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Difluorinative ring expansions of benzo-fused carbocycles and heterocycles are achieved with *p*-(difluoroiodo)toluene†

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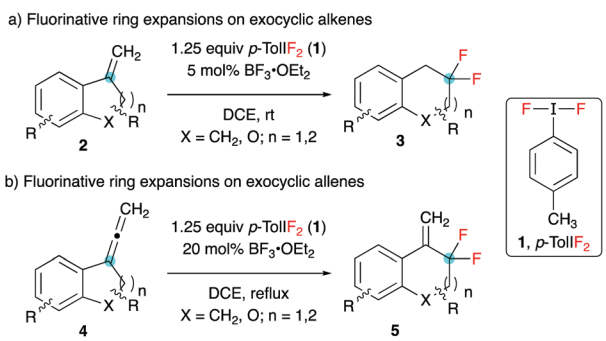
A chemoselective fluorinative ring expansion has been realized using the hypervalent iodine (HVI) reagent *p*-TolIF$_2$, which delivers β,β-difluoroalkyl arenes in yields up to 89% and allylic *gem*-difluorides in yields up to 78%. This rapid reaction exploits the ambiphilic nature of alkenes and allenes, and incorporates both fluorine atoms of the (difluoroiodo)arene in the products. The mechanism involves a 1,2-phenyl shift, which provides access in one step to important fluorinated building blocks for bioactive molecule synthesis.

Organofluorine compounds are critical to medicinal chemistry, agrochemistry, medical imaging, and materials sciences,[1] and there exists a critical need for new fluorination strategies. As part of this effort, the past decade has seen numerous new hypervalent iodine (HVI)-mediated fluorination reactions, as their inherent potential for addressing new or poorly accessible fluorinated motifs is realized.[2] HVI reagents are broadly reactive as oxidants,[3] owing to iodine's desire to return to its natural oxidation state, and in their fluorine-transfer reactions, this results in an apparent reversal of polarity of one of the fluoride ligands. For example, *p*-(difluoroiodo)toluene (*p*-TolIF$_2$, **1**),[4] a stable solid readily prepared from iodotoluene and aqueous fluoride *via* oxidation and ligand transfer, provides an "electrophilic" fluorine atom[5] analogous to other reagents derived from fluorine gas.

(Difluoroiodo)arenes have been employed in numerous fluorination processes, transferring one or both of their ligands. They fluorinate nucleophiles such as silyl enol ethers[6] or β-dicarbonyls,[7] and difluorinate ambiphilic functional groups like alkenes[5b,8] or diazo compounds,[9] serving as fluorine gas surrogates that deliver both "electrophilic" and nucleophilic fluorine atoms. The *vic*-difluorination of alkenes can be interrupted by various intramolecular processes, such as attack by nucleophiles (*e.g.* alcohols, amines, carboxylic acid derivatives), leading to a wide array of (hetero)cyclic fluorinated motifs.[10]

Reactions with styrenes[8a,c,d] or phenylallenes[11] are interrupted by 1,2-phenyl or 1,2-alkyl shifts, giving *gem*-difluorides *via* rearrangements or ring contractions.[8c,12] The state-of-the-art of HVI-mediated fluorinations has been redefined, as many of these reactions are now possible as catalytic and/or asymmetric processes, where chiral iodoarene catalysts[13] are re-oxidized *in situ*.[14,15] Therefore, as new fluorination reactions are realized, the potential for further development is significant.

Fluorinative ring expansions mediated by **1** are surprisingly unknown, but they might occur if substrates containing exocyclic alkenes are as viable as the related endocyclic alkenes used in ring contractions. If α-exomethylene-containing benzocycloalkanes (*e.g.* **2**) also react with **1** *via* a 1,2-phenyl shift pathway, they would give a direct synthesis of β,β-difluoroalkyl arenes **3**, a motif extensively studied within many bioactive molecules (Scheme 1a).[16,17] Furthermore, if allene-containing substrates (Scheme 1b, *e.g.* **4**) are also viable,[18] it would afford a novel, one-step synthesis of allylic *gem*-difluorides **5**, another valuable fluorine-containing motif not currently accessible *via* direct fluorination.[19] We report here how indanes, tetralins and related heterocyclic derivatives possessing α-exocyclic alkenes or -allenes react with *p*-TolIF$_2$ (**1**) to undergo rapid and chemoselective fluorinative ring expansions.



Scheme 1 Fluorinative ring expansions of alkenes and allenes using *p*-TolIF$_2$.

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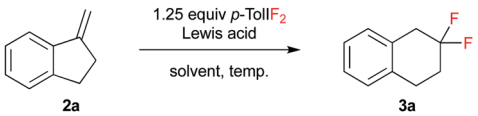
We began our investigation by reacting model indane **2a** with 1.25 equiv of *p*-TolIF$_2$ in DCE at reflux, using 20 mol% $BF_3{\cdot}OEt_2$ as activator, from which the β,β-difluoride **3a** was observed in 64% yield by ^{19}F NMR yield (Table 1, entry 1). Cooling the reaction to room temperature led to an increased yield (74%); however, further cooling to 0 °C resulted in a significantly decreased yield (entries 2 and 3). Chlorinated, polar and non-polar solvents were also tested, though none proved superior to DCE (entries 4–7, also see Table S1 for additional entries, ESI†). Of the other Lewis acidic activators tested, none proved as effective as $BF_3{\cdot}OEt_2$ (Table 1, entries 8–11, also see Table S2, ESI†). A 45% yield was even realized without an added activator, which we attribute to borosilicate activation of **1** (entry 12).[9d] The loading of $BF_3{\cdot}OEt_2$ was also studied, and while increasing to 30 mol% offered no improvement, decreasing it to 5 mol% was optimal, giving **4a** in 78% ^{19}F NMR yield, and 63% isolated yield after 20 minutes (entries 13 and 14). Therefore, reacting the α-exomethylene-containing indane **2a** with $BF_3{\cdot}OEt_2$-activated *p*-TolIF$_2$ gave a rapid and highly selective difluorinative ring-expansion, where both of the fluorine atoms derived from a single reagent.

We tested a series of α-exomethylene containing substrates in this reaction, first probing the effect of arene substitution on the indane-derived scaffold (Scheme 2). Halogenation was universally well tolerated, with the 5-bromo derivative **2b** giving **3b** in 75% yield. Halogenation at the 6-position included the bromo- (**2c**), fluoro- (**2d**) and chloro- (**2e**) derivatives, which gave **3c–e** in 72–77% yield. We were surprised that the 7-methyl derivative **2f** was converted to **3f** in only 43% yield, as neither steric or electronic biases were expected to interfere. Fluorination of the 7-bromo (**2g**) and 7-methoxy (**2h**) derivatives was also possible, giving the ring-expanded **3g** and **3h** in 57% and 49% yield, respectively. We then investigated the rearrangement homologous substrates derived from the tetralin scaffold, and found unsubstituted alkene **2i** to give **3i** in 75% yield.

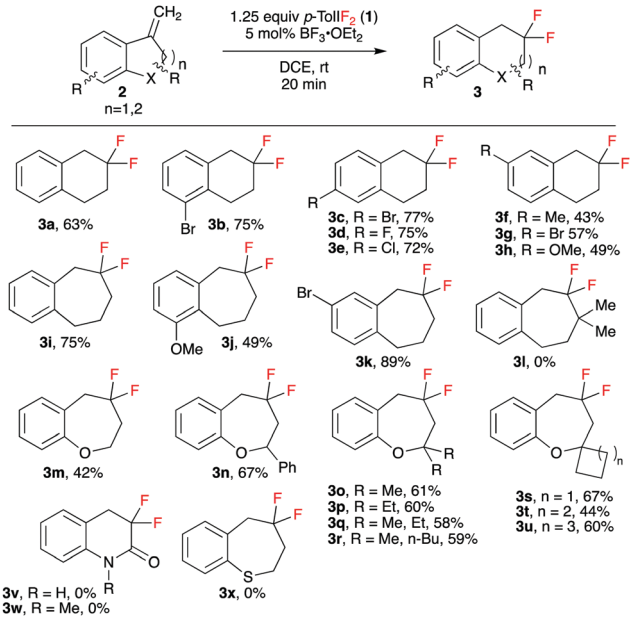
Table 1 Optimization of the fluorinative ring-expansion using indane **2a**



2a **3a**

Entry	Lewis acid (mol%)	Solvent	Temp. (°C)	Yield[a] (%)
1	$BF_3{\cdot}OEt_2$ (20)	DCE	Reflux	64
2	$BF_3{\cdot}OEt_2$ (20)	DCE	rt	74
3	$BF_3{\cdot}OEt_2$ (20)	DCE	0	35
4	$BF_3{\cdot}OEt_2$ (20)	DCM	rt	34
5	$BF_3{\cdot}OEt_2$ (20)	PhCl	rt	25
6	$BF_3{\cdot}OEt_2$ (20)	CH_3CN	rt	0
7	$BF_3{\cdot}OEt_2$ (20)	THF	rt	Trace
8	TiF_3 (20)	DCE	rt	31
9	TiF_4 (20)	DCE	rt	31
10	AlF_3 (20)	DCE	rt	27
11	InF_3 (20)	DCE	rt	34
12	—	DCE	rt	45
13	$BF_3{\cdot}Et_2O$ (30)	DCE	rt	57
14	$BF_3{\cdot}Et_2O$ (5)	DCE	rt	78 (63)[b]

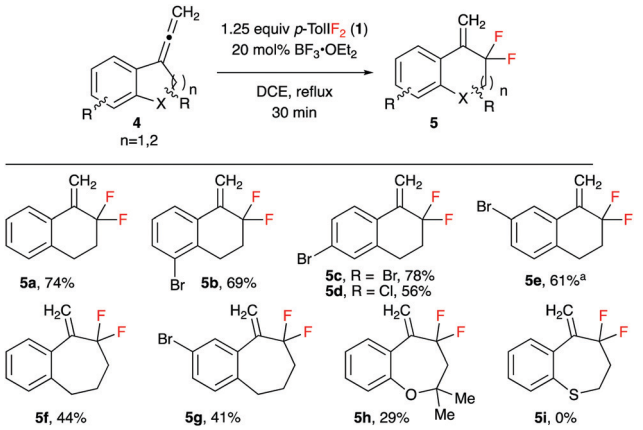
[a] ^{19}F NMR yield using 4-fluorotoluene as an internal standard. [b] Isolated yield.



Scheme 2 Fluorinative ring-expansion of various exocyclic olefins.

Methoxy substitution (**2j**) was moderately well-tolerated (**3j**, 49% yield); however, higher yields were achieved with the 3-bromo derivative **2k**, which gave **3k** in 89% yield. *gem*-Dimethylation adjacent to the reacting alkene inhibited the desired reaction, as alkene **2l** was fully consumed, and yet the reaction failed to produce **3l**.

Alkenes derived from the chromane skeleton were investigated, and the parent compound **2m** reacted to give **3m** in 42% yield. Derivatives of this scaffold were prepared with substituents at positions distal to exocyclic alkene, allowing us to test for remote steric effects.[20] Numerous substitution patterns were tolerated, such as the 2-phenyl derivative **2n**, which gave **3n** in 67% yield. 2,2-Dialkyl scaffolds included dimethyl- (**2o**), diethyl- (**2p**), and mixed dialkyl- (**2q**, **2r**) derivatives, which all gave their corresponding difluorides **3o–3r** in 58–61% yield. 2,2-Spirocyclic derivatives were also viable, with the spirocyclobutane (**3s**), -cyclopentane (**3t**) and -cyclohexane (**3u**) derivatives undergoing the fluorinative rearrangement in 44–67% yield. Substrates derived from the 2-oxindole scaffold (**2v**, **2w**) failed, which was surprising given the ease with which the related acyclic cinnamides undergo fluorinative rearrangements.[14c,p] Lastly, the thiochromane-derived alkene **2x** was also fully consumed in the reaction, but none of the desired product (**3x**) or any other identifiable products were observed, presumably due to the ease with which sulfides are oxidized by **1**.[21] Collectively, this ensemble of results demonstrates that *p*-TolIF$_2$ readily induces a rapid and chemoselective difluorinative ring-expansion on benzo-fused bicycles possessing α-exomethylene groups. While this study was not exhaustive, we discovered that various functional groups and substitution patterns were widely tolerated. Limitations included substitution adjacent to the alkene, and aryl methyl ethers were also low yielding, presumably due to their instability in the reaction media.[22] In any case, the ring-size and halogen substitution patterns realized herein provide



Scheme 3 Fluorinative ring-expansion of various exocyclic allenes. [a] ^{19}F NMR yield.

β,β-difluoroalkyl arenes with versatile handles for further manipulation.

We tested the fluorinative ring-expansion on the related allene-containing substrates, beginning with unsubstituted **4a** (Scheme 3). When subjected to the reaction conditions optimized above, only a trace of **5a** was observed. After screening reaction time, temperature and loading of the Lewis acid, we discovered that combining allene **4a**, 1.25 equiv. *p*-TolIF$_2$ and 20 mol% $BF_3{\cdot}OEt_2$ in DCE at reflux gives **5a** in 74% isolated yield. We found halogenation at any of the 5-, 6- or 7-positions on the arene was well tolerated, providing the products **5b–5e** in 56–78% yield. Two homologous derivatives were also tested, with allene **4f** giving difluoride **5f** in 44% yield, and with 7-bromo derivative **4g** giving **5g** in 41% yield. Oxygenation within the tether was tolerated (**5h**, 29% yield), whereas the related sulfide **4i** was not viable. The tolerance for substitution patterns and functional groups displayed by these allenes was consistent with that of the related alkenes; however, the yields decreased significantly for rearrangements leading to the medium-ring scaffolds.

Such fluorination reactions have attracted significant interest, and many efforts have been made to elucidate their mechanisms both computationally and experimentally.[23] The rearrangements reported here are proposed to begin with activation of the iodane by the Lewis acid (Fig. 1).[24] The activated iodane **A** is then attacked by the weakly nucleophilic π-system of the styrene (*e.g.* **2a**) or phenylallene derivative, *via* either concerted (shown) or stepwise (not shown) processes, leading to intermediate **B** in which the first C–F bond has been forged. The hypernucleofugal iodanyl leaving group[25] may be further activated by the Lewis acid, inducing the arene to participate in expelling iodotoluene, generating phenonium ion **C**. Ring expansion and rearomatization gives **3a**,

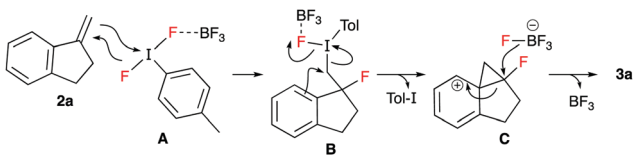


Fig. 1 Proposed mechanism of the ring-expansion.

where the second fluoride possibly derives from BF_4^-,[26] and where the regioselectivity is directed by the stabilizing effect of the existing fluorine atom.

In conclusion, we report a fluorinative ring-expansion of benzo-fused alkene- and allene-containing substrates mediated by *p*-TolIF$_2$. This reaction exploits the iodane's ability to deliver both "electrophilic" and nucleophilic fluorides, and the substrate's ability to undergo 1,2-phenyl migration, providing direct access to either β,β-difluorides or allylic *gem*-difluorides. The reactions were rapid and tolerant to a variety of functional groups, though steric hindrance and heteroatom (N,S) substitution were problematic. This mild and operationally-simple reaction constitutes a novel strategy for synthesizing fluorinated motifs not readily accessible *via* other direct fluorination methods, and our continued efforts will be reported in due course.

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Conflicts of interest

There are no conflicts to declare.

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