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Decarbonylative Thioetherification by Nickel Catalysis using Air- and Moisture-Stable Nickel Precatalysts

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A general, highly selective method for decarbonylative thioetherification of aryl thioesters by C–S cleavage is reported. These reactions are promoted by a commercially-available, user-friendly, inexpensive, air- and moisture-stable nickel precatalyst. The process occurs with broad functional group tolerance, including free anilines, cyanides, ketones, halides and aryl esters, to efficiently generate thioethers using ubiquitous carboxylic acids as ultimate cross-coupling precursors (cf. conventional aryl halides or pseudohalides). Selectivity studies and site-selective orthogonal cross-coupling/thioetherification are described. This thioester activation/coupling has been highlighted in the expedient synthesis of biorelevant drug analogues. In light of the synthetic utility of thioethers and Ni(II) precatalysts, we anticipate that this user-friendly method will be of broad interest.

The thioether functional group represents one of the privileged structural motifs in the synthesis of pharmaceuticals (Fig. 1A).[1,2] Most synthetic disconnections for the synthesis of aryl thioethers capitalize on transition-metal-catalyzed cross-coupling of aryl halides or pseudohalides with thiols (Fig. 1B).[3,4] Recently, significant progress has been made in the development of transition-metal-catalyzed decarbonylative processes that utilize ubiquitous carboxylic acids as ultimate cross-coupling precursors in the oxidant free, redox-neutral decarbonylative pathway.[5] Carboxylic acids are among the most appealing chemical building blocks in organic synthesis.[5b] Of note, carboxylic acids are (1) cheaper and there are more carboxylic acids commercially available than aryl halides; (2) derived from a different pool of precursors than aryl halides and pseudohalides; (3) inert to a variety of reaction conditions allowing for ring prefunctionalization.[6] Likewise, significant effort has been devoted to the cross-coupling of inert C–S bonds.[7] Notably, Morandi and co-workers have developed a versatile method for carbon-sulfur bond metathesis,[8] while Yorimitsu and co-workers have shown that Pd-NHC systems catalyze the coupling of aromatic thioethers with N- and C-nucleophiles.[9] In another important development, Niwa, Hosoya and co-workers established the feasibility of Rh-catalyzed decarbonylative borylation of thioesters.[10] The recent surge of efforts to capture sulfur intermediates in metal-free pathways[11] engenders the appeal of assembling thioethers from carboxylic acid-based substrates using robust, operationally-simple protocols that could be widely adapted in various areas of chemical science.

In the past decade, there has been an increasing interest in nickel catalysis due to more facile oxidative addition, abundance and economic advantages compared with Pd catalysis.[12] Generally speaking, the use of air- and moisture-stable precatalysts is strongly preferred in modern cross-coupling applications.[13] In this context, the groups of Monteiro,[14] Percec,[15] Buchwald,[16] Jamison,[17] Doyle,[18] Monfette[19] and others[15–19] have reported well-defined Ni(II) precatalysts, which enable a variety of cross-coupling transformations. The fact that the use of robust, bench-stable Ni(II) precatalysts enables broad applications of metal catalysis in industrial research[13] in lieu of the limited options available with air-sensitive and capricious Ni(0)-complexes.

Inspired by our recent studies in decarbonylative olefination,[20] arylation,[21] cyanation[22] and phosphorylation[23] of amides,[24] in this report we communicate our findings on decarbonylative thioetherification of aryl thioesters by selective C–S cleavage enabled by user-friendly, air- and moisture-stable nickel precatalysts (Fig. 1C). While this work was in progress, a Ni(0)-catalyzed decarbonylative thioether synthesis by C–S cleavage using a combination of air-sensitive Ni(cod)$_2$ (10 mol%) and PCy$_3$ (20 mol%) was reported.[25] Since our method (1) utilizes Ni(II) precatalysts that are air-stable, easy to handle and manipulate, (2) is significantly broader in scope, and (3) enables the use of operationally-simple and robust decarbonylative thioetherification for wide applications within both industry and academia, we anticipate that the protocol will be of general interest to the broad synthetic community.[1–4,13]

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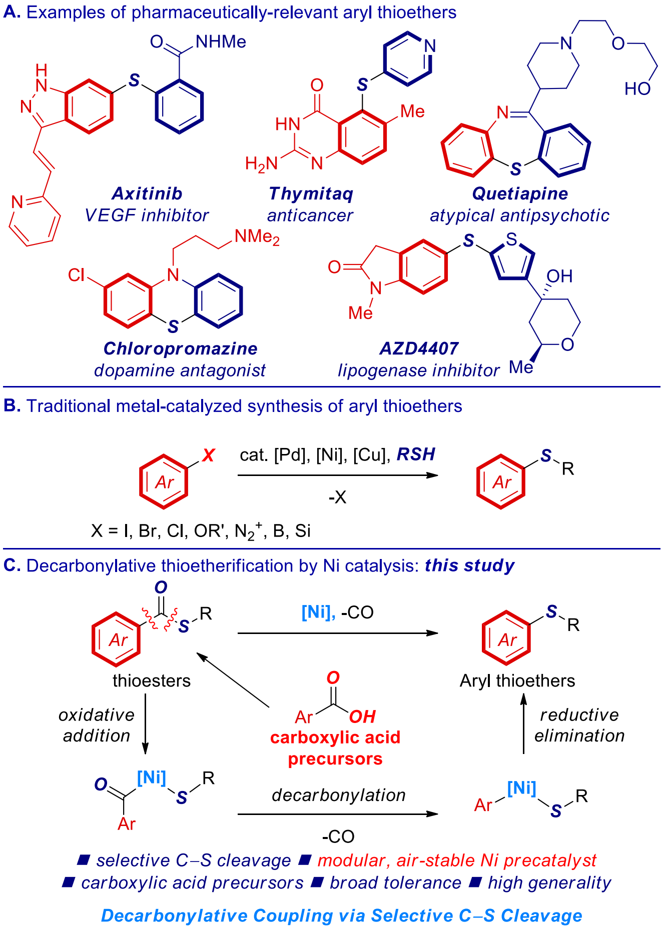
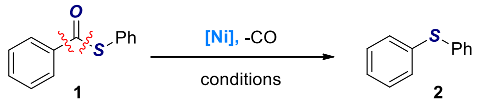


Fig. 1 (a) Examples of pharmaceutically important aryl thioethers. (b) Conventional synthesis. (c) Decarbonylative thioetherification using air- and moisture-stable Ni precatalysts (this study).

The reaction was optimized using *S*-phenyl benzothioate as a model substrate. Key optimization experiments are summarized in Table 1. Using our optimized conditions, Ni(dppp)Cl_2, (10 mol%), Na_2CO_3 (1.5 equiv), dioxane, 160 °C, *S*-phenyl benzothioate undergoes selective C–S insertion/CO extrusion in excellent yield (entry 1). Under these conditions, $Ni(PCy_3)_2Cl_2$ is also a highly effective catalyst (entry 2). As expected, no reaction is observed in the absence of base (entries 3-4) or nickel precatalyst (entry 5). Examination of various reaction parameters revealed a significant dependence on the Ni(II) complex used (entries 6-10), with Ni(dppp)Cl_2, Ni(dppe)Cl_2, and $Ni(PCy_3)_2Cl_2$ showing similar performance. As expected, no reaction was observed in the absence of phosphine ligand (entry 11). An extensive screen of bases revealed that the best results were obtained with Na_2CO_3 (entries 12-14). Dioxane was identified as the optimal solvent (entries 15-17). We were pleased to find that decreasing the nickel loading to 5 mol% delivered the product under the optimized conditions (entries 18-19). Low conversions were observed in the presence of oxygen (not shown). Finally, we note that substantial conversion was observed as 120 °C, consistent with facile decarbonylation by this catalytic system (entry 20).

Table 1 Reaction Optimization: Ni-Catalyzed Decarbonylative Thioetherification[a]



Entry	Catalyst	Base	*T* (°C)	Yield (%)[b]
1	Ni(dppp)Cl_2	Na_2CO_3	160	>95
2	$Ni(PCy_3)_2Cl_2$	Na_2CO_3	160	>95
3	Ni(dppp)Cl_2	-	160	<2
4	$Ni(PCy_3)_2Cl_2$	-	160	<2
5	-	Na_2CO_3	160	<2
6	Ni(dppp)Cl_2	Na_2CO_3	140	>95
7	$Ni(PCy_3)_2Cl_2$	Na_2CO_3	140	>95
8	$Ni(PPh_3)_2Cl_2$	Na_2CO_3	140	43
9	Ni(dppe)Cl_2	Na_2CO_3	140	>95
10	Ni(dppf)Cl_2	Na_2CO_3	140	18
11	$Ni(OAc)_2$	Na_2CO_3	140	<5
12	$Ni(PCy_3)_2Cl_2$	K_2CO_3	140	27
13	$Ni(PCy_3)_2Cl_2$	Cs_2CO_3	140	<5
14	$Ni(PCy_3)_2Cl_2$	K_3PO_4	140	15
15[c]	$Ni(PCy_3)_2Cl_2$	Na_2CO_3	140	87
16[d]	$Ni(PCy_3)_2Cl_2$	Na_2CO_3	140	>95
17[e]	$Ni(PCy_3)_2Cl_2$	Na_2CO_3	140	>95
18[f]	$Ni(PCy_3)_2Cl_2$	Na_2CO_3	140	27
19[f]	$Ni(PCy_3)_2Cl_2$	Na_2CO_3	160	>95
20	$Ni(PCy_3)_2Cl_2$	Na_2CO_3	120	52

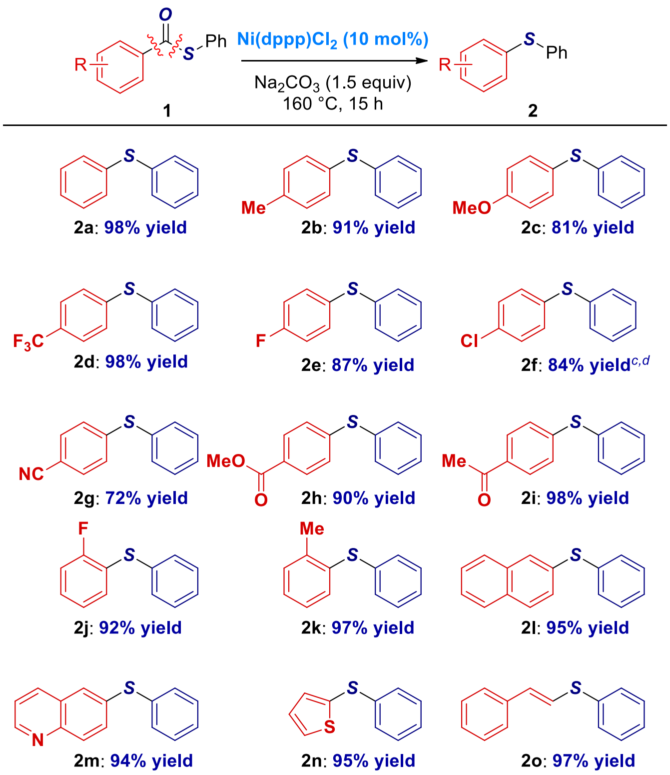
[a]Conditions: thioester (1.0 equiv), catalyst (10 mol%), base (1.5 equiv), 1,4-dioxane (0.20 M), *T*, 15 h. [b]GC/^{1}H NMR yields. [c]toluene. [d]CH_3CN. [e]DMF. [f]catalyst (5 mol%). See ESI for details.

The reaction exhibits broad substrate scope (Scheme 1). Electron-rich (**2b-c**) and electron-deficient (**2d**) substrates performed well in this protocol. Notable examples include halides (**2e-f**) and electrophilic functional groups (**2g-i**), providing handles for further functionalization. Ortho-substitution was well-tolerated under these conditions (**2j-k**). Furthermore, this protocol could be extended to polyaromatic (**2l**), heterocyclic (**2m-n**) and vinyl substrates (**2o**), providing the desired products in good to excellent yields. Finally, the scope of the thiol component was briefly examined (Table 2). A selection of electron-rich (entry 2), electron-deficient (entry 3), halide-containing (entry 4) and sterically-hindered (entry 5) substrates were converted into the desired thioethers in high yields. Important from a practical point of view, all of these reactions were conveniently set-up on a bench-top, which provides a very attractive feature of this protocol.[13–19] Furthermore, the scope supersedes the $Ni(cod)_2$ system[25] in that cyanides, ketones, halides, unprotected anlines (vide infra) and aryl esters (vide infra) are readily tolerated.

Preliminary studies demonstrate that cross-coupling of an aryl-alkyl thioester is also feasible (Scheme 2), providing another advantage of this user-friendly method. Note that alkyl thioesters are not tolerated using air-sensitive $Ni(cod)_2$.[25] Studies to expand the scope of aryl–alkyl coupling to chiral thioesters are ongoing and will be reported in due course.

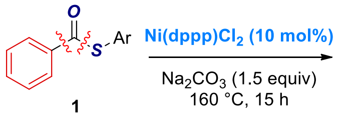
To investigate the potential utility of this cross-coupling method, we tested this protocol in the rapid derivatization of flufenamic acid, a selective COX-2 inhibitor (Scheme 3).[26] As shown, the reaction proceeded uneventfully, delivering the desired thioether product in high overall yield.[10]

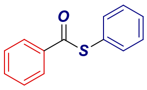
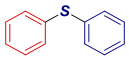
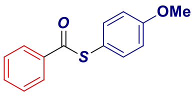
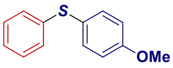
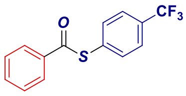
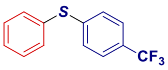
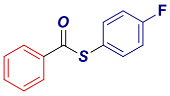
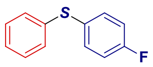
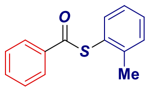
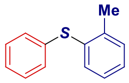
Scheme 1 Substrate Scope: Ni-Catalyzed Decarbonylative Thioetherification[a,b]



[a]Conditions: thioester (1.0 equiv), Ni(dppp)Cl$_2$ (10 mol%), Na$_2$CO$_3$ (1.5 equiv), dioxane (0.20 M), 160 °C, 15 h. [b]Isolated yields. [c]Ni(PCy$_3$)$_2$Cl$_2$. [d]140 °C. See ESI for details.

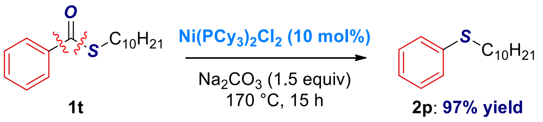
Table 2 Substrate Scope: Ni-Catalyzed Decarbonylative Thioetherification[a]



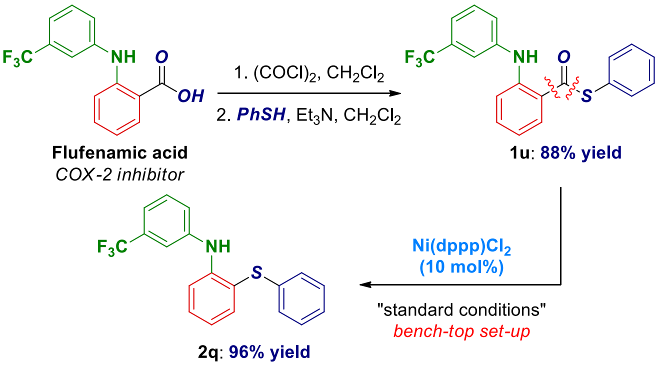
Entry	Thioester	1	Product	2	Yield (%)
1		**1a**		**2a**	98
2		**1p**		**2c’**	85
3		**1q**		**2d’**	98
4		**1r**		**2e’**	91
5		**1s**		**2k’**	96

[a]Conditions: thioester (1.0 equiv), Ni(dppp)Cl$_2$ (10 mol%), Na$_2$CO$_3$ (1.5 equiv), dioxane (0.20 M), 160 °C, 15 h. [b]Isolated yields. See ESI for details.

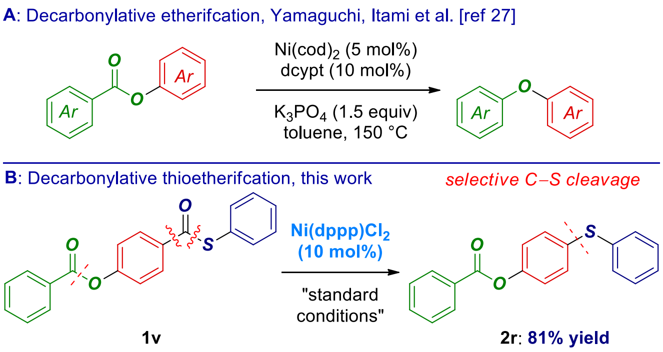
Scheme 2 Ni-Catalyzed Decarbonylative Thioetherification of *S*-Alkyl Benzothioate



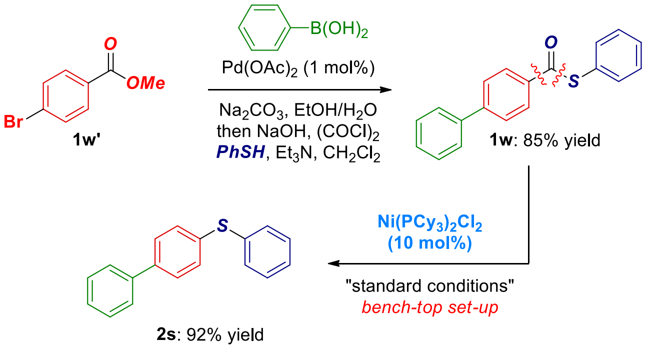
Scheme 3 Expedient Synthesis of Flufenamic Acid Thioether



Scheme 4 Selective Decarbonylative Thioetherification



Scheme 5 Site-Selective Cross-Coupling/Decarbonylative Thioetherification



Yamaguchi, Itami and co-workers recently reported a Ni-catalyzed decarbonylative diaryl ether synthesis by C–O cleavage.[27] We were intrigued to find that the present coupling proceeds in the presence of the sensitive aryl ester linkage (Scheme 4), demonstrating high chemoselectivity of the present method.

To further showcase the utility of this new thioetherification, sequential orthogonal cross-couplings were investigated (Scheme 5). This sequence highlights the potential of decarbonylative thioetherification to selectively generate thioethers from readily available carboxylic acids.[5,6,10]

In conclusion, we have reported a general method for decarbonylative thioetherification by C–S cleavage using a commercially-available, user-friendly, inexpensive, air- and moisture-stable nickel(II) precatalyst. The process provides a synthetic entry to the biologically-relevant thioether functional group exploiting abundant carboxylic acids as ultimate cross-coupling precursors. In view of the synthetic utility of thioethers and Ni(II) precatalysts, we anticipate that the method will be of broad interest.[28] Further studies on related decarbonylative cross-coupling transformations are ongoing.

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