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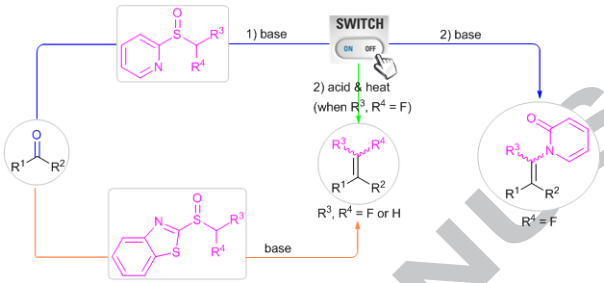

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Carbonyl Olefination of Diaryl Ketones with Heteroaryl Sulfoxides

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ABSTRACT

Heteroaryl sulfones are capable of converting the carbonyl functionalities to alkenyl motifs, which is well-known as Julia-Kocienski olefination reaction. However, their sulfoxide analogues have failed in such an olefination reaction for over twenty years. In this manuscript, we demonstrate that the heteroaryl sulfoxides-participated carbonyl olefination reaction can be realized under certain conditions. Furthermore, a novel defluorinative olefination of diaryl ketones has been achieved with 2-pyridyl sulfoxides.

The one-pot conversion of carbonyl compounds to alkenes with heteroaryl sulfones is well-documented as the Julia-Kocieski olefination,[1,2] which has found broad application in synthetic community due to its high efficacy, excellent functional group compatibility, and controllable stereoselectivity.[3,4] It is a typical cascade process that involves three sequential steps: 1) the nucleophilic addition of a sulfonyl carbanion to a carbonyl group, 2) the *ipso*-substitution of the addition adduct at the heteroaryl ring (also known as the Smiles rearrangement[5]), and 3) the fragmentation of the resulting sulfinate salt to give an alkene. A set of heteroaryl sulfones have been applied in this reaction, among which 1,3-benzothiazol-2-yl (BT), 1-phenyl-1H-tetrazol-5-yl (PT), 1-tert-butyl-1H-tetrazol-5-yl (TBT) sulfones are frequently used as the most effective reagents (Fig 1). Nevertheless, their sulfoxide analogues have never been successfully applied in such a transformation since its first report in 1991.[1a] A related report by Hild group demonstrated that the in-situ formed addition adduct of a lithiated methyl 2-pyridyl sulfoxide and benzaldehyde afforded disulfide rather than alkene.[6] Similar results were also observed in the reaction of β-hydroxysulfoxides of BT.[7] Both groups ascribed the failure of the olefination to the distinct reactivity of the sulfenate salt,[8] as compared to the sulfinate salt (in sulfones chemistry),[9,10] and it seems of special challenge to achieve the heteroaryl sulfoxides-participated carbonyl olefination.

We recently found that difluoromethyl 2-pyridyl sulfone (2-$PySO_2CF_2H$) was a more robust carbonyl *gem*-difluoroolefination reagent than the BT, TBT, and PT analogues, despite the fact that non-fluorinated 2-pyridyl sulfone derivatives were barely used in conventional Julia-Kocienski olefination reactions.[10,11] Mechanistic studies revealed that fluorine-substitution significantly altered the reactivity of corresponding heteroaryl sulfones.[10b,10c] This result prompted us to reassess the feasibility of fluorinated heteroaryl sulfoxides in the Julia-Kocienski type olefination reaction, and herein we disclose our results on this topic. It is found that the 2-pyridyl sulfoxide derivatives, as well as the BT sulfoxide, can indeed be used to accomplish carbonyl olefinations under certain conditions. We have also discovered a novel defluorinative olefination reaction of diaryl ketones with fluorinated 2-pyridyl sulfoxides.

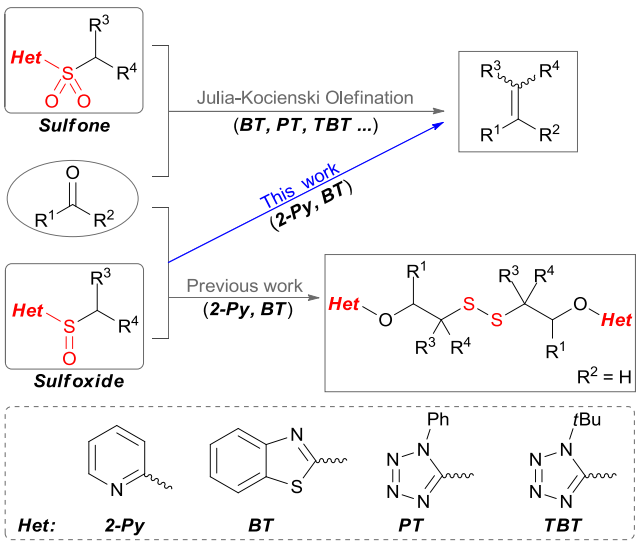

Fig 1. Current status of heteroaryl sulfones and sulfoxides participated reactions with carbonyl compounds.

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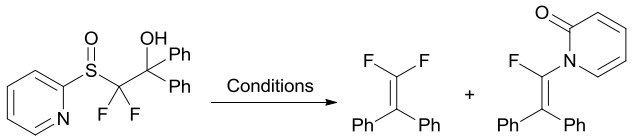
To examine the feasibility of each step in a typical Julia-Kocienski olefination reaction, a stepwise investigation was carried out. Since the nucleophilic addition reaction between 2-$PySOCF_2H$ (**1**) and benzophenone (**2a**) proceeded smoothly and gave **3a** in excellent yield,[12] We next focused on examining the *ipso*-substitution of **3a** under various conditions. When it was treated with DBU (Table 1, entry 2) in DMF at room temperature, to our surprise, neither the *gem*-difluoroolefin **4a** nor a disulfide (Figure 1) was obtained. Instead, compound **5a** was detected as the sole fluorine-containing product according to the ^{19}F NMR spectrum, and it was later confirmed as a monofluorinated alkene via X-ray crystallography analysis (see supporting information). The use of other bases, such as LiHMDS, KO*t*Bu, and K_2CO_3, also gave **5a** but in decreased yields (entry 3-6). When KOH was used, a 4% yield of **4a** was detected along with 49% yield of **5a** (entry 5). Further screening of the reaction conditions revealed no improvement on the yield of either **4a** or **5a**.

Table 1. The transformations of **3a** under different reaction conditions.[a]

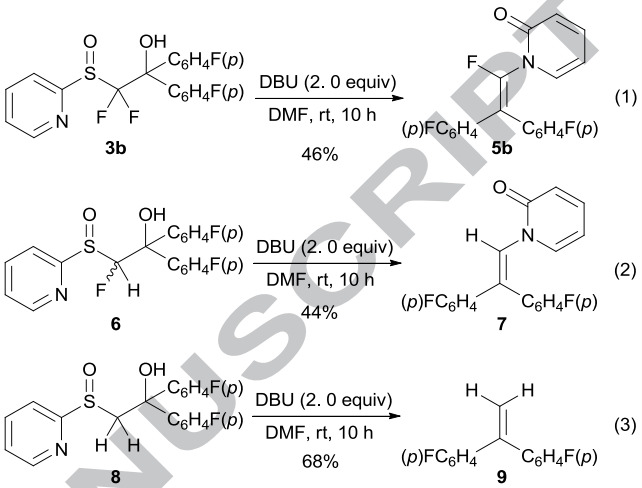


Entry	Additives (2.0 equiv)	T (°C)/t (h)	Solvent	Yield (%)[b] 4a	5a
1	Et_3N	rt/10 h	DMF	N.R	N.R
2	DBU	rt/10 h	DMF	0	58
3	LiHMDS	rt/10 h	DMF	0	38
4	KO*t*Bu	rt/10 h	DMF	0	25
5	KOH	rt/10 h	DMF	4	49
6	K_2CO_3	rt/10 h	DMF	0	17
7	DBU	rt/10 h	THF	0	39
8	—	90 °C/4 h	DMF	N.R	N.R
9	—	120 °C/4 h	DMF	28	0
10	—	150 °C/4 h	DMF	51	0
11	—	150 °C/4 h	Xylene	10	0
12	—	120 °C/4 h	DMSO	24	0
13	HCl (12M)	150 °C/4 h	DMF	24	0
14	CF_3CO_2H	150 °C/4 h	DMF	51	0
15	$ZnCl_2$	150 °C/4 h	DMF	56	0
16	$FeCl_3$	150 °C/4 h	DMF	62	0

[a] The reaction was conducted on 0.15 mmol scale in 1.0 mL of solvent. [b] ^{19}F NMR yield with $PhCF_3$ as an internal standard. LiHMDS = Lithium bis(trimethylsilyl)amide, DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene. N.R = no reaction.

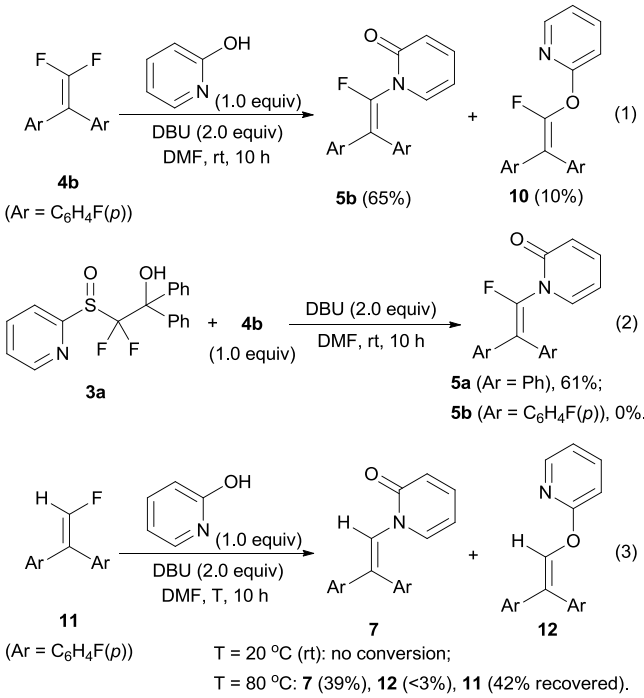
The transformations of **3a** under either neutral or acidic conditions were investigated. When **3a** was heated below 120 °C in different solvents, no conversion were observed. However, after being heated to 150 °C for 4 hours in DMF, *gem*-difluoroalkene **4a**, instead of monofluoroalkene **5a**, was obtained in 51% yield. Acid additives (either Brønsted acid or Lewis acid, entries 13-16) did not alter the reaction output but had subtle impact on the yields. The results obtained under neutral/acidic reaction conditions were in good accordance with that of the *gem*-difluoroolefination of diaryl ketones with 2-$PySO_2CF_2H$.[10b] However, the distinct results obtained under basic reaction conditions, the monofluorinated alkenes, seemed quite confusing.

To probe the fluorine-substitution effects on the reactivity of reagent **1**,[13] the following controlled experiments were carried out as depicted in Scheme 1. The difluoromethylated addition adduct **3b** gave **5b** in 46% yield under basic reaction conditions (eq 1). Its monofluorinated analogue **6** was treated with identical reaction conditions, and a nonfluorinated alkene **7** possessing similar skeleton was isolated in 44% yield (eq 2). Most intriguingly, their nonfluorinated analogue **8** also reacted smoothly, but to give a conventional Julia-Kocienski type olefination product **9** (68% yield, eq 3), rather than the 2-pyridinone substituted alkene. This was also in sharp contrast to Hild group's result that disulfide was obtained as major product.[6] Addition adduct of **1** and aldehydes were also investigated, but those reaction systems turned out quite complicated and gave neither an alkene nor a disulfide.



Scheme 1. The controlled experiments to evaluate the fluorine-substitution effects.

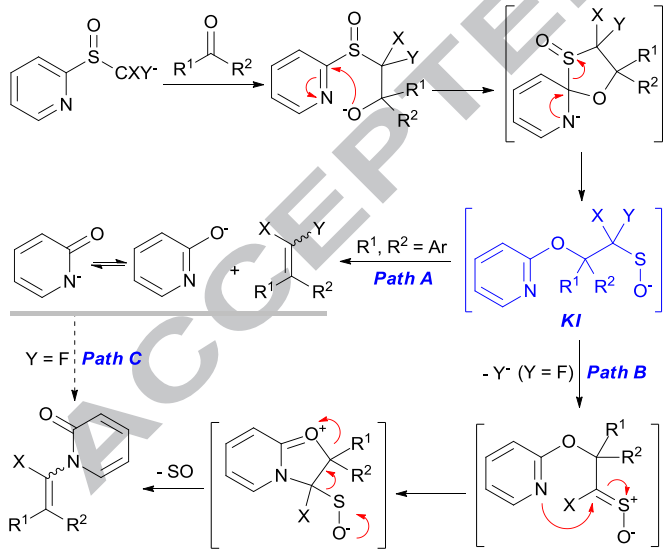
Considering that fluoroalkenes were electrophilic due to the inducing effect of fluorine(s) and the electron-repulsion effect between fluorine(s) and the double bond,[14] we speculated product **5** (or **7**) might result from the in-situ nucleophilic substitution of 2-pyridinone anion to **4** (or **11**) under basic reaction conditions,[15] both of which were the products of 2-$PySO_2CF_2H$-promoted Julia-Kocienski olefination.[10] To verify our hypothesis, *gem*-difluoroalkene **4b** (this compound was suitable for ^{19}F NMR spectrum monitoring) was treated with pyridine-2-ol (1.0 equiv) and DBU (2.0 equiv) in DMF at room temperature for 10 h. Monofluorinated alkene **5b** was indeed isolated in 65% yield along with its isomer **10** in 10% yield (Scheme 2, eq 1). However, product **10** was not observed in the base-promoted reactions of



Scheme 2. The controlled experiments for mechanistic study.

3b (Scheme 1, eq 1). Meanwhile, when 1.0 equivalent of **4b** was added to the reaction system of **3a**, no cross-substituted product **5b** was detected while **5a** was isolated in 61% yield (Scheme 2, eq 2). Accordingly, free 2-pyridinone anion seemed unlikely to exist in current reaction system. Fluoroalkene **11** was also subjected to the pyridine-2-ol/DBU/DMF reaction condition (Scheme 2, eq 3), but no conversion was observed at room temperature after 10 hours of standard reaction period. The reaction proceeded slowly even at elevated temperature, indicating that the in-situ nucleophilic substitution mechanism seemed unlikely.

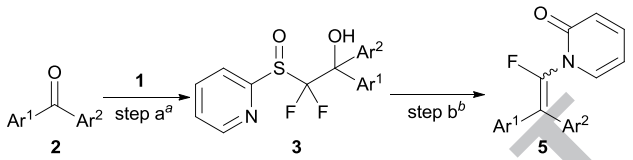
On the basis of the controlled experiments, potential reaction pathways of 2-pyridyl sulfoxide derivatives with carbonyl compounds are postulated in Scheme 3. The reactions are dominantly affected by the sulfenate salt intermediate (or sulfenic acids, ***KI***), which is highly unstable and its reactivity is extremely sensitive to proximal substituents.[8,16] The carbonyl olefination do take place under the acidic reaction conditons with fluorinated sulfoxides, and also under the basic reaction conditions with non-fluorinated sulfoxides, when diaryl ketone substrates are employed in both cases (**Path A**). For the fluorinated sulfoxides under basic reaction conditions, **Path B** is proposed. The formal oxidation state of sulphur in sulfenate is +2, and therefore it can function as a nucleophile to induce β-fluoride elimination.[17] The newly formed sulfine intermediate further undergoes intramolecular reaction with the pyridyl functionality,[18,19] followed by SO extrusion to give the final product. **Path C** is unlikely responsible for the defluorinative olefination because 1) the substitution isomer **10** is not observed under the base-promoted reaction with **3b**, 2) the free 2-pyridinone anions are not captured, and 3) the nucleophilic substitution of monofluorinated alkene with 2-pyridinone anions can hardly take place at ambient temperature.



Scheme 3. Plausible reaction pathways of 2-pyridyl sulfoxides with carbonyl compounds.

Finally, diaryl ketones with different substituents were examined under current base-promoted carbonyl defluorinative olefination reaction conditions. As depicted in Table 2, the monofluorinated olefination products were only obtained in moderate yield due to uncontrollable side reactions of the sulfenic intermediate.[8,16,17] A one-pot Julia-Kocienski type olefination procedure with substrate **2a** was also carried out, directly giving **5b** in 27% yield (entry 2). Electron-withdrawing substituents on the aryl rings would slightly decrease the yield of corresponding ketones (entry 8-9).

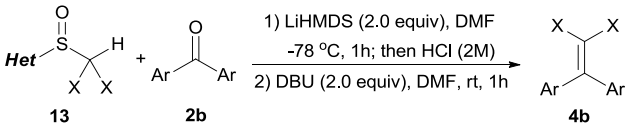
Table 2, Defluorinative olefination of diaryl ketones under basic conditions.



entry	substrates	yield (step a, %)	yield (step b, %)
1	**2a** [Ar^1 = Ar^2 = Ph]	**3a** (90)	**5a** (52)
2	**2a** [Ar^1 = Ar^2 = Ph]		**5a** (27)[c]
3	**2b** [Ar^1 = Ar^2 = $C_6H_4F(p)$]	**3b** (90)	**5b** (46)
4	**2c** [Ar^1 = Ar^2 = $C_6H_4Cl(p)$]	**3c** (84)	**5c** (45)
5	**2d** [Ar^1 = Ar^2 = $C_6H_4Br(p)$]	**3d** (98)	**5d** (45)
6	**2e** [Ar^1 = Ph, Ar^2 = $C_6H_4Ph(p)$]	**3e** (95)[d]	**5e** (55)[e,l]
7	**2f** [Ar^1 = Ph, Ar^2 = $C_6H_4OMe(p)$]	**3f** (84)[f]	**5f** (70)[g,l]
8	**2g** [Ar^1 = Ph, Ar^2 = $C_6H_4OMe(m)$]	**3g** (74)[h]	**5g** (57)[i,l]
9	**2h** [Ar^1 = Ph, Ar^2 = $C_6H_4CF_3(p)$]	**3h** (80)[j]	**5h** (47)[k,l]

[a] **1** (3.0 mmol), **2** (2.0 equiv), KHMDS (2.0 equiv), DME (20 mL), -70 °C, 1 h; then HCl (2M, 1 mL), -70 °C to rt. [b] **3** (1.0 mmol), DBU (2.0 equiv), DMF (1.0 mL), rt, 10 h. [c] **1** (0.5 mmol), LiHMDS (2.0 equiv), DMF (4.0 mL), -50 °C to rt. [d] 58:42 dr. [e] 68:32 (*Z*/*E* mixture). [f] 50:50 dr. [g] 96:4 (*Z*/*E* mixture). [h] 52:48 dr. [i] 48:52 (*Z*/*E* mixture). [j] 48:52 dr. [k] 76:24 (*Z*/*E* mixture). [l] the absolute configuration was not determined.

Heteroaryl sulfoxides of BT and PT were also examined. The nucleophilic addition adduct of methyl 1,3-benzothiazol-2-yl sulfoxide and **2b** afforded olefin **4b** in 60% yield with the treatment of 2.0 equivalents of DBU in DMF, indicating a similar substrates-effect as compared to the reported results.[7] But its difluorinated analogue failed to give the addition product with diaryl ketone under current and modified reaction conditions, so as it was with the PT analogues (Scheme 4).



* *Het* = *BT*, X = H, 82% yield (*step 1*), 60% yield (*step 2*); X = F, failed in *step 1*;
* *Het* = *PT*, X = H, F, failed in *step 1*.

Scheme 4. The generality of heteroaryl sulfoxides in carbonyl olefination reactions.

In summary, we have evaluated the feasibility of heteroaryl sulfoxides (especially 2-pyridyl sulfoxides) in the Julia-Kocienski type olefination reactions. Our results disclose that heteroaryl sulfoxides react with carbonyl compounds in tunable pathways as compared to that of the sulfone analogues. Carbonyl olefination can indeed be realized with both 2-pyridyl (2-Py) sulfoxides and 1,3-benzothiazol-2-yl (BT) sulfoxide under certain reaction conditions for the first time. Meanwhile, fluorine-substitution can alter their reactivity of 2-pyridyl sulfoxides to give a novel defluorinative olefination of diaryl ketones. Results in this manuscript also provide helpful insights in understanding the intrinsic difference of reactivity between sulfones and sulfoxides.

Acknowledgments

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Supplementary Material

Electronic Supplementary Information (ESI) available: Experimental details, characterization and copies of ^{1}H, ^{19}F NMR, ^{13}C NMR spectra and CCDC 1041858..

- The first example of sulfoxide-mediated one-pot carbonyl olefination reaction is described.
- De-fluorinative olefination was observed.
- Add new mechanistic insights into the Julia-Kocienski olefination reaction.