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Copper promoted *N*-alkylation of sulfoximines with alkylboronic acid under mild condition

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Copper meditated *N*-methylation of sulfoximines using methylboronic acid is reported. The reactions provide excellent yields in a short span of time under mild condition. The optimized condition was also found to be suitable for the *N*-alkylation of sulfoximine with different alkylboronic acids. In addition, *N*-methylation and cyclopropylation of bioactive L-methionine sulfoximine derivative was demonstrated under standard reaction condition.

In synthetic organic chemistry, sulfoximines have been explored as building blocks, chiral auxiliaries, organocatalysts, fluorophores, trifluoromethylating agents as well as directing groups for C-H activation reactions (Figure 1).[1] On the other hand, sulfoximine derivatives have also been identified as drugs and insecticides (Figure 1).[2-3] In particular, *N*-methylated sulfoximine motifs were found in many bioactive compounds.[4] From a synthetic perspective, *N*-methylated sulfoximines are considered stable *N*-protected sulfoximines in which a selective functionalization at the α-carbon *via* lithiation can be performed.[5] Such lithiated sulfoximines are extensively used as precursors for the asymmetric synthesis of various bioactive compounds.[5a]

N-Methylation of sulfoximines is typically achieved using the Eschweiler-Clarke reaction (*i.e.* formaldehyde/formic acid under reflux condition) which requires longer reaction time.[4c, 5b] In lieu of this, methyl iodide/K_2CO_3[4a] or Me_3OBF_4/NaOH[6] is also occasionally used for the *N*-methylation of sulfoximines. However, these methods provide low yields owing to poor nucleophilicity of the nitrogen atom present in sulfoximines.[7] Recently, *N*-methylation of sulfoximines using di-*tert*-butyl peroxide was demonstrated in the presence of copper acetate.[8] Nevertheless, requirement of inert reaction condition, prolonged reaction time and moderate yield limit the extensive use of this protocol for *N*-methylation reaction. Therefore, development of an amenable route for the synthesis of *N*-methylsulfoximines is an important task.

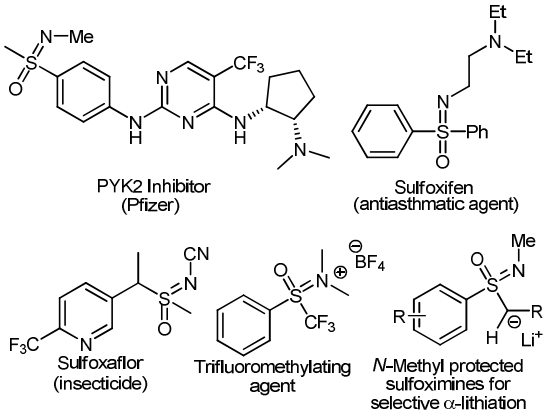
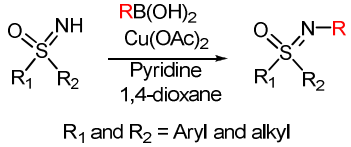


Figure 1. Biologically and chemically relevant some *N*-functionalized sulfoximines.



Scheme 1. *N*-alkylation of sulfoximine with alkylboronic acid.

In the series of organoboron compounds, boronic acids have received significant attention in synthetic organic chemistry.[9] These compounds are known to be non-toxic and stable, enabling ease of handling and storage. Copper mediated C-N bond formation reactions with arylboronic acids have emerged as a powerful tool for the synthesis of various bioactive compounds and natural products.[9] In this context, *N*-arylation of sulfoximines with arylboronic acid was successfully demonstrated by Bolm research group.[3a]

In contrast, the application of alkylboronic acids as *N*-alkylating agents is less explored.[9a] Recently, few reports have demonstrated a copper mediated Chan-Lam type *N*- and *O*-alkylation of organic compounds with different alkylboronic acids.[10] Notably, the reaction conditions used for *N*-alkylation with alkylboronic acids are

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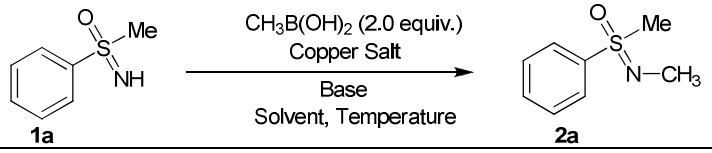
quite different from the *N*-arylation reactions carried out with arylboronic acids.[11]

Methylboronic acid has been used as a reagent for mono-methylation of anilines and esterification of carboxylic acids with different copper salts.[10a, 10b] To best of our knowledge, *N*-methylation or alkylation of sulfoximines with respective alkylboronic acid is not explored. Nevertheless, development of such protocol would provide not only an alternative route, but also conceptually different approach for the efficient preparation of *N*-alkyl sulfoximines under mild condition (Scheme 1). For instance, previous methods proceed through simple substitution reaction between a nucleophile (sulfoximine) and an electrophile (alkyl halide) while this approach discloses a reaction in which two nucleophiles (*i.e.* sulfoximine and alkylboronic acid) undergo coupling in the presence of Cu (II) species.

Table 1. Optimization of reaction condition for *N*-methylation of sulfoximine using methylboronic acid.[a]



1a 2a

Entry	Solvent	Metal salt (equiv.)	Base	Temperature (°C)	Time (h)	Yield (%)[b]
1	MeOH	$Cu(OAc)_2$ (0.1)	-	rt	12 h	NR[c]
2	MeOH	$Cu(OAc)_2$ (1.0)	-	rt (or) 80	12 h	NR
3	MeOH	$Cu(OAc)_2$ (1.0)	Py	rt (or) 80	12 h	NR
4	THF	$Cu(OAc)_2$ (1.0)	Py	80	12 h	33
5	AcCN	$Cu(OAc)_2$ (1.0)	Py	80	12 h	17
6	DCE	$Cu(OAc)_2$ (1.0)	Py	80	12 h	10
7	1,4-Dioxane	$Cu(OAc)_2$ (1.0)	Py	80	12 h	86
8	1,4-Dioxane	$Cu(OAc)_2$ (1.5)	Py	100	30 min	94
9	1,4-Dioxane	$CuSO_4$ (1.5)	Py	100	30 min	18
10	1,4-Dioxane	$CuCl_2$ (1.5)	Py	100	30 min	23
11	1,4-Dioxane	$CuBr_2$ (1.5)	Py	100	30 min	27
12	1,4-Dioxane	CuOAc (1.5)	Py	100	30 min	87
13	1,4-Dioxane	CuCl (1.5)	Py	100	30 min	14
14	1,4-Dioxane	Cu_2O (1.5)	Py	100	30 min	<5
15	1,4-Dioxane	$Cu(OAc)_2$ (1.5)	Et_3N	100	30 min	80
16	1,4-Dioxane	$Cu(OAc)_2$ (1.5)	DMAP	100	30 min	92
17	1,4-Dioxane	$Cu(OAc)_2$ (1.5)	K_2CO_3	100	30 min	<5
18	1,4-Dioxane	$Cu(OAc)_2$ (1.5)	NaOH	100	30 min	NR

[a]Reaction Condition: Sulfoximine (1.0 mmol), methylboronic acid (2.0 equiv.), base (2.4 equiv.), and copper salt were stirred in different solvents (8 mL) at appropriate temperature. [b]Isolated Yield. [C] Condition used for the *N*-arylation of sulfoximine by Bolm *et.al* (see ref 3a)

To execute the challenge, *N*-methylation of *S,S*-methylphenyl sulfoximine (**1a**) was studied with methylboronic acid in the presence of copper salts in various solvents. Initially, the reaction was performed with 0.1 equiv. copper (II) acetate in methanol using 2.0 equiv. of methylboronic acid at room temperature (Table 1, entry 1). In fact, this is the condition employed for the *N*-arylation

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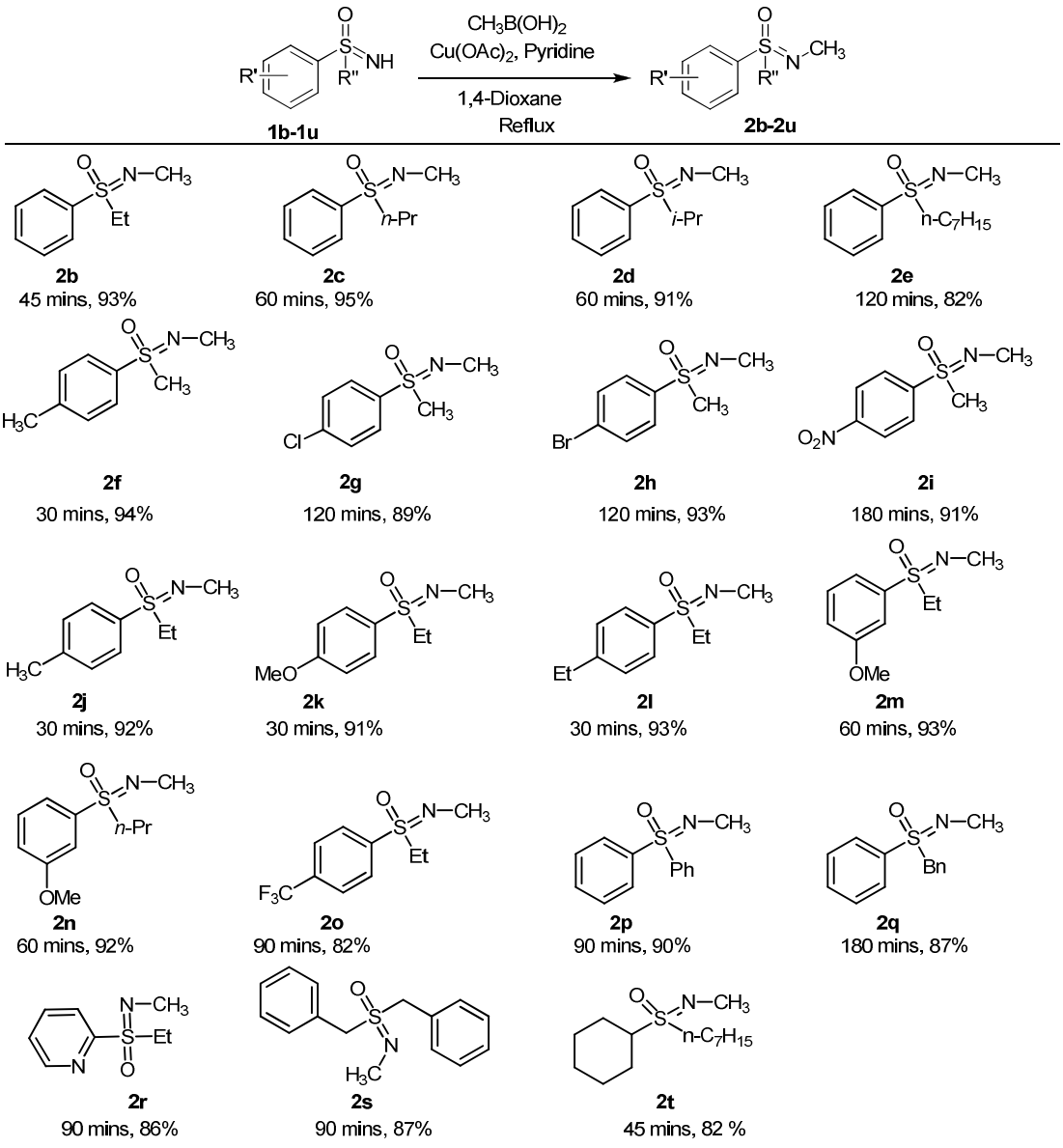
of sulfoximines with arylboronic acids by Bolm *et.al*.[3a] However, no reaction was detected under this condition after 12h. In addition, no reaction takes place with an equimolar amount of copper (II) acetate with or without base (*i.e.* pyridine, 2.4 equiv.) at room temperature as well as under reflux condition (*i.e.* 80 ^{o}C) in methanol (Table 1, entries 2 and 3). Thus, the reactions were carried out in different aprotic solvents such as THF, acetonitrile, dichloroethane and 1,4-dioxane with one equivalent of copper (II) acetate and pyridine at 80 ^{0}C (Table 1, entries 4-7). We were pleased to see a significant conversion of sulfoximine **1a** to the desired *N*-methylated sulfoximine **2a** (*i.e.* 86%) in 1,4-dioxane (Table 1, entry 7), while low yields were obtained with other solvents after 12h. Encouraged, we further modified the reaction condition where the reaction was carried out with 1.5 equiv. of copper (II) acetate at 100^{o}C in 1,4-dioxane (Table 1, entry 8). To our delight, under this condition, *N*-methyl *S,S*-methylphenyl sulfoximine (**2a**) was obtained in 94% yield within 30 mins.

Further, the optimization of reaction condition was continued with different copper (I) and copper (II) salts in the presence of pyridine in 1,4-dioxane at 100 ^{o}C (Table 1, entries 9-14). Surprisingly, most of the copper salts failed to provide significant amount of desired product while copper (I) acetate showed a comparable reactivity to that of copper (II) acetate (Table 1, entry 12). Furthermore, the reactions were carried out with different organic and inorganic bases in the presence of copper (II) acetate (Table 1, entries 15-18). The reactions with Et_3N and 4-DMAP provided good yields whereas negligible yield was observed in the case of K_2CO_3 and NaOH. In fact, 4-DMAP showed an equal reactivity to that of pyridine in the *N*-methylation reaction (Table 1, entry 16).

Table 2. *N*-Methylation of various sulfoximines with methylboronicacid under optimized conditions.[a,b]



[a]Reaction Condition: Sulfoximine (1 mmol), alkylboronic acid (2.0 equiv.), $Cu(OAc)_2$ (1.5 equiv.), and Pyridine (2.4 equiv.) was refluxed in 1,4-dioxane (8 mL) at 100 ^{o}C in a pressure tube. [b]Isolated yield.

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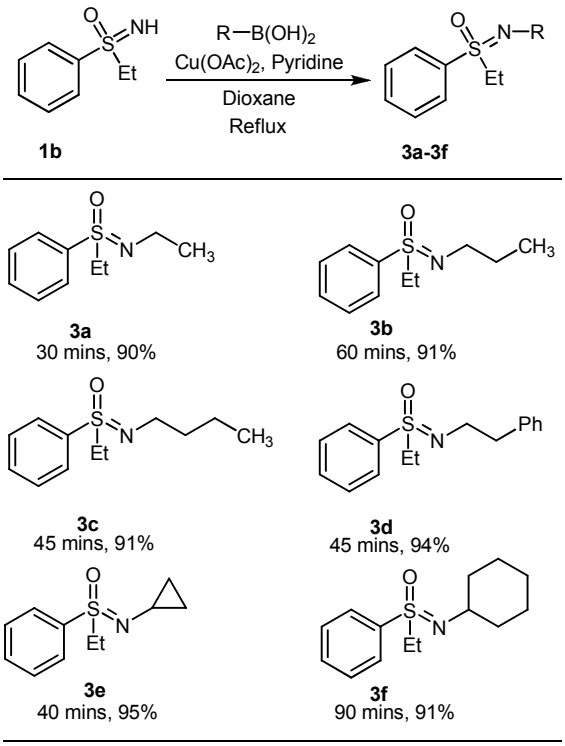
With optimized condition in hand, *N*-methylation of various sulfoximines was performed using methylboronic acid in the presence of copper (II) acetate and the results are summarized in Table 2. *S,S*-alkylphenylsulfoximines bearing linear or branched alkyl chains were *N*-methylated successfully in excellent yields under the optimized condition (Table 2, **2b**-**2e**). It is noteworthy that the sterically hindered *S,S*-phenyl *iso*-propyl sulfoximine was also methylated in 91% yield within 60 mins (Table 2, **2d**). In the case of *S,S*-heptylphenyl sulfoximine, a long alkyl substituent led to slightly longer reaction time to yield *N*-methylated sulfoximine **2e** in 82% yield. The substrates with electron donating or withdrawing substituents on the phenyl ring also underwent *N*-methylation in 89-94% yields (Table 2, **2f-2i**). In general, we observed that the electron withdrawing group substituted phenyl sulfoximines (e.g. *p*-NO_2, *p*-Br, *p*-Cl) required slightly longer time for *N*-methylation when compared with electron donating group substituted sulfoximines (e.g. *p*-Me). In order to demonstrate the versatility of the current methodology, *N*-methylation of various functionalised *S,S*-arylalkyl, *S,S*-arylbenzyl and *S,S*-diaryl sulfoximines were performed under optimized condition (Table 2,**2j**-**2q**). All these substrates were successfully *N*-methylated in 82-95% yield with methylboronic acid in a short span of time. Further, *N*-methylation of heterocylic sulfoximine (*i.e. S,S*-ethylpyridyl sulfoximine) was also accomplished in excellent yield in 90 mins (Table 2, **2r**). Similar to arylsulfoximines, *S,S*-dibenzyl and *S,S*-dialkyl sulfoximines underwent *N*-methylation in high yields (Table 2, **2s** and **2t**), which shows the versatility and broad scope of the current methodology.

Similar to *N*-methylated sulfoximines, other *N*-alkylated sulfoximines also play an important role in chemistry and biology.[4] However, only limited methods are available for the introduction of alkyl groups in sulfoximines.[7,12] Due to poor nucleophilicity of sulfoximines, *N*-alkylation requires strong bases like alkali metal hydrides or *n*-butyl lithium.[7, 12a, 12b] Alternatively, a two-step protocol is required, *i.e. N*-acylation followed by reduction, to achieve *N*-alkylated sulfoximines.[12c] Recently, Bolm *et. al.* have successfully demonstrated *N*-alkylation of various sulfoximines using alkylhalides with KOH in DMSO.[12d]

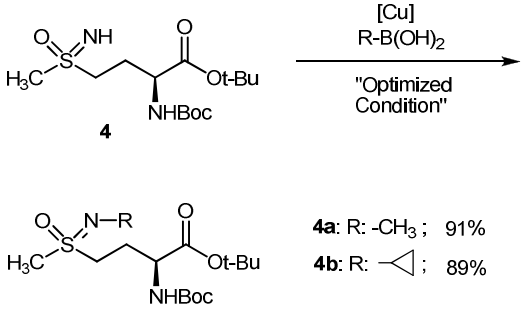
Favourable results in *N*-methylation of sulfoximines with methylboronic acid have spurred us to further explore the *N*-alkylation of sulfoximines with different alkylboronic acids. Initially, *N*-ethylation of *S,S*-ethylphenylsulfoximine (**1b**) with ethylboronic acid was examined under optimized condition. To our surprise, the reaction proceeds smoothly with similar efficiency to that of *N*-methylation and gave the desired product **3a** in 90% yield. Encouraged, we further tested *N*-propylation, butylation and phenethylation of sulfoximine **1b** with respective boronic acids. These reactions gave the desired *N*-alkylated products in excellent yields (Table 3, **3b**-**3d**) within 60 mins.

The cyclopropyl group, which appears frequently in preclinical and clinical drug molecules, has received significant attention in medicinal chemistry due to its unique structural properties.[13] Thus, we have examined the *N*-cyclopropylation of sulfoximine **1b** with cyclopropylboronic acid under optimized condition. Interestingly, the reaction provides the *N*-cyclopropyl *S,S*- ethylphenylsulfoximine (**3e**) in 95% yield within 45 mins. Similarly, *N*-cyclohexylsulfoximine **3f** was obtained in 91% yield.

Table 3. *N*-Alkylation of *S,S*-ethylphenyl sulfoximine (**1b)** with different alkylboronic acids.[a,b]



[a]Reaction Condition: Sulfoximine (1 mmol), alkylboronic acid (2.0 equiv.), $Cu(OAc)_2$ (1.5 equiv.), and Pyridine (2.4 equiv.) was refluxed in 1,4-dioxane (8 mL) at 100 °C. [b]Isolated yield.

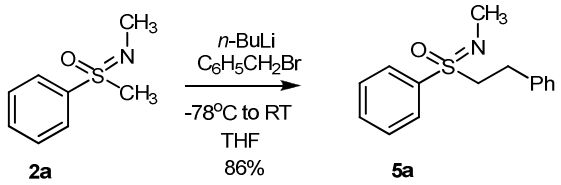


Scheme 2. *N*-Alkylation of L-methionine sulfoximine derivative under optimized reaction condition.

L-Methionine sulfoximine is a bioactive molecule which inhibits glutamine synthetase and g-glutamylcysteine synthetase.[14] In this respect, L-methionine sulfoximine shows considerable therapeutic applications in animal models for many human diseases.[14a] To expand the scope of our methodology, *N*-methylation and cyclopropylation of bioactive L-methionine sulfoximine derivative **4** was tested with corresponding alkylboronic acids. To our delight, the optimized reaction condition was well suited to the task and gave *N*-methylated and cyclopropylated L-methionine sulfoximine derivatives in 89-91% yield. It is remarkable that Boc-protected

primary amine was found to be intact during the *N*-methylation of L-methionine sulfoximine with methylboronic acid.

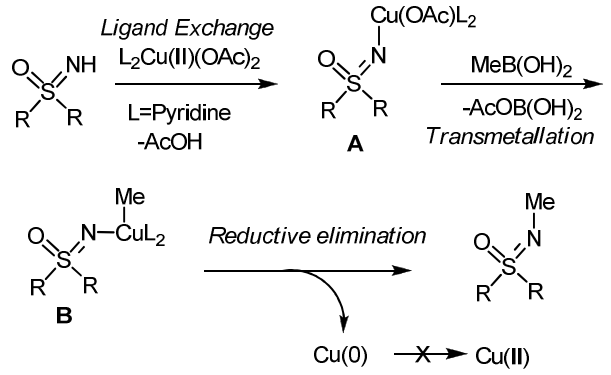
Finally, a synthetic application of *N*-methyl sulfoximine was demonstrated as shown in Scheme 3. Selective lithiation of *S*-methyl group in *N,S*-dimethyl *S*-phenyl sulfoximine (**2a**) was performed using n-butyl lithium in dry THF, which was subsequently reacted with benzyl bromide to obtain *N*-methyl *S*-phenyl *S*-(2-phenylethyl) sulfoximine **(5a**) in 86% yield.



2a **5a**

Scheme 3. A selective functionalization of N-methyl sulfoximine *via* lithiation.

A proposed mechanism for the *N*-methylation of sulfoximine is shown in Scheme 4.[9] In the first step, sulfoximine undergoes ligand exchange reaction with copper (II) acetate to form intermediate **A**. Further, methylboronic acid undergoes transmetallation with intermediate **A** to form intermediate **B,** which subsequently undergoes reductive elimination to yield the desired products. During the reductive elimination process, Cu(II) species is converted to Cu(0) which is basically inactive for the coupling reaction, hence stoichiometric amount of $Cu(OAc)_2$ is required for completion of the reaction.



Scheme 4. Proposed mechanism for *N*-methylation reaction.

In summary, we have established a copper mediated *N*-methylation of sulfoximines using methylboronic acid under mild condition. The reaction proceeds smoothly to provide the desired products in excellent yields in a short span of time. In addition to *N*-methylation, *N*-alkylation of sulfoximine with different alkylboronic acids was demonstrated. Under optimized condition, *N*-methylation and cyclopropylation of bioactive L-methionine sulfoximine derivative was achieved in high yields.

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11. In general, *N*-arylation reactions with arylboronic acid require catalytic amount of copper salts in the absence of any base. Reaction also proceeds at room temperature in methanol (See ref 3a). On the other hand, *N*-alkylation reaction with alkylboronic acid requires equivalent amount of copper salts with base or ligands (see ref. 10a). Reaction proceeds only in aprotic solvents at high temperature.
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