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Divergent, stereospecific mono- and difluoromethylation of boronic esters

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Abstract: There is considerable interest in incorporating fluorine in agrochemicals and pharmaceuticals to improve their biological properties. Whilst a number of methods have been reported for installing CH₂F and CHF₂ groups, they are mainly limited to radical reactions which are invariably racemic. Herein, we report the divergent, stereospecific reaction of fluoroiodomethyl lithium with boronic esters which give α-fluoro-boronic esters. These unique intermediates can be readily transformed into the corresponding mono- or difluoromethylated compounds, via proto- or fluoro-deboronation, respectively. The use of the highly unstable fluoroiodomethyl lithium was key to allowing rapid 1,2-migration over competing decomposition of the carbanion. DFT calculations informed and supported the experimental findings.

Organofluorine compounds are finding increasing applications, particularly in medicinal chemistry, where replacing a C–H bond with a C–F bond often provides more potent lead molecules. For example, mono-, di-, and trifluoromethyl groups are frequently introduced in agrochemicals and pharmaceuticals to enhance their metabolic stability, lipophilicity, as well as to increase their binding affinity. Of these fluoromethyl groups, the introduction of CF₃ is the most common because of the well-established reactivity of various commercially available reagents (e.g. Umemoto, Ruppert-Prakash, or Langlois). However, synthetic routes for direct mono- and difluoromethylation are more limited (Scheme 1a). The introduction of CH₂F or CHF₂ groups at sp² centres usually involves metal catalyzed cross-couplings, while installation on sp³-carbons is mainly achieved by radical mono- and difluoromethylation of alkenes. As radicals are involved in these processes, controlling asymmetry is especially challenging.

Since CH₂F and CHF₂ groups are bioisosteric with methyl and hydroxyl groups, respectively, their stereoselective incorporation into organic molecules is highly desirable. We considered the possibility of transforming enantioenriched boronic esters into CH₂F or CHF₂ groups by a stereospecific Matteson-type homologation (via 1,2-migration) with a mono- or difluorinated carbene precursor, followed by subsequent removal of the boron moiety (Scheme 1b). These transformations would require carbene precursors such as LiCH(F)X and LiCF₂X. However, such entities are highly unstable reagents, being prone to carbene formation, and so careful consideration of suitable leaving groups (X) was required. There were three main factors governing the nature of X that we needed to consider: (i) X must be a good leaving group to promote 1,2-migration but not too good that it results in elimination of LiX with formation of a fluorine-stabilized carbene (ii) X must not stabilize the lithiated species otherwise dissociation of the boronate complex back to its constituents will occur leading to decomposition of the carbanion (iii) X must not stabilize the potential carbone as this will promote α-elimination of LiF leading to decomposition of the carbanion. DFT calculations were performed to help guide and understand the effect of the X substituent on the homologation process (M06-2X/6–311G(d,p)+LANL2DZ (5d, 7f), with a polarizable continuum model of solvation [PCM,THF]). MeBpin and [CH(F)Br] were chosen for the model reaction (Scheme 2A). The lithium cation was not modelled explicitly as a previous report on related 1,2-migrations observed minimal structural differences between the optimized structures of boronate complexes with and without the cation.}

Supporting information for this article is given via a link at the end of the document.
The DFT calculations suggested that boronate complex \( \text{I}_{\text{B2}} \) would undergo 1,2-migration (\( \Delta G^* = 11.7 \text{ kcal mol}^{-1} \)) affording the thermodynamically stable, homologated product \( \text{II}_{\text{B2}} \). Boronate \( \text{I}_{\text{B2}} \) can also potentially dissociate back to the carbanion \( \text{III}_{\text{B2}} \). Although we were unable to find a transition state for this dissociation, it must be higher than the energy of the anion loosely bound to MeBpin (\( \Delta G = 21.7 \text{ kcal mol}^{-1} \)), and so homologation should occur. Calculations were also conducted for difluorinated and non-fluorinated carbeneboids \( \text{[CF}_2\text{Br]}_2 \) and \( \text{[CH}_3\text{Br]}_2 \) (\( \text{III}_{\text{B2}} \) and \( \text{III}_{\text{B2}} \), respectively), and clear trends emerged: the more fluorne atoms attached to carbon the higher the barrier to 1,2-migration and the lower the barrier to dissociation (Scheme 2B). In fact, Li\( \text{CF}_2\text{Br} \) underwent dissociation in preference to 1,2-migration making it an unsuitable reagent for the proposed homologation reaction. Having identified the monofluoro-carbenoid as a promising candidate, the effect of the X group on \( \alpha \)-elimination of fluoride was evaluated. DFT calculations were performed to determine \( \Delta G \) for the equation in Scheme 2C as this would give an indication of the relative propensity for carbene formation for different X groups. For the second period elements N, O and F, it was found that \( \alpha \)-elimination of fluoride followed the order N>O>F, making the most electronegative halide optimum. Moving down the halogen series, \( \alpha \)-elimination of fluoride was less and less favoured (the reaction became more endothermic), making iodide optimum. The trend mirrors the mesomeric effect of X to stabilise a carbene by donating electron density into the empty p-orbital of the carbene carbon (\( \text{NR}_3 > \text{OR} > \text{F} > \text{Cl} > \text{Br} > \text{I} \)). Thus, fluorodimethylmethylithium emerged as the ideal candidate for the homologation since (i) iodide is least able to stabilise the carbene, thereby promoting stability of the carbanion and (ii) iodide is the optimum leaving group, thereby promoting 1,2-migration. In fact, Luisi and Pace recently found that fluorodimethylmethylithium was able to add to carbonyl compounds under Barbier conditions and gave higher yields than \( \text{LiCH(F)Br} \). Guided by our computational analysis and the literature precedent,\textsuperscript{22-23} we began our investigation by treating a mixture of boronic ester 1 and fluoroiodomethane with LDA at \( -78 \degree \text{C} \) (Scheme 3). After optimization we obtained boronic ester 2 in 90% yield (see Table T1 in the SI for full optimisation). Fluoroboronic ester 2 was unstable to chromatography, but a simple aqueous work up gave material of sufficient purity to be used directly in the subsequent transformations. It should be noted that 2 represents a unique example of an isolated alkyl \( \alpha \)-fluoroboronic ester outside the tetracoordinated MIDA and trifluoroborates.\textsuperscript{24-26} The ready preparation of these intermediates will now enable their broader applications in synthesis.

Having identified a suitable reagent and conditions for homologation, our attention focused on the subsequent protodeboronation step which would give access to the CH\( _2\text{F} \) functionality. Benzyllic boronic esters undergo protodeboronation using \( \text{XF}_2\text{H}_2\text{O} \) (\( X = \text{Cs, } n\text{Bu}_3\text{N} \)) but application of these conditions resulted in recovery of the starting material at room temperature or decomposition at elevated temperatures (\( 100 \degree \text{C} \)). This indicated that, unlike an aromatic ring, fluoride was not able to stabilize an incipient negative charge\textsuperscript{28}. Acidic conditions (treatment with \( \text{EtCO}_2\text{H} \) or \( \text{H}_2\text{PO}_4\text{H} \)) were also unsuccessful and led mainly to \( \alpha \)-elimination. We then considered a radical-based approach since it is known that fluoride can stabilize an adjacent radical.\textsuperscript{30} In particular, Renaud had shown that pinacol boronic esters could undergo radical-mediated protodeboronation by acid catalysed transterification to a catechol boronic ester followed by oxidation and hydrogen atom transfer.\textsuperscript{31} To our delight, following screening of different acid and solvent combinations (see Table T2 in the SI for full optimisation) we found that using TFA and 4-tBu-catechol in \( \text{CH}_2\text{Cl}_2 \) gave the corresponding alkylfluoride 3 in high yield (Scheme 4). Notably, the reaction had to be performed under an inert atmosphere otherwise oxidation of the boronic ester occurred, with subsequent HF elimination providing the corresponding aldehyde product.

With our optimised conditions in hand, the substrate scope of the homologation-protodeboronation sequence was explored, without purification of the intermediate \( \alpha \)-fluoro-boronic ester (Scheme 5). NMR and isolated yields over two steps are reported, with the latter usually being lower due to the increased volatility caused by the replacement of the boryl moiety with the CH\( _2\text{F} \) group.\textsuperscript{1} Primary boronic esters bearing different aromatic rings were initially explored. The two-step process tolerated electron-rich/neutral \( (3a-3e) \) and electron-rich aromatics \( (3f-3l) \). Notably, we observed no competing addition of \( \text{LiCH(F)I} \) to electrophilic functional groups, such as methyl esters \( (3b) \) and nitriles \( (3c) \). The homologation-protodeboronation sequence was also successfully applied to the synthesis of perfluorinated product \( 3j \) but its high volatility complicated its isolation. Amino acid derivatives were also suitable substrates giving \( 3k \) and \( 3l \), the latter without racemization. Notably, the acid sensitive Boc group was tolerated during the acidic protodeboronation step. The methodology could also be extended to secondary boronic esters, as demonstrated by \( 3m-3o \), although yields tended to be slightly lower (compare \( 3f \) with \( 3o \)). Complete stereospecificity was observed with \( 3o \), thereby providing a route to a chiral fluorinated isopropyl group. The homologation-protodeboronation sequence was also applied to biologically relevant molecules such as derivatives of cholesterol, diosgenin, and lithocholic acid \( (3p, 3q, \text{and } 3r, \text{respectively}) \). Again, no loss in diastereoselectivity was observed for \( 3p \) and \( 3q \), indicating the stereospecificity of the 1,2-migration.\textsuperscript{15-16} Furthermore, functional groups such as alkenes \( (3p \text{ and } 3q) \), acetals \( (3q) \) and silyl ethers \( (3r) \) were well tolerated under the reaction conditions. However, tertiary boronic esters were unreactive, probably reflecting a slower rate of boronate formation and competing decomposition of \( \text{LiCH(F)I} \).
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Scheme 5. Homologation-protodeboronation scope. $^{19}$F NMR yields over two steps using 1-fluoropentane as standard (in brackets, isolated yields). For 3i, the amino alcohol protecting group was lost during the reaction sequence.

We then turned our attention to the fluordeboronation of 2 which would give access to the CHF₂ functionality. Two procedures have been reported for the fluordeboronation of boronic esters: (i) reaction of arylboronate complexes with selectfluor$^{32}$ and (ii) reaction of pinacol boronic esters with selectfluor and AgNO₃. $^{33}$ Whilst the first method was unsuccessful, the second method bore fruit. Through modification of the reported conditions (see Table T3 in the SI for full optimization) fluordeboronation of 2 to the desired product 4 could be realized (Scheme 6). Notably, reducing the reaction time (usually to 3-4 hours) avoided unwanted benzylic oxidation of the product 4. Having identified suitable conditions, we explored the substrate scope of the homologation-fluordeboronation sequence, again without purification of the intermediate α-fluoro-boronic ester (Scheme 7). Primary boronic esters bearing different aromatic rings were initially explored. Whilst electron neutral/rich aromatics worked well (4a-4c), electron deficient aromatics resulted in diminished reactivity, and so further optimization was conducted (see Table T4 in the SI for full optimization).

By increasing the stoichiometry of selectfluor and using AgOAc in place of AgNO₃ enabled the homologation-fluordeboronation sequence to be extended to primary boronic ester substrates containing electron-poor aromatic rings (4d-4g) and a range of other functional groups (4h-4i). A notable example is amino acid 4h, a bioisostere of homoserine in which the hydroxyl group has been replaced with the lipophilic H-bond donor CHF₂. The reaction was also extended to a lithocholic acid-derived boronic ester, leading to 4i. These conditions were also successfully applied to secondary boronic esters (4j-4m). Furthermore, the reaction was fully stereospecific as shown by transforming an enantioenriched secondary boronic ester into difluoromethylated product 4l in high enantiomeric excess. The stereospecificity was also demonstrated in the transformation of a cyclic boronic ester into 4m. The yield and substrate scope of the homologation-fluordeboronation sequence is more limited than the homologation-protodeboronation, and further methodology development is currently ongoing in our lab.
In conclusion, a novel conversion of boronic esters into mono- and difluoromethyl groups has been reported. Guided by DFT calculations on a series of potential fluorinated carbenoids, fluoroiodomethylboration was selected as the ideal reagent for stereoselective homologation of boronic esters to generate unique α-fluoroboronic esters, which can be converted into CH₂F₂ or CH₂F₂ groups via protodeboronation or fluordeboronation, respectively. The methodology uses commercially available reagents (including the carbenoid precursor - fluoroiodomethane), proceeds under mild reaction conditions and with perfect stereoselection.

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Keywords: Fluoromethylation • Boronic esters • 1,2-migration • fluorocarbon • stereoselectivity

Fluoro divergence: Upon homologation of a boronic ester with fluoroiodomethyllithium, the intermediate α-fluoro-boronic ester can be converted into -CH₂F (via protodeboronation) or -CHF₂ (via fluorodeboronation). The choice of the fluorocarbenoid was key to success, requiring a substituent that was both a good leaving group and poor at stabilizing a carbene. Exploiting the stereospecificity of the 1,2-migration, this approach enables complete control of asymmetry.

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