Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX-XXX

pubs.acs.org/OrgLett

Catalyst Selection Facilitates the Use of Heterocyclic Sulfinates as General Nucleophilic Coupling Partners in Palladium-Catalyzed Coupling Reactions

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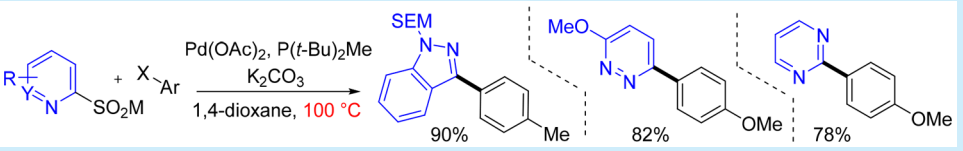
Supporting Information

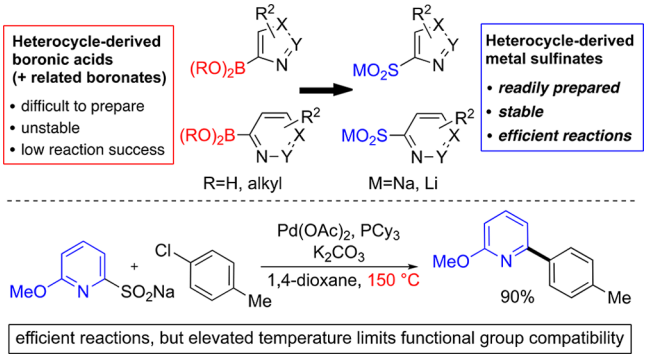


ABSTRACT: A range of 5- and 6-membered heterocycle-derived sulfinates are shown to be effective nucleophilic coupling partners with aryl chlorides and bromides using Pd(0) catalysis. The use of optimal reaction conditions, specifically incorporating a P(*t*-Bu)$_2$Me-derived Pd catalyst, allowed reactions to be performed at moderate temperatures and enabled the inclusion of a variety of sensitive functional groups. Challenging heterocyclic sulfinates, including pyrazine, pyridazine, pyrimidine, pyrazole, and imidazole, were all shown to perform well.

The ability to use cross-coupling methods to access substituted heteroaromatics is crucial to medicinal chemistry, where functionalized heterocycles are key components of many target structures.[1] However, heteroaromatic reactants are notoriously challenging substrates for a variety of cross-coupling reactions. One of the most documented challenges is the poor performance of heterocycle-derived boronic acids, and related boronates, in palladium-catalyzed Suzuki–Miyaura reactions.[2] Several factors contribute to these difficulties, but the propensity of heteroaryl boronic acid derivatives to undergo rapid proto-deboronation[3] is the major problem.[4] *N*-Heterocycles are notorious in this regard. To address these issues, we recently reported on the preparation and use of pyridine sulfinates as replacements for pyridine boronates in palladium-catalyzed coupling reactions with aryl halides.[5] Pyridine sulfinates are straightforward to prepare, stable under extended storage times, and conductive to high-yielding coupling reactions when combined with a broad range of aryl halides (Scheme 1). Despite the success of this chemistry, there were some notable constraints due to the elevated reaction temperature required (150 °C) and the corresponding functional group compatibility limitations.[6] The use of elevated temperatures has also been noted by others as being a potential drawback from a process chemistry perspective.[7] In this paper, we show how the use of an alternative catalyst allows the reaction temperature to be dramatically reduced, thus delivering improved functional group tolerance. We also report the preparation and successful coupling chemistry of a broad range of 5- and 6-membered-ring heteroaromatic sulfinates.

In order to address the stated limitations, we undertook a systematic evaluation of all reaction parameters (Scheme 2).

Scheme 1. Heterocyclic Boronic Acids vs Heterocyclic Sulfinates in Coupling Reactions and an Example Pyridine-2-sulfinate Coupling Reaction

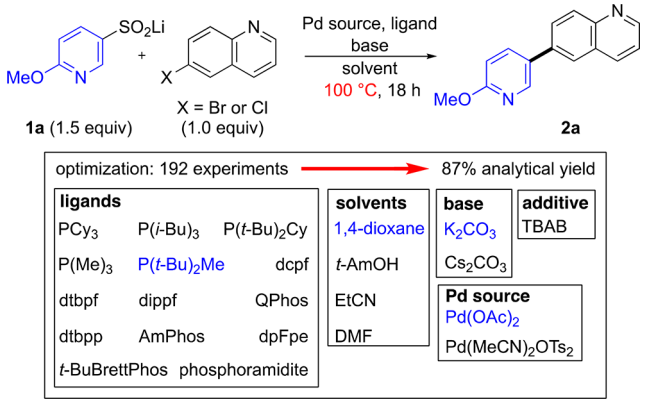


We hypothesized that a more active catalyst would permit lower reaction temperatures and, with our previous results in hand, selected for further screening a set of seven ligands including and close-in to the existing high-performers as well as seven ligands that represented unexplored. We also selected for evaluation (1) a range of solvents with boiling points above the screening temperature, (2) bases and Pd sources having shown promise in our previous screening campaign, and (3) a phase transfer catalyst (PTC) to understand its possible influence on this heterogeneous reaction. Screening was conducted against both chloro and bromo electrophiles in plate format at 100 °C, a temperature that we considered to be reasonable for use in

Received: September 20, 2017

DOI: 10.1021/acs.orglett.7b02944
Org. Lett. XXXX, XXX, XXX−XXX

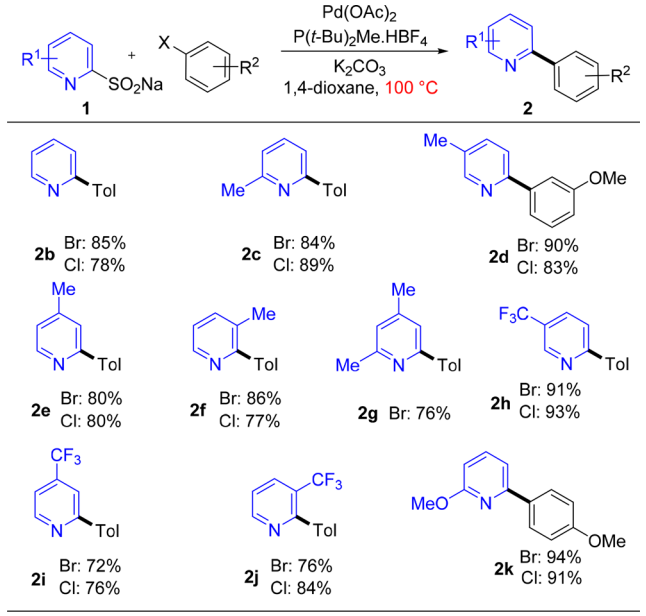
Scheme 2. Catalyst and Reaction Optimization



both array and large-scale reactions. Analysis of the screening results identified P(*t*-Bu)$_2$Me (used as its HBF$_4$ salt) as a highly active ligand, affording analytical yields up to 87%.[8] Despite the thorough screening, we resettled on Pd(OAc)$_2$, K$_2$CO$_3$, and dioxane. Validation of these results in singleton experiments performed on preparative scale (0.2 mmol) delivered isolated yields of 90% for coupling with the aryl bromide, and 85% for the chloride, respectively. A 1.0 mmol scale reaction using the Br-quinoline coupling partner delivered the coupled product in 87% yield.

To test the generality of these newly optimized reaction conditions and ligand selection, we evaluated the coupling of 10 pyridine 2-sulfinates, featuring a variety of substitution patterns, with simple aryl halides (Scheme 3). High-yielding reactions were achieved in all cases, with both aryl chloride and aryl bromide coupling partners performing well under these new conditions. Importantly, the yields obtained in these coupling

Scheme 3. Evaluation of Pyridine-2-sulfinate Coupling Partners[a]

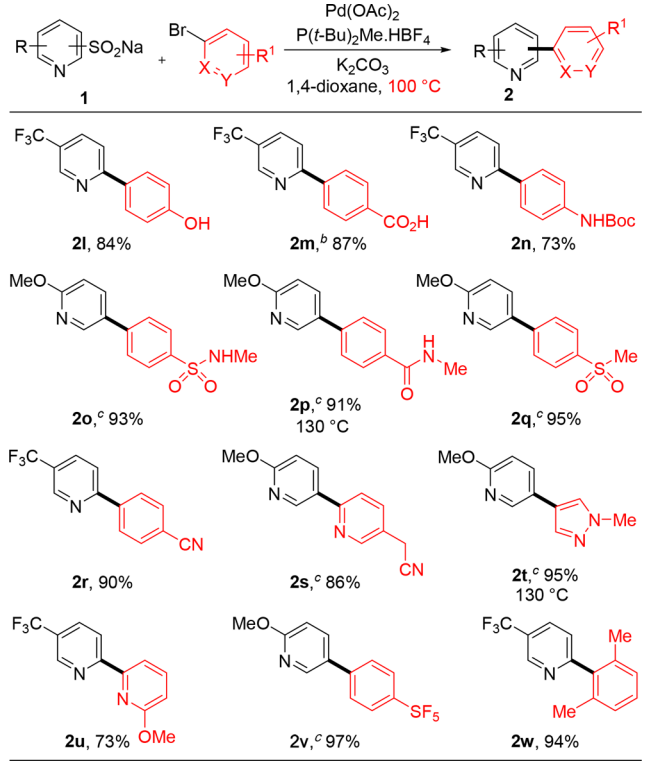


[a]Reaction conditions: pyridine sulfinate (1.5 equiv), aryl halide (1.0 equiv), Pd(OAc)$_2$ (5 mol %), P(*t*-Bu)$_2$Me (10 mol %), K$_2$CO$_3$ (1.5 equiv), 1,4-dioxane, 100 °C, 18 h. Isolated yields.

reactions were comparable to those achieved with our earlier, higher temperature, conditions.[5]

Having validated these new reaction conditions, we then wanted to test our hypothesis that a more active catalyst and milder reaction conditions would allow for greater functional group tolerance. Accordingly, a trifluoromethyl-substituted pyridine-2-sulfinate and a methoxy-substituted pyridine-3-sulfinate were combined with a selection of functionalized coupling partners, all of which had failed under our original reaction conditions (Scheme 4). Pleasingly, a broad range of

Scheme 4. Demonstration of Functional Group Compatibility[a]



[a]Reaction conditions: pyridine sulfinate (1.5 equiv), aryl halide (1.0 equiv), Pd(OAc)$_2$ (5 mol %), P(*t*-Bu)$_2$Me (10 mol %), K$_2$CO$_3$ (1.5 equiv), 1,4-dioxane, 100 °C, 18 h. Isolated yields. [b]Isolated as the methyl ester after treatment with TMSCH$_2$N$_2$ due to isolation difficulties with the free acid. [c]Lithium sulfinate used.

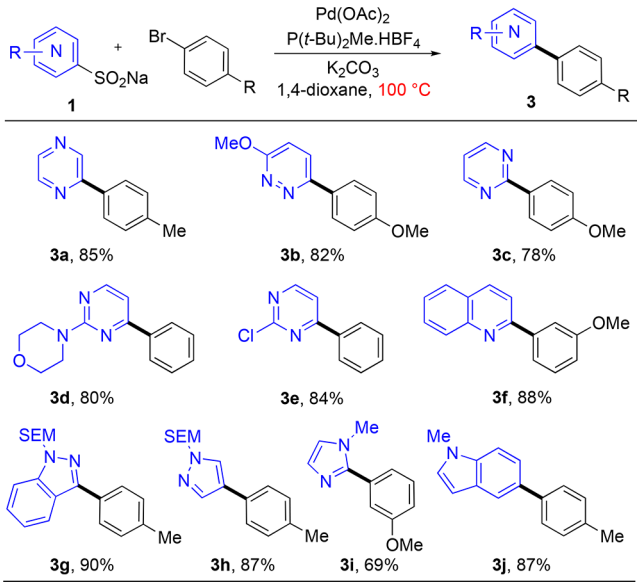
reactive functional groups were shown to be compatible with the reaction conditions, delivering coupled products in good to excellent yields. Specifically, acidic OH and NH groups, present in phenol (**2l**), carboxylic acid (**2m**), carbamate (**2n**), sulfonamide (**2o**), and amide (**2p**) substituted arenes, were all tolerated. Sulfone (**2q**) and cyano-containing substrates (**2r**, **2s**) also performed well. A 4-bromo-*N*-methylpyrazole coupling partner could also be employed (**2t**), although in this case a reaction temperature of 130 °C was needed. 2,2′-Bipyridine **2u** was obtained in 73% yield, establishing the validity of these new conditions to promote challenging heterocycle−heterocycle coupling reactions. Medicinally relevant pentafluorosulfide groups were also tolerated (**2v**). Finally, a sterically demanding 2,6-dimethyl-substituted benzene underwent efficient coupling (**2w**).

Although the challenges of using pyridine-derived boronic acids and related boronates in Suzuki−Miyaura coupling

DOI: 10.1021/acs.orglett.7b02944
Org. Lett. XXXX, XXX, XXX−XXX

reactions are well documented, a number of other heterocyclic partners are also known to be particularly problematic.[2] Consequently, we evaluated the preparation and coupling chemistry of a variety of 5- and 6-membered heterocyclic sulfinates (Scheme 5).[9] The sulfinates were prepared from

Scheme 5. 5- and 6-Membered Heterocyclic Sulfinates As Nucleophilic Coupling Partners with Aryl Bromides[a]



[a]Reaction conditions: heterocycle sulfinate (1.5 equiv), aryl halide (1.0 equiv), $Pd(OAc)_2$ (5 mol %), $P(t\text{-}Bu)_2Me$ (10 mol %), K_2CO_3 (1.5 equiv), 1,4-dioxane, 100 °C, 18 h. Isolated yields.

either oxidation of the corresponding thiol[10] or using SMOPS chemistry from the corresponding halide.[11] All of the sulfinates used in Scheme 5 are stable solid reagents. Diazene derivatives performed well in the coupling reactions, with pyrazine (**3a**), pyridazine (**3b**), and pyrimidine sulfinates (**3c**) providing the aryl-coupled products in high yields. A 2-quinoline sulfinate produced **3f** in 88% yield. Sulfinates derived from 5-membered heterocycles were also effective coupling partners, with 3-indazole (**3g**), 4-pyrazole (**3h**), 2-imidazole (**3i**), and 5-indole (**3j**) substituted sulfinates all delivering efficient reactions.

In conclusion, we show that the use of a new catalyst system allows the use of lower temperature reaction conditions for the palladium-catalyzed coupling of heteroaryl sulfinates with aryl halides. Excellent functional group tolerance is demonstrated. We also report the preparation and use of a range of medicinally relevant 5- and 6-membered heterocyclic sulfinates. Given the challenges associated with the use of the corresponding boronic acids, we anticipate that these reagents will find wide use in discovery chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02944.

Experimental procedures and full characterization for all compounds (PDF)

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Notes

The authors declare the following competing financial interest(s): B.N.R., D.C.B., and V.M. are employees of Pfizer, Inc. and may own stock in the company.

■ ACKNOWLEDGMENTS

We thank Pfizer and EPSRC for support of this study. In addition, we acknowledge Greg Steeno, Usa Reilly, and Neal Sach, all of Pfizer Medicine Design, for assistance with reaction screening.

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DOI: 10.1021/acs.orglett.7b02944
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