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

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Simple  $\alpha$ -(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  $\alpha$ -phenyl- $\beta$ -difluoro- $\gamma$ -bromo/chloro esters.

Structural editing with fluorine enables geometric and electronic variation to be explored in functional small molecules whilst mitigating steric drawbacks.<sup>1</sup> This expansive approach to manipulate structure–function interplay continues to manifest itself in bio-organic and medicinal chemistry.<sup>2</sup> Of the plenum of fluorinated motifs commonly employed, the *geminal* difluoromethylene group<sup>3</sup> has a venerable history.<sup>4</sup> This is grounded in the structural as well as electronic ramifications of CH<sub>2</sub> → CF<sub>2</sub> substitution, as is evident from a comparison of propane and 2,2-difluoropropane (Fig. 1, upper). Salient features include localized charge inversion (C–H<sup>δ+</sup> to C–F<sup>δ-</sup>) and a widening of the internal angle from 112° to 115.4°. Consequently, *geminal* difluoromethylene groups feature prominently in the drug discovery repertoire<sup>6</sup> 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.<sup>7–9</sup> 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  $\alpha$ -(bromomethyl)styrenes to *gem*-difluorinated linchpins: the primary C(sp<sup>3</sup>)–Br motif would facilitate downstream synthetic manipulations (Fig. 1, lower). To that end, *p*-Toll would function as a catalyst to generate *p*-TollIF<sub>2</sub> *in situ* in the presence of an external oxidant<sup>10</sup> and an amine·HF complex. Alkene activation (I) with subsequent bromonium ion formation (II)<sup>11</sup> would provide a pre-text for the

first C–F bond forming process (III) with regeneration of the catalyst. A subsequent phenonium ion rearrangement<sup>12</sup>/fluorination sequence (III and IV) would furnish the *geminal* difluoromethylene group and liberate the desired electrophilic building block.

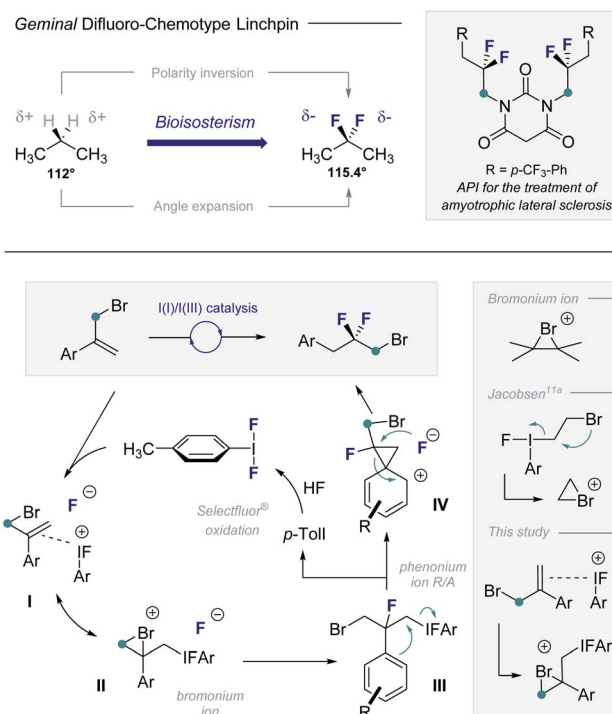


Fig. 1 The *geminal* difluoromethylene group: bioisosterism, and catalysis-based access from  $\alpha$ -(bromomethyl)styrenes via I(I)/I(III) catalysis.

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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)<sup>13</sup> and catalyst loading (Table 1). Initial reactions were performed with *p*-TolI (20 mol%), Selectfluor® (1.5 equiv.) as an oxidant, and CHCl<sub>3</sub> 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.<sup>9d,i</sup> 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  $\alpha$ -(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  $\alpha$ -(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-

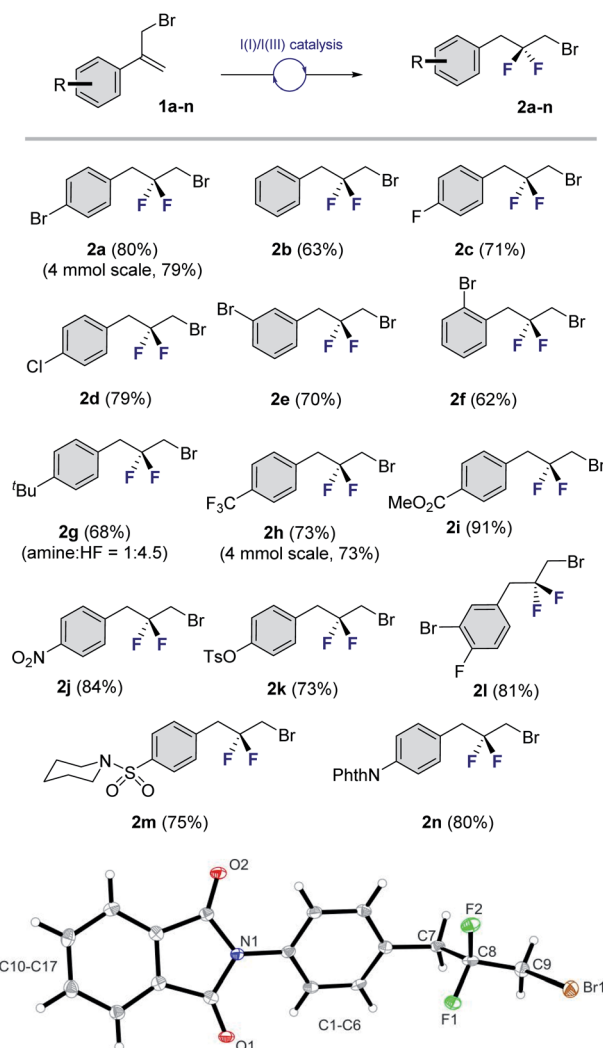


Fig. 2 Exploring the scope of the geminal difluorination of  $\alpha$ -(bromomethyl)styrenes via I(I)/I(III) catalysis. Isolated yields after column chromatography on silica gel are reported. X-ray crystal structure of compound **2n** (CCDC 2055892†). Thermal ellipsoids shown at 50% probability.

Table 1 Reaction optimization<sup>a</sup>

| Entry | Solvent           | Amine/HF | Catalyst loading [mol%] | Yield <sup>b</sup> [%] |
|-------|-------------------|----------|-------------------------|------------------------|
| 1     | CHCl <sub>3</sub> | 1 : 4.5  | 20                      | 72                     |
| 2     | CHCl <sub>3</sub> | 1 : 6.0  | 20                      | >95                    |
| 3     | CHCl <sub>3</sub> | 1 : 7.5  | 20                      | 94                     |
| 4     | CHCl <sub>3</sub> | 1 : 9.23 | 20                      | 87                     |
| 5     | CHCl <sub>3</sub> | 1 : 6.0  | 10                      | 87                     |
| 6     | CHCl <sub>3</sub> | 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 <sub>3</sub> | 1 : 6.0  | 0                       | <5                     |

<sup>a</sup> 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.  
<sup>b</sup> Determined by <sup>19</sup>F NMR using  $\alpha,\alpha,\alpha$ -trifluorotoluene as internal standard.

coupling protocols (**2a**, **2e** and **2f**). Modifying the amine : HF ratio to 1 : 4.5 provided conditions to generate the <sup>t</sup>Bu derivative **2g** in 68% yield.<sup>14</sup> 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).<sup>15</sup> The C9–C8–C7 angle was measured to be 112.6° (*cf.* 115.4° for 2,2-difluoropropane).<sup>5</sup> Intriguingly, the C(sp<sup>3</sup>)–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°).

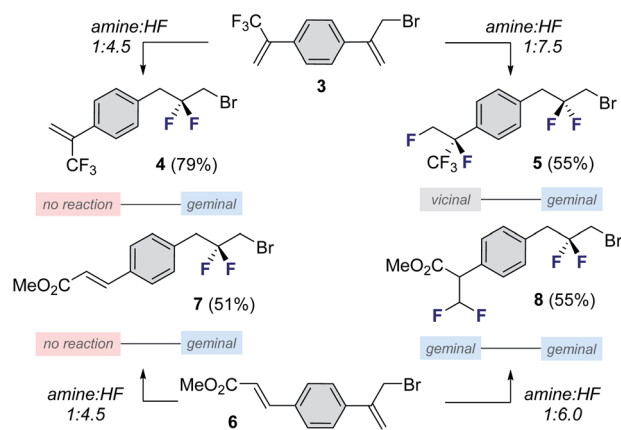
Cognizant of the influence of Brønsted acidity on the regioselectivity of I(I)/I(III) catalyzed alkene difluorination,<sup>9d</sup> the influence of the amine : HF ratio on the fluorination of



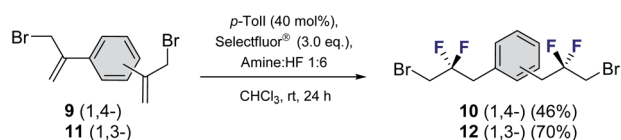
electronically non-equivalent divinylbenzene derivatives was explored (Fig. 3, top). Initially, compound **3** bearing an  $\alpha$ -(trifluoromethyl)styrene motif was exposed to the standard catalysis conditions with a 1 : 4.5 amine : HF ratio. Exclusive, chemoselective formation of **4** was observed 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* difluoromethylene<sup>16</sup> groups (55% yield. 20% of the *geminal-geminal* product was also isolated. See ESI†). Relocating the electron-withdrawing group ( $\alpha$ -CF<sub>3</sub>  $\rightarrow$   $\beta$ -CO<sub>2</sub>Me) and repeating the reaction with 1 : 4.5 amine : HF generated the *geminal* CF<sub>2</sub> 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

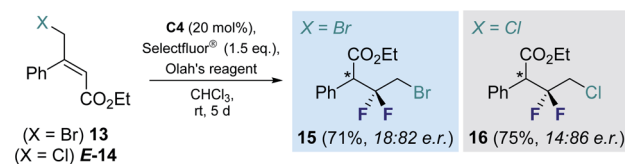
#### Chemoselective difluorination



#### Bidirectional reaction



#### Validation of an enantioselective difluorination



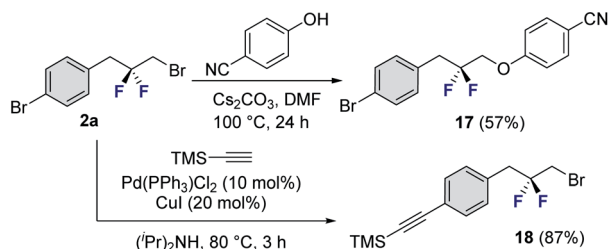
| Cat.      | R <sup>1</sup>    | R <sup>2</sup>  | R <sup>3</sup>                  | e.r.  |
|-----------|-------------------|-----------------|---------------------------------|-------|
| <b>C1</b> | OCH <sub>3</sub>  | Bn              | H                               | 31:69 |
| <b>C2</b> | OCH 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

Catalyst Optimization (X = Br)

**Z-14** (<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)

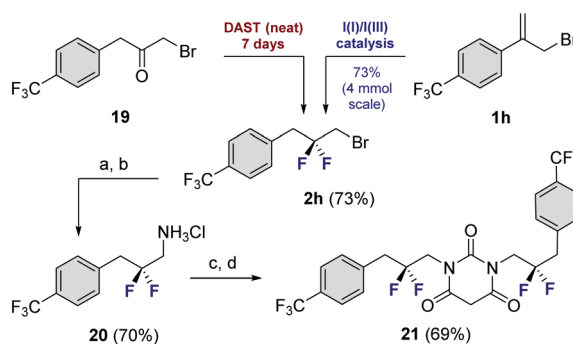


Fig. 4 Selected modification of building blocks **2a** and **2h**. Conditions: (a) NaN<sub>3</sub>, DMF, 110 °C, 16 h. (b) Pd(OH)<sub>2</sub>/C (10 mol%), EtOH, 1 M HCl, rt, 24 h; (c) CDI, Et<sub>3</sub>N, THF, 60 °C, 16 h; (d) malonyl chloride, DCM, 0 °C, 2 h.

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

Preliminary validation of an enantioselective variant<sup>8d</sup> was achieved using the trisubstituted alkene **13**. To that end, a series of *C*<sub>2</sub>-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 synthesis<sup>17</sup> requires the exposure of  $\alpha$ -bromoketone **19** to neat DAST over 7 days,<sup>18</sup> 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  $\alpha$ -(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  $\alpha$ -phenyl- $\beta$ -difluoro- $\gamma$ -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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