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Difluorination of α -(bromomethyl)styrenes via I(I)/I(III) catalysis: facile access to electrophilic linchpins for drug discovery†

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Simple α -(bromomethyl)styrenes can be processed to a variety of 1,1-difluorinated electrophilic building blocks via I(I)/I(III) catalysis. This inexpensive main group catalysis strategy employs *p*-Toll as an effective organocatalyst when combined with Selectfluor® and simple amine·HF complexes. Modulating Brønsted acidity enables simultaneous *geminal* and *vicinal* difluorination to occur, thereby providing a platform to generate multiply fluorinated scaffolds for further downstream derivatization. The method facilitates access to a tetrafluorinated API candidate for the treatment of amyotrophic lateral sclerosis. Preliminary validation of an enantioselective process is disclosed to access α -phenyl- β -difluoro- γ -bromo/chloro esters.

Structural editing with fluorine enables geometric and electronic variation to be explored in functional small molecules whilst mitigating steric drawbacks.¹ This expansive approach to manipulate structure–function interplay continues to manifest itself in bio-organic and medicinal chemistry.² Of the plenum of fluorinated motifs commonly employed, the *geminal* difluoromethylene group³ has a venerable history.⁴ This is grounded in the structural as well as electronic ramifications of CH₂ → CF₂ substitution, as is evident from a comparison of propane and 2,2-difluoropropane (Fig. 1, upper). Salient features include localized charge inversion (C–H^{δ+} to C–F^{δ-}) and a widening of the internal angle from 112° to 115.4°. Consequently, *geminal* difluoromethylene groups feature prominently in the drug discovery repertoire⁶ to mitigate oxidation and modulate physicochemical parameters. Catalysis-based routes to generate electrophilic linchpins that contain the *geminal* difluoromethylene unit have thus been intensively pursued, particularly in the realm of main group catalysis.^{7–9} Motivated by the potential of this motif in contemporary medicinal chemistry, it was envisaged that an I(I)/I(III) catalysis platform could be leveraged to convert simple α -(bromomethyl)styrenes to *gem*-difluorinated linchpins: the primary C(sp³)–Br motif would facilitate downstream synthetic manipulations (Fig. 1, lower). To that end, *p*-Toll would function as a catalyst to generate *p*-TollIF₂ *in situ* in the presence of an external oxidant¹⁰ and an amine·HF complex. Alkene activation (I) with subsequent bromonium ion formation (II)¹¹ would provide a pre-text for the

first C–F bond forming process (III) with regeneration of the catalyst. A subsequent phenonium ion rearrangement¹²/fluorination sequence (III and IV) would furnish the *geminal* difluoromethylene group and liberate the desired electrophilic building block.

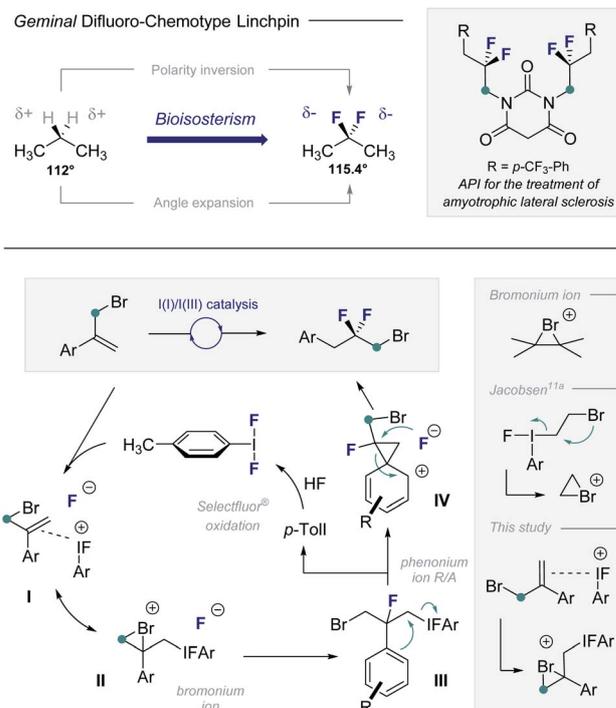


Fig. 1 The *geminal* difluoromethylene group: bioisosterism, and catalysis-based access from α -(bromomethyl)styrenes via I(I)/I(III) catalysis.

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† Electronic supplementary information (ESI) available. CCDC 2055892. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1sc01132d



To validate this conceptual framework, a short process of reaction optimization (**1a** → **2a**) was conducted to assess the influence of solvent, amine : HF ratio (Brønsted acidity)¹³ and catalyst loading (Table 1). Initial reactions were performed with *p*-TolI (20 mol%), Selectfluor® (1.5 equiv.) as an oxidant, and CHCl₃ as the reaction medium. Variation of the amine : HF ratio was conducted to explore the influence of Brønsted acidity on catalysis efficiency (entries 1–4). An optimal ratio of 1 : 6 was observed enabling the product **2a** to be generated in >95% NMR-yield. Although reducing the catalyst loading to 10 and 5 mol% (entries 5 and 6, respectively) led to high levels of efficiency (79% yield with 5 mol%), the remainder of the study was performed with 20 mol% *p*-TolI. Notably, catalytic vicinal difluorination was not observed at any point during this optimization, in contrast with previous studies from our laboratory.^{9d,i} A solvent screen revealed the importance of chlorinated solvents (entries 7 and 8): in contrast, performing the reaction in ethyl trifluoroacetate (ETFA) and acetonitrile resulted in a reduction in yield (9 and 10). Finally, a control reaction in the absence of *p*-TolI confirmed that an I(I)/I(III) manifold was operational (entry 11). An expanded optimization table is provided in the ESI.†

To explore the scope of this geminal difluorination, a series of α -(bromomethyl)styrenes were exposed to the standard reaction conditions (Fig. 2). Gratifyingly, product **2a** could be isolated in 80% yield after column chromatography on silica gel. The parent α -(bromomethyl)styrene was smoothly converted to species **2b**, as were the *p*-halogenated systems that furnished **2c** and **2d** (71 and 79%, respectively). The regioisomeric bromides **2e** and **2f** (70 and 62%, respectively) were also prepared for completeness to furnish a series of linchpins that can be functionalized at both termini by displacement and cross-

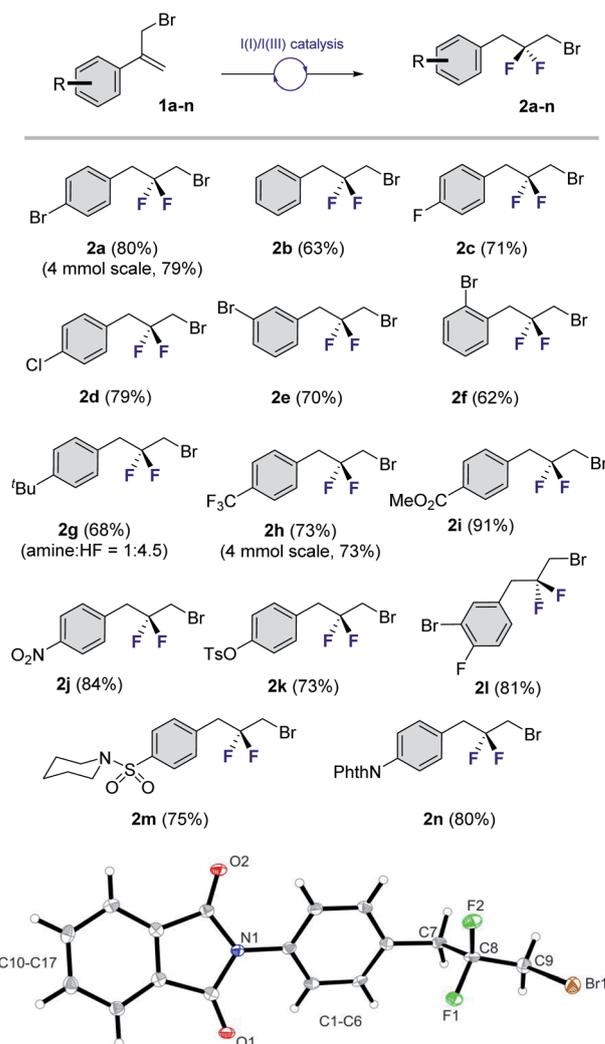
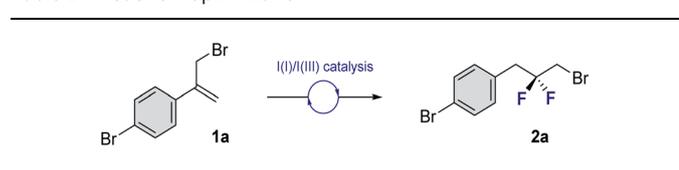


Fig. 2 Exploring the scope of the geminal difluorination of α -(bromomethyl)styrenes via I(I)/I(III) catalysis. Isolated yields after column chromatography on silica gel are reported. X-ray crystal structure of compound **2n** (CCDC 2055892†). Thermal ellipsoids shown at 50% probability.

Table 1 Reaction optimization^a



Entry	Solvent	Amine/HF	Catalyst loading [mol%]	Yield ^b [%]
1	CHCl ₃	1 : 4.5	20	72
2	CHCl ₃	1 : 6.0	20	>95
3	CHCl ₃	1 : 7.5	20	94
4	CHCl ₃	1 : 9.23	20	87
5	CHCl ₃	1 : 6.0	10	87
6	CHCl ₃	1 : 6.0	5	79
7	DCM	1 : 6.0	20	>95
8	DCE	1 : 6.0	20	93
9	ETFA	1 : 6.0	20	84
10	MeCN	1 : 6.0	20	50
11	CHCl ₃	1 : 6.0	0	<5

^a Standard reaction conditions: **1a** (0.2 mmol), Selectfluor® (1.5 equiv.), amine : HF source (0.5 mL), solvent (0.5 mL), *p*-TolI, 24 h, rt.
^b Determined by ¹⁹F NMR using α,α,α -trifluorotoluene as internal standard.

coupling protocols (**2a**, **2e** and **2f**). Modifying the amine : HF ratio to 1 : 4.5 provided conditions to generate the ^tBu derivative **2g** in 68% yield.¹⁴ Electron deficient aryl derivatives were well tolerated as is demonstrated by the formation of compounds **2h–2k** (up to 91%). Disubstitution patterns (**2l**, 81%), sulfonamides (**2m**, 75%) and phthalimides (**2n**, 80%) were also compatible with the standard catalysis conditions. Gratifyingly, compound **2n** was crystalline and it was possible to unequivocally establish the structure by X-ray crystallography (Fig. 2, lower).¹⁵ The C9–C8–C7 angle was measured to be 112.6° (*cf.* 115.4° for 2,2-difluoropropane).⁵ Intriguingly, the C(sp³)–Br bond eclipses the two C–F bonds rather than adopting a conformation in which dipole minimization is satisfied (F1–C8–C9–Br dihedral angle is 56.3°).

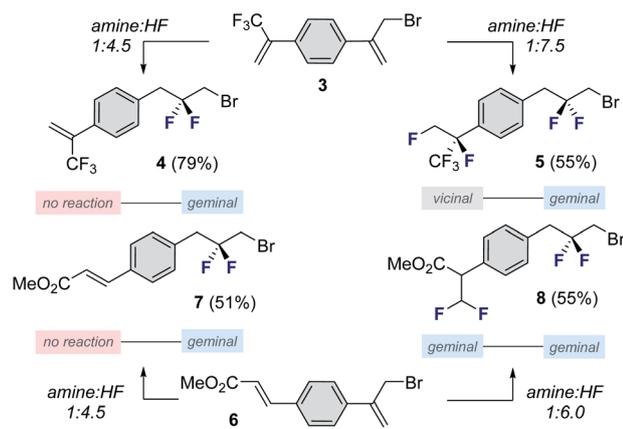
Cognizant of the influence of Brønsted acidity on the regioselectivity of I(I)/I(III) catalyzed alkene difluorination,^{9d} the influence of the amine : HF ratio on the fluorination of



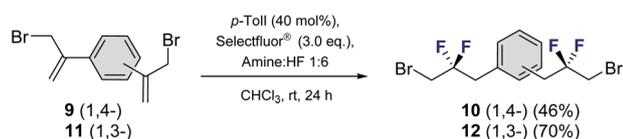
electronically non-equivalent divinylbenzene derivatives was explored (Fig. 3, top). Initially, compound **3** bearing an α -(trifluoromethyl)styrene motif was exposed to the standard catalysis conditions with a 1 : 4.5 amine : HF ratio. Exclusive, chemoselective formation of **4** was observed in 79% yield. Simple alteration of the amine : HF ratio to 1 : 7.5 furnished the tetrafluorinated product **5** bearing both the *geminal* and *vicinal* difluoromethylene¹⁶ groups (55% yield, 20% of the *geminal-geminal* product was also isolated. See ESI†). Relocating the electron-withdrawing group (α -CF₃ \rightarrow β -CO₂Me) and repeating the reaction with 1 : 4.5 amine : HF generated the *geminal* CF₂ species **7** in analogy to compound **4**. However, increasing the amine : HF ratio to 1 : 6.0 led exclusively to double *geminal* difluorination (**8**, 55%).

Similarly, bidirectional *geminal* difluorination of the divinylbenzene derivatives **9** and **11** was efficient, enabling the synthesis of **10** (46%) and **12** (70%), respectively. This enables

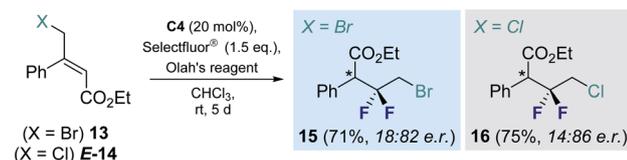
Chemoselective difluorination



Bidirectional reaction



Validation of an enantioselective difluorination



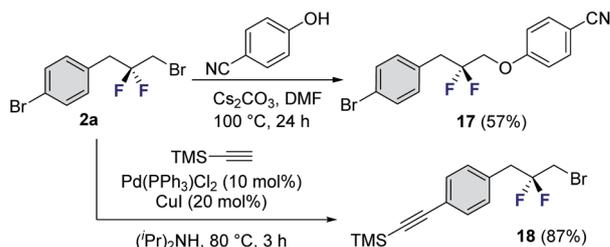
Catalyst Optimization (X = Br)

Cat.	R ¹	R ²	R ³	e.r.
C1	OCH ₃	Bn	H	31:69
C2	OCH ₃	CH ₃	CH ₃	33:67
C3	OCH ₃	CH ₃	CO ₂ CH ₃	23:77
C4	OCH ₃	<i>i</i> Pr	CO ₂ CH ₃	18:82
C5	OCH ₃	Bn	CO ₂ CH ₃	32:68
C6	NHCH ₃	CH ₃	CO ₂ CH ₃	31:69

Structure of **Z-14** is shown with R¹, R², and R³ substituents. <20% NMR yield using 20 mol% *p*-Toll.

Fig. 3 Exploring the synthetic versatility of this platform. (Top) Leveraging Brønsted acidity to achieve chemoselective fluorination. (Centre) Bidirectional functionalization. (Bottom) Preliminary validation of an enantioselective variant.

Site-selective functionalization



API 21 for amyotrophic lateral sclerosis (Cambria Pharmaceuticals)

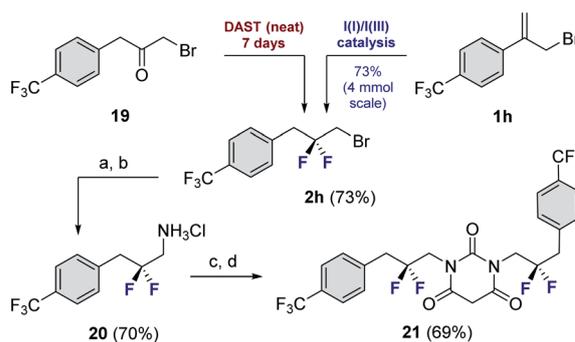


Fig. 4 Selected modification of building blocks **2a** and **2h**. Conditions: (a) NaN₃, DMF, 110 °C, 16 h. (b) Pd(OH)₂/C (10 mol%), EtOH, 1 M HCl, rt, 24 h; (c) CDI, Et₃N, THF, 60 °C, 16 h; (d) malonyl chloride, DCM, 0 °C, 2 h.

facile access to bis-electrophilic fluorinated linchpins for application in materials chemistry.

Preliminary validation of an enantioselective variant^{8d} was achieved using the trisubstituted alkene **13**. To that end, a series of *C*₂-symmetric resorcinol-based catalysts were explored (see Fig. 3, inset). This enabled the generation of product **15** in up to 18 : 82 e.r. and 71% isolated yield. It is interesting to note that this catalysis system was also compatible with the chlorinated substrate **E-14**. A comparison of geometric isomers revealed a matched-mismatched scenario: whilst **E-14** was efficiently converted to **16** (75%, 14 : 86 e.r.), **Z-14** was recalcitrant to rearrangement (<20%).

To demonstrate the synthetic utility of the products, chemoselective functionalization of linchpin **2a** was performed to generate **17** (57%) and **18** (87%), respectively (Fig. 4). Finally, this method was leveraged to generate an API for amyotrophic lateral sclerosis. Whereas the reported synthesis¹⁷ requires the exposure of α -bromoketone **19** to neat DAST over 7 days,¹⁸ compound **2h** can be generated using this protocol over a more practical timeframe (24 h) on a 4 mmol scale. This key building block was then processed, *via* the amine hydrochloride salt **20**, to API **21**.

Conclusions

In conclusion, an I(I)/I(III) catalysis manifold that facilitates the difluorinative rearrangement of α -(bromomethyl)styrenes is



disclosed. In addition to generating electrophiles with a single *geminal* difluoro motif, bidirectional processes are presented together with simultaneous *geminal* and *vicinal* difluorination. Preliminary validation of an enantioselective reaction is demonstrated, to enable the generation of versatile α -phenyl- β -difluoro- γ -bromo/chloro esters. Finally, the transformation has been leveraged to enable the synthesis of an amyotrophic lateral sclerosis drug: this provides an operationally simple alternative to common deoxyfluorinating reagents when preparing *gem*-difluoro linchpins for contemporary medicinal chemistry.

Author contributions

All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Note added after first publication

This article replaces the version published on 31st March 2021. The title contained a typesetting error. The oxidation state change in the title was incorrect and should read I(I)/I(III).

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