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The Copper-Catalyzed Oxidative *N*-Acylation of Sulfoximines

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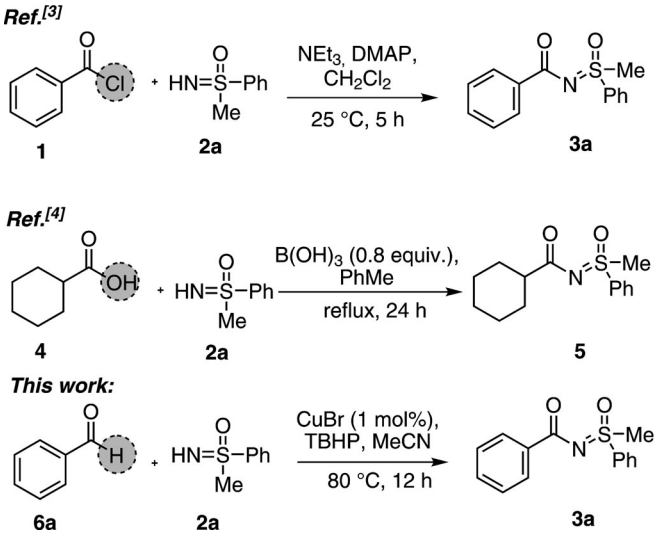
Abstract: An oxidative cross-coupling reaction between aldehydes and sulfoximines involving dual C–H/N–H functionalization has been developed. This reaction process is facilitated by a simple copper catalyst (1 mol% loading) and *tert*-butyl hydroperoxide (TBHP) as the oxidant and proceeds under mild reaction conditions to afford a series of valuable *N*-acylated sulfoximine derivatives in excellent yields.

Keywords: acylation; copper catalysts; oxidative coupling; sulfoximines



Scheme 1. Previous syntheses of *N*-acylsulfoximines and the new approach presented here.

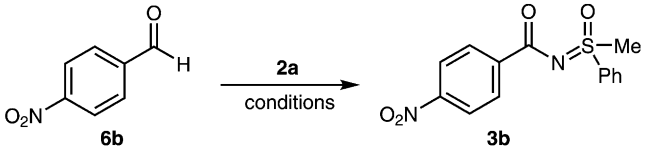
The recent increase in the utilization of the sulfoximine moiety in medicinal and agricultural applications is of significant interest to our research group and others.[1] In addition, chiral sulfoximine-based ligands have been successfully employed to induce high levels of stereochemistry during numerous bond forming processes.[2] One class of sulfoximines, namely the *N*-acylsulfoximines, have been traditionally prepared using pre-activated coupling partners, such as acyl chlorides,[3] or aliphatic carboxylic acids (Scheme 1).[4] To allow the sulfoximine moiety to be more widely applied in organic and medicinal chemistry, it is essential that new, efficient methods for their preparation and derivatization are realized.

In the last decade, significant progress has been made in the field of C–H activation, permitting the formation of new bonds between two coupling partners without the need for additional leaving groups or prior activation.[5] Among those, several transition metal-catalyzed oxidative (dehydrogenative) cross-coupling reactions have been developed for the synthesis of heterocycles, biaryl compounds, aryl halides, and substituted alkynes (such as ynamides).[6]

For the preparation of functionalized amides, imides, or ureas, coupling partners that include toxic isocyanates, sensitive acyl chloride substrates, or carboxylic acid derivatives (that require the use of activating agents such as carbodiimide-type additives) are commonly used. Recently, similar C–N bond forming transformations have been achieved using a combination of transition metal catalysts and oxidants facilitating an oxidative cross-coupling processes through dual C–H and N–H bond activation.[7] In such a catalysis, advantageously, readily available aldehydes can be used as coupling partners, and cheap transition metals serve as catalysts in low catalyst loadings under mild reaction conditions without requiring additional ligands or base. Hence, the previous need for additional derivatization or activation of carbonyl compounds during C–N bond formation is circumvented, and the subsequent generation of halide-containing waste is eliminated.

We herein disclose our recent efforts in the synthesis of *N*-acylsulfoximines from aldehydes, employing a copper-catalyzed oxidative coupling reaction through a dual C–H/N–H bond functionalization process (Scheme 1). The inclusion of an appropriate oxi-

Table 1. Optimization of the sulfoximine *N*-acylation conditions.[a]



Entry	Catalyst	Catalyst loading [mol%]	Oxidant	Yield [%]
1	CuBr	5	air	0
2	CuBr	5	O_2	0
3	CuBr	5	NBS	53
4	CuBr	5	*t*-BuOOH	95
5	$FeSO_4 \cdot 7H_2O$	5	*t*-BuOOH	90
6	$CuCl_2$	5	*t*-BuOOH	91
7	**CuBr**	**1**	***t*-BuOOH**	**95**
8	CuBr	0.1	*t*-BuOOH	94
9	–	–	*t*-BuOOH	trace

[a] *Reaction conditions:* **6b** (0.50 mmol), **2a** (0.75 mmol), catalyst, oxidant (1.00 mmol), MeCN (1 mL), 80 °C, 12 h.

dant in such dehydrogenative C–N cross-coupling protocols is also an essential requirement.[6d,8] Initial investigations into the oxidative *N*-acylation of sulfoximines focused on identifying a suitable transition metal catalyst and oxidant to facilitate this process (Table 1). Trial reactions were carried out combining *p*-nitrobenzaldehyde (**6b**, 1.0 equiv.) and *S,S*-methylphenylsulfoximine (**2a**, 1.5 equiv.) in acetonitrile in the presence of 5 mol% catalyst and an oxidant (2.0 equiv.).

The first reaction attempts used copper (I) bromide as a catalyst, and the oxidant was varied (Table 1, entries 1–4). These trials revealed that the use of *tert*-butyl hydroperoxide (TBHP, 70% solution in H_2O) was superior to NBS, air or dioxygen. In addition, although both iron sulfate (Table 1, entry 5) and $CuCl_2$ (Table 1, entry 6) afforded the desired product **3b** in excellent yields, the use of CuBr proved optimal, leading to the desired *N*-acylsulfoximine **3b** in 95% yield after 12 h. It was subsequently determined that the amount of catalyst employed could be decreased (Table 1, entries 7 and 8), with the sulfoximine product **3b** isolated in exceptional yields, when even a submolar catalyst loading (0.1 mol%, Table 1, entry 8) was used. In the absence of a metal salt (Table 1, entry 9), the *tert*-butyl ester derivative of the aldehyde was identified as the major product. Additional studies revealed that when the catalyst loading was reduced to less than 1 mol% when using substrates other than *p*-nitrobenzaldehyde (**6b**), poor levels of conversion to the product were observed. As such, a catalyst loading of 1 mol% was used for the remainder of the study.

With the optimal conditions in hand, we then investigated the substrate scope of this reaction process (Table 2). In addition to *S,S*-methylphenyl sulfoximine (**2a**), the reaction with aldehyde **6b** also proceeded smoothly with the *S,S*-dimethyl- (**2b**) and *S,S*-tetramethylenesulfoximines (**2c**) (Table 2, entries 1–3). Both *para*- and *meta*-nitrobenzaldehyde performed well, furnishing the corresponding *N*-acylsulfoximines in excellent yields (Table 2, entries 1–5). Advantageously, when the synthesis of *N*-acylsulfoximine **3b** was performed using enantiopure (*R*)-*S,S*-methylphenylsulfoximine, it was determined that the reaction process was entirely enantiospecific.[9]

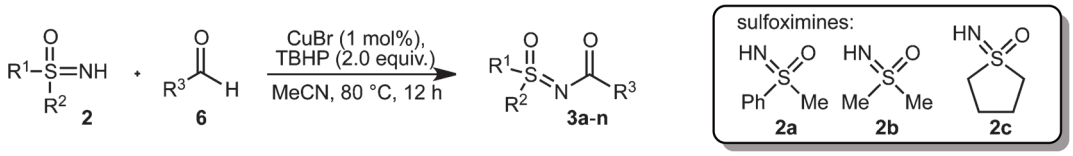
In general, both electron-withdrawing and electron-donating groups on the aryl ring of the initial aldehyde substrate were well tolerated, affording a series of *N*-benzoylsulfoximines containing additional functionality including aryl halide, *p*-methoxyphenyl, *tert*-butylphenyl and biphenyl groups (Table 2, entries 6–10). In addition, 1-naphthaldehyde and benzaldehyde were readily converted to the corresponding *N*-acylsulfoximines in high yields (Table 2, entries 11 and 12). Whereas the protocol previously reported by Garimallaprabhakaran and Harmata was only successful for the synthesis of *aliphatic* substituted *N*-acylsulfoximines,[4] the method reported herein afforded a diverse range of *aromatic* substituted *N*-acylsulfoximines. Additionally, isopropyl aldehyde reacted cleanly under our conditions (Table 2, entry 13). A keto-*N*-acylsulfoximine derivative **3n** was also readily obtained in 86% yield following the reaction of 2-oxo-2-phenylacetaldehyde with *S,S*-methylphenylsulfoximine (Table 2, entry 14).

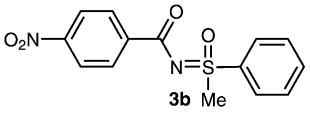
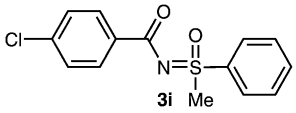
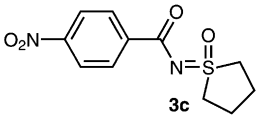
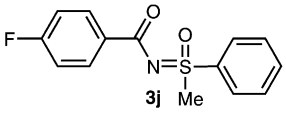
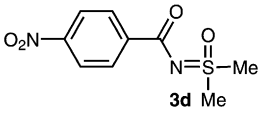
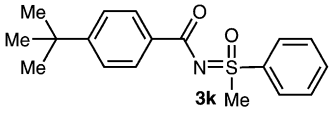
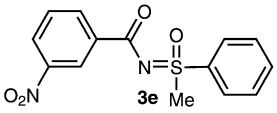
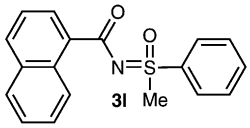
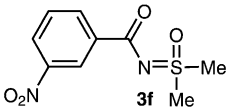
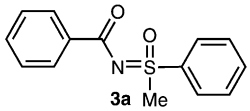
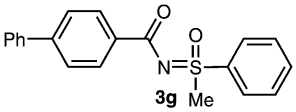
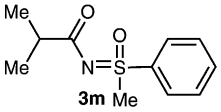
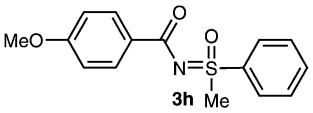
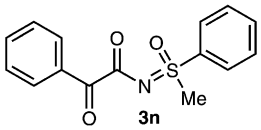
In Scheme 2, we propose a mechanistic pathway for the oxidative cross-coupling process. As this reaction also proceeded well using $CuCl_2$ as catalyst (see Table 1) and considering the presence of an excess of TBHP in the reaction mixture, we regard it highly unlikely that a Cu(I) species is active in the catalytic cycle. Most probably, the applied CuBr is immediately oxidized to a Cu(II)-based catalyst (Scheme 2).

In a recent related report, Zhu and co-workers suggested the presence of a radical acyl species formed by the copper/TBHP combination.[7a,9] Taking that scenario into account, a plausible pathway for the reaction process described herein involves a redox process (Scheme 2) whereby the Cu(II) catalyst interacts with sulfoximine **2** leading to an intermediate **I**, which reacts with an acyl radical formed from aldehyde **6**. Subsequent electron transfer processes result in the formation of the product, *N*-acylsulfoximine **3**, and a Cu(I) species, which is then re-oxidized to Cu(II) by TBHP, completing the catalytic cycle (Scheme 2).

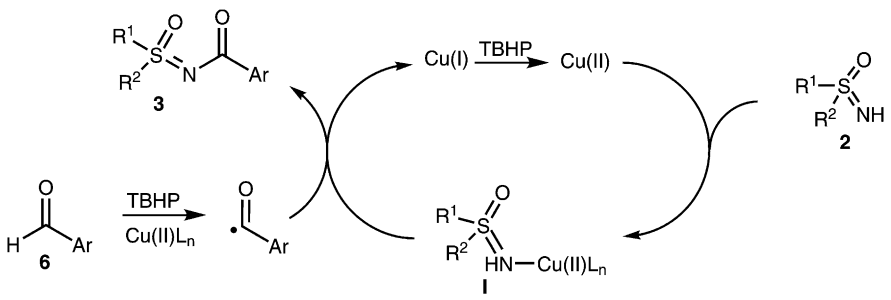
To further investigate the role of a radical species in this reaction process, the oxidative coupling reaction between *S,S*-methylphenylsulfoximine (**2a**) and *p*-nitrobenzaldehyde (**6b**) was repeated in the presence of TEMPO (3.0 equiv.). After 12 h of reaction time, as expected, none of the desired *N*-acylsulfox-

Table 2. Investigation into the substrate scope.[a]



Entry	Product	Yield [%]	Entry	Product	Yield [%]
1	 **3b**	95	8	 **3i**	88
2	 **3c**	85	9	 **3j**	89
3	 **3d**	83	10	 **3k**	80
4	 **3e**	85	11	 **3l**	80
5	 **3f**	78	12	 **3a**	85
6	 **3g**	85	13	 **3m**	72
7	 **3h**	78	14	 **3n**	86

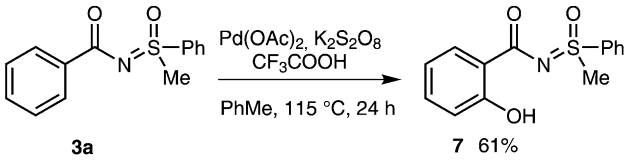
[a] *Reaction conditions:* sulfoximine (0.75 mmol), aldehyde (0.5 mmol), CuBr (1 mol%), TBHP (1.0 mmol), CH_3CN (1 mL), 80 °C, 12 h.



Scheme 2. The proposed mechanistic pathway of this oxidative coupling process.

imine **3b** could be detected and the TEMPO-aldehyde adduct was identified as the major product from this reaction mixture.[9]

Wondering about the subsequent functionalization of the *N*-acylsulfoximine products **3** we became interested in recent work by Sahoo and co-workers, who described the use of the *N*-acylsulfoximine moiety as a stable directing group in a palladium-catalyzed *ortho*-C–H acetoxylation process.[3e] This reaction was performed using palladium acetate as catalyst and po-



Scheme 3. Additional derivatization of an *N*-acylsulfoximine.

tassium persulfate as the oxidant in acetic acid and chloroform at 100 °C to introduce an acetate group at the 2-position of the phenyl ring of *N*-benzoyl-functionalized sulfoximines.

To further demonstrate the utility of the *N*-acylsulfoximines prepared using the method reported herein, we decided to investigate the application of a similar Pd-catalyzed C–H activation process to introduce an *ortho*-hydroxy group, negating the need for de-acetylation to access the hydroxy derivatives. In our hands, a simple modification of the Sahoo protocol employing two equivalents of trifluoroacetic acid in toluene directly afforded the *ortho*-hydroxylated *N*-acylsulfoximine **7** as the sole reaction product in good yield (Scheme 3).

In conclusion, a dual C–H/N–H functionalization protocol for the preparation of valuable *N*-acylsulfoximines under mild reaction conditions is reported. It involves the use of CuBr as catalyst and TBHP as oxidant, allowing a cross-coupling between aldehydes and sulfoximines. This new methodology provides an alternative method to rapidly access a diverse series of *N*-acylsulfoximines, circumventing the need for the traditional coupling partners that require pre-activation, for example acyl chlorides.

Experimental Section

General Procedure

In a 10-mL reaction vessel fitted with a magnetic stirring bar the aldehyde (0.5 mmol) and the sulfoximine (0.75 mmol) were dissolved in CH_3CN (1 mL), then *tert*-butyl hydroperoxide (1 mmol, 70% solution in water, 1.4 mL) and CuBr (1 mol%, 0.7 mg) were added to the solution. The reaction mixture was stirred at 80 °C for 12 h, and then cooled to room temperature, filtered over a short plug of silica gel, washed with CH_2Cl_2 and concentrated. The product was then purified by silica gel column chromatography to afford the *N*-acylsulfoximine **3**.

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[9] Refer to the Supporting Information for more details.

[10] See also: X. Li, B. Li, J. You, J. Lan, *Org. Biomol. Chem.* **2013**, *11*, 1925–1928, and references cited therein.

