.

Herein, we report a modular continuous flow platform for both deuteriodifluoromethylation and *gem*-difluoroalkenylation of aldehydes using the $ClCF_2H$ gas (Figure 1 d). Different downstream processing modules in the flow system diverts the fate of the difluorinated oxaphosphetane (OPA) intermediate to give desired products. The method is rapid, scalable and exhibits a broad substrate scope.

Results and Discussion

We initiated our study by investigating the use of $ClCF_2H$ gas for the *gem*-difluoroalkenylation of aldehydes in flow. *gem*-Difluoroalkenes are valuable synthetic intermediates towards functional organic materials and pharmaceutically relevant compounds.[18] Although different methods have been reported for the synthesis of *gem*-difluoroalkenes, including Suzuki coupling,[19] Negishi coupling,[20] and Julia–Kocienski olefination,[21] the Wittig-type reaction has received considerable attention recently due to its straightforward synthetic protocol.[15a,22] $ClCF_2H$ releases singlet difluorocarbenes ($:CF_2$) in the presence of base through deprotonation and α-elimination,[15b] in which it is expected to be subsequently trapped by triphenylphosphine to form a difluoromethyl triphenylphosphonium ylide ($Ph_3P{=}CF_2$) for the Wittig reaction with aldehydes.[22] A model flow system for optimization was established as depicted in Table 1. $ClCF_2H$ was infused into the system through an MFC (mass flow controller) and piperonal was chosen as a benchmarking substrate. We envisioned that LiO*t*-Bu (1 M in THF) would be a suitable base as it generates LiCl upon deprotonation and α-elimination of the chlorodifluoromethyl anion, thus ensuring a homogeneous mixture in THF. A BPR (back pressure regulator) set at 50 psi effectively pressurized the system and enabled complete dissolution of $ClCF_2H$ in the mixture. Initial solvent screening showed that THF was a promising candidate (Table S1), giving the *gem*-difluoroalkene product **1** in 47 % GC-FID yield (Table 1, entry 1). LiOMe in MeOH was not compatible with the reaction (Table S1, entry 10) while the use of KO*t*-Bu immediately clogged the microreactor and mixers due to undissolved KCl (Table S1, entry 11). The ylide ($Ph_3P{=}CF_2$) was reported to be a transient species in an interconversion between the ylide and difluorocarbene due to its low dissociation energy barrier.[22b,d] While

Table 1: Selected entries for optimization studies toward continuous flow *gem*-difluoroalkenylation.[a]



Entry	LiO*t*-Bu [equiv]	$ClCF_2H$ [equiv]	T [°C]	Solvent	t_R [min]	Yield [%][b]
1	2.0	2.5	60	THF	15.0	47
2	2.0	2.5	40	THF	15.0	57
3	2.0	2.5	20	THF	15.0	70
4	2.0	2.5	0	THF	15.0	80
5	2.0	2.5	0	THF	7.5	74
6	2.0	2.5	0	2-MeTHF	7.5	76
7	2.0	2.5	0	CPME	7.5	61
8	1.5	2.5	0	2-MeTHF	7.7	74
9	1.5	2.0	0	2-MeTHF	7.7	68
10	2.0	3.0	0	2-MeTHF	7.5	79
11	2.0	3.0	0	2-MeTHF	12.0	82

[a] Please see Supporting Information for detailed optimization tables. [b] GC-FID yields were reported.

literature precedents on the Wittig *gem*-difluoroalkenylation employed high reaction temperatures,[22c–e] we postulated that the enhanced heat transfer might also accelerate the dissociation of the ylide as well as dimerization of difluorocarbene to form tetrafluoroethylene.[23] We found that a decrease in temperature improved the reaction yields with 0 °C being the optimal (Table 1, entry 1–5). This is presumably due to the stabilization of the transient ylide. The use of subzero temperatures (−20 °C) led to reactor clogging. Screening of organic co-solvents further revealed an increase in yield by conducting the reaction with 2-MeTHF at 0 °C (Table 1, entry 5–7, Table S3). The stoichiometry of reagents was also optimized as shown in Table 1 (entry 8–10) and Table S4. Two equiv of LiO*t*-Bu and 3 equiv of $ClCF_2H$ was found to provide the best GC-FID yield of 82 % at t_R (residence time) = 12 min (Table 1, entry 11). However, **1** was isolated in only 20 % yield after column chromatography while addition of water or D_2O to the crude reaction mixture would afford the corresponding hydration products **2** and **3** (Scheme 1).

In the presence of stoichiometric amounts of triphenylphosphine, we initially postulated a phosphine-catalyzed hydration of the *gem*-difluoroalkenes which would resemble the hydration of activated olefins reported by Bergman and Toste.[24] Nonetheless, control experiments in which pure *gem*-difluoroalkene **4** was treated with PPh_3 under similar basic conditions gave no hydration products (Table S5). Additional experiments also excluded the possibility of side products in this reaction serving as the active catalyst. We further carried out a crossover experiment whereby *gem*-difluoroalkene **4** was subjected to the fresh crude mixture **A** from the flow reaction and subsequently quenched with water (Scheme 2 a). Interestingly, only compound **2** was provided in 72 % yield while *gem*-difluoroalkene **4** did not undergo the hydration. These results indicated that the former reaction halted at an intermediate state which reacted with water to afford the α-

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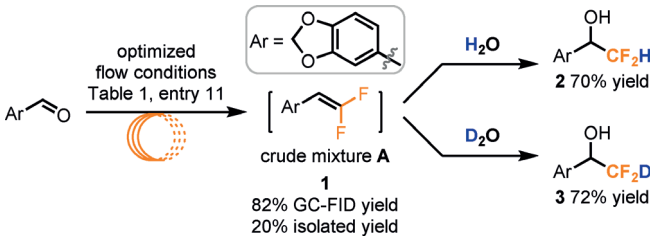
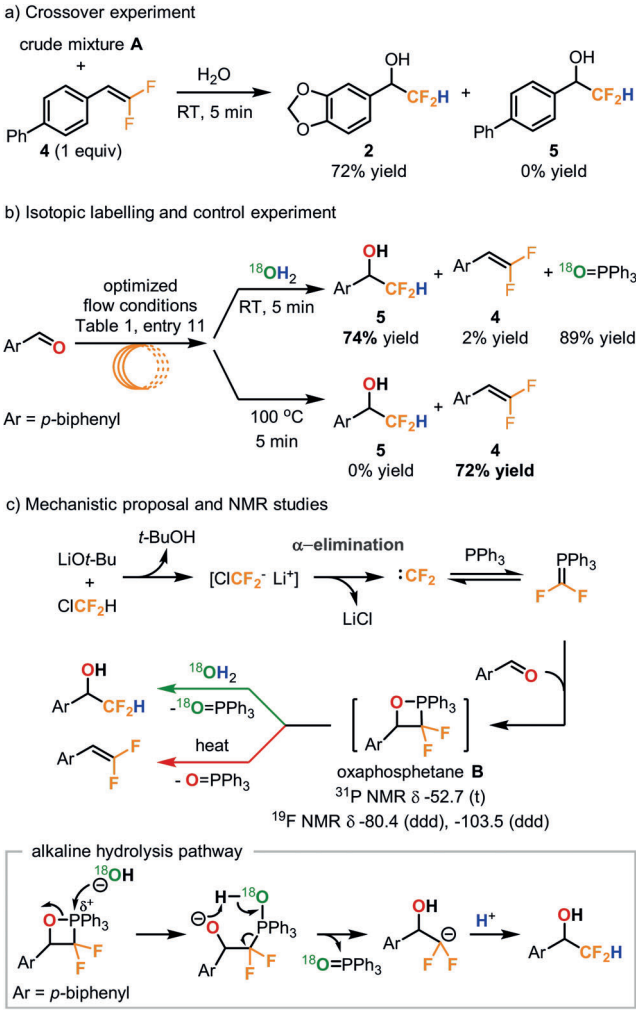


Scheme 1. Formation of hydration product from crude mixture **A**.



Scheme 2. Mechanistic studies.

difluoromethylated benzyl alcohols. Indeed, NMR studies of a crude reaction using 4-phenylbenzaldehyde as a substrate revealed a difluorinated oxaphosphetane species **B** at room temperature (Scheme 2c, ^{31}P NMR, THF, $\delta = -52.7$ ppm, t, $^{2}J_{P\text{-}F} = 76.0$ Hz; ^{19}F NMR, THF, $\delta = -80.4$ ppm, ddd, $^{2}J_{F\text{-}F} = 212.5$ Hz, $^{2}J_{P\text{-}F} = 70.9$ Hz, $^{3}J_{F\text{-}H} = 6.8$ Hz, 1F; $\delta = -103.5$ ppm, ddd, $^{2}J_{F\text{-}F} = 212.6$ Hz, $^{2}J_{P\text{-}F} = 80.5$ Hz, $^{3}J_{F\text{-}H} = 13.1$ Hz, 1F).[25] The P^{V} in **B** is more electron-deficient than typically observed in OPAs,[25] presumably due to the electron-withdrawing difluoromethylene group. We then hypothesized that the electrophilic P^{V} would be facile to the nucleophilic attack of hydroxide (Scheme 2c). The expelled alkoxide would abstract the hydroxyphosphorane proton to give phosphine oxide, forming a difluorocarbanion which would then be protonated to yield the difluoromethyl group. Substituting water with $^{18}OH_2$ gave the isotopically labelled phosphine oxide (Scheme 2b, characterized by HRMS), supporting the proposed alkaline hydrolysis of the OPA.

Recently, Byrne and co-workers reported the first observation of *P*-hydroxytetraorganophosphoranes as the intermediate in phosphonium salt alkaline hydrolysis,[26] but the same mechanism for an OPA has not been demonstrated. Although NMR observation of oxaphosphetanes was only known to be possible at low temperatures,[25] the difluorinated OPA in our reaction is relatively stable at room temperature and undergoes the retro [2+2] cycloaddition to give *gem*-difluoroalkenes overnight in the absence of water (Figure S1–S4). We anticipated that the Wittig pathway of OPA **B** is thermodynamically controlled and heating the crude mixture at 100 °C for 5 minutes successfully gave *gem*-difluoroalkene **4** in 72 % isolated yield (Scheme 2b), aligning with the high yields observed by GC-FID analyses.

With an understanding of the mechanism and the optimized flow system for generating difluorinated OPAs, we set out to develop different downstream processing modules to guide the outcome of the reaction. We first focused on the hydrolysis-deuteration module (Scheme 3) to provide α-deuteriodifluoromethylated benzyl alcohols via in situ hydrolysis of the intermediate OPA using D_2O. The use of 120 equiv of D_2O (39 μL min^{-1}) was found to provide the highest product yield while adding LiOH in the D_2O to increase the basicity gave no positive effect. Due to the low solubility of phosphine oxide in the 2-MeTHF/D_2O mixture, THF was used as the organic co-solvent to ensure homogeneity. Next, the generality of our continuous flow deuteriodifluoromethylation was explored. Both electron-rich (**3**, **6b**, **6h**) and electron-deficient aryl aldehydes (**6c**, **6j**) were converted to the corresponding products in good yields within a residence time of 15 minutes. A diverse range of functional groups were tolerated, including trifluoromethoxy (**6c**), thiomethyl (**6d**), halide (**6e**, **6f**, **6k**), extended π-system (**6i**) and trifluoromethyl groups (**6j**). α,β-Unsaturated (**6l**–**6m**) and heteroaryl aldehydes (**6n**–**6p**) successfully underwent the deuteriodifluoromethylation process in moderate to good yields. In the case of isophthalaldehyde, halving the substrate concentration provided product **6q** in 65 % yield and 97 % deuterium incorporation. It is notable that selectively deuterated fluorocarbon moiety ($CDCF_2D$) could be generated when C1-deuterated aldehyde was used (**6r**). We also successfully derived adapalene (**6s**), and ataluren (**6t**) which are pharmaceuticals used for the treatment of acne and Duchenne muscular dystrophy, respectively. In general, high to excellent deuterium incorporation levels have been obtained for all cases (95–97 %). Enolizable aldehydes were not applicable under the standard reaction conditions, and efforts to switch the addition/mixing sequence of substrates and reagents proved to be futile. We have observed by NMR analysis that approximately 0.5 to 1 equivalent of chlorodifluoromethane remained in the crude mixture after the course of reaction, and we believe that further development using in-line IR or NMR techniques would enable more efficient

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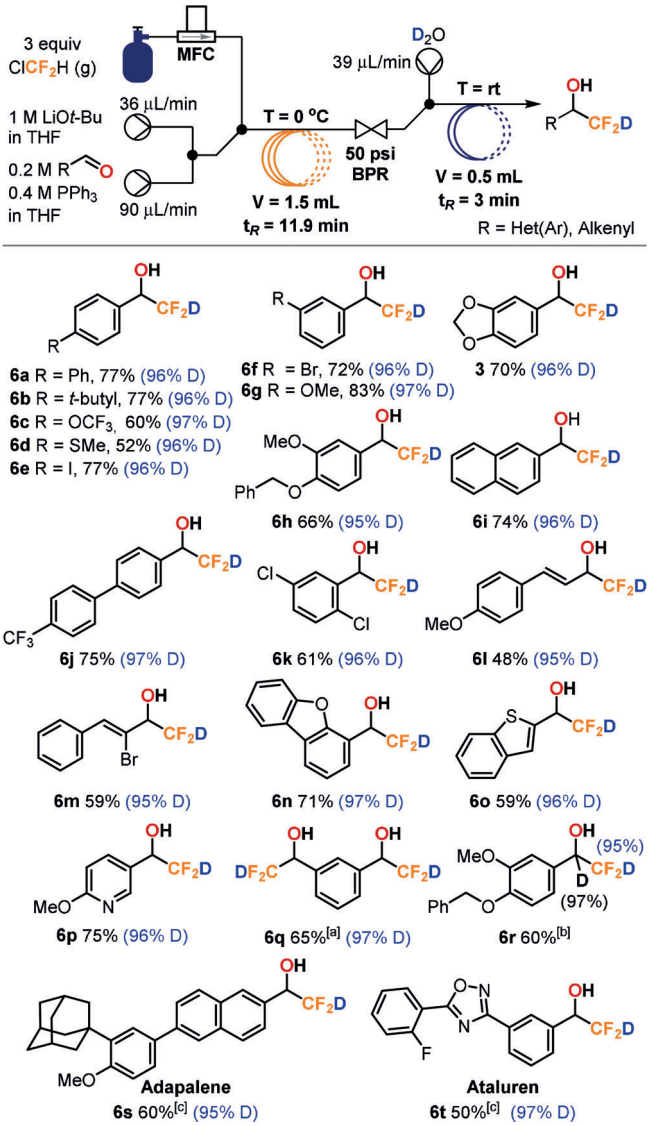
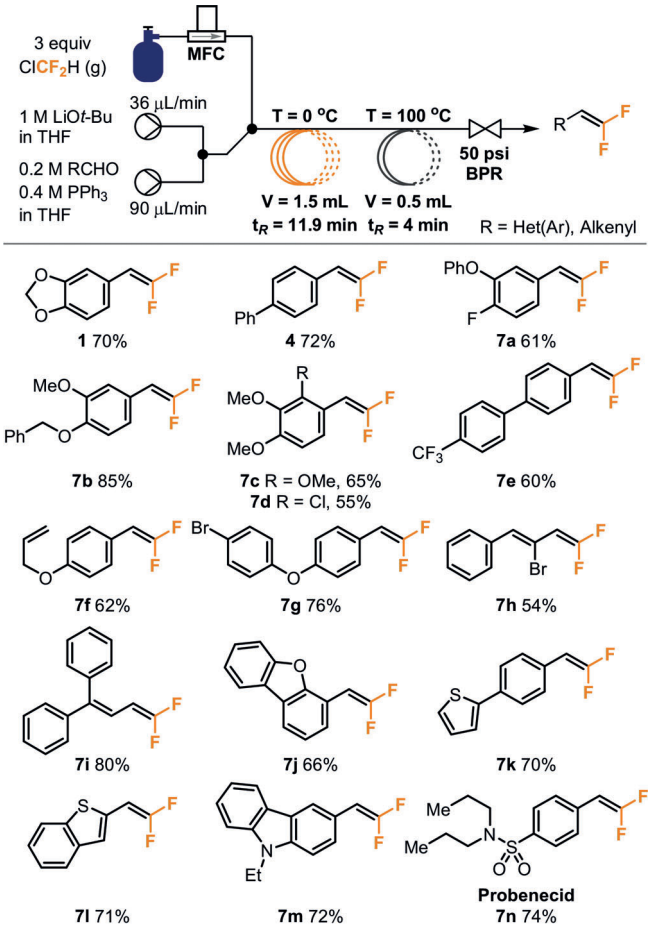


Scheme 3. Substrate scope of the continuous flow deuteriodifluoromethylation. Isolated product yields were reported. Deuterium incorporation levels are highlighted in parentheses. [a] 0.1 M of aldehyde was used. [b] C1-deuterated aldehyde was used. [c] A lower concentration of aldehyde was used, see the Supporting Information for details.



Scheme 4. Substrate scope of continuous flow *gem*-difluoroalkenylation. Isolated yields were reported.

consumption and destruction of the gas as demonstrated by Ley and co-workers.[27]

Having established the hydrolysis–deuteration module, we then turned our attention to develop a retro [2+2] cycloaddition module for our system (Scheme 4). The reactor coil for the heated fragmentation process was placed between the OPA generation module and the back pressure regulator (BPR), as the utilization of a 50 PSI BPR would allow for the superheating of THF at 100 °C without solvent vaporization. This highlighted the utility of the flow apparatus in executing reactions above the boiling point of the solvent and simultaneously maintaining homogeneity of a gas-liquid reaction. The substrate scope of the continuous flow *gem*-difluoroalkenylation was then investigated and a broad scope of *gem*-difluoroalkenes were obtained with a total residence time of 16 minutes. *gem*-Difluoroalkenylation of both electron-rich (**7b**–**7d**, **7f**–**7g**), electron-deficient (**7e**) and sterically hindered aldehydes (**7c**–**7d**) proceeded efficiently with $ClCF_2H$. In particular, the substrate containing an electron-rich allyloxy group (**7f**) did not undergo competing *gem*-difluorocyclopropanation,[28] thereby demonstrating chemoselectivity. The scope of our flow reaction could be further expanded to α- or β-substituted alkenyl aldehydes (**7h**–**7i**) while heterocycles (dibenzofuran, thiophenes, carbazole) were well tolerated (**7j**–**7m**) under the continuous flow conditions. The aldehyde derivative of the drug probenecid underwent the *gem*-difluoroalkenylation smoothly to give **7n** in 74% isolated yield.

To demonstrate the synthetic utility of our deuteriodifluoromethylation in a wider scope, we have carried out derivatizations of product **6a** (Scheme 5). Additional fluorination on the α-deuteriodifluoromethylated benzyl alcohols was possible using commercially available reagents and **8a** was isolated in 62% yield.[29] Amines are ubiquitous in pharmaceuticals and agrochemicals.[30] C–N bond forming reactions including Mitsunobu and Ritter reaction were applicable and transformed **6a** into **8b** and **8c** in excellent yields, whereas the phthalimide in **8b** could be removed to give an amino group ($-NH_2$). Dess–Martin oxidation of **6a** gave the α-CF_2D ketone **8d** in 98% yield while the deuterium incorporation level was unaffected. We were also pleased to

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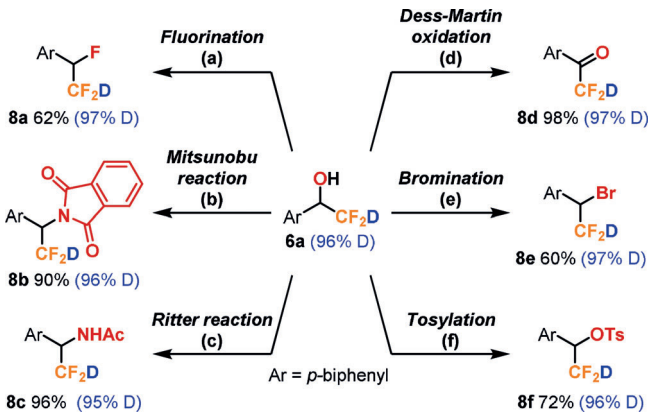
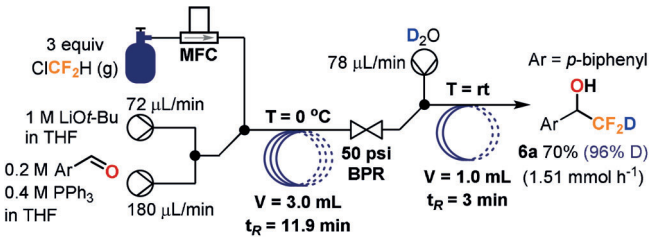


Scheme 5. Transformation of product **6a**. Reaction conditions: a) **6a** (0.3 mmol), NEt_3 (6 equiv), PBSF (2 equiv), $NEt_3{\cdot}3HF$ (2 equiv), THF (0.25 M), RT; b) **6a** (0.3 mmol), PPh_3 (1.1 equiv), phthalimide (1.1 equiv), DEAD (1.2 equiv), THF (0.15 M), RT; c) **6a** (0.3 mmol), H_2SO_4 (300 μL), MeCN (0.1 M), 80 °C; d) **6a** (0.3 mmol), Dess–Martin periodinane (1.2 equiv), DCM (0.25 M), RT; e) **6a** (0.3 mmol), NBS (1 equiv), $P(OPh)_3$ (1 equiv), DCM (0.3 M), 40 °C; f) **6a** (0.3 mmol), TsCl (1 equiv), DABCO (1.2 equiv), DCM (0.3 M), RT.

find that **6a** could be transformed to give the resulting bromide **8e** and tosylate **8f** in 60% and 72% yield, respectively. Additionally, we studied the scalability of our system and doubled the microreactor volumes and flow rates (Scheme 6). Product **6a** was isolated in 70% overall yield (1.4 grams) within a total residence time of 14.9 minutes. The production rate increased from 0.832 mmol h^{-1} (Scheme 3, entry **6a**) to 1.51 mmol h^{-1} (Scheme 6).



Scheme 6. Scaled-up continuous flow deuteriodifluoromethylation.

Conclusion

In conclusion, we have demonstrated the effective utilization of chlorodifluoromethane gas in the continuous flow synthesis of α-deuteriodifluoromethylated benzyl alcohols and *gem*-difluoroalkenes. The use of a flow system enabled efficient heat and mass transfer, and addressed several batch limitations such as inadequate gas–liquid interfacial contact. A broad scope of aldehydes with different conjugation, electron richness and steric profiles were successfully demonstrated as substrates, and a range of functional groups and heteroarenes were well tolerated. We further demonstrated the scale-up of our flow deuteriodifluoromethylation and the derivatization of an α-deuteriodifluoromethyl benzyl alcohol to a number of different products.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: chlorodifluoromethane · continuous flow · deuteration · difluoromethylation · *gem*-difluoroalkene

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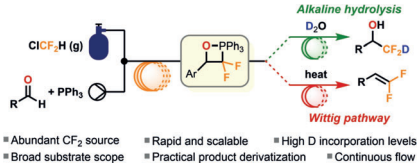
Research Articles

Difluoromethylation

W. C. Fu, T. F. Jamison* ____ ▮▮▮▮–▮▮▮▮

Deuteriodifluoromethylation and *gem*-Difluoroalkenylation of Aldehydes Using $ClCF_2H$ in Continuous Flow



$ClCF_2H$ gas is used in the continuous-flow deuteriodifluoromethylation and *gem*-difluoroalkenylation of aldehydes. Mechanistic studies reveal the difluorinated oxaphosphetane intermediate can proceed via alkaline hydrolysis in the presence of D_2O to provide α-deuteriodifluoromethylated benzyl alcohols or undergo a retro [2+2] cycloaddition under thermal conditions to provide the *gem*-difluoroalkenylated product.

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