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Decarbonylative Sulfide Synthesis from Carboxylic Acids and Thioesters via Cross-Over C–S Activation and Acyl Capture

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Method

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Chengwei Liu[a]* and Michal Szostak[a]*

A method for the synthesis of sulfides from carboxylic acids via thioester C–S activation and acyl capture has been accomplished, wherein thioesters serve as dual electrophilic activators to carboxylic acids as well as S-nucleophiles through the merger of decarbonylative palladium catalysis and sulfur coupling. This new concept engages readily available carboxylic acids as coupling partners to directly intercept sulfur reagents via redox-neutral thioester-enabled cross-over thioetherification. The scope of this platform is demonstrated in the highly selective decarbonylative thioetherification of a variety of carboxylic acids and thioesters, including late-stage derivatization of pharmaceuticals and natural products. This method operates under mild, external base-free, operationally-practical conditions, providing a powerful new framework to unlock aryl electrophiles from carboxylic acids and bolster the reactivity by employing common building blocks in organic synthesis.

Introduction

Sulfides represent one of the most fundamental moieties in all areas of chemistry and are of immense importance in pharmaceutical development (Figure 1).[1] Thus, new methods for the synthesis of sulfides are receiving increasing attention. Typical methods are centered on the synthesis of sulfides by alkylation of thiols,[2a] addition of organometallics to disulfides,[2b] hydrothiolation reactions,[2c] and Pummerer rearrangements.[2d] With the advent of transition-metal-catalyzed cross-coupling reactions, a variety of C–S coupling protocols for the synthesis of thioethers from aryl halides or pseudohalides have emerged as an increasingly powerful strategy for the synthesis of thioethers.[3] Further recent progress in the synthesis of thioethers involves thioetherification of amides[4,5] and esters[6] by a decarbonylative pathway. However, thioether synthesis from amides or esters is challenging since reductants, such as magnesium or manganese, are required for these transformations. In this context, intramolecular C(O)–S decarbonylation of thioesters by CO de-insertion represents one of the most direct and useful fragment couplings for the synthesis of thioethers.[7]

In this framework, thioesters have emerged as highly valuable building blocks in organic synthesis, while acetyl-CoA has long been established as the key acyl transfer reagent in enzymatic pathways.[8–10] Considering their high air- and moisture-stability, thioesters are well-tolerant to the chromatographic purification and significantly easier to handle than the corresponding acyl halides, while maintaining high electrophilic character of the C(O)–S group.[9] Thus, thioesters have been widely used in chemical synthesis. In this context, transition-metal-catalyzed cross-coupling of thioesters has been well-established, and this manifold typically operates via acyl-type coupling with the –SR moiety serving as a leaving group. Thus, substitution of the sulfur group with various nucleophiles has been widely studied, including Grignard reagents,[11] organozinc reagents,[12] boronic acids,[13] alcohols,[14] amines,[15] hydrides,[16] silanes[17] and alkynes.[18] In sharp contrast to the use of thioesters as C(O)–S electrophiles, the function of thioesters as nucleophiles to react with electrophiles has been rarely developed (Figure 2A).[19]

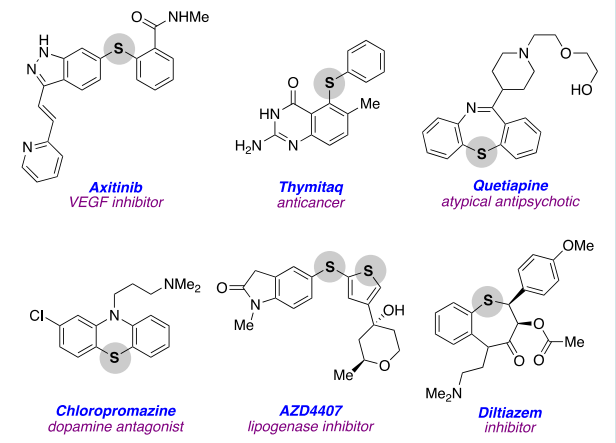

Figure 1. Commercial pharmaceuticals containing thioethers.

Although transition-metal-catalyzed thiolation of halides and pseudohalides with thiols is a fundamental method for the synthesis of thioethers, these protocols are inherently limited due to the formation of RS–M–H intermediates from free thiols, thus requiring the use of a base and leading to the generation of reduction by-products (Figure 2B). Thus, the development of new "protonless" sulfur reagents is highly desirable.

[a] *Department of Chemistry, Rutgers University, 73 Warren Street, Newark, NJ 07102, United States.*
* chengwei.liu@rutgers.edu; michal.szostak@rutgers.edu.
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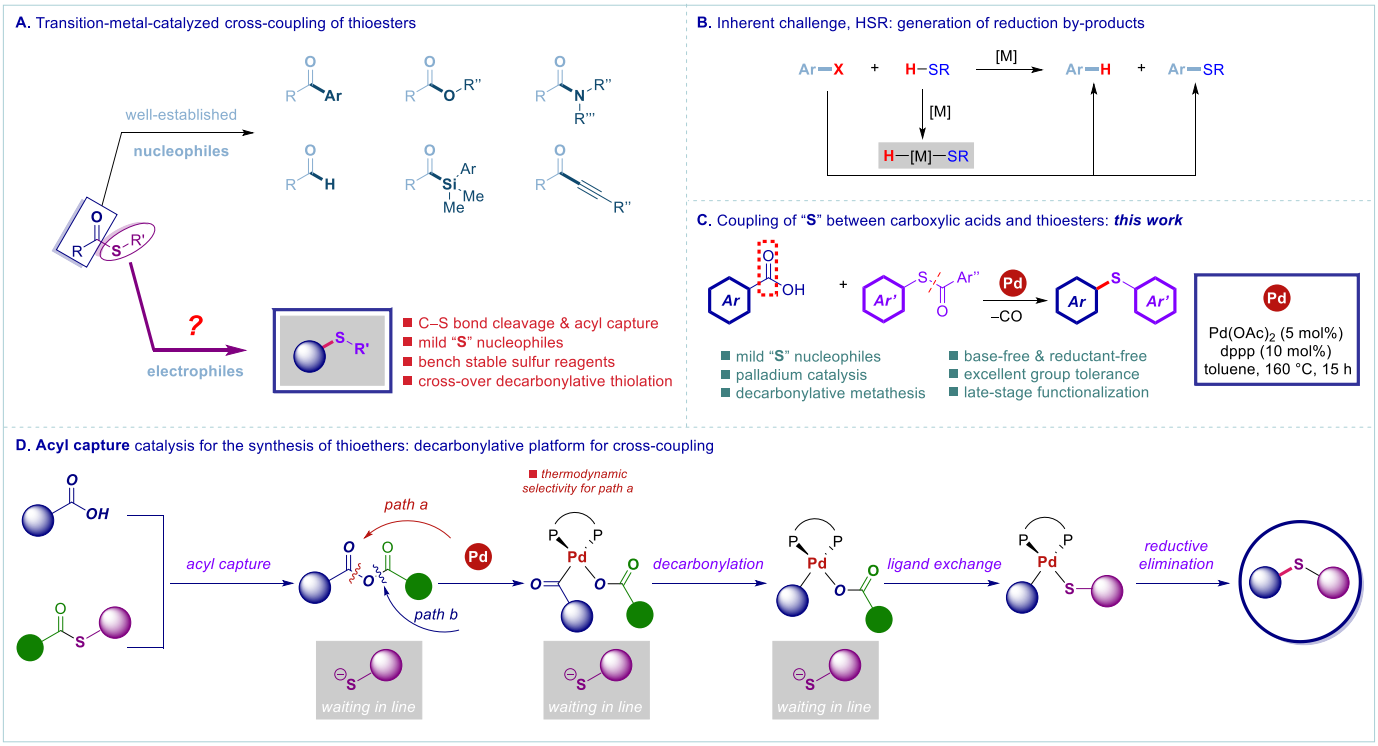

Figure 2. Acyl capture catalysis for the synthesis of sulfides via decarbonylative cross-over C–S bond activation.

Simultaneously, we recognized that carboxylic acids are fundamental building blocks in organic synthesis.[20,21] Transition-metal-catalyzed cross-coupling of carboxylic acids is highly attractive due to their pervasiveness as crystalline starting materials across various faces of chemical science.[22–24] Recently, compelling applications of cross-coupling of carboxylic acids by decarboxylative and decarbonylative mechanisms to form C–C and C–X bonds in a highly selective fashion have appeared.[25–31]

Our interest in the cross-coupling chemistry of carboxylic acid functional groups led us to take advantage of the dual reactivity of thioesters as cross-over C(O)–S nucleophiles to achieve the synthesis of sulfides via versatile acyl capture catalysis platform (Figure 2C). Further, given the widespread availability and the tremendous potential of carboxylic acids as unconventional cross-coupling electrophiles, we envisioned the simultaneous activation of a carboxylic acid moiety to provide a new general approach to the synthesis of thioesters from carboxylic acids and thioesters by acyl capture.

The proposed mechanism for this general strategy involves reversible carboxylic acid coupling with an acyl activator from thioester to form an active carboxylic acid (i.e. mixed anhydride) in situ by acyl capture exploiting the high reactivity of the C(O)–S carbonyl group, followed by oxidative addition of the C(acyl)–O bond to a transition-metal, decarbonylation, ligand exchange and reductive elimination, which results in engaging of carboxylic acids in a modular decarbonylative cross-coupling platform (Figure 2D). This strategy forges carbon–sulfur bonds via the classical oxidative addition mechanism operating under redox-neutral conditions in the absence of external bases and provides a general solution to the routine application of carboxylic acids for the synthesis of valuable sulfides with high chemoselectivity and excellent functional group tolerance. It should be noted that two pathways are possible in Figure 2D for the cleavage of the C–O bond in a mixed anhydride (path a and b). We hypothesized that given the thermodynamic nature of the process and the transient stability of acyl-metal complexes, one thioether product would be formed predominantly (path a) (*vide infra*). We further proposed that the mechanism for the formation of the mixed anhydride would involve metal-free acylation.

The following features of our study are noteworthy: (1) the first palladium-catalyzed decarbonylative thioetherification of carboxylic acids and related derivatives; (2) acyl capture catalysis that in principle is broadly applicable to exploiting carboxylic acids in a wide array of transition-metal-catalyzed cross-coupling protocols; (3) the first cross-over S-transfer from thioesters to carboxylic acids; (4) the use of mild "protonless" *S*-nucleophiles; (5) external-base-free and reductant-free conditions; (6) broad scope and applications to late-stage functionalization exploiting the ubiquity of carboxylic acid functional group.

Results and Discussion

The proposed acyl capture catalysis was first investigated using 2-naphthoic acid (**1a**) and *S*-phenyl benzothioate (**2a**) (**1a**:**2a**, 1:1 ratio) as model substrates (see SI). To our delight, after extensive optimization we identified the catalyst system consisting of $Pd(OAc)_2$ (5 mol%) and dppp (10 mol%) (dppp = 1,3-bis(diphenylphosphino)propane) in toluene at 160 °C as the optimum combination to deliver the desired sulfide product (**3a**) in quantitative yield.

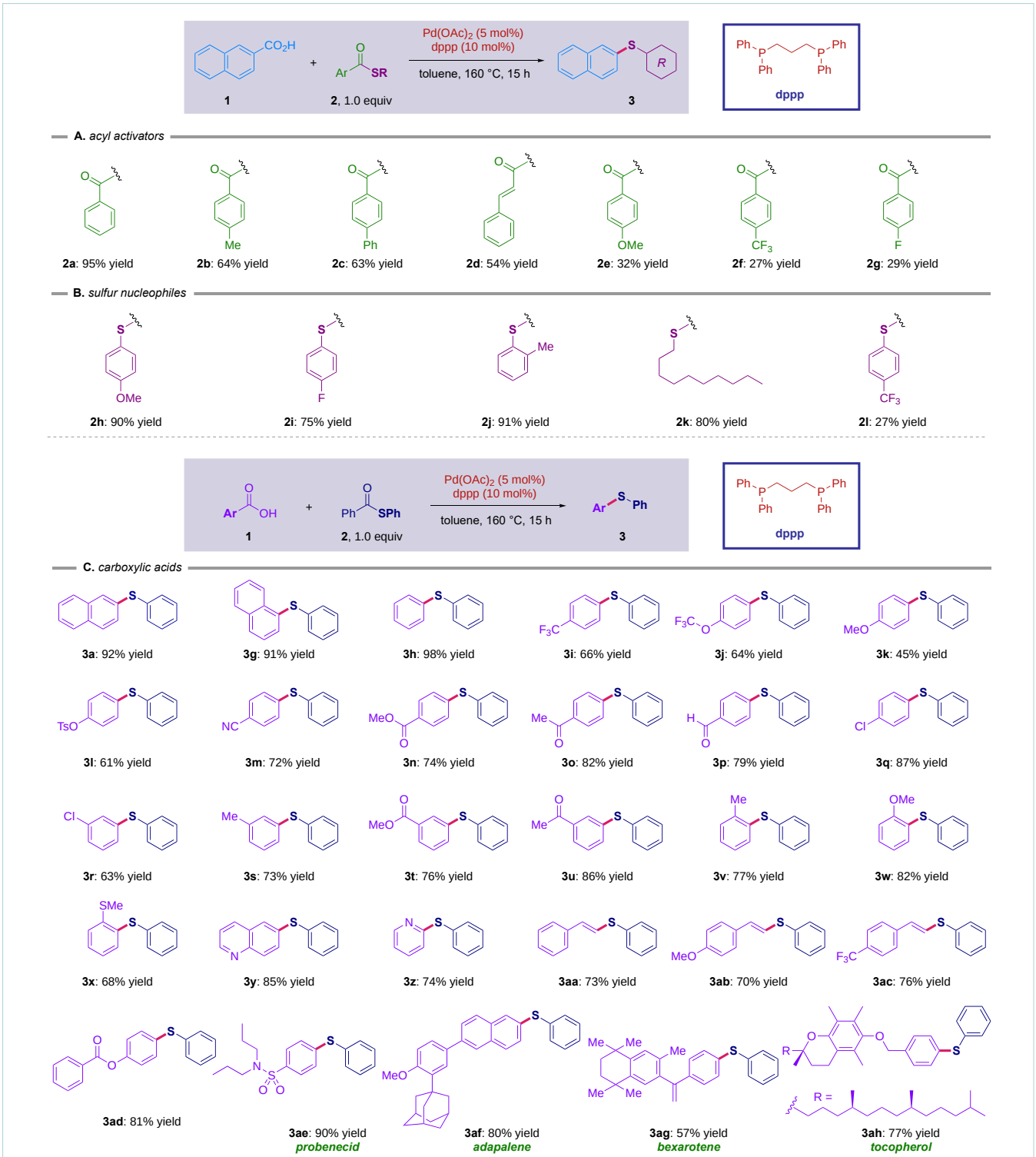

Figure 3. Acyl capture catalysis for the synthesis of sulfides via decarbonylative cross-over C–S bond activation. Conditions: 1 (1.0 equiv), 2 (1.0 equiv), $Pd(OAc)_2$ (5 mol%), dppp (10 mol%), toluene (0.25 M), 160 °C, 15 h. See SI for details.

A summary of key optimization results is presented in the SI. Several points are worth noting: (1) other phosphane ligands can be used, such as dppm (81%), dppe (82%), dppb (63%), dpppent (30%), dppf (73%), Xantphos (65%), however, bidentate phosphines are preferred cf. PCy_3 (<2%), PPh_3 (<2%); (2) the coupling ensues at temperatures as low as 120 °C, consistent with the efficient decarbonylation step (48% yield); (3) monitoring of the reaction indicates 75% conversion after 60 min, consistent with facile coupling. It should be noted that the carboxylic acid is activated in the absence of external-bases and additional external-activators, while the thioester provides an "internal" cross-over activator and offers nucleophilic sulfur to deliver the desired coupling product. Toluene is the preferred solvent for the reaction. Furthermore,

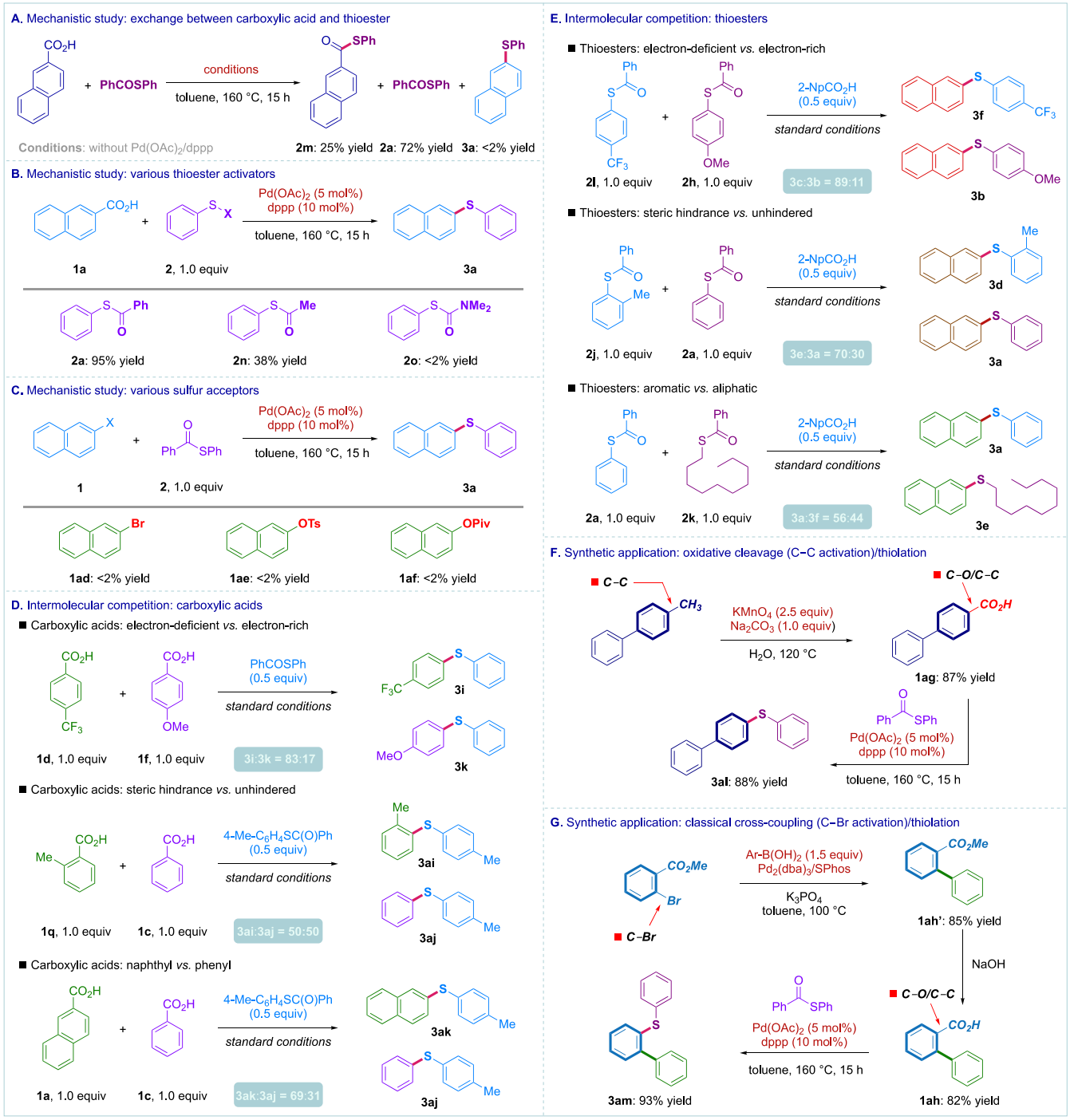

Figure 4. Acyl capture catalysis for the synthesis of sulfides via decarbonylative cross-over C–S bond activation. See SI for details.

dioxane is typically also a preferred solvent for decarbonylative couplings, while lower efficiency is observed in higher boiling solvents.

Considering that thioesters serve as the dual component in this transformation, we first explored the effect of thioester acyl and *S*-substitution on the reaction (Figure 3A-B). As shown, the acyl part accommodates benzoyl, alkyl-benzoyl, aryl-benzoyl as well as vinyl substitution in good to excellent yields, while modest yield is obtained with methoxy and electron-withdrawing substitution (Figure 3A). Thus, *S*-phenyl benzothioate (**2a**) emerges as the most reactive among a range of acyl functionalized thioesters. Furthermore, the scope of the *S*-substitution was investigated (Figure 3B). As shown, electron-neutral (**2a**), electron-rich (**2h**), fluoro-containing (**2i**), sterically-hindered (**2j**) and even alkyl (**2k**) thioesters delivered to desired products in excellent yields. The electron-deficient thioester (**2l**) gave a promising but lower efficiency due to the electronic mismatch with the acyl capture and ligand exchange steps. We note that only one product was generally observed in the coupling, selectivity >90:10 in all cases examined. We believe that the selectivity in Figure 3A is connected to the acylation/decarbonylation selectivity, which results in the optimum performance of electronically-unbiased substrates, while in general electron-rich S-substituents are preferred over

electron-deficient S-substituents (Figure 3B). An alternative mechanism might involve dehydration to symmetrical anhydride. Homo anhydrides have not been observed under the reaction conditions.

We next turned our attention to investigate the scope of the carboxylic acid component amenable to this transformation (Figure 3C). As shown, the method is compatible with a remarkably broad range of electronically- and sterically-functionalized carboxylic acids, attesting to its generic format. As shown, various electron-neutral (**3a, 3g, 3h, 3s**), electron-rich (**3k**) and electron-deficient (**3i**) carboxylic acids can be employed to deliver the desired products in good to excellent yields. We believe that in case of **3h** the reaction follows the proposed mechanism since decarbonylation of **2** is slower than acylation to form a mixed anhydride. Importantly, medicinally-privileged motifs, such as trifluoromethyl ethers (**3j**), as well as functional handles, such as tosyl (**3l**), nitrile (**3m**), esters (**3n, 3t, 3ad**), ketones (**3o, 3u**), aldehydes (**3p**), halides (**3q, 3r**) are well compatible. It is noteworthy that steric hinderance (**3v-x**) can be readily employed. Pleasingly, heterocycles, such as quinoline and pyridine (**3y-z**) are well-tolerated. Furthermore, cinnamic acids (3aa-ac) are also compatible in this transformation, providing vinyl sulfides. Overall, these results highlight the broad scope of carboxylic acids that can be employed in this redox-neutral decarbonylative coupling.

It is noteworthy that this protocol permits direct late-stage derivatization of pharmaceuticals, such as antihyperuricemics (Probenecid, **3ae**), retinoids (Adapalene, **3af**), antineoplastic agents (Bexarotene, **3ag**) and natural products (Tocopherol, **3ah**). This late-stage cross-coupling is feasible due to the innate presence of the carboxylic acid moiety; thus, the cross-coupling approach exploiting carboxylic acids as electrophiles through redox-neutral decarbonylation offers powerful alternative to the traditional cross-coupling of halides or pseudohalides and, as shown, may be readily applied to the late-stage thiolation.

Intrigued by the efficiency of this robust acyl capture catalysis, we sought to gain insight into the reaction mechanism of this process:

(1) To gain insight into the acyl capture step of the activator, we conducted the model reaction in the absence of Pd-catalyst (Figure 4A). The reaction resulted in the exchanged thioester (**2p**) in 25% yield, recovered thioester (**2a**) in 72% yield and sulfide (**3a**) in less than 2% yield. This finding suggests that a mixed anhydride reacts with SPh anion to form **2p**, which is the intermediate in this process. Typically, we did not observe homo anhydrides under these conditions.

(2) To investigate different activators, various C–S reagents were prepared and subjected to the standard reaction conditions (Figure 4B). As such, both S-phenyl benzothioate (**2a**) and S-phenyl ethanethioate (**2m**) delivered the desired product, albeit the latter was less effective, affording the coupling product in 38% yield. In contrast, less electrophilic S-thiocarbamate (**2n**) was unreactive under the reaction conditions, consistent with the relative $n_S \rightarrow \pi^*_{C=O}$ delocalization in the C(acyl)-S group.

(3) To evaluate the chemoselectivity of this activation method with respect to the classical electrophiles, we have applied a range of electrophiles to the standard reaction conditions (Figure 4C), such as aryl bromide (**1af**), aryl sulfonate (**1ag**) and aryl pivalate (**1ah**), which resulted in unproductive reactions and recovery of starting materials, highlighting the selectivity and unique complementarity of the method.

(4) To gain insight into the observed selectivity, we performed a range of intermolecular competition experiments (Figure 4D-E). Thus, competition experiments between different carboxylic acids revealed that electron-deficient substrates are inherently more reactive that their electron-rich counterparts (4-CF_3:4-MeO = 83:17), while sterically-hindered carboxylic acids showed similar reactivity to *ortho*-unsubstituted acids (2-Me:2-H = 50:50) and polycyclic aromatic acids showed comparable reactivity to benzoic acid (2-Np:Ph = 69:31) (Figure 4D). Interestingly, electron-deficient substrates are inherently more reactive than electron-rich counterparts, consistent with the ease of acyl capture and decarbonylation. Furthermore, *S*-aryl electron-deficient thioesters are inherently more reactive than their electron-rich counterparts (4-CF_3:4-MeO = 89:11), while sterically-hindered thioesters are more reactive than their ortho-unsubstituted counterparts (2-Me:H = 70:30) and aromatic thioesters are more reactive than alkyl substrates (Ph:*n*-$C_{10}H_{21}$ = 56:44) (Scheme 4E). At this stage, longer chain *S*-alky thiol has been used as representative to probe for β-hydride elimination/olefin migration (cf. Me, Et), which has not been detected under the reaction conditions. Overall, the observed effects give insight into the selectivity of the process and are a net result of acylation and decarbonylation steps.

Finally, in order to further demonstrate the selectivity and synthetic utility of this novel reaction manifold, we performed a series of sequential transformations (Figure 4F-G). Thus, "traceless" toluene oxidation merged with acyl capture catalysis delivered a 4-biphenyl-thioether in excellent yield, illustrating the use of hydrocarbons as carboxylic acid precursors (Figure 4F). Furthermore, "classical" Ar–Br cross-coupling merged with "decarbonylative" Ar–CO2H cross-coupling furnished a 2-biphenyl thioether in high yield, emphasizing the synthetic utility of the complementary cross-coupling manifolds (Figure 4G).

Conclusions

In conclusion, we have shown, for the first time, that acyl capture catalysis can be utilized for the direct decarbonylative base-free thioetherification of carboxylic acids using thioesters as thiolating reagents without external activators. Compared with the traditional pathway, thioesters serve as dual electrophilic activators to carboxylic acids as well as *S*-nucleophiles through the merger of decarbonylative palladium catalysis and sulfur coupling. The protocol exemplifies the utility of cross-over redox-neutral decarbonylative catalysis to accomplish highly selective thioetherification of a variety of carboxylic acids and thioesters, which represent some of the

most pervasive building blocks in chemical science. We fully expect that activation of carboxylic acids with cross-over electrophiles will lead to new cross-coupling concepts in transition-metal-catalysis.

Conflicts of interest

There are no conflicts to declare.

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