

Difluoromethyl 2-Pyridyl Sulfone: A New *gem*-Difluoroolefination Reagent for Aldehydes and Ketones

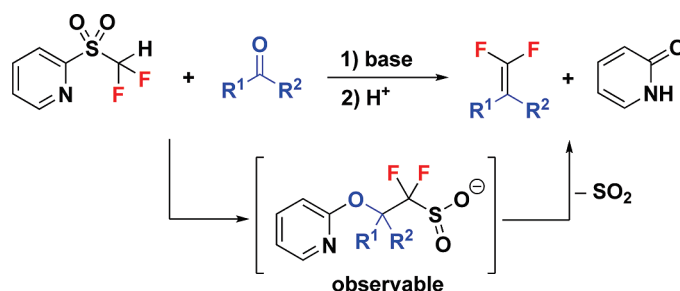
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ABSTRACT



Difluoromethyl 2-pyridyl sulfone, a previously unknown compound, was found to act as a novel and efficient *gem*-difluoroolefination reagent for both aldehydes and ketones. It was found that the fluorinated sulfinate intermediate in the reaction is relatively stable, which can be observed by ¹⁹F NMR and trapped with CH₃I.

Incorporation of fluorine atom(s) or fluorinated moieties into an organic molecule often results in profound changes of physical, chemical, and biological properties of the target molecule.¹ For instance, unlike other nonfluorinated alkenes, *gem*-difluoroalkene (*gem*-difluoroolefin) functionality is highly electrophilic and the fluorine atom(s) can be replaced by nucleophiles through an addition–elimination mechanism,^{2,3} which enables *gem*-difluoroalkenes to act as valuable intermediates for the synthesis of other important molecules, such

as 2-fluorinated indoles,^{3a} monofluoroalkenes,^{3b} esters, and carboxylic acids.^{3c} Moreover, *gem*-difluorovinyl functionality is known to act as a bioisostere for carbonyl group,⁴ and it is critical to many biologically active molecules such as mechanism-based enzyme inhibitors.^{1,5} Owing to their important applications, various approaches have been developed for the preparation of *gem*-difluoroalkenes, among which the *gem*-difluoroolefination reaction with aldehydes or ketones is one of the most straightforward methods.^{1,2} In

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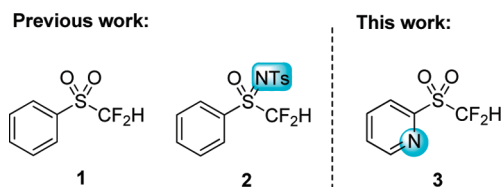
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Wittig-type reactions developed by Silverstein and Burton, difluoromethylene ylide generated from the reaction of PPh₃ and CF₂CICOONa or CF₂Br₂ successfully difluoromethylates aldehydes and activated ketones.⁶ For unactivated ketones, reagents such as HMPT/CF₂Br₂^{7a–c} or (CF₃)₂Hg/NaI/PPh₃^{7d} are needed. Horner–Wadsworth–Emmons-type and Horner–Wittig-type *gem*-difluoroolefination reactions provide more general routes suitable for both aldehydes and ketones.⁸ Alternatively, in classical Julia reaction, difluoromethyl phenyl sulfone is employed to achieve a three-step synthesis of *gem*-difluoroalkenes via a reduction–desulfonation protocol.⁹ In these *gem*-difluoroolefination reactions, however, low-boiling or toxic reagents, strictly anhydrous reaction conditions, and/or multistep procedures are often needed. Herein, we report a concise and efficient method for *gem*-difluoroolefination of both aldehydes and ketones via a Julia–Kocienski protocol.

Previously, we were interested in investigating the unique synthetic applications of fluorinated sulfones¹⁰ and sulfoximines.¹¹ Difluoromethyl phenyl sulfone (PhSO₂CF₂H, **1**) was found to be a robust nucleophilic difluoromethylation reagent (via its deprotonated form PhSO₂CF₂[−]), thanks to the excellent modulating ability of the phenylsulfonyl group on both the stability and nucleophilicity of the PhSO₂CF₂[−] anion species (Scheme 1).¹⁰ Recently, we found that when one oxygen atom in

Scheme 1. Difluoromethyl Sulfones and Sulfoximines (Ts = *p*-Toluenesulfonyl Group)

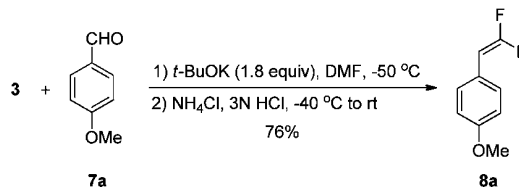


compound **1** was replaced by the NTs group (Ts = *p*-toluenesulfonyl), the chemical reactivity of the resulting compound *N*-tolyl-*S*-difluoromethyl-*S*-phenylsulfoximine **2** is significantly different from **1**. While compound **1** is a nucleophilic difluoromethylation agent, compound **2** behaves as an “electrophilic” difluoromethylation reagent through a difluorocarbene mechanism.^{11a} Intrigued by these results, we envisioned that as another analogous compound of **1**, difluoromethyl 2-pyridyl sulfone (2-PySO₂CF₂H, **3**¹²) may possess other interesting reactivities that are different from those of **1** and **2**. Furthermore, it would also be interesting to compare the reactivity of **3** with those of other difluoromethyl heteroaryl sulfones such as 1,3-benzothiazol-2-yl difluoromethyl sulfone (**4**), 1-phenyl-1*H*-tetrazol-5-yl difluoromethyl sulfone (**5**), and 1-*tert*-butyl-1*H*-tetrazol-5-yl difluoromethyl sulfone (**6**).

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With these considerations in mind, we attempted the reaction between **3**¹² and anisaldehyde (**7a**) using *t*-BuOK as a base (Scheme 2). Therefore, into an equimolar mixture

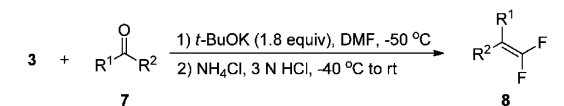
Scheme 2. Difluoromethylation of Anisaldehyde with 2-PySO₂CF₂H (**3**)



of sulfone **3** and aldehyde **7a** in DMF at $-50\text{ }^{\circ}\text{C}$ was slowly added a DMF solution of *t*-BuOK (2 equiv). The reaction mixture was subsequently warmed to $-40\text{ }^{\circ}\text{C}$ over a period of 15 min and then quenched with 3 N HCl. After routine workup and purification, we were able to isolate 1-(2,2-difluorovinyl)-4-methoxybenzene (**8a**) in 76% yield (Scheme 2). It became apparent that a Julia–Kocienski-type olefination¹³ occurred under the present reaction conditions. After a quick optimization of the reactant ratio (**3**/**7a**/*t*-BuOK = 1.0:1.2:1.8), the product yield of **8a** was increased to 86% (Table 1, entry 1). It should be noted that, to the best of our knowledge, this is the first example of Julia–Kocienski-type one-step *gem*-difluoroolefination reaction.

With the optimized reaction condition (reactant molar ratio **3**/**7a**/*t*-BuOK = 1.0:1.2:1.8), we examined the generality and substrate scope of this new *gem*-difluoroolefination reaction between **3** and carbonyl compounds **7**. As shown in Table 1, various aldehydes and ketones were treated with **3**, smoothly giving the corresponding *gem*-difluoroalkenes in good to excellent yields. This method tolerates various substituents on carbonyl compounds (entries 1–6, 9, 10, and 14–16), which is superior to Wittig-type *gem*-difluoroolefination reactions.^{6,7} It was found that aldehydes with electron-donating groups gave slightly higher yield than those with electron-withdrawing groups (entries 1–6). For the enolizable aldehyde **7h** (entry 8), lower yield was observed even when LiHMDS was used as a base to suppress the undesired aldol reaction. The reaction was also amenable to both aliphatic and aromatic ketones, leading to the formation of structurally diverse *gem*-difluoroalkenes **8k–p** (entries 11–16). It was reported that difluoroalkenes **8i** and **8o** were previously prepared from **7i** and **7o** in low yields ($\leq 41\%$) by using toxic (CF₃)₂Hg reagent,^{7d} but in our cases with reagent **3**, products **8i** and **8o** were obtained in 62% and 80% yield, respectively (entries 9 and 15). Furthermore, our method gave product **8p**, an intermediate for the synthesis of thrombin inhibitor SSR182289A, in 84% yield, which is also superior to the previously reported results (with 61% yield through a Wittig-type reaction using excess CF₂Br₂ and HMPT).^{5b} It should be noted that reagent **3** is a stable and crystalline solid¹² and the organic byproduct of the reaction is pyridin-2-ol (water-soluble), both factors making the current difluoroolefination reaction easy to handle.

Table 1. *gem*-Difluoroolefination of Carbonyl Compounds with Reagent **3**

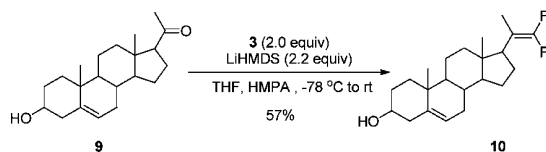


entry ^a	substrate	product	yield (%) ^b
1			8a R = <i>p</i> -MeO 86
2			8b R = <i>p</i> -tBu 74
3			8c R = 2, 4-Cl 72
4			8d R = <i>m</i> -NO ₂ 72
5			8e R = <i>p</i> -NMe ₂ 91
6			8f R = <i>p</i> -Br 72
7			92
8 ^c			40 ^d
9			62 ^d
10			93
11			87
12 ^e			81
13 ^c			72
14 ^e			77
15			80
16			84

^a For all cases, the molar ratio of reactants was **3**/*t*-BuOK = 1.0:1.2:1.8. ^b Isolated yield. ^c LiHMDS was used as a base. ^d Low yield is partially due to the high volatility of the product. ^e THF was added as a cosolvent due to the poor solubility of these substrates in DMF at low temperature.

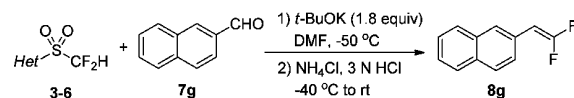
To further demonstrate the synthetic potency of our method with reagent **3**, we applied it in the synthesis of 21,21-difluoro-3-hydroxy-20-methylpregna-5,20-diene (**10**), a potential inhibitor of steroid C₁₇₍₂₀₎-lyase.^{5c} Compound **10** was previously prepared from pregnenolone acetate using (difluoromethyl)diphenylphosphine oxide in low yield (20%).^{5c} We found that by using **3**/LiHMDS/THF/HMPA system, **10** could be produced in 57% yield directly from unprotected pregnenolone **9** (with recycling of 30% unreacted **9**) (Scheme 3).

Scheme 3. Synthesis of **10**



Considering that in nonfluorinated Julia–Kocienski olefination reactions, 2-pyridyl sulfones generally give lower yield of olefins than other heteroaryl sulfones such as 1,3-benzothiazol-2-yl (BT), 1-phenyl-1*H*-tetrazol-5-yl (PT), and 1-*tert*-butyl-1*H*-tetrazol-5-yl (TBT) sulfones,¹³ we prepared other three difluoromethyl heteroaryl sulfones **4–6**¹² and investigated their reactivities in difluoroolefination reactions. As shown in Table 2, we were surprised to find that under

Table 2. *gem*-Difluoroolefination with Different Sulfones



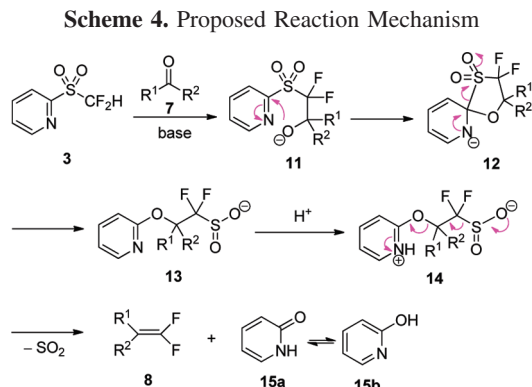
entry	reagent	yield (%) ^a
1	 3 (2-PySO ₂ CF ₂ H)	92
2	 4 (BTSO ₂ CF ₂ H)	42
3	 5 (PTSO ₂ CF ₂ H)	trace ^b
4	 6 (TBTSO ₂ CF ₂ H)	0 ^b

^a Isolated yield. ^b Determined by ¹⁹F NMR spectroscopy.

similar reaction conditions (as those for Table 1), sulfones **4–6** showed lower reactivity in the difluoroolefination reaction with 2-naphthaldehyde **7g**. The reaction with BTSO₂CF₂H (**4**) gave product **8g** in 42% yield, while both PTSO₂CF₂H (**5**) and TBTSO₂CF₂H (**6**) did not show significant reactivity with aldehyde **7g**. However, the reaction with reagent **3** provided alkene **8g** in 92% isolated yield. The sharp contrast between the reactivities of nonfluorinated heteroaryl sulfones¹³ and difluoromethyl sulfones **3–6** in Julia–Kocienski olefination was striking and never reported.¹⁴ We speculate that the high reactivity of sulfone **3** (compared with other sulfones **4–6**) may be due to the fact that 2-PySO₂CF₂[−] anion possesses the best nucleophilicity

(among four HetSO₂CF₂⁻ anions; Het = 2-Py, BT, PT, and TBT) toward carbonyl compounds.¹⁵

The reaction mechanism of the current difluoroolefination with **3** is proposed in Scheme 4, following the generally



accepted mechanism of the Julia–Kocienski reaction.¹³ First, sulfone **3** and carbonyl compound **7** condense under basic condition to afford the adduct **11**, which rearranges to a relatively stable sulfinate salt **13**. When protonated at pyridine, the leaving ability of the 2-pyridyloxyl group is

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(12) Similar to PhSO₂CF₂H, difluoromethyl sulfone compounds **3–6** can be readily prepared by difluoromethylation of the corresponding thiols, followed by simple oxidation (see the Supporting Information). Compounds **3**, **5**, and **6** were previously unknown, and the chemical reactivities of compounds **3–6** have never been reported.

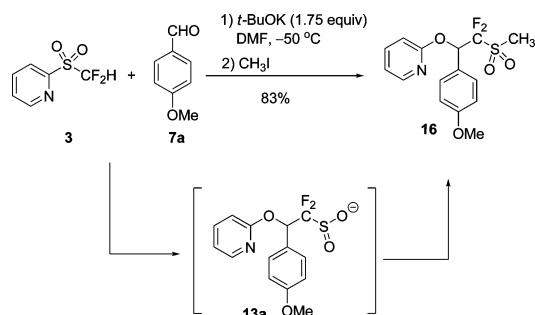
(13) See reviews of Julia–Kocienski olefination: (a) Aissa, C. *Eur. J. Org. Chem.* **2009**, 1831. (b) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. I* **2002**, 2565.

(14) The α -monofluoro sulfones (such as BT- and TBT-based sulfones) have been successfully used in Julia–Kocienski olefination, and the efficiency of the monofluoroolefination was similar to non-fluorinated systems. See selected examples: (a) Ghosh, A. K.; Zajc, B. *J. Org. Chem.* **2009**, *74*, 8531. (b) Ghosh, A. K.; Zajc, B. *Org. Lett.* **2006**, *8*, 1553. (c) Pfund, E.; Lebargy, C.; Rouden, J.; Lequeux, T. *J. Org. Chem.* **2009**, *72*, 7871. (d) Alonso, D. A.; Fuensanta, M.; Gomez-Bengoa, E.; Najera, C. *Adv. Synth. Catal.* **2008**, *350*, 1823.

(15) For discussion on the stability and nucleophilicity of fluorinated carbanions, see: (a) Ni, C.; Zhang, L.; Hu, J. *J. Org. Chem.* **2008**, *73*, 5699. (b) Ni, C.; Li, Y.; Hu, J. *J. Org. Chem.* **2006**, *71*, 6829. (c) Reference 10a,b.

enhanced, and the sulfinate salt **14** readily decomposes to the desired *gem*-difluoroalkene product **8**, sulfur dioxide, and 2-pyridone **15a** (or pyridin-2-ol **15b**). This mechanism is supported by our experimental observations: (a) species **13** was observed by ¹⁹F NMR [–127.9 ppm (dd, ²J_{F–F} = 230 Hz, ³J_{F–H} = 12 Hz), 1F; –129.0 ppm (dd, ²J_{F–F} = 230 Hz, ³J_{F–H} = 15 Hz), 1F; relative to CFCl₃], (b) when we quenched the reaction mixture (from **3** and aldehyde **7a**) with CH₃I, methylated compound **16** was isolated in 83% yield via difluorinated sulfinate intermediate **13a** (Scheme 5).

Scheme 5. Trapping the Sulfinate Salt with Iodomethane



In conclusion, difluoromethyl 2-pyridyl sulfone **3**, a previously unknown compound that can be readily prepared from 2-mercaptopyridine,¹² was found to be a novel and efficient *gem*-difluoroolefination reagent for preparing *gem*-difluoroalkenes from both aldehydes and ketones. Our experimental data suggest that the intermediate sulfinate salt is relatively stable under basic conditions and decomposes after protonolysis. The remarkable feature of the present new difluoroolefination method is its practical simplicity and broad scope of applicability, which promises it to find many applications in organic synthesis. The unusual reactivity difference of sulfones **3–6** (as shown in Table 2) provides some insights into both fluorinated sulfone chemistry and Julia–Kocienski reaction. Further exploration of this chemistry is currently underway in our laboratory.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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