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Cu(I)- or Ag(I)-Catalyzed Regio- and Stereocontrolled *trans*-Hydrofluorination of Ynamides

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Supporting Information

ABSTRACT: With $Et_3N{\cdot}3HF$ as the fluorinating reagent, a copper(I)- or silver(I)-catalyzed β/α-site-regiocontrolled *trans*-hydrofluorination of alkynamides has been achieved, affording the corresponding fluoro enamides in moderate to nearly quantitative yields with high regio- and stereoselectivity, respectively. The reaction proceeds under mild reaction conditions and exhibits good functional group tolerance. Further, the deuterium-labeling experiment confirmed the existence of the alkenylcopper intermediate.

The incorporation of a fluorine atom into molecules frequently renders remarkable changes in their physical, chemical, and biological properties when compared with their nonfluorinated analogues.[1] Thus, the development of mild and efficient methods to form carbon−fluorine bonds is of considerable significance in pharmaceuticals, agrochemicals, materials, and radiotracers for positron emission tomography (PET).[2] Recently, Sadighi,[3] Hammond,[4] and co-workers conducted pioneering work on (NHC)Au-catalyzed hydrofluorination of alkynes, which revealed a new pathway for the easy formation of C−F bonds. Following their reports, Miller[5] and Nolan[6] also described (NHC)Au-catalyzed hydrofluorination of functionalized alkynes. Despite notable recent advances in the field of fluorination of alkynes, comparable cheap transition-metal catalysts and exploration of new fluorination systems are still highly desired.

In recent years, ynamides have attracted the interest of an ever-increasing number of research groups due to their availability combined with their stability and unique reactivity.[7] Although a series of transformations from ynamides have been reported recently, only two examples in the literature focused on the hydrofluorination of ynamides. Thibaudeau[8] reported a *cis*-hydrofluorination of ynamides to (*E*)-α-fluoroenamides with superacid HF or HF/pyridine as both solvent and reactant (Scheme 1a). Zhu[9] developed a *trans*-hydrofluorination of *N*-sulfonylynamides with overstoichiometric amounts of AgF[10] as the fluorination reagent (Scheme 1b). However, to the best of our knowledge, the catalytic α/β-site regiocontrolled *trans*-hydrofluorination of ynamides has not been reported. In conjunction with our continuing interest in the chemistry of ynamides,[11] herein we present a Cu(I)- or Ag(I)-catalyzed nucleophilic fluorination of ynamides with high levels of regio- and stereoselectivities using a relatively benign fluorine source (Scheme 1c).

In initial experiments, we investigated the $(PPh_3)_3CuF$[12]-catalyzed hydrofluorination of 3-(2-phenylethynyl)oxazolidin-2-one (**1a**) with $Et_3N{\cdot}3HF$[13] in anhydrous solvents at 70 °C (Table 1). The reaction in DMSO afforded the β/α-site fluorinated alkenylamide mixture with a (*Z*)-**2a**[14]/(*Z*)-**3a**[15] ratio of 82/18 in poor yield (entry 1). Further screening revealed that the solvent effect played an important role in achieving high selectivity and yield (entries 1−6). To our delight, when the Cu(I)-catalyzed hydrofluorination was conducted in anhydrous THF, the desired β-site regiocontrolled fluoroenamide (*Z*)-**2a** could be afforded in 98% yield with excellent regioselectivity (entry 6), which has seldom been observed in the fluorination of ynamides.[8,9] Lowering the reaction temperature or reducing the amount of catalyst loading also resulted in good yields and excellent selectivity; however, both required prolonged reaction times (entries 7 and 8). In fact, the yield and selectivity of the hydrofluorination was still maintained at a parallel level even when 1.0 equiv of $Et_3N{\cdot}3HF$ was used (entry 9 vs entry 6). In contrast, $(PPh_3)_3CuF$ exhibited a better catalytic ability than CuCl (entry 11). Other fluorinating agents, such as pyridine/HF, LiF, CsF, and ZnF_2, significantly decreased the chemical yields

Scheme 1. Cu(I)- or Ag(I)-Catalyzed *trans*-Hydrofluorination of Ynamides

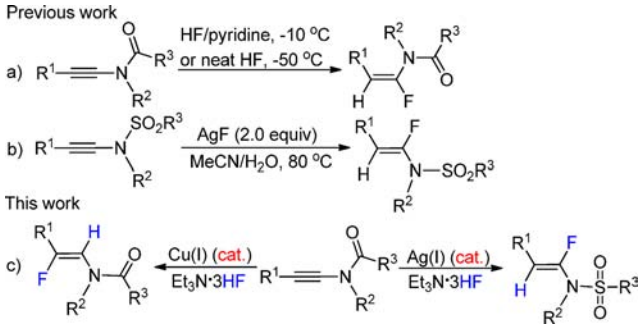

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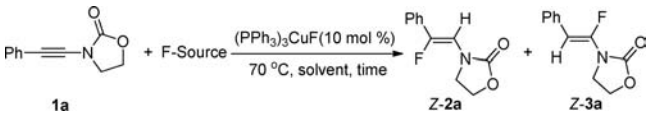
Table 1. Screening Reaction Conditions of Cu(I)-Catalyzed *trans*-Hydrofluorination of 3-(2-Phenylethynyl)oxazolidin-2-one (1a)[a]



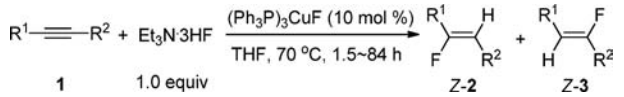
entry	F source (equiv)	solvent	time (h)	NMR yield of (*Z*)-**2a**(%)[b]	ratio of (*Z*)-**2a**/(*Z*)-**3a**[c]	recovery of **1a** (%)
1	$Et_3N{\cdot}3HF$ (2.0)	DMSO	50	9	82/18	73
2	$Et_3N{\cdot}3HF$ (2.0)	CH_3CN	48	0		100
3	$Et_3N{\cdot}3HF$ (2.0)	DMF	50	11	92/8	0
4	$Et_3N{\cdot}3HF$ (2.0)	DCE	15	80	96/4	0
5	$Et_3N{\cdot}3HF$ (2.0)	benzene	8	87	99/1	0
6	$Et_3N{\cdot}3HF$ (2.0)	THF	14	98	98/2	0
7[d]	$Et_3N{\cdot}3HF$ (2.0)	THF	23	88	98/2	0
8[e]	$Et_3N{\cdot}3HF$ (2.0)	THF	20	86	98/2	0
9	$Et_3N{\cdot}3HF$ (1.0)	THF	19	97 (92)[f]	98/2	0
10	$Et_3N{\cdot}3HF$ (0.5)	THF	15	92	98/2	0
11[g]	$Et_3N{\cdot}3HF$ (1.0)	THF	22	1	NA	93
12	pyridine/HF(3.0)	THF	28	3	25/75	11
13	LiF(3.0)	THF	48	13	>99/1	75
14	CsF(3.0)	THF	37	0		100
15	ZnF_2(3.0)	THF	28	13	>99/1	73
16[h]	$Et_3N{\cdot}3HF$ (1.0)	THF	46	0		100

[a]Reaction conditions: **1a** (0.3 mmol), $(PPh_3)_3CuF$ (0.03 mmol), solvent (3 mL), N_2, 70 °C. [b]NMR yield based on **1a** with mesitylene as the internal reference. [c]Determined by ^1H NMR analysis of the crude product. [d]$(PPh_3)_3CuF$ (5 mol %) was used. [e]The reaction was conducted at 50 °C. [f]Isolated yield. [g]CuCl (10 mol %) as catalyst. [h]Without catalyst.

under otherwise identical conditions (entries 12−15). No reaction took place in the absence of catalyst (entry 16).

With the optimized conditions in hand (Table 1, entry 9), we next investigated the scope and limitations of the Cu-catalyzed *trans*-hydrofluorination (Table 2). Generally, both *N*-arylalkynylated and *N*-alkylalkynylated oxazolidinones were all suitable for the *β*-site regioselective fluorination (entries 1−10). For *N*-arylalkynyl-substituted oxazolidinones, the alkynamide with a strong electron-donating group on the arene exhibited higher reactivity and regioselectivity than that with a strong electron-withdrawing group (compare entry 3 with entry 6), which presumably suggested that the coordination of Cu(I) cation to the alkyne was the determining step in the nucleophilic fluorination, and the alkenyl alkynyl-substituted substrate 3-[(3*E*)-4-phenyl-3-buten-1-yn-1-yl]oxazolidin-2-one (**1k**) could also undergo such a conversion to afford the corresponding (*Z*)-fluoroenamide in excellent yield (entry 11). Interestingly, the *β*-fluorination of the sterically demanding *tert*-butyl-substituted substrate with $Et_3N{\cdot}3HF$ still worked well and gave the desired product (*Z*)-**2l** with modest yield and regioselectivity (entry 12),

Table 2. Scope of the $(Ph_3P)_3CuF$-Catalyzed *trans*-Hydrofluorination of Alkynamides (1) with $Et_3N{\cdot}3HF$[a]



entry	R^1	R^2	yield of (*Z*)-**2** (%)	ratio of (*Z*)-**2**/(*Z*)-**3**[b]
1	Ph (**1a**)		92 (*Z*-**2a**)	98/2
2	*p*-MeC_6H_4 (**1b**)		85 (*Z*-**2b**)	99/1
3	*p*-$MeOC_6H_4$ (**1c**)		78 (*Z*-**2c**)	>99/1
4	*p*-BrC_6H_4 (**1d**)		74 (*Z*-**2d**)	96/4
5	*p*-AcC_6H_4 (**1e**)		72 (*Z*-**2e**)	93/7
6[c]	*p*-$NO_2C_6H_4$ (**1f**)		63 (*Z*-**2f**)	81/19
7	*n*-C_4H_9 (**1g**)		81 (*Z*-**2g**)	>99/1
8	*n*-C_5H_{11} (**1h**)		80 (*Z*-**2h**)	>99/1
9	*n*-C_8H_{17} (**1i**)		75 (*Z*-**2i**)	>99/1
10	(*S*)-Ph(CH_3)CH		61 (*Z*-**2j**)	99/1
11	(*E*)-styrenyl (**1k**)		92 (*Z*-**2k**)	>99/1
12	*t*-C_4H_9 (**1l**)		63 (*Z*-**2l**)	90/10
13[d]	Ph (**1m**)		83 (*Z*-**2m**)	>99/1
14[d]	*p*-$MeOC_6H_4$ (**1n**)		76 (*Z*-**2n**)	>99/1
15[c]	Ph (**1o**)		82 (*Z*-**2o**)	96/4
16[c]	*n*-C_4H_9 (**1p**)		83 (*Z*-**2p**)	>99/1
17	Ph (**1q**)		90 (*Z*-**2q**)	>99/1
18	(*E*)-styrenyl (**1r**)		86 (*Z*-**2r**)	>99/1
19	*n*-C_4H_9 (**1s**)		88 (*Z*-**2s**)	>99/1
20[e]	Ph (**1t**)		0 (*Z*-**2t**)	-

[a]Reaction conditions: **1** (0.30 mmol), $Et_3N{\cdot}3HF$ (0.30 mmol), $(Ph_3P)_3CuF$ (0.03 mmol), THF (3 mL), N_2, 70 °C. [b]Determined by ^1H NMR analysis of the crude product. [c]$Et_3N{\cdot}3HF$ (2.0 equiv) was used. [d]$(Ph_3P)_3CuF$ (0.33 mmol) was used instead of $Et_3N{\cdot}3HF$. [e]Compound **1t** (93%) was recovered.

while arylethynyl pyrrolidinones required 1.1 equiv of $(PPh_3)_3CuF$ for full completion as a result of their susceptibility to the acidic media (entries 13 and 14). Oxazolidinones bearing different substituents, including phenyl and benzyl groups, also participated in the reaction with the desired fluoro enamides being isolated in 82−90% yields (entries 15−19). The regio- and stereochemical issue was unambiguously confirmed by X-ray diffraction study of (*Z*)-**2a** (Figure 1).[14]

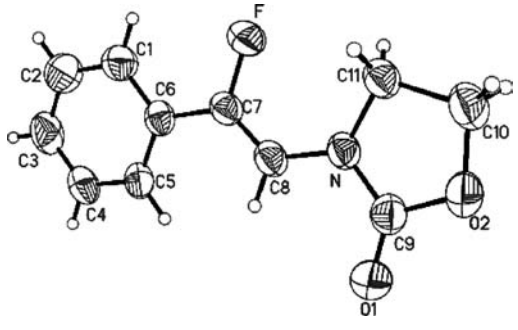


Figure 1. ORTEP drawing of the X-ray structure of (*Z*)-**2a** with 30% thermal ellipsoids.

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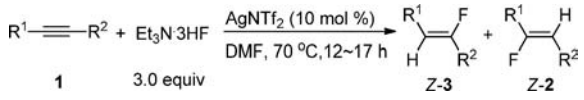
However, when *N*-sulfonyl acyclic ynamide **1t** was subjected to the standard reaction conditions, no desired *β*-site-fluorinated enamide (*Z*)-**2t** was detected (Table 1, entry 20). Further, no improvement was observed, whatever the conditions used, including changing reaction temperature, solvent, concentration, and addition of different types of Lewis acid, as only starting material was recovered. Considering that the silver cations have superior alkynophilicity due to *π*-coordination with a carbon−carbon triple bond,[16] we focused on familiar silver salts catalysts, such as AgF, AgOAc, AgOTs, and $AgNTf_2$. Gratifyingly, under the catalysis of $AgNTf_2$, the reaction of ynamide **1t** with $Et_3N{\cdot}3HF$ in DMF could lead exclusively to the (*Z*)-*α*-fluoroenamide (*Z*)-**3t**[17] in 98% isolated yield (Table 3, entry 1), which showed

Table 3. Scope of the $AgNTf_2$-Catalyzed *trans*-Hydrofluorination of Alkynamides (1) with $Et_3N{\cdot}3HF$[a]



entry	R^1	R^2	yield of (*Z*)-**3** (%)	ratio of (*Z*)-**3**/(*Z*)-**2**[b]
1	Ph (**1t**)	Ms, N, Bn	98 (*Z*-**3t**)	98/2
2	*n*-C_5H_{11} (**1u**)	Ms, N, Bn	85 (*Z*-**3u**)	94/6
3	Ph (**1v**)	Ts, N, Bn	94 (*Z*-**3v**)	>99/1
4	*n*-C_4H_9 (**1w**)	Ts, N, Bn	79 (*Z*-**3w**)	95/5
5	Ph (**1x**)	O, S, O, N	69 (*Z*-**3x**)	>99/1
6	(*E*)-styrenyl (**1y**)	O, S, O, N	83 (*Z*-**3y**)	>99/1

[a]Reaction conditions: **1** (0.30 mmol), $Et_3N{\cdot}3HF$ (0.90 mmol), $AgNTf_2$ (0.03 mmol), DMF (1 mL), air, 70 °C. [b]Determined by ^1H NMR analysis of the crude product.

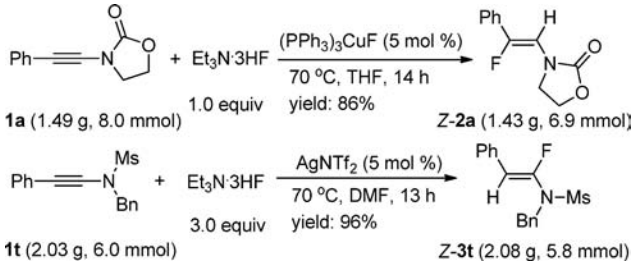
completely reversed regioselectivity in contrast to that observed in the Cu(I)-catalyzed hydrofluorination of ynecarbamates and ynepyrrolidinones. It should be noted that the *α*-site regiocontrolled *trans*-hydrofluorination of ynamides could be also achieved in good to excellent yields by means of catalytic amounts of silver salt in comparison with an excess of AgF in previous report (entries 1−6).[9] Although alkyl-substituted *N*-sulfonylynamides are highly sensitive to hydrolysis under acidic conditions, they were also found to be suitable substrates for the hydrofluorination reaction (entries 2 and 4). Furthermore, the *N*-sulfonyl cyclic ynamides were also effective to give the desired products with >99/1 *α*-site regioselectivity (entries 5 and 6).

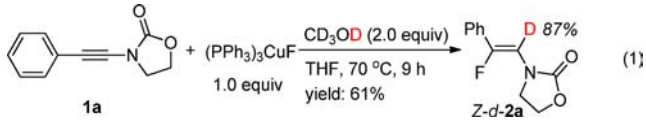
Despite the *trans*-hydrofluorination reaction being routinely run at 0.30 mmol scale, we confirmed that the process is amenable to 20-fold scale-up without loss of chemical efficiency, such as in the case of products (*Z*)-**2a** (6.9 mmol, 86%) and (*Z*)-**3t** (5.8 mmol, 96%). Additionally, we found that the Cu(I) or Ag(I) catalyst loading can be reduced to 5 mol % with comparable efficiency (Scheme 2).

To elucidate the mechanism of the Cu(I)-catalyzed *trans*-hydrofluorination of ynamides, we conducted the reaction of **1a** with 1.0 equiv of $(PPh_3)_3CuF$ in the presence of CD_3OD at 70 °C in THF, which as expected, afforded the fluorinated product (*Z*)-*d*-**2a** in 61% yield with 87% deuterium incorporation at the *α*-position. Thus, the deuterium-labeling experiment confirmed the existence of the alkenyl copper intermediate (eq 1).

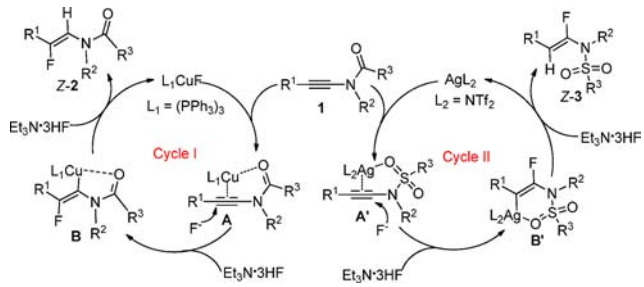
On the basis of the above experimental results and mechanistic considerations, a plausible mechanism of the Cu(I)- or Ag(I)-catalyzed *trans*-hydrofluorination of alkynamides is outlined in Scheme 3. The coordination[18] of a copper cation with the

Scheme 2. Scale-up Experiments





Scheme 3. Proposed Catalytic Cycles of $(Ph_3P)_3CuF$ or $AgNTf_2$-Catalyzed *trans*-Hydrofluorination of Alkynamides



carbonyl oxygen and the alkyne of the substrate occurs to generate a copper−alkyne complex **A**. Subsequent back-side nucleophilic attack of fluoride on the activated alkyne provides the alkenylcopper intermediate **B**. Protonolysis of the carbon−copper bond by $Et_3N{\cdot}3HF$ provides the *β*-site regiocontrolled fluoroenamide (*Z*)-**2** and regenerates the copper catalyst (cycle I). For the $AgNTf_2$-catalyzed *trans*-hydrofluorination of acyclic alkynamides, the formation of *α*-site regiocontrolled fluoro enamides (*Z*)-**3** probably proceeds via a six-membered chelated transition state **B′**, resulting from the cooperation of sulfonyl oxygen coordination[19] and polarization[9] of the triple bond of *N*-sulfonylynamides (cycle II).

Lastly, as a useful synthetic application, we examined the fluorination[20] of *β*-site-fluorinated alkenylamide (*Z*)-**2a**. As shown in eq 2, *α*,*α*′-difluoro imide **5** could be obtained directly from the hydroxyfluorinated *N*,*O*-hemiacetal intermediate **4** after Dess−Martin oxidation.

In summary, a Cu(I)- or Ag(I)-catalyzed *trans*-hydrofluorination of alkynamides has been achieved for the first time, affording *α*/*β*-fluorinated enamides in good to excellent yields with high regio- and stereoselectivity. The reaction employs mild $Et_3N{\cdot}3HF$ as the fluorinating agent and tolerates a variety of functional groups such as NO_2, Ac, Br, OMe, alkenyl, and other substituents. Future work will be directed toward further elucidating the detailed reaction mechanism and applying the catalytic process for the synthesis of complex fluorine-containing olefin.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00615.

Experimental procedures and characterization (PDF)
Spectra of compound (*Z*)-**2a**–**5** (PDF)

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Notes

The authors declare no competing financial interest.

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