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Synthetic Methods

gem-Difluoroolefination of Diaryl Ketones and Enolizable Aldehydes with Difluoromethyl 2-Pyridyl Sulfone: New Insights into the Julia–Kocienski Reaction

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Abstract: The direct conversion of diaryl ketones and enolizable aliphatic aldehydes into *gem*-difluoroalkenes has been a long-standing challenge in organofluorine chemistry. Herein, we report efficient strategies to tackle this problem by using difluoromethyl 2-pyridyl sulfone as a general *gem*-difluoroolefination reagent. The *gem*-difluoroolefination of diaryl ketones proceeds by acid-promoted Smiles rearrangement of the carbinol intermediate; the *gem*-difluoroolefination is otherwise difficult to achieve through a conventional Julia–Kocienski olefination protocol under basic conditions due to the retro-aldol type decomposition of the key intermediate. Efficient *gem*-difluoroolefination of aliphatic aldehydes was achieved by the use of an amide base generated in situ (from CsF and tris(trimethylsilyl)amine), which diminishes the undesired enolization of aliphatic aldehydes and provides a powerful synthetic method for chemoselective *gem*-difluoroolefination of multi-carbonyl compounds. Our results provide new insights into the mechanistic understanding of the classical Julia–Kocienski reaction.

Introduction

The synthesis of fluoroalkenes has attracted much attention due to their unique chemical and biological properties, especially relative to their nonfluorinated counterparts.[1,2] *gem*-Difluoroalkenes, for instance, are highly electrophilic toward many nucleophiles at the terminal difluoromethylene group (=CF_2),[3] therefore, they can be employed as valuable intermediates for the preparation of di- and tri-fluoromethylated compounds, monofluoroalkenes, monofluorinated heterocycles, carboxylic acids, and esters.[4] Moreover, the *gem*-difluorovinyl functionality (C=CF_2) is known to act as a bioisostere for the carbonyl group and has been used in the design of mechanism-based enzyme inhibitors.[2a,5] Synthetic methods for the preparation of *gem*-difluoroalkenes can be mainly divided into two categories: 1) the direct conversion of carbonyl compounds into *gem*-difluoroalkenes[6,7] and 2) the incorporation of *gem*-difluorovinyl-containing building blocks into the target molecules.[8] In this context, the direct deoxygenative *gem*-difluoroolefination of carbonyl compounds represents one of the most straightforward methods because of the ready availability of aldehydes and ketones. Among them, Wittig reactions that involve difluoromethylene phosphorus ylides (R_3P=CF_2) have been extensively exploited; however, transformations that involve reagent systems $PPh_3/ClCF_2CO_2Na$,[7b–d] PPh_3/CF_2Br_2,[7e] $PPh_3/FSO_2CF_2CO_2Me$,[7f] and $PPh_3/TMSCF_2Cl$[7o] are limited to aromatic aldehydes and activated ketones. Although examples of unactivated substrates have been illustrated for reactions with $P(NMe_2)_3/CF_2Br_2$[7g,h] and $PR_3/(CF_3)_2Hg/NaI$,[7i] they suffer from the disadvantages of toxic reagents, moderate yields, and/or production of undesired tetrafluorocyclopropanation products. Recently, Xiao and co-workers have prepared difluoromethylene phosphobetaines and applied them to the conversion of carbonyl compounds into *gem*-difluoroalkenes under base-free conditions.[7j] The Horner–Wadsworth–Emmons reaction with difluoromethyl phosphonate anions and Horner–Wittig reaction with difluoromethyl phosphine oxide anions seemed to be more general than the classical Wittig reactions, but the reactions with diaryl ketones were demonstrated with only a few examples.[7l–n] Therefore, an easily accessible and safe reagent for the direct and general *gem*-difluoroolefination of both diaryl ketones and enolizable aldehydes is highly desirable.

The Julia–Kocienski olefination reaction has been widely employed in synthetic chemistry for the direct construction of C=C bonds from carbonyl groups because of its easy manipulation, high efficiency, and excellent stereocontrol.[9] Recently, we reported the first example of a Julia–Kocienski type *gem*-difluoroolefination reaction of carbonyl compounds with difluoromethyl 2-pyridyl sulfone (2-$PySO_2CF_2H$, **1**; Figure 1).[10a] Reagent **1** is a bench-stable, crystalline solid that is now commercially available.[10d] Moreover, it is noteworthy that although 2-pyridyl sulfones are not commonly used in classical Julia–Kocienski olefination reactions,[9] reagent **1** unexpectedly shows better reactivity in *gem*-difluoroolefination reactions than other

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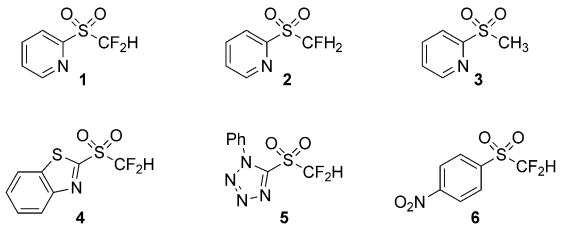


Figure 1. Heteroaryl sulfones for *gem*-difluoroolefination reactions

difluoromethyl heteroaryl sulfones, such as difluoromethyl 1,3-benzothiazol-2-yl (BT, **4**; Figure 1), difluoromethyl 1-phenyl-1*H*-tetrazol-5-yl (PT, **5**; Figure 1), and difluoromethyl 1-*tert*-butyl-1*H*-tetrazol-5-yl (TBT) sulfone.[10a] We also realized that our *gem*-difluoroolefination reaction with reagent **1** may provide new insights into the classical Julia–Kocienski reaction. For instance, we found that the *gem*-difluorinated sulfinate salt, a key intermediate from the Smiles rearrangement in the Julia–Kocienski reaction that has been overlooked in the past, was indeed a stable species.[10a–c]

On the other hand, although our reported procedure showed good compatibility with aromatic aldehydes, preliminary exploration of the *gem*-difluoroolefination of diaryl ketones and aliphatic aldehydes proved to be less efficient. In view of the importance of 2,2-diaryl-1,1-difluoroethenes and aliphatic *gem*-difluoroalkenes,[8i,j] we have carried out further investigations and tried to solve these synthetic problems with reagent **1**. Herein, we report our recent success in the carbonyl *gem*-difluoroolefination of diaryl ketones and aliphatic aldehydes with reagent **1** based on our new mechanistic insights into the Julia–Kocienski reaction.

Results and Discussion

Thermal-stability evaluation of different aryl sulfones under basic conditions

Since the initial exploration of the olefination reaction of carbonyl compounds with BT sulfones by Julia and co-workers,[11] other heteroaryl sulfones (such as PT sulfones and TBT sulfones)[12] have been successively developed and applied in organic synthesis.[13] These sulfones are believed to increase the stability of the corresponding metalated sulfone carbanions. In a typical olefination reaction, the heteroaryl sulfone is first deprotonated in solution by a strong non-nucleophilic base [lithium diisopropylamide (LDA) or potassium hexamethyl disilazide (KHMDS)], then the carbonyl compound is added to react with the metalated sulfone carbanion. Finally Smiles rearrangement[14] and SO_2 extrusion give the alkene product. The fact that the metalated nonfluorinated sulfone carbanions are sufficiently stable in solution (even in the absence of electrophiles) allows the scope of the Julia–Kocienski olefination to be extended to base-sensitive carbonyl substrates.[12] To explore the potential impact of fluorine substitution on the chemical properties of heteroaryl sulfones in Julia–Kocienski reactions, we carried out thermal stability (lifetime) analysis of different aryl sulfone carbanions.

Table 1. Thermal stability of the carbanions of sulfones **1**–**6**.

Sulfone	Recovery in DMF [%][a,b]	Recovery in THF [%][a,c]
1	41	0
2	73	62
3	90[d]	99[d]
4	5	0
5	14	0
6	26	<1

[a] Recovery was determined by ^{19}F NMR spectroscopy with trifluoromethylbenzene as an internal standard. [b] Conditions: sulfone (1 equiv) and LiHMDS (2.0 equiv) in DMF (0.5 mmol) at $-50\,^{\circ}C$ for 1 h; then CF_3COOH (excess) quench. [c] Sulfone (1 equiv) and LiHMDS (2.0 equiv) in THF (0.5 mmol) at $-78\,^{\circ}C$ for 1 h; then CF_3COOH (excess) quench. [d] Isolated yield.

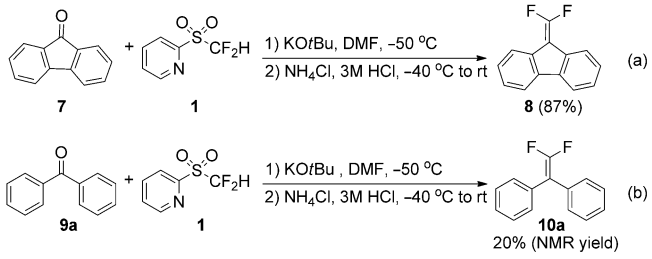
Compounds **2**–**6** (Figure 1) were prepared by the procedure reported for the synthesis of **1**.[10a] As shown in Table 1, sulfones **1**–**6** were treated with strong base (lithium hexamethyl disilazide (LiHMDS), 2.0 equiv) in both high-polarity solvent DMF ($-50\,^{\circ}C$, 1 h) and low-polarity solvent THF ($-78\,^{\circ}C$, 1 h) in the absence of electrophiles. Each reaction mixture was quenched with excess CF_3COOH after 1 h. For compounds **1**, **2**, and **4**–**6**, the amount of unreacted sulfone in the reaction mixture was monitored by ^{19}F NMR spectroscopy with trifluoromethylbenzene as an internal standard. In the case of sulfone **3**, the isolated yield was obtained after flash chromatography.

It was found that the carbanions of sulfones **1, 2**, and **4**–**6** in THF showed less thermal stability than in DMF, whereas the carbanion of sulfone **3** exhibited excellent thermal stability in both THF and DMF. The order of thermal stability of the difluoromethyl aryl sulfone carbanions ($\mathbf{1} > \mathbf{6} > \mathbf{5} \approx \mathbf{4}$) was in agreement with that of the corresponding nonfluorinated aryl sulfones.[9] There is a clear tendency of the thermal stability of the carbanions to decrease as the number of the fluorine substituents increases ($\mathbf{3} > \mathbf{2} > \mathbf{1}$). This is also in agreement with the "negative fluorine effect" that we found during our investigation of fluoroalkylations of epoxides.[15] In general, the difluoromethyl carbanions tend to decompose into difluorocarbene ($:CF_2$) by α elimination and the difluorocarbene species further degrades into fluoride ions or other products.[16]

The better performance of **1** in the *gem*-difluoroolefination reaction relative to **4** and **5** can be partly attributed to the higher thermal stability of its anion ($2\text{-}PySO_2CF_2^-$).[10] It should be noted that the highly unstable nature of the difluoromethyl carbanion makes conventional stepwise manipulation impossible and Barbier-type conditions[17] must be adopted. However, the Barbier-type process intrinsically prevents the efficient olefination of base-sensitive carbonyl compounds like aliphatic aldehydes.[11,12] With these considerations in mind, we next sought to tackle the problems encountered in the *gem*-difluoroolefination of diaryl ketones and aliphatic aldehydes.

gem-Difluoroolefination of diaryl ketones

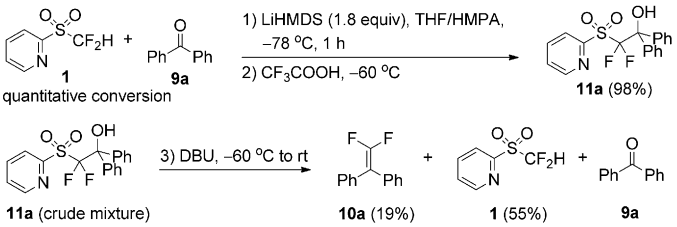
The direct synthesis of 2,2-diaryl-1,1-difluoroethenes from diaryl ketones possesses significant advantages in terms of convenience and efficiency relative to multistep cross-coupling reactions.[8e] In our previous report, the *gem*-difluoroolefination of fluorenone (**7**) was demonstrated; alkene **8** was produced in 87% yield (Scheme 1a).[10a] In sharp contrast, the reaction



Scheme 1. The *gem*-difluoroolefination of **7** and **9a**.

with benzophenone (**9a**) under identical conditions gave only 20% yield of the corresponding *gem*-difluoroalkene **10a** (Scheme 1b). The poor results seemed general for a broad range of diaryl ketones (for example, under identical conditions, **10b**, **10f**, and **10l** (see Table 3 below for structures) were obtained in 19, 3, and 23% yield, respectively).

To gain a better understanding of this phenomenon, we performed careful investigation of the reaction (Scheme 2). The reaction between **1** and **9a** was conducted in THF/HMPA (hexamethylphosphoramide) at −78 °C for 1 h. The mixture was quenched with trifluoroacetic acid (TFA) and alcohol **11a** was obtained in 98% yield (determined by ^{19}F NMR spectroscopy) with nearly quantitative conversion of **1** (Figure 2, spectrum **A** versus **B**). Treatment of the crude product **11a** with excess 1,8-diazabicycloundec-7-ene (DBU) at −60 °C, followed by gradual



Scheme 2. A stepwise mechanistic study of the *gem*-difluoroolefination of **9a**. All reactions were monitored by ^{19}F NMR spectroscopy with trifluoromethylbenzene as an internal standard.

warming of the reaction mixture to room temperature, directly afforded product **10a** in 19% yield (^{19}F NMR spectroscopy) without the observation of sulfinate salts. However, the regeneration of **1** (55%) was detected by ^{19}F NMR spectroscopy (Figure 2, spectrum **B** versus **C**).

On the basis of the generally accepted reaction mechanism of the Julia–Kocienski reaction, we speculated that the different performances of **7** and **9a** might originate from decomposition of the alcoholate intermediate **13** at elevated temperatures (Scheme 3).[11,12] In the case of **9a**, the two untied aryl groups would cause strong steric hindrance around the quaternary carbon center (O-substituted carbon atom) of intermediate **13** due to their large size and free rotation and, as a consequence, the competing decomposition process would outstrip the rearrangement process. On the contrary, when the two aryl groups are tied together, as in **7**, free rotation is minimized to some extent and the rigid geometry may even accelerate the rearrangement process by lowering the energy barrier. Overall, these results indicate that it is difficult to achieve efficient *gem*-difluoroolefination of normal diaryl ketones by the typical Julia–Kocienski reaction under basic conditions.

Considering that intermediate **13** can be captured at low temperatures by acid to afford the relatively stable alcohol **11**,

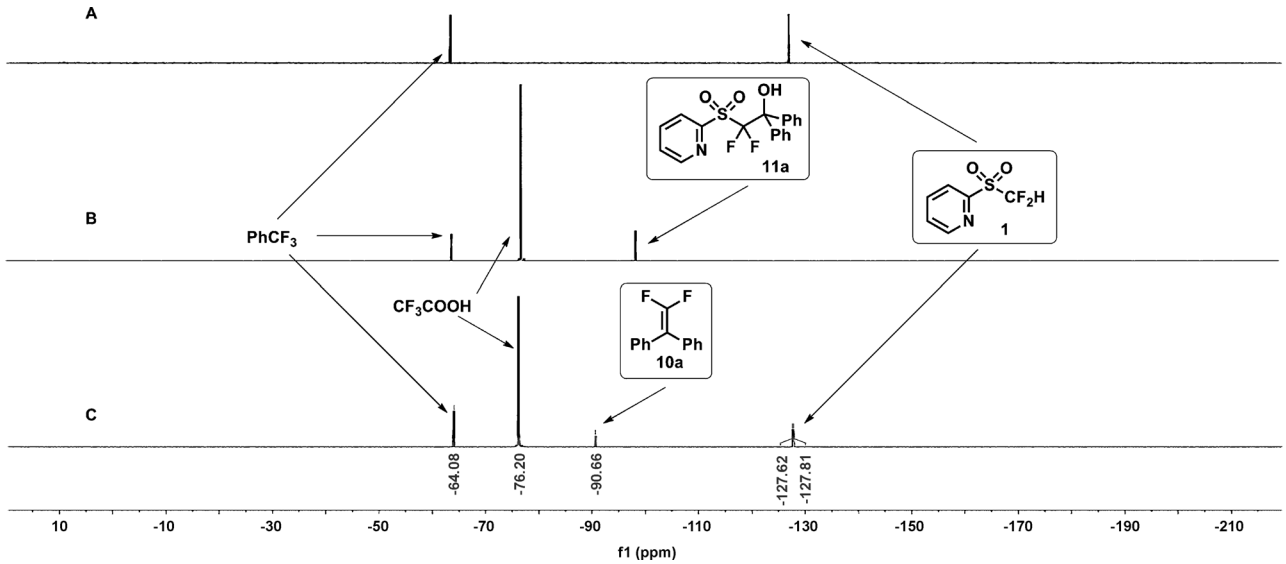
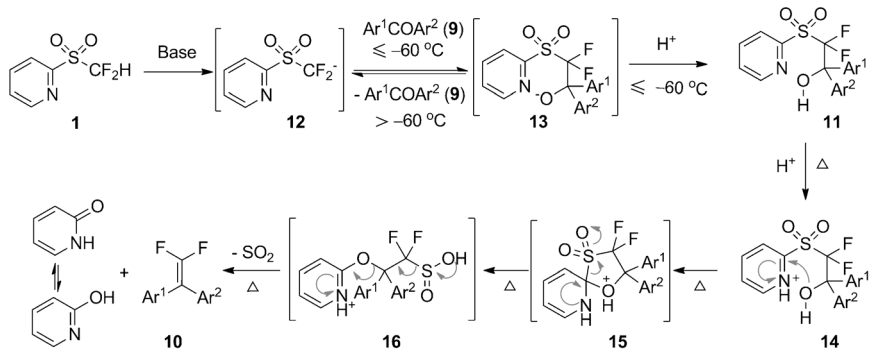
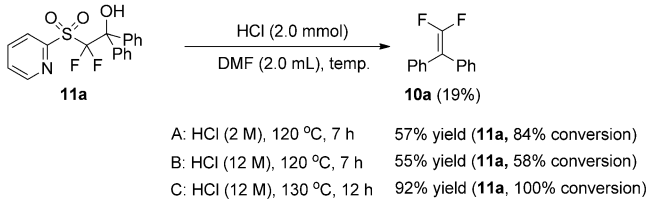


Figure 2. ^{19}F NMR spectroscopic study of the stepwise *gem*-difluoroolefination of **9a**.



Scheme 3. Mechanistic consideration of the *gem*-difluoroolefination of **9a**.

we speculated whether a Smiles rearrangement of **11** under acidic conditions could generate alkene **10** (Scheme 3). Although the base-promoted Smiles rearrangement of heteroaryl sulfones is well known, neither the acid-promoted Smiles rearrangement,[18] nor its application in Julia–Kocienski olefination reactions are widely reported. To test the feasibility of our hypothesis, we first tested the transformation of alcohol **11a** by using HCl as the promoter under different conditions (Scheme 4). This strategy was successful; both the high reaction temperatures and high acid concentration were beneficial to the transformation. When the reaction was performed with concentrated HCl (12 M) at 130 °C for 12 h, an excellent yield (92%) of **10a** was obtained, with full conversion of **11a**.

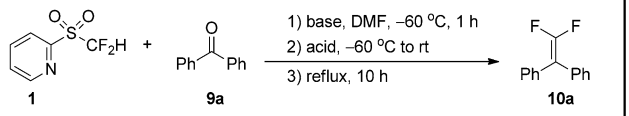


Scheme 4. Acid-promoted transformations of **11a** into **10a**.

Encouraged by these results, we next investigated the possibility of a one-pot synthesis of **10a** from **9a** (Table 2). The addition reaction between **1** and **9a** was conducted with our previously developed KO*t*Bu/DMF system[10a] at −60 °C for 1 h. Thereafter, the reaction mixture was quenched with excess HCl (12 M) at −60 °C. The reaction mixture was warmed to ambient temperature, then heated at reflux at 120–130 °C for 10 h to afford **10a** in 48% yield (Table 2, entry 1). When NaO*t*Bu was used instead of KO*t*Bu, difluoroalkene **10a** was obtained in a much higher yield (75%; Table 2, entry 2). CF_3COOH was found to be an inferior promoter for the olefination reaction relative to HCl (12 M) (Table 2, entry 3). LiHMDS was also screened and the addition of HMPA (10% *v/v*) as co-solvent in DMF with a 1:2 molar ratio of **1**/**9a** gave an improved result.[19] Although NaO*t*Bu showed better performance in the reaction than LiHMDS (Table 2, entries 2 and 7) on model substrate **9a**, the LiHMDS-mediated reaction conditions proved more general to a broad range of diaryl ketones, especially those with poor solubility in DMF at low temperatures (Table 2, entries 9–14).

With the optimized reaction conditions in hand (Table 2, entry 7), we next investigated the generality of the *gem*-difluoroolefination reaction with various diaryl ketones. The results shown in Table 3 indicated that, by the one-pot protocol, both symmetric and asymmetric diaryl ketones smoothly gave *gem*-difluoroalkenes in moderate-to-good yields. The reaction conditions tolerate electron-donating (phenyl (**9e**) and methoxy (**9f–h**) groups) and electron-withdrawing substituents (halogen (**9b–d, 9k–m**) and trifluoromethyl (**9i**) groups). It was reported that difluoroalkenes **10c** and **10f** were prepared in 56 and 45% overall yield, respectively, by a two-step palladium-catalyzed cross-coupling reaction from 2,2-difluoro-1-tributylstannylethenyl *p*-toluenesulfonate;[8e] by our method, **10c** and **10f** were obtained in 83 and 69% yield, respectively (Table 2, entries 3 and 9). *gem*-Difluoroalkene **10m**, which is difficult to prepare by palladium-catalyzed transformation due to the inevitable C–Br bond cleavage by Pd^0,[8f–h] was prepared in 77% yield from the readily available ketone **9m**. The reaction conditions also worked well with some heteroaryl ketones. For example, the reaction of phenyl 2-thienyl ketone (**9n**) gave alkene **10n** in 63% yield

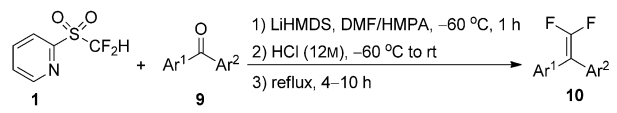
Table 2. Optimization of the reaction conditions for one-pot synthesis of **10a**.



Entry	Base	Ratio [**1**/**9a**/base]	Acid[b]	Yield of **10a** [%][a]
1	KO*t*Bu	1.0:2.0:1.8	HCl	48[c]
2	NaO*t*Bu	1.0:2.0:1.8	HCl	75
3	NaO*t*Bu	1.0:2.0:1.8	CF_3COOH	65
4	NaO*t*Bu	2.0:1.0:3.0	HCl	60
5	LiHMDS	1.0:1.2:2.0	HCl	25
6	LiHMDS	1.0:2.0:2.0	HCl	56
7[d]	LiHMDS	1.0:2.0:2.0	HCl	61
8	LiHMDS	2.0:1.0:3.0	HCl	59
9[e]	NaO*t*Bu	1.0:2.0:1.8	HCl	48[f]
10[e]	LiHMDS	1.0:2.0:2.0	HCl	67[f]
11[g]	NaO*t*Bu	1.0:2.0:1.8	HCl	51[h]
12[g]	LiHMDS	1.0:2.0:2.0	HCl	83[h]
13[i]	NaO*t*Bu	1.0:2.0:1.8	HCl	15[j]
14[i]	LiHMDS	1.0:2.0:2.0	HCl	77[j]

[a] Isolated yield. [b] $c = 12$ M. [c] Yield determined by ^{19}F NMR spectroscopy. [d] 10% *v/v* of HMPA was added as co-solvent. [e] **9b** served as substrate. [f] Yield of **10b**. [g] **9c** served as substrate. [h] Yield of **10c**. [i] **9l** served as substrate. [j] Yield of **10l**. See Table 3 (entries 2, 3, and 12) below for structures other than **9a** and **10a**.

Table 3. *gem*-Difluoroolefination of diaryl ketones **9** with reagent **1**.

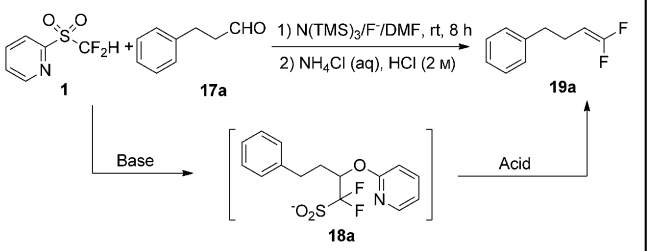


1 + **9** → **10**

Entry[a]	Ar^1	Ar^2	Yield [%][b]
1[c]	Ph	Ph, **9a**	**10a**, 75
2	Ph	*p*-F-C_6H_4, **9b**	**10b**, 67
3	Ph	*p*-Cl-C_6H_4, **9c**	**10c**, 83
4	Ph	*p*-Br-C_6H_4, **9d**	**10d**, 75
5	Ph	*p*-Ph-C_6H_4, **9e**	**10e**, 70
6	Ph	*p*-MeO-C_6H_4, **9f**	**10f**, 69
7	Ph	*m*-MeO-C_6H_4, **9g**	**10g**, 80
8	Ph	*o*-MeO-C_6H_4, **9h**	**10h**, 72
9	Ph	*p*-CF_3-C_6H_4, **9i**	**10i**, 67
10	*p*-MeO-C_6H_4	*p*-CF_3-C_6H_4, **9j**	**10j**, 64
11	*p*-F-C_6H_4	*p*-F–C_6H_4, **9k**	**10k**, 79
12	*p*-Cl-C_6H_4	*p*-Cl-C_6H_4, **9l**	**10l**, 77
13	*p*-Br-C_6H_4	*p*-Br-C_6H_4, **9m**	**10m**, 77
14	Ph	2-thiophenyl, **9n**	**10n**, 63
15	Ph	2-pyridyl, **9o**	**10o**, 0

[a] Reactions were conducted on 0.5 mmol scale with DMF (4 mL) and HMPA (0.4 mL) as co-solvents. [b] Isolated yield. [c] NaO*t*Bu was used (Table 2, entry 2).

Table 4. Survey of the reaction conditions for *gem*-difluoroolefination of aldehyde **17a** with **1**.



1 + **17a** → **19a** (via **18a**)

Entry	F^-	Ratio [**1**/**17a**/F^-/$N(TMS)_3$]	Yield of **18a** [%][a]
1	TMAF	1.0:1.5:2.0:2.0	78
2	TBAF	1.0:1.5:2.0:2.0	88
3	TBAT	1.0:1.5:2.0:2.0	63
4	CsF	1.0:1.5:2.0:2.0	95 (74)[b]
5	CsF	1.0:2.0:2.5:2.5	95
6	CsF	1.0:1.2:2.0:2.0	77
7	CsF	1.0:1.5:0.05:2.0	trace

[a] The yield of **18a** was determined by ^{19}F NMR spectroscopy. [b] The yield of **19a** determined by ^{19}F NMR spectroscopy is given in parentheses.

(Table 2, entry 14). Notably, even the *ortho*-methoxy-substituted diaryl ketone **9h** could be converted to **10h** in 72% isolated yield.

Compared to the reported methods for the synthesis of 2,2-diaryl-1,1-difluoroethenes **10**, this protocol possesses several advantages, such as one-pot operation, good functional-group tolerance, and high efficiency. Limitations mainly derive from the reaction with nitrogen-containing ketones, such as phenyl 2-pyridyl ketone (**9o**). In this case, the difluoro[(2-pyridyl)sulfonyl]methylated carbinol intermediate failed to undergo the Smiles rearrangement, which probably results from the decreased nucleophilicity of the OH group caused by protonation of the α-(hetero)aryl substituents.

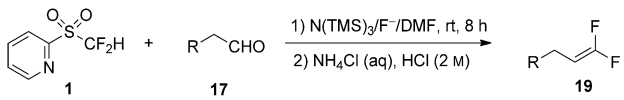
gem-Difluoroolefination of enolizable aldehydes

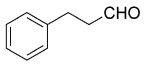
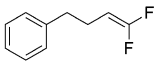
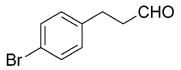
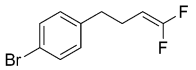
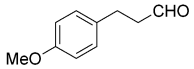
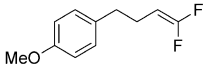
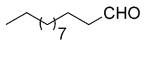
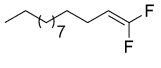
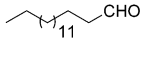
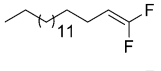
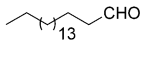
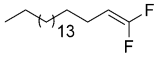
The direct carbonyl *gem*-difluoroolefination of aliphatic aldehydes remains another challenge in fluorine chemistry. Methods reported in the literature seldom employ aldehydes with long-chain alkyl groups as substrates because the α-hydrogen atom of the corresponding carbonyl groups are quite acidic and would easily result in self-condensation under strongly basic conditions.[20] Preliminary efforts to expand the **1**/KO*t*Bu/DMF reaction system to the enolizable aldehyde **17a** proved only moderately successful; product **19a** was obtained in only 40% yield, even when LiHMDS was used as the base. We hypothesized that the competing aldol condensation reaction might have a direct relationship with the concentration of the base; if the base concentration was controlled at a relatively low level by a slow-release strategy, the side reaction might be suppressed to some extent.

Inspired by Langlois' seminal work on the trifluoromethylation of ketones and formamides with CF_3H by using a substoichiometric amount of base generated in situ from tris(trimethylsilyl)amine ($N(TMS)_3$) and a F^- source,[21] we thought a similar strategy might be applicable to our reaction. The *gem*-difluoroolefination of aldehyde **17a** with **1** was examined first and the results are shown in Table 4. When Langlois' method (CsF (5 mol%); Table 4, entry 7) was used,[21a,b] only a trace amount of sulfinate **18a** was detected by ^{19}F NMR spectroscopy, accompanied by nearly quantitative recovery of the starting material **1**. The failure of this reaction can probably be ascribed to the weak nucleophilicity of sulfinate **18a**, which is unreactive toward $N(TMS)_3$ (and the regeneration of the amide anion is therefore stopped). When an excess of CsF was used, sulfinate **18a** was obtained in excellent yield (95%; Table 4, entry 4) and could be easily converted to difluoroalkene **19a** in 74% yield after acidic workup. Other fluoride sources, such as tetramethylammonium fluoride (TMAF), tetrabutylammonium fluoride (TBAF), and tetrabutylammonium triphenyldifluorosilicate (TBAT) were also examined, and it was found that CsF gave the best result (Table 4, entries 1–4). A brief optimization of the reaction conditions provided the appropriate molar ratio of **1**/**17a**/$N(TMS)_3$/CsF to be 1.0:1.5:2.0:2.0 (Table 4, entry 4).

With the optimal reaction conditions obtained, we examined the substrate scope of the *gem*-difluoroolefination of aliphatic aldehydes **17** with **1**. The results summarized in Table 5 show that *gem*-difluoroalkenes **19a–f** were obtained in moderate-to-good yields. Aldehyde **17b**, with a Br substituent, could be converted to alkene **19b** in 85% yield (Table 5, entry 2), which is potentially useful for further functionalization by metal-catalyzed cross-coupling.[22] For the long-chain alkyl aldehydes, such as undecanal (**17e**) and palmitaldehyde (**17f**), excess (2.5 equiv) $N(TMS)_3$ and CsF were required due to the poor solubility of these aldehydes in DMF (Table 5, entries 5 and 6).

Table 5. *gem*-Difluoroolefination of aliphatic aldehydes with **1**.



Entry	Substrate		Product		Yield[b] [%]
1[c]		**17a**		**19a**	60 (74)[d]
2		**17b**		**19b**	85
3		**17c**		**19c**	71
4		**17d**		**19d**	80
5[e]		**17e**		**19e**	66
6[e]		**17f**		**19f**	64

[a] Reactions were performed on 0.5 mmol scale in DMF (4 mL). [b] Isolated yield. [c] The low yield is partially due to the volatility of the product. [d] The yield of **19a** determined by ^{19}F NMR spectroscopy is given in parentheses. [e] CsF (2.5 equiv) and $N(TMS)_3$ (2.5 equiv) were used.

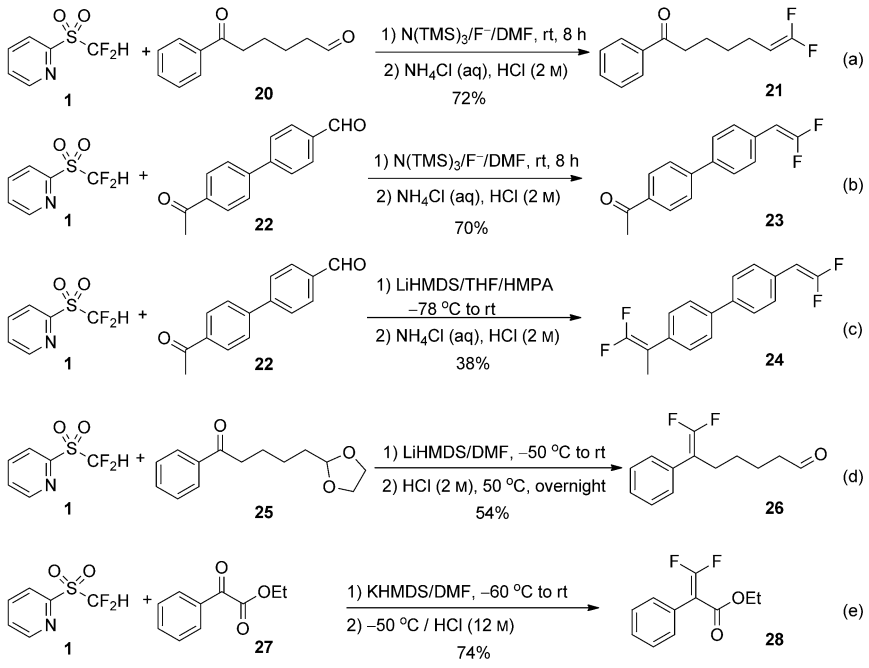
ined, the aromatic aldehyde was also exclusively transformed with high efficiency (70%; Scheme 5b). These two examples demonstrate that extra steps to protect the keto-carbonyl group of keto-aldehydes would be unnecessary if only the *gem*-difluoroolefination of the aldehyde is desired. In comparison, when a stoichiometric amount of base was used, both the ketone and aldehyde groups of **22** were *gem*-difluoroolefinated to give **24** in a single step (Scheme 5c). Protection of the aldehyde was required for selective *gem*-difluoroolefination of the ketone group. For example, reaction of keto-acetal **25** with **1**, followed by acid workup, afforded alkene **26** in 54% yield (Scheme 5d).[24]

β,β-Difluoroacrylates are potential precursors for compounds used in coatings, polymerization, special optical materials, etc.[25] We found that the reaction between keto-ester **27** and **1** with KHMDS as the base proceeded smoothly to give the difluorinated sulfinate intermediate in high yield; subsequent workup with concentrated HCl at −50 °C afforded the desired olefin **28** in 74% yield (Scheme 5e).

Chemoselective transformations of dicarbonyl compounds

During the investigation of the *gem*-difluoroolefination of enolizable aldehydes, we found that generation of the base in situ also worked well with aromatic aldehydes, however, ketones failed to undergo the transformation under identical reaction conditions. Taking into account that various ketones can be successfully *gem*-difluoroolefinated by using a stoichiometric amount of base, we decided to make a comparison of the chemoselectivity of the *gem*-difluoroolefination of dicarbonyl compounds by using different base systems (Scheme 5).[23]

The *gem*-difluoroolefination of substrates that contained both aldehyde and ketone functional groups were investigated; such substrates have not been demonstrated in previously reported deoxygenative *gem*-difluoroolefination reactions. When compound **20** was treated with **1** under the $N(TMS)_3$/CsF/DMF reaction conditions, the aldehyde group was selectively converted to the corresponding alkene **21** in 72% yield, and the ketone was left untouched (Scheme 5a). When an analogous substrate **22** was examined, the aromatic aldehyde was also exclusively transformed with high efficiency (70%; Scheme 5b). These two examples demonstrate that extra steps to protect the keto-carbonyl group of keto-aldehydes would be unnecessary if only the *gem*-difluoroolefination of the aldehyde is desired. In comparison, when a stoichiometric amount of base was used, both the ketone and aldehyde groups of **22** were *gem*-difluoroolefinated to give **24** in a single step (Scheme 5c). Protection of the aldehyde was required for selective *gem*-difluoroolefination of the ketone group. For example, reaction of keto-acetal **25** with **1**, followed by acid workup, afforded alkene **26** in 54% yield (Scheme 5d).[24]



Scheme 5. Chemoselective transformations of dicarbonyl compounds.

Conclusion

We have described an efficient carbonyl *gem*-difluoroolefination of diaryl ketones, enolizable aldehydes, and dicarbonyl compounds by using difluoromethyl 2-pyridyl sulfone as a robust deoxygenative *gem*-difluoroolefination reagent. We have demonstrated that the substitution of fluorine atoms reduces the thermal stability of corresponding carbanion and, as a consequence, all reactions need to be conducted under Barbier-type reaction conditions. Our investigation reveals that the *gem*-difluoroolefination of diaryl ketones under conventional basic Julia–Kocienski reaction conditions is difficult due to retro-aldol type decomposition of the key intermediate. However, a modified acid-promoted one-pot procedure can be used to successfully tackle this problem. So far as we know, these findings represent the first example of a Julia–Kocienski olefination performed under acidic conditions. Moreover, this reaction is also potentially applicable to the nonfluorinated olefination of sterically hindered carbonyl compounds.[26] The *gem*-difluoroolefination of aldehydes with a substoichiometric amount of base generated in situ not only tackles the problem of enolization of the aliphatic aldehydes, but also provides a synthetically useful method for the selective functionalization of multi-carbonyl compounds. The results reported in this article provide an intriguing example of fluorine chemistry research as a powerful tool to probe reaction mechanism, which can provide inspiration to solve existing synthetic problems.[27]

Experimental Section

General procedure for the synthesis of 2,2-diaryl-1,1-difluoroethenes 10 from diarylketone 9

Under N_2 atmosphere, HMPA (0.4 mL) was added into an oven-dried 20 mL Schlenk tube that contained **1** (96.6 mg, 0.5 mmol) and **9** (1.0 mmol) in DMF (4.0 mL) and a stirrer bar. The reaction mixture was cooled to −60 °C with a dry ice/acetone cold bath. A solution of $(TMS)_2NLi$ (1.0 M in THF, 1.0 mL, 1.0 mmol) was added dropwise over 5 min, and the reaction mixture was stirred at −60 °C for 1 h. An aqueous solution of HCl (2.0 M, 1.0 mL, 2.0 mmol) was quickly injected to quench the reaction. After being warmed to rt, another portion of HCl (12 M, 1.5 mL, 18 mmol) was added and the reaction mixture was heated at reflux (120–130 °C) for 4–10 h by using an oil bath between. When the reaction was complete (monitored by ^{19}F NMR spectroscopy), the mixture was poured into an ice/water mixture (50 mL) and extracted with diethyl ether (3×20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Difluoroalkene **10** was obtained after purification by column chromatography on silica gel (eluent = hexane).

General procedure for the *gem*-difluoroolefination of aliphatic aldehydes 17

Under N_2 atmosphere, DMF (2.0 mL) was added to an oven-dried 20 mL Schlenk tube that contained **1** (38.6 mg, 0.2 mmol), **2b–g** (0.3 mmol), $N(TMS)_3$ (93.4 mg, 0.4 mmol), and CsF (75.6 mg, 0.4 mmol). The mixture was stirred at rt until full conversion of **1** was detected by ^{19}F NMR spectroscopy. The mixture was cooled to 0 °C, then a saturated aqueous solution of NH_4Cl (1.0 mL) and aqueous HCl (2 M, 1.5 mL, 3.0 mmol) were added sequentially, and the reaction mixture was stirred for another 30 min at 50 °C until complete consumption of the sulfinate intermediate was determined by ^{19}F NMR spectroscopy. The mixture was poured into water (50 mL) and extracted with diethyl ether (3×20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Difluoroalkene **19** was obtained after purification by column chromatography on silica gel (eluent = hexane).

Acknowledgements

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Keywords: chemoselectivity · difluoromethyl 2-pyridyl sulfone · Julia–Kocienski reaction · olefination · rearrangements

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