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Continuous Flow as Enabling Technology: Synthesis of Heteroaromatic Sulfinates as Bench Stable Cross-Coupling Partners

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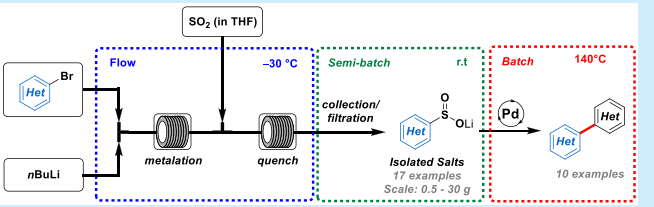
ABSTRACT: An enabling continuous flow setup for handling of unstable organolithium intermediates and synthesis of heteroaryl sulfinates on a multigram scale is described. The developed continuous flow process allows for the synthesis and simple isolation of heteroaryl sulfinates which are otherwise challenging to access in classical batch mode. The lithium sulfinate salts prepared by this method were shown to be efficient reaction partners in palladium catalyzed C(sp^2)−C(sp^2) cross-coupling to access medicinally relevant bis-heteroaryl motifs.



Biaryls, containing at least one aza-heterocyclic core, are privileged and recurrent pharmacophoric features in the small-molecule pharmaceutical landscape.[1−3] An assessment of 146 WHO-registered kinase inhibitors, a compound class of paramount importance in the pharmaceutical industry, showed that 33 compounds possess the biaryl motif, of which 18 drugs embody the heteroaryl−heteroaryl and 15 the heteroaryl−aryl motif (see Figure 1).[4] The high recurrence and value of the

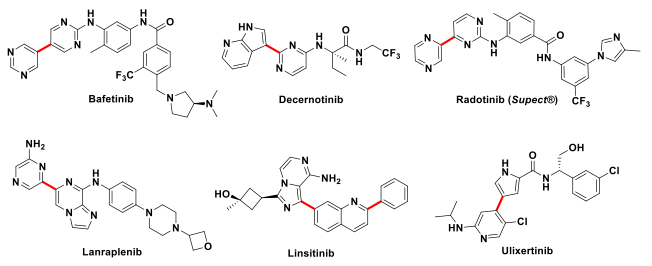


Figure 1. C(sp^2)−C(sp^2) in a selection of kinase inhibitors.

biaryl motif has propelled the development of a vast array of synthetic protocols to access these scaffolds,[5] with the palladium-catalyzed Suzuki−Miyaura coupling being acknowledged as the most popular method for C(sp^2)−C(sp^2) bond formation in the pharmaceutical industry.[6−8]

Despite its widespread usage, this catalytic system reveals limitations when heterocyclic boronic acids need to be cross-coupled. On the basis of internal experience and also supported by a survey performed by Pfizer,[9] this phenomenon becomes even more pronounced when 2-substituted pyridine boronate heterocycles are involved as these desirable building blocks show a tendency to rapidly protodeborylate under a wide pH range.[10] These stability issues can be mitigated by derivatization of the boronic acids to stabilized boronic esters and boronates such as triolborates, *N*-methyl iminodiacetic acid (MIDA) boronates, or *N*-phenyldiethanolamine boronates.[9,11,12]

Although these measures can improve the stability of the coupling partner, they are in contrast to the green chemistry principals due to reduced atom efficiency as well as generation of extra organic waste and boron-containing aqueous waste streams.[13] An additional aspect relates to preclinical safety and the high likelihood of boronic acid derivatives to trigger an in silico alert for mutagenicity, which can require the development of challenging and time-consuming analytical control and testing strategies.[14,15]

In this context, the substitution of heteroaryl boronic acid derivatives by their corresponding sulfinate salts opens the opportunity to circumvent the above-mentioned concerns and allows access to a complementary cross-coupling strategy. Recently, Willis et al. described the use of heteroaryl sulfinates (especially pyridyl) as alternative nucleophilic partners for palladium-catalyzed C(sp^2)−C(sp^2) cross-couplings.[16−20] These salts are known to be bench-stable and greener compared to stabilized boronates, with sulfur dioxide (SO_2)[21] being one of the only byproducts of the desulfinative coupling reactions.

Various methodologies for the preparation of aryl (and some heteraryl) sulfinate salts have been described as outlined in Scheme 1.[19,22] Aryl and heteroaryl sulfinates are accessible via redox or other reactions[23] of prefunctionalized organosulfur

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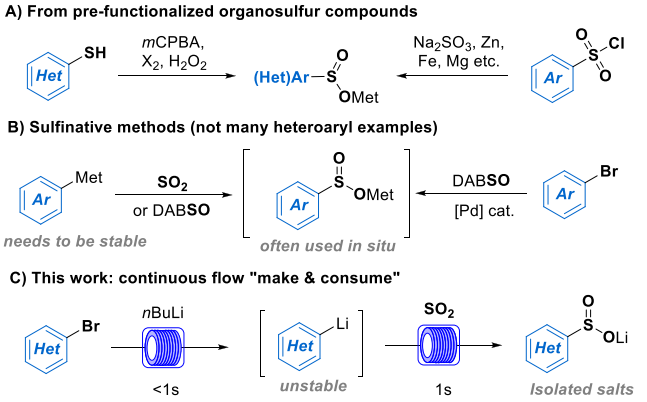
Scheme 1. Selected Methods for the Synthesis of Aryl (Ar) and Heteroaryl (Het) Sulfinate Salts



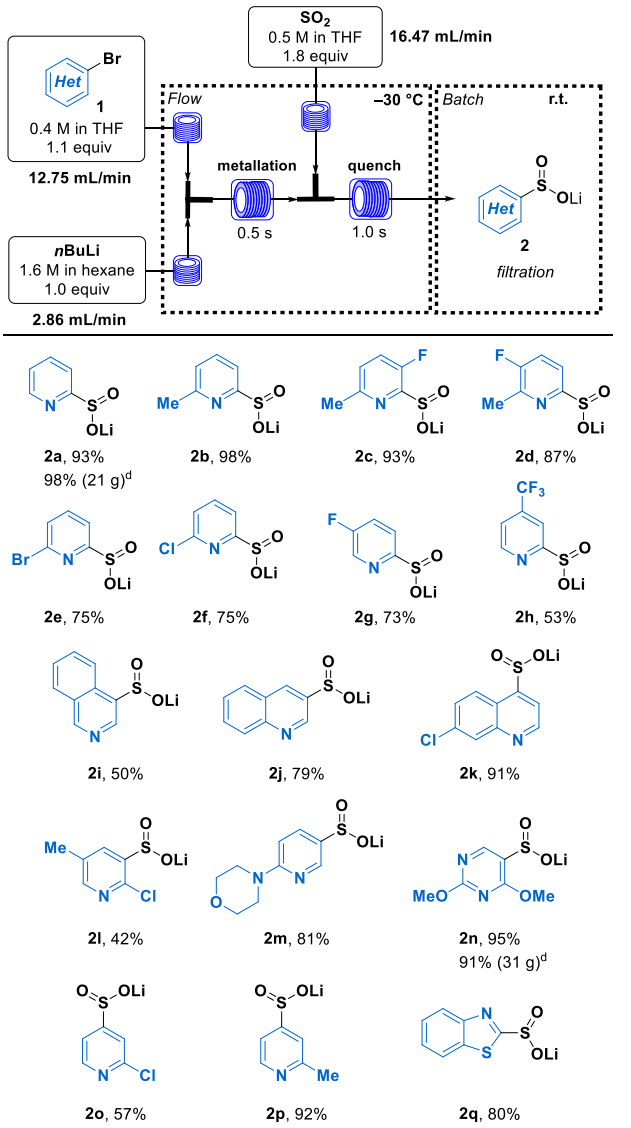
compounds (**A**). Sulfinative approaches (**B**) occur either via palladium-catalyzed sulfination of aryl halides[15,19−21] or by reaction of an organometallic species with electrophilic SO_2 or its surrogate DABSO.[19,23−26] Of note, aryl sulfinates are rarely described as isolated compounds and are typically used in situ for consecutive reactions.[22]

From an atom economy perspective, the reaction of an (hetero)aryllithium species with SO_2 appears the most appealing, however the limited half-life of certain heteroaryl aryllithium intermediates render this approach challenging in conventional batch mode. We therefore hypothesized that a continuous flow "make and consume" approach would allow for rapid generation and electrophilic quench of an unstable aryllithium intermediate and thereby extend the scope of this methodology to access a wide range of advanced heteroaryl sulfinate species.[24−26]

Significantly reduced residence times (≤1 s) as well as enhanced heat- and mass-transfer in flow mode compared to batch mode operation facilitates the handling of unstable intermediates and enables chemistries which are highly challenging or even impossible in conventional batch reactors.[27−29]

Here, we describe the synthesis of aryl sulfinates via a metalation−sulfination sequence in continuous flow mode (**C**). On the basis of our previous work in the field of organometallic reactions, we reverted to our established continuous flow setup which is a reliable work horse in our process development laboratory for the synthesis of aryl boronic acids.[30,31] The utilized flow setup integrates precooling loops for all reagent streams: three Syrdos2 continuous syringe pumps and pressure sensors for each reagent stream (Scheme 2). The automated flow platform[32] consists of simple PTFE T-pieces (ID = 0.5 mm) as mixing elements, and PFA tubing (ID = 0.8 mm) providing two tubular reactors. Pleasingly, we realized that only minimal adjustment to the established boronic acid protocol was required to establish a flow procedure for the synthesis of aryl sulfinates. Side-reaction of *n*-butyllithium (*n*BuLi) with SO_2 leads to the formation of *n*-butyllithium sulfinate as a major process impurity, which is difficult to separate from the desired heteroaryl sulfinate moiety. Therefore, *n*-butyllithium was defined as the limiting reagent while sacrificing small amounts (10 mol %) of aryl bromide. This comes at a price, however, it simplifies the workup significantly because all nonsulfinate, nonpolar impurities can be depleted from the product filter cake by a washing cycle. High purity compounds are obtained

Scheme 2. Metallation−Quench Sequence for the Synthesis of Heteroaryl Sulfinates[a]



[a](a) Reactions were performed on 4.6 mmol scale in flow (1.0 min collection at steady-state). (b) Isolated yields are given. Yield is calculated on *n*BuLi as limiting reagent. (c) Scale up was realized by collecting at steady-state for 31 min (**2a**) and 35 min (**2n**), amounts isolated in parentheses.

without the requirement of chromatographic purification or recrystallization.

Optimal conversion for the preparation of sulfinates **2a−q** was achieved using a 0.4 M concentration of aryl bromide (**1**) in tetrahydrofuran, a commercially available 1.6 M solution of *n*-butyllithium in hexanes, and a 0.5 M solution of sulfur dioxide[33] in tetrahydrofuran. The sulfinate immediately precipitates at the mixing point with sulfur dioxide and consisted of very fine, hard, and nonsticky particles which did not show a tendency to accumulate and cause clogging issues under these conditions.

To demonstrate the substrate scope and synthetic value of the continuous flow process, standard conditions for the conversion of various aryl bromides to lithium sulfinates were devised. In total, 17 pharmaceutically relevant heteroaryl sulfinates were synthesized in moderate to excellent yield. Heteroaromatic bromides such as pyridines in all three positions (**2a−h, 2l−m**),

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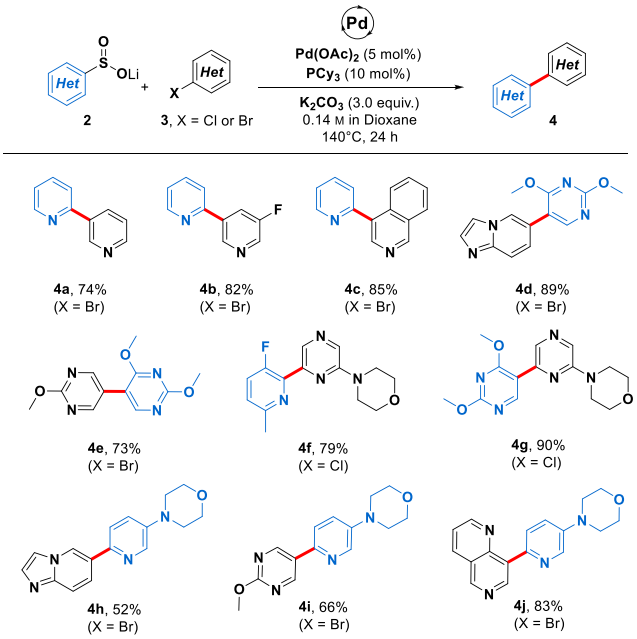
and isoquinoline (**2i**), quininolines (**2j**,**k**), pyrimidine (**2n**), and benzthioxalzole (**2q**) were successfully transformed to their corresponding sulfinate salts.

We considered the scale-ups to be an important proof-of-concept effort due to the exothermic nature of the two consecutive reaction steps, and the potential clogging of the reactor system with sulfinate salts during extended run-time. Over 35 min, the unit delivered 31 g of the desired sulfinate **2n** in excellent purity and with only neglectable fluctuation in the back-pressure.

To validate the quality and reactivity of the lithium sulfinates synthesized via the continuous flow procedure, with the desulfinylative cross-coupling results reported by Willis,[16,20] we investigated the reaction of **2** with **3** toward bis-heteroaryls **4** (see Scheme 3).

Scheme 3. Paladium-Catalyzed Desulfinative Cross-Couplings of Heteroaromatic Lithium Sulfinates towards bis-Heteroaryls[a]



[a](a) Reactions were performed using 1.0 mmol of heteroaryl halide **3** and 1.5 mmol of heteroaryl sulfinate **2** in a sealed vessel. (b) Isolated yields after column chromatography are given.

Under the described palladium-catalyzed cross-coupling conditions, the lithium sulfinates originating from the continuous flow procedure gave excellent yield and quality of the cross-coupled products. In total, 10 pharmaceutically relevant bis-heteroaryls were synthesized in moderate to excellent yield following the Willis protocol (**4a**−**j**).

Despite the application of heteroaryl sulfinates in palladium-catalyzed desulfinative cross-coupling reactions, they also embody versatile building blocks for transition-metal-free desulfinative cross-couplings[34] or other useful transformations toward sulfonyl fluorides,[35,36] sulfones,[37−45] and sulfonamides.[46−50] Investigations in these areas are underway in our laboratories.

To finally confirm the use of these building blocks as a replacement to potentially mutagenic boronate species for pharmaceutical synthesis, in-house in silico assessment for the presence of structural alerts for mutagenicity of **2a**−**q** (17 heteroaryl lithium sulfinates) was carried out. These assessments revealed that **2a**, **2b**, and **2p** showed equivocal results, and the molecules were not covered in the in silico systems used (Derek Nexus v 6.0.0, Sarah Nexus v 3.0.0, and Case Ultra v 1.7.0.5). However, reverse mutation assay Ames tests performed for theses three heteroaryl sulfinates (**2a**, **2b**, **2p**) demonstrated absence of a mutagenic potential (see Supporting Information (SI) mutagenicity study data). Hence, they are considered as nonmutagenic impurities, and no analytical control and testing strategy would be necessary.

In concluson, we expanded on an established and reliable continuous flow protocol for boronic acid preparation[31] and Matterson chemistry[51] to synthesize a broad range of heteroaryl sulfinates, which serve as valuable building blocks for the formation of pharmaceutically relevant heterocyclic, biaryl motifs. This emphasizes the usefulness and scope of this flow platform and showcases the synthetic utility of organolithium chemistry. The reported flow setup is equally suitable for the delivery of small quantities for medicinal chemistry purposes or for larger quantities for early development phases. We feel that the straightforward concept will serve to reduce development times and will generally appeal to the scientific community.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02155.

Detailed experimental procedures and spectral data for all compounds. Computational toxicological report: in silico prediction of potential mutagenic properties of aryl sulfinates, bacterial reverse mutation assays of lithium pyridine-2-sulfinate (**2a**), lithium 6-methylpyridine-2-sulfinate (**2b**) and lithium 2-methylpyridine-4-sulfinate (**2p**) (PDF)

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Notes

The authors declare no competing financial interest.

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