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Palladium and Nickel-Catalyzed Decarbonylative C–S Coupling to Convert Thioesters to Thioethers

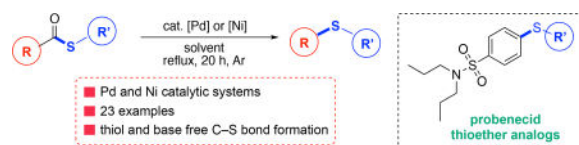
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Abstract

This Letter describes the development of a catalytic decarbonylative C–S coupling reaction that transforms thioesters into thioethers. Both Pd- and Ni-based catalysts are developed and applied to the construction of diaryl, aryl-alkyl, and heterocycle-containing thioethers.

Graphical abstract



The aryl thioether functional group appears in a variety of pharmaceuticals and agrochemicals.¹ For instance, a number of top-selling drugs,² including Seroquel,³ Trintellix,⁴ Teflaro,⁵ and Inlyta,⁶ contain aryl thioether moieties (Figure 1). Aryl thioethers are most commonly prepared via the coupling of an aryl halide or pseudohalide with a thiol in the presence of base.^{7–10} With electron deficient aryl halides, these reactions often proceed via an uncatalyzed S_NAr pathway,⁷ while Pd or Cu catalysis⁸ is commonly employed to forge the C–S bond with electron rich (hetero) aryl halides (Figure 2a).

In this Letter, we report an alternate approach to aryl thioethers, involving a metal-catalyzed intramolecular decarbonylative coupling of thioesters (Figure 2b). This process offers several advantages over conventional aryl halide/thiol cross-couplings. First, carboxylic acids (the precursors to thioesters) are often more readily available and less expensive than their aryl halide counterparts.^{11–14} Second, this transformation proceeds under base-free conditions and without the requirement for exogenous thiol¹⁵ nucleophiles.¹⁶ Finally, we demonstrate that both Pd and Ni complexes are competent catalysts for this transformation, and further that they exhibit complementary reactivity and selectivity profiles with some substrates.

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details, characterization, and NMR data for isolated compounds (PDF)

At the outset of our studies, we noted sporadic literature reports of metal-mediated decarbonylative thioetherification reactions.^{17–19} However, most prior examples employed stoichiometric quantities of Ni or Rh complexes. Furthermore, the reported reactions were demonstrated with a narrow scope of unfunctionalized substrates. Our work in this area was inspired by recent reports of the Ni and/or Pd-catalyzed intramolecular decarbonylation of aryl esters²⁰ and aroyl chlorides²¹ to form C(sp²)-O and C(sp²)-Cl bonds, respectively. As shown in Figure 2b, we hypothesized that a similar process involving: (i) oxidative addition of a thioester to form an acyl metal thiolate (**A**), (ii) decarbonylation to form an aryl thiolate intermediate (**B**), and finally (iii) C-S bond-forming reductive elimination would enable the catalytic formation of diverse thioether products.

We initiated our studies with *S*-phenyl benzene thiolate **1a** as the substrate. Our previous work on the decarbonylative coupling of aroyl chlorides showed that Pd complexes bearing bulky mono-phosphine ligands (e.g., P(*o*-tol)₃ and BrettPhos) were the most effective catalysts. Thus, we initially explored the use of 10 mol % of Pd[P(*o*-tol)₃]₂ as the catalyst. As shown in Table 1, entry 1, these conditions afforded the desired product, diphenylsulfide **2a**, in 28% yield in xylene at 150 °C. We next explored the use of Pd[P(*o*-tol)₃]₂ in conjunction with various mono- and bisphosphine ligands.²² As shown in Table 1, many of these ligands afforded improvements in yield, and the best result (78% yield) was obtained with the sterically bulky monophosphine PAD₂Bn (entry 7).

We also pursued an analogous Ni-catalyzed reaction, since Ni-based catalysts have been much more widely used for decarbonylative couplings than their Pd analogues.²³ The combination of 10 mol % of Ni(cod)₂, and 20 mol % of PAD₂Bn (the optimal ligand for the Pd system) in toluene at 130 °C afforded **2a** in 85% yield. Furthermore, switching to PCy₃ resulted in the formation of **2a** in nearly quantitative yield (entry 10).

We next examined the scope of these Pd- and Ni-catalyzed C-S coupling reactions. As shown in Scheme 1, substrates bearing electron-donating and electron withdrawing substituents on the thiol-derived fragment underwent high yielding decarbonylative thioetherification to afford products **2i-l** under both Pd and Ni catalysis. A wide variety of substituents were well-tolerated on the carboxylic acid-derived portion of the substrate. For instance, benzylic C-H bonds (**2b**), carboxylic acid esters (**2e**), and boronate esters (**2f**) were compatible with the reaction conditions. Notably, the low (27%) yield observed with 4-anisoyl phenylthiolate **2c** under Pd catalysis is due to the formation of diaryl sulfides as by-products.²⁴ In contrast, under Ni catalysis **2c** was obtained in 75% yield. Sterically hindered thioesters also reacted to form the corresponding thioether products (**2g,h**), and the Ni catalyst provided higher yields with these substrates. Finally, heterocycles including thiophene (**2m**), pyridine (**2n**), and chromenone (**2o**) were well tolerated, particularly with the Ni catalyst.

The decarbonylation of *S*-phenyl (*E*)-3-phenylprop-2-enethioate proceeded to form **2p** under both Pd and Ni catalysis with retention of the olefin geometry. However, the *E/Z* ratio in the product varied significantly as a function of metal. Under Pd catalysis, **2p** was obtained as a 9:1 mixture of the *E/Z* isomers, while the Ni catalyst afforded the product with an *E/Z* ratio of >20:1. Benzylic (**2q**) and allylic (**2r**) thioethers were formed in moderate to high yields from *S*-phenyl 2-phenylethanethioate and *S*-phenyl (*E*)-4-phenylbut-3-enethioate,

respectively. With these two substrates, the Pd catalyst afforded significantly higher yields than the Ni. Alkyl thioesters were also found compatible under the Pd catalysis forming alkyl thioether products **2s** and **2t** in good yields. However, these reactions did not proceed under Ni catalysis.

We also applied this method to the functionalization of the carboxylic acid-containing drug, probenecid.²⁵ A series of probenecid thioesters (**1s-u**) were prepared and then subjected to the optimal Ni and Pd catalytic conditions. As summarized in Scheme 1, these transformations afforded thioether derivatives **2s-u** in good to excellent yields, highlighting the potential of this transformation for the late stage derivatization of bioactive carboxylic acids.

A final set of experiments was conducted to probe the relative reactivity of thioester substrates with the two different catalyst systems. First, a 1:1 mixture of **1c** and **1d** was heated at 130 °C under Pd or Ni catalysis (Table 2a). The reactions were analyzed by ¹H and ¹⁹F NMR spectroscopy after 0.5 and 2 h to assay both the yield and ratio of aryl thioether products at each time point. As summarized in Table 2, **1d** (bearing an electron withdrawing *para*-trifluoromethyl substituent) reacted faster than **1c** (bearing an electron donating *para*-methoxy substituent) under both Pd and Ni catalysis. However, the Pd catalyst afforded lower overall yield and higher selectivity for **1d** at both time points. We next examined the *ortho*-methyl-substituted thioester substrate **1g** with both catalysts (Table 2b). These studies revealed that this relatively sterically hindered substrate undergoes much faster reaction with the Pd catalyst, affording >99% yield of thioether **2g** after just 0.5 h. In contrast, the Ni catalyst afforded **2g** in just 40% yield under analogous conditions. These studies provide preliminary insights into the different electronic/steric preferences of the two catalyst systems.

In summary, this Letter describes the development, optimization, and scope of the Pd and Ni-catalyzed intramolecular decarbonylative conversion of thioesters to thioethers. This method provides access to diaryl thioethers, heteroaryl thioethers, and aryl-alkyl thioethers under base- and thiol-free conditions. In general, the Pd and Ni catalysts exhibit similar substrate scopes, but several complementarities are demonstrated with respect to the selectivity, yields, and reaction rates with each of the two catalyst systems.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

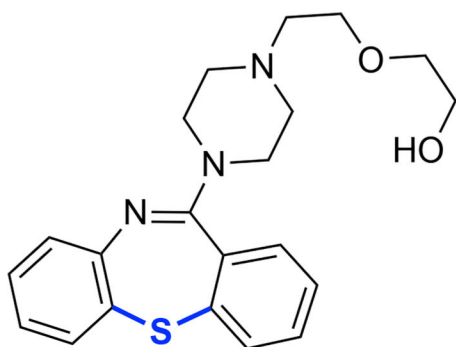
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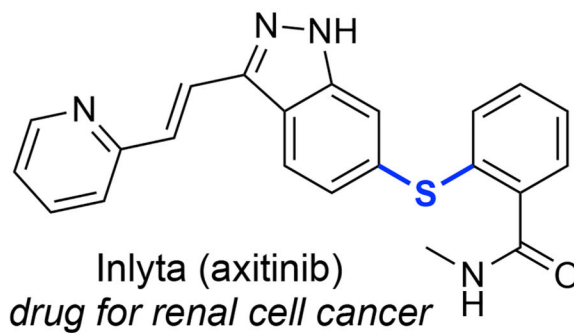
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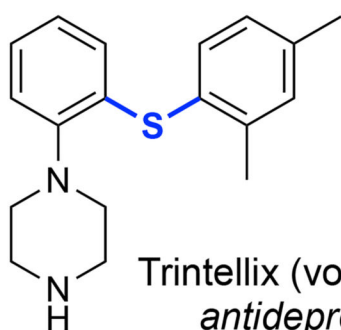
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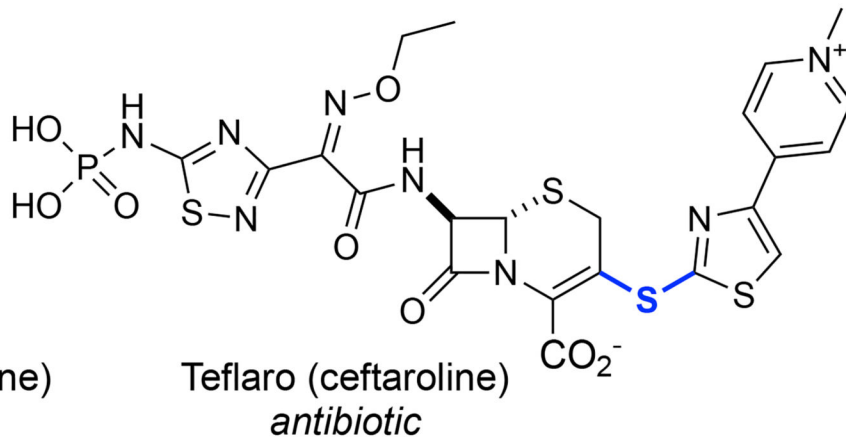
Seroquel (quetiapine)
antipsychotic



Inlyta (axitinib)
drug for renal cell cancer



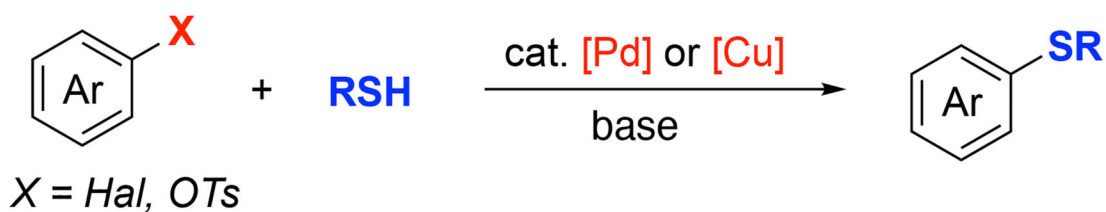
Trintellix (vortioxetine)
antidepressant



Teflaro (ceftaroline)
antibiotic

Figure 1.
Examples of pharmaceuticals containing aryl thioethers.

(a) Traditional Pd- and Cu-catalyzed C–S bond forming cross-couplings



(b) Pd- and Ni-catalyzed decarbonylative C–S bond formation (*this work*):

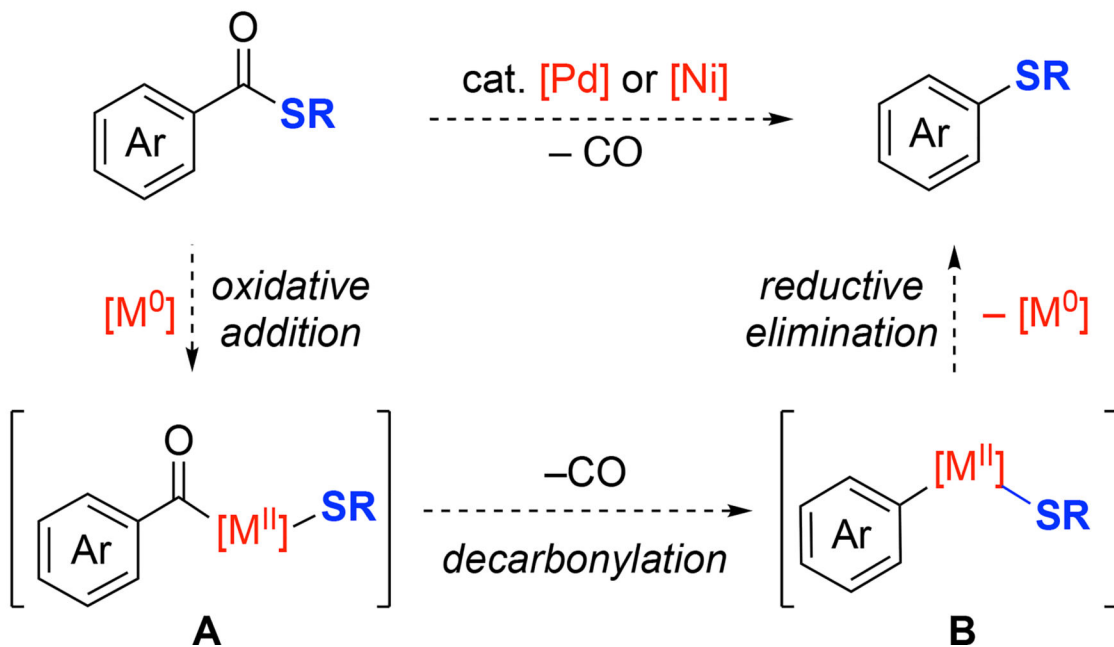
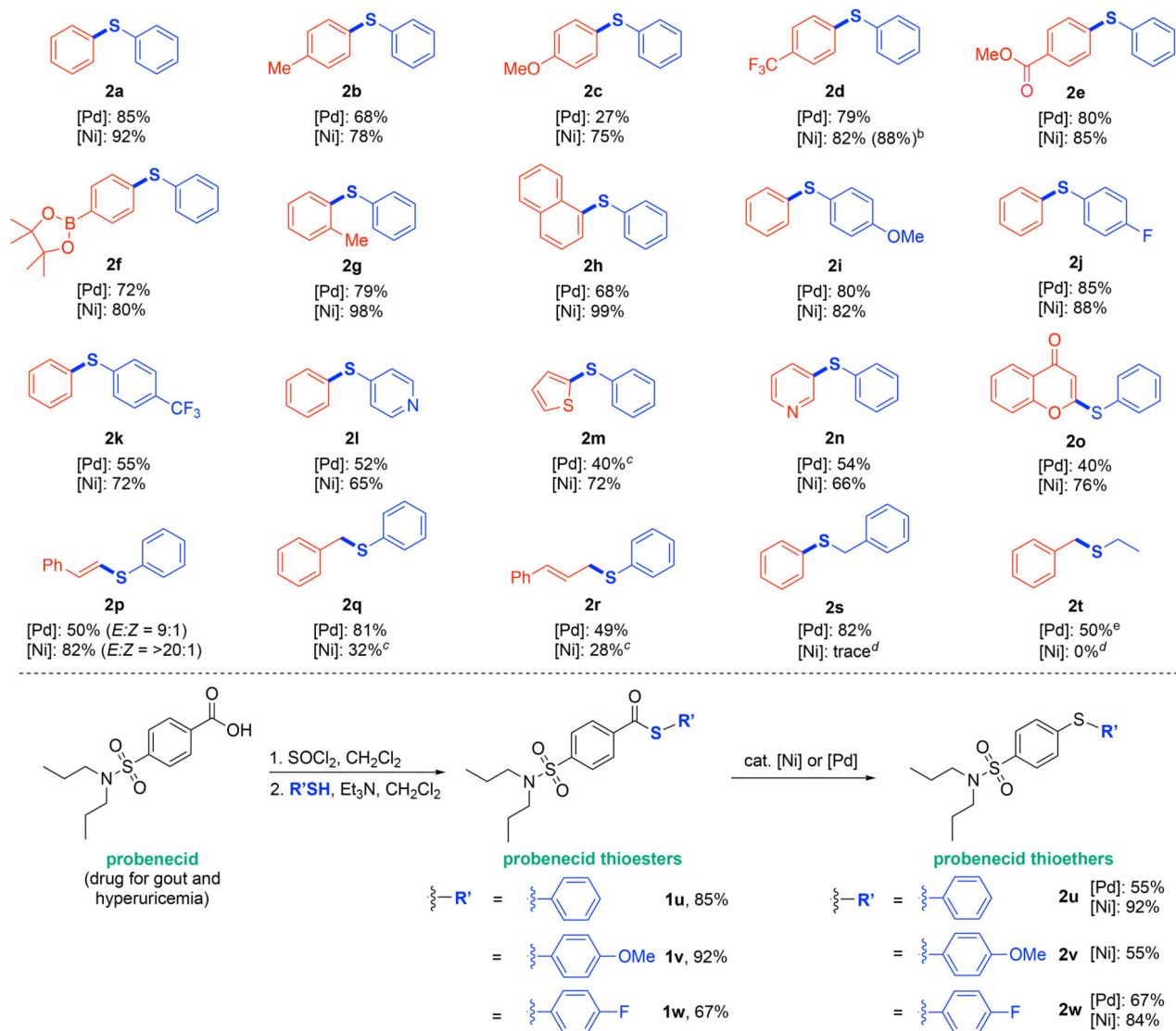
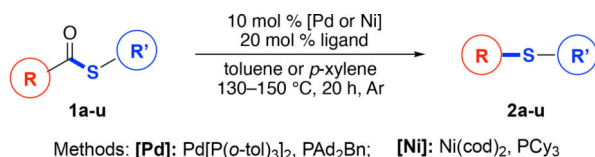


Figure 2. Transition metal-catalyzed synthesis of aryl thioethers by (a) traditional cross-coupling reaction, and (b) decarbonylation of thioesters.

**Scheme 1.**Scope of Pd and Ni-Catalyzed Decarbonylative Thioetherification^a

^aConditions: with [Pd]: substrate **1** (0.3 mmol, 1 equiv), Pd[P(*o*-tol)₃]₂ (0.03 mmol, 0.1 equiv), PdAd₂Bn (0.06 mmol, 0.2 equiv) in *p*-xylene (0.2 M) with 5 Å molecular sieves at 150 °C. With [Ni]: substrate (0.3 mmol, 1 equiv), Ni(cod)₂ (0.03 mmol, 0.1 equiv), PCy₃ (0.06 mmol, 0.2 equiv) in toluene (0.2 M) at 130 °C. Isolated yields. For experimental details, see the Supporting Information. ^bIsolated yield from 1.0 mmol scale. ^cGC yields obtained from 0.05 mmol scale substrate using neopentyl benzene as internal standard.

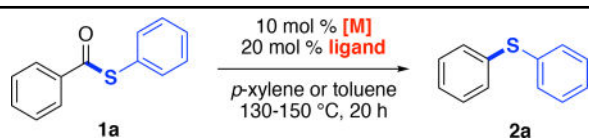
^dBased on ¹H NMR and GCMS analysis of the crude mixture. ^eYield based on ¹H NMR of the crude mixture, **2t** was found inseparable with starting material.

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Table 1Evaluation of Ligands for Pd- and Ni-catalyzed Decarbonylative Thioetherification^a

entry	[M]	ligand (L)	L (mol %)	2a (% yield) ^b
1	Pd[P(<i>o</i> -tol ₃) ₂] ₂	none	0	28
2		Brettphos	10	58
3		dppe	20	19
4		dppf	20	61
5		^t BuXantphos	20	15
6		PAd ₂ <i>n</i> -Bu	20	67
7		PAd ₂ Bn	20	78
8	Ni(cod) ₂	PAd ₂ Bn	20	85
9		P(<i>n</i> -Bu) ₃	20	92
10		PCy ₃	20	>99

^aConditions: phenyl thiolate **1a** (0.05 mmol), [M] (0.005 mmol, 0.1 equiv), ligand (0.01 mmol, 0.2 equiv). Entries 1–7 were performed in *p*-xylene (0.2 M), 150 °C, 20 h; entries 8–10 were performed in toluene, 130 °C, 20 h. See the Supporting Information for additional details.

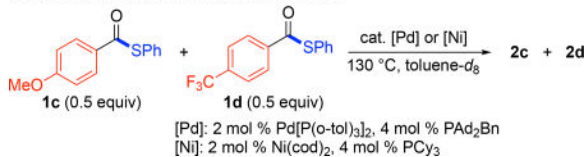
^bGC yields obtained using neopentylbenzene as an internal standard.

Table 2

Competition experiments of various thioesters under Pd and Ni methods^a

(a) Effect of electronics on thioester substrates

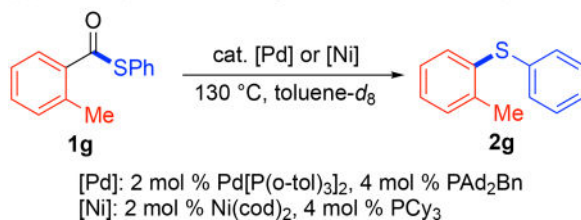
(a) Effect of electronics on thioester substrates



entry	[M]; <i>t</i> (h)	2c+2d (% yield) (ratio 2c:2d) ^b	unreacted 1c (%) ^b	unreacted 1d (%) ^b
1	[Pd]; 0.5	18 (1:99)	>49	32
2 ^c	[Pd]; 2	35 (4:96)	48	12
3	[Ni]; 0.5	31 (6:94)	48	21
4	[Ni]; 2	49 (9:91)	46	5

(b) Reactivity of thioester 1g under Pd and Ni catalysis

(b) Reactivity of thioester 1g under Pd and Ni catalysis



entry	[M]; <i>t</i> (h)	2g (% yield) ^b	unreacted 1g (%) ^b
1	[Pd]; 0.5	>99	<1
2 ^c	[Pd]; 2	>99	<1
3	[Ni]; 0.5	40	60
4	[Ni]; 2	70	30

^aConditions: (a) **1c** (0.05 mmol), **1d** (0.05 mmol), [M] (0.002 mmol), ligand (0.004 mmol), toluene-*d*₈, 130 °C, 0.5 and 2 h. (b) **1g** (0.1 mmol), [M] (0.002 mmol), ligand (0.004 mmol), toluene-*d*₈, 130 °C, 0.5 and 2 h.

^bRatio and yield analyses were obtained by ¹H and ¹⁹F NMR.

^cUnwanted biarylsulfide byproducts (~5%) were observed (ref 24). See the Supporting Information for additional details.