A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

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Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201706798
Angew. Chem. 10.1002/ange.201706798

Link to VoR: http://dx.doi.org/10.1002/anie.201706798
http://dx.doi.org/10.1002/ange.201706798

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Fluorinative Rearrangements of Substituted Phenylallenes Mediated by (Difluoroiodo)toluene: Synthesis of α-(Difluoromethyl)styrenes

Zhensheng Zhao, [a] Léanne Racicot[a] and Graham K. Murphy*[a]

Abstract: Phenylallenes undergo a fluorinative rearrangement by the action of (difluoroiodo)toluene, in the presence of 20 mol% BF_3•OEt_2, to yield α-difluoromethyl styrenes. This unprecedented reaction was entirely chemoselective for the internal allene π-bond, and showed remarkable regioselectivity during the fluorination event. Substituted phenylallenes, phenylallenes possessing both phenyl- and α-allenyl substituents, and diphenylallenes were investigated, and good functional group compatibility was observed throughout. The ease with which allenes can be prepared on large scale, and the operational simplicity of this reaction have allowed us to rapidly access fluorine-containing building blocks that have not been accessed by conventional deoxyfluorination strategies.

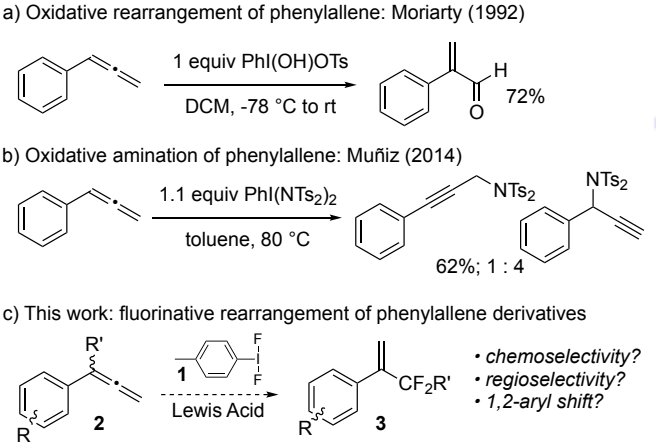
Organofluorine compounds play important roles in medicinal chemistry, agrochemistry, as well as material sciences. [1,2,3] The development of new reagents and strategies to synthesize fluorine-containing building blocks, especially those not readily accessible using existing methodologies, is critical to meeting investigators' current and future needs.

The recent upswing in reactions involving aryl-λ^3 organic hypervalent iodine (HVI) reagents[4] is because they serve as sources of "electrophilic ligands", in addition to their myriad applications as oxidants. This is advantageous in fluorination chemistry, as HVI-based fluorination reagents are easily prepared from fluoride ions, unlike other electrophilic fluorinating agents manufactured using fluorine gas.[5] (Difluoroiodo)toluene ($TolIF_2$, **1**) possesses two fluorine ligands on the iodine atom, and as a source of both "electrophilic" and nucleophilic fluorine atoms, it is a stable, easy to handle solid, making it an attractive alternative to fluorine gas.[6] The efficient and highly selective fluorinating ability of $TolIF_2$ is driven by the concomitant reduction of iodine. Thus, $TolIF_2$ holds significant potential for discovering valuable new fluorination reactions.[7,8]

Gem-difluoride compounds can be accessed through denitrogenative difluorination of diazo compounds by $TolIF_2$.[9] While isolated alkenes react with $TolIF_2$ to give *vicinal*-difluorides,[10] reactions with styrenes are interrupted by a 1,2-phenyl shift to give the isomeric *gem*-difluorides.[7h, 11] The unrealized potential of HVI-mediated fluorination is with structural classes where deoxygenative fluorination strategies are unknown. Though α-(difluoromethyl)styrenes are precursors to poly-substituted fluoroalkenes,[12] and to novel fluorinated polymers,[13,14] there are no deoxyfluorination strategies reported for these.[15] They have been prepared by direct fluorination using cesium fluoroxysulfate ($CsSO_4F$);[16] however, the typical approach involves olefination[12,17] or dehydration[13,18] of a fluorine-containing precursor. We wished to develop a direct synthesis of α-(difluoromethyl)styrenes via a $TolIF_2$-mediated fluorinative rearrangement of phenylallene derivatives.

To our knowledge, there are only two reports related to the envisioned reaction, and they disclosed widely differing outcomes. Moriarty and co-workers reported that phenylallene was unreactive with $PhI(OAc)_2$, but it reacted with Koser's reagent to give α-formylstyrene (Scheme 1, a).[19] Conversely, Muñiz and co-workers recovered regioisomeric propargyl amines from the oxidative amination reaction between phenylallene and $PhI(NTs_2)_2$ (Scheme 1, b).[20] If $TolIF_2$ were to react chemo- and regioselectively with the internal, conjugated olefin of **2**, and were the fluorination sequence interrupted by a 1,2-phenyl shift, α-(difluoromethyl)styrenes would result (Scheme 1, c). We report here the first HVI-mediated fluorination reaction of phenylallenes, which is a mild and rapid synthesis of fluorinated styrenyl building blocks.

The investigation began with the synthesis of *p*-phenyl-allene (**2a**) prepared from 4-phenylstyrene through the Doering-Moore-Skattebøl reaction.[21] Allene **2a** was treated with $TolIF_2$ in DCE at room temperature and at reflux, but no reaction was observed (Table 1, entries 1, 2). BF_3•OEt_2 was added to activate the iodane, which gave traces of **3a** at room temperature, and **3a** in 64% yield at reflux (entries 3, 4). Increasing the loading of $TolIF_2$ to 1.2 equiv failed to further improve the yield, possibly due to over fluorination of **3a** (entry 5). Various non-nucleophilic solvents compatible with $TolIF_2$ reactions were screened, but none were as effective as DCE (entries 6-8). Other Lewis acidic activating agents were



Scheme 1. Reactions of substituted phenylallenes with HVI reagents.

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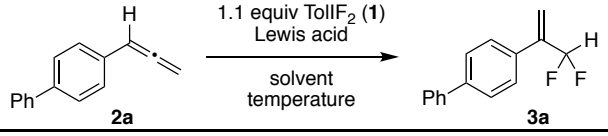
10.1002/anie.201706798

explored,[22] but none proved as effective as BF_3•OEt_2 (entries 9-14, also see Table SI-1). The loading of BF_3•OEt_2 was varied, and 20 mol% was found to be optimal, giving **3a** in 70% isolated yield (entry 15). Therefore, the rearrangement of allene **2a** with BF_3•OEt_2-activated $TolIF_2$ occurs chemoselectively in good yield.

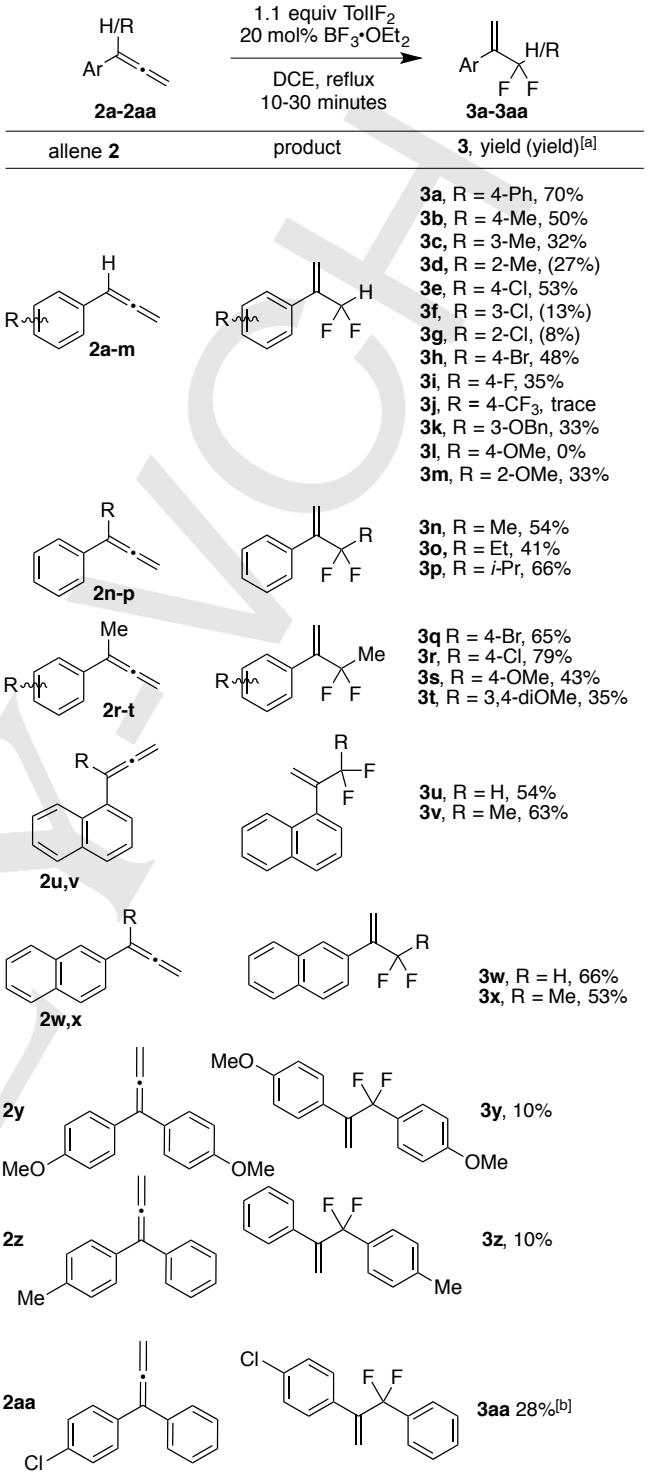
Table 1. Optimization of the fluorinative rearrangement of phenylallene.



entry	Lewis acid (mol%)	solvent	temperature	Yield[a]
1	-	DCE	r.t.	n.r.
2	-	DCE	reflux	n.r.
3	BF_3•OEt_2 (10)	DCE	r.t.	trace
4	BF_3•OEt_2 (10)	DCE	reflux	64%
5[b]	BF_3•OEt_2 (10)	DCE	reflux	52%
6	BF_3•OEt_2 (10)	PhCl	reflux	10%
7	BF_3•OEt_2 (10)	Toluene	reflux	39%
8	BF_3•OEt_2 (10)	DCM	reflux	trace
9	TiF_3 (25)	DCE	reflux	28%
10	TiF_4 (25)	DCE	reflux	36%
11	BiF_3 (25)	DCE	reflux	36%
12	InF_3 (25)	DCE	reflux	32%
13	SnF_2 (25)	DCE	reflux	15%
14	SbF_3 (25)	DCE	reflux	20%
15	BF_3•OEt_2 (20)	DCE	reflux	71%(70%)[c]

[a] ^{1}H NMR yield using HMDSO as internal standard. [b] 1.2 equiv $TolIF_2$ used. [c] Isolated yield.

We prepared a series of aryl- and α-allenyl-substituted phenylallenes (**2a**-**2aa**), and subjected these to the optimized reaction conditions (Scheme 2). In addition to the 4-phenyl substituent (**2a**), phenylallenes with alkyl (**2b-d**) and halogen substituents (**2e-i**) were all viable in the reaction, though the yields were generally lower for *ortho*- and *meta*-substituted derivatives than for the analogous *para*-substituted substrates (also, see Scheme SI-1). The 4-CF_3-substituted phenylallene **2j** only gave a trace of **3j**, presumably due to its strong electron-withdrawing nature and the resulting diminished ability to undertake electrophilic aromatic substitution. The alkoxy derivatives **2k**-**m** proved interesting, in that the 4-OMe substrate (**2l**) failed to provide any trace of **3l**, however the 3-OBn (**2k)** and 2-OMe (**2m**) substrates were both viable, undergoing the fluorinative rearrangement in modest yield. Phenylallenes with α-methyl (**2n**), α-ethyl (**2o**) and α-*i*-propyl (**2p**) substituents were all viable, with yields ranging from 41-66%. α-Methyl phenylallenes possessing aryl substituents were then investigated, with the 4-Br and 4-Cl substrates giving **3q** and **3r** in 65% and 79% yield. The alkoxy-substituted derivatives again proved



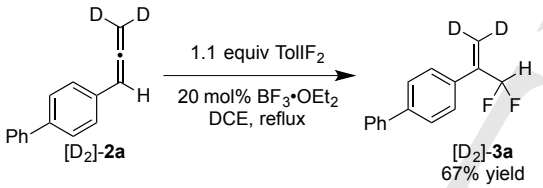
Scheme 2. Fluorinative rearrangement of various aryl-substituted allenes. [a] ^{1}H NMR yield using HMDSO as internal standard. [b] A mixture of aryl migration products was recovered.

interesting, in that both the 4-OMe (**2s**) and 3,4-diOMe (**2t**) substrates were viable, implying a beneficial effect of α-alkyl substitution with strongly electron donating substituents (compare **3l** and **3s**).

10.1002/anie.201706798

Four related 1-naphthyl- (**2u**,**v**) and 2-naphthyl- (**2w**,**x**) allenes were exposed to the reaction conditions, and the α-difluoromethyl and α-difluorethyl products of the 1-naphthyl series were obtained in 54% and 63% yield (scheme 2). The analogous products of the 2-naphthyl series were formed in 66% and 53% yield. We attempted to further increase the substrate scope by subjecting a series of 1,1-diarylallenes to the fluorinative rearrangement reaction. When 1,1-(bis-4-methoxyphenyl)allene (**2y**) was employed, product **3y** was recovered in 10% yield. Mono-methyl-substituted 1,1-diphenylallene **2z** afforded **3z** in 10% yield, with only the more electron rich *p*-tolyl group undergoing the 1,2-shift. Lastly, α-(4-chlorophenyl)phenylallene (**2aa**) was also investigated, and while the products were recovered in a slightly improved 28% yield, a mixture of products, resulting from competitive arene migration, was recovered. Overall, a variety of electronically different groups were acceptable as aryl substituents, and while alkyl substituents at the α-allenyl position were well tolerated, 1,1-diphenylallenes were generally poor yielding.[23]

To gain insight into the mechanism and regioselectivity of the rearrangement, we prepared a deuterated version of phenylallene [D_2]-**2a** (Scheme 3, also see Supporting Information). It was subjected to the general reaction conditions, and it underwent the fluorinative rearrangement to give β,β-D_2-α-diflurormethyl styrene [D_2]-**3a** in 67% yield. No indication of deuterium scrambling was observed by either ^{1}H, ^{2}H or ^{19}F NMR, confirming that the allene's terminal olefin is not involved in the reaction.



Scheme 3. Fluorinative rearrangement of a deuterium-enriched phenylallene.

There has been significant recent interest in elucidating the mechanisms of reactions mediated by fluoroiodane reagents. Molecular modelling has provided valuable mechanistic insights into the HVI-mediated *gem*-difluorination reactions of styrenes[24] or fluorination/cyclization sequences,[25] which are believed to involve four distinct steps: iodane activation, fluorination, 1,2-aryl migration and termination.[26] Because $TolIF_2$ and the fluoroiodane studied *in silico* have similar reactivity, the computational studies have guided our mechanistic proposal. $TolIF_2$ activation by BF_3•OEt_2 increases its electrophilicity enabling attack by the weakly nucleophilic allene (Figure 1). Two pathways are proposed for transit from **2** to the 1,2-phenyl shift precursor **B**. The first, path a, invokes the often reported iodane attack to give benzylic cation **A**, in which additional stabilization might be achieved by formation of iodocyclopropylium cation **A'**.[7h,11] Fluorination of this intermediate produces the first C-F bond, giving **B**. The second possibility derives from the studies of Szabó and Himo,[25] with iodofluorination occurring through ligand metathesis, and where the regioselectivity is dictated by the electronics inherent to the allene (path b). Once intermediate **B** is formed, the arene will displace iodotoluene and fluoride, possibly with assistance from BF_3•OEt_2, to generate phenonium ion **C**. Nucleophilic attack by fluoride (possibly from BF_4^-)[27] occurs exclusively at the fluorinated carbon, avoiding the alternate S_N2' pathway leading to 1,3-difluorides. Presumably, this is due to hyperconjugative stabilization resulting from fluorine substitution. This attack re-establishes aromaticity and forges the second C-F bond of **3**. This hypothesis is consistent with the elevated temperature required for the endothermic 1,2-phenyl shift to occur, the failure of the *p*-CF_3 substrate **1f** to undergo electrophilic aromatic substitution, and the lack of deuterium scrambling observed in the labelling study.

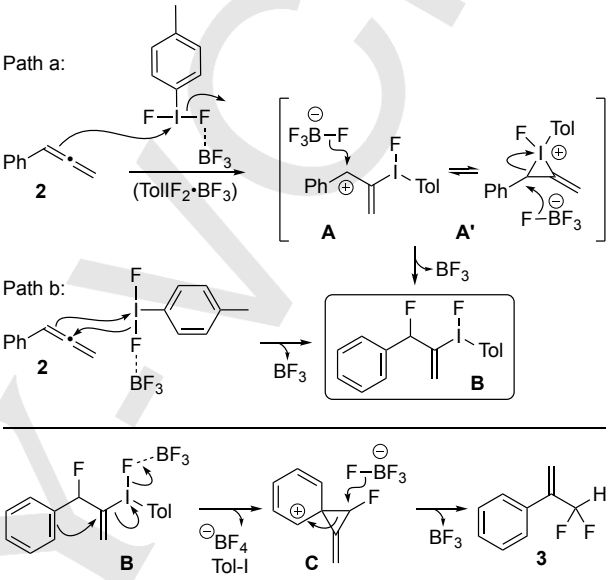


Figure 1. Proposed mechanism of the reaction.

In conclusion, we reported the first example of a fluorinative rearrangement of substituted phenylallene derivatives that provides direct access to the α-difluoromethylstyrene class of fluorinated building blocks. This rearrangement of substituted phenylallenes was tolerant to a variety of functional groups, apart from strongly electron deficient substituents. α-Alkyl substituents of varying steric demand were well tolerated, however the rearrangement of 1,1-diphenylallenes were generally poor. This operationally simple reaction, using safe and reliable hypervalent iodine reagents, offers a novel strategy for investigating the synthesis of fluorinated building blocks not readily accessible by standard deoxyfluorination protocols.

Acknowledgements

This work was supported by the Natural Sciences and Engineering Research Council (NSERC) of Canada and the University of Waterloo. We also thank Dr. Val Goodfellow of the UWaterloo Mass Spectrometry Facility.

Keywords: allenes • halogenation • hypervalent compounds • rearrangement • synthetic methods

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Layout 2:

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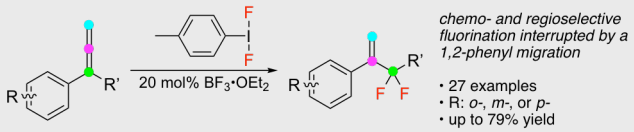

Reacting substituted phenylallenes with $TolIF_2$ results in a regio- and chemoselective synthesis of α-difluoromethyl styrenes. Fluorination of the internal olefin is interrupted by a 1,2-phenyl shift, leading to *geminal* instead of *vicinal* difluorides.

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