N-Arylation of NH-Sulfoximines via Dual Nickel Photocatalysis

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ABSTRACT: The pharmaceutically underexplored sulfoximine moiety has emerged as a potentially active pharmaceutical ingredient. We developed a scalable synthetic route to N-arylated sulfoximines from the respective “free” NH-sulfoximines and bromoarenes. Our strategy is based on a dual nickel photocatalytic approach, is applicable for a broad scope of substrates, and exhibits a highly functional group tolerance. In addition, we could demonstrate that other sulfoximidoyl derivatives like sulfonimidamides and sulfonamides proceed smoothly under the developed reaction conditions.

Most organic chemists consider sulfoximines mainly as chiral auxiliaries or ligands, being applied in asymmetric reactions or catalysis.1 However, recently, sulfoximines emerged as potentially active pharmaceutical ingredients (APIs) in medicinal and agricultural research.2 Although their bioactivity is already long known, their exploration as APIs was scarce. Recently, it was found that the sulfoximines’ mode of binding to biological receptors can be very different compared to established ligands. For example, the sulfoximine-based insecticide Sulfoxaflor is capable of bypassing many cross-resistances of pest species because of its differing mechanism of binding.3 Discoveries as such call for efficient synthetic routes to sulfoximines. In particular, N-arylated sulfoximines are of interest for medicinal chemists, as they could serve as potent drug analogues.4

Various Pd-, Cu-, or Fe-catalyzed N-arylations of NH-sulfoximines with different types of electrophiles were developed by Bolm, Harmata, and others since the late 1990s (Figure 1A).1i,n,5 However, demanding reaction conditions such as high catalyst loadings, specialized ligands, elevated reaction temperatures, and long reaction times often limit the practicability or the scope of substrates. This set of limitations already indicates that NH-sulfoximines often behave as a rather special and challenging class of N-nucleophiles for transition-metal-catalyzed N-arylations. In particular, the coupling of pharmaceutically relevant heteroaromatic scaffolds to NH-sulfoximines is rather unexplored. Consequently, there is still a great demand for general, mild, and efficient synthetic solutions toward N-functionalized aliphatic, aromatic, and heteroaromatic sulfoximines. Very recently, we reported the first photocatalytic approach for the N-arylation of NH-sulfoximines.6 At the same time, Meier at al. published a similar method, showing that the mildness of the photocatalytic reaction also allows late-stage sulfoximation of complex molecules in the industrial context.7

Stimulated by the continuous interest in sulfoximines, we wondered whether the N-arylation of NH-sulfoximines could be realized by the combination of classic transition-metal catalysis with visible-light photocatalysis (metallaphotocatalysis) (Figure 1B). Dual nickel photocatalysis has emerged as a powerful strategy and a remarkably efficient tool for organic cross-coupling reactions in the last years.8 In particular, N-arylation was reported for anilines, aliphatic amines, and also sulfonamides.9 We considered that NH-sulfoximines might be

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suitable substrates for such a strategy, keeping in mind that a prac-
ticable synthetic method should work not only on a milligram labo-
atory scale but also on a preparative multigram scale.

We started our investigations using similar reaction condi-
tions as reported by MacMillan et al.\textsuperscript{9c} NH-sulfoximine
\(1\text{a} \) (1.5 equiv) and bromoarene \(2\text{a} \) (1.0 equiv) as model
substrates were reacted with 1.0 mol % of [Ir]-Cat ([Ir-
(ppy)\(_2\)(dtbbpy)]PF\(_6\)) as photocatalyst, 5.0 mol % of [Ni-1]-
Cat (NiBr\(_2\) and dtbbpy as ligand (1.0:0.2 equiv) added
separately), and TMG (1,1,3,3-tetramethylguanidine, 1.5
equiv) as base in dry and degassed DMSO (0.25 M, 1.0 mL)
under nitrogen atmosphere. Irradiation with blue light of
455 nm for 3 h at 25 °C yielded the desired N-arylated sulfoximine
\(3\text{a} \) in an excellent yield of 94% (Table 1, entry 1).

Yields were determined by GC analysis with naphthalene
as internal standard.

With the optimized reaction conditions in hand (Table 1,
entry 6), we started to explore the scope of the reaction. First,
we focused on the scope of brominated arenes and
heteroarenes (Figure 2). Both electron-rich and electron-
deficient brominated arenes reacted smoothly with
NH-sulfoximine \(1\text{a} \), giving the respective N-arylated sulfoximines
\(3\text{a}−\text{r} \) in high to excellent yields (Figure 2A). For this type of
brominated substrates, we selected MeCN as solvent as it is
easily removed under reduced pressure. Many functional
groups, including thioethers (3c), cyanides (3f), ethers (3h
and 3j), amides (3k), or carbamates (3r), were tolerated under
the reaction conditions. Interestingly, the reaction of 1,3-
dibromobenzene stopped after 1-fold substitution, yielding
monobrominated \(3\text{l} \) as product. This observation could give
the opportunity for further functionalizations in other cross-
coupling reactions. In particular, the compatibility of
pharmaceutically relevant substrate classes like sulfoxides
(3m) or sulfones (3n) and bioisosteric scaffolds like −OCF\(_3\)
(3o), −SCF\(_3\) (3p), or −SF\(_5\) (3q) was investigated. Gratifying-
ly, all these moiety were found to be tolerated under the
reaction conditions and afforded the respective sulfoximines in
moderate to excellent yields. It has to be mentioned that the
lower yield of SF\(_5\)-containing sulfoximine \(3q \) is due to
decomposition of the brominated arene during the reaction.
In addition, we conducted a large-scale version of the reaction
in a custom-made reactor commonly used in our laboratories.
The reaction was carried out on a 27 mmol scale, affording 8.8
(g 99%) of product, using only 37 mg of [Ir]-Cat (0.15 mol 
%) and 26 mg of [Ni-2]-Cat (0.20 mol %).\textsuperscript{12}

The scope of brominated heteroarenes was explored with
common heteroaromatic scaffolds, occurring in pharmaceutical
agents or natural products (Figure 2B). Introducing the
sulfoximine moiety to established bioactive cores like indoles,
pyridines, quinolines, pyrimidines, pyrazines, and quinoxalines
reacted in high yield. Brominated \(2\text{a} \) reacted smoothly with
\(2\text{a} \) (0.25 mmol, 1.0 equiv), \(2\text{a} \) (0.28 mmol, 1.1 equiv), [Ir]-
Cat (0.15 mol %), [Ni-2]-Cat (0.20 mol %), TMG (0.30 mmol, 1.2
equiv), dry and degassed DMSO (0.25 M, 1.0 mL), irradiation at 455
nm for 3 h. Yields were determined by GC analysis with naphthalene
as internal standard.\textsuperscript{10} Reaction was up-concentrated to 0.75 M and
run for 17 h, and the yield is reported after purification via automated
flash-column chromatography.

Table 1. Optimization of the Reaction Conditions\textsuperscript{a,b}

| entry | \(1\text{a}/2\text{a} \) (equiv) | [Ir]-Cat (mol %) | [Ni]-Cat (mol %) | TMG (equiv) | yield (%) |
|-------|----------------|----------------|----------------|------------|----------|
| 1     | 1.5:1.0        | 1.0            | [Ni-1]-Cat (5.0)| 1.5        | 94       |
| 2     | 1.5:1.0        | 0.15           | [Ni-1]-Cat (5.0)| 1.5        | 96       |
| 3     | 1.5:1.0        | 0.15           | [Ni-1]-Cat (5.0)| 1.5        | 95       |
| 4     | 1.5:1.0        | 0.15           | [Ni-2]-Cat (0.20)| 1.5        | 76       |
| 5     | 1.0:1.1        | 0.15           | [Ni-2]-Cat (0.20)| 1.5        | 99       |
| 6     | 1.0:1.1        | 0.15           | [Ni-2]-Cat (0.20)| 1.2        | 99       |
| 7     | 1.0:1.1        | 0.15           | [Ni-2]-Cat (0.20)| 1.2        | 99\textsuperscript{d} |

\textsuperscript{a}[Ir]-Cat = [Ir(ppy)\(_2\)(dtbbpy)]PF\(_6\), [Ni-1]-Cat = NiBr\(_2\) + dtbbpy (1.0:0.2 equiv) added separately, and [Ni-2]-Cat = preformed [Ni-
dtbbpy]Br\(_2\). TMG = 1,1,3,3-tetramethylguanidine, \textsuperscript{b}Reaction conditions:
\(1\text{a} \) (0.25 mmol, 1.0 equiv), \(2\text{a} \) (0.28 mmol, 1.1 equiv), [Ir]-
Cat (0.15 mol %), [Ni-2]-Cat (0.20 mol %), TMG (0.30 mmol, 1.2
equiv), dry and degassed DMSO (0.25 M, 1.0 mL), irradiation at 455
nm for 3 h. Yields were determined by GC analysis with naphthalene
as internal standard. \textsuperscript{c}Reaction was up-concentrated to 0.75 M and
run for 17 h, and the yield is reported after purification via automated
flash-column chromatography.
A) Scope of brominated arenes:

B) Scope of brominated hetero arenes:

Figure 2. Substrate scope of bromoarenes. Reaction conditions: 1a (0.25 mmol, 1.0 equiv), bromo arene (2) (0.275 mmol, 1.1 equiv), [Ir]-Cat (0.15 mol %), [Ni-2]-Cat (0.20 mol %), TMG (1.2 equiv), dry and degassed MeCN (*) or DMA (**) (0.25 M), irradiation at 455 nm for 17 h; (a) 3.5 h; 17 h for the large-scale reaction; (b) 0.5 mol % of [Ir]-Cat, 1.0 mol % of [Ni-2]-Cat; (c) 0.2 mol % of [Ir]-Cat, 1.0 mol % of [Ni-2]-Cat; (d) 1,3-dibromobenzene (0.24 mmol, 1 equiv) as limiting reagent; (e) 0.5 mol % of [Ni-2]-Cat; (f) 0.5 mol % of [Ir]-Cat; (g) 1.0 mol % of [Ir]-Cat, 5.0 mol % of [Ni-2]-Cat; (h) 1.0 mol % of [Ni-2]-Cat; (i) 0.5 mol % of [Ir]-Cat, 3.0 mol % of [Ni-2]-Cat; (j) 0.5 mol % of [Ir]-Cat, 2.0 mol % of [Ni-2]-Cat; (k) 2.0 mol % of [Ni-2]-Cat; (l) 0.15 mol % of [Ir]-Cat, 2.0 mol % of [Ni-2]-Cat, 0.04 M.

99%), and the reaction with 2-bromobenzothiazole afforded sulfoximine 3ag in a moderate yield of 44%. Furthermore, methylxanthine alkaloid caffeine was tested as a substrate. The reaction of brominated caffeine afforded the respective N-arylated sulfoximine 3ah in an isolated yield of 29%.

Next, we focused on the scope of different NH-sulfoximines and conducted the reactions using methyl 4-bromobenzoate (2j) as model substrate (Figure 3A). Electron-rich as well as electron-deficient alkyl- and aryl-substituted NH-sulfoximines were suitable for the N-arylation reaction and afforded good to excellent yields of the desired products. Cyclopropyl moieties (3ai), benzyl positions (3ak), and heterocyclic scaffolds (3ap and 3aq) were well tolerated and yielded the respective products in moderate to excellent yields.

To further demonstrate the practicability of our method, we investigated whether the chiral information on an enantiopure NH-sulfoximine is conserved throughout the reaction to yield the respective enantiopure N-arylated sulfoximine. This allows the rapid generation of enantiopure substrate libraries. We investigated the reaction of an enantiopure NH-sulfoximine with various brominated arenes and heteroarenes (Figure 3B) and verified the optical purity of the products by chiral HPLC analysis. To our delight, the reaction of enantiopure NH-sulfoximine yielded the respective chiral cross-coupling products ((S)-3at−(S)-3ax), and no racemization was observed.

Finally, we decided to also test other sulfoximidoyl derivatives under the N-arylation conditions, optimized for NH-sulfoximines (Figure 3C). NH2-Sulfinamide 4 was reacted with methyl 4-bromobenzoate (2j) and afforded the respective product 5 in an excellent yield of 93%. Furthermore, applying
NH-sulfonimidamide 6 yielded the respective N-arylated sulfonimidamide 7 in a yield of 96%.

In conclusion, we demonstrated that NH-sulfoximines can be N-arylated with brominated arenes and heteroarenes as coupling partners, by using a dual nickel photocatalyzed strategy. For the conversion of most of the benzene-based NH-sulfoximines and brominated arenes, catalyst loadings of only 0.15 mol % of [Ir]-Cat and 0.20 mol % of [Ni-2]-Cat were sufficient and afforded up to 99% yield of the desired products. In addition, by careful adjustment of the catalyst loadings a diverse range of heteroaromatic substrates could be applied, including a series of relevant scaffolds occurring in natural products and bioactive compounds. Additionally, the reaction was carried out on a preparative scale of 27 mmol (8.8 g product) without any decrease in yield. Furthermore, it was shown that enantiopure products can be obtained by using enantiopure NH-sulfoximines as starting materials. Finally, we demonstrated that the same reaction conditions are suitable for structurally related sulfoximidoyl derivatives, like NH2-sulfinamides and NH-sulfonimidamides. The method extends the synthetic toolbox for the synthesis of sulfoximidoyl derivatives, and applications in the development of molecules for use in pharmaceutical industry or crop protection can be readily envisaged.

**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00698.
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(10) A comprehensive version of the optimization of the reaction conditions and all of the control reactions is displayed in the SI.
(11) For a mechanistic proposal and further experimental details, see the SI. Electron-transfer processes between the applied photocatalyst and nickel catalyst species cannot be ruled out.
(12) For further experimental details, see the SI.
(13) Due to the higher solubility of the brominated heteroarenes, mainly DMAC was used as solvent in this part of the substrate scope.
(14) The amounts of [Ir]-Cat and [Ni-2]-Cat used in these cases vary between 0.15–1.0 mol% and 0.20–5.0 mol%, respectively, and are displayed for every substrate in Figure 2.
(15) For further experimental details, see SI.