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Copper-Catalyzed Trifluoromethylation of Alkenes: Synthesis of Trifluoromethylated Benzoxazines

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A simple base and ligand free copper catalyzed method for the construction of trifluoromethylated benzoxazines has been developed by using Umemoto's reagent. It involves the oxidative difunctionalization of alkenes through tandem C-O and C-CF_3 bond formations. Furthermore, synthesized benzoxazines were selectively converted into trifluoromethylated allylic and *(E)*-vinylic benzamides by the treatment of KO^{t}Bu and CH_3Li, respectively.

Benzoxazines, *N,O*-containing six membered heterocycles are present in many drug molecules and herbicides and also widely used as building blocks for bioactive molecules. It shows interesting biological and pharmaceutical properties such as progesterone receptor (PR) modulators, anti-anxiety, anti-HIV, agonist, and antagonist activities (Fig.1).[1,2]

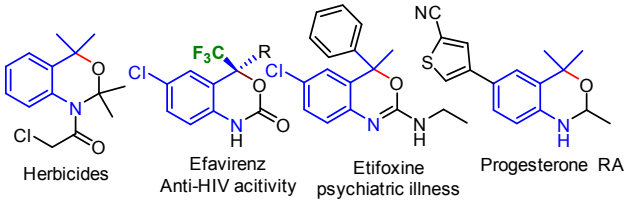
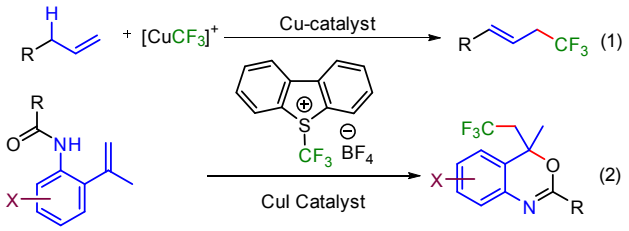


Fig 1. Benzoxazine and related drugs

Incorporation of CF_3 group in the organic molecule enhances several biological properties such as solubility, lipophilicity, metabolic stability, binding selectivity etc.[3] As a result, several trifluoromethylated heterocycles such as efavirenz and celecoxib were used as potential drugs for the treatment of HIV infection, arthritis, and spondylitis, respectively.[4]

As a consequence, versatile methodologies are being established for the introduction of CF_3 moiety into heterocycles and related organic molecules.[5-12] However, the synthesis of CF_3-containing heterocycles through intramolecular cyclization has been less explored. In 2013, Buchwald *et al*. had reported copper-catalyzed intramolecular oxytrifluoromethylation of unactivated alkenes using Togni's reagent for the synthesis of trifluoromethylated lactones.[6] Subsequently, intramolecular aminotrifluoromethylation[7] and carbotrifluoromethylation[8] of simple alkenes have been successfully established. Fu group had developed transition metal-free synthesis of trifluoromethylated oxazolines exploiting CF_3SO_2Na as a CF_3 source.[9]



Scheme 1. Synthesis of trifluoromethylated of alkenes and benzoxazines

Construction of benzoxazine ring has been achieved by the intramolecular cyclization of alkenes using electrophiles such as Br^+, I^+, and KSCN, $K_2S_2O_8$ combination.[13,14] Benzoxazines comprising CF_3 group remained as an unexplored area. Recently, Xiao *et al*. has demonstrated photocatalytic oxytrifluoromethylation of *N*-allylamides for the synthesis of trifluoromethylated benzoxazines using expensive $Ru(bpy)_3(PF_6)_2$ catalyst and a base by radical pathway.[15d]

Copper-catalyzed trifluoromethylation of terminal alkenes through allylic C-H bond activation has been accomplished by Fu and Liu *et al*. exploiting copper catalyst, Umemoto's reagent, and 2,4,6-trimethyl pyridine reaction system (scheme 1, eq 1).[10a] In view of recent advances in Cu-catalyzed functionalization of alkenes,[16,17] we envisioned, trifluoromethylation of terminal alkene followed by intramolecular addition of oxygen for the synthesis of trifluoromethylated benzoxazines keeping allylic C-H bond intact (eq 2). Herein, we present a simple base and ligand-free Cu-catalyzed synthesis of trifluoromethylated benzoxazine heterocycles from *N*-(2-(prop-1-en-2yl)benzamide substrates **1** using Umemoto's reagent **2** (scheme 1, eq 2). Synthesized trifluoromethylated benzoxazines were also selectively

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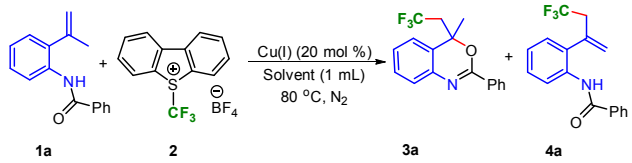
converted into trifluoromethylated allylic and (*E*)-vinylic benzamides.

Table 1 Optimization of the reaction conditions [a]

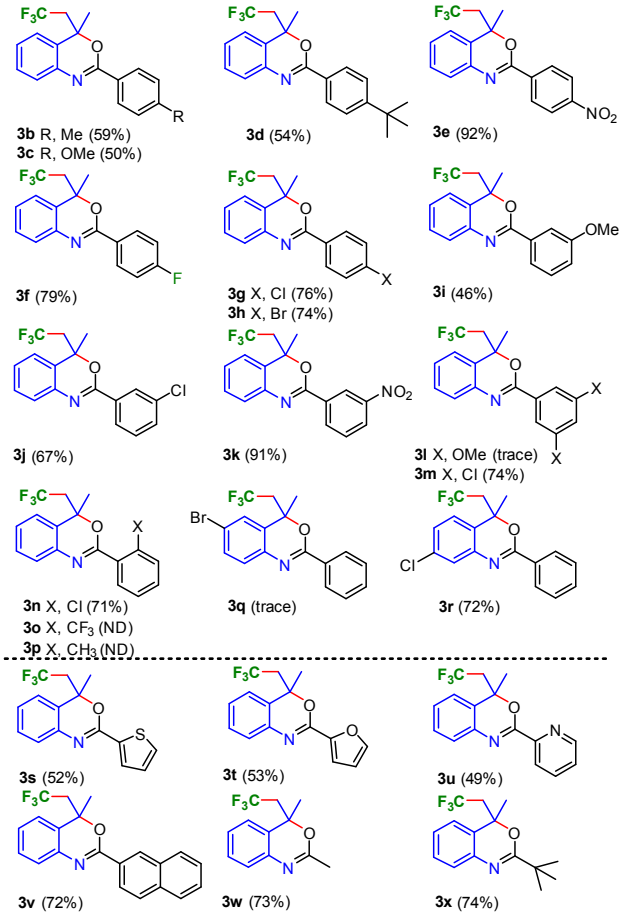


entry	catalyst + CF_3 Source	solvent	Yield of 3a[b]
1	CuI + Togni's reagent	DCE	30[b], 45[c]
2	CuI + $TMSCF_3$	DCE	ND
3	CuI +Shreeves' reagent	DCE	37
4	CuI + 2	DCE	52
5	- + 2	DCE	ND
6	CuTc + 2	DCE	17
7	CuCN + 2	DCE	26
8	$[Cu(CH_3CN)_4]BF_4$ + 2	DCE	5
9	$[Cu(CH_3CN)_4]PF_6$ + 2	DCE	6
10	CuI + 2	DMF	52
11	CuI + 2	DMAc	58
12	CuI + 2	NMP	39
13	**CuI + 2**	**DMSO**	**68**
14	Cu	DMSO	18

[a]All reactions were carried out using 0.2 mmol of **1a,** 0.35 mmol of **2** in 1 mL solvent at 80 °C in a Schlenk tube under nitrogen and progress of the reaction was monitored by TLC upto 35 h. [b]Percentage yield was determined by ^{19}F-NMR using fluorobenzene as an internal standard. [c]Yield of **4a**, ND = Not detected, CuTc = Thiophene-2-carbonyloxylate copper(I)

We initially examined the reaction of *N*-(2-(prop-1-en-2-yl) benzamide **1a** with CuI (20 mol %) and various trifluoromethylating reagents in DCE (Table 1, entries 1-4). $TMSCF_3$ noticed to be sluggish and the formation of desired product was not realized. Togni's reagent gave a mixture of desired trifluoromethylated product **3a** in low yield (30%) along with 45% allylic trifluoromethylated product **4a** (entry 1, Table 1). Shreeves' reagent, a triflate analogue of **2** provided 37% yield of **3a**. The use of Umemoto's reagent **2**, led to further increase in the yield by 15% of the desired product **3a**. The presence of copper is crucial for trifluoromethylation as the reaction failed to provide even traces of **3a** in the absence of copper (entry 5, Table 1). Although, various Cu sources (Table 1, entries 6-9, 14), ligands, and bases were screened (See SI, Table S1, page S5-S6 for detailed optimization study), CuI alone was noticed to be effective. The change in the solvent from DCE to DMAc, DMF, and DMSO (Table 1, entries 10-13) led to further improvement in the yield and best yield (68%) was obtained in DMSO (entry 13, Table 1).

Next, substrate scope of trifluoromethylation of the alkenes using 20 mol% of CuI at 80 °C in DMSO was studied. The substitution in the amide ring of **1a** was explored (Scheme 2). Alkenes with electron donating substituents such as CH_3, OCH_3, and ^{t}Bu at *para*-position of benzamide ring, gave trifluoromethylated benzoxazines **3b**-**3d** in moderate yields (50-59%) whereas electron withdrawing groups such as NO_2 F, Cl, and Br favoured the trifluoromethylation which indeed led good yields (74-92%) of **3e**-**3h**.



Scheme 2. Synthesis of CF_3-benzoxazines: scope with respect to amide and aniline rings

Structures of CF_3-benzoxazines **3f** and **3z** are also established by single crystal structure study (Fig 2, for **3z** and crystallographic details, please see SI page S202-S232). *meta*-Methoxy substituted benzoxazine **3i** was obtained in moderate yield (46%) whereas Cl and NO_2 substituted benzoxazines **3j** and **3k** were obtained in 67 and 91% yields, respectively. The reaction of *meta*-di-OCH_3-subtituted substrate noticed to be sluggish and only trace of respective trifluoromethylated benzoxazine **3l** was isolated. On the other hand, *meta*-di-chloro-substituted benzoxazine **3m** was obtained in 74% yield.

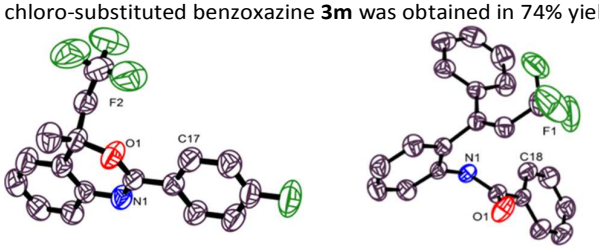


Fig 2. ORTEP diagrams of **3f** and **5d**

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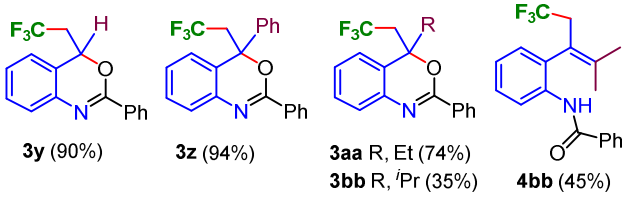
Similarly, the substrate with *ortho*-chloro substitution in amide ring, gave desired trifluoromethylated benzoxazine **3n** in good yield (71%). *ortho*-Methyl and trifluoromethyl substituted substrates failed to yield trifluoromethylated benzoxazines **3o** and **3p** and recovered quantitatively and this could be due to the steric effect of CH_3 and CF_3 which may prevent the coordination of –CONHPh group with the $CuCF_3$ (*vide infra*).

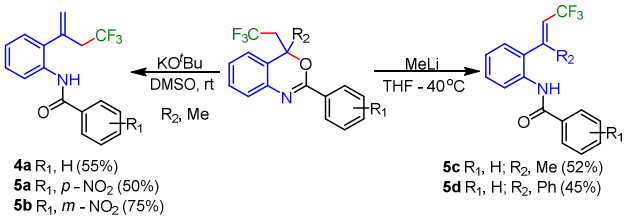
On the other hand, bromo-substitution in the aniline ring *para* to NH has negative effect on the trifluoromethylation reaction as only trace of **3q** was obtained. Substrate with chloro substituent in the aniline ring, *para* to alkene, underwent trifluoromethylation smoothly and yielded chloro benzoxazines **3r** in 72% yield.



Scheme 3. Substrate scope with regards to olefins

Next, substrates with various *N*-aromatics such as naphthyl heteroaromatics; thiophenyl, furanyl, and pyridinyl were subjected for trifluoromethylation reaction. Indeed, reaction also showed compatibility with naphthyl and heteroaryl containing substrates and respective trifluoromethyl benzoxazines **3s**-**3v** were obtained in 49-72% yields.

Substrates not only with various aryl benzamides but also with alkyl amides such as methyl and tert-butyl substituents were also tolerated and yielded trifluormethylated benzoxazines **3w** and **3x** in 73 and 74% yields, respectively.

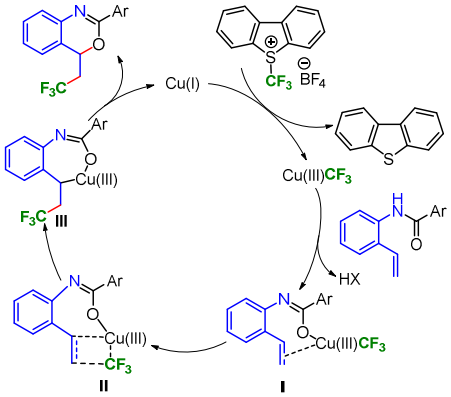


Scheme 4. Further modification of CF_3-benzoxazines

After studying various *N*-aryl, alkyl and benzamide substrates, C-2 substituted alkenes were explored in the copper-catalyzed C-CF_3 and C-O bond formation reaction (Scheme 3). Alkenes with H and Ph substituents at C-2 position provided excellent yields (90 and 94%) of trifluoromethylated benzoxazines **3y** and **3z**. C-2 substituted methyl, ethyl, and *iso*-propyl benzoxazines (**3a**, *vide supra*), **3aa**, and **3bb** were obtained in 68, 74, and 35% yields, respectively. In the case of **3bb**, formation of trifluoromethylated uncyclized product **4bb** in 45% yield was also observed.

Next, the synthetic utility of trifluoromethylated benzoxazines was explored (Scheme 4). An addition of KO^{t}Bu to benzoxazines **3a**, **3e**, and **3k** provided trifluoromethylated allylic benzamides **4a**, **5a**, and **5b**, respectively. Interestingly, treatment of **3a** and **3y** with CH_3Li provided trifluoromethylated (*E*)-vinyl benzamides **5c** and **5d**, respectively. Structure of **5d** is also established by X-ray single crystal study (Figure 2). It seems that KO^{t}Bu removes the less hindered methyl proton whereas CH_3Li prefers abstraction of highly acidic proton adjacent to CF_3 group.

In the mechanistic consideration, copper(I) can form Cu(III)CF_3 intermediate by the reaction of Umemoto's reagent **2** (Scheme 5).[10a] The formation of Cu(I)CF_3 intermediate is also possible by the disproportionation of Cu(I) into Cu(II) and Cu(0) followed by the reaction of Cu(0) with Umemoto's reagent (please see SI, page S8-S13 for details).[12e,18] Nevertheless, both Cu(I)CF_3 and Cu(III)CF_3 could act as trifluoromethylating reagent.[12e] Ligand exchange with alkenamide substrate would lead to the substrate –copper intermediate I.[19]



Scheme 5. Mechanism for Cu-catalyzed trifluoromethylation

Intramolecular coordination of alkene followed by the formation of Heck-type four-membered ring would generate transition state **II**. This could allow the formation of C-CF_3 bond leading to **III**, subsequent reductive elimination may give benzoxazine, by concomitant release of catalyst. It seems unlikely that the reaction proceeds *via* radical pathway because reaction mixture failed to give any signal in EPR spectrum.

The non-reactive nature of *ortho*-methyl and trifluoromethyl substituted substrates (*vide supra*, **3o** and **3p**) and formation of trifluoromethylated allylic product **4bb** could be rationalized based on the proposed intermediates **I**-**III**. It seems that allylic trifluoromethylation of alkene through allylic C-H bond activation process[10a] also occurred along with the formation of new C-CF_3 and C-O bonds. This may be due to the steric effect of *iso*-propyl substituent, therefore, gave a mixture of C-CF_3 and C-O bond forming product **3bb** and trifluoromethylated allylic product **4bb**.

In Conclusion, we have developed a simple, ligand and base free copper catalyzed method for the construction of trifluoromethylated benzoxazines by using Umemoto's reagent. As the reaction involves mild conditions, trifluoromethylated benzoxazines with functionalities such as nitro and bromo could be constructed which are useful for the later stage modifications. Synthetic utility of trifluoromethylation reaction has also been demonstrated by converting CF_3-containing benzoxazines into allylic and *(E)*

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vinylic benzamides. The stereoselective synthesis utilizing chiral ligand and copper catalytic system as well as biological study of trifluoromethylated benzoxazines are under investigation in our laboratory.

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