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Zinc-Catalyzed Stereo- and Regioselective 1,4-Hydrative Fluorination of 3-En-1-ynamides with Selectfluor

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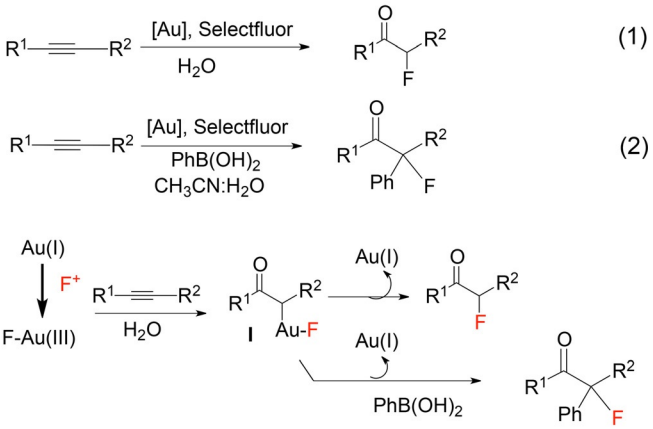
Abstract: Zinc-catalyzed 1,4-oxofluorinations of 3-en-1-ynamides with Selectfluor in acetonitrile/water proceeded with high regio- and stereoselectivity, giving *E*-configured γ-fluoro-α,β-unsaturated amides efficiently. Our control experiments indicate that kinetically unstable C-bound zinc dienolates are chemically reactive to undergo S_E2'-electrophilic fluorinations whereas the detectable O-bound dienolates preferably undergo protodemetalation reactions instead.

Keywords: S_E2'-electrophilic fluorinations; 1,4-oxofluorinations; Selectfluor; zinc dienolates

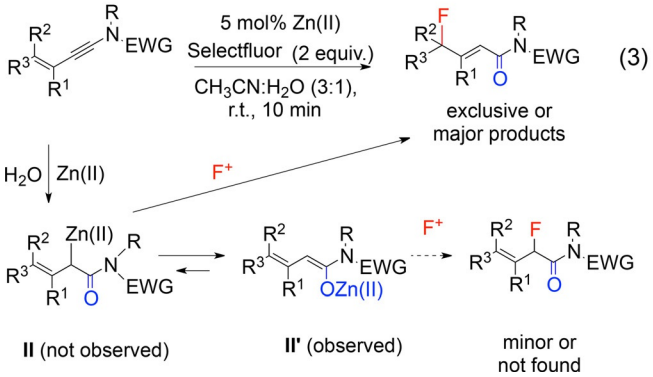
Considerable interest has focused on fluoroorganic compounds due to their potential use in material chemistry, fine chemicals, agrochemicals, polymer and fiber-related industries. The presence of a fluorine atom in the organic compound can largely alter its biological functions; such organofluoro compounds are hence pharmaceutically important.[1] Despite many synthetic methods, syntheses of organofluoro compounds under mild conditions are still limited.[2] The advent of gold catalysis has inspired considerable interest in the 1,2-hydrative fluorination of alkynes to produce α-fluoro ketone derivatives using Selectfluor[3] as the fluorine source.[4,5] Nevado and co-worker reported gold-catalyzed hydrative fluorinations on alkynes to afford α-fluoro ketones [Eq. (1)].[4] Hammond and co-worker reported remarkable hydrative fluorination/aryl cascade reactions of alkynes using Selectfluor and boronic acid to yield α,α-fluoroaryl ketones [Eq. (2)].[5] The mechanisms of these reactions involve initial oxidations of neutral Au(I) complexes to F–Au(III) species, enabling the alkyne hydrations to form α-oxo fluorogold intermediates (**I**) before proceeding to α-fluoro ketones and α,α-fluoroaryl ketones.

γ-Fluoro-α,β-unsaturated carbonyl species constitute a class of versatile intermediates in organic synthesis, and are important functionalities in biologically active compounds.[6] Common methods for the synthesis of these compounds include electrophilic fluorinations of conjugated enol ethers[7] and Wittig-type

1,2-Oxofluorination of alkynes *via* Au(III) (previous work)



1,4-Oxofluorination *via* Zn(II) (this work)

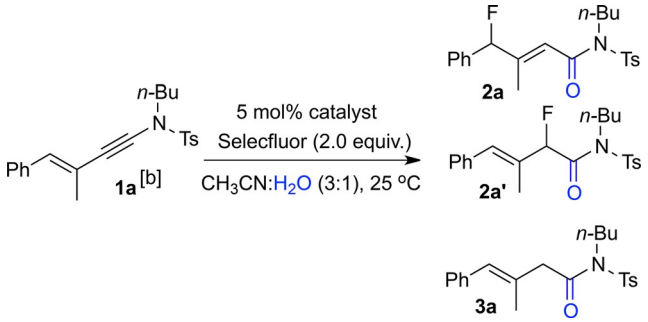


reactions of α-fluoroaldehydes and ketones,[8] vinylogous fluorinations of vinyldiazo esters.[9] We are aware of no examples aiming at γ-fluoro-α,β-unsaturated amides.

We envisaged that metal-catalyzed hydrative fluorinations of 3-en-1-ynamides might be a convenient tool to access γ-fluoro-α,β-unsaturated amides because possibly existing C- and O-bound dienolates (**II** and **II′**) would direct the 1,4- and 1,2-regioselectivities of their electrophilic activations. We recently reported zinc-catalyzed 1,2-hydrative aldol reactions of 3-en-1-ynamides *via* the aldol reactions of their O-bound zinc dienolates intermediates (**II′**) that were detectable in solution.[10] In contrast with our previous results, the present work reports 1,4-regioselectivity in the zinc-catalyzed hydrative fluorinations of 3-en-1-ynamides to furnish *E*-configured 4-fluoro-2-en-1-amides **2a** with excellent regio- and stereoselectivity. The occurrence of such a 1,4-regioselectivity is attributed to the S_E2' electrophilic fluorinations of C-bound zinc-dienolates (**II**) that are undetectable in solution.

Table 1 shows the realization of a 1,4-oxofluorination of 3-en-1-ynamide **1a**[11] with Selectfluor (2.0 equiv.) that is soluble in water. In the absence of catalyst, the reaction of 3-en-1-ynamide **1a** with Selectfluor in CH_3CN/water (3:1) at 25 °C gave 1,4- and 1,2-oxofluorination products **2a** and **2a′** in a combined 81% yield (**2a/2a′** = 2.6:1) that were inseparable on a silica column (entry 1). The structure of **2a′** was assigned based on an observed C–F coupling of its amide carbonyl ($J_{C,F}$ = 24 Hz). In entry 2, we followed the methods of Nevado[4] and Hammond[5] to treat 3-en-1-ynamide **1a** with Ph_3PAuCl (5 mol%) and Selectfluor to attain a complete conversion, yielding *E*-configured **2a** in only 37% yield together with hydration product **3a** in 24% yield. Fluorogold(III) intermediate [**I**, Eqs. (1) and (2)] is not a viable route for the desired 1,4-hydrative fluorinations. We thus employed cationic gold catalysts including $Ph_3PAuCl/AgNTf_2$ and $P(t\text{-}Bu)_2(o\text{-biphenyl})AuCl/AgNTf_2$ which afforded the same product **2a** in good yields (63–65%, entries 3 and 4). We tested the reactions with less acidic $IPrAuCl/AgNTf_2$ [IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene] that gave the desired **2a** in 48% yield together with a hydration product **3a** and unreacted **1a** in minor proportions (16–17%); the reaction time was long (*ca.* 4 h) although this catalyst was reported to be very efficient for alkyne hydration (entry 5).[12] Notably, the yield of **2a** was greatly improved to 85% with $Zn(OTf)_2$ after a brief period (10 min, entry 6) whereas $ZnCl_2$ maintained the high efficiency to deliver the same product **2a** in 83% (entry 7). The use of AgOTf was troubled with the reaction chemoselectivity to yield compounds **2a**, by-product **3a** and unreacted **1a** in 62%, 12%, and 15%, respectively (entry 8). Other metal catalysts such as $Cu(OTf)_2$, $In(OTf)_3$, and $Sc(OTf)_3$, gave the desired product **2a** in moderate yields (47–52%) along with undesired 3-alkenylamide **3a** in 12–16% (entries 9–11). The *E*-configured geometry of 4-fluoro-2-en-1-amide **2a** was confirmed by ^1H NOE effects. We hypothesize that selective formation of product **2a** is due to a rapid Zn(II)-catalyzed hydration of alkynes to yield C-bound zinc dienolates **II** (see Scheme 1). In the absence of metal catalyst, F^+ can coordinate with alkene or alkyne before the attack of water, further affording 1,4- and 1,2-oxofluorination reactions.

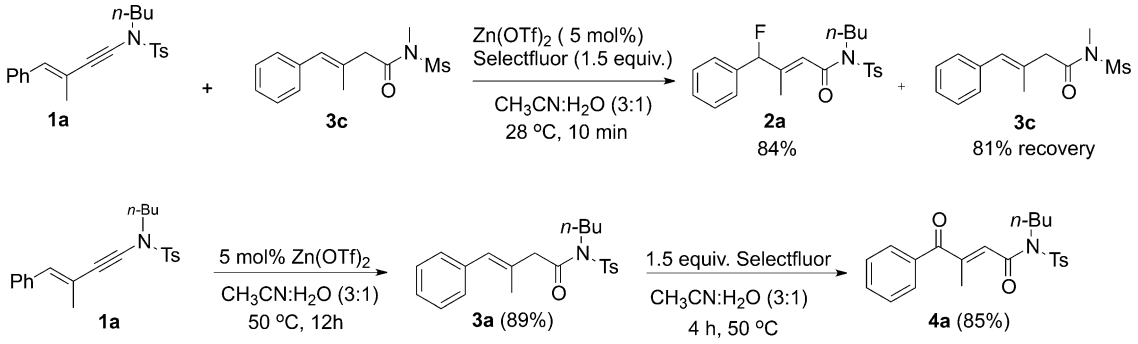
Table 1. Catalyst screening for 1,4-oxofluorination.



Entry	Catalysts[a]	Time [h]	Compounds (yields)[c]		
			2a/2a′	**3a**	**1a**
1	–	0.6	81(2.6:1)	–	–
2	Ph_3PAuCl	2.0	37/–	24	–
3	$Ph_3PAuCl/AgNTf_2$	2.0	65/–	–	–
4	$LAuCl/AgNTf_2$	2.0	63/–	–	–
5	$IPrAuCl/AgNTf_2$	4.0	48/–	16	17
6	$Zn(OTf)_2$	0.15	85/–	–	–
7	$ZnCl_2$	0.50	83/–	–	–
8	AgOTf	2.0	62/–	12	15
9	$Cu(OTf)_2$	2.0	47/–	16	–
10	$Sc(OTf)_3$	2.0	50/–	14	–
11	$In(OTf)_3$	2.0	52/–	12	–

[a] L = $P(t\text{-}Bu)_2(o\text{-biphenyl})$; IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene).
[b] [**1a**] = 0.13 M.
[c] Product yields are reported after purification by using a silica gel column.

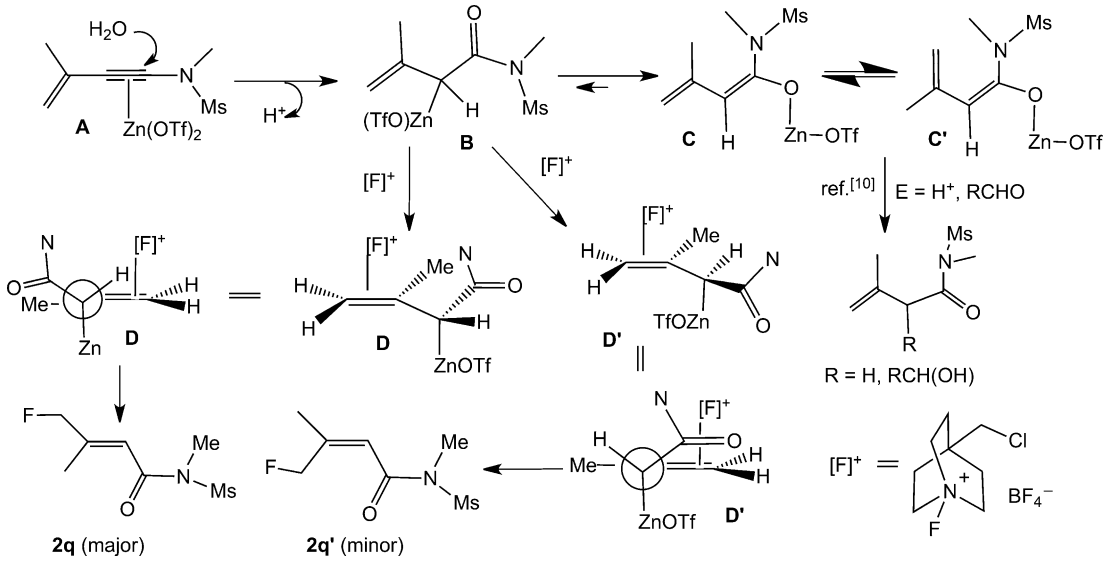
We prepared various 3-en-1-ynamides **1b–r** to assess the scope of applicable substrates; the results are presented in Table 2. Initially, 3-en-1-ynamides **1b**–**1q** were prepared in *E*-configurations with R^2 being larger than R^1. The 1,4-oxofluorination reactions were performed with $Zn(OTf)_2$ (5 mol%) following the same procedure as in Table 1 (entry 6). The resulting 4-fluoro-2-en-1-amides **2b**–**2p** were obtained as single diastereomeric products (entries 1–15) whereas compounds **2q** and **2r** were present with two isomeric products. For 3-en-1-ynamides **1b–e** bearing various sulfonamide groups including cyclopropyl tosylsulfonamide, methyltosylsulfonamide, benzyltosylsulfonamide, and oxazolidine, their zinc-catalyzed reactions gave the desired 1,4-oxofluorination products **2b–2e** in satisfactory yields (76–87%, en-



Scheme 1. Control experiments.

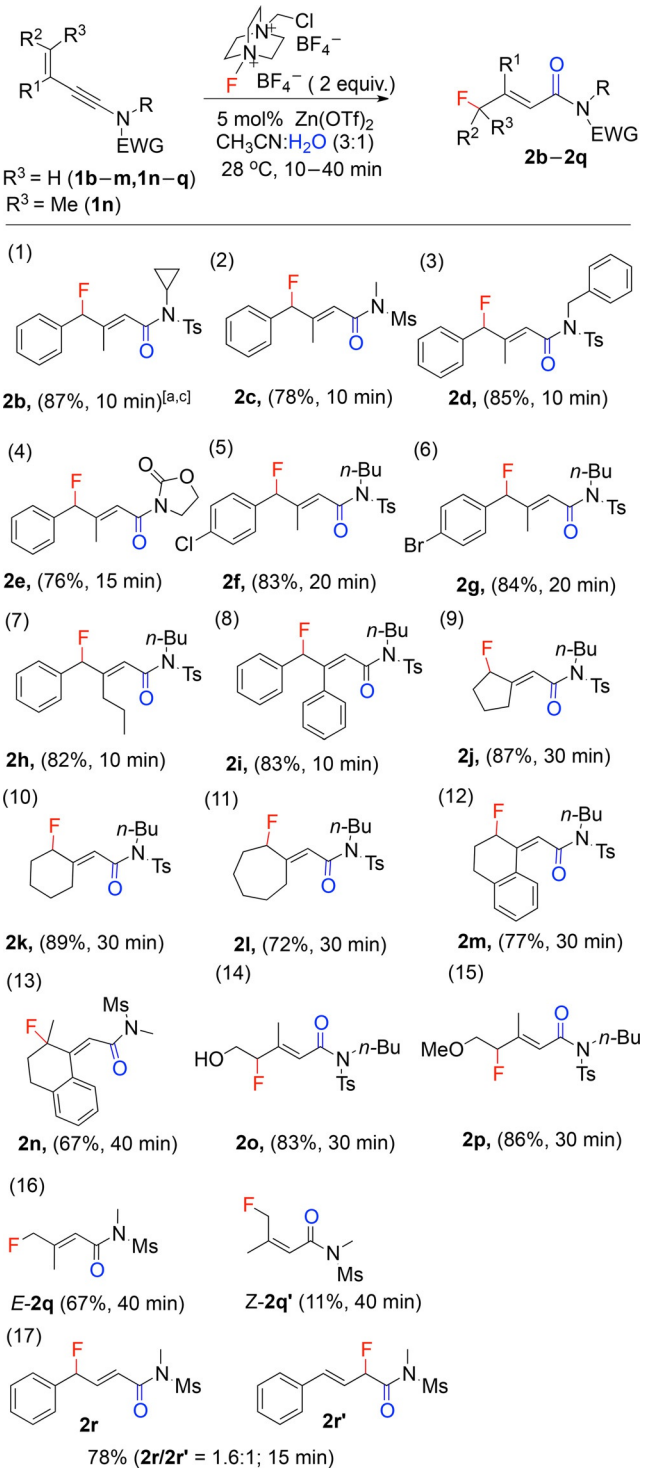
tries 1–4). The reactions were compatible with substrates **1f** and **1g** bearing $R^2 = 4\text{-}ClC_6H_4$, and $4\text{-}BrC_6H_4$, yielding the expected 1,4-oxofluorinatiton products **2f** and **2g** in satisfactory yields (83–84%, entries 5 and 6). We prepared additionally 3-en-1-ynamides **1h** and **1i** containing $R^1 = n$-propyl and phenyl, giving the desired **2h** and **2i** in 82 and 83% yields respectively (entries 7 and 8). To further expand the substrate scope, we tested the reactions on starting species **1j–1l** bearing a cycopentenyl, cyclohexenyl and cycloheptenyl ring, respectively (R^1, $R^2 = C_5H_6$, C_6H_8 and C_7H_{10}); the corresponding products **2j–l** were obtained with satisfactory yields (72–89%, entries 9–11). These zinc-catalyzed reactions were extendable to substrates **1m** and **1n** bearing a dihydronaphthalene ring, the desired products **2m** and **2n** resulted in 77% and 67% yields, respectively (entries 12 and 13). We performed X-ray diffraction studies to characterize the molecular structure of **2n**, confirming its *E*-configuration.[13] We also prepared 3-en-1-ynamides **1o** and **1p** bearing $R^3 = H$, $R^2 = CH_2OH$ and CH_2OMe to test the tolerance of a functional group, their Zn(II)-catalyzed 1,4-oxofluorination reactions gave the desired **2o** and **2p** in 83 and 86% yields, respectively (entries 14 and 15). The reaction was further compatible with 2-en-1-ynamide **1q** bearing a vinyl group ($R^2 = R^3 = H$); two isomeric products *E*-**2q** and *Z*-**2q′** were obtained in *E*- and Z-configurations, respectively, with corresponding yields of 67% and 11% (entry 16). ^1H NOE was used to determine the olefin geometries of the two isomers. The reaction is less compatible with substrate **1r** bearing a 1,2-substituted alkene, yielding 1,4- and 1,2-oxofluorination products **2r** and **2r′** in a combined 78% yield (entry 17).

Scheme 1 presents data to assist in an understanding of the reaction mechanism. Treatment of a 1:1 molar ratio of 3-en-1-ynamide **1a** and a hydration product **3c**, together with Selectfluor (2 equiv.) and $Zn(OTf)_2$ (5 mol%) in $MeCN/H_2O$ (3:1) for a brief



Scheme 2. Rationale for the stereo- and regioselectivity.

Table 2. 1,4-Oxofluorination of various 3-en-1-ynamides.



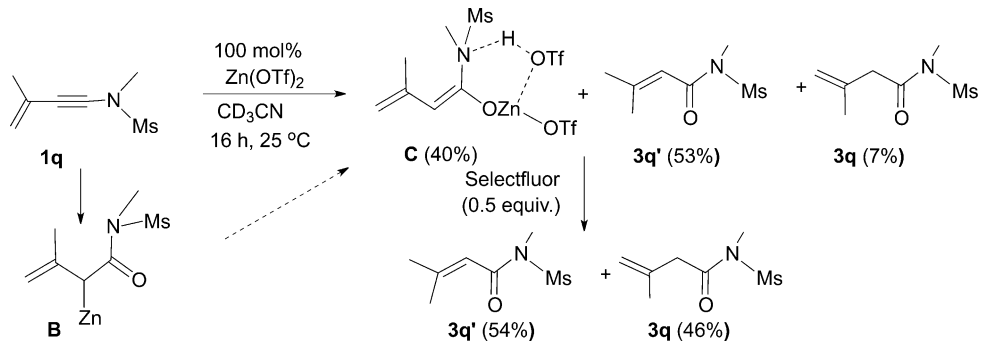
[a] *Reaction conditions:* **1** (0.27 mmol), $Zn(OTf)_2$ (0.013 mmol), Selectfluor (0.54 mmol).
[b] **1a** (0.13 M).
[c] Product yields are reported after separation on a silica gel column.

period (25 °C, 10 min) delivered **2a** in 85% yield whereas species **3c** was recovered exclusively. This information indicates that a hydration product like **3c** is unlikely to be an intermediate for this 1,4-oxofluorination reaction. We examined also the reactivity of species **3a** toward Selectfluor (1.5 equiv.) in MeCN/H_2O (3:1) at 50 °C, the reaction proceeded smoothly to yield 4-oxo-2-en-1-amide **4a** in 85% yield instead.[11c]

Scheme 2 provides a plausible mechanism to rationalize the excellent regio- and stereocontrol of the 1,4-oxofluorination reactions of 3-en-1-ynamide **1q**. In our previous work,[10] we identified an O-bound dienolate **C/C′** *via* a slow hydration of 3-en-1-ynamide **1q** with $Zn(OTf)_2$, this O-bound zinc dienolate reacted with aldehydes at the Cα-addition, inconsistent with a distinct Cγ-addition regioselectivity observed for our fluorination products **2**. We postulate that C-bound dienolate **B** is actually active despite being undetectable. The S_E2'-reaction of this enolate (**B**) with Selectfluor likely proceeds in two possible conformations with state **D** being more favorable than state **D′** because the latter has a large and proximate amide group to impede Selectfluor from approaching the olefin group according to an S_E2' model, in which the Zn–C bond is parallel to the electrophile to exert a hyperconjugation.

To verify our hypothesis, we followed our reported procedure[10] to generate O-bound zinc dienolate **C** through the treatment of 3-en-1-ynamide **1q** with H_2O (5 equiv.) in CD_3CN (25 °C, 16 h) to attain a complete consumption of initial **1q**; the resulting solution contained O-bound zinc dienolate **C** and 2-en-1-amide **3q′** and 3-en-1-amide **3q** in 40%, 53% and 7% yields, respectively, as depicted in Scheme 3. A subsequent treatment of this solution provided mainly two hydration products **3q′** and **3q** in 54% and 46% yields, respectively. This information suggests that O-bound zinc dienolate **C** is inactive toward Selectfluor in the presence of HOTf, but preferably formed the hydration product **3q**. With this information, we envisage that initial hydration product **3q′** arises from C-bound enolate **B**, further supporting our postulated mechanism.

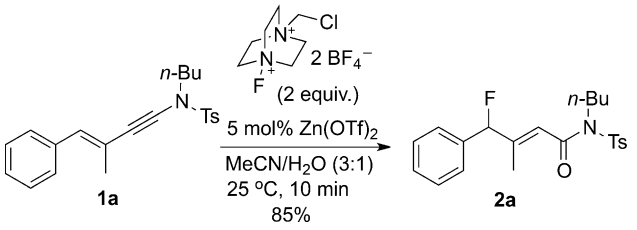
This work continues our interest in the zinc-catalyzed hydrative functionalizations of 3-en-1-ynamides *via* dienolate intermediates. In contrast with our reported 1,2-regioselectivity of the hydration and hydrative aldol reactions of these 3-en-1-ynamides, the present 1,4-oxofluorinations proceeded through 1,4-addition regioselectivity with high *E*-stereoselectivity, yielding diverse 4-fluoro-2-en-1-amides efficiently.[14] As a result of a series of control experiments to confirm the intermediacy of dienolate intermediates,[15] we postulate C-bound dienolates to control the regio- and stereochemical course for the final fluorination reactions.



Scheme 3. Reactivity of the O-bound zinc dienolate.

Experimental Section

Standard Catalytic Procedure (Scheme 4)



Scheme 4. Standard procedure for 1,4-oxidative fluorination.

A glass vial was charged with an MeCN/H_2O (2 mL, 3:1) solution of $Zn(OTf)_2$ (5.0 mg, 0.013 mmol), 3-en-1-ynamide **1a** (100 mg, 0.27 mmol) and Selectfluor (191 mg, 0.54 mmol); the resulting mixture was stirred at room temperature for 10 min before it was filtered through a short silica bed. The filtrate was dried over $MgSO_4$ and purified by column chromatography to obtain compound (*E*)-*N*-butyl-4-fluoro-3-methyl-4-phenyl-*N*-tosylbut-2-enamide (**2a**) as a brown viscous liquid; yield: 93 mg (0.23 mmol, 85%). IR (neat): $\nu =$ 3037 (m), 1627 (s), 1543 (s), 1247 (m), 813 cm^{-1} (s); ^1H NMR (600 MHz, $CDCl_3$): $\delta = 7.74$ (dd, $J = 6.8$, 1.8 Hz, 2H), 7.37~7.35 (m, 3H), 7.29 ~7.26 (m, 4H), 6.64 (dd, $J =$ 2.6, 1.3 Hz, 1H), 5.68(d, $J = 47.2$ Hz, 1H), 3.82(t, $J = 6.7$ Hz, 2H,) 2.40 (s, 3H), 1.73–1.68 (m, 5H), 1.38–1.34 (m, 2H), 0.94 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta =$ 165.9, 151.4 (d, $J = 18.1$ Hz), 144.5, 137.0, 136.4 (d, $J =$ 20.5 Hz), 129.6, 129.2, 128.7, 127.6, 127.0 (d, $J = 5.4$ Hz), 117.0 (d, $J = 11.1$ Hz), 96.0 (d, $J = 179.2$ Hz), 46.6, 32.0, 21.6, 19.9, 15.0, 13.6 (d, $J = 17.6$ Hz); HR-MS: $m/z = 403.1612$, calcd. for $C_{22}H_{26}FNO_3S$: 403.1617.

Acknowledgements

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[13] CCDC 1030662 contains the supplementary crystallographic data for this paper (compound **2n**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.
[14] In ref.[11c] it is reported that a zinc-catalyzed 1,4-dioxo functionalization was produced *via* sequential treatment of 3-en-1-ynamides with water at 50 °C, followed by Selectfluor oxidations. These 4-oxo-2-en-1-amides actually arose from the Selectfluor oxidation of hydration products (see Scheme 1) rather than zinc dienolate intermediates.
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