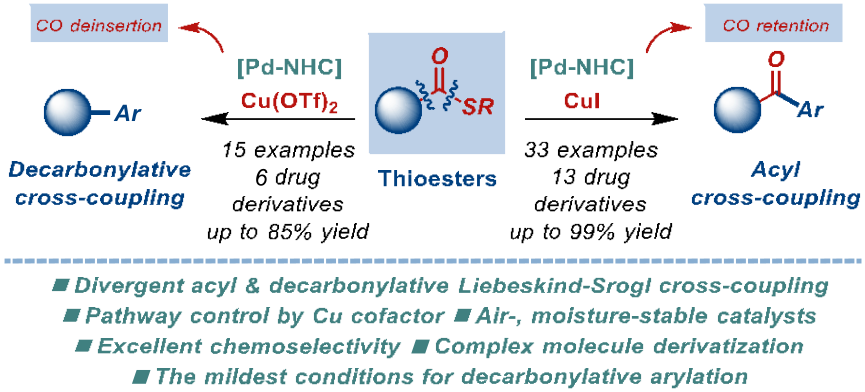
Divergent Acyl and Decarbonylative Liebeskind-Srogl Cross-Coupling of Thioesters by Cu-Cofactor and Pd–NHC (NHC = N-Heterocyclic Carbene) Catalysis

Shiyi Yang, Xiang Yu, and Michal Szostak*

Department of Chemistry, Rutgers University, 73 Warren Street, Newark, New Jersey 07102, United States



ABSTRACT: Transition-metal-catalyzed cross-coupling reactions of thioesters by selective acyl C(O)–S cleavage have emerged as a powerful platform for the preparation of complex molecules. Herein, we report divergent Liebeskind-Srogl cross-coupling of thioesters by Pd–NHC (NHC = N-heterocyclic carbene) catalysis. The reaction provides straightforward access to functionalized ketones by highly selective C(acyl)–S cleavage under mild conditions. Most crucially, the conditions enable direct functionalization of a range of complex pharmaceuticals decorated with a palette of sensitive functional groups, providing attractive products for medicinal chemistry programs. Furthermore, decarbonylative Liebeskind-Srogl cross-coupling by C(acyl)–S/C(aryl)–C(O) cleavage is reported. Cu metal cofactor directs the reaction pathway to acyl or decarbonylative pathway. This reactivity is applicable to complex pharmaceuticals. The reaction represents the mildest decarbonylative Suzuki cross-coupling discovered to date. The Cu-directed divergent acyl and decarbonylative cross-coupling of thioesters opens up chemical space in complex molecule synthesis.

KEYWORDS: *cross-coupling; N-heterocyclic carbenes; Pd–NHCs; C–S activation; acyl coupling; biaryls; Liebeskind-Srogl*

The Liebeskind-Srogl cross-coupling reaction represents one of the most fundamental and well-studied methods for the synthesis of functionalized ketones of broad importance in organic synthesis (Figure 1A).[1–3] This highly discriminating cross-coupling method exploits thiophilic Cu(I)–carboxylate as a metal cofactor, enabling cross-coupling under "baseless" conditions. The role of Cu(I) cofactor is twofold: (1) to activate the C(O)–S bond towards oxidative addition, (2) to facilitate boron to palladium transmetalation.[4] However, despite the major advances of this cross-coupling method, a major challenge is limitation to palladium–phosphine catalysis.[5]

In parallel, N-heterocyclic carbenes have emerged as tremendously powerful ancillary ligands for transition-metal catalysis.[6–8] In particular, the strong σ-donation, variable sterics and availability of various ligand architectures provide numerous avenues to facilitate elementary steps of catalytic cycle and enable a range of challenging cross-coupling processes. However, exploiting the reactivity of NHC ligands to enable selective cross-coupling by the activation of inert C(acyl)–S bonds[4] in thioesters and advance this powerful platform to the preparation of complex molecules[5] has not been accomplished thus far.

Given our interest in C(acyl)–X bond cross-coupling together with NHC catalysis,[9,10] we set out to investigate the Liebeskind-Srogl cross-coupling by Pd–NHC catalysis. Herein, we report the first divergent Liebeskind-Srogl cross-coupling of thioesters by Pd–NHC catalysis (Figure 1B). Most crucially: (1) the method displays extraordinary broad substrate scope and functional group compatibility,

enabling direct functionalization of complex pharmaceuticals;[5] (2) a divergent decarbonylative activation by C(acyl)–S/C(aryl)–C(O) cleavage, controlled by a different Cu cofactor enables to direct the reaction to acyl[11] or decarbonylative pathway[12] for the first time; (3) the reaction represents the mildest decarbonylative Suzuki cross-coupling discovered to date.[12,13] It is worthwhile to note the broad functional group tolerance of the Liebskind-Srogl coupling and the use of this reaction in total synthesis and medicinal chemistry patents.[1-3]

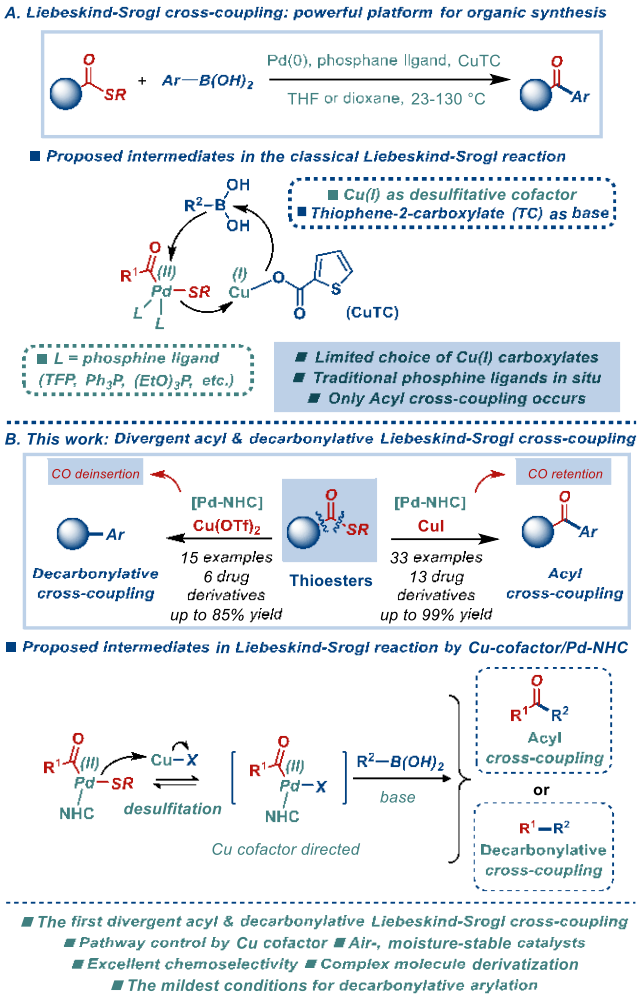
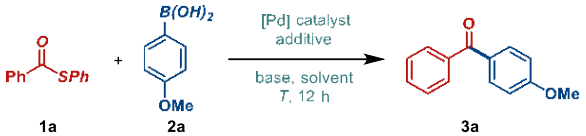


Figure 1. (a) Liebeskind-Srogl cross-coupling of thioestres. (b) This work: Divergent acyl and decarbonylative Liebeskind-Srogl cross-coupling by Cu-cofactor/Pd–NHC catalysis and application to complex pharmaceuticals.

A summary of optimization is presented in Table 1. Additional results are presented in the SI (Table S1, page S38). The cross-coupling between *S*-phenyl benzothioate (**1a**) and 4-methoxyphenyl boronic acid (**2a**) was selected as a model system. After very extensive studies, we identified a system of [Pd(IPr)(μ-Cl)Cl]$_2$ (1 mol%), CuI (1.5 equiv), K_3PO_4 (1.5 equiv) in THF at 50 °C, promoting the cross-coupling in 96% yield (entry 1). From the outset, we selected Pd(II) chloro dimers, [Pd(NHC)(μ-Cl)Cl]$_2$ (Chart 1), as the first-choice Pd–NHC catalysts owing to their fast activation to the monoligated Pd(0) by dimer dissociation, excellent air- and bench-stability of Pd(II)–NHC precatalysts, broad commercial and synthetic availability, and green profile in the absence of extraneous throw-away ligands.[6,10e] [Pd(NHC)(μ-Cl)Cl]$_2$ are well-defined, air- and moisture-stable, enabling operational-simplicity by synthetic chemists and operate in the ideal 1:1 Pd/ligand ratio.[6,11]

Several optimization results are worth noting. Control experiments revealed that all reaction components are critical (entries 2-4). 50 °C is the optimum temperature (entries 5-7). Evaluation of different Pd(II)–NHC precatalysts, including halo dimers, allyl-based and heterocycle-based catalysts, revealed that [Pd(IPr)(μ-Cl)Cl]$_2$ provided the best results (entries 8-14). Of note, screening of different throw-away ligands revealed that chloro dimer is the preferred catalyst, albeit the promising reactivity of the cinnamyl-based [(IPr)Pd(cin)Cl] catalyst should be noted (entries 8-11). Saturated imidazolin-2-ylidene SIPr provided inferior results (entry 12). Imidazol-2-ylidene IPr congeners, such as less sterically-demanding IMes as well as more sterically-

Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a

entry	[Pd]	additive	base	solvent	*T* (°C)	yield (%)
1[b]	[Pd(IPr)(μ-Cl)Cl]$_2$	CuI	K_3PO_4	THF	50	96
2	-	CuI	K_3PO_4	THF	50	0
3	[Pd(IPr)(μ-Cl)Cl]$_2$	-	K_3PO_4	THF	50	0
4	[Pd(IPr)(μ-Cl)Cl]$_2$	CuI	-	THF	50	0
5	[Pd(IPr)(μ-Cl)Cl]$_2$	CuI	K_3PO_4	THF	50	75
6	[Pd(IPr)(μ-Cl)Cl]$_2$	CuI	K_3PO_4	THF	80	78
7	[Pd(IPr)(μ-Cl)Cl]$_2$	CuI	K_3PO_4	THF	23	<5
8	[Pd(IPr)(μ-Br)Br]$_2$	CuI	K_3PO_4	THF	50	55
9	[Pd(IPr)(μ-I)I]$_2$	CuI	K_3PO_4	THF	50	52
10	[Pd(IPr)(cin)Cl]	CuI	K_3PO_4	THF	50	70
11	[Pd(IPr)(3-Clpy)Cl$_2$]	CuI	K_3PO_4	THF	50	59
12	[Pd(SIPr)(μ-Cl)Cl]$_2$	CuI	K_3PO_4	THF	50	57
13	[Pd(IMes)(μ-Cl)Cl]$_2$	CuI	K_3PO_4	THF	50	44
14	[Pd(Ipr*)(μ-Cl)Cl]$_2$	CuI	K_3PO_4	THF	50	<5
15[c]	$Pd_2(dba)_3$/IPrHCl	CuI	K_3PO_4	THF	50	69
16[c]	$Pd_2(dba)_3$/P(2-fur)$_3$	CuI	K_3PO_4	THF	50	48

[a]Conditions: thioester (1.0 equiv), ArB(OH)$_2$ (1.2 equiv), base (1.5 equiv), [Pd] (2 mol%), solvent (0.25 M), *T*, 12 h. [b]ArB(OH)$_2$ (3.0 equiv), base (2.0 equiv). [c]ligand (3 mol%).

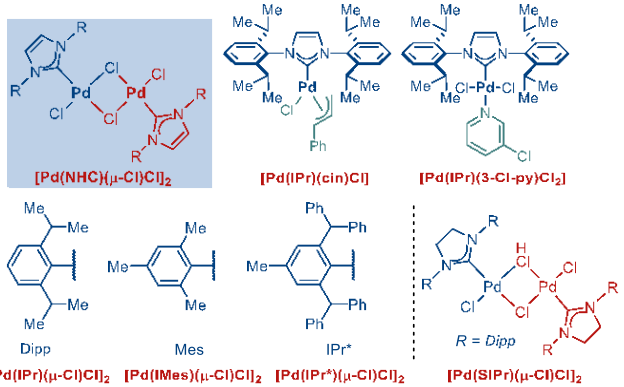
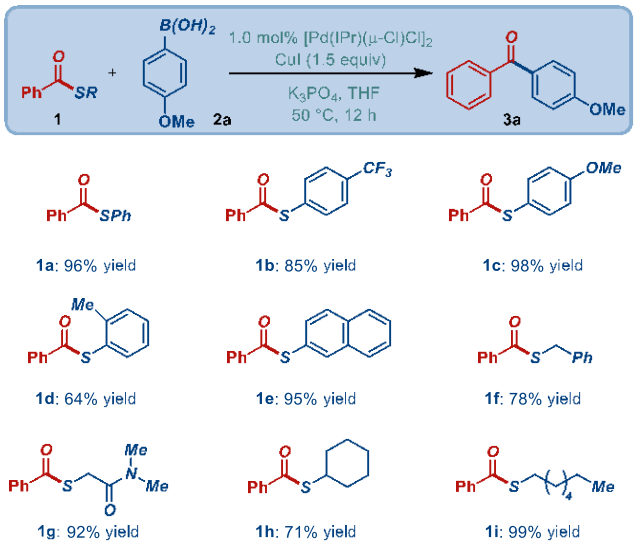


Chart 1. Structures of Pd–NHC catalysts.

Scheme 1. Liebeskind-Srogl Cross-Coupling: *S*-Group Variation on the Thioester Component[a]



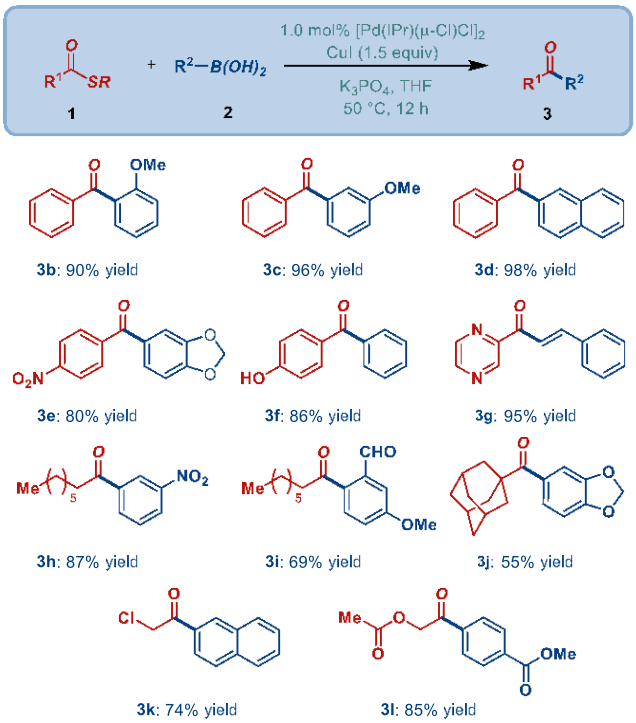
[a]Conditions: thioester (1.0 equiv), 4-MeO-C_6H_4-$B(OH)_2$ (3.0 equiv), K_3PO_4 (2.0 equiv), $[Pd(IPr)(\mu\text{-}Cl)Cl]_2$ (1.0 mol%), CuI (1.5 equiv), THF (0.25 M), 50 °C, 12 h. See SI for details.

hindered IPr* were less effective (entries 13-14). The combination of strongly σ-donating NHC ligand and mild phosphate base provides excellent reactivity and functional group compatibility.[6–8] As expected, the use of well-defined Pd(II)–NHC precatalyst is vastly preferred over the in situ protocol using either imidazolium or P(2-Fur)$_3$ as the preferred phosphine ligand[1a] (entries 15-16). It should be noted that the optimized conditions use 3 equiv boronic acid. Various stoichiometries were tested and the best conditions utilize the optimized stoichiometry. Decomposition of boronic acid is observed under the reaction conditions.

With optimal conditions in hand, we next explored the scope of the Pd(II)–NHC-catalyzed Liebeskind-Srogl cross-coupling. First, we evaluated the capacity of various *S*-groups on the thioester component (Scheme 1). As shown, the developed conditions are broad and tolerate electronically- and sterically-differentiated *S-Ar* groups (**1a–1e**) as well as *S-alkyl* groups, such as benzyl (**1f**), CH_2CONMe_2 (**1g**), 2° alkyl (**1h**) and long chain 1° alkyl (**1i**), furnishing the desired cross-coupling products in uniformly high yields irrespective of the electronic nature of the *S*-activating group.

Next, we assessed different thioesters in the cross-coupling (Scheme 2). For this evaluation we explored the same set of substrates as the original Liebeskind-Srogl conditions.[1a] As shown, the Pd(II)–NHC catalyst system is compatible with a broad range of N, O and X functional groups, including nitro (**3e**), unprotected hydroxy (**3f**), heterocyclic nitrogens (**3g**), aldehydes (**3i**), sterically-hindered substrates (**3j**) as well as very sensitive α-halogens (**3k**) and α-*O*-leaving groups (**3l**). These reactions lead to highly attractive molecular architectures for medicinal chemistry research using well-defined and operationally-simple Pd(II)–NHC catalysis in combination with electrophilic sulfur activation by a thiophilic Cu(I) cofactor.

Scheme 2. Liebeskind-Srogl Cross-Coupling: Thioester Variation[a]

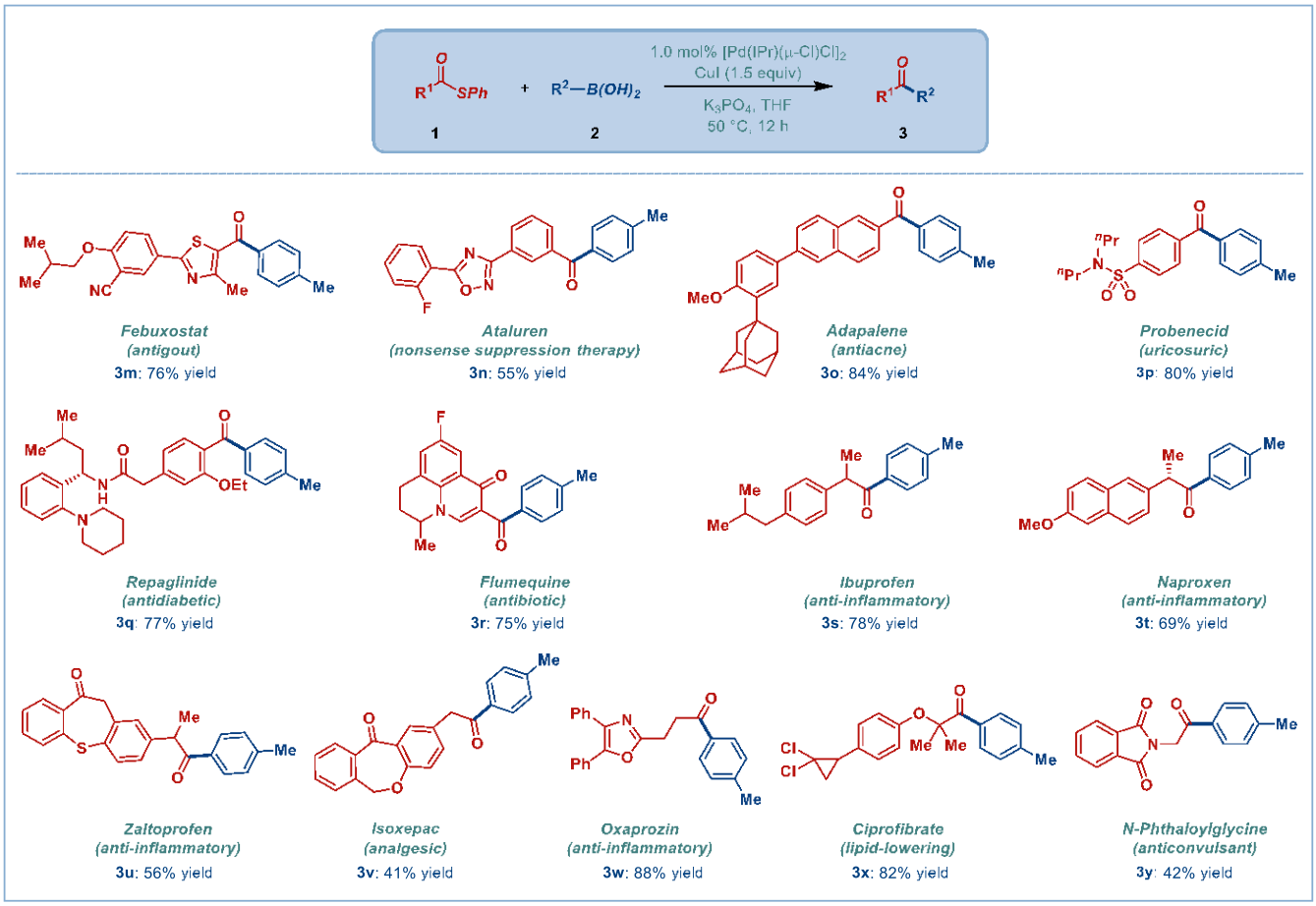


[a]Conditions: thioester (1.0 equiv), Ar-$B(OH)_2$ (3.0 equiv), K_3PO_4 (2.0 equiv), $[Pd(IPr)(\mu\text{-}Cl)Cl]_2$ (1.0 mol%), CuI (1.5 equiv), THF (0.25 M), 50 °C, 12 h. See SI for details.

Most importantly, the Pd(II)–NHC catalysis enables Liebeskind-Srogl cross-coupling of complex pharmaceuticals for the first time (Scheme 3).[5b,d,e] As shown, these reactions proceed with excellent functional group tolerance and reaction scope within the complex contexts, highlighting a significant capacity of the method in medicinal chemistry research. The cross-coupling of thioesters derived from *Febuxostat* (**3m**), *Ataluren* (**3n**), *Adapalene* (**3o**), *Probenecid* (**3p**), *Repaglinide* (**3q**), *Flumequine* (**3r**), *Ibuprofen* (**3s**), *Naproxen* (**3t**), *Zaltoprofen* (**3u**), *Isoxepac* (**3v**), *Oxaprozin* (**3w**), *Ciprofibrate* (**3x**), and *N-phthaloylglycine* (**3y**) proceeded in high to excellent yields. The excellent functional group tolerance (cyano, sulfonamide, chloro, amido, thio, amino, thiazole, oxazole, enaminone, cyclopropyl, ether, oxadiazole, thiepin, oxepin) renders this protocol of practical interest in pharmaceutical settings.[5b,d,e]

Serendipitously, we discovered the first divergent decarbonylative Liebeskind-Srogl cross-coupling by C(acyl)–S/C(aryl)–C(O) cleavage (Scheme 4). This reaction is fully controlled Cu source as a metal cofactor and the electronic nature of the thioester electrophile. We found that when the cross-coupling was performed using $[Pd(IPr)(\mu\text{-}Cl)Cl]_2$ and $Cu(OTf)_2$ under otherwise identical reaction conditions, a switch of the reaction pathway from acyl to decarbonylative product by a formal C(acyl)–S/C–C activation takes place. *In sharp contrast, using CuI as the Cu(I) cofactor, acyl product is the only observed product.* Remarkably, the decarbonylative coupling occurred at exceedingly mild temperature (50 °C). *This reaction represents the mildest decarbonylative Suzuki cross-coupling reported to date.*[12]

Scheme 3. Liebeskind-Srogl Cross-Coupling of Complex Pharmaceuticals[a]

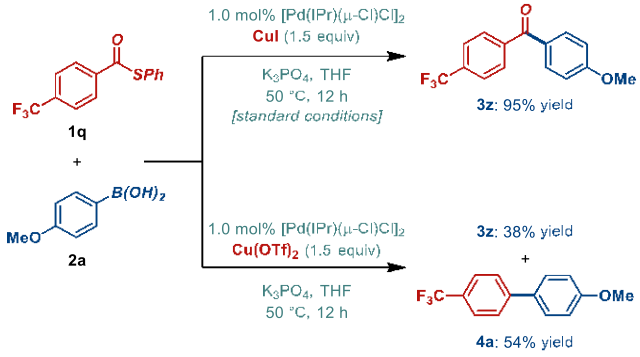


[a]Conditions: thioester (1.0 equiv), 4-Tol-B(OH)$_2$ (3.0 equiv), K_3PO_4 (2.0 equiv), [Pd(IPr)(μ-Cl)Cl]$_2$ (1.0 mol%), CuI (1.5 equiv), THF (0.25 M), 50 °C, 12 h. See SI for details.

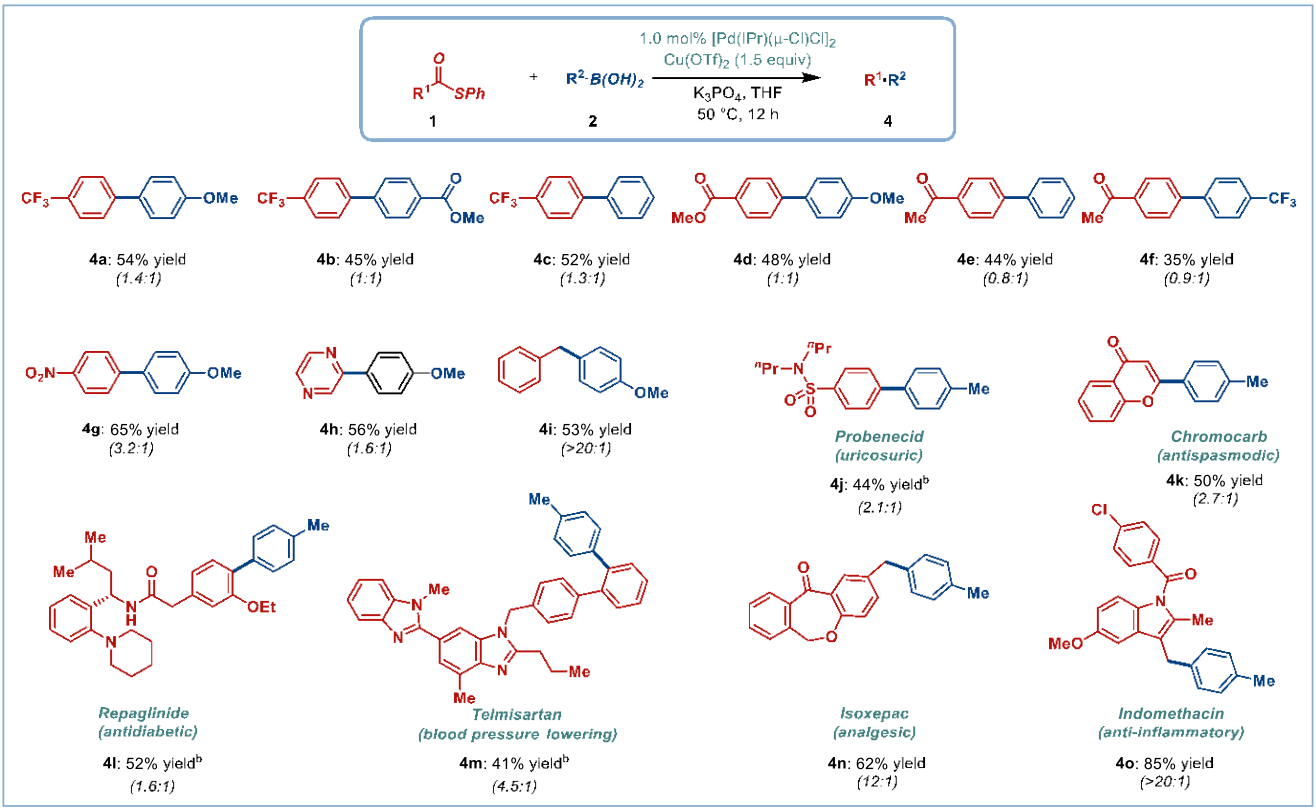
The scope of the decarbonylative Liebeskind-Srogl reaction was briefly investigated (Scheme 5). We found that the process enables for the synthesis of biaryls from electronically-activated thioesters in good to high yields. As shown, the reaction is compatible with CF_3 (**4a–4c**), ester (**4d**), ketone (**4e–4f**), nitro (**4g**) and heterocyclic (**4h**) activating groups. In these cases, acyl product is also observed. Furthermore, benzylic electrophiles are suitable cross-coupling partners as demonstrated by (**4i**). *Most importantly, this novel process can be readily applied to complex pharmaceuticals, demonstrating its capacity for the direct conversion of medicinally relevant pharmacophores.* As such, *Probenecid* (**4j**), *Chromocarb* (**4k**), *Repaglinide* (**4l**), *Telmisartan* (**4m**), *Isoxepac* (**4n**) and *Indomethacin* (**4o**) readily participated in this C(acyl)–S/C(aryl)–C(O) cleavage to furnish decarbonylative arylation products. Optimization of the reaction conditions for the decarbonylative coupling is presented in the SI (Table S3, page S41). Variation of bases, NHCs, temperature and solvents, identified K_3PO_4, 50 °C, THF and [Pd(IPr)Cl$_2$]$_2$ as the most effective combination at the present stage of reaction development.

The proposed mechanism for the divergent acyl and decarbonylative Liebeskind-Srogl coupling is shown in Scheme 6. The key feature is oxidative addition of C(acyl)–S bond to NHC ligated Pd facilitated by the electronic character of the carbene and chelation of the thiophilic sulfur to Cu(I) cofactor.[14] The decarbonylative pathway is triggered by the OTf exchange facilitated by sulfur chelation, resulting in a highly electrophilic Pd(II) center, which is prone to CO deinsertion.[12]

Scheme 4. Discovery of the Divergent Liebeskind-Srogl Cross-Coupling by Pd–NHC Catalysis with Different Cu Cofactor

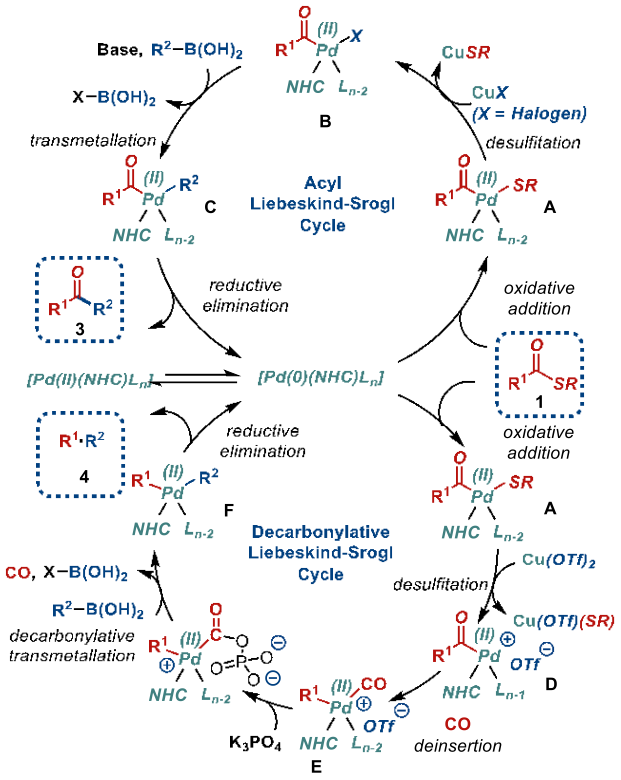


Scheme 5. Decarbonylative Liebeskind-Srogl Cross-Coupling[a]



[a]Conditions: thioester (1.0 equiv), Ar-B(OH)2 (3.0 equiv), K3PO4 (2.0 equiv), [Pd(IPr)(μ-Cl)Cl]2 (1.0 mol%), Cu(OTf)2 (1.5 equiv), THF (0.25 M), 50 °C, 12 h. [b][Pd(IPr)(μ-Cl)Cl]2 (2.5 mol%). Decarbonylative:acyl ratio is indicated in parenthesis (determined by crude ^{1}H NMR). See SI for details.

Scheme 6. Proposed Mechanism: Divergent Catalysis



Mechanistically, the role of OTf is likely to allow access to a cationic Pd, which opens up a coordination site for CO deinsertion. The base can then add to the CO ligand to generate species suitable for transmetallation with the aryl boronic acid. The base has a significant effect on the reaction efficiency. Ongoing research is focused on studies to elucidate the mechanistic pathway and investigation of cationic precursors for CO deinsertion.

In summary, we reported the first divergent acyl and decarbonylative Liebeskind-Srogl cross-coupling of thioesters. This reaction is enabled by Pd–NHC catalysis, enabling an unprecedented broad scope of the thioester cross-coupling and functionalized products. Most crucially, the reaction is readily applicable to complex pharmaceuticals, demonstrating the utility for the synthesis of intricate building blocks for the first time. The use of different Cu source as a metal cofactor and the innate nature of the thioester switches the reaction pathway to afford medicinally-relevant pharmacophores from complex pharmaceuticals. The decarbonylative Liebeskind-Srogl cross-coupling represents the mildest conditions for decarbonylative arylation reported to date. This divergent C(Acyl)–S and C(Aryl)–S cross-coupling represents a powerful entry for reaction discovery in medicinal and synthetic chemistry.

ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

michal.szostak@rutgers.edu

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