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Metal-Free Approach for the Synthesis of *N*-Aryl Sulfoximines via Aryne Intermediate

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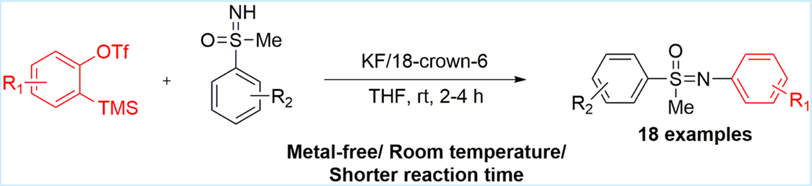
Supporting Information

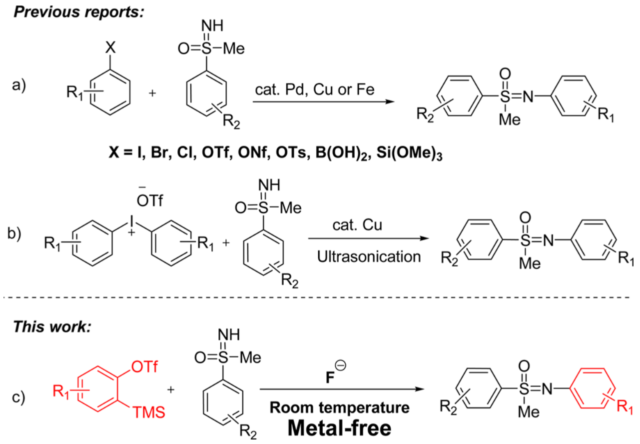


ABSTRACT: A metal-free and operationally simple *N*-arylation of *NH*-sulfoximines with aryne precursors is reported. Transition metal-free reaction conditions and shorter reaction times are the highlights of the present method. The mild optimized condition was also found to be suitable with enantiopure substrates.

Sulfoximines are a versatile class of compounds in organic chemistry because of their applicability as chiral auxiliaries,[1] as ligands in asymmetric catalysis,[2] and as building blocks in pseudopeptides.[3] In the current decade, sulfoximines have also gained significant attention in medicinal chemistry.[4] Considering their importance, extensive work has been done regarding the synthesis and functionalization of sulfoximines, but new mild methods are still highly desired. Regarding the functionalization of sulfoximines, *N*-arylated sulfoximines have been greatly explored since the pioneering work of Bolm in 1998 via transition-metal catalysis.[5] After this, several metal-catalyzed (Pd, Cu, Ni, and Fe) approaches have been developed using various donors such as aryl halides, aryl triflates, nonaflates, tosylates, arylboronic acids, and diaryliodonium salts (Scheme 1, approaches a and b).[6,7]

In the present decade, metal-free and mild methods involving readily available starting materials are the choice. In this context, arynes offer an attractive alternative and, due to their distinct electronic properties, they are recognized as good substrates for metal-free organic transformations.[8] To this end, we have recently developed a metal-free method for the synthesis of variety of sulfones through an aryne intermediate.[9] Considering the electronic properties of arynes (electrophilic) and sulfoximines (nucleophilic), we envisioned that the arylation of *NH*-sulfoximines could be achieved with arynes under metal-free conditions, which to the best of our knowledge, has not yet been explored. Herein, we report the first metal-free method for the synthesis of *N*-aryl sulfoximines by the reaction between arynes and *NH*-sulfoximines at room temperature (Scheme 1, approach c).

Scheme 1. Previous and Present Approaches for the Synthesis of *N*-Aryl Sulfoximines



We commenced our investigation using readily available 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1a** and *S*,*S*-methylphenylsulfoximine **2a** as the model substrates (Table 1).

When the reaction was performed with CsF as the fluoride source (to generate benzyne) at room temperature in acetonitrile, the desired product **3a** was obtained in a modest yield of 38% (Table 1, entry 1). In the next reaction, an increase in the quantity of CsF had a minor effect on the product yield (Table 1, entry 2). Other fluoride sources such as KF/18-crown-6,[10] TBAF,[11] and TBAT[12] were also tried. Among the fluoride sources used (Table 1, entries 3−5) KF/18-crown-6 furnished the desired product **3a** in 50% yield. To

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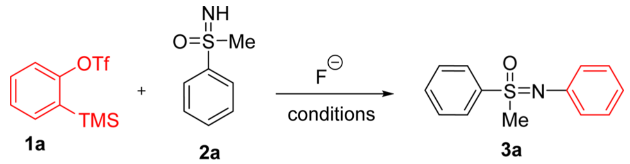
our delight, a significant increase in the yield up to 72% of **3a** was observed when THF was used as the solvent (Table 1, entry 6). Further, the use of dioxane as the solvent did not show any improvement (Table 1, entry 7). Using THF as the solvent, other fluoride sources such as TBAF, CsF, and TBAT also showed no advantage (Table 1, entries 8−10). Further, a decrease in the amount of KF/18-crown-6 also reduced the yield of **3a** (Table 1, entry 11).

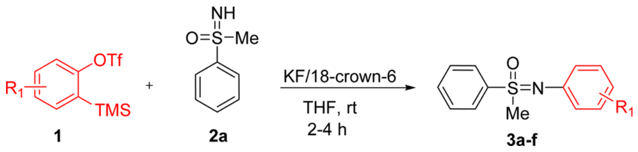
Table 1. Optimization Studies[a]

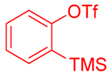
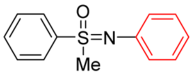
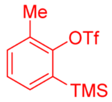
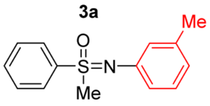
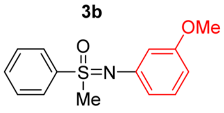
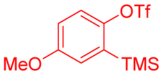
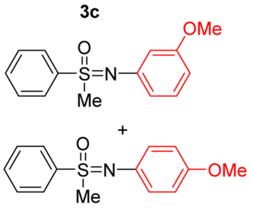
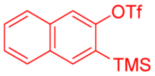
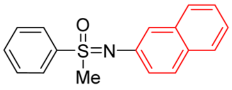
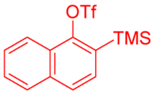
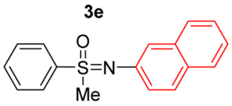
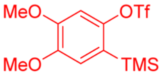
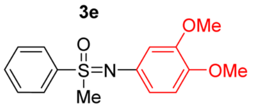


entry	F⁻ source	equiv	solvent	yield (%)[b]
1	CsF	3.0	CH$_3$CN	38
2	CsF	4.0	CH$_3$CN	40
3	TBAF[c]	2.0	CH$_3$CN	42
4	TBAT[d]	2.0	CH$_3$CN	40
5	KF/18-crown-6	2.5	CH$_3$CN	50
6	KF/18-crown-6	2.5	THF	72
7	KF/18-crown-6	2.5	dioxane	58
8	TBAF	1.5	THF	60
9	CsF	3.0	THF	25
10	TBAT	2.0	THF	57
11	KF/18-crown-6	2.0	THF	65

[a] Reaction conditions (unless otherwise stated): **1a** (0.2 mmol, 1.0 equiv), **2a** (0.2 mmol, 1.0 equiv), F⁻ source, solvent 2 mL, under N$_2$, at room temperature for 4 h. [b] Isolated yield. [c] Tetrabutylammonium-fluoride. [d] Tetrabutylammonium difluorotriphenylsilicate.

Table 2. Substrate Scope of Various Aryne Precursors[a]



entry	aryne precursor	product	yield (%)[b]
1	 **1a**	 **3a**	72
2	 **1b**	 **3b**	63
3	 **1c**	 **3c**	65
4	 **1d**	 **3c/3d = 1:1.5**	63
5	 **1e**	 **3e**	45
6	 **1f**	 **3e**	42
7	 **1g**	 **3f**	58

[a] Reaction conditions (unless otherwise stated): **1** (0.2 mmol, 1.0 equiv), **2a** (0.2 mmol, 1.0 equiv), KF/18-crown-6 (0.5 mmol, 2.5 equiv), THF 2 mL, under N$_2$, at room temperature for 2−4 h. [b] Isolated yield.

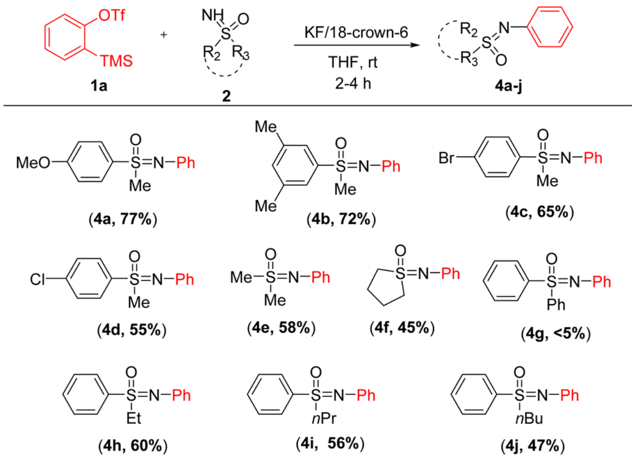
With the optimized reaction conditions in hand, we examined the substrate scope with various aryne precursors, and the results are depicted in Table 2. Aryne precursors **1b** and **1c** (having substitutions *ortho* to "yne" bond) when tried, sulfoximine **2a** attacked at the remote site exclusively (*meta* to substitution) and produced corresponding *N*-aryl sulfoximines **3b** and **3c** in 63% and 65% yields, respectively. However, in the case of aryne precursor **1d** (substitution *meta* to "yne" bond), nucleophile **2a** reacted at two possible sites (*meta* and *para*) and produced a mixture of inseparable regioisomers **3c**/**3d** in a ratio of 1:1.5 with an overall yield of 63%. Further, naphthyl based aryne precursors **1e** and **1f** furnished only the 2-substituted regioisomer **3e** in moderate yields, 45% and 42%, respectively. Symmetrical and highly electron-rich aryne precursor **1g** also proceeded well and afforded **3f** in a yield of 58%.

Next, the reactivity of different sulfoximines was investigated, and the results are summarized in Scheme 2. An array of sulfoximines having different electon-donating (OMe and Me) as well as electron-withdrawing substituents (Br and Cl) were tried. These underwent the desired transformation smoothly and furnished the corresponding *N*-aryl sulfoximines **4a−d** in good to high yields of 77%, 72%, 65%, and 55%, respectively. Notably, *S*,*S*-dimethylsulfoximine was also found to be a good substrate under optimized conditions, affording the corresponding product **4e** in a yield of 58%. Further, *S*,*S*-tetramethylenesulfoximine also furnished the expected product **4f** in a moderate yield of 45%. Unfortunately, when *S*,*S*-diphenylsulfoximine was used under standard conditions, the desired product **4g** was obtained in a yield of less than 5%. Interestingly, sulfoximines having different aliphatic chain substituents at S-center also proceeded well under the optimized conditions and afforded the corresponding products **4h−j** in moderate to good yields of 47−60%.

To determine the tolerance of the present optimized conditions toward chiral substrates, 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1a** was treated with enantiopure sulfoximine, (*S*)-(+)-*S*-methyl-*S*-phenylsulfoximine. The corresponding product (*S*)-(+)-**3a** was observed in a yield of 70% with retention of configuration (Scheme 3), suggesting that the chiral substrates are also tolerable under present reaction conditions.

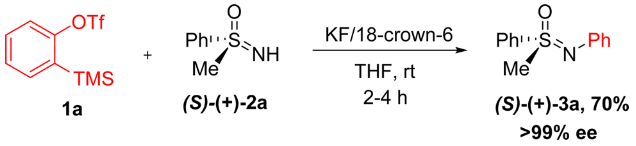
In conclusion, we have demonstrated a simple and metal-free method for the synthesis of *N*-aryl sulfoximines via an aryne intermediate. The present method enables very mild conditions and requires shorter reaction times when compared with previous reports.

Scheme 2. Substrate Scope of Various Sulfoximines[a]



[a]Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2** (0.2 mmol, 1.0 equiv), KF/18-crown-6 (0.5 mmol, 2.5 equiv), THF 2 mL, under N_2, at room temperature for 2–4 h.

Scheme 3. Reaction with Enantiopure Sulfoximine[a]



[a]Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2a** (0.2 mmol, 1.0 equiv), KF/18-crown-6 (0.5 mmol, 2.5 equiv), THF 2 mL, under N_2, at room temperature for 2–4 h.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02804.

General procedures regarding the synthesis of sulfoximines and *N*-aryl sulfoximines along with ^{1}H and ^{13}C spectra of all synthesized compounds (PDF)

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Notes

The authors declare no competing financial interest.

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