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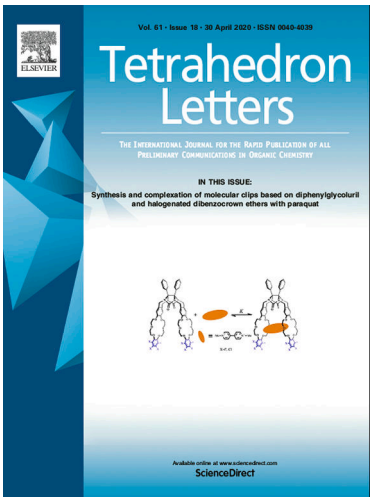

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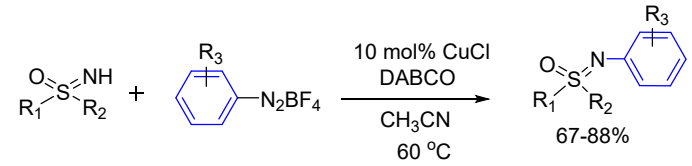

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ABSTRACT

N-Arylation of sulfoximines with aryldiazonium tetrafluoroborates is demonstrated in the presence of copper chloride and DABCO. A wide range of aryl and alkyl sufoximines are participated in the coupling reaction with different aryldiazonim salts bearing electron donating and withdrawing groups and provided the desired products in 67-88% yields. The reaction proceeds through a radical mechanism.

Introduction

Sulfoximines are aza-analogues of sulfones that have been considered as an important pharmacophore in drug discovery (Figure 1).[1] Currently few sulfoximine compounds are in the different phases of clinical trials for the treatment of different diseases including cancer.[1b] On the other hand, sulfoximines were also explored as building blocks, chiral ligands and auxiliaries, organocatalysts, directing groups for CH-activation, etc. in organic synthesis.[2]

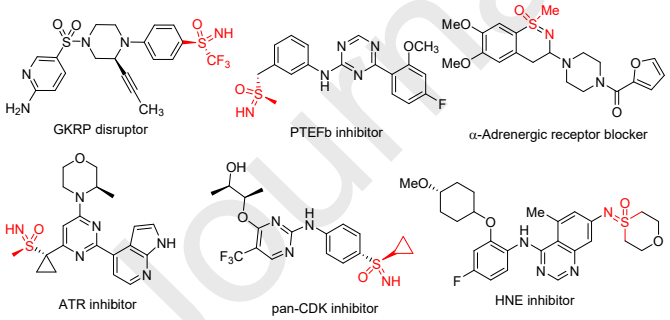
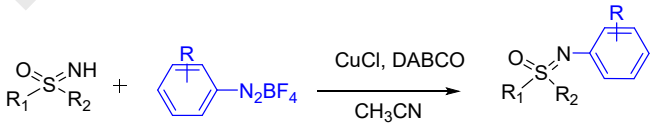


Figure 1: Structures of Some biologically important sulfoximines.

From a synthetic as well as biological perspectives, *N*-functionalization of sulfoximine received significant interest over the decades.[1-3] In this context, *N*-arylation of sulfoximine has been reported with aryl halides, arylboronic acids, diaryliodonium salts, aryl sulfonates, aryl siloxanes, etc., in the presence of metal catalysts.[4] However, most of these developed methods require harsh reaction conditions, expensive ligands, longer reaction time, etc. We have recently reported a copper catalysed *N*-arylation of sulfoximines with different arylboronic acids.[5] Our reported method provides clean access to various *N*-aryl sulfoximines, including a sterically hindered *N*-aryl sulfoximines as well as biologicaly relavent *N*-aryl L-methionine sulfoximines, in good to excellent yields. However, arylboronic acids are relatively expensive, hence the development of alternative and complementary method, is of great interest.



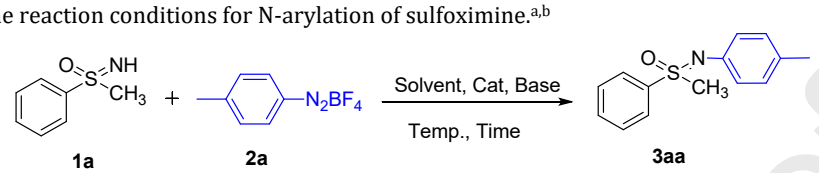
Scheme 1: N-Arylation of sulfoximines using aryldiazonium tetrafluoroborates.

Aryldiazonium salts are highly useful aryl donors and that have been utilized extensively in many palladium catalyzed cross-coupling reactions in the place of aryl halides and arylboronic acids.[6] In this context, we have recently reported a palladium catalyzed aryldizonium salts mediated stereo-controlled synthesis of *C*-aryl glycosides from glycals at room temperature.[7] Besides C-C coupling reactions, aryldizonium salts were also explored in many C-S bond forming reactions.[8] In contrast, their applications in C-N bond forming reactions are underexplored.[9] In the last few years, our research group has been focused on the chemistry of sulfoximines and explored various *N*-functionalization reactions, including *N*-arylation,[5] alkylation,[10] acylation[11] and phosphorylation[12] using copper catalysts. In continuation of these works, here we report a copper catalyzed *N*-arylation of sulfoximines using aryldiazonium salts under mild conditions (Scheme 1).

At the outset, the optimization of the reaction condition was investigated using (*S,S*)-methylphenyl sulfoximine (**1a**) and 4-methylbenzenediazonium tetrafluoroborate (**2a**) as model substrates. Initially, the reaction was tested in different solvents including methanol, dimethyl sulfoxide (DMSO) and acetonitrile at

additives (Table 1, entry 1). However, no reaction was observed. Hence, the optimization was performed with different copper (I) and copper (II) catalysts in acetonitrile (Table 1, entries 2-7). Among the different copper salts, CuCl showed better activity by providing the desired product **3aa** in 36% yield. Further, the reaction was carried out with different bases including potassium carbonate, cesium carbonate, pyridine, *N,N* dimethylaminopyridine (DMAP), triethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,4-diazabicyclo[2.2.2]octane (DABCO) in the presence of 10 mol% CuCl (Table 1, entry 8 to 14). Among these bases, DABCO was found to be superior that provides **3aa** in 51% yield in 10 hours. Further, the reaction was attempted in elevated temperatures, i.e. 45-75 °C in acetonitrile in the presence of CuCl and DABCO (Table 1, entry 15 to 17). To our delight, the desired product **3aa** was obtained in 88% yield at 60 °C within 6 hours. Relatively low yields of **3aa** were observed at 45 °C and 75 °C.

Table 1: Optimization of the reaction conditions for N-arylation of sulfoximine.[a,b]



1a 2a 3aa

Entry	Solvent	Catalyst (10 mol%)	Base (1.0 eq.)	Temp. (°C)	Time (h)	Yield[b] (%)
1	MeOH/DMSO/ ACN	-	-	30	10	ND
2	Acetonitrile	CuOAc	-	30	10	13
3	Acetonitrile	CuBr	-	30	10	10
4	Acetonitrile	CuCl	-	30	10	36
5	Acetonitrile	CuI	-	30	10	17
6	Acetonitrile	$CuCl_2$	-	30	10	~10
7	Acetonitrile	$Cu(OAc)_2$	-	30	10	~10
8	Acetonitrile	CuCl	K_2CO_3	30	10	40
9	Acetonitrile	CuCl	Cs_2CO_3	30	10	47
10	Acetonitrile	CuCl	Pyridine	30	10	41
11	Acetonitrile	CuCl	DMAP	30	10	45
12	Acetonitrile	CuCl	Et_3N	30	10	43
13	Acetonitrile	CuCl	DBU	30	10	40
14	Acetonitrile	CuCl	DABCO	30	10	51
15	Acetonitrile	CuCl	DABCO	45	6	63
16	Acetonitrile	CuCl	DABCO	60	6	88
17	Acetonitrile	CuCl	DABCO	75	6	81
18	Water	CuCl	DABCO	60	6	ND
19	MeOH	CuCl	DABCO	60	6	30
20	DMSO	CuCl	DABCO	60	6	69
21	Dioxane	CuCl	DABCO	60	6	72
22	Acetonitrile	$Ni(OAc)_2$/$Pd(OAc)_2$ /$PdCl_2$	DABCO	60	6	ND

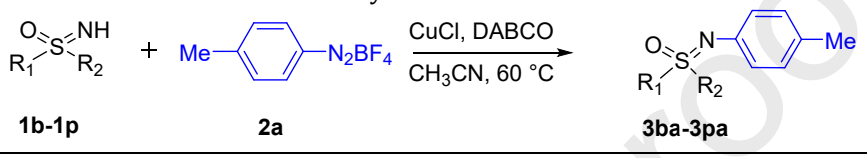
[a]S,S-methylphenyl sulfoximine (50 mg, 0.32 mmol), 4-methylbenzenediazonium tetrafluoroborate (99 mg, 0.48 mmol) and solvent (2 mL). [b]Isolated yield.

Furthermore, the optimization of the reaction condition was investigated in different solvents in the presence of 10 mol% CuCl and DABCO. However, acetonitrile remained the best out of the solvents used in this study. Moreover, other metal catalysts including $Ni(OAc)_2$, $Pd(OAc)_2$ and $PdCl_2$ were failed to yield the desired

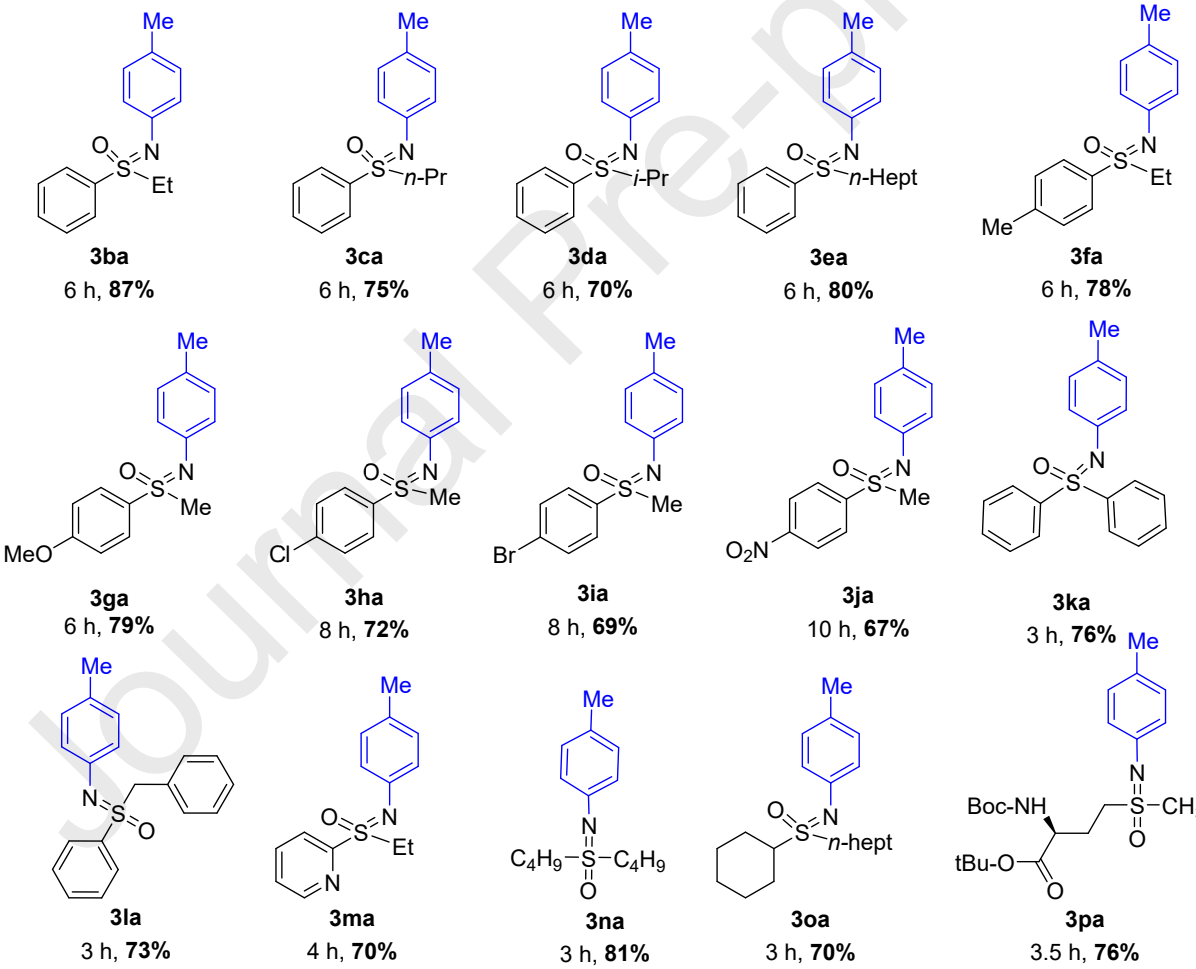
product (Table 1, entry 22). Overall, the optimization study indicated that *N*-arylation of sulfoximine with aryl diazonium salts can be achieved efficiently using 10% CuCl in the presence of DABCO in acetonitrile at 60 °C.

Having developed optimized condition, we have investigated the scope of different of sulfoximines in C-N bond forming reactions with 4-methylbenzenediazonium tetrafluoroborate (**2a**) and summarized in Table 2. (*S,S*)-alkyl-Phenyl sulfoximines bearing different length of side alkyl chains, including sterically hindered *iso*-propyl, provided the corresponding *N*-arylated products in good yields under optimized condition (Table 2, **3ba–3ea**). On the other hand, (*S,S*)-alkyl-phenyl sulfoximines bearing different electron donating and withdrawing substituents on the aryl ring underwent *N*-arylation with 67–79% yields (Table 2, **3fa–3ja**). It was noted that the electron withdrawing group functionalized phenyl sulfoximines (e.g. *p*-NO_2, *p*-Br, *p*-Cl, etc.) required slightly longer time for the *N*-arylation when compared with electron donating group substituted sulfoximines (e.g. *p*-Me and *p*-OMe). Likewise (*S,S*)-aryl-aryl, aryl-benzyl and heteroaryl-alkyl sulfoximines were successfully arylated with 70-76% yields (Table 2, **3ka–3ma**). Furthermore, to our delight, *N*-arylation of (*S,S*)-dialkyl sulfoximines as well as biologically relevant L-methionine sulfoximine were also successfully accomplished in 70-81% yields, which demonstrates the broad applicability of the present method (Table 2, **3na–3pa**).

Table 2: *N*-Arylation of various sulfoximines with 4-methylbenzenediazonium tetrafluoroborate.[a,b]



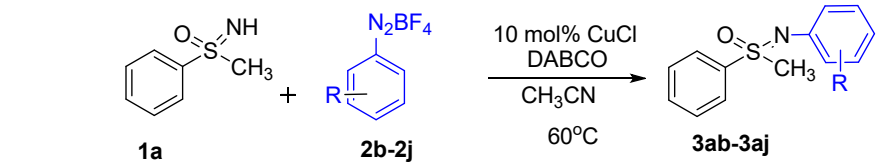
1b-1p **2a** **3ba-3pa**



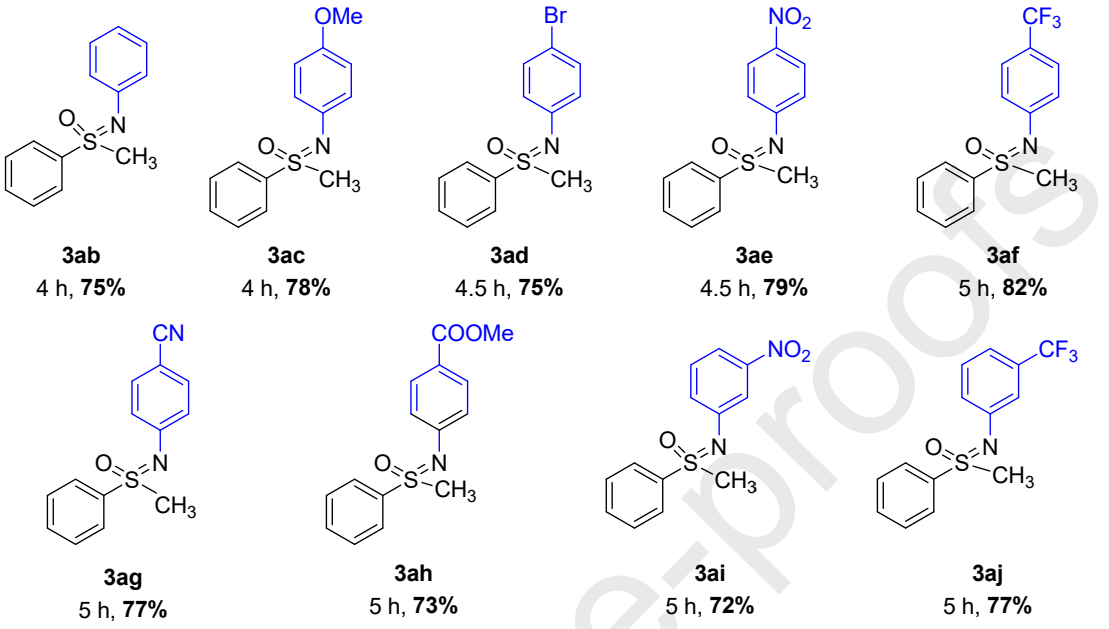
[a]Sulfoximine (0.5 mmol), 4-methylbenzenediazonium tetrafluoroborate (1.5 eq.), DABCO (1 eq.) and acetonitrile (5 mL). [b] Isolated yield.

Encouraged, we further investigated the scope of different readily accessible aryldiazonium tetrafloroborate salts in the arylation reaction with *S,S*-methylphenyl sulfoximine (**1a**) and summarized in Table 3. To our delight, aryl diazonium salts bearing electron donating and withdrawing groups participated efficiently in the C-N forming reactions and provided the desired *N*-arylated sulfoximines in 72-82% yields (Table 3, **3ab-3aj**).

Table 3: *N*-Arylation of (*S,S)*-phenylmethyl sulfoximine with various diazonium salts.[a,b]

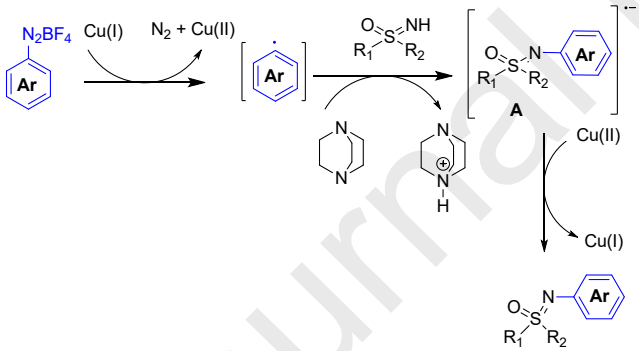


1a 2b-2j 3ab-3aj



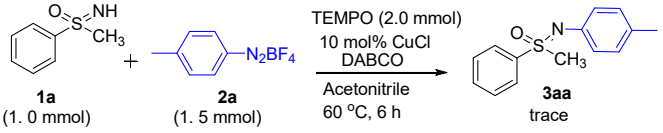
3ab 4 h, **75%**
3ac 4 h, **78%**
3ad 4.5 h, **75%**
3ae 4.5 h, **79%**
3af 5 h, **82%**
3ag 5 h, **77%**
3ah 5 h, **73%**
3ai 5 h, **72%**
3aj 5 h, **77%**

[a](*S,S)*-Phenylmethyl sulfoximine (0.5 mmol, 1eq), aryldiazonium tetrafloroborate (1.5 eq.) DABCO (1 eq.) and acetonitrile (5 mL). [b]Isolated yield.



Scheme 2. Plausible mechanism for the *N*-arylation of sulfoximines.

A plausible mechanism for the imino-arylation of sulfoximine is shown in Scheme 2.[9] In the first step, aryl radical is generated from arenediazonium salt in the presence of Cu(I) *via* single electron transfer. During this process, Cu(I) turns into Cu(II). Simultaneously, sulfoximine reacts with aryl radical in the presence of DABCO and generates radical anion intermediate **A.** The intermediate **A** converted into product in the presence of copper (II). During this process, Cu (I) is regenerated to resume the catalytic cycle. To strengthen the proposed mechanism, the N-arylation reaction was performed in the presence of radical scavenger TEMPO (2,2,6,6-tetramethylpiperidine-1-yl)oxyl. The desired product was obtained only in trace amount, suggesting that the reaction proceeds through a radical mechanism.



1a (1. 0 mmol) **2a** (1. 5 mmol) **3aa** trace

Scheme 3. Control experiment with TEMPO

In conclusion, a simple and efficient method for the *N*-arylation of sulfoximines is demonstrated using arenediazonium salts as an aryl source in the presence of a copper catalyst and DABCO. A wide range of aryl and alkyl sufoximines, including a biologically relevant L-methionine sulfoximine, are participated in the coupling reaction with different aryldiazonim salts bearing electron donating and withdrawing groups. The desired products i.e. *N*-aryl sulfoximines were obtained in good to excellent yields. Controlled experiment suggets that the reaction proceeds throguh a radical mechanism. The present methodology appears to be more general, hence expected to find promising applications in organic synthesis.

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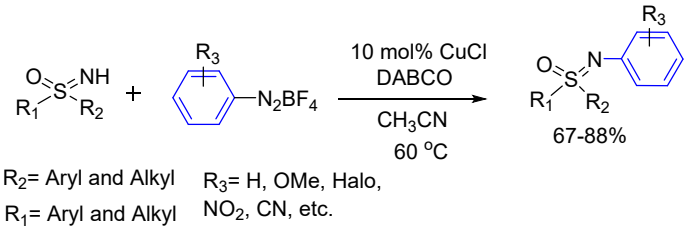

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Highlights

- *N*-Arylation of sulfoximines was achieved using aryldiazonium tetrafluoroborates as aryl donors.
- The coupling reaction proceeds in the presence of copper chloride and DABCO.
- The reaction proceeds through a radical mechanism.
- Broad substrate scope and good yields are the advantages of the current protocol