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Nickel Metallaphotoredox Catalysis Enabling Desulfurative Cross Coupling Reactions

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Abstract: Metallaphotoredox processes have emerged as powerful methods for C–C bond formations. The Ni-photoredox catalyzed desulfurative cross-coupling of thiol derivatives with aryl bromides has now been established. This procedure provides access to simple and complex unsymmetrical diarylmethane molecules under mild reaction conditions with a broad functional group tolerance. The key steps of the reaction involve a silane-mediated halogen-atom transfer (XAT) and a subsequent intramolecular homolytic substitution (S_H2), forming C-centered radicals from various thiol derivatives as shown by mechanistic studies. This study paves the way for new transformations of abundant, naturally occurring thiols.

Keywords: Photoredox; Nickel; Thiols; Catalysis; Radicals

Transition-metal catalyzed cross-coupling reactions represent in the field of chemistry one of the greatest innovations and discoveries of the last century allowing the fast and selective generation of C–C bonds.^[1] Since the initial seminal reports involving palladium, numerous developments and new breakthrough concepts have enriched this field. Among them, metallaphotoredox catalysis, which merges photoredox and transition-metal catalysis, has been established as a valuable alternative to traditional palladium catalyzed C–C cross-couplings.^[2] Indeed metallaphotoredox reactions present the benefits of employing base transition metals, mainly nickel, and organic coupling partners that can be readily available, such as carboxylic acids (Figure 1A).^[3] Even though metallaphotocatalyzed C–C couplings have been intensively explored in recent years, so far, no protocol has addressed the challenge of forming C–C

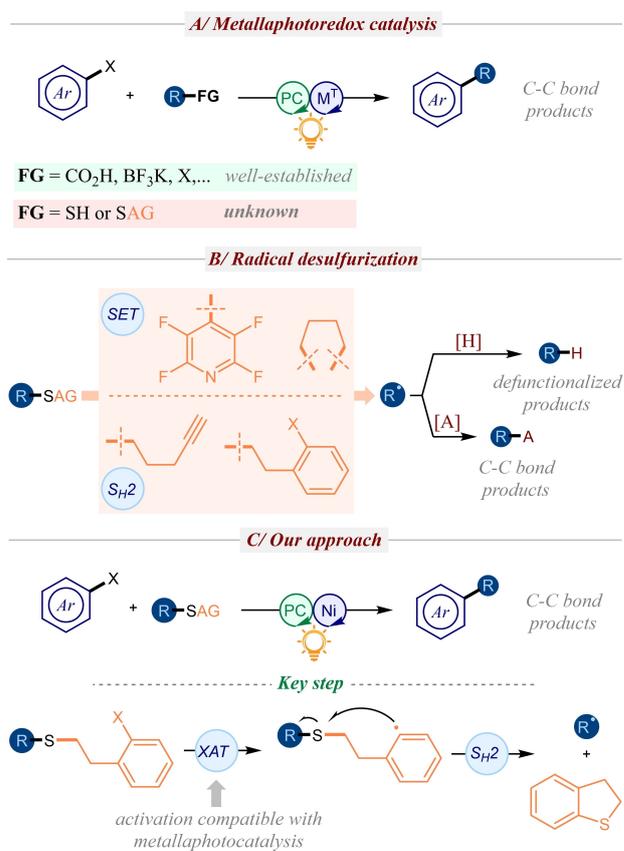


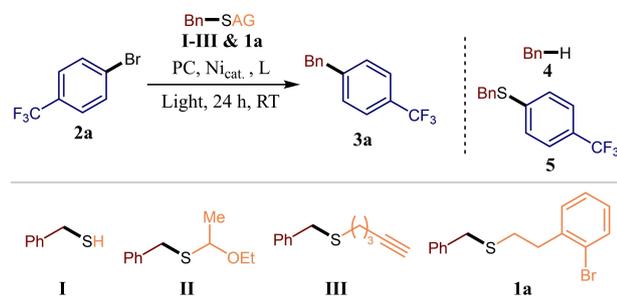
Figure 1. A/Overview of metallaphotoredox catalysis. B/Overview of radical desulfurization. C/Our approach.

bond products by desulfurative cross-coupling, involving the C–S bond activation of thiol derivatives (Figure 1A).^[2–3] This is rather surprising as desulfurization processes of sulfur-based materials are well-known in radical chemistry (Figure 1B).^[4] Indeed, over the years, diverse methods have been developed for achieving the C–S activation of thiol derivatives, including the naturally occurring amino acid

cysteine.^[5] These desulfurative procedures, which often lead to defunctionalized compounds (R–H) and to a much lesser extent to C–C bond products (R–A), often require the pre-installation of an activatable group (AG) (Figure 1B). Two main reactivity patterns allow to trigger the generation of C-centered radicals by desulfurization using AGs, (i) the single electron transfer (SET) reduction^[6–7] or (ii) the homolytic substitution reaction (S_H)^[8] (Figure 1B).

For instance, recent methodologies showed that perfluoropyridinyl^[6] or sulfonium^[7] derivatives could be reduced by a SET event conducting to carbon radical intermediates (Figure 1B). Unfortunately, given that one-electron reduction of substrates cannot be undertaken in nickel metallaphotocatalysis, such compounds are not good candidates for desulfurative coupling processes. In contrast, some of the AGs following the S_H mechanism might be compatible with the metallaphotoredox chemistry. Indeed, the desulfurization by homolytic substitution consists in the intramolecular radical addition of a transient radical species to the S-center (Figure 1C).^[8b] The transient radicals are either formed by initial radical addition (AGs bearing a triple bond) or by initial halogen atom transfer (XAT) (AGs bearing a halide) (Figure 1B & 1C). Therefore, we considered these AGs for developing the first desulfurative C–C cross-coupling in the metallaphotoredox field (Figure 1C). Herein, we describe preliminary results demonstrating that thiol derivatives can be used as radical precursors for forming simple and complex unsymmetrical diarylmethane molecules^[9] by desulfurative cross-coupling reactions.

At the beginning of the project, we explored the desulfurative coupling of various thiol precursors with aryl bromide **2a** (Scheme 1). Four thiol derivatives have been intensively studied in such couplings (see supporting information for more details and choice criteria). When thiol derivatives **I–III** were used, the reaction was not effective, affording the compound **3a** in poor to modest yields along with by-

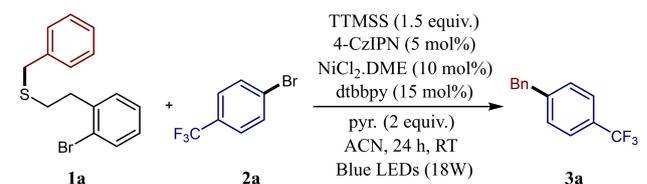


Scheme 1. Initial attempts for the desulfurative coupling using various thiol precursors. See supporting information for more details. PC = Photocatalyst. Ni_{cat} = Nickel catalyst. L = ligand.

products **4** and **5** (Scheme 1).^[10] Promising results were obtained by using the thiol precursor **1a**, allowing at the beginning, the formation of **3a** in modest yield (around 30%), however without the formation of by-products.

After optimization, the best reaction conditions were obtained with sulfur-based compound **1a** (1 equiv.), aryl bromide **2a** (1.5 equiv.), supersilane (TTMSS, 1.5 equiv.), pyridine (2 equiv.), NiCl₂·DME (10 mol%), dtbbpy (15 mol%) and the 4-CzIPN as photocatalyst (5 mol%) in acetonitrile under blue light irradiation at room temperature (Table 1, entry 1). Those conditions allowed the formation of **3a** in 64% NMR yield, isolated in 45% yield. The use of other silane or silanol sources resulted in a drastic drop of yields (Table 1, entries 2–4). Variation of the power of the light or solvents did not lead to the formation of **3a** in better yields (Table 1, entries 5–7). The use of inorganic bases such as KOAc, KH₂PO₄ or KO^tBu either provided **3a** in poor yields or resulted in no reaction (Table 1, entries 8–10). While the use of unsubstituted bipyridine ligand (bpy) resulted in a slight drop of yield (Table 1, entry 11), the use of the 4,4'-diOMe-bpy derivative appeared to be deleterious to the formation of **3a** (Table 1, entry 12). The

Table 1. Optimization of the desulfurative cross-coupling.^[a]



Entry	Deviations from standard conditions	Yield 3a (%) ^[b]
1	none	64 (45) ^[c]
2	Et ₃ SiH (1.5 equiv.)	N.R.
3	Ph ₃ SiH (1.5 equiv.)	N.R.
4	(TMS) ₃ SiOH (1.5 equiv.)	34
5	Blue LEDs (30 W)	44
6	Acetone, Blue LEDs (30 W)	34
7	DCE, Blue LEDs (30 W)	33
8	KOAc	0
9	KH ₂ PO ₄	22
10	KO ^t Bu	N.R.
11	bpy	54
12	4,4'-diOMe-bpy	23
13	NaBr (1.5 equiv.)	25
14	No TTMSS, no PC, no light, no Ni _{cat} , no ligand	N.R.

^[a] Reaction conditions: **1a** (0.3 mmol), **2** (0.45 mmol) in ACN (3 mL).

^[b] Yields were determined by ¹H NMR using trichloroethylene as an internal standard.

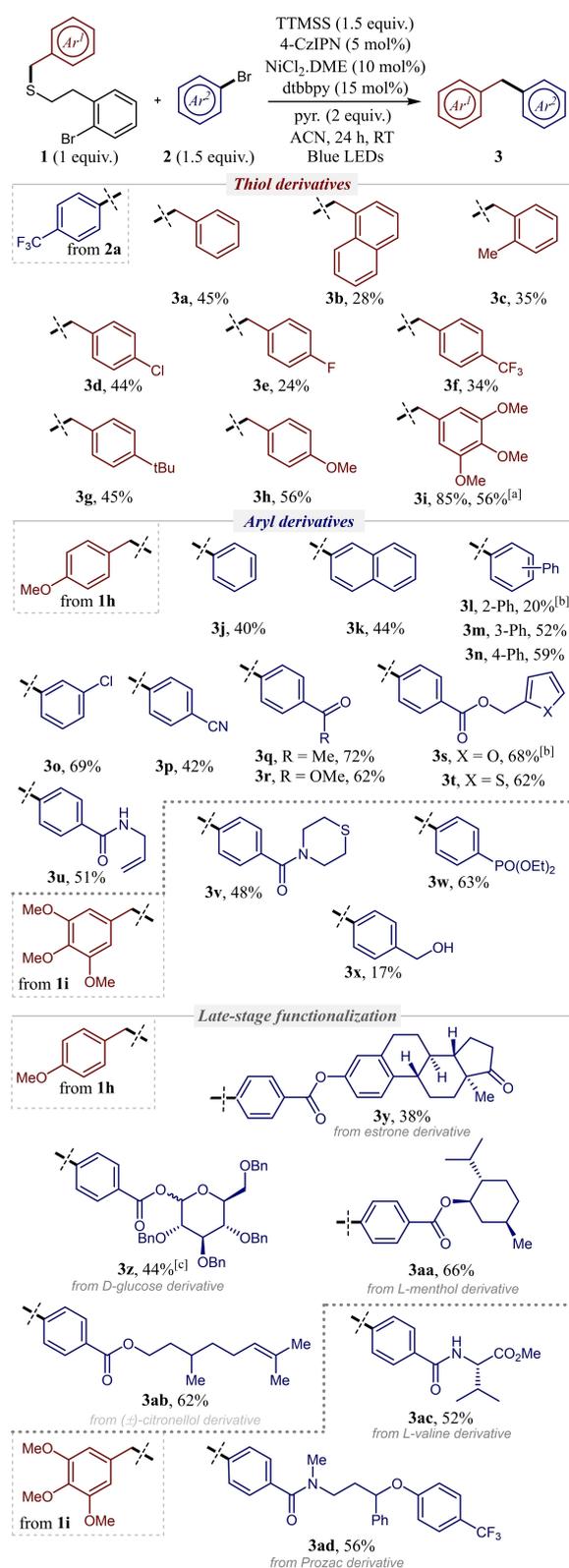
^[c] Isolated yield. N.R. = no reaction. TTMSS = (TMS)₃SiH. dtbbpy = 4,4'-Di-tert-butyl-2,2-dipyridyl. PC = 4-CzIPN.

reaction in the presence of NaBr as additive did not lead to any improvement (Table 1, entry 13).^[11] Finally, control experiments demonstrated that all the components of the reaction were essential for achieving desulfurative cross-coupling (Table 1, entry 14).^[12]

With the optimized conditions in hand, the scope of the desulfurative cross-coupling was further investigated (Scheme 2). First, we explored the reaction evaluating thiol derivatives.

While the coupling reaction with sterically hindered thiol derivatives, such as naphthyl or *o*-methylbenzyl groups, delivered the compounds **3b** and **3c** with modest yields, the reaction was effective with *para*- and *meta*-substituted benzyl derivatives (products **3d–3i**). However, the evaluation of the effect of the electronic-nature of substituents on these positions showed that benzyl moieties having electron-rich substituents gave better results compared to electron-poor counterparts. For instance, benzyl thiols bearing a fluorine atom or a trifluoromethyl group (**3e–3f**) gave modest yields, while benzyl thiols with alkyl or ether groups furnished the products **3g**, **3h** and **3i** in good yields (Scheme 2). To our regret, all the attempts using alkyl thiol derivatives, such as cyclohexanethiol, which are less stabilized than benzyl ones, did not lead to the effective formation of compounds **3** (<20% yields). Additionally, reactions performed with secondary benzyl thiols, such as 1-phenylethane-1-thiol, did not lead to the formation of expected products **3**. However, we were pleased to see that our protocol could be applied on a 5 mmol semi-preparative scale giving the compound **3i** in a good yield of 56%. Then, we explored the scope of the reaction changing aryl bromide partners (Scheme 2). Pleasingly, a large variety of aryl bromides **2** were successfully coupled with sulfur-based materials **1h** and **1i**, affording the corresponding compounds **3** in moderate to good yields. Interestingly, while the reaction was inefficient with *ortho*-substituted aryls (**3l**), *meta*- and *para*-substituted aryls afforded the products **3m** and **3n** in good yields. Additionally, while electron-poor aryl bromide partners led to compounds **3p–3w** in good yields, the use of electron-rich aryl derivatives resulted in the formation of product **3x** in poor yield. Nevertheless, the coupling in the presence of a free alcohol is quite remarkable.

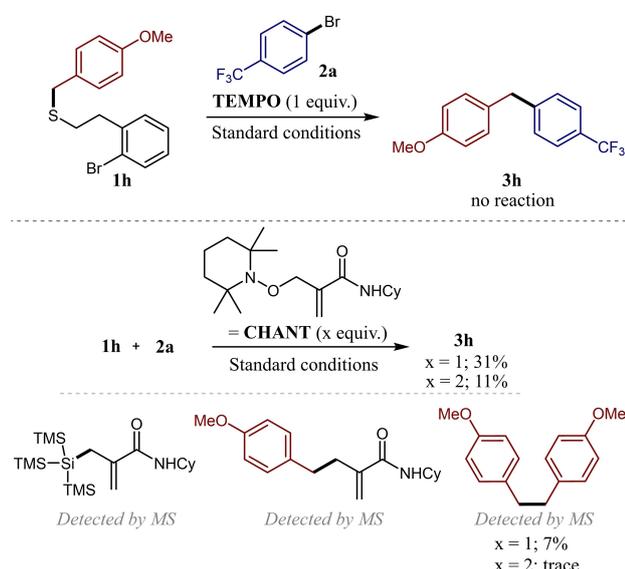
Finally, the late-stage functionalization of complex natural and bioactive molecules was explored (Scheme 2). We were pleased to find that our method could be readily applied without further optimization to the synthesis of a large variety of complex molecules in moderate to good yields, including compounds derived from estrone, D-glucose, L-menthol, L-valine, citronellol, and Prozac. Overall, this desulfurative coupling is well compatible with a



Scheme 2. Scope of the desulfurative cross-coupling reaction. Reaction conditions: **1** (0.5 mmol), **2** (0.75 mmol), TTMS (0.75 mmol), 4-CzIPN (5 mol%), NiCl₂·DME (10 mol%), dtbbpy (15 mol%) in ACN (5 mL). Yields refer to isolated products.^[a] On a 5 mmol scale, 48 h.^[b] ¹H NMR yield is given.^[c] On a 0.16 mmol scale.

wide range of functional groups including halides, ethers, thioethers, nitriles, ketones, esters, amides, alkenes, phosphites, thiophenes, furans, alcohols.

We then turned our attention to the elucidation of the reaction mechanism (Scheme 3). It should be noted that during the scope exploration, we observed in all cases the formation of the sulfur-containing heterocycle, 2,3-dihydrobenzo[*b*]thiophene in stoichiometric amount (Figure 2).^[13] The formation of this compound is fully consistent with the key step (S_H) proposed for the desulfurative process (Figure 1). Additionally, to gain further insights, we performed radical trapping experiments. First, the standard reaction was performed in the presence of the 2,2,6,6-tetramethyl-1-piperidinyloxy reagent (TEMPO; 1 equiv.). In those conditions, the reaction was completely inhibited (Scheme 3). Therefore, we were not able to detect any TEMPO-adduct by mass



Scheme 3. Mechanistic investigations: Radical trapping experiments. Yields were determined by ^1H NMR using trichloroethylene as an internal standard.

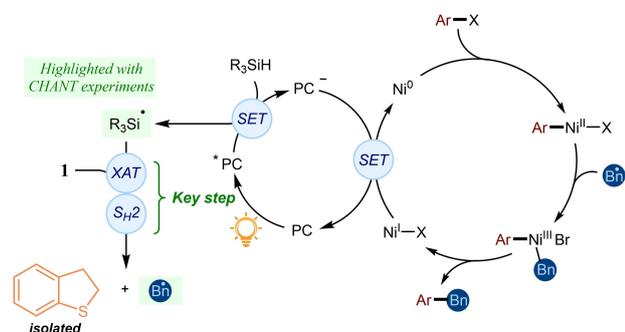


Figure 2. Mechanistic proposal for the nickel metallaphotocatalyzed desulfurative cross-coupling.

spectroscopy (MS) analysis. Consequently, we considered to use the *N*-cyclohexyl-2-(((2,2,6,6-tetramethylpiperidin-1-yl)oxy)methyl)acrylamide (CHANT) that has been recently designed for trapping short-lived radical intermediates (Scheme 3).^[14] In presence of CHANT (1 and 2 equiv.), reactions afforded the product **3a** in lower yields, respectively 31% and 11%. Moreover, these reactions allowed us to detect several compounds stemming from radical intermediates by MS analysis. Indeed, we were able to identify products derived from addition of $(\text{TMS})_3\text{Si}^\bullet$ and Bn^\bullet radical to CHANT, as well as from the dimerization of benzyl radicals (Scheme 3).

In view of the obtained mechanistic evidences and literature precedents, our desulfurative cross-coupling likely operates following the mechanism depicted in Figure 2. The process would start by the photoexcitation of the PC, which in the excited-state would oxidize the silane derivative, affording the corresponding silyl radical species $(\text{TMS})_3\text{Si}^\bullet$. The latter would be involved in an XAT with compound **1**, forming an aryl radical intermediate that would be engaged in an S_H process. This step would then give rise to the concomitant formation of benzyl radical and the 2,3-dihydrobenzo[*b*]thiophene.^[12] At the same time, the $\text{Ni}(0)$ complex would undergo oxidative addition with the aryl bromide, yielding the ArNi(II)X complex. The latter would intercept the benzyl radical, forming the Ni(III) intermediate, which after reductive elimination would release the C–C bond product along with a Ni(I) intermediate. Finally, SET reduction of the Ni(I) complex by the reduced form of the PC would close the two catalytic cycles (Figure 2).

In summary, we have established a desulfurative protocol enabling the formation of C–C bond products by nickel-photoredox catalysis. A broad range of diarylmethanes could be accessed from diverse thiol and aryl halide precursors. The reactions showed very good functional group tolerance and could therefore be successfully employed in the late-stage functionalization of complex scaffolds. Based on the mechanistic insights obtained during this study, we are currently focusing our efforts to exploit this reactivity for securing desulfurative C–C cross-coupling reactions involving alkyl thiols, especially cysteine derivatives.

Experimental Section

General Procedure

Preparation of diarylmethanes 3. In a Schlenk tube, TTMSS (233 μL , 0.75 mmol, 1.5 equiv.) was added to a solution of the selected thiol derivative **1** (0.5 mmol, 1 equiv.), the corresponding aryl bromide **2** (0.75 mmol, 1.5 equiv.), pyridine (83 μL , 1 mmol, 2 equiv.), $\text{NiCl}_2 \cdot \text{DME}$ (11 mg, 0.05 mmol,

10 mol%), dtbbpy (20 mg, 0.075 mmol, 15 mol%) and 4-CzIPN (20 mg, 0.025 mmol, 5 mol%) in ACN (5 mL). The reaction mixture was degassed via a freeze pump thaw procedure, and then placed in the EvoluChem™ PhotoRedOx reactor fitted with a 450 nm (18 W) EvoluChem lamp. The reaction was stirred under light irradiation at room temperature for 24 h. Then the reaction mixture was filtered over celite and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, appropriate mixture of hexane/ethyl acetate) to afford the corresponding product 3.

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- [11] Literature precedents have proposed that bromide can be oxidized to bromine radicals, which initiate the formation of silyl radicals, see ref **3 e**. Therefore, the use of bromide source as additive can affect beneficially the reaction outcome.
- [12] Additionally to these control experiments, a reaction in the dark without the use of 4-CzIPN and in presence of 20 mol% of AIBN at 50 °C during 24 h has been performed. In these conditions the formation of **3 a** was not observed.
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COMMUNICATIONS

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Adv. Synth. Catal. **2022**, *364*, 1–7

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