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# Iron-Catalyzed Hetero-Cross-Dehydrogenative Coupling Reactions of Sulfoximines with Diarylmethanes: A New Route to *N*-Alkylated Sulfoximines

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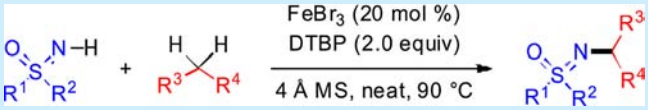
Supporting Information

**ABSTRACT:** An efficient iron-catalyzed C−N bond formation by hetero-cross-dehydrogenative coupling (CDC) between sulfoximines and diarylmethanes is described. The reaction shows good functional group tolerance and provides *N*-alkylated sulfoximines in moderate to good yields.




The first sulfoximine was reported by Whitehead and Bentley in the early 1950s,[1] and since then sulfoximidoyl-containing compounds have gained significant attention.[2] Johnson and others demonstrated the synthetic power of sulfoximines in stoichiometric asymmetric synthesis,[2a−d] and our work has predominantly been focused on applying such compounds in enantioselective catalysis.[2e−g] Others made use of sulfoximines in crop protection and medicinal chemistry.[3] In all such areas, *N*-alkylated derivatives proved particularly interesting because in those compounds the nitrogen substituent allowed modulation of important properties such as molecular dimension, H-bonding capability, acidity, etc. Unfortunately, the preparation of such *N*-alkylated sulfoximines has often proven difficult, and only a few efficient routes toward such compounds have been reported. Those include, for example, based-catalyzed Michael-type additions,[4] Eschweiler−Clark-type methylations,[5] nucleophilic substitutions,[6] and two-step acylation/reduction sequences.[7] Most of those methods involve strong bases such as lithium reagents or metal hydrides for the *N*-H deprotonation (under strict dry conditions) and the presence of a crown ether or phase transfer catalyst to overcome the low nucleophilicity of the resulting anion. Even more difficult is the introduction of $\alpha$-branched alkyl groups on the sulfoximine nitrogen.

Transition-metal-catalyzed cross-dehydrogenative coupling (CDC) reactions have emerged as powerful tools for organic synthesis.[8] Being highly atom- and step-economical they can have a significant impact on green chemistry. By involving unactivated C−H and X−H bonds (where X is carbon or a heteroatom such as N), CDC reactions allow new C−C and C−X bonds to be prepared in a highly efficient manner. Recently, several interesting couplings between ($sp^2$)C−H and N−H bonds of amines and amides have been reported.[9] Less known are analogous C−N bond formations at $sp^3$ carbons. Examples include work by Powell and co-workers, who reported copper-catalyzed amidations of allylic and benzylic $sp^3$ carbons with sulfonamides and *tert*-butyl peroxyesters as oxidants.[10] Fu and co-workers described oxidative amidations of molecules with $sp^3$ carbons next to nitrogen atoms with amides under copper catalysis.[11] Iron salts have successfully been applied as catalysts in analogous couplings starting from compounds with benzylic ($sp^3$)C−H bonds[12] and $sp^3$ carbons adjacent to oxygen atoms.[13,14]

Following our interest in sulfoximine chemistry, we have studied hetero-CDC reactions of *N*-H sulfoximines with arenes,[15a] aldehydes,[15b] and terminal alkynes.[15c,d] We now wondered if such an approach could also be used in challenging *N*-alkylations of sulfoximines, in particular those leading to products with $\alpha$-branched alkyl groups. Here, we report on iron-catalyzed hetero-CDC reactions between sulfoximines and diarylmethanes.

The investigation was started by searching for a suitable metal/oxidant combination using sulfoximine **1a** and diphenylmethane (**2a**) as test substrates (Table 1). In the initial screening, various copper, palladium, and iron salts were applied in 1,2-dichloroethane (DCE) using di-*tert*-butyl peroxide (DTBP) as the oxidant (Table 1, entries 1−10). While in most reactions none of the targeted *N*-alkylated sulfoximine **3aa** was detected, the use of $FeBr_3$ led to a promissing 35% yield (entry 10). To our delight, the yield of **3aa** increased to 85% when the reaction was performed in the absence of solvent (entry 11). Attempts to use alternative oxidants such as *tert*-butyl hydroperoxide (TBHP), dioxygen, and others proved less efficient affording **3aa** in lower yields (Table 1, entries 12−16).

With the optimal conditions in hand, the applicability of other sulfoximines in hetero-CDC reactions with diphenylmethane (**2a**) were examined. In general, the couplings proceeded well, leading to the desired products in good to high yields (Table 2). In reactions of methyl aryl sulfoximines (**1a−g**) the substitution pattern on the arene had only a minor impact on the effectiveness of the catalysis. For example, substrates **1b** and **1c** with electron-donating groups in the *meta* and *para* position of the sulfoximidoyl moiety provided the corresponding products **3ba** and **3ca** in 83% and 82% yield,

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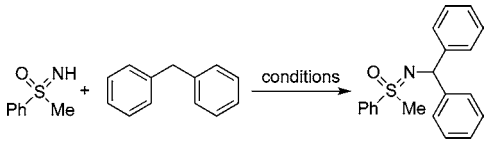
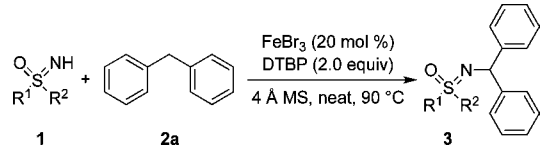
**Table 1. Optimization Studies for the Hetero-CDC Reaction of Sulfoximine 1a with Diphenylmethane (2a)[a]**




| entry | catalyst | oxidant | solvent | yield (%) |
|---|---|---|---|---|
| 1 | CuI | DTBP | DCE | – |
| 2 | CuBr | DTBP | DCE | – |
| 3 | CuCl | DTBP | DCE | – |
| 4 | $Cu(OTf)_2$ | DTBP | DCE | – |
| 5 | $Pd(OAc)_2$ | DTBP | DCE | – |
| 6 | $PdCl_2$ | DTBP | DCE | – |
| 7 | $Fe(acac)_3$ | DTBP | DCE | – |
| 8 | $FeCl_2$ | DTBP | DCE | 10 |
| 9 | $FeCl_3$ | DTBP | DCE | 30 |
| 10 | $FeBr_3$ | DTBP | DCE | 35 |
| **11**[b] | **$FeBr_3$** | **DTBP** | – | **85** |
| 12[b] | $FeBr_3$ | TBHP | – | 65 |
| 13[b] | $FeBr_3$ | oxygen | – | 16 |
| 14[b] | $FeBr_3$ | $K_2S_2O_8$ | – | 48 |
| 15[b] | $FeBr_3$ | oxone | – | 50 |
| 16[b] | $FeBr_3$ | $PhI(OAc)_2$ | – | 53 |

[a]Reaction conditions: Sulfoximine **1a** (0.3 mmol, 1.0 equiv), diphenylmethane (**2a**, 1.5 mmol, 5.0 equiv), catalyst (20 mol %, 0.06 mmol), oxidant (0.6 mmol, 2.0 equiv), and 4 Å MS (100 mg) in solvent (3.0 mL) were stirred at 90 °C for 48 h. [b]Use of 1 mL of **2a** (6.0 mmol, 20 equiv).

**Table 2. Scope of Sulfoximines[a]**



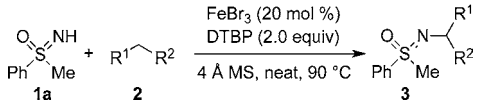

| entry | $R^1$, $R^2$ (**1**) | **3** | yield (%) |
|---|---|---|---|
| 1 | Ph, Me (**1a**) | **3aa** | 85 |
| 2 | 3-$MeC_6H_4$, Me (**1b**) | **3ba** | 83 |
| 3 | 4-$MeOC_6H_4$, Me (**1c**) | **3ca** | 82 |
| 4 | 4-$O_2NC_6H_4$, Me (**1d**) | **3da** | 72 |
| 5 | 4-$ClC_6H_4$, Me (**1e**) | **3ea** | 76 |
| 6 | 4-$BrC_6H_4$, Me (**1f**) | **3fa** | 75 |
| 7 | 2-naphthyl, Me (**1g**) | **3ga** | 68 |
| 8 | Me, Me (**1h**) | **3ha** | 62 |
| 9 | Ph, Et (**1i**) | **3ia** | 84 |
| 10 | Ph, *i*-Pr (**1j**) | **3ja** | 80 |
| 11 | Ph, cyclopropyl (**1k**) | **3ka** | 81 |
| 12 | Ph, Ph (**1l**) | **3la** | 82 |

[a]Reaction conditions: Sulfoximine **1** (0.3 mmol, 1.0 equiv), diphenyl methane (**2a**, 1.0 mL, 6.0 mmol, 20 equiv), $FeBr_3$ (20 mol %, 18 mg, 0.06 mmol), DTBP (88 mg, 0.6 mmol, 2.0 equiv), and 4 Å MS (100 mg) were stirred at 90 °C for 48 h.

respectively (Table 2, entries 2 and 3). In comparison, *N*-alkylations of sulfoximines **1d–f** with electron-withdrawing nitro and halo groups in the *para* position led to **3da–3fa** in yields ranging from 72% to 76% (Table 2, entries 4–6). Presumably due to the steric crowding induced by the *ortho* substitution of the arene, methyl 2-naphthyl sulfoximine (**1g**) afforded the corresponding product **3ga** in only 68% yield (Table 2, entry 7). The lowest yield was observed in the reaction between dimethylsulfoximine (**1h**) with diphenylmethane (**2a**), which gave *N*-alkylated **3ha** in 62% yield (Table 2, entry 8). Varying the alkyl substituent in alkyl phenyl sulfoximines had almost no effect, as indicated by conversions of **1i–1k**, which all led to product yields of >80% (Table 2, entries 9–11). Finally, diphenyl sulfoximine (**1l**) reacted with **2a** providing **3la** in 82% yield (Table 2, entry 12).

Next, the substrate scope with respect to diarylmethanes was investigated. As a representative reaction partner, sulfoximine **1a** was chosen. Both unsymmetrical and symmetrical diarylmethanes (**2b–k** and **2l–2n**, respectively) reacted well, affording the corresponding *N*-alkylated sulfoximines (**3ab–3an**) in good yields (Table 3). In general, electronic factors

**Table 3. Scope of Diarylmethanes[a]**




| entry | $R^1$, $R^2$ (**2**) | **3** | yield (%) |
|---|---|---|---|
| 1 | Ph, 4-$MeOC_6H_4$ (**2b**) | **3ab**[b] | 70 |
| 2 | Ph, 4-$MeC_6H_4$ (**2c**) | **3ac**[b] | 75 |
| 3 | Ph, 4-$FC_6H_4$ (**2d**) | **3ad**[b] | 85 |
| 4 | Ph, 4-$ClC_6H_4$ (**2e**) | **3ae**[b] | 88 |
| 5 | Ph, 4-$BrC_6H_4$ (**2f**) | **3af**[b] | 85 |
| 6 | Ph, 3-$MeC_6H_4$ (**2g**) | **3ag**[b] | 80 |
| 7 | Ph, 3-$ClC_6H_4$ (**2h**) | **3ah**[b] | 87 |
| 8 | Ph, 3-$CF_3C_6H_4$ (**2i**) | **3ai**[b] | 86 |
| 9 | Ph, 2-$MeOC_6H_4$ (**2j**) | **3aj**[b] | 56 |
| 10 | Ph, 2-$BrC_6H_4$ (**2k**) | **3ak**[b] | 58 |
| 11 | 4-$MeC_6H_4$, 4-$MeC_6H_4$ (**2l**) | **3al** | 75 |
| 12 | 4-$FC_6H_4$, 4-$FC_6H_4$ (**2m**) | **3am** | 88 |
| 13 | 4-$BrC_6H_4$, 4-$BrC_6H_4$ (**2n**) | **3an** | 82 |

[a]Reaction conditions: Sulfoximine **1a** (0.3 mmol, 1.0 equiv), diarylmethane **2** (1.0 mL), $FeBr_3$ (20 mol %, 18 mg, 0.06 mmol), DTBP (88 mg, 0.6 mmol, 2.0 equiv), and 4 Å MS (100 mg) were stirred at 90 °C for 48 h [b]Obtained as a ca. 1:1 mixture of diastereomers.

induced by substituents on the arenes had only a minor impact and the yield remained essentially unaffected. Conversions of diarylmethanes **2j** and **2k** showed that the presence of *ortho*-substituents lowered the yield of the respective products (**3aj** and **3ak**; Table 3, entries 9 and 10). With unsymmetrical diarylmethanes, diastereomeric mixtures (in ca. 1:1 ratios) were obtained (Table 3, entries 1–10).[16]

A plausible mechanism for the hetero-CDC process exemplified by the iron-catalyzed *N*-alkylation of sulfoximine **1a** with diphenylmethane (**2a**) to give **3aa** is shown in Scheme 1. The first step involves a DTBP cleavage initiated by an iron(II) species to give a *tert*-butoxy anion and a *tert*-butoxy radical.[13,17] The latter abstracts a benzylic hydrogen of **2a** providing diphenylmethane radical **A**.[18] Single-electron transfer from **A** onto the generated iron(III) species leads to benzylic cation **B**, which reacts with the anion formed by deprotonation of sulfoximine **1a** by the *tert*-butoxy anion affording product **3aa**.

Assuming the intermediacy of radical species, a control experiment with 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) as a radical inhibitor was performed. Confirming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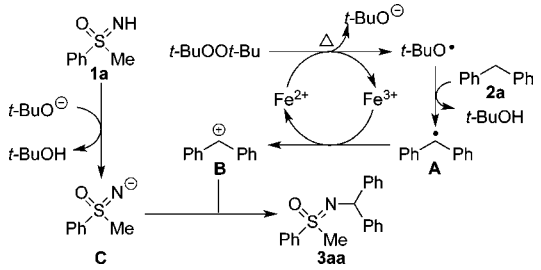
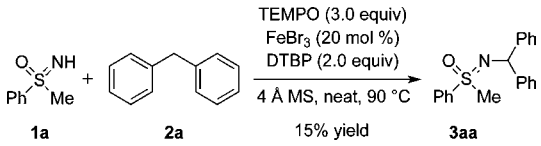
**Scheme 1. Plausible Mechanism**




our hypothesis, diphenylmethane radical **A** was trapped by TEMPO, and the yield of **3aa** dropped to 15% (Scheme 2).

**Scheme 2. Control Experiment**




In summary, we developed iron-catalyzed hetero-cross-dehydrogenative coupling reactions for *N*-alkylations of *N*-H sulfoximines with diarylmethanes. The transformation provides a new strategy for the synthesis of *N*-alkylated sulfoximines with $\alpha$-branched substituents, which are otherwise difficult to prepare. Further studies along those lines are in progress.

## ■ ASSOCIATED CONTENT

### Supporting Information

General experimental procedure and characterization details. This material is available free of charge via the Internet at http://pubs.acs.org

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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