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Predominant Intermolecular Decarbonylative Thioetherification of Carboxylic Acids using Nickel Precatalysts

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RESEARCH ARTICLE

Predominant Intermolecular Decarbonylative Thioetherification of Carboxylic Acids using Nickel Precatalysts

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We report a general method for the direct decarbonylative thioetherification of carboxylic acids using air- and moisture-stable nickel precatalysts. In this approach, ubiquitous carboxylic acids are directly employed as aryl electrophiles and common thiols serve as sulfide donors. This protocol features excellent functional group tolerance and broad substrate scope using robust, bench- and air-stable catalysts, offering rapid entry for the synthesis of valuable aryl sulfides. The synthetic potential is showcased in the late-stage modification of pharmaceuticals directly utilizing carboxylic acid functional group. Nickel-catalyzed intermolecular decarbonylative thioetherification via C(O)–O cleavage is merged with intramolecular decarbonylation via C(O)–S cleavage, wherein thioesters are formed by thioesterification of activated carboxylic acids. Considering the significant interest in synthesis thioethers and the great utility of Ni(II) precatalysts as the privileged class of operationally-simple catalysts, we anticipate that this method will find broad applications in organic synthesis.

Aryl thioethers represent prevalent and highly valuable structural motifs in organic chemistry with broad applications ranging from the industrial production of surfactants through functional materials and pharmaceuticals (Figure 1A).[1,2] Transition-metal-catalyzed thioetherification of halides or pseudohalides (Ar–X) is one of the most common industrial and academic methods for the synthesis of aryl thioethers (Figure 1B).[3-5] However, this method by necessity relies on the availability of halide or pseudohalide starting materials.

In this context, decarbonylative cross-couplings have emerged as a powerful approach to use carboxylic acid derivatives (Ar–CO_2R) as electrophiles as an alternative paradigm to aryl halides and pseudohalides, while exploiting the highly desirable orthogonal availability and reactivity of carboxylic acids.[6,7] This decarbonylative platform heavily benefits from the ubiquitous presence of carboxylic acids in late-stage intermediates and pharmaceuticals, enabling for new reactivity pathways and functional group interconversions not accessible from aryl halides.[5l,6,7] To date, amides,[7-8] esters,[9] thioesters,[10] carboxylic acids[11] and acyl halides[6] have been employed as electrophiles for decarbonylative cross-coupling reactions. These carboxylic acid derivatives combine facile oxidative addition of the C(O)–X bond into a transition metal with bench-stability and availability of various precursors that could be used to tune the decarbonylative cross-coupling reactivity. From the synthetic standpoint, the most desirable is the direct use of carboxylic acids.[11] This pathway can be achieved after in situ conversion into a mixed anhydride, which obviates preactivation steps and enables to directly engage ubiquitous carboxylic acids for the formation of new C–C and C–X bonds.

Recently, there has been a surge of interest in the decarbonylative synthesis of aryl sulfides.[12] Most notably, in 2018 the Sanford group[13a] and our group[13b] concurrently reported Ni-catalyzed synthesis of thioethers by intramolecular decarbonylation of thioesters. Furthermore, transition-metal-catalyzed decarbonylative thioetherifications of different precursors have been reported.[9a,b,12-16] However, all of these methods are limited by the preparation of acyl electrophiles requiring separate synthetic and isolation steps, which restricts applicability of these approaches especially in the context of late-stage functionalization of pharmaceuticals. Thus, we hypothesized that a method directly using carboxylic acids as pervasive and widely available electrophiles would offer a major advantage in the decarbonylative synthesis of aryl thioethers. Furthermore, we were cognizant of the recent advances in the use of well-defined, air- and moisture-stable Ni(II) precatalysts as vastly preferred catalysts for industrial and academic research.[17] In particular, the area of well-defined Ni(II) precatalysts has been thriving in recent years due to economic and reactivity advantages of nickel,[18] where the use of bench-stable, operationally-simple precatalysts has been deemed essential to extend the applicability of nickel in organic synthesis, drug discovery and medicinal chemistry.[19,20]

Herein, we report a general method for the direct decarbonylative thioetherification of carboxylic acids using air-

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and moisture-stable nickel precatalysts. The method uses air-stable, well-defined Ni(II) catalysts that are operationally-easy to handle and permits for a direct decarbonylative thioetherification of carboxylic acids for broad applications in organic synthesis, we anticipate that this approach will significantly expand the synthetic toolbox available to researchers in academic and industrial settings (Figure 1C).

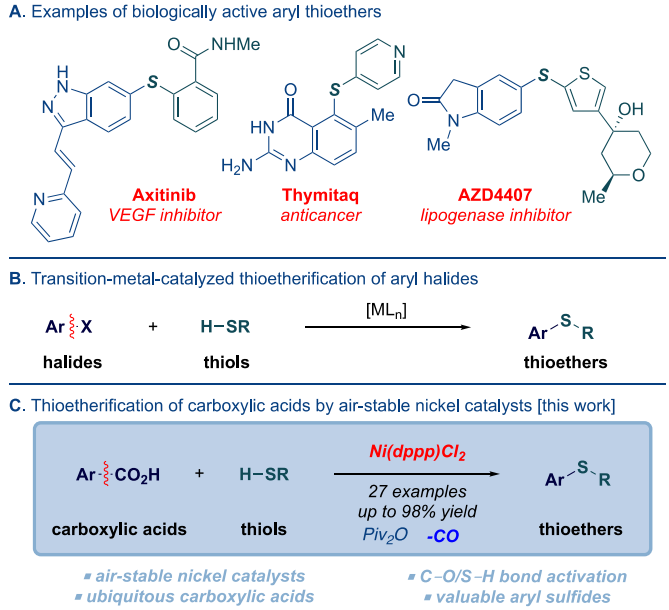
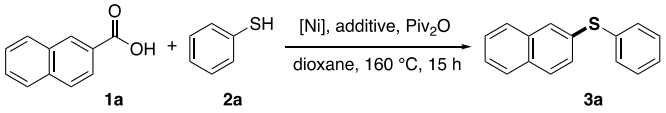


Figure 1 (A) Examples of biologically active thioethers. (B) Direct synthesis of aryl thioethers from aryl halides. (C) Direct decarbonylative synthesis of aryl thioethers from carboxylic acids by air- and moisture-stable nickel catalysts (this work).

The following features of our study are noteworthy: (1) direct one-step decarbonylative synthesis of aryl thioethers from widely available carboxylic acids and thiols; (2) air-stable, well-defined and readily available Ni(II) precatalysts, enabling operational-simplicity, modularity, robustness and bench-top set-up; (3) broad substrate scope and functional group tolerance using directly carboxylic acids for the synthesis of aryl thioethers, including applications to the late-stage functionalization of pharmaceuticals.

The optimization results are summarized in Table 1. 2-Naphthoic acid **1b** and thiophenol **2a** were selected as modular substrates for reaction optimization. After unpromising results using Pd and Rh, we were delighted to identify that a combination of Ni(dppp)Cl_2 as a catalyst, Piv_2O as an activator and Et3N as a base afforded the desired 2-naphthyl phenyl sulfide **3b** in 15% yield (Table 1, entry 1). Further screening showed that using excess of thiophenol dramatically decreased the yield due to competing acylation of Piv_2O (Table 1, entries 2-3). Furthermore, DMAP (4-dimethylaminopyridine) was identified as a superior base to Et_3N, providing the aryl thioether product in much higher yield (Table 1, entries 4-5). The catalyst loading was next investigated and 20 mol% catalyst loading was identified as the optimal choice (Table 1, entries 6-7). Furthermore, inorganic bases and protic additives were screened, showing that organic bases are preferred for this process (Table 1, entries 8-10). Different air- and moisture-stable Ni(II)–phosphine precatalysts were screened, showing that precatalysts with monodentate phosphine ligands, such as Ni$(PCy_3)_2Cl_2$ or Ni$(PPh_3)_2Cl_2$ are ineffective (Table 1, entries 11-12). Interestingly, Ni(dppe)Cl_2 showed high reactivity (Table 1, entry 13), however, no product was observed using Ni(dppf)Cl_2 as a precatalyst (Table 1, entry 14). Furthermore, toluene was identified as another suitable solvent for the reaction (Table 1, entry 15). Finally, as expected, no product was observed in the absence of Piv_2O, in agreement with the C–O acyl activation pathway (Table 1, entry 16, vide infra).

Table 1. Optimization of Reaction Conditions.[a]

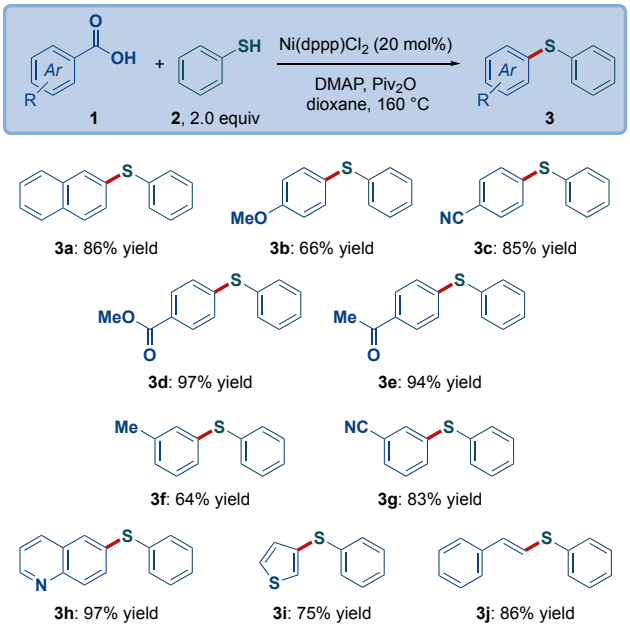


entry	[Ni]	cat loading	additive	Yield(%)
1	Ni(dppp)Cl_2	10 mol%	Et_3N	15
2[b]	Ni(dppp)Cl_2	10 mol%	Et_3N	<2
3[c]	Ni(dppp)Cl_2	10 mol%	Et_3N	<2
4	Ni(dppp)Cl_2	40 mol%	Et_3N	34
5	Ni(dppp)Cl_2	40 mol%	DMAP	88
6	Ni(dppp)Cl_2	20 mol%	DMAP	86
7	Ni(dppp)Cl_2	10 mol%	DMAP	45
8	Ni(dppp)Cl_2	20 mol%	Na_2CO_3	<2
9	Ni(dppp)Cl_2	20 mol%	K_2CO_3	<2
10	Ni(dppp)Cl_2	20 mol%	H_3BO_3	<2
11	Ni$(PCy_3)_2Cl_2$	20 mol%	DMAP	<2
12	Ni$(PPh_3)_2Cl_2$	20 mol%	DMAP	<2
13	Ni(dppe)Cl_2	20 mol%	DMAP	85
14	Ni(dppf)Cl_2	20 mol%	DMAP	<5
15[d]	Ni(dppp)Cl_2	20 mol%	DMAP	78
16[e]	Ni(dppp)Cl_2	20 mol%	DMAP	<5

a) Conditions: 2-naphthoic acid **1a** (0.20 mmol), thiophenol **2a** (2.0 equiv), [Ni] (x mol%), additive (1.2 equiv), Piv_2O (1.2 equiv), dioxane (0.20 M), 160 °C, 15 h. b) thiophenol (3.0 equiv). c) thiophenol (4.0 equiv). d) toluene. e) without Piv_2O.

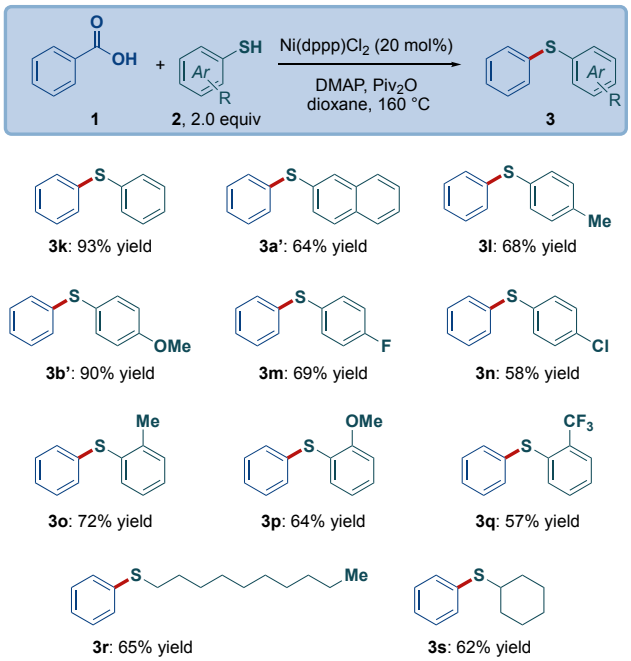
With the optimized conditions in hand [**1** (1.0 equiv), **2** (2.0 equiv), Ni(dppp)Cl_2 (20 mol%), DMAP (1.2 equiv), Piv_2O (1.2 equiv), dioxane (0.2 M), 160 °C, 15 h], the scope of this direct decarbonylative thioetherification of carboxylic acids was next investigated (Scheme 1). As shown, this transformation shows broad functional group tolerance and compatibility, resulting in an operationally-simple, chemoselective synthesis of aryl thioethers, permitting all reactions to be performed on a bench-top without resorting to air-sensitive and capricious Ni(0) catalysts. The C–O bond of the aromatic acyl part is selectively activated, rather than the C–O bond on the side of the acyl side of the *tert*-butyl group, demonstrating high chemoselectivity of this approach. As such, a range of electronically-varied carboxylic acids is well-tolerated in this reaction, including electron-neutral (**3a**), electron-rich (**3b**), and electron-deficient (**3c**) substrates. Moreover, the approach tolerates substrates containing sensitive functional groups, such as ester (**3d**) and ketone (**3e**).

It is particularly noteworthy that meta-substituted (**3f-3g**) carboxylic acids are also compatible in this process. Furthermore, the method tolerates heterocyclic substrates, such as quinolinyl (**3h**) and thienyl (**3i**). Finally, this approach could be extended to cinnamic acids, affording vinyl thioethers in high yields (**3j**).



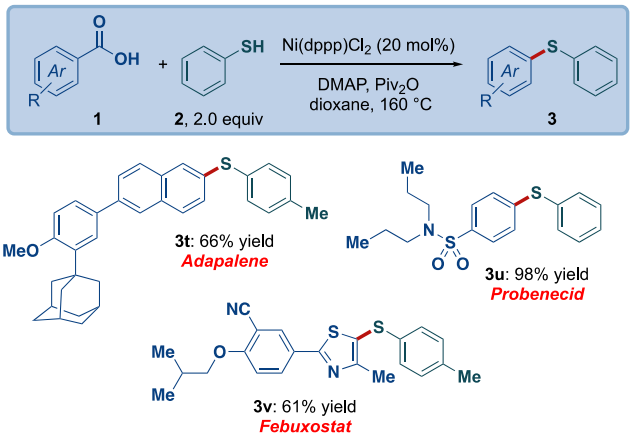
Scheme 1. Decarbonylative thioether synthesis: carboxylic acid scope.

Next, the thiol scope in this decarbonylative thioetherification was briefly investigated (Scheme 2). As shown, electronically- and sterically-differentiated thiols are well-accommodated by this process, including electron-neutral (**3k**, **3a'**, **3l**), electron-rich (**3b'**) and electron-deficient substrates (**3m-3n**). Furthermore, ortho-substituted thiols (**3o-3q**) and even alkyl thiols (**3r-3s**) are well compatible with this method, affording desired thioethers in high yields. As expected, aliphatic carboxylic acids are not compatible due to competing β-hydride elimination.



Scheme 2. Decarbonylative thioether synthesis: thiol scope.

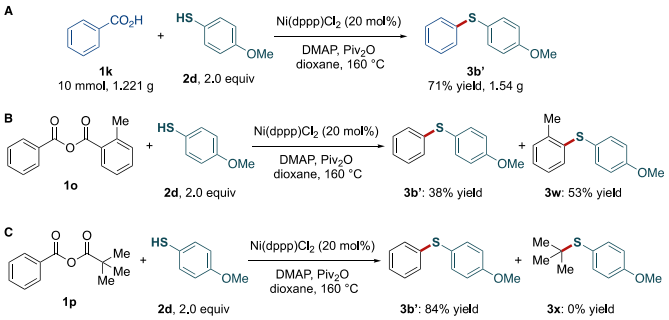
Owing to the prominent role of sulfur as a pharmacophore, aryl thioethers represent an increasingly important functional group in drug molecules and are widely utilized in medicinal chemistry research.[2,12] To highlight the synthetic potential of this decarbonylative synthesis of aryl thioethers, we applied this protocol to the late-stage functionalization of pharmaceuticals (Scheme 3). The synthesis of aryl thioethers from carboxylic acids derived from Adapalene (**3t**), Probenecid (**3u**) and Febuxostat (**3v**) demonstrate the synthetic potential of this method, providing direct access to valuable thioethers from ubiquitous carboxylic acids.



Scheme 3. Late-stage thioetherification of pharmaceuticals.

Gram scale reaction was performed, resulting in high yield on this scale (Scheme 4A). Nonsymmetrical aryl anhydride was synthesized and applied to this reaction (Scheme 4B). The reaction showed that both sides of the aryl anhydride can be converted into aryl sulfide products, while the side with ortho-substitution showed higher reactivity. Furthermore, aryl/*tert*-butyl nonsymmetrical anhydride was synthesized and applied to the reaction conditions (Scheme 4C). As expected, the aryl

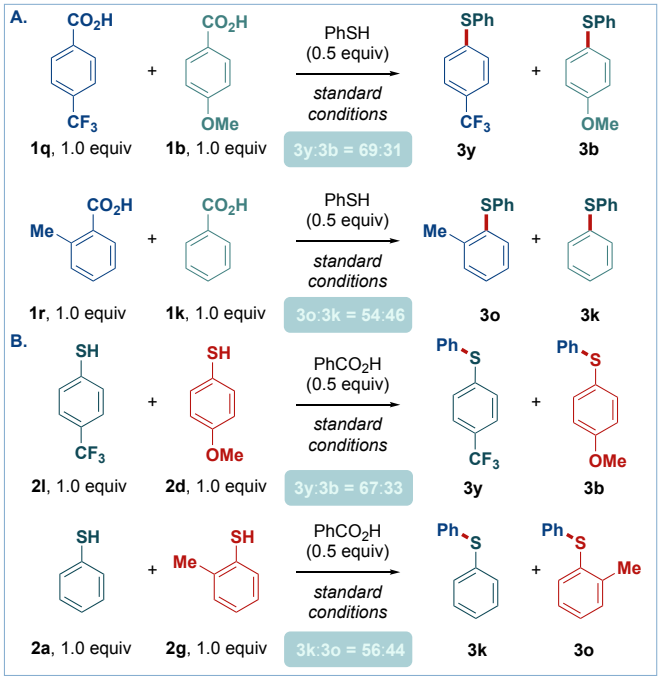
side was efficiently converted into the aryl product, while the *tert*-butyl side did not react.



Scheme 4. Mechanistic studies.

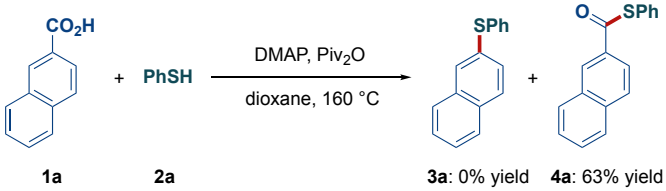
Mechanistic studies were performed to gain insight into this decarbonylative process (Schemes 5-7).

(1) Intermolecular competition experiments showed that electron-deficient carboxylic acids are inherently more reactive than electron-rich counterparts (4-CF_3:4-OMe = 69:31), while sterically-hindered substrates showed higher reactivity than unsubstituted substrates (2-Me:2-H = 54:46) (Scheme 5A). Furthermore, electron-deficient thiophenols showed higher reactivity than electron-rich counterparts (4-CF_3:4-OMe = 67:33), while unsubstituted substrates are more reactive than sterically-hindered substrates (2-H:2-Me = 56:44) (Scheme 5B). These effects are consistent with decarbonylation favored by the steric demand of carboxylic acid (cf. thiophenol) and reductive elimination as kinetically relevant step.



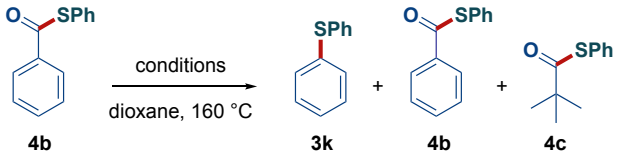
Scheme 5. Competition studies.

(2) The reaction without metal catalyst resulted in high yield of thioester formed by acylation of carboxylic acids with thiophenol, while thioether formation was not observed (Scheme 6). This finding is consistent with thioester as a potential intermediate in the process. This result further demonstrates that in the absence of a transition metal decarboxylation and decarbonylation reactions are not occurring under the reaction conditions.[9a]



Scheme 6. Mechanistic studies.

(3) To gain further insight into the decarbonylative pathway, control reactions with thioesters have been performed (Scheme 7). As shown, **3a** formed as a minor product under standard conditions, and only trace **3a** formed without base (entries 1-2). Furthermore, similar results were obtained in the absence of Piv_2O (entries 3-4). Overall, these results are consistent with intermolecular C(O)–O cleavage as the major pathway in this process.



entry	[Ni]	additive	activator	yield (**3k**)	yield (**4b**)	yield (**4c**)
1	$Ni(dppp)Cl_2$	DMAP	Piv_2O	22%	42%	35%
2	$Ni(dppp)Cl_2$	-	Piv_2O	<2%	71%	27%
3	$Ni(dppp)Cl_2$	DMAP	-	23%	76%	-
4	$Ni(dppp)Cl_2$	-	-	<2%	97%	-

Scheme 7. Mechanistic studies.

The proposed mechanism is shown in Figure 2. First, aryl carboxylic acid is activated by Piv_2O to give unsymmetrical anhydride, which can be converted to thioester by acylation. Divalent nickel precatalyst is activated to nickel(0) by a Ni–N or by a nickel–nickel transmetallation.[17e] Next, oxidative addition of the C(O)–O bond of carboxylic anhydride and C(O)–S bond of thioester afford the respective acyl-metal intermediates, followed by decarbonylation. In the C(O)–O thioetherification cycle, ligand exchange of Ar–Ni–OPiv gives Ar–Ni–SR intermediate, which undergoes reductive elimination. In the C(O)–S cycle, the product is formed by reductive elimination of the Ar–Ni–SR decarbonylation intermediate.

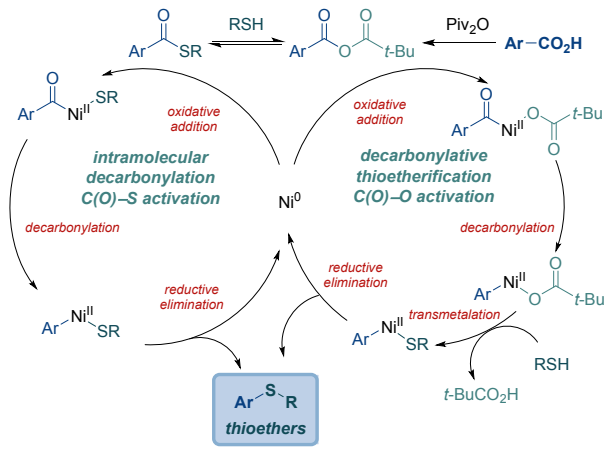


Figure 2. Plausible mechanism.

Conclusions

In conclusion, we have reported a general method for the direct decarbonylative thioetherification of carboxylic acids using air- and moisture-stable nickel precatalysts. The method is operationally-simple, robust and modular using well-defined, air- and bench-stable Ni(II) precatalysts. This method shows broad substrate scope and excellent functional group tolerance, enabling the synthesis of valuable thioethers from ubiquitous carboxylic acids and thiols. The utility of this process has been highlighted in the late-stage derivatization of pharmaceuticals, exploiting the prevalent carboxylic acids. Considering the interest in decarbonylative synthesis of thioethers and the great utility of Ni(II) precatalysts as the privileged class of operationally-simple catalysts, we anticipate that this method will find broad applications in organic synthesis, drug discovery and medicinal chemistry.

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Author contributions

[+]These authors contributed equally to this work.

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