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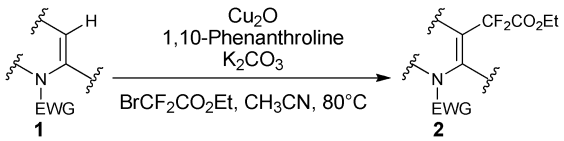
Copper-catalyzed olefinic difluoroacetylation of enamides *via* direct C–H bond functionalization using $BrCF_2CO_2Et$ is reported for the first time. It constitutes an efficient radical-free method for the regioselective synthesis of β-difluoroester substituted enamides which exhibits broad substrate scope, and thus demonstrates its potent application in a late stage fluorination strategy.



Scheme 1 Present work.

Organofluorine chemistry is a rapidly expanding field. The ubiquity of fluorinated compounds has been particularly highlighted in the fields of pharmaceutical research and agrochemistry.[1,2] Recently, fluorinated compounds and particularly those containing a fluorinated methyl group (CF_3, CF_2R) have attracted much attention, spurring research groups to discover new access to fluorine containing molecules.[3–7] These remarkable efforts gave birth to efficient and selective methods towards the introduction of CF_3 and CF_2R groups particularly by means of direct C–H bond functionalization which recently became one of the most attractive research fields in organic synthesis.[8–10] Rather surprisingly, less attention has been paid to the direct introduction of pre-functionalized fluorinated building blocks (*i.e.* CF_2SO_2Ph, CF_2CO_2Et) that can be used in further transformations.[11] The CF_2CO_2Et moiety appeared notably as an interesting manifold to access a wide range of fluorinated substituents. Noteworthily, its introduction mainly focused on the use of radical processes or transition metal catalyzed cross-coupling reactions between a halo-derivative and an organometallic partner.[12] Stimulated by our recent findings on the copper-catalyzed direct β-arylation of enamides[13] and on the dihydropyran series,[11b] herein, we would like to report the regioselective synthesis of β-difluoroester substituted enamides by using the commercially available $BrCF_2CO_2Et$ (Scheme 1).

Within this protocol and as an extension of our interest in alkene functionalization, copper catalysis, which is a field of tremendous expansion due to its abundance, low cost and low toxicity, was adopted to perform carbon–carbon bond formation. Moreover, enamides have been widely used as valuable building blocks to introduce nitrogen based functionalities into various aromatic or non-aromatic heterocycles.[14] In the present case, the resulting difluoroester substituted enamides are thus of immediate relevance for the target-oriented synthesis of derivatives comprising a fluorinated heterocyclic subunit. To the best of our knowledge, the Cu-catalyzed olefinic difluoroacetylation of non-aromatic enamides *via* direct C–H bond functionalization is unprecedented and would constitute a powerful, selective and atom-economic strategy to reach the fluorinated π-electron-rich olefin, which is still in great demand.

At the outset of our study, the reaction condition was optimized using six-membered cyclic enamide **1a** as a model substrate. Standard screening of solvents, catalysts, temperature, and the ratio of reagents established that the optimized conditions[15] were Cu_2O (10 mol%) and 1,10-phenanthroline (12 mol%) as a ligand in the presence of $BrCF_2CO_2Et$ (2 equiv.), K_2CO_3 (2 equiv.) in CH_3CN at 80 °C (Table 1). Accordingly, we were pleased to isolate **2a** in 91% yield along with a complete β-regioselectivity (entry 1). Modification of the $BrCF_2CO_2Et$ stoichiometry did not provide further improvements and the reaction was ineffective in the presence of 1 equiv. of $BrCF_2CO_2Et$ (entries 2 and 3). A catalyst screening showed that $Cu(OTf)_2$, CuI, $Cu[MeCN]_4{\cdot}PF_6$ were less

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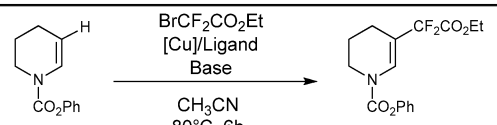
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra of products. See DOI: 10.1039/c4cc01994f

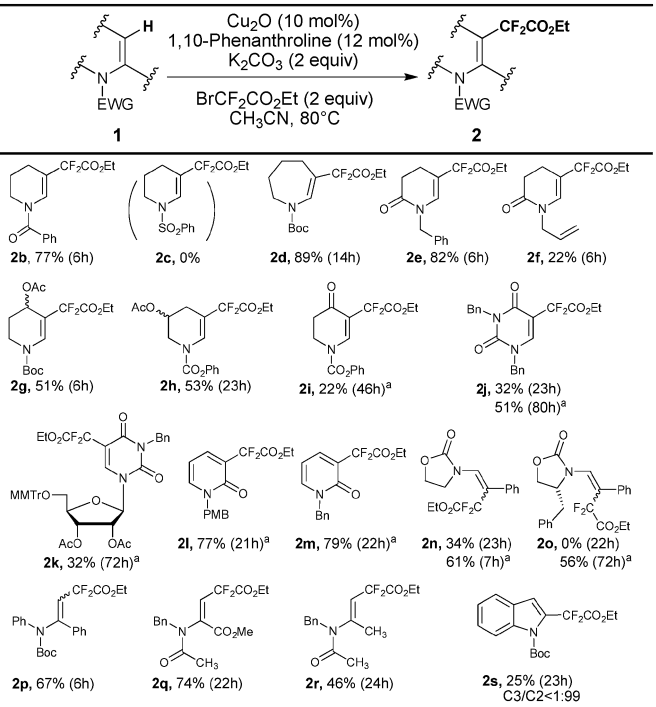
Table 1 Optimization of the copper-catalyzed difluoroacetylation of enamide **1a**[a]



Entry	Catalyst	Ligand	Base	Yield[b] (%)
1	Cu_2O	1,10-Phenanthroline	K_2CO_3	91
2[c]	Cu_2O	1,10-Phenanthroline	K_2CO_3	88
3[d]	Cu_2O	1,10-Phenanthroline	K_2CO_3	Traces
4	$Cu(OTf)_2$	1,10-Phenanthroline	K_2CO_3	25
5	CuI	1,10-Phenanthroline	K_2CO_3	26
6	$Cu[MeCN]_4{\cdot}PF_6$	1,10-Phenanthroline	K_2CO_3	24
7	Cu_2O	1,10-Phenanthroline	Cs_2CO_3	88
8[c]	Cu_2O	1,10-Phenanthroline	Et_3N	Traces
9[c]	Cu_2O	1,10-Phenanthroline	dtbpy	0
10	Cu_2O	Bathophenanthroline	K_2CO_3	38
11	Cu_2O	Neocuproine	K_2CO_3	Traces
12	Cu_2O	2,2′-Bipyridine	K_2CO_3	41
13	—	1,10-Phenanthroline	K_2CO_3	0
14[c]	Cu_2O	1,10-Phenanthroline	—	0
15	Cu_2O	—	K_2CO_3	0

[a] Reaction conditions unless otherwise specified: $BrCF_2CO_2Et$ (2 equiv.), copper catalyst (10 mol%), ligand (12 mol%), base (2 equiv.), CH_3CN, 80 °C, 6 h. [b] Isolated yield after purification by flash chromatography. [c] 4 equiv. of $BrCF_2CO_2Et$ were used. [d] 1 equiv. of $BrCF_2CO_2Et$ was used. dtbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine.

Table 2 Scope of the Cu-catalyzed difluoroacetylation reaction by varying enamides **1**

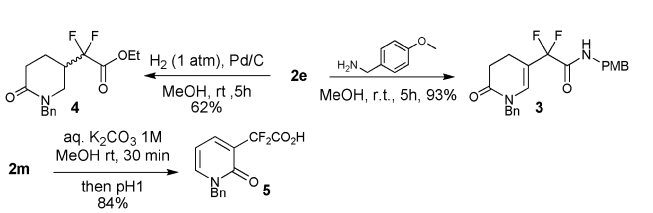


[a] With 4 equiv. of $BrCF_2CO_2Et$.

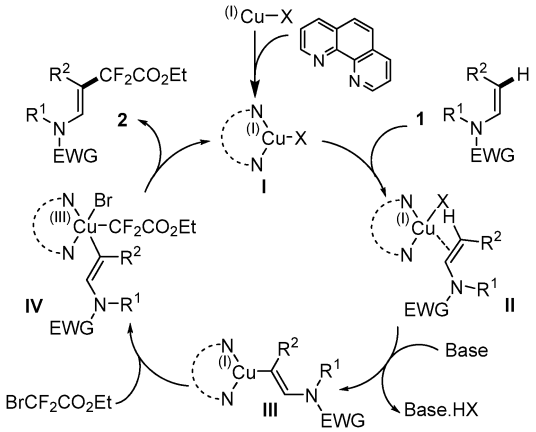
active, furnishing the desired product **2a** in lower yield (entries 4–6).[16] An examination of the nature of the base revealed that K_2CO_3 gave the best results (entry 7). Organic bases did not allow the formation of **2a** (entries 8 and 9). Other ligands, such as bathophenanthroline, neocuproine and 2,2′-bipyridine, were tested, but no enhancement of the reaction yield was measured (entries 10–12). It is worth mentioning that no reaction occurred in the absence of a copper catalyst, base or a ligand (entries 13–15).

Having established the reaction conditions, a wide range of cyclic and acyclic enamides **1** were examined, as depicted in Table 2. The scope, site selectivity, and functional group tolerance are notable aspects of this original methodology. We were delighted to note that all transformations worked well and afforded the corresponding β-difluoroester substituted enamides **2** with complete regioselectivity. Modifications concerning both the protecting group on the nitrogen atom and the size of the heterocycle were envisaged. While enecarbamate **1a**, **1d** and enamide **1b** gave very satisfying results, sulfonamide **1c** proved not to be activated enough to react. The desired fluorinated endo-enamides **2e** and **2f**[17] were isolated, respectively, in good and low yields. Furthermore, the reaction turned out to be compatible with a variety of functional groups, which were amenable to further useful transformations (**2g**, **2h**, **2i**). Uracil and uridine derivatives, giving, respectively, **2j**[18] and **2k**, were also proved to be applicable in this reaction. This result points out the functional group tolerance of our process and its potent application in a late stage fluorination strategy.[19] Expectedly, when a thymine derivative[20] was used as a substrate, no coupling product was obtained, ruling out the possibility of a coupling at the α-position. Notably, the vinylogous β-difluoroester pyridones **2l** and **2m** were isolated in good yields.[21] It is worth noting that to date only the trifluoromethylpyridone derivative has been reported in the literature.[22] Furthermore, experiments were also carried out on the valuable acyclic substrates affording the desired β-difluoroester enamides **2n–r** with complete regio- and stereoselectivity, as only one diastereoisomer (*E* or *Z*) could be detected.[21,23] Evans oxazolidinone was also a suitable substrate; **2o** was isolated in 56% isolated yield.[24] Importantly, acyclic β-difluoroester enamides were readily available *via* Cu-catalyzed C–H functionalization, setting up the possibility of developing new unprecedented access to either non-natural fluorine containing amino acids or fluorinated heterocycles.[25] Our method also proved applicable to aromatic enamides such as indole **1s**. The corresponding α-fluorinated derivative **2s** was isolated albeit with low yield.[26] The α-selectivity is a result of the higher acidity of the hydrogen at the C-1 position (*cf.* Scheme 3) and extends the scope of our reaction beyond existing other methods.[27]

Then, in order to showcase the versatility of these difluoroester enamides **2**, further transformations were carried out (Scheme 2). First, aminolysis of enamide **2e** worked smoothly which generated the corresponding fluorinated amide **3** with an excellent 93% yield. Hydrogenation of **2e** at room temperature and atmospheric pressure afforded the difluoroacetylated lactam **4** in 62% yield.



Scheme 2 Transformations from fluorinated enamide **2e** or **2m**.



Scheme 3 Plausible reaction mechanism.

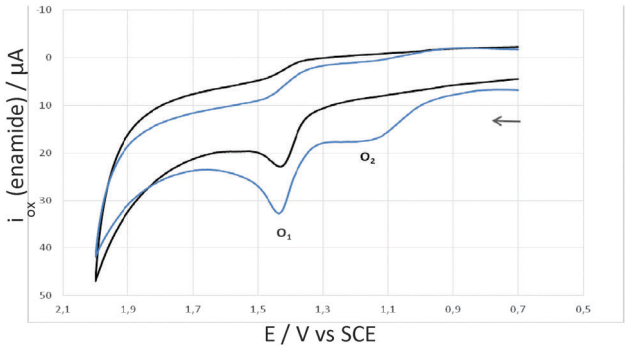


Fig. 1 CV performed in CH_3CN containing nBu_4NBF_4 (0.3 M) at a steady glassy disk electrode (d = 1 mm), at a scan rate of 0.5 V s^{-1}, at 20 °C. (a) Oxidation of the enamide **1a** (2 mM) (in black); (b) oxidation of the enamide **1a** in the presence of $Cu^{I}(phen)S_3^+$ (1 equiv.) (in blue).

It should be noted that, under the conditions used, only the double bond of the enamide was reduced, while the benzyl group was not removed and no fluorine abstraction occurred. Noteworthily, this reduction gave unique access to β-CF_2CO_2Et-piperidones, which are key scaffolds in the quest for new pharmaceuticals.[22] Finally, hydrolysis of the ester function of **2m** under basic conditions led to the corresponding carboxylic acid **5** with good yield.

In an effort to understand the mechanism of the reaction, we initiated an investigation in the presence of a catalytic amount (20 mol%) of radical inhibitors or scavengers: TEMPO, benzoquinone and TBHT. In all cases, no inhibition of the coupling reaction was observed. Although the reaction required a longer reaction time, the fluorinated product was formed in similar yield when one equivalent of TEMPO was added to the reaction mixture. These observations prompted us to do not consider a radical mechanism as a plausible pathway for this transformation.

Then, to gain further insight into the reaction mechanism, studies were undertaken *via* electrochemical techniques. Cyclic voltammetry (CV) was performed with the tetrakisacetonitrile copper(I) hexafluorophosphate $Cu^{I}S_4^+$ PF_6^- as the copper source to analyze a homogeneous mixture. $Cu^{I}(phen)S_3^+$,[28] formed in the presence of phenanthroline (phen) in acetonitrile (S), did not react with the $BrCF_2CO_2Et$.[29] However, the CV of the enamide, characterized by its oxidation peak at +1.42 V (O_1), evolved after addition of $Cu^{I}(phen)S_3^+$ (1 equiv.) and a pre-wave appeared at O_2[30] before O_1 (Fig. 1). This pre-wave indicates that a new complex is formed, $Cu^{I}(phen)(enamide)S_2^+$ in equilibrium with the free enamide. The plateau shape of the new wave typically characterizes a CE mechanism, in which the equilibrium is shifted in the diffusion layer by the first oxidation of $Cu^{I}(phen)(enamide)S_2^+$ at O_2.[31] Therefore, one can conclude that $Cu^{I}(phen)S_3^+$ reacts preferentially with the enamide in the first step of the catalytic cycle. Addition of K_2CO_3 (1 equiv.) at room temperature did not modify the CV, attesting to a slow deprotonation of the ligated enamide giving intermediate III.[15] However, III was detected by ESI^+ (m/z 446.0924 for $[M + H]^+$).[15] Although the mechanism of this copper catalytic reaction is still under investigation, our preliminary data render a standard redox cycle with Cu(I)/Cu(III) involving a complexation of the nucleophile to Cu(I) prior to deprotonation (Scheme 3).[32]

In summary, we have developed a mild, simple and efficient Cu-catalyzed radical free synthesis of the β-difluoroester substituted enamide. This original transformation is completely regioselective and exhibits broad substrate scope, good functional group tolerance and thus demonstrates its potent application in a late stage fluorination strategy. Beyond this elegant method, the resulting original difluoroester enamides could be versatile building blocks for the synthesis of various N-containing aromatic or non-aromatic heterocycles. Moreover, mechanistic studies were carried out to elucidate the reaction pathway. Cyclic voltammetry along with MS-ESI experiments led us to propose a Cu(I)/Cu(III) catalytic cycle. Further investigations of the mechanism, scope and applications of this method are underway.

This work has been partially supported by Université d'Orléans, INSA de Rouen, Université de Rouen, CNRS, and LABEX SynOrg (ANR-11-LABX-0029). G.C. thanks LABEX SynOrg for a postdoctoral fellowship. M.-C.B. thanks the MESR for a doctoral fellowship. The authors thank A. Jutand for fruitful discussions.

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15 See the ESI† for further details.

16 Others copper salts were screened without improvement of the reaction yield *e.g.* CuCl, CuBr, $CuCl_2$, $CuBr_2$.

17 It is worth noting that despite our careful attention the high volatility of fluorinated products prevented their isolation in high yield in spite of good and fast conversions.

18 In this case the reaction time was slower and usually required a higher amount of $BrCF_2CO_2Et$ (*i.e.* 4 equiv.).

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23 The configuration of the alkenes was confirmed for **2q** and **2r** from 2D NOESY analysis (see the ESI† for details). Unfortunately, no evidence of the *Z* or *E* alkene stereochemistry for **2n–p** derivatives could be observed.

24 Noteworthy when reaction was carried out with **2n** a decomposition of the product was observed after a longer reaction time. To tackle this drawback a shorter reaction time and an excess of $BrCF_2CO_2Et$ was required to ensure decent yields.

25 A longer reaction time is required, probably because of the steric hindrance.

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29 The reduction peak of $Cu^{I}(phen)S_3^{+}$ (−1.65 V *vs.* SCE)[25] was not affected after addition of the $BrCF_2CO_2Et$ in large excess, attesting that no reaction takes place at room temperature between the catalyst and the bromofluoroester within 2 hours. These results were also confirmed by ^{19}F and ^{1}H NMR analyses.

30 It is noticeable that the complex $Cu^{I}(phen)S_3^{+}$ is not oxidized in the potential scale investigated[28].

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