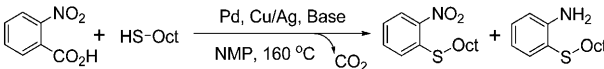


Synthesis of Aryl Sulfides by Decarboxylative C–S Cross-Couplings

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Aryl sulfides are used in advanced materials and industrial chemicals such as organic semiconductors, herbicides, lubricants, and high boiling point solvents.^[1] They are also key intermediates for the preparation of pharmaceuticals.^[2] Despite the phenomenal growth in diverse synthetic methodologies, the primary method for the synthesis of aryl sulfides is limited to the condensation reaction between a metal thiolate and an alkyl or aryl halide.^[3] Organohalides are a health and environmental concern, and organohalide waste requires costly remediation, particularly on an industrial scale. In contrast, carboxylic acids are generally environmentally benign and readily prepared reagents. Decarboxylation of carboxylic acids by loss of carbon dioxide (CO₂) has recently emerged as a promising coupling reaction, but only in the context of C–C, C–N, and C–Se bond-forming transformations.^[4] To the best of our knowledge, a process for decarboxylative C–S bond formation has never been proposed or experimentally validated in the literature. We reasoned that the direct decarboxylative C–S coupling of aryl carboxylic acids and thiols,

Table 1. Decarboxylative C–S coupling under different conditions.^[a]

				
Entry	Pd (mol %)	Cu/Ag (equiv)	Yield ^[b] [%]	
			-NO ₂	-NH ₂
1	Pd(OAc) ₂ (5.0)	–	<3	<3
2	–	CuCO ₃ ·Cu(OH) ₂ (1.5)	18	8
3	AgBF ₄ (10.0)	CuCO ₃ ·Cu(OH) ₂ (1.5)	10	<3
4	Ag ₂ O (5.0)	CuCO ₃ ·Cu(OH) ₂ (1.5)	15	<3
5	Pd(OAc) ₂ (5.0)	AgBF ₄ (1.0)	<3	<3
6	Pd(OAc) ₂ (5.0)	Ag ₂ O (1.0)	<3	<3
7 ^[c]	Pd(OAc) ₂ (5.0)	CuCO ₃ ·Cu(OH) ₂ (1.5)	26	46
8	Pd(OAc) ₂ (5.0)	CuCO ₃ ·Cu(OH) ₂ (1.5)	<3	96(90)
9 ^[d]	Pd(OAc) ₂ (5.0)	CuCO ₃ ·Cu(OH) ₂ (1.5)	57	12
10 ^[e]	Pd(OAc) ₂ (5.0)	CuCO ₃ ·Cu(OH) ₂ (1.5)	41	48
11	Pd(OAc) ₂ (2.5)	CuCO ₃ ·Cu(OH) ₂ (1.5)	56	24
12	Pd(OAc) ₂ (5.0)	CuCO ₃ ·Cu(OH) ₂ (1.0)	19	69
13	Pd(OAc) ₂ (5.0)	CuCO ₃ ·Cu(OH) ₂ (0.75)	66(52)	10
14	Pd(OAc) ₂ (5.0)	CuCO ₃ ·Cu(OH) ₂ (0.50)	59	13
15	Pd(OAc) ₂ (5.0)	CuCO ₃ ·Cu(OH) ₂ (0.38)	22	10

[a] Reaction conditions: aryl acid (0.5 mmol), 1-octanethiol (0.75 mmol), KF (3 equiv), NMP (3 mL), 160 °C, 24 h. [b] GC yield. Isolated yield is in parenthesis. [c] Without KF. [d] Under a nitrogen atmosphere. [e] KOH (3 equiv) was used as the base for KF.

if possible, would provide an alternative access to aryl sulfides without the need for halocarbon precursors. Herein, we describe the integration of these concepts into the transition-metal-catalyzed synthesis of a broad range of aryl and diaryl sulfides.

To test our hypothesis and also to identify an effective catalyst system, coupling reactions of 2-nitrobenzoic acid with 1-octanethiol (1.5 equiv) were first carried out in the presence of different combinations of transition-metal catalysts at elevated temperatures. Selected results from our screening experiments are summarized in Table 1. Our studies showed that these reactions formed decarboxylative coupling products containing a mixture of nitrobenzene and aminobenzene sulfides. Reactions conducted with monometallic Pd^{II}, Cu^{II} or bimetallic Cu^{II}/Ag^I, Pd^{II}/Ag^I catalysts resulted in low conversions of starting materials (Table 1, entries 1–6). The reactions with bimetallic Pd^{II}/Cu^{II} catalysts occurred with moderate to excellent conversions (Table 1,

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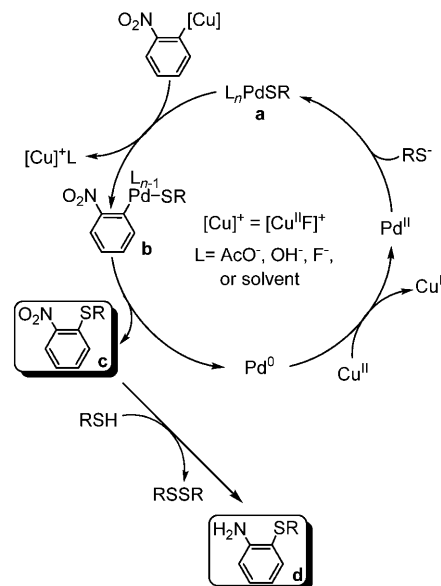
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/chem.200900133>.

entries 7–15). Importantly, optimal conversion to aminobenzene sulfide was achieved with a catalytic amount of Pd(OAc)₂ (5 mol %) combined with CuCO₃·Cu(OH)₂ (1.5 equiv) and KF (3 equiv) in *N*-methyl-2-pyrrolidone (NMP) at 160 °C for 24 h (Table 1, entry 8). In contrast to KF, a control reaction conducted by using KOH as the base only gave a relatively low yield of the coupling product (Table 1, entry 10). This can be attributed to an increase in Pd^{II} catalyst solubility and stability in the presence of the KF relative to KOH. It should be noted that the reaction was carried out without the exclusion of oxygen and moisture. Our studies also indicated that equimolar amounts of 2-nitrobenzoic acid and 1-octanethiol under the same conditions afforded a mixture of nitrobenzene and aminobenzene sulfides (see the Supporting Information, Table S1).

In a further set of experiments, a series of thiols and 2-nitrobenzoic acid were evaluated under the optimal conditions, and the results are summarized in Table 2. Primary aliphatic thiols such as 1-decanethiol and 1-butanethiol were successfully transformed to aminobenzene sulfides in high yields (Table 2, entries 1–3), while cyclohexanethiol and aromatic thiols yielded nitrobenzene sulfides as major products (Table 2, entries 4–8). Notably, disulfide precursors also resulted in high yields of nitrobenzene sulfides (Table 2, en-

tries 9, 10), providing an alternative to the use of more reactive and odiferous thiols.

A hypothetical mechanism for the decarboxylative C–S coupling reaction is depicted in Scheme 1. The organometallic nucleophile formed upon decarboxylation initially reacts



Scheme 1. Proposed mechanism for the synthesis of aryl sulfides by decarboxylative C–S cross-coupling of 2-nitrobenzoic acid and thiols.

Table 2. Decarboxylative coupling of 2-nitrobenzoic acid with thiols or disulfides.^[a]

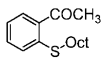
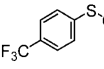
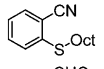
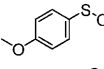
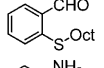
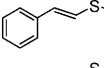
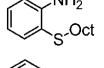
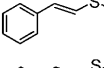
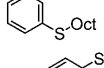
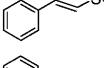
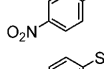
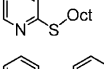
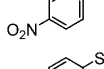
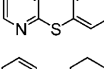
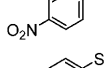
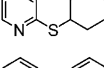
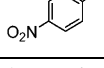
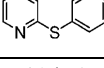
$ \begin{array}{c} \text{NO}_2 \\ \\ \text{C}_6\text{H}_4 \\ \\ \text{CO}_2\text{H} \end{array} + \begin{array}{c} \text{HSR} \\ \text{or} \\ \text{RSSR} \end{array} \xrightarrow[\text{KF, NMP, 160 }^\circ\text{C, 24h}]{\text{Pd(OAc)}_2, \text{CuCO}_3 \cdot \text{Cu(OH)}_2} \begin{array}{c} \text{NO}_2 \\ \\ \text{C}_6\text{H}_4 \\ \\ \text{S-R} \end{array} + \begin{array}{c} \text{NH}_2 \\ \\ \text{C}_6\text{H}_4 \\ \\ \text{S-R} \end{array} $			
Entry	HSR or RSSR	Product	Yield ^[b] [%]
1	HS-(CH ₂) ₁₁ CH ₃		85
2	HS-CH ₂ CH ₂ CH ₂ CH ₃		80
3			70
4			75
5			68
6			73
7			81
8			73
9			85
10			77

[a] All the reactions were carried out with aryl acid (0.5 mmol) and thiols (0.75 mmol) in the presence of Pd(OAc)₂ (5.0 mol %), CuCO₃·Cu(OH)₂ (1.5 equiv), and KF (3.0 equiv). [b] Yields of isolated products are the average of at least two experiments.

with an electrophilic Pd^{II} thiolate (**a**) intermediate to form an aryl palladium(II) species (**b**). Subsequent reductive elimination generates the aryl sulfide coupling product (**c**), followed by Cu^I-mediated oxidation of the previously reduced Pd⁰ species to regenerate the Pd^{II} compound and thus continue the catalytic cycle for the palladium.^[5] The conversion to aminobenzene sulfide (**d**) through use of alkyl thiols is possibly ascribed to the more facile auto-oxidation of the alkyl thiols relative to aryl thiols. In the presence of a palladium catalyst, an excessive amount of alkyl thiols promotes the reduction of the coupling product **c** to the aminobenzene sulfide **d**. This hypothesis was further confirmed by control experiments on the reduction of nitrobenzene with alkyl thiols (see the Supporting Information, Table S2). In the absence of the alkyl thiol, a very low yield (5 %) of aniline product was observed in the control experiment.

To expand the scope of the method, a wide range of aryl carboxylic acids were tested as substrates for C–S coupling (Table 3). Benzoic acids with electron-withdrawing substituents in the *ortho*-position give the coupling products in moderate to high yield (Table 3, entries 1–3). In contrast, benzoic acid with an electron-donating substituent in the *ortho*-position did not proceed under the identical conditions (Table 3, entry 4). In addition, the use of benzoic acids without a substituent (Table 3, entry 5) or with a *para*-substituent (Table 3, entries 6–11) resulted in a low yield of the coupling

Table 3. Decarboxylative coupling of carboxylic acid with thiols or disulfides.^[a]

$\text{R}^1\text{-COOH} + \text{HSR or RSSR} \xrightarrow[\text{KF, NMP, 160 } ^\circ\text{C, 24 h}]{\text{Pd(OAc)}_2, \text{CuCO}_3 \cdot \text{Cu(OH)}_2} \text{R}^1\text{SR}$					
Entry	Product	Yield ^[b] [%]	Entry	Product	Yield ^[b] [%]
1		55	10		27
2		76	11		28
3		85	12		90
4 ^[c]		< 3	13		88
5		31	14		85
6		25	15		95
7		70	16		92
8 ^[d]		47	17		90
9		14	18		80

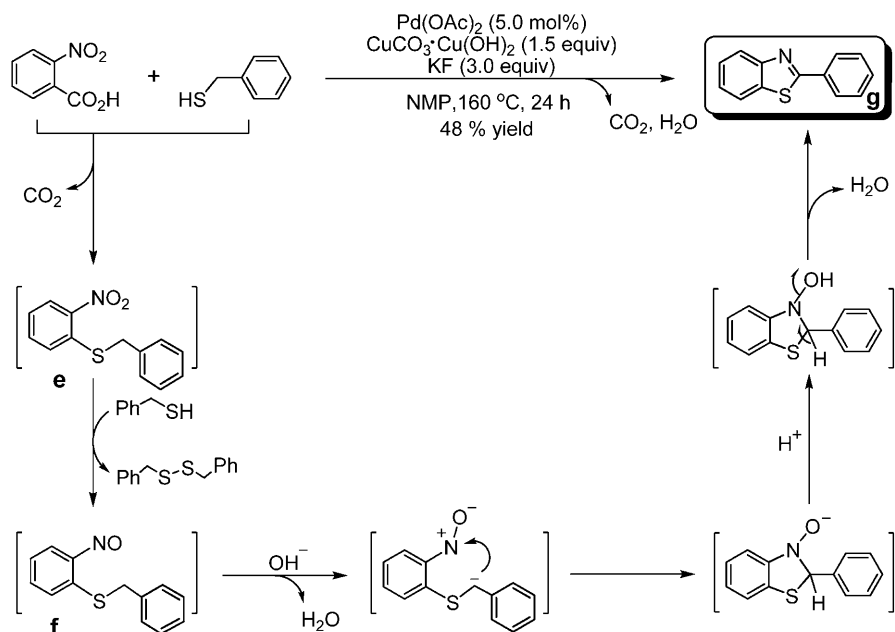
[a] All the reactions were carried out with aryl acid (0.5 mmol) and thiols (0.75 mmol) in the presence of Pd(OAc)₂ (5.0 mol %), CuCO₃·Cu(OH)₂ (1.5 equiv), and KF (3.0 equiv) in NMP (3 mL) at 160 °C. [b] Yields of isolated products are the average of at least two experiments. [c] GC Yield. [d] Ethyl disulfide was used.

product, possibly due to the inefficiency in the decarboxylation of these arylcarboxylic acids under the current conditions.^[4p] Importantly, this C–S coupling strategy can be extended to vinyl and heteroaromatic substrates (cinnamic acid and pyridine-2-carboxylic acid). These carboxylic acid derivatives were converted to the corresponding sulfides in excellent yields for most cases (Table 3, entries 12–18).

Another notable application of the newly developed direct decarboxylative C–S cross-coupling is the synthesis of a benzothiazole compound and possibly its derivatives that have found many uses as industrial dyes and antitumor drug candidates.^[6] Conventional methods typically rely on the cyclization

of 2-haloanilides in the presence of Lawesson's reagent.^[7] Alternatively, benzothiazoles can be synthesized by a C–H functionalization/intramolecular C–S bond-formation process.^[8] We discovered that a benzothiazole compound can be alternatively obtained in a moderate yield by a decarboxylative cross-coupling of 2-nitrobenzoic acid with benzyl thiol under our standard reaction conditions (Scheme 2). Once refined, this approach may prove particularly attractive because it utilizes readily prepared aryl carboxylic acids and generates CO₂ and H₂O as by-products rather than hydrogen halides, which are formed from the analogous synthesis with the aryl halide reagent. We attributed this organic transformation to a process that possibly involves a nitroso intermediate (**f**), which is formed via reduction of the decarboxylative coupling product (**e**) by the benzyl thiol (Scheme 2). The nitroso intermediate subsequently undergoes intramolecular cyclization by preferential attack on the benzyl carbon in the presence of a base, followed by acidification and dehydration to afford the benzothiazole product (**g**).

The first identification of direct decarboxylative C–S cross-couplings is important because these proof-of-concept reactions shall provide a valuable and versatile synthetic method for a broad range of aryl sulfides without the need for a halocarbon precursor. On the basis of the above findings, further mechanistic investigation and catalyst optimization by introducing small organic ligands for enhanced decarboxylative C–S bond-forming reactions under relatively mild conditions are currently in progress.



Scheme 2. Proposed mechanism for the synthesis of 2-phenyl-benzothiazole by decarboxylative C–S cross-coupling.

Experimental Section

Typical procedure: $\text{CuCO}_3 \cdot \text{Cu}(\text{OH})_2$ (165 mg, 0.75 mmol), $\text{Pd}(\text{OAc})_2$ (5.6 mg, 0.025 mmol), and KF (87 mg, 1.5 mmol) were added to a solution of *N*-methyl-2-pyrrolidone (NMP) (3 mL) charged with carboxylic acid (0.5 mmol) and thiol (0.75 mmol). The resulting mixture was stirred at 160 °C and monitored by TLC. Upon completion of the reaction (ca. 24 h), the mixture was cooled to room temperature, poured into a solution of HCl in water (1 N, 15 mL), and extracted several times with ethyl acetate (15 mL). The combined organic layers were washed with water and brine, dried over Na_2SO_4 , and filtered. The solvent was removed in vacuo and the residue was purified by column chromatography (silica gel, eluent: hexane/ethyl acetate) to afford the coupling product.

Acknowledgements

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Keywords: carboxylic acid • cross-coupling • decarboxylation reaction • thiols • transition metals

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