C–H Activation

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Palladium- and Copper-Catalyzed Stereocontrolled Direct C–H Fluoroalkenylation of Heteroarenes using *gem*-Bromofluoroalkenes**

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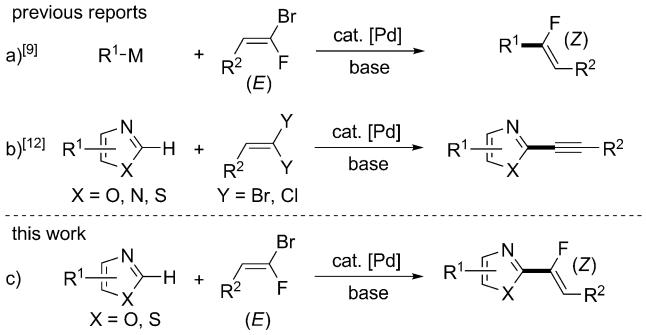
The development of efficient and mild methods for the synthesis of organofluorinated molecules is raising substantial interest in various fields of chemistry. Indeed, these compounds occupy a significant place in the pharmaceutical/medicinal,[1,2] agrochemical[1–3] and material sciences[1a–4] owing to the unique properties of the fluorine atom. Monofluorinated alkenes are an important organic moiety[5] that is found in various pharmaceuticals[6] and heavily exploited as nonhydrolyzable peptide bond mimics on the basis of electronic and geometric similarities.[7]

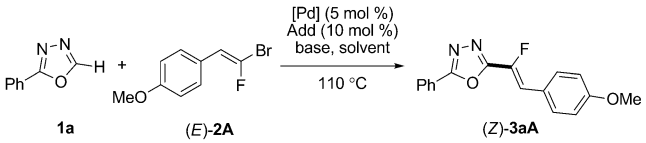
Among the readily available fluorinated building blocks for the construction of fluoroolefins, *gem*-bromofluoroalkenes are easily accessible[8] and versatile substrates for highly useful cross-coupling reactions (Scheme 1 a).[9] The development of catalytic direct C–H bond functionalization methods currently constitutes an important new tool in organic chemistry that avoids the preparation of organometallic intermediates as coupling partners.[10] To the best of our knowledge, *gem*-bromofluoroalkenes remain unemployed as electrophiles in any transition-metal catalyzed direct C–H bond alkenylation of (hetero)arenes.[11] Indeed, the *gem*-dibromo(dichloro)alkene structural analogs have only been used for direct C–H alkynylation of heterocycles, the non-coupled second halogen being eliminated during the process (Scheme 1 b).[12] Herein, we report the first base-assisted direct C–H haloalkenylation of heterocycles using various *gem*-bromofluoroalkenes as electrophiles, a method which offers novel, step-economical and stereocontrolled access to heteroarylated monofluoroalkenes (Scheme 1 c).



Scheme 1. Direct functionalization of C–H bonds using *gem*-dihaloalkenes.

Our initial investigations were focused on the base-assisted direct fluoroalkenylation of 2-phenyl-1,3,4-oxadiazole (**1a**) with (*E*)-1-(2-bromo-2-fluorovinyl)-4-methoxybenzene (**2A**),[8] and the results are summarized in Table 1. Whereas $Pd(OAc)_2$ under ligand-free conditions was ineffective (entry 1), a $PdCl_2(PPh_3)_2$ precatalyst could achieve the desired transformation under mildly basic conditions: CsF in 1,4-dioxane (entry 2).[13] However, a CuBr cocatalyst dramatically impacts the success of the CsF-assisted reaction; the resulting Pd^0/Cu^I bimetallic catalytic system[14] showed a much better performance, affording the expected olefinated oxadiazole (**3aA**) in 60% and 84% yields in 1,4-dioxane and toluene, respectively (entries 3 and 4). Subsequently, the reaction was conducted with this catalyst system under either mild or hard basic conditions with the use of Cs_2CO_3 or *t*BuOLi bases, respectively, which are conventionally employed in the palladium-catalyzed direct C–H functional-

Table 1: Pd-catalyzed direct C–H fluoroalkenylation under various reaction conditions.[a]



Entry	Base	Additive	Solvent	*t* [h]	Yield [%][b]
1[c]	CsF	–	1,4-dioxane	24	n.r.
2[d]	CsF	–	1,4-dioxane	24	20
3[d]	CsF	CuBr	1,4-dioxane	24	60
4[d]	CsF	CuBr	toluene	2	84
5[d]	Cs_2CO_3	–	1,4-dioxane	24	81
6[d]	Cs_2CO_3	CuBr	1,4-dioxane	2	83
7[d]	Cs_2CO_3	CuBr	toluene	24	n.r.
8[d]	*t*BuOLi	–	1,4-dioxane	4	79
9[d]	*t*BuOLi	CuBr	1,4-dioxane	0.5	83
10[d]	*t*BuOLi	CuBr	toluene	24	63

[a] Reaction Conditions: [Pd] (5 mol%), additive (10 mol%), base (2 equiv), solvent (0.27 M), 110°C. [b] Yield of isolated product after flash chromatography. [c] $Pd(OAc)_2$. [d] $PdCl_2(PPh_3)_2$. n.r. = no reaction.

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ization of less acidic heterocycles.[10] Remarkably, good results were obtained under both conditions with both the copper-free Pd^0 and Pd^0/Cu^I bimetallic catalytic systems in 1,4-dioxane (entries 5, 6, 8, and 9), without formation of an alkynylated side-product by a dehydrofluorination process.

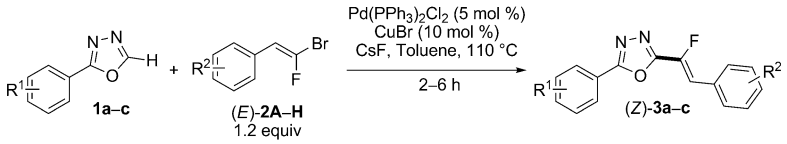
Both Cs_2CO_3- and *t*BuOLi-assisted processes proceed much more rapidly under Cu^I-co-catalysis (Table 1, entries 6 and 9).[14] All these observations are in complete accordance with a conventional Pd^0/Cu^I bimetallic catalytic system[15] model, in which the palladium cycle activates the electrophile and the copper-mediated process reinforces the acidity of the substrate through the formation of a 2-azolylcopper transmetalating agent. The configuration of 4-phenyloxadiazolylmonofluoroarylalkene **3aA** was confirmed by single crystal X-ray analysis (see the Supporting Information) demonstrating that this base-assisted Pd^0/Cu^I-catalyzed direct C–H alkenylation process proceeds with complete control of stereochemistry.

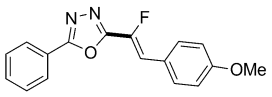
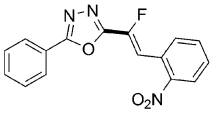
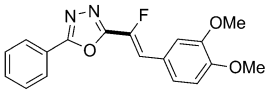
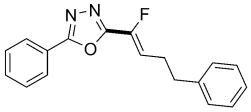
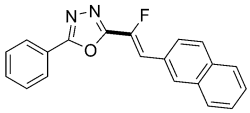
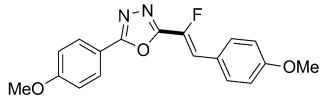
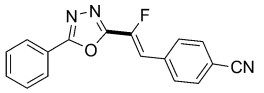
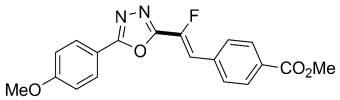
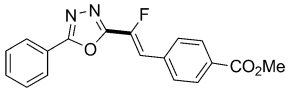
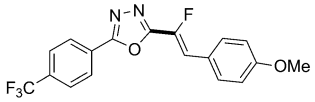
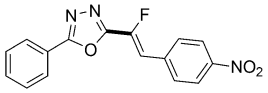
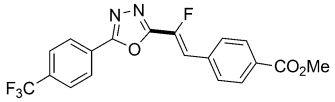
To extend the scope of the method, a broad range of arylated (*E*)-*gem*-bromofluoroalkenes **2A–G**, which bear electron-donating and -withdrawing groups on the aromatic unit, was tested for direct C–H alkenylation with **1a** (Table 2, entries 1–7). We were pleased to observe in all cases the formation of the expected (*Z*)-5-phenyloxadiazolylmonofluoroalkenes **3aA–G**, which were isolated in excellent yields. Thus, the mild basic conditions used may prevent any fluorine elimination side-reaction, even when highly activated nitro-substituted (*E*)-*gem*-bromofluoroalkenes **2F** and **2G** were used in the reaction. The procedure was also applied to the preparation of the alkylated (*Z*)-*gem*-bromofluoroalkene **3aH** in 83% yield (Table 2, entry 8). Importantly, the reaction could be scaled up from 0.41 to 2.05 mmol without any loss in effectiveness (Table 2, entry 1).

To further demonstrate the versatility of the method, the direct C–H alkenylation of methoxylated and trifluoromethylated 2-phenyl-1,3,4-oxadiazoles (**1b** and **1c**, respectively) was also achieved with (*E*)-*gem*-bromofluoroalkenes **2A** and **2F** (Table 2, entries 9–12).[8] Invariably, the electronic effect of the substituent on the aromatic units of both coupling partners had no influence on the success of the direct C–H alkenylation, which provided the expected (*Z*)-4-aryloxadiazolylmonofluoroarylalkenes **3bA**, **3bE**, **3cA**, and **3cE** in excellent yields (entries 9–12).

We further examined the selective direct C2–H monofluoroalkenylation of various 1,3-diazoles, heterocycles which are less acidic than the oxadiazole series, with the more basic Cs_2CO_3 and *t*BuOLi-based experimental conditions (Table 1, entries 6–9). Naturally, the use of more basic conditions are fraught with the inherent difficulty of preventing side dehydrofluorination, most notably with the more sensitive (*E*)-*gem*-bromofluoroarylalkenes, which bear electron-withdrawing groups on the aromatic moiety. A first set of

Table 2: Scope of the direct C–H fluoroalkenylation reaction with various *gem*-bromofluoroalkenes and 1,3,4-oxadiazoles.[a,b]



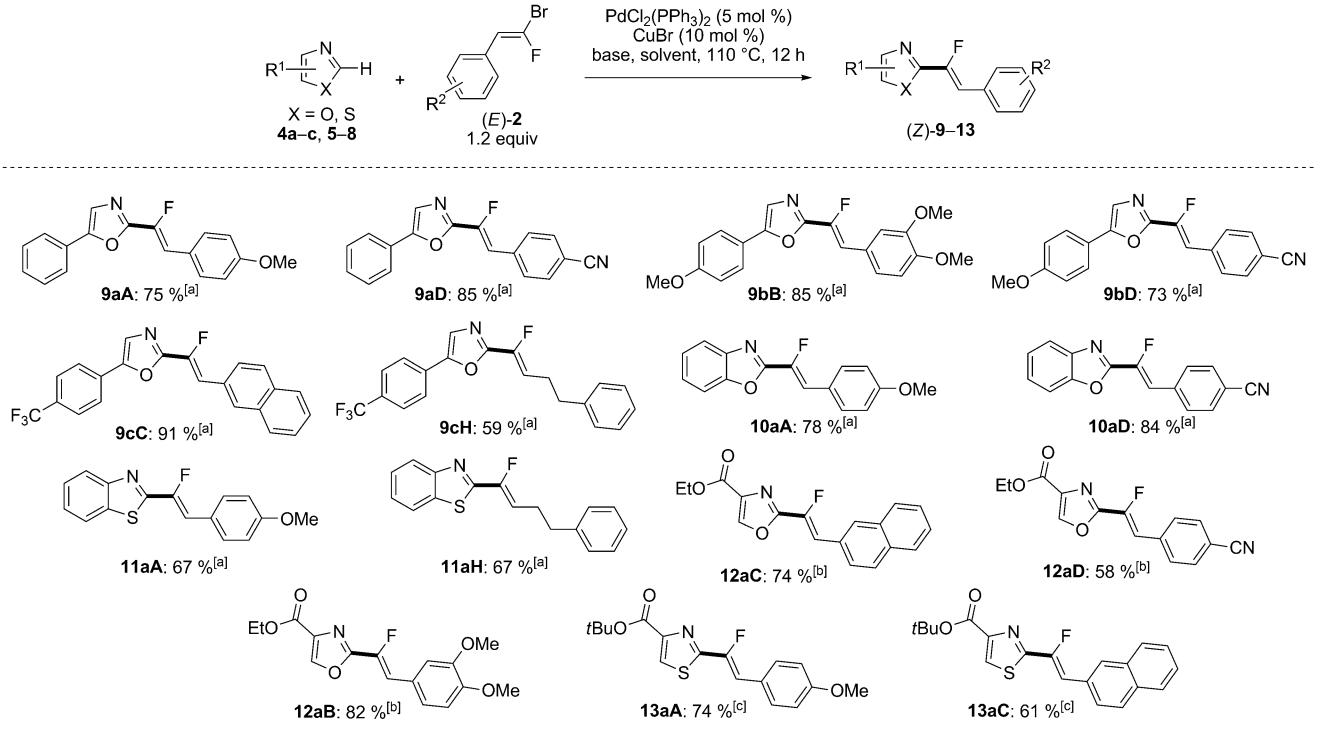
Entry	Product	Yield [%][c]	Entry	Product	Yield [%][c]
1		**3aA**: 84%[d]	7		**3aG**: 84%
2		**3aB**: 96%	8		**3aH**: 83%
3		**3aC**: 88%	9		**3bA**: 91%
4		**3aD**: 88%	10		**3bE**: 82%
5		**3aE**: 77%	11		**3cA**: 95%
6		**3aF**: 86%	12		**3cE**: 92%

[a] Reaction conditions: $PdCl_2(PPh)_3$ (5 mol%), CuBr (10 mol%), CsF (2 equiv), **2A–H** (1.2 equiv), anhydrous toluene, 110°C, 6 h. [b] The reaction was performed on a 0.41 mmol scale. [c] Yield of isolated product after flash chromatography. [d] The reaction was performed on a 2.05 mmol scale.

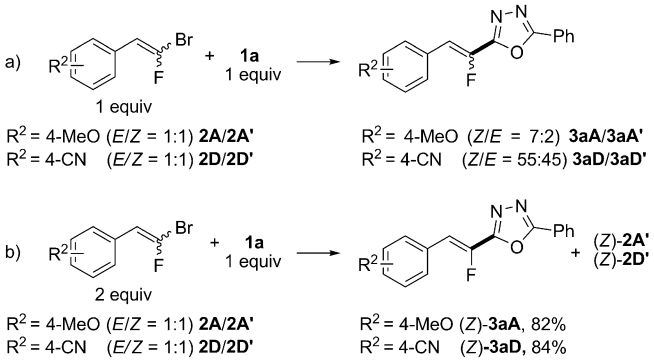
experiments employing 5-phenyloxazole (**4a**), benzoxazole (**5**), benzothiazole (**6**), and the more challenging and highly valuable 4-oxa(thia)zoles (**7** and **8**) with the (*E*)-*gem*-bromofluoroalkene **2A**, as a coupling partner, produced the expected monofluoroalkenes **9aA**–**13aA** in good yields (Scheme 2). Thus, the harder *t*BuOLi base was the base of choice for the direct C–H coupling of the less-acidic 1,3-diazoles **4**–**6**,[16] whereas the Cs_2CO_3-based reaction gave excellent results only with the carboxylated 1,3-diazoles **7** and **8** in 1,4-dioxane and DMF, respectively. In accordance with our previous observations on the base-assisted palladium-catalyzed direct C–H functionalization of 4-carboxylate oxa-(thia)zoles with halides under the same basic conditions,[17] the monofluoroalkenylation of **7** and **8** also occurred selectively at the C2 position of the oxazole and thiazole rings. We next examined the scope of the method in each 1,3-diazole series by conducting the direct C–H monofluoroalkenylation with various highly electronically different (*E*)-*gem*-bromofluoroalkenes coupling partners, and the results are summarized in Scheme 2. Remarkably, the majority of arylated and alkylated (*E*)-*gem*-bromofluroalkenes **2A**–**G**, including the challenging 4-cyanoarylated bromofluoroalkene **2D**, displayed good reactivity with 5-arylated oxazoles **4a**–**c**, as well as the selected 1,3-diazoles **5**–**8**. In fact, only the nitroarylated *gem*-bromofluoroalkenes **2F** and **2G** were found to be sensitive to both Cs_2CO_3-based and *t*BuOLi-based experimental conditions. The method allows for fast access to heteroaryled monofluoroaryl(alkyl)alkenes in good yields and may open the way to the design of innovative and useful fluorinated intermediates for further applications in medicinal and agrochemical chemistry, as well as material science.

In the final part of this study, we explored the reactivity of the (*Z*)-isomer coupling partner using the previously described direct C–H alkenylation procedure. For that purpose, the direct C–H fluoroalkenylation reaction of 1,3,4-oxadiazole **1a** was carried out with an equimolar mixture of *E*/*Z*-isomers (1:1 ratio) under the previous optimized conditions (Scheme 3a). Thus, when an equimolar mixture of either methoxylated (**2A/2A′**) or cyanated (**2D/2D′**) *gem*-bromofluoroalkenes were used, mixtures of the corresponding monofluoroalkenes **3aA**/**3aA′** or **3aD**/**3aD′** were obtained in ratios of 7:2 and 11:9, respectively, by ^{19}F and ^{1}H NMR analyses of the crude products. Both isomers could be separated using standard chromatographic techniques, resulting in the isolation of (*E*)-**3aA′** (15% yield) and (*Z*)-**3aA** (40% yield), as well as (*E*)-**3aD′** (31% yield) and (*Z*)-**3aD** (39% yield). As already observed in different cross-coupling reactions,[9,18] the (*E*)-monofluoroalkenes **3aA** and **3aD** could be produced alone in good yield, when two equivalents of a mixture of (*E*/*Z*)-*gem*-bromofluoroalkenes **2A/2A′** or **2D/2D′** were employed. In this case, the (*Z*)-*gem*-bromofluoroalkenes **2A′** and **2D′** were recovered (**2A′**/**3aA** = 2:7 and **2D′**/**3aD** = 9:11, as determined by ^{19}F NMR analyses of the crude products), owing to the faster oxidative addition of the less steric hindered (*E*)-*gem*-bromofluoroalkenes to the Pd^0 complex (Scheme 3b).

In summary, we have reported a novel and versatile stereocontrolled route to valuable trisubstituted monofluoroalkenes through the base-assisted Pd^0/Cu^I-catalyzed stereospecific direct C–H alkenylation of various 1,3-diazoles using *gem*-bromofluoroalkenes as electrophiles. The reaction is functional-group tolerant, step-economical, and proceeds in



Scheme 2. Direct C–H fluoroalkenylation using various azoles derivatives. [a] *t*BuOLi (1.5–2 equiv), 1,4-dioxane. [b] Cs_2CO_3 (2 equiv), 1,4-dioxane. [c] Cs_2CO_3 (2 equiv), dimethylformamide.



Scheme 3. Direct C–H fluoroalkenylation with a mixture of (*E*/*Z*)-*gem*-bromofluoroalkenes. a) Reaction conditions: $PdCl_2(PPh)_3$ (5 mol%), CuBr (10 mol%), CsF (2 equiv), anhydrous toluene, 110°C, 6 h. Yields: (*E*)-**3aA′** = 15%, (*Z*)-**3aA** = 40% and (*E*)-**3aD′** = 31%, (*Z*)-**3aD** = 39%. b) Reaction conditions: $PdCl_2(PPh)_3$ (5 mol%), CuBr (10 mol%), CsF (3 equiv), anhydrous toluene, 110°C, 6 h. **2A′**/**3aA** = 2:7, **2D′**/**3aD** = 9:11.

moderate to good yields with a wide range of heteroaryls and *gem*-bromofluoroalkenes. In the active research area of novel functionalizing agents for use in transition-metal-catalyzed direct C–H modification, this work reports the first examples of the direct C–H alkenylation of heterocycles using *gem*-dihaloalkenes as coupling partners.

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[14] Reaction time could be reduced by the use of CuBr as cocatalyst; see the Supporting Information.

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[16] For complete details concerning the screening of solvents and bases, see the Supporting Information.

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