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Organic Letters

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https://doi.org/10.1021/acs.orglett.3c03873

OL Organic Letters

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A Platform for the Liebeskind–Srogl Coupling of Heteroaromatic Thioethers for Medicinal-Chemistry-Relevant Transformations

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Cite This: https://doi.org/10.1021/acs.orglett.3c03873 Read Online

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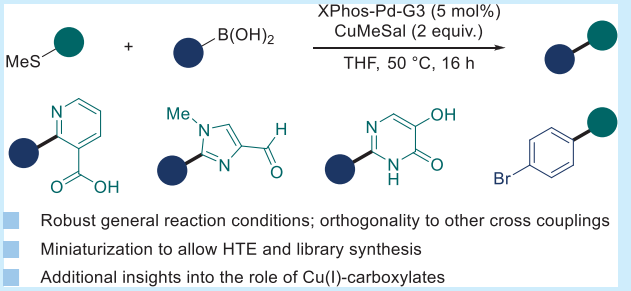
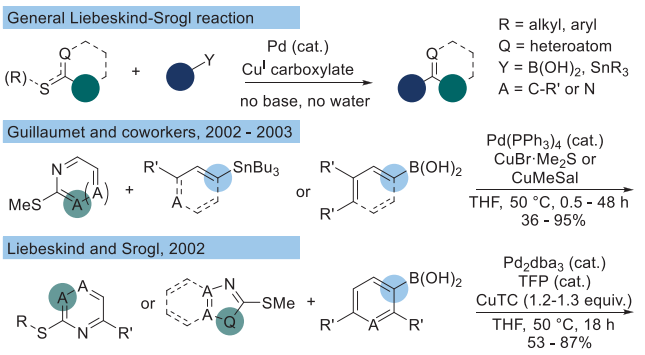
ABSTRACT: General and robust conditions for the Liebeskind–Srogl coupling were developed and used in functionalization of medicinal-chemistry-relevant heterocyclic substrates. Applicability in HTE and library synthesis, combined with its orthogonality to other cross-coupling reactions, make it highly attractive for discovery chemistry workflows. Additionally, the results suggest that the nature of the Cu(I)-carboxylate plays a more prominent role in the reaction performance than the nature of Pd-catalysts, which is rather uncommon for Pd-catalysis and can be used in further optimization of Liebeskind–Srogl coupling.



The Liebeskind–Srogl coupling (LSC) is the most recent cross-coupling reaction that bears the name of its inventors.[1−3] The original publication describes the Pd-catalyzed and Cu(I)-carboxylate-mediated cross-coupling of thioesters with boronic acids to form ketones (Scheme 1).[4] Not long after, this mechanistically unique reaction was expanded to heteroaromatic thioethers with either boronic acids[5,6] or stannanes.[7]

Scheme 1. Overview of the Liebeskind–Srogl Coupling



Particularly the transformation of heterocycles can be of great interest to medicinal chemists, as it can not only help overcome inherent limitations of other cross-couplings reactions and their respective starting materials but also offer a high degree of orthogonality as, for example, halides or thioethers can be carried unscathed through the Liebeskind–Srogl or other cross-coupling reactions, respectively.

Given its potential, the authors found the number of Liebeskind–Srogl couplings in the Boehringer Ingelheim internal electronic lab notebook to be highly underrepresented. We speculate that the lack of early success, abundance of starting materials *for*—and experience *with*—"competing" cross-coupling reactions, and absence of general "go-to" conditions—or best practices—were the main drivers for the slow adoption of this chemistry. There were, however, also examples where the endeavors of the synthesis teams to explore the LSC had paid off with highly improved yields or even enabled reactions altogether, where other cross-couplings had failed. In the current project, we aimed to establish a set of general and easy-to-use "go-to" conditions, including a workup and purification workflow, a LSC platform, for coupling of heteroaromatic thioethers. This LSC platform will provide a set of conditions amenable to the largest set of substrates possible, although not necessarily affording the highest possible yield, to quickly determine whether a Liebeskind–Srogl coupling is a feasible strategy for a medicinal chemistry program or, perhaps more importantly, enable parallel synthesis (library synthesis) with a single set of conditions for the largest set of substrates possible.[8]

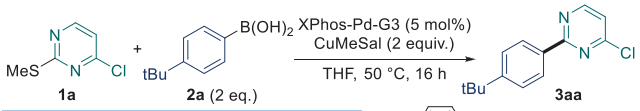
As a starting point for the development of a LSC platform we selected seemingly robust and general conditions from seminal papers,[5,6] involving 5 mol % of palladium, 2 equiv of boronic acid, and 2 equiv of CuMeSal in THF at 50 °C over 16 h. Our exploration started by investigating how amenable these

Special Issue: Organic Chemistry Driven by Academic-Industrial Collaborations

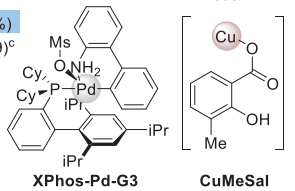
Received: November 17, 2023
Revised: December 7, 2023
Accepted: December 12, 2023

conditions were to variations (Scheme 2, more details in the Supporting Information). We found that THF was indeed the

Scheme 2. Sensitivity to the Variation of the Reaction Conditions[a]



Entry	Deviation standard conditions	3aa[b] (%)
1	none	91 (79)[c]
2	**Pd(PPh$_3$)$_4$** instead of XPhos-Pd	68
3	**10 mol%** XPhos-Pd-G3	95
4	**2.5 mol%** XPhos-Pd-G3	76
5	**1,4-dioxane** instead of THF	75
6	**1 equiv.** CuMeSal	63
7	**1 equiv.** of **2a**	92



[a]Compound **1a** (0.31 mmol), compound **2a** (0.62 mmol), CuMeSal (0.62 mmol), and XPhos-Pd-G3 (5 mol %) in THF (0.1 M) at 50 °C for 16 h. [b]HPLC yields using 4,4′-di-*tert*-butyl-biphenyl as the standard. [c]Isolated yield.

most suitable solvent for this transformation, although it should be noted that the much greener 2-MeTHF worked almost equally well,[9] and the use of 1,4-dioxane leads to acceptable yields while offering the possibility to increase the reaction temperature beyond what is possible for THF. A brief examination of the reaction temperature confirmed that 50 °C was the optimal trade-off between speed, tolerance, and cleanness, which was later corroborated in more extensive kinetics studies (see Figure 1A). Interestingly, a variation of phosphine ligands (Buchwald ligands, Xantphos, or NHC carbenes) did not result in significant changes in reaction performance (*vide infra*). Thus, we opted to continue the optimization with XPhos-Pd-G3,[10] a convenient bench-stable Pd(II) precatalyst, which is readily available at reasonable cost, and already a "commodity" in many medicinal chemistry laboratories. Importantly, use of XPhos-Pd-G3 allows us to minimize any batch or storage variations, which in our experience occasionally lead to unexpected results when less stable palladium sources are used. Lastly, we looked at the nature of the copper species, where indeed the use of Cu(I) carboxylates, or phosphinate, was required for conversions. The use of both CuTC and CuMeSal could lead to a nearly quantitative HPLC yield of the desired product. However, the use of CuMeSal led to more consistent results when less strict oxygen-free and anhydrous conditions were applied. Further differences were noted during our kinetic studies, *vide infra*. A similar observation was made for the stoichiometry of the boronic acid; although not strictly necessary for a good conversion when the reaction could stringently be kept under inert and anhydrous conditions, using 2 equiv rendered the reaction more robust in case those conditions could not be met.

Regarding the product isolation, we found that a relatively simple workup including washing with aqueous ammonia to remove most of the Cu-species remaining after filtration and finally a semiautomatic preparative-HPLC purification constitute the desired robust and general conditions to allow the rapid generation of medicinal-chemistry-relevant heterocycles.

A general scope covering functional group tolerance for both electrophiles and nucleophiles has already been covered to quite some extent in the literature.[1−3,5−7] We therefore focused on medicinal-chemistry-relevant examples that had proven to

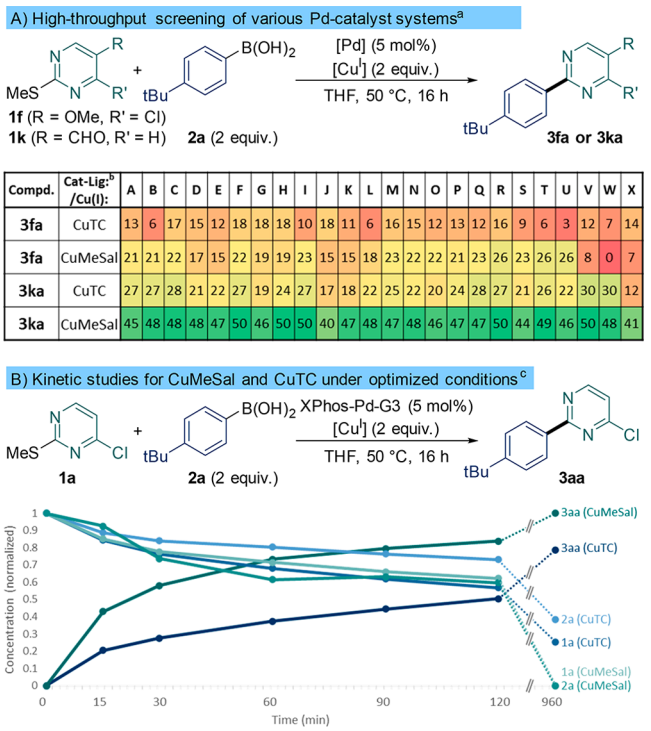


Figure 1. HTE and kinetic experiments. [a]Compound **1** (2.0 μmol), compound **2** (4.0 μmol), CuMeSal (4.0 μmol), and XPhos-Pd-G3 (0.1 μmol) in THF (0.4 M) at 50 °C for 16 h. HPLC yields were obtained using 4-*tert*-butylbiphenyl as the standard. [b]Ligands (see the Supporting Information for full details): A = QPhos; B = TFP; C = RuPhos; D = BrettPhos; E = tBuBrettPhos; F = BINAP; G = Xantphos; H = Bippyphos; I = cataCXium A; J = JosiPhos; K = di-Cl-PEPPSI-ipent; L = AlPhos; M = PPh_3; N = dppf; O = dtbpf; P = tBuXPhos; Q = cataCXium PlCy; R = JackiePhos; S = MordalPhos; T = (tBu)Ph-CPhos; U = GPhos; V = PAd_3; W = AdBrettPhos; X = joYPhos. [c]Compound **1a** (1.6 mmol), compound **2a** (3.2 mmol), CuMeSal/CuTC (3.2 mmol), and XPhos-Pd-G3 (0.08 mmol) in THF (0.1 M). Analysis by HPLC using 4-*tert*-butylbiphenyl as the standard at 15, 30, 60, 90, 120, and 960 min.

be challenging substrates in other cross-couplings or substrates that could demonstrate orthogonal reactivity when compared to other cross-coupling reactions (Scheme 3). The scope of the electrophilic partner (**1**) generally followed the expected trends for cross-coupling reactions, where electron-poor reagents tend to give better yield, such as **3ba** for example. The product of 2-methylsulfide-4-chloro-pyrimidine (**3aa**) was isolated in good yield, with negligible coupling product in the 4-position, whereas a selective transformation from the 2-halo-4-chloropyrimidine often is challenging using orthogonal methods.[11] Such a strategy allows us to selectively synthesize material that bears variations at the 2-position and can subsequently be submitted to a Suzuki−Miyaura cross-coupling library. However, when we moved to the more challenging 2-methylsulfide-5-bromo-pyrimidine (**3ca**), the formation of a side-product from the competing Suzuki−Miyaura reaction was observed (see the Supporting Information), although the desired product could still be isolated in a yield acceptable for a compound library. Other examples of such orthogonal reactivity can be seen, for example, **3da**, **3fa**, and **3ia**. Heterocyclic electrophiles bearing unprotected functional groups, such as alcohols (**3da**, **3ma**), unprotected primary lactams (**3ma**),[12,13] nicotinic acids (**3la**; hexafluoro-2-propanol (HFIP) was added to increase the yield),[14] and basic

https://doi.org/10.1021/acs.orglett.3c03873
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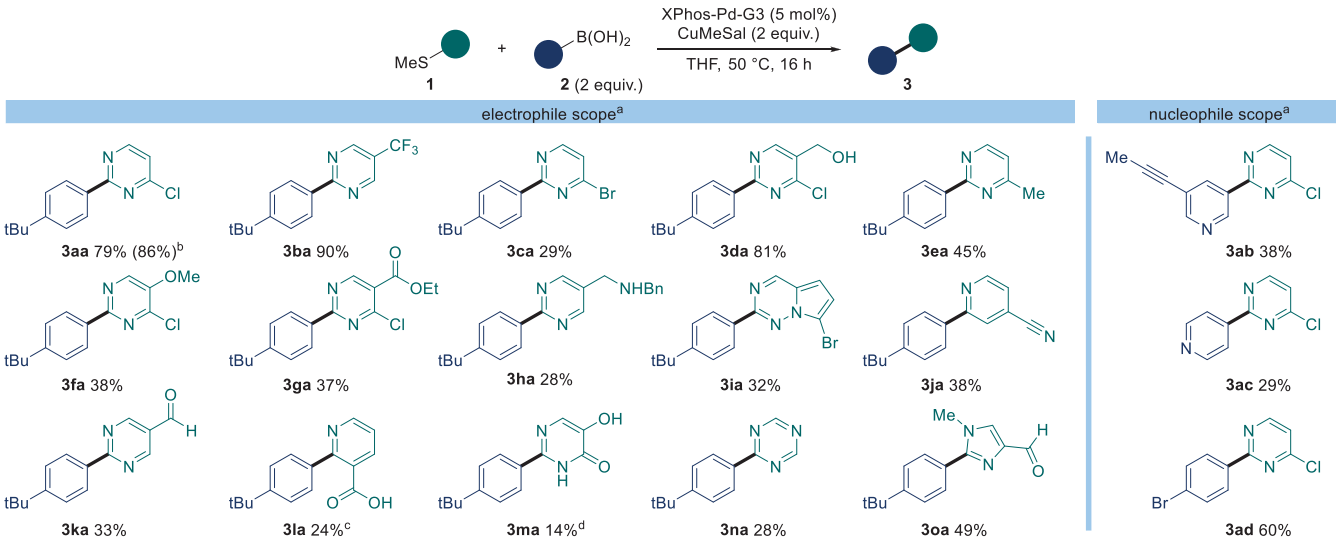
Scheme 3. Scope and Limitations of the LSC Platform Applied to Medicinal-Chemistry-Relevant Heteroaromatic Substrates[a]



[a]Compound **1** (0.31 mmol, 1 equiv), compound **2** (0.62 mmol, 2 equiv), CuMeSal (0.62 mmol, 2 equiv), and XPhos-Pd-G3 (0.06 mmol, 5 mol %) in THF (0.1 m) at 50 °C for 16 h. Isolated yields are reported. [b]Isolated yield at a 1.6 mmol scale. [c]The reaction was performed with added HFIP (3.1 mmol, 10 equiv). [d]The reaction was performed using CuTC (0.62 mmol, 2 equiv) instead of CuMeSal and DMF (0.1 m) instead of THF.

amines (**3ha**), were tolerated, whereas, for orthogonal cross-couplings, synthetic variations or nonstandard conditions had to be applied. 5-Membered heterocycles are often considered to pose challenging substrates in cross-coupling reactions, and a similar trend was unfortunately also observed for our LSC platform (more details in the Supporting Information). However, *N*-alkylated 5-membered heterocycles like imidazoles proved to be suitable substrate partners that gave appreciable yields (**3oa**). The scope of boronic acid nucleophiles (**2**) was also further explored. For common boronic acids the scope of LSC is already well-established.[5−7] We investigated several heteroaromatic and 5-membered aromatic boronic acids, which are known to be notoriously difficult because of their propensity to undergo protodeborylation.[15] Unfortunately, for pyridine-2-ylboronic acids, various imidazolyl boronic acids, oxazolyl boronic acids, and thiazolyl boronic acids, no formation of LSC product was observed (more details in the Supporting Information). But when the nitrogen atom is not adjacent to the boronic acid, reasonable yields can be obtained (**3ab**, **3ac**). Boronic acids with a halogen reacted well to give products with multiple handles for further functionalization, such as **3ad**.

In parallel to identifying the scope of our LSC platform, we worked on rendering it amenable to high-throughput experimentation (HTE): We enabled 96-well screening at the micromolar scale using ChemBead technology.[16−18] Using two example transformations, we juxtaposed the outcomes of a Pd-ligand screen to explore trends in stereoelectronic properties of Pd-catalysts using a standard Buchwald-ligand kit, with the ones for two commercially available copper species (Figure 1A). To our surprise, we did not observe any significant difference between the Pd species, where we would normally expect the effects of electron-releasing abilities and steric bulk to display a certain trend. On the other hand, a clear trend was outlined by the copper species, where markedly improved yields were observed for CuMeSal in nearly all cases. Interestingly, the last three entries (Figure 1A; V−X) actually showed inferior results for the CuMeSal for substrate **3fa** yet a similar trend for **3ka**, but we were not able to simply ascribe these observations to either steric or electronic effects.[19,20] Kinetic studies corroborated that there was no appreciable rate enhancement when varying the Pd species. In addition, it was observed that the boronic acid reagent slowly disappears from the reaction mixture under the reaction conditions, even in the absence of the thioether substrate. We ascribe this effect to protodeborylation and suspect the involvement of copper in accelerating this process under reaction conditions that are not strictly inert and anhydrous. Most surprising was the observation made around the copper species: (1) a significantly higher reaction rate was observed for CuMeSal compared to CuTC, leading to a nearly complete conversion in 3 h at 50 °C, as opposed to more than 12 h for CuTC (Figure 1B); (2) the CuMeSal system was less oxygen sensitive than the CuTC variant; deliberate exposure of the reaction mixture to small amounts of air decreased the reaction rate and the final yield for both systems, but the effect was significantly more pronounced for CuTC. Taking no precautions against air entering the reaction mixture proved detrimental in both cases.

During the development of our LSC platform, we noted that the reaction seems almost agnostic to the nature of the Pd source. Although not exceptional, this observation is different from common cross-coupling reactions for challenging substrates and could serve as an indication of the LSC reaction mechanism. Mechanistic studies of LSC are, unfortunately, rather scarce. In the computational studies by Liebeskind and Musaev, the requisite role of copper carboxylate in the reaction was attributed to the enhancing effects during phosphine dissociation, transmetalation, and reductive elimination steps.[21] Our observations could correspond to the mechanism already proposed, where a "Cu-side" transmetalation of the boronic acid species could be the rate-limiting step, followed by the non-rate-limiting reductive elimination from a three-coordinate palladium complex. Although the role of carboxylate was considered to be vital for the reaction mechanism, the effect of the carboxylate anion structure was not systematically studied. Our studies highlight the prominent role of the carboxylate ligand in the reaction,

https://doi.org/10.1021/acs.orglett.3c03873
Org. Lett. XXXX, XXX, XXX−XXX

and the comprehensive exploration of this effect is currently ongoing in our laboratories.

In conclusion, we have successfully identified a LSC platform, a set of robust reaction conditions, suitable workup procedures, and miniaturization applicable for HTE, which, we believe, will allow medicinal chemistry synthesis teams to quickly assess whether the LSC is a viable path forward worthy of further optimization or rather to be abandoned quickly. Additionally, we have shown that some substrates, which are challenging for other cross-couplings, can lead to appreciable yields under our conditions. We have further demonstrated useful orthogonality between the LSC and other cross-coupling reactions, allowing us to carry the thioether through these reactions for late-stage functionalization or, reversely, functionalize at an otherwise inaccessible position early on, to access a library building block. Finally, we have observed a strong influence of the nature of the copper carboxylate on the success of LSC, which we believe is worth further exploration.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c03873.

Additional details, experimental procedures, and characterization data (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. V.K., R.S., Martin S., and B.H. performed and conceptualized the experiments. A.B., E.B., and Matthias S. performed and conceptualized the HTE experiments. F.M.M. and B.H. conceptualized the work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors gratefully thank Boehringer-Ingelheim's analytical department for the measurements and structure elucidation. We thank our colleagues at Boehringer Ingelheim, namely, Dr. Hannes F. Koolman, Dr. Garazi Talavera, Dr. James M. Fordham, and Dr. Marco Santagostino for their valuable input during our discussions.

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https://doi.org/10.1021/acs.orglett.3c03873
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