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C–F bond formation with fluoride anions – highly selective iodofluorination of simple allenes†

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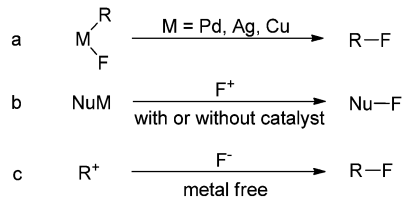
A highly regioselective (up to 99 : 1) iodofluorination reaction of simple allenes occurs under mild conditions with $Et_3N{\cdot}3HF$ or Py·9HF to afford 2-iodoalken-3-yl fluorides.

As we know that the introduction of a fluorine atom into organic molecules would have a remarkable effect on the chemical, physical and biological properties due to its mimic effect and very high electronegativity,[1,2] thus, much attention has been directed towards regio- and stereoselective monofluorination. Recently, there have been numerous reports on the metal-mediated C–F bond formation: an actively explored process leading to aryl fluoride is direct reductive elimination from [ArPdF] intermediates *via* either a Pd(0)/Pd(II)[3,4] or Pd(II)/Pd(IV)[3,5] cycle; the conversion of aryl boronic acids (AgOTf),[6] silanes (Ag_2O),[7] stannanes (AgOTf),[8] and halides ($CuOTf(CH_3CN)_4$)[9] to arylfluorides with electrophilic fluorine reagents[6–9] has also been reported (Scheme 1a); transition metal-catalyzed tandem cyclization and fluorination of alkenes, alkynes, or allenes are reported to be efficient ways to construct fluorinated heterocycles;[10] palladium-[11] or iridium-mediated[12] nucleophilic fluorination of allylic electrophiles has been developed as the regio- and enantioselective route to allylic fluorides; C–F bond formation has also been realized through the Au(I)-catalyzed hydrofluorination of alkynes;[13] in addition, a five-coordinate fluoro complex of ruthenium(II)-catalyzed fluorination of allylic or alkyl bromide with TlF (1.1 equiv.) has also been reported.[14] On the other hand, due to the toxicity and the cost of transition metal catalysts or metallic reagents, metal-free processes with readily available fluorine sources has always been attracting the attention of chemists, although fluorination using elemental fluorine[15] and pyrolysis of diazonium tetrafluoroborate[16] are less attractive due to harsh or dangerous reaction conditions and the limited substrate scopes: for example, highly regio- and stereoselective electrophilic fluorination reactions of 2,3-allenoic acids,[17] 3-aryl-1,2-allenes,[18] 1,2-allenyl phosphine oxides,[19] or 2,3-allenoates[20] with Selectfluor have been observed; electrophilic fluorination of allylic silanes was reported to afford allylic fluorides with a branch selectivity;[21] α-fluorination of carbonyl compounds,[22] such as ketones, aldehydes, and esters, with electrophilic fluoride reagents has also been established (Scheme 1b). We envisioned a C–F bond formation *via* the reaction of cationic species generated from electrophilic addition of allenes[18,19,23,24] with a fluoride anion (Scheme 1c).[22,25–28]



Scheme 1 Monofluorination reactions of typical organic intermediates.

We chose trideca-1,2-diene **1a** and NIS to conduct the iodofluorination reaction in DCE. The effect of the fluoride anion was studied first: no fluorine-containing products were afforded when applying NH_4F, $(NH_4)HF_2$, $NaHF_2$, and KHF_2 in the reaction (entries 1–4, Table S1, ESI†); interestingly, with Py·9HF,[28] a mixture of regio- and stereoisomeric iodofluorination products, 3-fluoro-2-iodotridec-1-ene **2a**, (*Z*)-1-fluoro-2-iodotridec-2-ene (*Z*)-**3a** and (*E*)-1-fluoro-2-iodotridec-2-ene (*E*)-**3a** (**2a** : (*Z*)-**3a** : (*E*)-**3a** = 88 : 8 : 4), were obtained in 53% combined yield (entry 5, Table S1, ESI†); when $Et_3N{\cdot}3HF$ was used, the reaction at 0 °C could afford a better yield with a similar regioselectivity (entry 6, Table S1, ESI†). Increasing the amount of $Et_3N{\cdot}3HF$ had almost no impact on the yields and selectivity (entries 7–9, Table S1, ESI†). Running the reaction at a lower temperature led to a much slower conversion (entries 10 and 11, Table S1, ESI†), while there was a slight decrease in regioselectivity when the reaction was conducted at room temperature (entry 12, Table S1, ESI†). No reaction occurred in anhydrous DMF (entry 1, Table S2, ESI†); only trace amounts

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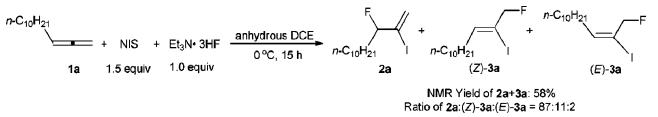
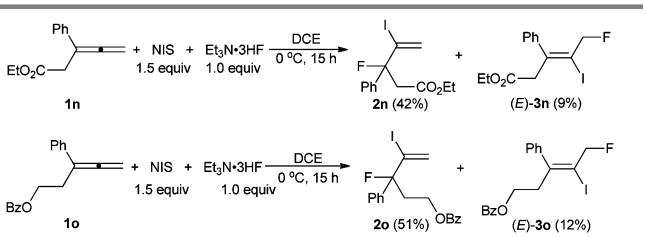
of fluorinated products were detected by the analysis of ^{1}H and ^{19}F NMR spectra when using toluene, acetone, THF, and dioxane as the solvent (entries 2–5, Table S2, ESI†); only a mixture of **2a** and **3a** (**2a**:(*Z*)-**3a**:(*E*)-**3a** = 90:9:1) in 23% combined yield was afforded when CH_3CN was used as the solvent (entry 6, Table S2, ESI†); with CH_3NO_2 as the solvent, there was almost no improvement (entry 7, Table S2, ESI†); the reaction in DCM or $CHCl_3$ afforded very similar results as compared to DCE (entries 8 and 9, Table S2, ESI†). By considering the yields together with the regio- and stereoselectivities, the reaction conditions presented in entry 6 of Table S1 (ESI†) have been defined as the standard for further studies (eqn (1)). It should be noted that no reaction occurred on the remaining C=C bonds in these products.[29–31]



(1)

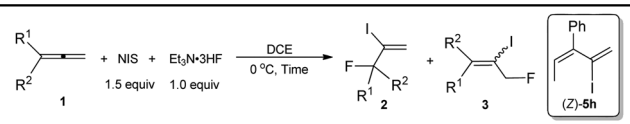
Then we attempted the iodofluorination reaction of geminally disubstituted allenes with different types of R^1 and R^2 under the optimized reaction conditions, with the results being summarized in Table 1. To our delight, when R^1 is an aryl group and R^2 is a cyclic alkyl group, such as ^{t}Bu or ^{i}Pr, the reaction could afford iodofluorination products **2** in good yields with an excellent regioselectivity (up to 99:1) (entries 1–6, Table 1). Even with R^2 being normal alkyl groups, the regioselectivity of the iodofluorination reaction is also satisfactory (entries 8 and 9, Table 1); in addition, a trace amount of elimination product, *i.e.*, (*Z*)-2-iodo-3-phenylpent-1,3-diene (*Z*)-**5h** (9%) (entry 8, Table 1), was detected. The presence of an aryl group within R^2 led to a slightly lower regioselectivity (entry 11, Table 1); with R^2 as the allyl group, the electrophilic addition reaction occurred exclusively to the allene unit (entries 12 and 13, Table 1); with R^1 and R^2 both being alkyl groups, the yields and selectivity are still remarkable (entries 14 and 15, Table 1). It is noted that when Py·9HF was used instead of Et_3N·3HF, the yield of **2g**, **2i**, and **2k** were slightly lower, however, with a better regioselectivity (entries 7, 10, and 13, Table 1).

The iodofluorination reactions of geminally disubstituted allenes containing an oxygen-related functionality **2n** and **2o** may also proceed with a nice selectivity (Scheme 2).



Scheme 2 Iodofluorination reactions with functionalized allenes.

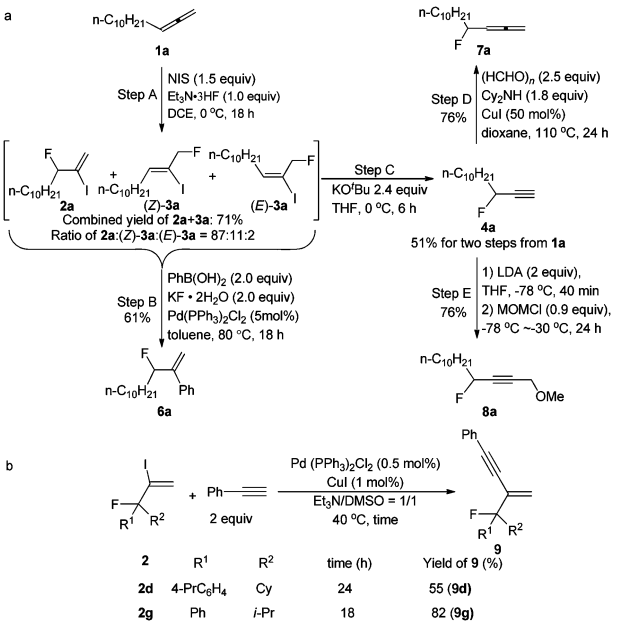
Table 1 Iodofluorination reaction of geminally disubstituted allenes with a nucleophilic fluoride anion[a]



Entry	R^1	R^2	Time (h)	Isolated yield of **2** (%)	**2**:**3**[b]
1	Ph	*c*-C_6H_{13} (**1b**)	11	65 (**2b**)	99:1
2[c]	Ph	*c*-C_5H_{11} (**1c**)	16	68 (**2c**)	99:1
3[c]	4-PrC_6H_4	*c*-C_6H_{13} (**1d**)	11	71 (**2d**)	99:1
4[c]	4-FC_6H_4	*c*-C_6H_{13} (**1e**)	9	75 (**2e**)	99:1
5	Ph	*t*-Bu (**1f**)	13	71 (**2f**)	99:1
6	Ph	i-Pr (**1g**)	15	85 (**2g**)	98:2
7[d]	Ph	i-Pr (**1g**)	15	73 (**2g**)[e]	99:1
8	Ph	Et (**1h**)	10	67 (**2h**)[f]	94:6
9[c]	Ph	$Ph(CH_2)_3$ (**1i**)	12	60 (**2i**)[e]	91:9
10[c,d]	Ph	$Ph(CH_2)_3$ (**1i**)	12	45 (**2i**)	93:7
11	Ph	Ph (**1j**)	19	72 (**2j**)[g]	84:16
12	Ph	Allyl (**1k**)	15	54 (**2k**)	88:12
13[d]	Ph	Allyl (**1k**)	12	36 (**2k**)	93:7
14	*n*-Bu	*n*-Bu (**1l**)	11	69 (**2l**)[h]	92:8
15	$Ph(CH_2)_3$	*n*-Bu (**1m**)	19	63 (**2m**)[h]	92:8

[a] Conditions: 1.0 equiv. of **1**, 1.5 equiv. of NIS, 1.0 equiv. of Et_3N·3HF or Py·9HF, DCE as a solvent, reacted at 0 °C. [b] The ratios were determined by the analysis of ^{19}F NMR spectra of crude products. [c] The scale of the reaction is 6 mmol. [d] Py·9HF was used instead of Et_3N·3HF. [e] The yields were detected by ^{1}H NMR spectra of crude products using mesitylene as the internal standard. [f] (*Z*)-**5h** (9%) was afforded. [g] Separated using low temperature column chromatography with a −18 to −16 °C circulating EtOH outside the column. [h] There were trace products obtained by the elimination of HF of the main product **2**.

These 2-iodoallylic fluorides have been demonstrated to be very attractive building blocks in organic synthesis as shown in Scheme 3. The 6 mmol scale reaction of **1a** affording a mixture of **2a** and **3a** (**2a**:(*Z*)-**3a**:(*E*)-**3a** = 87:11:2) in 71% combined yield (Step A, Scheme 3a) could afford pure 3-fluoro-2-phenyltridec-1-ene **6a** after a highly selective Pd-catalyzed Suzuki coupling reaction with $PhB(OH)_2$ (Step B, Scheme 3a);[32] pure 3-fluorotridec-1-yne **4a** was obtained *via* simple extraction,



Scheme 3 (a) The iodofluorination reaction of **1a** and the subsequent conversion of 2-iodoalken-3-yl fluoride **2a**. (b) Sonogashira coupling of 2-iodoallylic fluorides **2d** and **2g** with phenylacetylene.

concentration of the mixture of **2a** and **3a** and subsequent treatment with KO^{t}Bu (2.4 equiv.) in anhydrous THF at 0 °C for 6 h in 51% combined isolated yield for two steps from **1a** (Steps A and C, Scheme 3a);[33] alkyne **4a** may be further converted to 4-fluorotetradeca-1,2-diene **7a** by its treatment with $(HCHO)_n$ and Cy_2NH (Step D, Scheme 3a),[34] and alkyne **8a** by its sequential treatment with LDA and MOMCl, respectively (Step E, Scheme 3a). The synthetic potential of these 2-iodoallylic fluorides has been further demonstrated by applying the Sonogashira reaction of **2d** and **2g** with phenylacetylene affording 2-(1-fluoro-1-phenyl-2-methylpropyl)-4-phenyl-buten-3-yne **9d** and 2-(1-fluoro-1-phenyl-2-methylpropyl)-4-phenyl-buten-3-yne **9g**, respectively (Scheme 3b).[35] These **2a**, **4a**, **6a**, **7a**, **8a**, **9d**, and **9g**-type products are difficult to prepare by following conventional synthetic methods.

In summary, we have developed a highly regioselective iodofluorination reaction for the convenient synthesis of 2-iodoallylic fluorides. Considering the potential of the electrophilic monofluorination products and the ready availability of the starting materials,[36] this method shall open a new window for the chemistry of organofluorine compounds based on allenes. Further studies in this area including the asymmetric version of this reaction are undergoing in our laboratory.

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