COMMUNICATION

Defluoroalkylation of sp^3 C–F Bonds of Industrially Relevant Hydrofluoroolefins

Nicholas A. Phillips,[a] Gregory J. Coates,[a] Andrew J. P. White[a] and Mark R. Crimmin*[a]

Dedication ((optional))

Abstract: *A simple, one-pot procedure is reported for the selective defluoroalkylation of trifluoromethyl alkene derivatives with aldehydes and ketones. The reaction sequence allows construction of a new C–C bond in a highly selective manner from a single sp^3 C–F bond of a CF$_3$ group in the presence of sp^2 C–F bonds. The scope incorporates industrially relevant fluorocarbons including HFO-1234yf and HFO-1234ze. No catalyst, additives or transition metals are required, rather the methodology relies on recently developed boron reagent. Remarkably, the boron site of this reagent plays a dual role in the reaction sequence, being nucleophilic at boron in the C–F cleavage step (S$_N$2') but electrophilic at boron en route to the carbon–carbon bond forming step (S$_E$2'). The duplicitous behaviour is underpinned by a hydrogen atom migration from boron to the carbon atom of the carbene ligand*

The trifluoromethyl group (CF_3) is widely used in chemical synthesis.[1,2] This functional group is common amongst fluorinated pharmaceuticals and agrochemicals. The majority of modern refrigerants also contain at least one trifluoromethyl group. This includes 2,3,3,3-tetrafluoropropene (HFO-1234yf),[3] which is being positioned as a direct replacement for 1,2,2,2-tetrafluoroethane (HFC-134a) the most abundant refrigerant in the automotive sector. The ubiquity of the trifluoromethyl group stems in part from its chemical robustness. The sp^3 C–F bonds are strong and reluctant to further chemical transformations. When reactions do occur, they are often complicated by low chemoselectivity as C–F bond strengths become weaker across the series $CF_3 > CF_2H > CFH_2$.[4]

Only recently have synthetic methods emerged for the selective alkylation or arylation of a single sp^3 C–F bond of the trifluoromethyl group.[5,6] These transformations are highly desirable, not only because they reveal the trifluoromethyl moiety as a point for functional group interconversions, but also because they generate a difluoromethylene unit through a modular carbon–carbon bond forming step. The difluoromethylene group (–CF_2–) itself is a target of interest due to its inclusion in a number of isosteres in medicinal chemistry.[7-9] To give some examples, the selective alkylation of trifluoromethyl benzene derivatives with ketones or alkenes has been achieved through reactions that generate either carbocation or radical intermediates.[10,11] The latter species can be produced electrochemically[12] or by carefully constructed photoredox catalytic cycles.[13-15] In contrast, methods for selective carbon–carbon bond formation from vinylic trifluoromethyl groups are far less well advanced, likely due to the difficulty in controlling the reactivity of the adjacent C=C π-system.[16-19]

Ito and coworkers have reported the enantioselective defluoroalkylation of trifluoromethyl-substituted alkenes.[20] The key step in this report was the defluoroborylation of the substrate using a chiral copper(I) catalyst. Both racemic and enantioselective variants of this reaction have been widely studied.[21-26] Despite this elegant advance, to the best of our knowledge defluoroalkylation of industrially relevant hydrofluoroolefins (HFOs), such as HFO-1234yf remains elusive. These types of substrate pose an additional challenge as they contain both sp^3 C–F and sp^2 C–F bonds, hence chemoselectivity becomes a central concern. We hypothesised that the defluoroalkylation of HFO-1234yf could be achieved by a stepwise S$_N$2' / S$_E$2' reaction sequence mediated by main group reagents.[27,28] The key challenge being the identification of reagent that allows control of the selectivity of both steps without loss of fidelity over which site (α or γ) of the allylic system reacts (Figure 1).

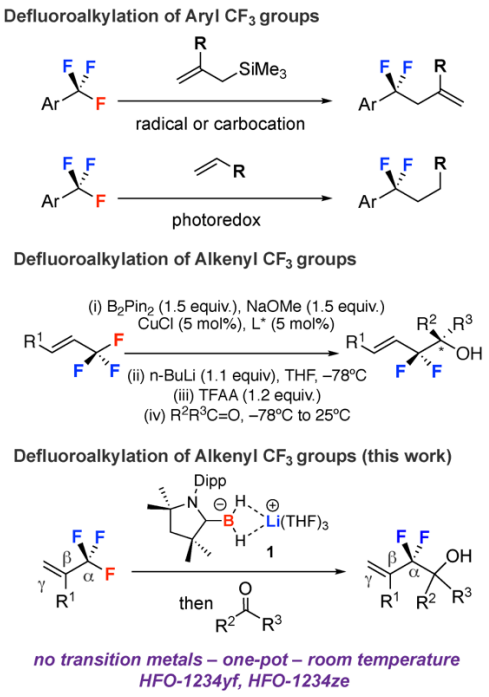

Figure 1. Defluoroalkylation and defluoroarylation of trifluoromethyl benzenes and trifluoromethyl alkenes.

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In this paper, we detail a selective defluoroalkylation of a single sp^3 C–F bond of commercial HFO-1234s by a one-pot procedure. The new transformation relies on the boron reagent **1**. **1** is supported by a cyclic amino alkyl carbene (cAAC) ligand and was originally reported by Braunschweig and co-workers (Figure 1).[29] Reaction of **1** with a series of industrially relevant hydrofluoroolefins (HFOs) in benzene-d_6 solution results in rapid defluoroborylation to form **2a-c** *via* an apparent S_N2' mechanism in 90 – 94% spectroscopic yield (Figure 2).

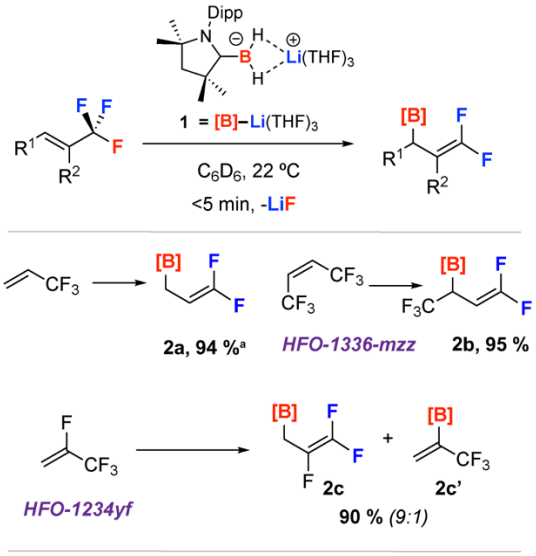

Figure 2. Reaction of **1** with industrially relevant HFOs. [a]yield measured by NMR spectroscopy against 1-fluorohexane as an internal standard.

The reactions occur within seconds at 22 °C upon admission of the HFO (1 bar), as evidenced by a colour change of the reaction mixture from orange to colourless. In a representative case, reaction of **1** with 3,3,3-trifluoropropene is characterised by a shift of the resonance in the ^{11}B NMR spectrum from δ_B = 0.7 (br) ppm to δ_B = –21.4 (t, $^1J_{BH}$ = 85 Hz) ppm. The product **2a** is characterised by diagnostic ^{19}F NMR resonances at δ_F = –96.1 (d, $^2J_{FF}$ = 65 Hz) and –99.1 (d, $^2J_{FF}$ = 65 Hz) ppm. In the case of HFO-1234yf, two isomers derived from substitution at the terminal (γ – **2c**) and internal (β – **2c'**) position were observed in a 9:1 ratio. The minor isomer is proposed to derive from a direct S_NV mechanism.[27]

Attempts to crystallise **2a-c** proved unsuccessful. Isolation was likely compromised by the slow decomposition of these reagents in hydrocarbon solutions. Nevertheless, **2a** and **2c** were found to react with carbonyls under mild conditions (22 ºC) and short reaction times (10 min – 3 h). For example, naphthaldehyde was reacts with **2a** to generate the corresponding α,α-difluoroalcohol **3a** following work-up with aqueous acetic acid (Figure 3). **3a** demonstrates resonances in the $^{19}F\{^1H\}$ NMR spectrum at δ_F = –113.8 (d, $^2J_{FF}$ = 264 Hz) and δ_F = –116.4 (d, $^2J_{FF}$ = 264 Hz) ppm assigned to the diastereotopic fluorine atoms of the difluoromethylene group. No other fluorine containing products were observed and carbon–carbon bond formation occurs exclusively at the α-position, consistent with an S_E2' type pathway. The fluoroallylboration of aldehydes with related three-coordinate boranes has been reported before.[30]

The reaction sequence **1** → **2** → **3** can be carried out in one-pot at ambient temperature within several hours. Boron reagents derived from 3,3,3-trifluoropropene (**2a**) and HFO-1234yf (**2c**) participate in the reaction sequence while those from HFO-1336-mzz (**2b**) do not. For HFO-1234yf, the minor isomer **2c'** is unreactive. As a result, the two selectivity events in C–F bond breaking (S_N2') and C–C bond forming step (S_E2') are mutually reinforcing and products derived from **2c'** are not observed. Both electron-rich and electron-deficient aldehydes and ketones are tolerated as reaction partners. A number of functional groups survive the carbon–carbon bond forming step, including remote alkenes, aryl methyl ethers and aryl bromides. While an α,β-unsaturated carbonyl reacts by selective 1,2-addition, under the conditions examined there was no evidence for carbon–carbon bond formation for imines, esters or amides. The method is selective for sp^3 C–F over sp^2 C–F bonds and does not proceed past synthetic modification of a single C–F bond of the CF_3 group.

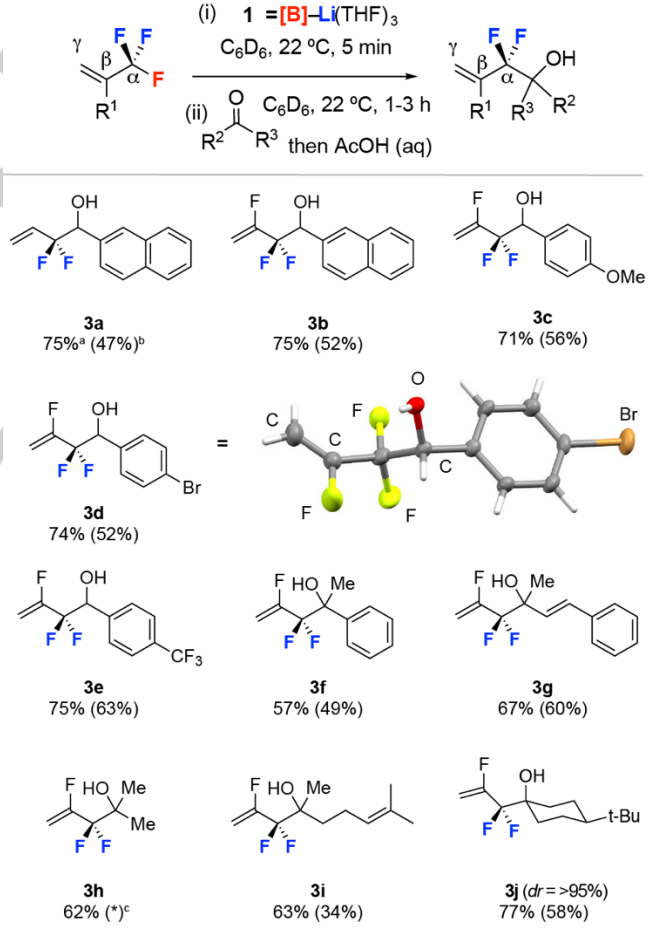

Figure 3. Reaction scope for the one-pot defluoroalkylation procedure. [a]yield over two steps measured by NMR spectroscopy against 1-fluorohexane as an internal standard. [b] isolated yield. [c] isolated by vacuum transfer as a solution in C_6D_6.

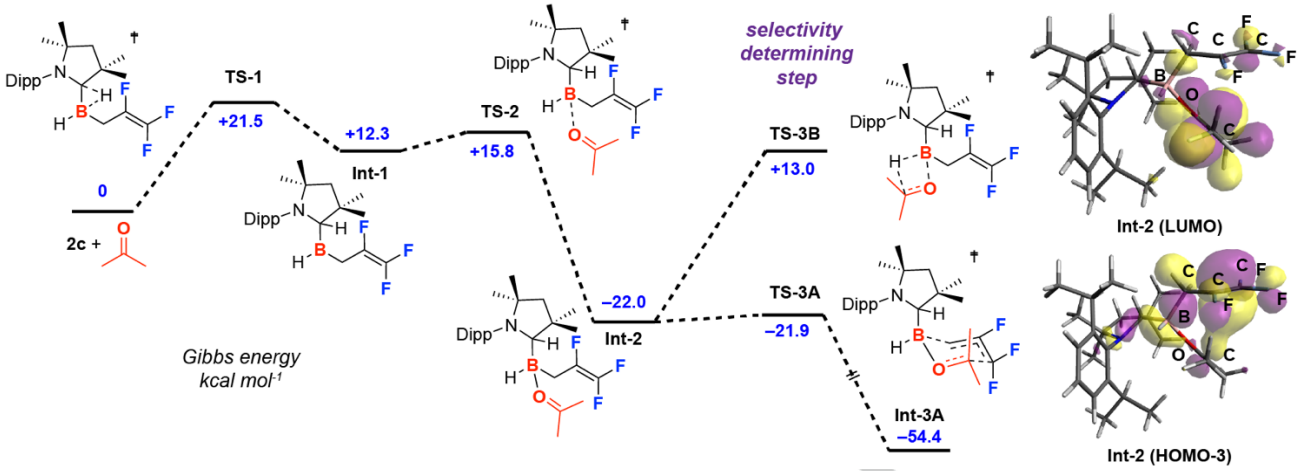

Figure 4. DFT calculated pathway for the carbon–carbon bond forming step from reaction of **2c** with acetone. The B3LYP functional with 6-31G** basis set was applied, with single point GD3BJ dispersion and PCM(benzene) solvent corrections.

DFT calculations were conducted to gain some mechanistic insight into the carbon–carbon bond forming step and the remarkable role the boron reagent plays in facilitating this transformation in the absence of external catalysts or reagents. Calculations were conducted using Gaussian09. The B3LYP functional with 6-31G** basis set was applied, with single point GD3BJ dispersion and PCM(benzene) solvent corrections. Discussion is limited to the reaction of **2c** with acetone (Figure 4).

In line with its strong σ-donor properties, dissociation of the cAAC ligand from **2c** is calculated to be extremely endergonic, $\Delta G°_{(298K)}$ > 50 kcal mol^{-1}. The high Gibbs free energy effectively rules out dissociation of the cAAC ligand under the reaction conditions. Thus, an alternative route to generate a vacant site at the boron centre must be in operation. It was found that hydrogen atom transfer from boron to the electrophilic carbon atom of the cAAC ligand to form **Int-1** is only mildly endergonic $\Delta G°_{(298K)}$ = +12.3 kcal mol^{-1} and occurs by **TS-1** with an accessible barrier of $\Delta G^{‡}_{(298K)}$ = +21.5 kcal mol^{-1}. **Int-1** possesses a vacant p-orbital to which a substrate may bind. Acetone coordination occurs by **TS-2** with a local Gibbs activation barrier of only $\Delta G^{‡}_{(298K)}$ = +3.5 kcal mol^{-1}. Adduct formation leads to **Int-2** in an exergonic step, $\Delta G°_{(298K)}$ = –22.0 kcal mol^{-1}. Two bond forming pathways are possible from **Int-2**, C–C bond formation by **TS-3A** - a highly organised 6-membered transition state - or C–H bond formation by **TS-3B**. Although C–H bond formation (hydroboration) was calculated to be the thermodynamically favoured pathway with $\Delta G°_{(298K)}$ = –59.2 kcal mol^{-1}, **TS-3B** is prohibitively high energy to be accessible, $\Delta G^{‡}_{(298K)}$ = +35 kcal mol^{-1}. In contrast, the C–C bond forming process occurs through **TS-3A** and is essentially a barrierless process $\Delta G^{‡}_{(298K)}$ = +0.1 kcal mol^{-1} leading to **Int-3B**, $\Delta G°_{(298K)}$ = –54.4 kcal mol^{-1} and ultimately the experimentally observed reaction product. The difference in energy between the two key transition states for the selectivity determining step can be explained by: *(i)* the difference in angle strain in the four-membered versus the six-membered (Zimmerman-Traxler) transition states, and *(ii)* consideration of the frontier molecular orbitals of **Int-2**. The HOMO-3 and HOMO-4 of **Int-2** are localised primarily on alkene π-bond and the B–H σ-bond respectively, these MOs differ in energy by ~ 10 kcal mol^{-1}. The LUMO involves the π*-orbital of the C=O fragment. Hence, the HOMO-3 / LUMO combination determine the selectivity.

1,2-Hydrogen atom migration has been invoked by Braunschweig and co-workers during the study of related cAAC stabilised boron reagents. Reactions of nucleophiles with [(cAAC)BH_3] have been shown to occur at the boron centre, but are accompanied by a 1,2-hydrogen atom shift from boron to the electrophilic carbon of the carbene ligand.[31] More recently, this 1,2-hydrogen shift has been exploited in the reduction chemistry of a dihydroboryl cation.[32] Evidence for the intermediate **Int-1** was acquired by trapping it as a 4-dimethylaminopyridine (DMAP) adduct **Int-1·DMAP**. While **Int-1·DMAP** could not be isolated, it was characterised by resonances in the expected region of the ^{11}B NMR spectrum at δ_B = –2.3 ppm and ^{19}F{^{1}H} NMR spectrum at δ_F = –112.8 (dd, J_{FF} = 105 Hz, 26 Hz), –131.2 (dd, J_{FF} = 105 Hz, 105 Hz) and –165.0 ppm (dd, J_{FF} = 105 Hz, 26 Hz).

Attempts to expand the reaction scope to HFO-1234ze, another industrial refrigerant gas, led to a remarkable double C–F bond functionalisation sequence (Figure 5). Reaction of *E*-HFO-1234ze with **1** followed by addition to naphthaldehyde and work-up led to the isolation of **3a**. The same product that formed from the defluoroalkylation of 3,3,3-trifluoropropene with this aldehyde. Monitoring the reaction as a function of time allowed characterisation of the intermediate **2d**. The structure of **2d** was further substantiated by derivatisation to form the 4-coordinate adduct **2d·DMAP**. Compound **2d·DMAP** is a four-coordinate boron fluoride characterised by diagnostic resonances at δ_B = +6.8 ppm and δ_F = –93.9 (d, $^{2}J_{FF}$ = 63 Hz), –98.9 (d, $^{2}J_{FF}$ = 63 Hz) and –188.4 (broad, BF) in the ^{11}B NMR and ^{19}F NMR spectrum respectively. **2d** is proposed to derive from a double C–F bond functionalisation. The first C–F functionalisation parallels that described for **2a-c** and involves the addition of **1** to HFO-1234ze by an S_N2' mechanism with elimination of 1 equiv. of LiF. The second C–F functionalisation is proposed to involve both a 1,2-hydrogen atom migration from boron to the cAAC ligand and

fluorine for hydrogen atom exchange on the γ-site of the fluoroalkyl chain. This latter exchange reaction results in a hydrodefluorination of a specific and single site of alkyl chain and undoubtedly benefits from a large thermodynamic driving force due to the formation of the B–F bond (Figure 5). We have proposed a related mechanism in the hydrodefluorination of hexafluoropropene by borane reagents.[3] Hence it is likely that, **3a** derives from a selective sp^3 C–F defluoroalkylation and sp^2 C–F hydrodefluorination sequence.

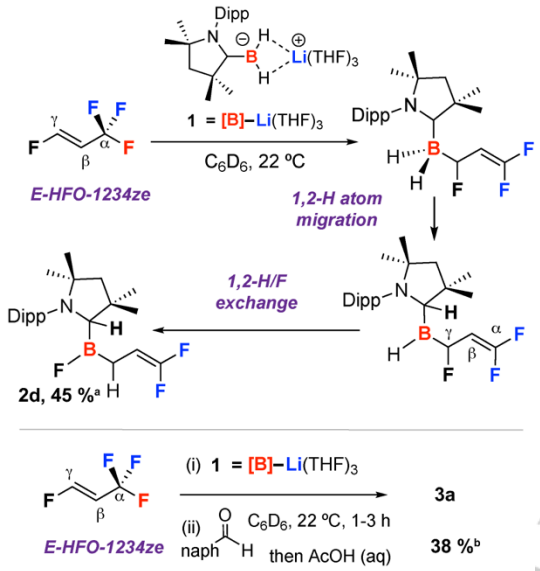

Figure 5. Stepwise reaction of *E*-HFO-1234ze with **1** and naphthaldehyde. [a]yield measured by NMR spectroscopy against 1-fluorohexane as an internal standard. [b] isolated yield.

In summary, we report a simple synthetic route that results in the highly selective defluoroalkylation of a single sp^3 C–F bond of a vinylic trifluoromethyl group. Reactions proceed at room temperature and do not require the use of transition metals or additives. The high selectivity can be attributed to two mutually reinforcing selectivity determining events that occur along a S_N2' S_E2' reaction sequence. This new method allows the upgrading of 3,3,3-trifluoropropene, HFO-1234yf and HFO-1234ze. The latter two fluorinated gases are being marketed as next generation refrigerants and are set to be used on increasing scales as the demand for refrigeration increases.

Acknowledgements

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Keywords: fluorine • trifluoromethyl • C–F functionalisation • defluoroalkylation • HFOs

Declaration of Conflict of Interest: Aspects of the work are the subject of a UK patent application 19066657.0

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Layout 1:

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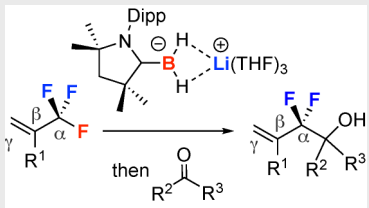

high selectivity (S_N2' / S_E2' sequence)
no transition metals
one-pot – room temperature
HFO-1234yf, HFO-1234ze

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