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Base-mediated direct fluoroalkenylation of 2-phenyl-1,3,4-oxadiazole, benzothiazole and benzoxazole with *gem*-difluoroalkenes†

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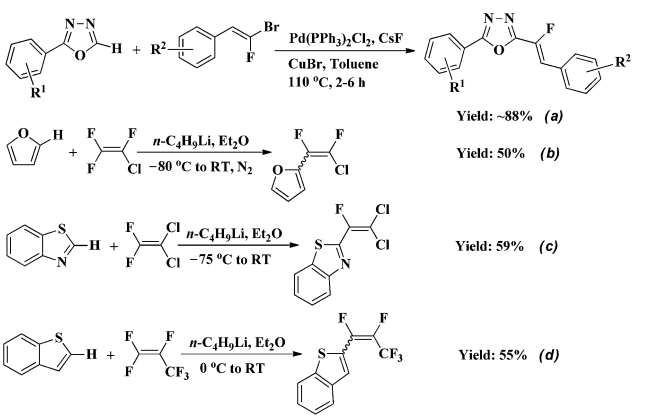
Direct α-fluorovinylation of 2-phenyl-1,3,4-oxadiazole, benzothiazole and benzoxazole with *gem*-difluoroalkenes *via* nucleophilic vinylic substitution reaction (S_NV) under the assistance of KHMDS or NaH at room temperature is described.

The alkenylated heteroarenes have gained much attention over the past decades due to their widespread applications as versatile building blocks for the synthesis of pharmaceuticals, agrochemicals and functional materials.[1] As a consequence, considerable efforts have been made to develop efficient methods for the synthesis of alkenyl-substituted heteroarenes.[2] The traditional method to prepare the alkenyl-substituted heteroarene is the Knoevenagel-type condensation of 2-methyl heteroarene with the appropriate aldehyde.[3]

Nowadays, the direct conversion of C–H bonds into C–C bonds is a very useful methodology for the construction of complex molecules.[4] At the same time, direct C–H alkenylation through C–H bond cleavage has been developed into a powerful tool for the synthesis of alkenylated arenes and particularly alkenylated heteroaromatics.[5] Among the protocols for the direct C–H alkenylation of (hetero)arenes, the alkenylation of (hetero) arenes with alkenyl halides by using palladium or copper as catalyst is becoming more popular.[6]

Monofluoroalkenes are useful fluorinated synthons in synthetic organic chemistry and precursors of biologically active compounds.[7] In medicinal chemistry and peptide chemistry, they are often considered as peptide bond isosteres.[8] However, very few reports are available on the synthesis of fluoroalkenyl-substituted heterocycles. In 2013, Schneider *et al.* reported a novel and facile approach to heteroarylated monofluoroalkenes through the base-assisted Pd- and Cu-catalyzed direct C–H alkenylation of various 1,3,4-diazoles using *gem*-bromofluoroalkenes as electrophiles (Scheme 1a).[9]

Generally, alkenyl chlorides, bromides or iodides could be served as alkenylating agents in the coupling with heteroarenes.[10] However, unreactive alkenyl fluorides are rarely used as coupling partners or substrates in alkenylation reaction due to the unique nature of the carbon–fluorine bond.[11] Up to now, there are only three examples of direct C–H alkenylation of heterocycles with fluoroalkenes (Scheme 1b–d).[12] The drawbacks of these methods are the lithiation of heterocycles with the moisture sensitive *n*-butyllithium in the first step, very low reaction temperature, relatively low yield, the mixture of *E*/*Z* isomers and the need for highly electron-deficient polyfluoroalkenes. Furthermore, *n*-butyllithium is prone to nucleophilic attack of fluorine atom in fluoroalkene, followed by fluorine elimination to produce undesired product.[12a] Thus, a simple method for the direct C–H alkenylation of heterocycles with fluoroalkenes under mild conditions is highly desirable. In continuation of our research on the functionalization of *gem*-difluoroalkenes,[13] in this communication, we report a straightforward protocol for direct C–H bond monofluoroalkenylation of 2-phenyl-1,3,4-oxadiazole,



Scheme 1 C–H alkenylation of heterocycle with alkenyl bromide or alkenyl fluoride.

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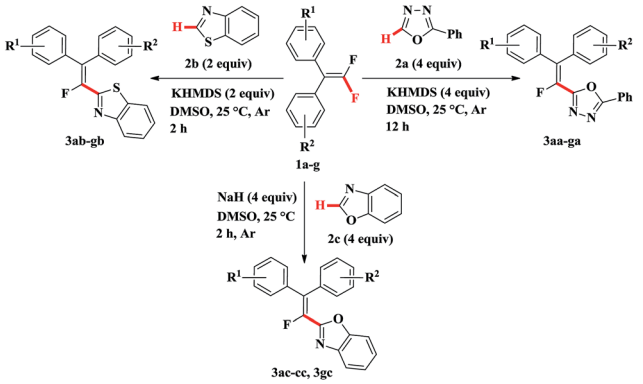
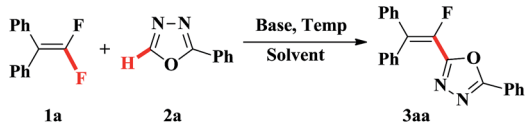


Scheme 2 Synthesis of fluoroalkenyl substituted heterocycles.

benzothiazole and benzoxazole with *gem*-difluoroalkenes under the assistance of base (KHMDS or NaH) at room temperature (Scheme 2).

We began our investigation by using (2,2-difluoroethene-1,1-diyl)dibenzene **1a** and 2-phenyl-1,3,4-oxadiazole **2a** as the model substrates to optimize the reaction conditions and the results are summarized in Table 1. Initially, the effect of base on the reaction was examined. In the absence of the base, the

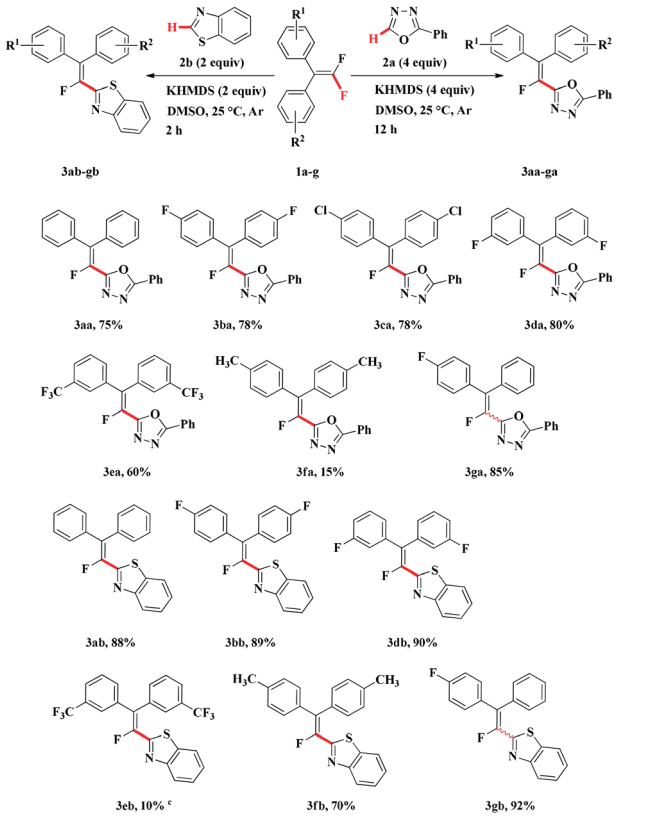
Table 1 Optimization of reaction conditions[a]



Entry	2a (equiv.)	Base (equiv.)	Temp (°C)	Solvent	Yield of 3aa[b] (%)
1	4	—	25	DMSO	0
2	4	LiOH (4)	25	DMSO	20
3	4	*t*-BuOK (4)	25	DMSO	27
4	4	*t*-BuOLi (4)	25	DMSO	64
5	4	*n*-BuLi (4)	25	DMSO	68
6	4	KOH (4)	25	DMSO	70
7	4	NaOH (4)	25	DMSO	71
8	4	LiHMDS (4)	25	DMSO	55
9	4	NaHMDS (4)	25	DMSO	50
10	4	KHMDS (4)	25	DMSO	81
11	4	KHMDS (5)	25	DMSO	26
12	4	KHMDS (3)	25	DMSO	17
13	3	KHMDS (4)	25	DMSO	23
14	2	KHMDS (4)	25	DMSO	16
15	4	KHMDS (4)	25	DMF	17
16	4	KHMDS (4)	25	DMA	8
17	4	KHMDS (4)	25	THF	0
18	4	KHMDS (4)	25	Dioxane	Trace
19	4	KHMDS (4)	25	Et_2O	0
20	4	KHMDS (4)	70	DMSO	22
21	4	KHMDS (4)	40	DMSO	21
22	4	*n*-BuLi (4)	25	Et_2O	0

[a] *Reagents and conditions*: **1a** (1.0 mmol), KHMDS (4.0 mmol, 1.0 mol L^{-1} in THF), DMSO (5 mL), 12 h. [b] Yields were determined by GC-MS analysis and based on **1a**.

Table 2 Reactions of *gem*-difluoroalkenes **1a–g** with 2-phenyl-1,3,4-oxadiazole **2a** and benzothiazole **2b**[a,b]

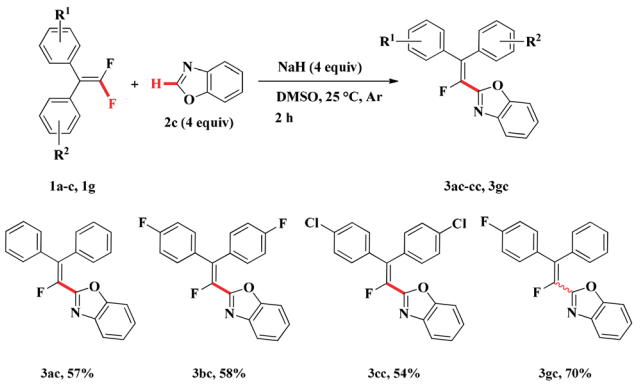


[a] *Reaction conditions*: *gem*-difluoroalkenes **1a–g** (1.0 mmol), **2a** (4.0 mmol) or **2b** (2.0 mmol), KHMDS (4.0 mmol or 2.0 mmol), DMSO (5 mL). [b] Isolated yields. [c] GC-MS yield.

reaction hardly proceeded and no expected product **3aa** was observed (entry 1). Among the various bases evaluated, KHMDS was better than the other bases such as *t*-BuOLi, *n*-BuLi, KOH, NaOH, LiHMDS and NaHMDS, and could provide the highest yield (entries 2–10). Although KOH and NaOH are cheaper and commercially more readily available than KHMDS, the lower yields of the valuable desired products render them less economically attractive. Too much or too little KHMDS led to a remarkable decrease in the yield (entries 11–12). Decreasing the amount of **2a** resulted in low yield of **3aa** (entries 13–14). The results also indicated that the solvent has a dramatic effect on the reaction. Only DMSO could afford the expected product **3aa** in good yield (entries 10, 15–19). Moreover, increasing reaction temperature obviously diminished the yield (entries 20–21). Finally, we also used the reaction system of literatures (*n*-BuLi/Et_2O, entry 22), however, no desired product was detected.

With the optimized reaction conditions established (Table 1, entry 10), we proceeded to investigate the direct C–H alkenylation of 2-phenyl-1,3,4-oxadiazole **2a** with several *gem*-difluoroalkenes (Table 2, **3aa–ga**). The results indicated that *gem*-difluoroalkenes bearing electron-withdrawing groups on the benzene ring were somewhat more reactive and provided the alkenylated

Table 3 Reactions of *gem*-difluoroalkenes **1a–c**, **1g** with benzoxazole **2c**[a,b]



[a] *Reaction conditions*: *gem*-difluoroalkenes **1a–c**, **1g** (1.0 mmol), **2c** (4.0 mmol), NaH (4.0 mmol), DMSO (5 mL). [b] Isolated yields.

1,3,4-oxadiazoles in good yields (**3ba–da**). However, the *gem*-difluoroalkenes bearing strong electron-withdrawing group such as CF_3 was unfavorable for the reaction (**3ea**). *gem*-Difluoroalkene having electron-donating group such as CH_3 was not a suitable substrate for this transformation and furnished only small amount of alkenylated product (**3fa**). Unsymmetrical *gem*-difluoroalkene could also furnish high yield of desired product (**3ga**), but with poor *E*/*Z* selectivity (4 : 3, the ratio of *E*/*Z* isomers in the crude reaction mixture was determined by ^{19}F NMR). When 1-(2,2-difluorovinyl)-4-methoxybenzene was used as substrate, no reaction was observed. It appears that two diaryl groups attached at the C–C double bond of *gem*-difluoroalkenes is necessary, which could stabilize carbanion transition state. Furthermore, the replacement of phenyl group in 2-phenyl-1,3,4-oxadiazole with hydrogen or alkyl group can not make the reaction proceed smoothly.

To explore the scope of the novel alkenylation reaction, we next evaluated the reaction of benzothiazole **2b** with different *gem*-difluoroalkenes (Table 2, **3ab–gb**). Much to our delight, 2.0 equiv. KHMDS and 2.0 equiv. benzothiazole **2b** were enough to make the reaction proceed smoothly. Furthermore, *gem*-difluoroalkenes were almost completely consumed within 2 hours, affording the desired products in high yield (**3ab**, **3bb**, **3db**, **3fb**). This might be in part due to the ease of dissociation of the C–H bond in benzothiazole **2b** in the presence of base. Contrary to the reactions of 2-phenyl-1,3,4-oxadiazole **2a**, the reaction of benzothiazole **2b** with *gem*-difluoroalkene bearing electron-donating group such as CH_3 could give good yield of alkenylated product (**3fb**), whereas *gem*-difluoroalkene bearing CF_3 resulted in very low conversion (**3eb**). Unsymmetrical *gem*-difluoroalkene could react with benzothiazole **2b** smoothly and the expected product (**3gb**) was isolated in excellent yield but in a poor stereoselectivity. It should be noted that when NaOH or KOH were used as base, which were suitable for the reaction of *gem*-difluoroalkenes with 2-phenyl-1,3,4-oxadiazole **2a**, the reaction could not proceed efficiently.

Under the above-mentioned two optimized conditions, the scope of the direct C–H alkenylation reaction involving C–F bond breaking was expanded to benzoxazole **2c** (Table 3). However, KHMDS as well as other bases such as *t*-BuOLi, *t*-BuOK, KOH and LiHMDS failed to furnish the desired products. Gratifyingly, we found that the alkenylation of benzoxazole **2c** with *gem*-difluoroalkenes **1a–c**, **1g** could occur in presence of NaH and give the expected alkenylated products in moderate yield at room temperature (**3ac–cc**, **3gc**). Unfortunately, both compound **1f** having electron-donating group and compound **1e** bearing strong electron-withdrawing group on benzene ring were not suitable substrates for the transformation and only trace amounts of alkenylated products were detected.

Based on the above observations, we suggest that the mechanism is analogous to those proposed in the literatures.[14] *gem*-Difluoroalkenes undergo nucleophilic vinylic substitution (S_NV) with heteroarenes in the presence of base *via* addition–elimination processes to afford fluoroalkenylated heteroaromatics. The abstraction of the C–H proton of heteroaromatics with assistance of base to generate the corresponding sp^2 carbanion on the heterocycles is essential for efficient transformation. The presence of benzene group in 2-phenyl-1,3,4-oxadiazole, benzothiazole and benzoxazole is favorable for the activation of the C–H bond.

In conclusion, we have developed a mild and efficient method for the KHMDS or NaH-mediated alkenylation of three azole heterocycles, including 2-phenyl-1,3,4-oxadiazole, benzothiazole and benzoxazole with various *gem*-difluoroalkenes. Although, at present stage, the substrate scope of this new approach was relatively limited due to the fact that the cleavage of heteroaromatic C–H bonds is much more difficult in absence of metal catalyst, it will pave the way for realizing direct C–H alkenylation of heterocycles without prefunctionalization of Csp^2–H of heterocycles such as halogenation. Further studies to expand the substrates and increase yields are in progress in our laboratory.

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