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Gold-Catalyzed Hydrofluorination of Electron-Deficient Alkynes: Stereoselective Synthesis of β-Fluoro Michael Acceptors

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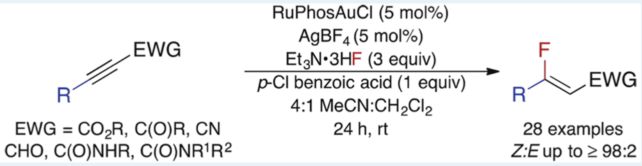
Supporting Information

ABSTRACT: The gold(I)-catalyzed, stereoselective hydrofluorination of electron-deficient alkynes with triethylamine trihydrogen fluoride ($Et_3N\cdot 3HF$) is described. Fluorinated α,β-unsaturated aldehydes, amides, esters, ketones, and nitriles were isolated in moderate to good yields as single diastereomers. In all but four cases, the (Z)-vinyl fluorides were initially formed in ≥97% diastereoselectivity. This work constitutes the first catalytic example of the diastereoselective preparation of a variety of β-alkyl, β-fluoro Michael acceptors from alkynes. Additionally, the described work expands access to β-aryl, β-fluoro Michael acceptors to the synthesis of β-fluoro-α,β-unsaturated amides and nitriles. The monofluoroalkenes formed through this strategy were readily transformed into other fluorine-containing compounds, and the developed method was applied to the synthesis of a fluorinated analogue of Exoderil, a topical antimycotic.



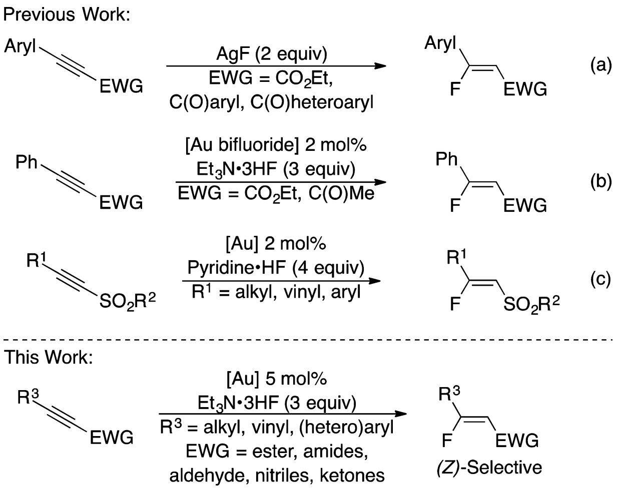
KEYWORDS: *monofluoroalkenes, michael acceptors, hydrofluorination, gold catalysis, fluorine*

New routes toward the selective fluorination of small molecules have been targeted in recent years due to the differences in the physical and biological properties between fluorinated compounds and those of their nonfluorinated analogues.[1] A fluorinated motif of particular interest is the monofluoroalkene. Monofluoroalkenes are isosteric with peptide bonds, and several bioactive compounds containing this motif have been reported.[2] Although several synthetic protocols exist to access α-fluoro, α,β-unsaturated carbonyl compounds—the Horner−Wadsworth−Emmons reaction,[3] the Julia Olefination,[4] the Peterson Olefination,[5] and the Reformatsky reaction[6]—the stereoselective synthesis of β-fluoro, α,β-unsaturated carbonyl compounds has proven to be a challenge, especially if β-alkyl substituents are desired.[7] Previous methods to access (Z)-β-fluoro-α,β-unsaturated carbonyl compounds are limited by the formation of products with low diastereoselectivities or yields,[8] the requirement for prefunctionalized starting materials,[9] and narrow functional group tolerance.[9b,c,10] Because of these limitations, a stereoselective and functional-group-tolerant method to access (Z)-β-alkyl, β-fluoro-α,β-unsaturated carbonyl compounds would be highly desirable.

The hydrofluorination of electron-deficient alkynes is perhaps the most direct method to generate (Z)-β-fluoro α,β-unsaturated carbonyl compounds from commercially available starting materials. Although some electron-deficient alkynes can undergo hydrofluorination in the absence of a catalyst, the diastereoselectivities of these reactions are generally moderate, especially for β-alkyl substrates.[8a,b,10] Traditional chromatographic techniques often fail to separate (E) and (Z) isomers of monofluoroalkenes; therefore, it is essential that the desired monofluoroalkenes are synthesized with high diastereomeric ratios.[11]

Since Sadighi's seminal report of the gold-catalyzed hydrofluorination of internal alkynes in 2007, other research groups have expanded the use of coinage metals for alkyne hydrofluorination.[12] Both Jiang, with excess AgF (Scheme 1a), and Nolan, with a catalytic amount of gold (Scheme 1b), prepared β-aryl, β-fluoro-α,β-unsaturated esters or ketones

Scheme 1. Generation of β-Fluoro Michael Acceptors from Alkynes with Coinage Metals



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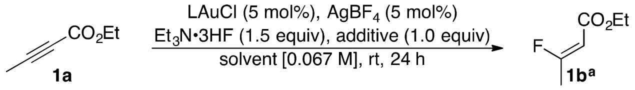
from electron-deficient, unsymmetrical alkynes.[12c,e] However, neither procedure reported the synthesis of β-alkyl, β-fluoro Michael acceptors or utilized alternative electron-withdrawing groups such as nitriles or amides. Alternative conditions were described by Hammond and Xu for the gold-catalyzed hydrofluorination of alkynes with a new DMPU/HF fluorinating reagent, but this procedure did not expand access to (*Z*)-β-fluoro-α,β-unsaturated carbonyl compounds.[12d] The first gold-catalyzed synthesis of a β-alkyl-β-fluoro Michael acceptor was demonstrated by Hammond and Xu in 2017 (Scheme 1c).[12f]

Although β-alkyl-β-fluorovinylsulfones could be accessed in a (*Z*)-selective manner, alkynes that did not bear a sulfonyl group—such as aroyl and phosphonyl—failed to undergo hydrofluorination. Despite these advances in alkyne hydrofluorination by coinage metals, a general procedure to synthesize a variety of (*Z*)-β-alkyl, β-fluoro Michael acceptors from electron-deficient alkynes is still an unsolved challenge.

Herein, we report a method for the preparation of a diverse array of β-alkyl, β-fluoro Michael acceptors from the gold-catalyzed hydrofluorination of electron-deficient alkynes. In addition to forming β-fluoro-α,β-unsaturated esters and ketones, this method is the first gold-catalyzed procedure to generate β-fluoro-α,β-unsaturated amides, nitriles, and aldehydes. A variety of β-alkyl as well as β-aryl substituents were tolerated; notably, 3° alkyl, alkenyl, and *o*-tolyl. Furthermore, we demonstrate that the monofluoroalkene products are synthetically versatile fluorinated building blocks.

The hydrofluorination of ethyl 2-butynoate (**1a**) with $Et_3N\cdot 3HF$ to form ethyl (*Z*)-3-fluorobut-2-enoate (**1b**) was selected as a model reaction. Monofluoroalkene **1b** formed in moderate yields and low stereoselectivities under conditions similar to those reported by Sadighi (see Table 1, entry 1).[12a] Reactions employing $AgBF_4$ as the silver salt afforded alkene **1b** in greater chemical yield compared to reactions conducted in the presence of other silver salts (entry 1 and 2, see the Supporting Information for further details). Upon switching from gold catalysts bearing NHC-ligands to gold catalysts bearing phosphine ligands, modest improvements in both yield and stereoselectivity were observed (entries 3 and 4). Unfortunately, reactions conducted with several triaryl or trialkyl phosphine gold(I) complexes as catalysts generated a purple hue after several hours in the presence of $Et_3N\cdot 3HF$, which has been reported by others as a visual indication of catalyst decomposition.[13]

Table 1. Effect of the Reaction Conditions on the Hydrofluorination of 1a



entry	L	solvent	additive	yield [%] (*Z*:*E*)[b]
1	IPr	CH_2CI_2	$KHSO_4$	50 (66:34)
2[c]	IPr	CH_2CI_2	$KHSO_4$	43 (70:30)
3	PPh_3	CH_2CI_2	$KHSO_4$	55 (60:40)
4	PCy_3	CH_2CI_2	$KHSO_4$	64 (75:25)
5	CyJohnPhos	CH_2CI_2	$KHSO_4$	84 (55:45)
6	RuPhos	CH_2CI_2	$KHSO_4$	57 (56:44)
7[d]	RuPhos	CH_2CI_2	$KHSO_4$	62 (97:3)
8[e]	RuPhos	CH_2CI_2	*p*-CI BA[e]	66 (97:3)
9	RuPhos	CH_3CN	*p*-CI BA	70 (97:3)
10	RuPhos	1:4 CH_2CI_2:CH_3CN	*p*-CI BA	76 (96:4)
11[f]	RuPhos	1:4 CH_2CI_2:CH_3CN	*p*-CI BA	71 (96:4)
12	RuPhos	1:4 CH_2CI_2:CH_3CN	none	65 (96:4)
13[g]	RuPhos	1:4 CH_2CI_2:CH_3CN	*p*-CI BA	80 (96:4)

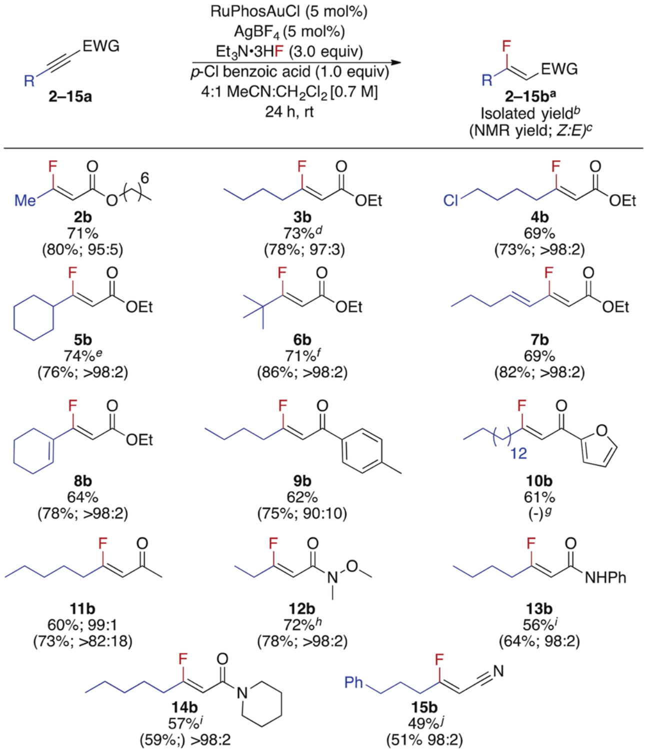
[a] General reaction conditions: 0.2 mmol **1a**, plastic vial. [b] Yields and *Z*:*E* ratios were determined by ^{19}F NMR spectroscopy with 2,4-dinitrofluorobenzene as an internal standard. [c] 5 mol % AgSbF6. [d] 4 h. [e] *p*-chlorobenzoic acid. [f] 10 mol % *p*-CI BA. [g] 3.0 equiv $Et_3N\cdot 3HF$.

Cationic-gold(I) complexes with dialkylbiarylphosphine ligands are known to be more stable toward decomposition pathways than cationic gold(I) complexes triaryl or trialkyl phosphines.[14] Upon switching the gold catalyst to CyJohnPhosAuCl, monofluoroalkene **1b** was generated in 84% yield. However, the stereoselectivity of the reaction conducted with CyJohnPhosAuCl decreased relative to the stereoselectivity of the reaction conducted with Cy_3PAuCl as the catalyst (entry 3 and 4). Examination of a variety of dialkylbiaryl phosphinegold(I) complexes revealed that only reactions with RuPhos as the ligand afforded the greatest *Z*:*E* selectivity of **1b** (entries 6 and 7). For instance, in the presence of CyJohnPhos the yield of **1b** after 4 h was 85% but with a *Z*:*E* of 77:23.

In addition to the ligand effect on the reaction, both the solvent and additive were found to influence the yield and stereoselectivity of the hydrofluorination of alkynoate **1a**. Switching from potassium bisulfate to *p*-chlorobenzoic acid (*p*-Cl BA), a more soluble acid coadditive, resulted in a modest improvement in the yield of monofluoroalkene **1b** (entry 8). Reactions conducted with RuPhosAuCl and CH_3CN as the solvent afforded the hydrofluorination product in a further improved yield while maintaining the *Z*-selectivity observed at shorter reaction times (entry 8 and 9). The change in solvent also ensured that the *Z*:*E* ratio did not decrease over time, permitting easier reaction monitoring as alkene isomerization was largely suppressed. Ultimately, reactions conducted in a solvent mixture of CH_3CN:CH_2Cl_2 maintained the high stereoselectivity of the hydrofluorination of alkyne **1a** while affording alkene **1b** in an improved yield (entry 9 and 10). The beneficial improvement in the yield of **1b** was observed with as little as 10 mol % *p*-Cl BA (entry 11 and 12). Other acid additives were examined, but benzoic acid derivatives appeared to provide an optimal pK_a range (see Supporting Information, Table S4). Increasing the equivalents of $Et_3N\cdot 3HF$ did not have a significant influence on the reaction (entry 13); however, reactions with $Et_3N\cdot 2HF$, $Et_3N\cdot HF$, and pyridine·HF (70% HF) failed to generate alkene **1b** (See Supporting Information).

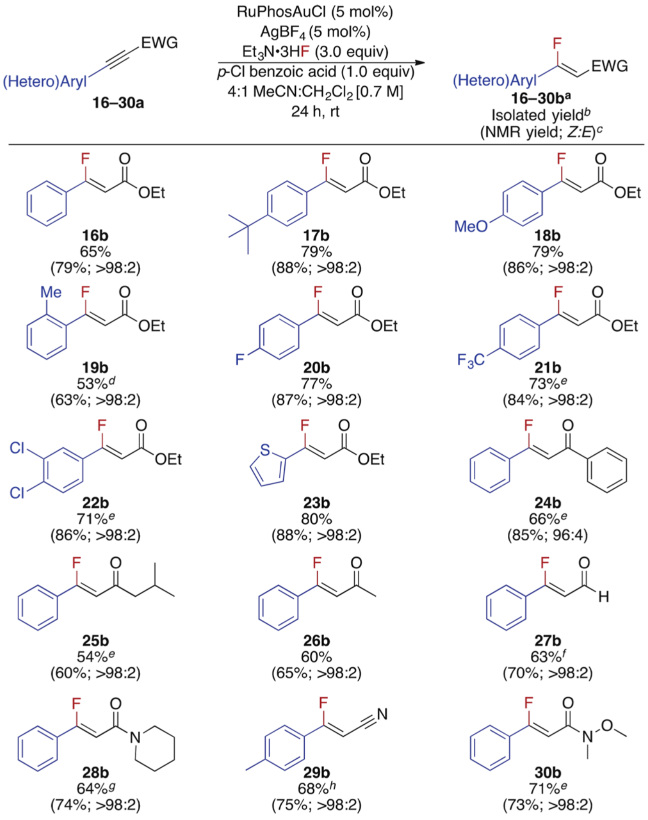
Having identified suitable reactions conditions for the hydrofluorination of alkyne **1a**, we investigated the hydrofluorination of β-alkyl alkynoates, alkynones, alkynamides, and alkynenitriles (Table 2). Methyl, 1° alkyl, 2° alkyl, and vinyl β-substituted alkynoates underwent hydrofluorination in the presence of $Et_3N\cdot 3HF$ in a *Z*-selective manner in good yields. Notably, the final products were all isolated as a single diastereomer after standard silica gel column chromatography. Importantly, these results highlight this operationally simple, one-step route to β-alkyl, β-fluoro Michael acceptors from alkynes. The hydrofluorination reaction was also shown to be scalable, as fluoroalkenes **3b** and **5b** were both prepared on a gram scale in good yield and with excellent *Z*-selectivity. For substrate **6a** with a bulky β-substituents, a higher reaction temperature was required to obtain the product in moderate yield (**6b**). The hydrofluorination of alkynoates bearing β-vinyl substituents provided straightforward access to fluorinated dienes **7b** and **8b**. Hydrofluorination of the γ,δ-alkene of either

Table 2. Scope of *β*-Alkyl, *β*-Fluoro Michael Acceptors



[a] Standard reaction conditions: 0.5 mmol **2–15a**, 3.0 equiv $Et_3N{\cdot}3HF$, 1.0 equiv *p*-Cl BA, 5 mol % RuPhosAuCl, 5 mol % $AgBF_4$, 4:1 $MeCN:CH_2Cl_2$ [0.7M], rt, 24 h. [b] **2–15b** isolated as a single isomer except **11b**. [c] Detemined by ^{19}F NMR spectroscopy with PhF as an internal standard. [d] 6.0 mmol scale. [e] 5.0 mmol scale. [f] 55 °C [g] insoluble product. [h] 1.25 M, 4.0 equiv $Et_3N{\cdot}HF$. [i] 1.25 M, 4.0 equiv $Et_3N{\cdot}3HF$. [j] 1.43 M, 4.5 equiv $Et_3N{\cdot}3HF$, 50 °C.

Table 3. Scope of *β*-aryl, *β*-fluoro Michael acceptors



[a] Standard reaction conditions: 0.5 mmol **16–30a**, 3.0 equiv $Et_3N{\cdot}3HF$, 1.0 equiv *p*-Cl BA, 5 mol % RuPhosAuCl, 5 mol % $AgBF_4$, 4:1 $MeCN:CH_2Cl_2$ [0.7M], rt, 24 h. [b] **16–30b** isolated as a single isomer. [c] Determined by ^{19}F NMR spectroscopy with PhF as an internal standard. [d] 1.43 M, 45 °C. [e] 45 °C. [f] 4.5 mmol. [g] 1.25 M, 55 °C, 4.0 equiv $Et_3N{\cdot}3HF$. [h] 45 °C, 48 h, 4.0 equiv $Et_3N{\cdot}3HF$.

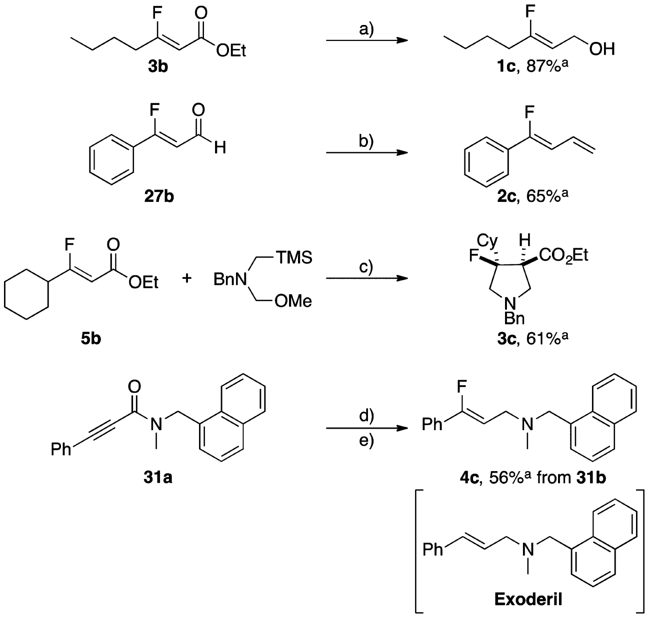
7a or **8a** was not detected by ^{19}F NMR spectroscopy. The reaction conditions for the hydrofluorination of *β*-alkyl alkynoates were also suitable for the hydrofluorination of *β*-alkyl (hetero)aryl alkynones **9b** and **10b**. Although methyl ketone **11a** proved to be a challenging substrate, **11b** was isolated in good yield with only a trace amount of the *E*-isomer. Both 2° and 3° *β*-alkyl alkynamides (**12–14a**) as well as alkynonitrile derivative **15a** underwent hydrofluorination to provide **12–15b** in moderate yields. Dec-2-ynal was the only substrate that did not undergo hydrofluorination in a diastereoselective manner under the standard conditions in Table 2 (72%, *Z*:*E* = 51:49). However, conducting the reaction at 5 °C did afford a *Z*:*E* ratio of >98:2 and 22% yield after 24 h. Unfortunately, after 96 h at 5 °C, the yield increased to 51% but the *Z*:*E* ratio decreased to 70:30.

To showcase the generality of this method, the hydrofluorination reactions of a variety of electron deficient alkynes bearing *β*-aryl substituents were also explored (Table 3). Generally, the yields of *β*-aryl-monofluoroalkenes **16–30b** were comparable to those of their *β*-alkyl-analogues **2–15b**. In contrast to previous procedures, even a monofluoroalkene bearing an *ortho*-substituted aryl group (**19b**) was generated in modest yield.[12e] Compared with the esters and ketones, even the more electrophilic 2-phenylpropiolaldehyde afforded **27b** in a *Z*-selective manner. Moreover, both *β*-aryl alkynonitriles and alkynamides were suitable substrates, generating otherwise difficult to access fluorinated motifs (**28–30b**). Finally, this methodology was found to be complementary to that reported by Hammond and Xu (See Supporting Information, Table S5)[12f]

The monofluoroalkenes generated from our catalytic process underwent a series of transformations demonstrating that *β*-fluoro Michael acceptors are valuable fluorinated building blocks (Scheme 2). For example, ester **3b** was reduced in the presence of DIBAL–H to yield the fluorinated allylic alcohol **1c** in high yield.[15] Aldehyde **27b** underwent Wittig olefination in modest yield to afford a 1-fluoro-2,4-diene **2c.**[16] In the presence of a suitable 1,3-ylide, ester **5b** underwent a regioselective [3 + 2] cycloaddition to generate a pyrrolidine with a quaternary fluorine center (**3c**).[17] Finally, amide **31b** was reduced in the presence of Meerwein's salt to furnish a fluorine-containing analogue of Exoderil **4c.**[18]

In conclusion, we have developed a stereoselective hydrofluorination of electron-deficient alkynes catalyzed by a RuPhos-ligated gold(I) complex. For the first time, direct access to a variety of (*Z*)-*β*-alkyl, *β*-fluoro Michael acceptors was achieved. In addition, (*Z*)-*β*-aryl, *β*-fluoro *α*,*β*-unsaturated amides and nitriles were conveniently accessed with the disclosed method. The synthetic potential of the resulting monofluoroalkene was demonstrated with various transformations of the products without the loss of the newly installed fluorine atom, and with the synthesis of a fluorinated analogue of Exoderil.

Scheme 2. Diversification of Fluorinated Michael Acceptors



[a]Yield given is for isolated product at specified scale. (a) **3b** (2.32 mmol), DIBAL−H, CH_2CI_2, 0 °C. (b) ^{n}BuLi, Ph_3PMeBr, **27b** (0.3 mmol), THF, 0 °C. (c) **5b** (0.3 mmol), ylide, TFA, 0 °C−rt. (d) **31a** (1.96 mmol), 5 mol % RuPhosAuCI, 5 mol % $AgBF_4$, 1.0 equiv *p*-CI BA, 4.0 equiv $Et_3N·3HF$, 45 °C, 48 h, 4:1 MeCN:CH_2CI_2[1.25 M]. (e)Me_3OBF_4, 2,6-DI-^{t}Bu-pyridine, **31b** (0.54 mmol), CH_2CI_2, rt; $NaBH_4$, MeOH, −10 °C.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.8b01341.

Experimental details and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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