Visible-Light-Mediated Photoredox-Catalyzed *N*-Arylation of *NH*-Sulfoximines with Electron-Rich Arenes

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.201800607

Abstract: The direct C–H/N–H dehydrogenative cross-coupling of *NH*-sulfoximines with electron-rich arenes was realized by oxidative visible-light photoredox catalysis, applying 9-mesityl-10-methylacridinium perchlorate as an organic photocatalyst. Sulfoximines display diverse desirable properties for medicinal chemistry and the pharmaceutical industry. However, their preparation is still challenging. Our reaction proceeds without sacrificial oxidant, at room temperature and is highly selective for the C–N bond forming reaction. The scope of the reaction includes mono- and multi-alkylated and halogenated arenes, which are reacted with aromatic and aliphatic electron-rich and electron-poor *NH*-sulfoximines, giving moderate to excellent yields of the *N*-arylated sulfoximines. In addition, we successfully conducted the developed reaction on a gram scale (1.5 g). Mechanistic investigations show that both arene and *NH*-sulfoximine interact with the excited-state of the photocatalyst. We propose a radical-based mechanism, where both the arene and the *NH*-sulfoximine are photo-oxidized to their respective radical intermediates. Radical-radical cross-coupling subsequently leads to the *N*-arylated sulfoximine. Two electrons and two protons are released during the reaction and are subsequently converted into H_2 by a proton-reducing cobalt-catalyst.

Keywords: visible-light; photocatalysis; *N*-arylation; dehydrogenation; sulfoximines; radical reactions; cross-coupling

Introduction

Sulfoximines, the monoaza analogues of sulfones, are a rather uncommon class of substrates to many chemists, although their discovery goes back into the early 1950s.[1] Due to their chemical and configurational stability, first applications mainly focused on asymmetric reactions or catalysis where they act as chiral auxiliaries or ligands.[2] Only recently, it was realized that the diverse structure of sulfoximines has much more to offer, especially in medicinal chemistry and the pharmaceutical industry. Recent reports attest sulfoximines to be relevant bioactive structures, which display desirable metabolic stability and physicochemical properties in combination with hydrogen-bond acceptor/donor functionalities.[3] Consequently, pharmaceutical companies developed sulfoximine-based drugs or pharmaceutical agents. Several kinase inhibiting drug candidates for the treatment of cancer have already been introduced to clinical trials such as roniciclib, BAY 1143572 and AZD 6738 (Figure 1). Nevertheless, very limited synthetic procedures associated with safety concerns hampered the application of sulfoximines in drug discovery for a long time.[4]

Ideal sulfoximines for further functionalization and derivatization are unprotected *NH*-sulfoximines. Classic synthetic strategies proceed *via* three steps including oxidation and imination of sulfides and a final deprotection to the respective unsubstituted *NH*-sulfoximine.[5] Very recently, the groups of Bull and
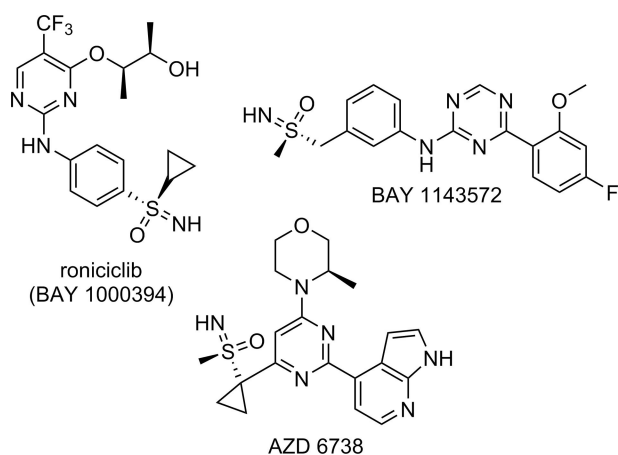
Figure 1. Examples for kinase inhibiting candidates for the treatment of cancer in clinical trials.

Scheme 1. Established transition-metal-catalyzed methods for the *N*-arylation of *NH*-sulfoximines and our new synthetic approach.

Luisi reported the direct synthesis of unsubstituted *NH*-sulfoximines from the respective sulfides in a "one-pot-synthesis".[6] This approach significantly facilitates the access to "free" *NH*-sulfoximines and further *N*-functionalization reactions. The direct *N*-arylation of *NH*-sulfoximines was first reported by the group of Bolm in 1998. Inspired by the palladium-catalyzed amination of aryl halides with amines by Buchwald[7] and Hartwig,[8] they successfully applied this concept to the cross-coupling of aryl bromides with *NH*-sulfoximines.[9] In the following years, various transition-metal-catalyzed (Pd, Cu, Ni and Fe) approaches have been developed, enabling the cross-coupling also with other aryl halides, aryl triflates, nonaflates, tosylates, arylboronic acids, diaryliodonium salts, arylsiloxanes, sodium arylsulfinates and acyl peroxides.[2i,n,10]

In order to avoid the need of pre-activated substrates Bolm and Jeganmohan described the direct transition-metal-catalyzed C–H bond activation and subsequent C–N bond formation with *NH*-sulfoximines (Scheme 1a. and b.).[11] However, such metal-catalyzed processes often require high reaction temperatures, pre-activated substrates or expensive metals combined with special ligands. Furthermore, in late-stage functionalization of complex molecules, the functional group compatibility can be challenging and metal-derived impurities can cause elaborative purification. In this context, it is surprising that only very few metal-free reports for the *N*-arylation of *NH*-sulfoximines have been reported. On one hand electrophilic azine *N*-oxides were found to be reactive enough to be coupled with *NH*-sulfoximines after activation with phosphonium salts.[12] On the other hand, in-situ generated arynes were successfully reacted with nucleophilic *NH*-sulfoximines by the group of Singh and Hosoya very recently.[13]
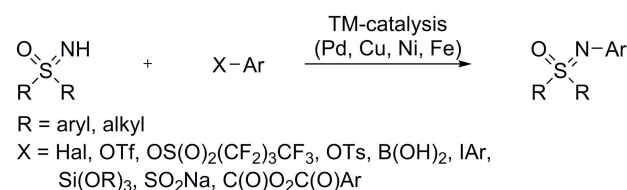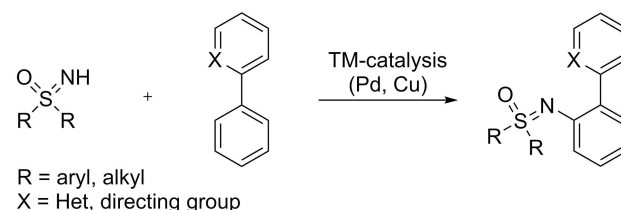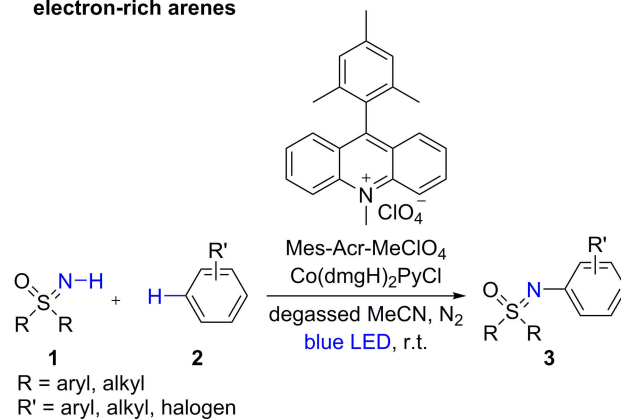
The reported methods for the *N*-arylation of *NH*-sulfoximines use transition-metal catalysis or require special reactive precursors or reagents. Visible-light photoredox catalysis enables the generation of highly reactive intermediates, but at the same time proceeds under very mild reaction conditions. This may facilitate selective and unique bond formations, which are inaccessible by classic synthetic methods. High-intensity, visible-light emitting diodes are commercially available and simple reaction set-ups now allow every chemist to conduct photoredox-catalyzed reactions without expended effort or expensive equipment.[14]

Very recently, metal-free organic photoredox catalysts were applied for the direct oxidative *N*-arylation of amines by the groups of Nicewicz and Lei.[15] These approaches demonstrate the advantages of visible-light photoredox catalysis in developing challenging unique bond formations in a very sustainable and

atom-economic manner. To the best of our knowledge, no visible-light photoredox-catalyzed approach for the *N*-arylation of *NH*-sulfoximines exists in the current literature. We therefore focused on developing a new synthetic strategy for the direct oxidative C–H/N–H dehydrogenative cross coupling of arenes and *NH*-sulfoximines *via* organic visible-light photoredox catalysis (Scheme 1c.).

Results and Discussion

Optimization of the reaction conditions

Inspired by the group of Lei utilizing a proton-reducing cobalt[15c,16] catalyst instead of sacrificial electron-donors for their photoredox-catalyzed systems, we wondered if such an approach also could be suitable for our envisioned cross-coupling system. We began our studies by employing *NH*-sulfoximine **1a** (0.1 mmol) and arene **2a** as model substrates for the dehydrogenative cross-coupling, together with 10 mol% 9-mesityl-10-methylacridinium (**A**) as organic photocatalyst and 10 mol% proton-reducing catalyst **D** in degassed acetonitrile (0.1 M) under nitrogen-atmosphere and irradiation with blue light of 455 nm for 20 hours at 25 °C (Table 1). To our delight, the desired product **3a** could be observed in a moderate yield of 41% (Entry 1). Exchanging the counter-anion of **A** to tetrafluoroborate did not improve the reaction (Entry 2). It has been previously reported that **A** can be unstable in the presence of nucleophiles or radicals, leading to decomposition of the photocatalyst. *NH*-Sulfoximines are reasonable nucleophilic. Therefore, we decided to exchange **A** by its modified version **C**, which has been reported to be more stable towards nucleophiles.[15a] Unfortunately, the yield of **3a** even decreased to 19% (Entry 3), which indicates that instability of **A** might not be a problem in our reaction. We further investigated the best ratio and catalyst loadings of **A** and **D** and found that 20 mol% of **A** and 10 mol% of **D** gave 67% of the *N*-arylated product **3a** (Entry 4). Being already quite satisfied with these results, we wondered if we could lower the amount of arene **2a**. Applying only four equivalents of **2a**, still gave a good yield of 55% of **3a**, whereas further decrease to only one equivalent significantly diminishes the reaction efficiency (Entries 5 and 6). Applying 4-fold excess of **1a** and therefore reversing the ratio of the substrates confirmed the observed trend (Entry 7). Considering methyl-arenes as one of the most readily available and cheap raw chemical materials,[17] further experiments were conducted with an excess of 10 equivalents. Although cobalt-catalyst **D** reacts highly efficient in our developed system, we were also interested if classic terminal oxidants like dioxygen, nitrobenzene or persulfate work as well in our reactions. We observed that the sulfoximine-

moiety was not stable in the presence of strong oxidants like dioxygen or persulfate under photo-irradiation conditions, but was transformed into the respective sulfone and sulfoxide, which were identified by GC-MS analysis (Entries 8 and 10). These results show that an oxygen-free atmosphere is highly important for our reaction system. Using nitrobenzene did not lead to decomposition of **1a**, but gave a yield of only 7% of the desired product (Entry 9). Further test reactions revealed that solvents like DCM, DCE, DMSO, MeOH or EtOH were not suitable for the reaction and afforded only small amounts of **3a**. Conducting the reaction without **A**, without **D** or without blue light irradiation (reaction in the dark) gave no product, which indicates that the reaction proceeds *via* a light-mediated process (Entries 11, 12 and 4[b], respectively).

Table 1. Optimization of the reaction conditions.

Entry	PC [mol%]	Co-cat [mol%] or oxidant (equiv.)	1a (equiv.)	2a (equiv.)	Yield[a] [%]
1	10 (**A**)	10 (**D**)	1	10	41
2	10 (**B**)	10 (**D**)	1	10	34
3	10 (**C**)	10 (**D**)	1	10	19
4	20 (**A**)	10 (**D**)	1	10	67 (0)[b]
5	20 (**A**)	10 (**D**)	1	4	55
6	20 (**A**)	10 (**D**)	1	1	27
7	20 (**A**)	10 (**D**)	4	1	27
8	20 (**A**)	O$_2$[c]	1	10	traces
9	20 (**A**)	1 PhNO$_2$	1	10	7
10	20 (**A**)	1 (NH$_4$)$_2$S$_2$O$_8$	1	10	0
11	No (**A**)	10 (**D**)	1	10	0
12	20 (**A**)	No (**D**)	1	10	0

[a] Yields were determined by GC analysis with chlorobenzene as internal standard.
[b] No yield when the reaction is conducted in the dark.
[c] A balloon filled with O$_2$ was connected to the vial *via* a syringe needle.

Scope of the reaction

With the optimized reaction conditions in hand, we were interested in the applicability of our method. Therefore, we first explored the scope of different arenes for the dehydrogenative cross-coupling with *NH*-sulfoximine **1a** (Table 2). Compared t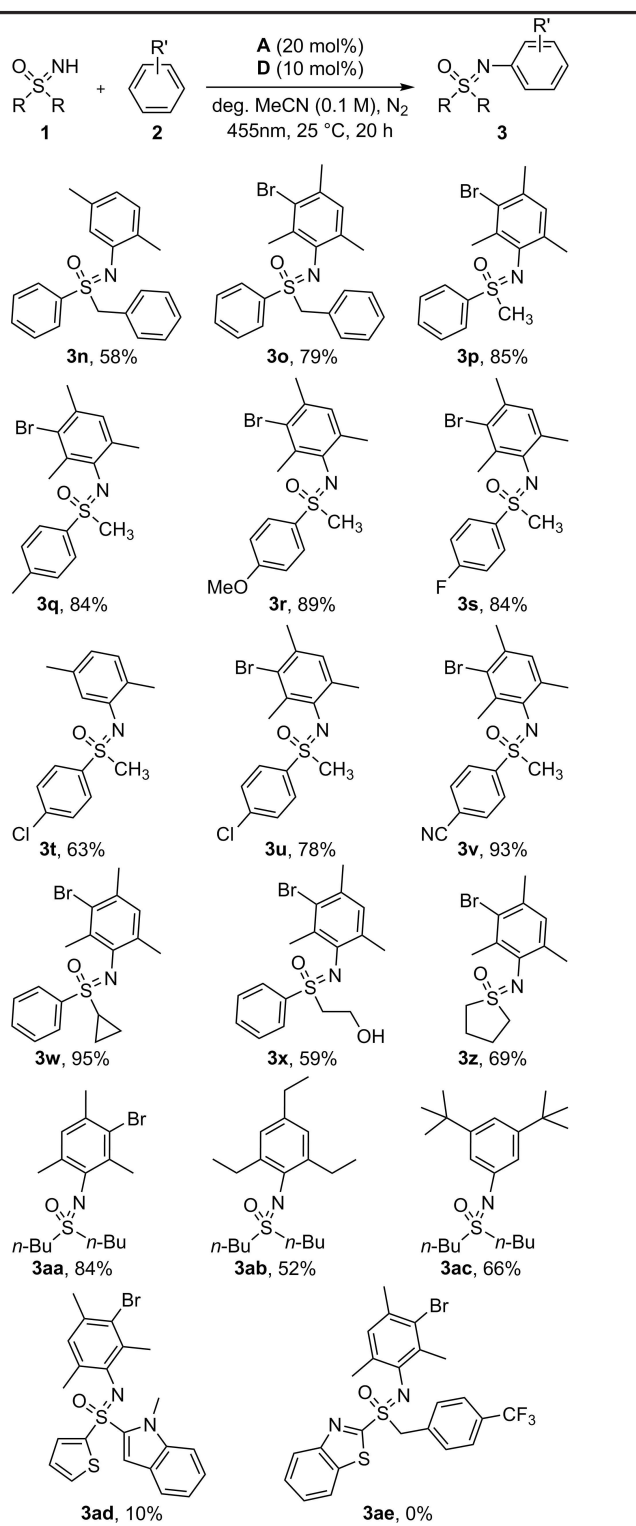o **3a**, which gave 61% of the desired product, the *ortho*- and *meta*-analogues afforded slightly lower, but still moderate yields. We also observed that in these unsymmetrical substrates the inductively more stabilized C–H-position of the arene is favorably functionalized. This also was recently highlighted in several reports and is due to better stabilization of the radical-cationic intermediate.[18]
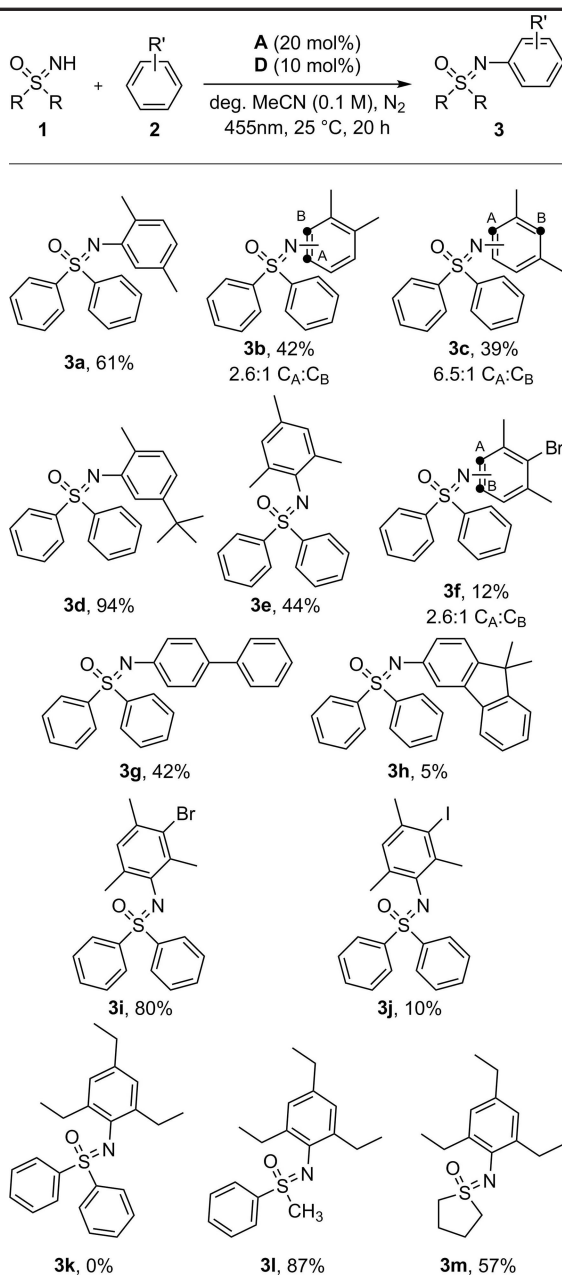
The coupling product with 4-*tert*-butyltoluene (**1d**) could be obtained in an excellent yield of 94%. We assume that on one hand the *tert*-butyl group donates even more electrons, to stabilize the radical-cationic intermediate, which subsequently leads to a higher yield. On the other hand, it is also bulky enough to block efficiently its *ortho*-C–H-position, giving only one regioisomer. Applying 1,3,5-trimethylbenzene or biphenyl as arene coupling partners, moderate yields of **3e** (44%) and **3g** (42%) could be obtained, whereas only trace amounts of the coupling product **3h** could be observed. To our delight, brominated and iodinated arenes were tolerated under our reaction conditions, giving the opportunity for further product functionalizations. Compound **3i** could be isolated in high yield (80%) while only using 5.3 equivalents, whereas 2-iodo-1,3,5-trimethylbenzene only afforded 10% of the coupling product (**3j**). Applying bulky 1,3,5-triethylbenzene we recognized, that steric hindrance can play a decisive role for our system. The reaction with **1a** did not proceed at all, whereas cross coupling with smaller *NH*-sulfoximines proceeded well and gave **3l** and **3m** in moderate to high yields. More electron-rich substrates like anisole or heterocyclic substrates like pyrroles and indoles were not suitable for the reaction and the substrates could be re-isolated in quantitative amounts. Simple benzene or toluene also did not react with *NH*-sulfoximine **1a**. The scope of the arene coupling partner is therefore limited to mono- and multi-alkylated and halogenated arenes, affording moderate to high yields.

Next, we investigated different *NH*-sulfoximines for our *N*-arylation procedure (Table 3). Benzylic positions or a free *S*-methyl substituent in sulfoximines were tolerated and afforded moderate to good yields. In addition, electron-donating *para*-methyl and *para*-methoxy substituents react smoothly. Electron-poor *NH*-sulfoximines containing fluorine-, chlorine or cyano-substituents were tolerated and gave up to 93% of the cross-coupling products. Even a cyclopropyl moiety was stable under the reaction conditions, yielding *N*-arylated sulfoximine **3w** in an excellent yield of 95%. *NH*-sulfoximine **1x** containing a free hydroxyl-group was selectively converted to the *N*-arylated product, which proves that our method is very selective for the formation of the C–N-bond, instead of a C–O-bond.

Furthermore, we could apply various aliphatic *NH*-sulfoximines, giving also moderate to high yields of the desired product. It has to be mentioned, that the

**Table 2.** Scope of electron-rich arenes for the *N*-arylation of *NH*-sulfoximines.

Reactions were carried out under optimized conditions in a scale of 0.1 mmol of *NH*-sulfoximine **1**. Yields of the products are reported as the average yield of two isolated reactions. Isomeric ratios were calculated by ^{1}H-NMR.

Table 3. Scope of *NH*-sulfoximines for the *N*-arylation arenes **2**.

3n, 58%	**3o**, 79%

(Products shown: **3n**, 58%; **3o**, 79%; **3p**, 85%; **3q**, 84%; **3r**, 89%; **3s**, 84%; **3t**, 63%; **3u**, 78%; **3v**, 93%; **3w**, 95%; **3x**, 59%; **3z**, 69%; **3aa**, 84%; **3ab**, 52%; **3ac**, 66%; **3ad**, 10%; **3ae**, 0%)

Reactions were carried out under optimized conditions in a scale of 0.1 mmol of *NH*-sulfoximine **1**. Yields of the products are reported as the average yield of two isolated reactions. Isomeric ratios were calculated by ¹H-NMR.

reaction with 1,3,5-tri-*tert*-butylbenzene leads to the *ipso*-substituted product **3ac**. The relatively facile replacement of the *tert*-butyl group is well known and can be attributed to the high stability of the respective *tert*-butyl radical cation as leaving group.[19] More complex *NH*-sulfoximines showed low or no conversion to the respective products. Only 10% of **3ad** could be isolated and no **3ae** could be obtained. Again, quantitative amounts of the unconverted substrates could be re-isolated. In general, a diverse scope of *NH*-sulfoximines was applicable for the cross-coupling reaction with different arenes. Both aromatic and aliphatic *NH*-sulfoximines containing electron-donating and electron-withdrawing functional groups, as well as benzyl, cyclopropyl and free hydroxyl moieties were tolerated and gave moderate to excellent product yields. However, more complex substrates, like **1ad** and **1ae**, showed low or no conversion to the respective *N*-arylated products.

Preparative-Scale Reaction

We also were interested in performing our reaction on a little larger preparative scale. Therefore, we conducted the reaction shown in Scheme 2 with 1.00 g of *NH*-sulfoximine **1a** (4.6 mmol, 1.0 equiv.) in a large-scale reactor developed in our laboratories (see also Supporting Information, section 3.). After 24 hours of irradiation with blue LEDs (455 nm) 1.50 g (79%) of the *N*-arylated sulfoximine **3i** was isolated.
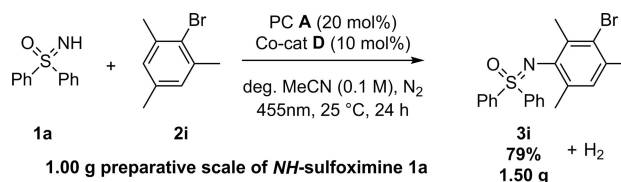
Scheme 2. Photoredox-catalyzed *N*-arylation reaction of **1a** in preparative scale.

The result shows that larger scale reactions can be realized for the developed reaction without decrease in yield or longer reaction times.

Mechanistic investigations

First, we performed a series of Stern-Volmer emission quenching studies (Figure 2 and Figure 3). The applied organic photocatalyst 9-mesityl-10-methylacridinium (Mes-Acr⁺-Me, **A**) exhibits an excited charge-transfer singlet-state with a reduction potential (E_{Red}^*) of +2.08 V vs. SCE upon irradiation with blue light of 455 nm.[20] The single-electron oxidation of **2a** (E_{Red} = +2.01 V vs. SCE[21]) to the corresponding radical cation is therefore thermodynamically feasible. The

emission intensity as well as the lifetime of the excited-state of the organic photocatalyst significantly decrease upon titration with **2a**, following a linear Stern-Volmer behavior (see also Supporting Information, Figure S8 and S11). In contrast to literature reports,[15a,c] where the applied nucleophiles did not quench the excited-state of the photocatalyst, also titration with **1a** decreased the fluorescence intensity and lifetime of the excited-state photocatalyst in a linear Stern-Volmer behavior, however with a smaller rate constant (see also Supporting Information, Figure S7 and S10). The observed quenching can be rationalized by the measured reduction potential for **1a** of $+2.00$ V vs. SCE (see Supporting Information, Table S1). These results show that the arene and the *NH*-sulfoximine both interact with the excited-state of the photocatalyst and a single-electron oxidation can lead to the respective radical cationic species.
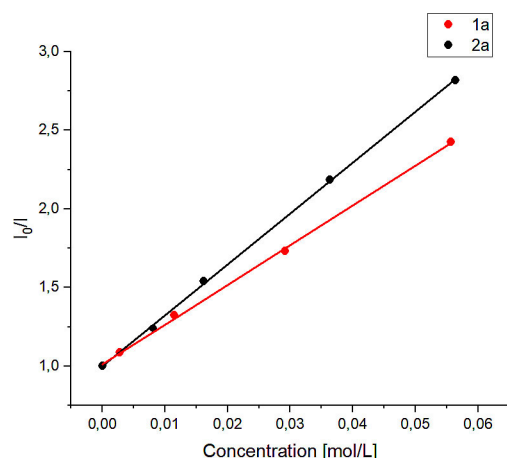
Figure 2. Steady-state Stern-Vomer plot of Mes-Acr$^+$-Me (**A**) emission quenching with *NH*-sulfoximine **1a** and arene **2a**.
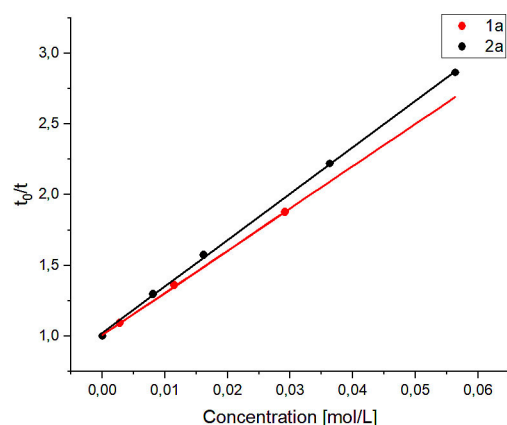
Figure 3. Time-resolved Stern-Vomer plot of Mes-Acr$^+$-Me (**A**) fluorescence lifetime quenching with *NH*-sulfoximine **1a** and arene **2a**.

Sulfoximine **1ae** did not react under our reaction conditions. Investigating the excited-state quenching by **1ae**, no decrease of the emission intensity of the photocatalyst was observed (see Supporting Information, Figure S9). Upon titration, the emission-intensity of the photocatalyst increased, which is explained by an accompanied slight increase of the absorbance in the UV-Vis spectrum (see Supporting Information, Figure S5 and S6). This may be due to changes in polarity in the microenvironment of the photocatalyst upon addition of **1ae**. However, no quenching of the excited-state of the photocatalyst could be observed and the reaction resulted in no product formation. We tried to determine the reduction potential of **1ae** by cyclic voltammetric measurements, but could not observe any corresponding oxidation signal up to $+2.4$ V vs SCE. We assume that the reduction potential of **1ae** is too high for a reaction with the photocatalyst in the excited-state, therefore no photo-oxidation to the reactive species occurs and consequently no cross-coupling reaction.

These results reveal that *NH*-sulfoximines, which do not quench the emission, cannot be converted in our developed reaction. This gives the opportunity for a facile selection of suitable substrates by emission quenching measurements.

Reactive radical intermediates can be trapped by TEMPO, yielding stable adducts of the respective intermediates.[22] As shown in Scheme 3 we conducted our standard reaction with one equivalent of TEMPO as additive and were able to identify the radical trapping product of TEMPO with the arene radical cation by LC-MS analysis (see Supporting Information section 4). Unfortunately, we could not observe any coupling with a potential *N*-centered radical of the *NH*-sulfoximine, which may be explained by competing fast hydrogen atom abstraction[23] from the solvent.
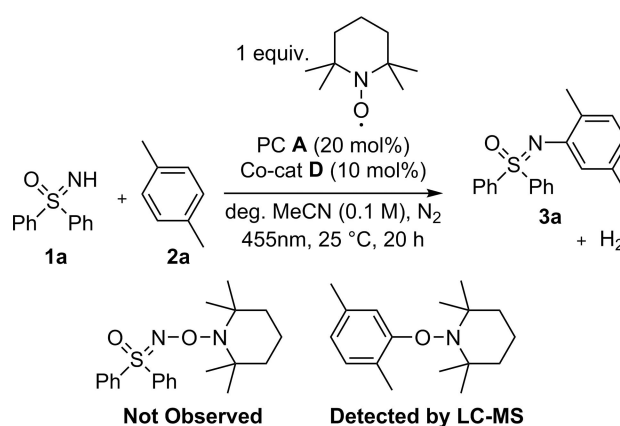
Scheme 3. TEMPO trapping experiment conducted with 1 equivalent of TEMPO under standard conditions.

Regarding the cobalt-catalyzed part of the mechanism, it is reported that step-wise reduction of the Co(III) complex leads to Co(II) and Co(I) species.[15c,16,24] We were able to visualize the formed Co(II) and Co(I) species by in-situ UV/Vis measurements (Figure 4). At the beginning of the reaction, the UV/Vis spectrum solely reflects the spectrum of the pure catalyst. Upon irradiation, characteristic absorption bands at 450 nm and 550–700 nm arise, which can be attributed to Co(II) and Co(I) species,[25] respectively. In addition, by headspace GC-TCD measurements we could detect nearly equimolar amounts of H_2 (89%) produced in the cross-coupling reaction yielding **3r**.
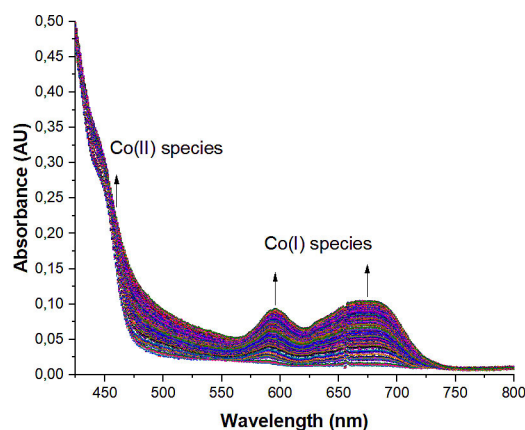
Figure 4. In-situ UV-Vis investigation of the reaction of **1a** with **2a** at a reaction concentration scale dependent on the photocatalyst concentration (**A**, 50 μM). Spectra are recorded every 10 seconds over a period of 30 minutes.

Mechanistic proposal

Based on the reported mechanism for the C–H/N–H dehydrogenative cross-coupling applying the Co(III) complex as proton-reducing catalyst, recent literature on radical-radical cross-coupling reactions and our experiments, we propose the following mechanism for the *N*-arylation of *NH*-sulfoximines (Scheme 4[26]): Upon irradiation with blue light the photocatalyst is excited to its charge-transfer singlet-state (**Mes•+-Acr•-Me**). Single-electron oxidation of arene **2** leads to the arene radical cation **2•+** and Mes-Acr•-Me radical. The photocatalytic cycle is closed *via* oxidation by the Co(III) complex, generating the ground-state Mes-Acr+-Me and a Co(II) species. In addition, *NH*-sulfoximine **1** is photo-oxidized by the excited photocatalyst, leading first to the radical cationic intermediate **1•+**, which can undergo fast deprotonation to the respective neutral *N*-centered radical intermediate **1•**. Now electrophilic **2•+** can cross-couple[27] with **1•**,

yielding the cationic intermediate **3+**. The final product **3** is formed *via* deprotonation and rearomatization. The Co(II) complex again is reduced to Co(I) by Mes-Acr•-Me to close the photocatalytic cycle. Addition of a proton leads to a Co(III)-hydride complex and releases H_2 upon addition of a second proton.
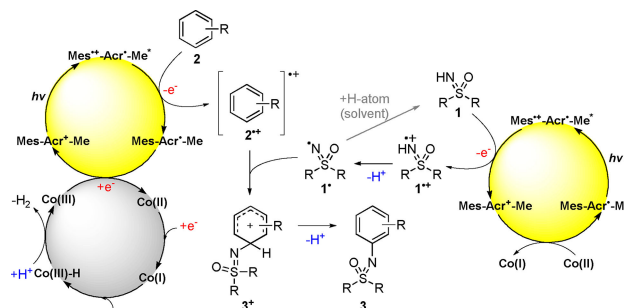
Scheme 4. Proposed mechanism for the *N*-arylation of *NH*-sulfoximines with electron-rich arenes.

Conclusion

In conclusion, we report the first visible-light photoredox-catalyzed direct *N*-arylation of *NH*-sulfoximines with alkylated arenes. A series of mono- and multialkylated and halogenated arenes react in the C–H/N–H cross-coupling with a diverse scope of aromatic and aliphatic electron-rich and electron-poor *NH*-sulfoximines. In addition, we conducted the reaction on a gram scale (1.5 g, 4.6 mmol). We could show, that our reaction proceeds *via* single-electron transfer steps initiated by the excited state of the photocatalyst 9-mesityl-10-methylacridinium perchlorate. A second, cobalt-catalyzed cycle closes the photocatalytic cycle and produces H_2 as the only byproduct. Stern-Volmer emission quenching studies indicate that both, arene and *NH*-sulfoximine interact with the excited state of the photocatalyst. Therefore, we propose a radical-radical cross-coupling mechanism initiated by visible-light photocatalysis. Our method can serve as a mild and selective synthetic tool for accessing *N*-arylated sulfoximines, which are of increasing importance in drug development and crop protection compounds.

Experimental Section

For full experimental data see Supporting Information.

General procedure for the photoredox-catalyzed N-arylation of NH-sulfoximines

A 5 mL crimp cap vial was equipped with solid *NH*-sulfoximine **1** (0.10 mmol, 1.0 equiv.), solid arene **2** (1.00 mmol, 10 equiv.; except **1i**, 0.53 mmol, 5.3 equiv.), 9-mesityl-10-methylacridinium perchlorate (**A**) (8.2 mg,

0.02 mmol, 20 mol%) as organic photocatalyst, Co(dmgH)$_2$ PyCl (**D**) (4.0 mg, 0.01 mmol, 10 mol%) as co-catalyst and a magnetic stirring bar and was capped with a septum. All liquid substrates were added *via* syringe after degassing. Nitrogen atmosphere was introduced *via* three cycles vacuum/nitrogen (2 min. at 7 mbar/2 min. nitrogen atmosphere). Degassed MeCN (1 mL, 0.1 M) was added *via* syringe under nitrogen atmosphere. The reaction mixture was stirred and irradiated using a blue LED (455 nm) for 20 hours at 25 °C under nitrogen atmosphere in a typical irradiation set-up used in our laboratories (see Supporting Information, Figure S1). The progress of the reaction could be monitored by GC analysis and GC/MS analysis. The reaction mixture was diluted with brine (10 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were dried with Na$_2$SO$_4$, filtered and the solvent was removed under reduced pressure. Evaporation of volatiles led to the crude product. Purification was performed by automated flash column chromatography (PE/EtOAc) yielding the corresponding pure product **3**.

Acknowledgements

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