Copper-Catalyzed Direct C-H Fluoroalkenylation of Heteroarenes

Journal:	*Organic & Biomolecular Chemistry*
Manuscript ID	OB-ART-10-2015-002213.R1
Article Type:	Paper
Date Submitted by the Author:	12-Nov-2015
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Copper-Catalyzed Direct C–H Fluoroalkenylation of Heteroarenes

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Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Copper-catalyzed direct C-H fluoroalkenylation of heterocycles using various *gem*-bromofluoroalkenes as electrophiles is reported. This efficient method offers a step-economical, low-cost and stereocontrolled access to relevant heteroarylated monofluoroalkenes. The synthesis of fluorinated analogues of biomolecules and therapeutic agent for the treatment of Duchenne muscular dystrophy as application is reported.

Introduction

The importance of fluorinated compounds in agrochemicals,[1,2] pharmaceuticals/medicinals,[1,3] and materials science[1,4] has triggered an explosion of research efforts in developing new and efficient methods to introduce fluorinated functional group into organic molecules. Of particular relevance is the emergence of fluoroalkenes,[5] versatile compounds that have found many applications as, for examples, peptidomimetics,[6] drugs[7] and materials.[8] In peptide synthesis and fine organic chemistry, fluoroalkenes are widely looked upon as stable isosteric and isoelectronic mimics of the amide bond,[6] and bioisosteres in structure/activity relationship studies.

Within the readily available fluorinated building blocks for the construction of fluoroolefins, *gem*-bromofluoroalkenes are easily accessible[9] and versatile reagents for the achievement of highly useful cross-coupling reactions.[10] The development of catalytic direct C-H bond functionalization methodologies using transition metals as catalysts has received considerable attention avoiding thus the preparation of organometallic intermediates as coupling partners.[11] For a realistic catalyst loading of these precious metals, less expensive transition elements such as copper have received significant attention. Indeed, since the breakthroughs made by Daugulis,[12] Miura[13] and Piguel,[14] remarkable advances have been made in copper-catalyzed direct arylation[15], alkynylation[16] and alkenylation[17,18] of azoles from monohalogenoalkenes (Figure 1, eqs 1 and 2). However, no example of copper-catalyzed direct C-H halogenoalkenylation so far has been reported from *gem*-dihalogenoalkenes. Indeed, these latter have been only used for copper-catalyzed C-H alkynylation of heterocycles, the non-coupled second halogen being eliminated during the catalytic process (Figure 1, eq 3).[19] Recently, Cao has described an elegant metal-free base mediated nucleophilic vinylic substitution reaction between tetrasubstituted *gem*-difluoroalkenes and azoles (Figure 1, eq 4).[20a] In that case, only tetrasubstituted *gem*-difluoroalkenes can be used as substrates, the trisubstituted ones would directly lead to dehydrofluorination process. This year, Loh have successfully engaged *gem*-difluoroalkenes in an innovative Rh(III)-catalyzed ortho-directed C-H activation, migratory insertion to double bond and defluorination sequence to produce fluoroalkenylated (hetero)aromatics.[20b] Our group has previously reported the first Pd-catalyzed direct C-H halogenoalkenylation of heterocycles demonstrating that *gem*-bromofluoroalkenes are suitable building blocks for this transformation (Figure 1, eq 5).[21] During this study, a combination of copper salt with palladium catalyst led to a cooperative Pd(0)/Cu(I) catalysis which was found very

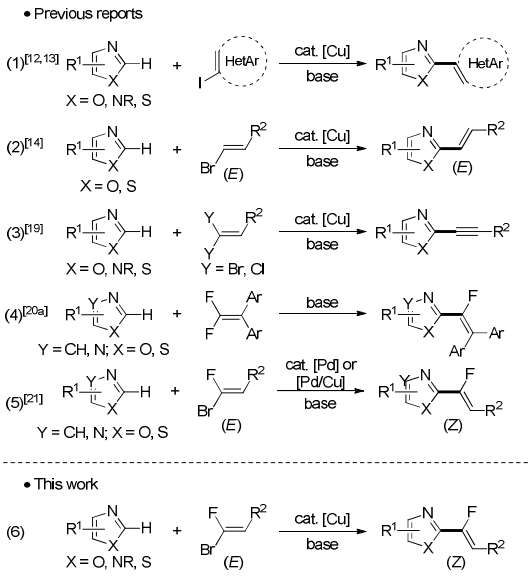

Fig. 1. Direct functionalization of ubiquitous C-H bonds using halogenoaryls/alkenes and gem-dihalogenoalkenes

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†Electronic Supplementary Information (ESI) available: Experimental procedures, optimization tables, characterization data and NMR spectra of new compounds See DOI: 10.1039/x0xx00000x

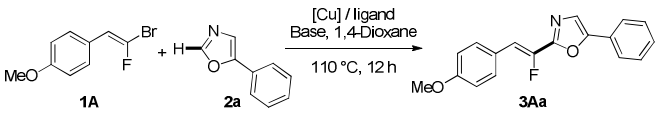
performant to achieve the direct C-H alkenylation of a broad range of 1,3-diazoles with any *gem*-bromofluoroalkenes as electrophiles. This efficiency was based upon the catalytic generation of an heteroaryl copper intermediate reacting as transmetallating agent.[22] In our ongoing project devoted to the production of fluorinated biomolecule analogues, we recently turned our attention to the evaluation of the reactivity of the heteroaryl copper intermediate towards *gem*-bromofluoroalkenes in view of developing a novel palladium free copper-catalyzed direct C-H fluoroalkenylation of heterocycles offering a step-economical, low-cost and stereo-controlled access to heteroarylated monofluoroalkenes (Figure 1, eq 6). Moreover, taking into account that the direct fluoroalkenylation is very scarce in the literature, it could represent an efficient alternative to produce fluorinated fine chemicals. We reported herein this methodology giving access to a wide variety of trisubstituted monofluoroalkene[5,23] derivatives including fluorinated analogues of therapeutic agents.

Results and discussion

We initiated our investigation by probing various reaction conditions for the direct C-H fluoroalkenylation of 5-phenyl-oxazole (**2a**) with easily accessible (*E*)-*gem*-bromofluoroalkene[9] **1A** (Table 1). Indeed, whereas a set of experiments with our model substrate, phenyloxadiazole, under optimized previously reported procedure found unsuccessful without palladium catalyst,[24] **2a** proved to be suitable substrate for direct fluoroalkenylation without palladium source, providing **3Aa** in 63% yield compared to 75% yield under bimetallic Pd/Cu catalysis (Entries 1-2). Switching the nature of the copper source for CuI led to a slight enhancement of the yield (Entry 3). Among the bases, *t*-BuOLi proved to be the most effective without formation of alkynylated side-product via dehydrofluorination process (Entries 4-5). Subsequently, common ligands of copper have been screened, such as Phen and derivatives, diamine ligand or mono- and bidendate phosphines (Entries 4-10), and surprisingly, dppe revealed considerable efficiency affording the desired product in almost quantitative yield (Entry 10). Crucially, formation of **3Aa** was not observed if copper was omitted from the reaction mixture (Entry 11). We then performed the reaction with different copper sources (Entries 12-14). The best performance of the reaction was thus attained by using CuI as catalyst; however, we observed than the monofluoroalkenylation was slightly insensitive to the copper source (Cu(I) or Cu(II)).

Under these optimized reaction conditions, the heteroarylated fluoroalkene **3Aa** was produced in 96% isolated yield as pure (*Z*)-isomer, demonstrating that the reaction proceeds with a complete retention of the stereochemistry.

Table 1. Optimization of the fluoroalkenylation reaction[a]

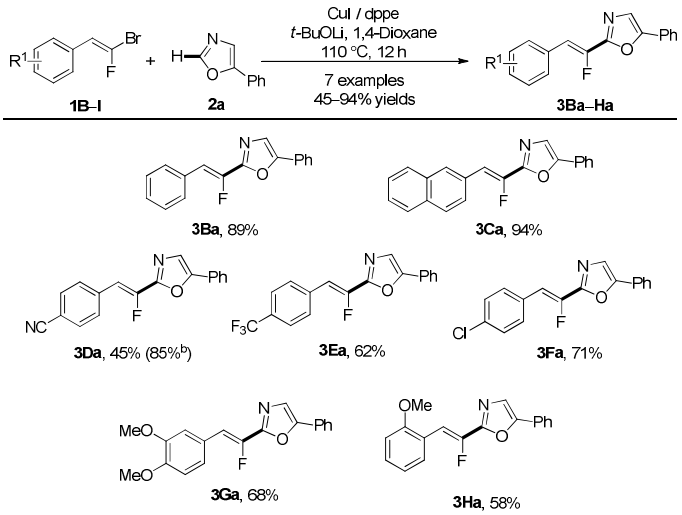


Entry	[Cu]	Ligand	Base	Yield[b] (%)
1[c]	CuBr	-	*t*-BuOLi	75
2	CuBr	-	*t*-BuOLi	63
3	CuI	-	*t*-BuOLi	65
4	CuI	Phen	*t*-BuOLi	51
5	CuI	Phen	K_2CO_3	-
6	CuI	L_1[d]	*t*-BuOLi	51
7	CuI	L_2[e]	*t*-BuOLi	81
8	CuI	PPh_3	*t*-BuOLi	83
9	CuI	PCy_3•HBF_4	*t*-BuOLi	51
10	*CuI*	*dppe*	*t*-BuOLi	*96*
11	-	dppe	*t*-BuOLi	-
12	CuBr	dppe	*t*-BuOLi	66
13	$CuCl_2$	dppe	*t*-BuOLi	73
14	$Cu(OTf)_2$	dppe	*t*-BuOLi	65

[a]All reactions were performed using **1A** (1.1 equiv.), **2a** (0.2 mmol, 1.0 equiv.), copper source (10 mol%), ligand (20 mol%), base (3 equiv.) in 1,4-dioxane (0.25 M) at 110°C [b]Yield based on isolated product after flash chromatography. [c]In presence of $PdCl_2(PPh_3)_2$ (5 mol%). [d]L1 = 3,4,7,8-$(Me)_4$-1,10-Phen; [e]L2 = *trans*-*N*,*N'*-dimethylcyclohexane-1,2-diamine.

With the optimized conditions in hands, the establishment of the scope of the direct C-H fluoroalkenylation was undertaken on 5-phenyloxazole (**2a**) with various readily accessible (*E*)-*gem*-bromofluoroalkenes[9] (Table 2). These latter flanked indifferently with electron-donating or electron-withdrawing groups on the aromatic unit at the ortho, meta and para positions, reacted at the C-2 position of the 5-phenyloxazole in moderate to excellent yields.

Table 2. Copper-Catalyzed C-H fluoroalkenylation of 5-phenyloxazole with various *gem*-bromofluoroalkenes[a]



[a]All reactions were performed using **1** (1.1 equiv.), **2a** (0.2 mmol, 1.0 equiv.), CuI (10 mol%), dppe (20 mol%), *t*-BuOLi (3 equiv.) in 1,4-dioxane (0.25 M) at 110°C. Yields are based on isolated product after flash chromatography. [b]Yield obtained under bimetallic Pd/Cu catalysis.

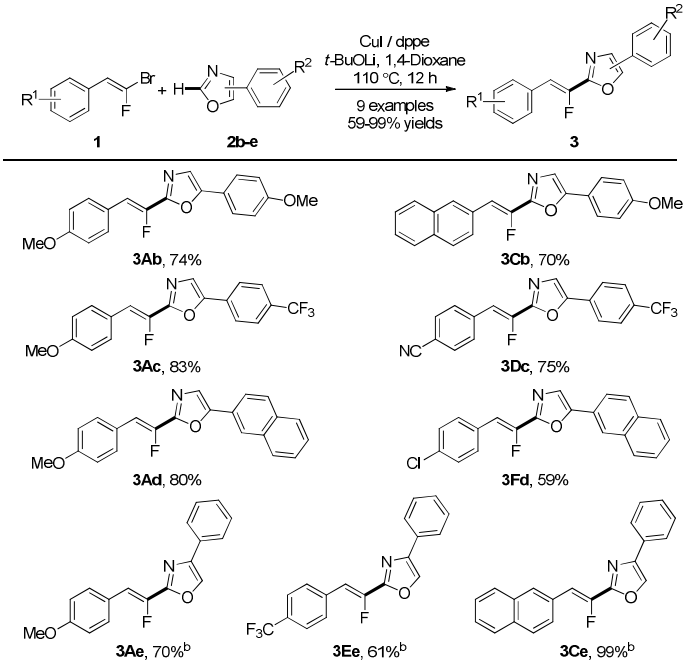
Interestingly, (*E*)-*gem*-bromofluoroalkenes bearing cyano group (**1D**) or chlorine atom (**1F**) on the aromatic ring, both valuable functional groups for further post-functionalizations, displayed good reactivity, even if, in the case of **3Da**, the reaction yield was lower than that obtained under Pd/Cu catalysis.

Alkylated or tetrasubstituted *gem*-bromofluoroalkene proved to be unreactive under Cu-catalysis whereas the reaction occurred under Pd/Cu catalysis.[21,25] Aromatic bearing an electron-withdrawing group in ortho position proved to be unstable in these reaction conditions.[25]

We next examined the substrate scope of various aryloxazoles (**2b-e**) with a panel of *gem*-bromofluoroalkenes in this transformation (Table 3). The reaction was efficient whatever the electronic nature of the substituents on the benzene ring of the 5-phenyloxazole **2b-d**. It is noteworthy that the use of Phen instead of dppe as ligand with 4-phenyloxazole **2e** as substrate was crucial to obtain trisubstituted *Z*-fluoroalkenes **3Ae**, **3Ee** and **3Ce** in good yields.[25]

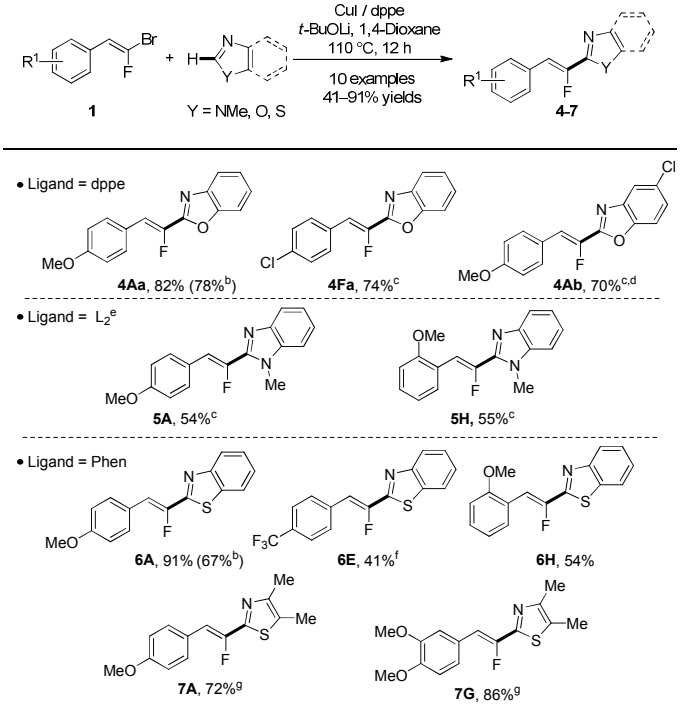
We then applied our reaction conditions to various relevant 1,3-diazoles (Table 4). A first set of experiments engaging benzoxazole **4a** with the (*E*)-*gem*-bromofluoroalkenes **1A** and **1F**, as coupling partners was adressed. Through the expected monofluoroalkenes **4Aa** was obtained in good 82% yield, the chlorinated benzoxazolylfluoroalkene **4Fa** was produced in poor 20% yields (^{19}F NMR yield). Nevertheless, when the temperature was increased from 110 to 130 °C, full completion of benzoxazole **4a** was attained to provide the product **4Fa** in 74% yield.

Table 3. Copper-catalyzed C-H fluoroalkenylation of various aryloxazoles[a]



[a]All reactions were performed using **1** (1.1 equiv.), **2** (0.2 mmol, 1.0 equiv.), CuI (10 mol%), dppe (20 mol%), *t*-BuOLi (3 equiv.) in 1,4-dioxane (0.25 M) at 110°C. Yields are based on isolated product after flash chromatography. [b]Phen (20 mol%) has been used as ligand instead of dppe.

Table 4. Extension of the reaction to various heterocycles[a]



[a]All reactions were performed using **1** (1.1 equiv.), heterocycle (0.2 mmol, 1.0 equiv.), CuI (10 mol%), dppe (20 mol%), *t*-BuOLi (3 equiv.) in 1,4-dioxane (0.25 M) at 110°C. Yields are based on isolated product after flash chromatography. [b]Yield obtained under bimetallic Pd/Cu catalysis. [c]Reaction performed at 130 °C. [d]Reaction performed on 1 mmol scale. [e]L2 = *trans-N,N'*-dimethylcyclohexane-1,2-diamine. [f]Reaction performed at 90 °C. [g]CuI (20 mol%) and Phen (40 mol%) were used.

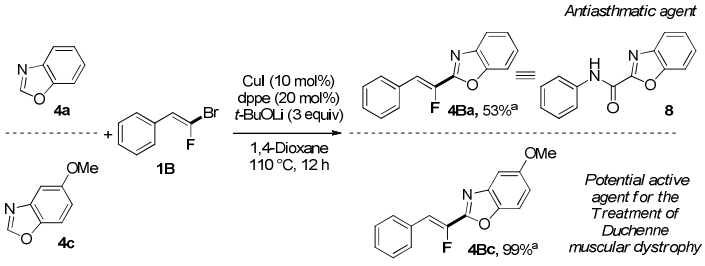
The reaction performed with chlorinated benzoxazole **4b** at the same 130 °C temperature delivered the expected benzoxazolylfluoroalkene **4Ab** in good 70% yield and importantly, the reaction could be scaled up from 0.2 mmol to 1 mmol without any loss of efficiency. We then examined the selective C-H monofluoroalkenylation with the *N*-methyl-benzimidazole **5** as heterocycle under our optimized conditions and, unfortunately no desired product was obtained. A careful screening of bases, solvents and ligands at different reaction temperatures,[25] led to select *trans-N,N'*-dimethylcyclohexane-1,2-diamine as ligand and a reaction temperature of 130 °C to produce the fluoroalkenes **5A** and **5H** in optimized 54 and 55% yields respectively. Finally, the reaction was investigated in thiazoles series. In that case phenanthroline ligand was found highly performant to achieve the cross-coupling at 110 °C of para-, ortho- or disubstituted *gem*-bromofluoroalkenes **1A**, **1G** and **1H** with benzothiazole **6** and 4,5-dimethythiazole **7** giving the fluoroalkenes in fair 54% to excellent 91% yields. However, the reaction performed with the trifluoromethylated (*E*)-*gem*-bromofluoroalkenes **1E** provided the desired product **6E** in poor 20 % isolated yield mainly due to the degradation of the coupling partner **1E**. Fortunately, the yield was significantly improved to 41% when operating at lower 90°C. It has to be noted than the yields obtained in **4Aa** and **6A** under these experimental conditions

were better than the yields obtained under bimetallic catalysis.[21]

Finally, we applied this copper-catalyzed fluoroalkenylation to the synthesis of relevant biomolecules as depicted in Scheme 1. Taking into account the similarities between fluoroolefin moiety and the amide bond,[6] we first synthetized a fluorinated analogue **4Ba**, in 53 % yield, of the antiasthmatic agent **8**,[26] starting from benzoxazole **4a** and *gem*-bromofluoroalkene **1B**. Then, we decided to apply our methodology as an alternative pathway to produce potential active molecules used in the treatment of Duchenne muscular dystrophy exemplified by the molecule **4Bc**[27] which was produced in quantitative yield by reacting 5-methoxybenzoxazole **4c** with *gem*-bromofluoroalkene **1B** (Scheme 1). Interestingly, a library of compounds may be ready produced for further SAR study introducing various substituents on both aromatic rings bear by heterocycle **4** or *gem*-bromofluoroalkene partner **1**.

Conclusions

In summary, an efficient Cu(I)/*t*-BuOLi catalyst has been employed for direct C-H fluoroalkenylation of 1,3-diazoles with readily available *gem*-bromofluoroalkenes as coupling partners. Althought phenyloxadiazole remained unreactive, as well as the use of alkylated *gem*-bromofluoroalkenes as electrophiles were inappropriate under these experimental conditions compared to the bimetallic Pd/Cu catalysis, the palladium free copper catalyzed fluoroalkenylation proved to be very efficient with *gem*-bromofluorostyrenes. Remarkably, a broad scope of 1,3-diazoles was accomplished modulating the nature of the ligand. Notably, (benzo)oxazole, (benzo)thiazole and benzimidazole series were successfully coupled with various *gem*-bromofluoroalkenes using diarylphosphine, phenanthroline and diamine ligands. The methodology gave access to innovative and valuable heteroarylated fluoroalkenes **3-7** produced in fair to excellent yields. It was finally applied to the synthesis of valuable benzoxazolylfluoroalkenes **4Ba**, a fluorinated analogue of antiasthmatic agent, and **4Bc** which is potentially active in the treatment of the Duchenne muscular dystrophy.



Scheme 1 Synthesis of fluorinated therapeutic agents. [a]Yields based on isolated product after flash chromatography.

Acknowledgements

This work has been partially supported by INSA Rouen, Rouen University, CNRS EFRD, Labex SynOrg (ANR-11-LABX-0029).

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25 See SI for more details.

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