Organic LETTERS

Letter

Cite This: Org. Lett. 2018, 20, 1576–1579

pubs.acs.org/OrgLett

Controlled Single and Double Iodofluorination of Alkynes with DIH- and HF-Based Reagents

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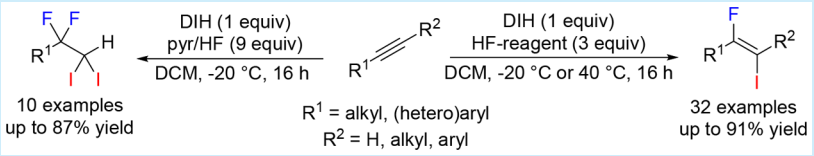
Supporting Information

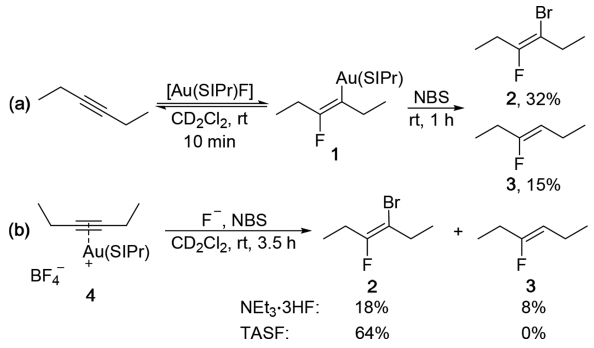


ABSTRACT: A novel protocol for the regio- and stereoselective iodofluorination of internal and terminal alkynes using 1,3-diiodo-5,5,-dimethylhydantoin and HF-based reagents is disclosed. This approach is used to prepare a fluorinated tamoxifen derivative in two steps from commercially available starting materials. A facile method enabling controlled regioselective double iodofluorination of terminal alkynes is also presented.

A classical strategy for the halofluorination of alkynes uses electrophilic halogenating reagents in combination with sources of HF.[1] These methods are typically associated with low yields,[1c,e,f] poor selectivity,[1d−f] and a substrate scope restricted to unfunctionalized hydrocarbons.[1e,f] These limitations have prompted the use of alternative reagents such as hypervalent iodine species.[2] These reactions that proceed via the formation of (*E*)-(fluoroalkenyl)iodonium fluorides[2b] suffer from byproduct formation for terminal alkyne substrates.[2c] Rozen and co-workers reported the addition of BrF and IF, generated from the elements, to unfunctionalized alkynes, leading to the formation of stereoisomeric mixtures, and in some cases uncontrolled single and double addition products.[3] Isolated examples of iodofluorination of 3-hexyne employing bis(pyridine)iodonium tetrafluoroborate and fluoride salts,[4] or a combination of elemental iodine and XeF_2, have also been disclosed.[5] In quest of a reliable simpler protocol, the *cis*-bromofluorination of terminal alkynes using *N*-bromosuccinimide and an excess of AgF was developed by Jiang,[6] and Hara reported the iodofluorination of internal and terminal alkynes using IF_5−pyridine−HF.[7] From this survey, it is apparent that the development of a regioselective iodofluorination method compatible with functionalized alkynes and using easily accessible reagents is still highly desirable.

Given our interest in transition metal mediated C−F bond formation,[8] our initial approach considered Au-catalysis to activate the alkyne. Hashmi[9] reported that an alkenyl-Au(I) species can undergo halodeauration when treated with an electrophilic halogen source, and Sadighi[10] demonstrated that internal alkynes reversibly form *β*-(fluorovinyl)gold(I) complexes in the presence of [Au(SIPr)F]. Building on these precedents, a preliminary experiment consisted of adding *N*-bromosuccinimide (NBS) to the equilibrium mixture of 3-hexyne and *β*-(fluorovinyl)gold(I) complex **1**; this reaction led to 32% of (*E*)-3-bromo-4-fluorohex-3-ene, **2**, and 15% of (*Z*)-3-fluorohex-3-ene, **3** (Scheme 1a), being formed. The treatment

Scheme 1. Au-Mediated Bromofluorination of Alkynes



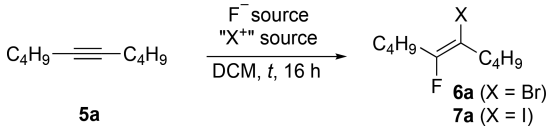
of the preformed gold(I)−alkyne *π*-complex **4** with NBS and either $NEt_3{\cdot}3HF$ or $(Me_2N)_3S(Me)_3SiF_2$ (TASF) gave **2** in 18% and 64% yield, respectively (Scheme 1b).

These results encouraged further investigation. The reaction of 3-hexyne with NBS in the presence of $[Au(SIPr)BF_4]$ (5 mol %) led to no (TASF) or only traces ($NEt_3{\cdot}3HF$) of bromofluorinated product **2** (Table 1, entries 1 and 2). The replacement of NBS with 1,3-dibromo-5,5,-dimethylhydantoin (DBH) afforded the desired product in 54% yield, and a control experiment revealed that **6a** was also formed *in the absence of a Au-catalyst* (Table 1, entries 3 and 4). Screening of alternative sources of fluoride, electrophilic bromine sources, and solvents identified $NEt_3{\cdot}3HF$ and DBH in DCM as optimum for this reaction (Table 1, entries 5−7; Tables S2−S5). Only HF-based reagents were effective (Table S2). By lowering the temperature to 0 °C (Table 1, entry 8) and increasing the amount of $NEt_3{\cdot}3HF$ to 3 equiv (Table 1, entries 9 and 10), **6a** was isolated in 80% yield but as a mixture with 15% of (*E*)-5,6-

Received: January 29, 2018
Published: March 1, 2018

DOI: 10.1021/acs.orglett.8b00321
Org. Lett. 2018, 20, 1576–1579

Table 1. Optimization of Halofluorination of 5a



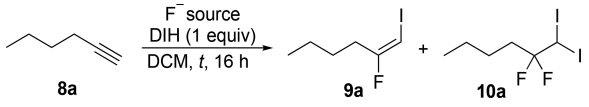
entry	F⁻ source (equiv)	"X⁺" source (equiv)	t [°C]	6a/7a[a] [%]
1[b,c]	TASF (1)	NBS (1)	rt	0
2[b,c]	NEt_3·3HF (1)	NBS (1)	rt	<5
3[b,c]	NEt_3·3HF (1)	DBH (1)	rt	54
4	NEt_3·3HF (1)	DBH (1)	rt	45
5	pyr/HF (3)[d]	DBH (1)	rt	29
6[e]	NEt_3·3HF (1)	DBH (1)	rt	32
7[f]	NEt_3·3HF (1)	DBH (1)	rt	43
8	NEt_3·3HF (1)	DBH (1)	0	53
9	NEt_3·3HF (2)	DBH (1)	0	72
10	NEt_3·3HF (3)	DBH (1)	0	81 (80)[g]
11	DMPU/HF (3)[d]	DBH (1)	0	8
12	NEt_3·3HF (3)	DIH (1)	0	30
13	NEt_3·3HF (3)	DIH (1)	40	91 (91)
14	pyr/HF (3)[d]	DIH (1)	−20	81

[a]Determined by ^{1}H and ^{19}F NMR of crude reaction mixture (1-fluoro-3-nitrobenzene as internal reference). Isolated yields in parentheses. [b]3-Hexyne is used as substrate affording bromofluorinated alkene **2**. [c]With 5 mol % of [Au(SIPr)BF_4]. [d]Amount (equiv) of HF. [e]In DCE. [f]In $CHCl_3$. [g]Isolated in a mixture with 15% of (*E*)-5,6-dibromodec-5-ene.

dibromodec-5-ene, which could not be separated by silica gel column chromatography (Conditions A). DMPU/HF was not satisfactory for this reaction (Table 1, entry 11).[11] When using 1,3-diiodo-5,5,-dimethylhydantoin (DIH) instead of DBH, the reaction was best performed using NEt_3·3HF at 40 °C and gave (*E*)-5-fluoro-6-iododec-5-ene, **7a**, isolated pure in 91% yield (Conditions B) (Table 1, entries 12−14; Table S6).

These conditions applied to the terminal alkyne 1-hexyne **8a** afforded the iodofluoroalkene **9a** in 35% yield as a single diastereomer (Table 2, entry 1). Increasing the amount of

Table 2. Optimization of Selective Single and Double Iodofluorination of Terminal Alkynes

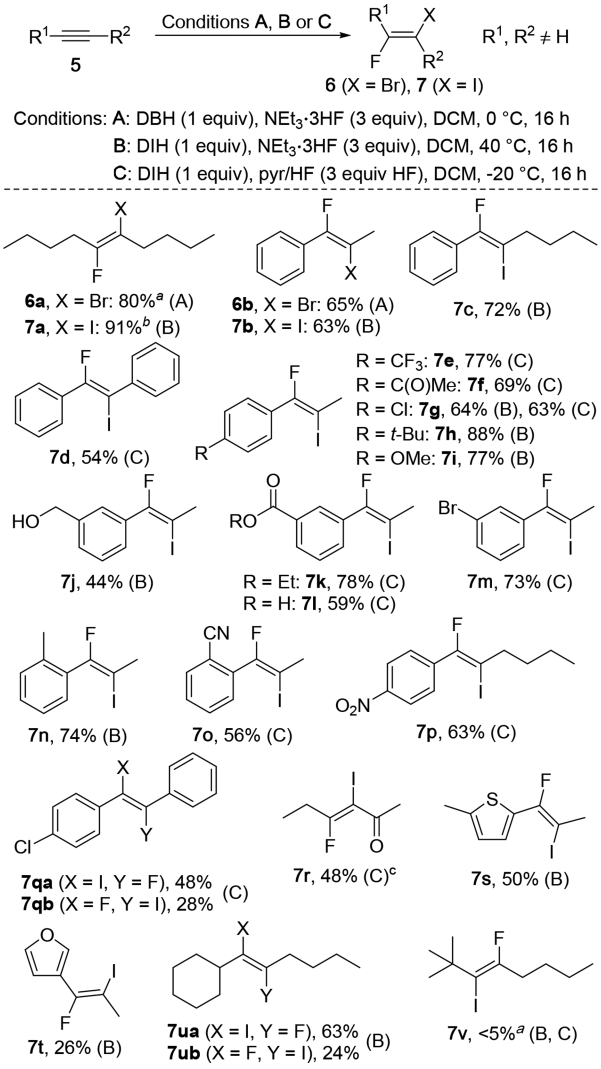


entry	F⁻ source (equiv)	t [°C]	9a[a] [%]	10a[a] [%]
1	NEt_3·3HF (3)	40	35	0
2	NEt_3·3HF (5)	40	28	0
3	NEt_3·3HF (3)	rt	31	0
4	pyr/HF (3)[b]	rt	14	29
5	pyr/HF (3)[b]	0	33	20
6	pyr/HF (3)[b]	−20	77 (74)	8
7	pyr/HF (9)[b]	−20	0	87 (80)

[a]Determined by ^{1}H and ^{19}F NMR of crude reaction mixture (1-fluoro-3-nitrobenzene as internal reference). [b]Amount (equiv) of HF.

NEt_3·3HF or lowering the temperature had detrimental effects on the outcome of the reaction (Table 2, entries 2 and 3). Switching to pyr/HF gave 14% of monoiodofluorinated **9a** along with 29% of double iodofluorinated **10a** (Table 2, entry 4). By lowering the temperature to −20 °C, **9a** could be isolated in 74% yield (Conditions C) (Table 2, entries 5 and 6).

Scheme 2. Halofluorination of Internal Alkynes[a]



[a]Conditions used are shown in parentheses. [b]Yield determined by ^{19}F NMR (hexafluorobenzene as internal reference). [c]93% on 5 mmol scale. [d]Reaction at rt using pyr/HF (4 equiv of HF).

An increase of the amount of pyr/HF to 9 equiv led to the exclusive formation of double iodofluorinated product **10a** in 80% yield using 1 equiv of DIH (Conditions D) (Table 2, entry 7). This later transformation absorbs fully the iodine content of this reagent.[12]

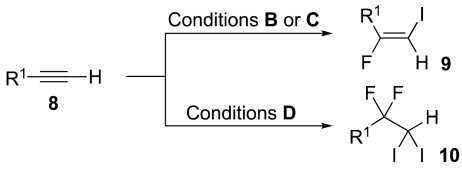
In this study, the difference in reactivity of the DIH/NEt_3·3HF and DIH/pyr/HF systems is notable. It is known that halogenating reagents can be activated either with Brønsted and Lewis acids or with nucleophilic promoters. Brønsted acid activation is more plausible for DIH/pyr/HF (pK_{aH}(pyr) = 5.2) than for DIH/NEt_3·3HF (pK_{aH}(NEt_3) = 10.7).[13] In contrast, nucleophilic activation could be more effective for DIH/NEt_3·3HF than DIH/pyr/HF considering the reduced hydrogen bond accepting potential of pyridine (pK_{BHX} = 1.86) versus NEt_3 (pK_{BHX} = 1.98).[14]

Having established the optimum conditions for the iodofluorination of internal and terminal alkynes, we studied the substrate scope of these transformations. For internal alkynes (Scheme 2), conditions B (3 equiv of NEt_3·3HF, 40 °C) gave good to excellent yields for the iodofluorination of electron-neutral as well as electron-rich substrates **5a**−**5c**, **5h**−

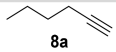
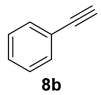
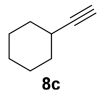
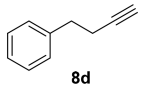
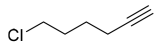
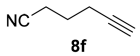
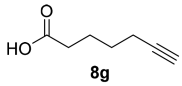
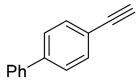
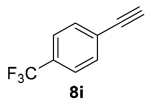
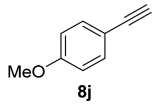
DOI: 10.1021/acs.orglett.8b00321
Org. Lett. 2018, 20, 1576−1579

5j, 5n, 5s, and 5u, with a lower yield of 26% for furan derivative 5t. The *p*-Cl-substituted alkyne 5g gave almost identical yields

Table 3. Substrate Scope for the Single and Double Iodofluorination of Internal Alkynes



Conditions: **B**: DIH (1 equiv), NEt_3·3HF (3 equiv), DCM, 40 °C, 16 h
C: DIH (1 equiv), pyr/HF (3 equiv HF), DCM, −20 °C, 16 h
D: DIH (1 equiv), pyr/HF (9 equiv HF), DCM, −20 °C, 16 h

entry	substrate	9[a] [%]	10[a] [%]
1	 8a	74 (C)	80 (D)
2	 8b	43 (C)	42 (D)
3	 8c	54 (C)	87 (D)
4	 8d	78 (C)	53 (D)
5	 8e	53 (C)	59 (D)
6	 8f	74 (C)	78 (D)
7	 8g	37 (C)	57 (D)
8	 8h	35 (B)	17 (D)
9	 8i	68 (C)	76 (D)
10	 8j	12[b] (B)	<5[b] (D)

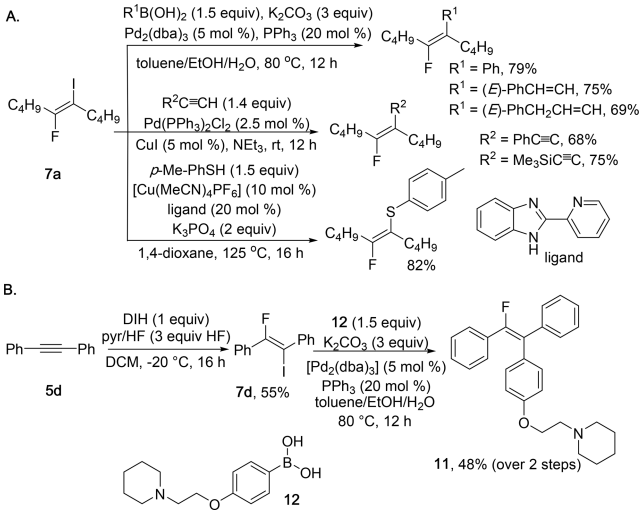
[a]Conditions are shown in parentheses. [b]Yield determined by ^{19}F NMR (hexafluorobenzene as internal reference).

with conditions B and C (pyr/HF, −20 °C). Conditions C were superior for the iodofluorination of electron-poor substrates 5d−5f, 5k−5m, and 5o−5q. Overall, different functionalities, among them unprotected alcohols (7j) and carboxylic acids (7l) as well as esters (7k), cyano groups (7o), ketones (7f), and aromatic halides (7g, 7m, and 7q), are tolerated under these conditions. The $^{19}F-^{1}H_{alkyl}$ coupling constants <4 Hz for products derived from alkyl aryl alkynes served to determine the sense of regiocontrol of the reaction. α-Ketoalkyne 5r also underwent regioselective iodofluorination using 4 equiv of pyr/HF at rt, affording 7r in 48% yield.[15] The influence of electronics on regioselectivity was studied using the unsymmetrically substituted stilbene derivative 5q. Under conditions C 5q gave an inseparable mixture of the two regioisomers 7qa and 7qb, which were obtained in a 1.7:1 ratio, favoring fluoride attack on the more electron-rich position as confirmed by $^{19}F-^{1}H$ heteronuclear NOE (HOESY) analysis. When placing a primary and a secondary carbon substituent on the triple bond (5u) a 2.6:1 ratio of regioisomers was obtained, favoring fluoride attack on the less sterically congested alkyne carbon.[16] The presence of a tertiary carbon substituent (5v) resulted in only a trace amount of product being formed under conditions B or C. Both 5a and 5b underwent successful bromofluorination under conditions A. The iodofluorination of 5a was performed starting from 5.00 mmol of alkyne giving 1.32 g (93%) of 7a, demonstrating the robustness of this protocol toward scale-up.

Next, we examined the substrate scope for the single and double iodofluorination of terminal alkynes (Table 3). Good yields were obtained with unfunctionalized alkyl and aryl substrates 8a−8d (Table 3, entries 1−4), chloro- and cyano-substituted compounds 8e and 8f (Table 3, entries 5 and 6), and electron-poor alkyne 8i (Table 3, entry 9). Alkyne 8g bearing a carboxylic acid functionality gave lower yields especially in the monoiodofluorination (Table 3, entry 7). For the single iodofluorination of 4-Ph- and 4-OMe-substituted phenylacetylenes 8h and 8j, conditions C only gave trace amounts of the desired products, whereas conditions B resulted in yields of 35% and 12%, respectively (Table 3, entries 8 and 10). Likewise, double iodofluorination gave 17% (10h) and a trace amount (10j) of the desired products, respectively. Products 10 bearing the 1,1-diiodo-2,2-difluoroethyl functionality are rare and accessed from the reaction of 1-hexyne or phenylacetylene with IF.[3] These products hold great potential as versatile intermediates, for example, for subsequent use in olefinations under Takai's conditions[17] or via reaction with α-sulfinyl carbanions,[18] as well as double functionalization with a Grignard[19] or organozinc[20] reagent followed by quenching with an electrophile. The (*E*)-configuration of 7b and 9d was unambiguously confirmed using NOESY and $^{19}F-^{1}H$ HOESY NMR experiments.[21]

Iodofluoroalkenes are useful products for the preparation of highly substituted fluoroalkenes as they are amenable to Suzuki, Sonogashira, or Ullmann-type cross-couplings (Scheme 3A).[21]

Scheme 3. Cross-Coupling Reactions with 7a, and Two-Step Synthesis of Fluorinated Tamoxifen Derivative 11 from Alkyne 5d



DOI: 10.1021/acs.orglett.8b00321
Org. Lett. 2018, 20, 1576−1579

This chemistry was applied to the preparation of the fluorinated tamoxifen derivative **11**, a compound shown to exhibit higher growth inhibition against four tested human cancer cell lines compared to the parent compound.[22] By applying our methodology, **7d** was prepared and subsequently coupled to boronic acid **12** to afford **11** in 48% overall yield (Scheme 3B). This two linear steps synthesis constitutes a significant improvement from the original six-step procedure, for which no overall yield was provided.[22]

In conclusion, we have developed synthetic protocols enabling controlled iodofluorination of internal and terminal alkynes relying on the unique reactivity of the DIH/"HF" system. Our method for single iodofluorination tolerates a wide range of functionalities and has successfully been performed on gram scale. It allowed facile access to a potent fluorinated tamoxifen derivative in two steps from commercially available starting materials. We have also developed a highly efficient strategy for double iodofluorination using the entire iodine content of DIH.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00321.

Experimental procedures, optimization tables, characterization data, and ^{1}H, ^{13}C, and ^{19}F spectra of all novel compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Generous financial support by the EU (FP7-PEOPLE-2012-ITN-RADIOMI-316882 to L.P.) is gratefully acknowledged. V.G. thanks the Royal Society for a Wolfson Research Merit Award (2013−2018).

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(12) The multiplicity as well as coupling constants of the ^{19}F NMR signals of **9a** (td, J = 22.6, 17.8 Hz) and **10a** (td, J = 16.6, 12.2 Hz) were used to determine the regiochemistry of these products.

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(15) ^{19}F NMR: −66.3 ppm (tq, J = 22.8, 6.6 Hz).

(16) ^{19}F NMR: −91.2 ppm (t, J = 23.8 Hz) (**7ua**) vs −105.3 ppm (d, J = 28.9 Hz) (**7ub**).

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DOI: 10.1021/acs.orglett.8b00321
Org. Lett. 2018, 20, 1576−1579