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Heterocyclic Allylsulfones as Latent Heteroaryl Nucleophiles in Palladium-Catalyzed Cross-Coupling Reactions

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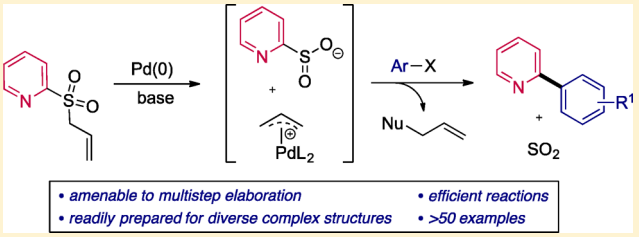
Supporting Information

ABSTRACT: Heterocyclic sulfinates are effective reagents in palladium-catalyzed coupling reactions with aryl and heteroaryl halides, often providing high yields of the targeted biaryl. However, the preparation and purification of complex heterocyclic sulfinates can be problematic. In addition, sulfinate functionality is not tolerant of the majority of synthetic transformations, making these reagents unsuitable for multistep elaboration. Herein, we show that heterocyclic allylsulfones can function as latent sulfinate reagents and, when treated with a Pd(0) catalyst and an aryl halide, undergo deallylation, followed by efficient desulfinylative cross-coupling. A broad range of allyl heteroarylsulfones are conveniently prepared, using several complementary routes, and are shown to be effective coupling partners with a variety of aryl and heteroaryl halides. We demonstrate that the allylsulfone functional group can tolerate a range of standard synthetic transformations, including orthogonal C- and N-coupling reactions, allowing multistep elaboration. The allylsulfones are successfully coupled with a variety of medicinally relevant substrates, demonstrating their applicability in demanding cross-coupling transformations. In addition, pharmaceutical agents crizotinib and etoricoxib were prepared using allyl heteroaryl sulfone coupling partners, further demonstrating the utility of these new reagents.



INTRODUCTION

Aromatic aza-heterocycles linked to a second heteroarene are common motifs in a wide range of bioactive molecules,[1] in materials,[2] and in ligands for metal catalysts.[3] The presence of a key C(sp^2)−C(sp^2) bond joining the two heterocycles results in metal-catalyzed cross-coupling being a popular disconnection for this fragment assembly.[4] Unfortunately, the Suzuki−Miyaura reaction, usually the most versatile of coupling processes, is notoriously difficult when applied to reactions involving aza-heterocycle-derived boron coupling partners.[5] These heteroarene boron reagents are difficult to prepare and store and, due to rapid protodeboronation,[6] deliver poor-yielding reactions.[7,8] To address many of these issues, we recently introduced a variety of heteroarene-derived metal sulfinate reagents[9] and demonstrated that they function as efficient nucleophilic reaction partners in palladium-catalyzed cross-coupling reactions with aryl and heteroaryl halides (Scheme 1a).[10] Specifically, these sulfinate reagents are straightforward to prepare, are stable during storage for many months, and deliver high-yielding coupling reactions. These attributes allowed desulfinylative heteroaryl−aryl coupling reactions of broad scope to be developed.[9]

Despite the success of heteroarene sulfinates as coupling partners, there remained several issues to consider: (1) Although simple heteroaromatic sulfinate salts can be prepared and isolated efficiently by a variety of methods, the purification of more complex analogues has been challenging. (2) The anionic and nucleophilic character of the sulfinate salts makes them unsuitable for functionalization and therefore not amenable to elaboration. These two issues are intrinsically linked, as it is with functionalized, more complex substituted sulfinate reagents, that the ability to perform functional group manipulations is attractive. This second issue holds for many nucleophilic coupling partners, although masked boronic acids, such as aryl potassium trifluoroborate salts,[11] have been shown to be tolerant of a series of transformations[12] and aryl MIDA-[13] and DAN-boronates[14] have been used in iterative coupling reactions.[15] Transformations of alkyl and alkenyl boronic esters are also known.[16] Significantly, aza-heterocyclic reagents are conspicuous by their absence from these studies.

We wanted to capitalize on the exceptional reactivity of heterocyclic sulfinates in challenging coupling reactions but in a variant that allowed for simpler purification of the reagents, for multistep elaboration of secondary functional groups, and ultimately for greater diversity of the nucleophilic coupling partners. For the design of our latent sulfinate reagents, we considered a traditional protecting group strategy,[17] but this was rejected as it would require a formal deprotection step before the coupling reaction. A more attractive scenario was the design of a reagent that would release the sulfinate functionality under the reaction conditions used for the cross-

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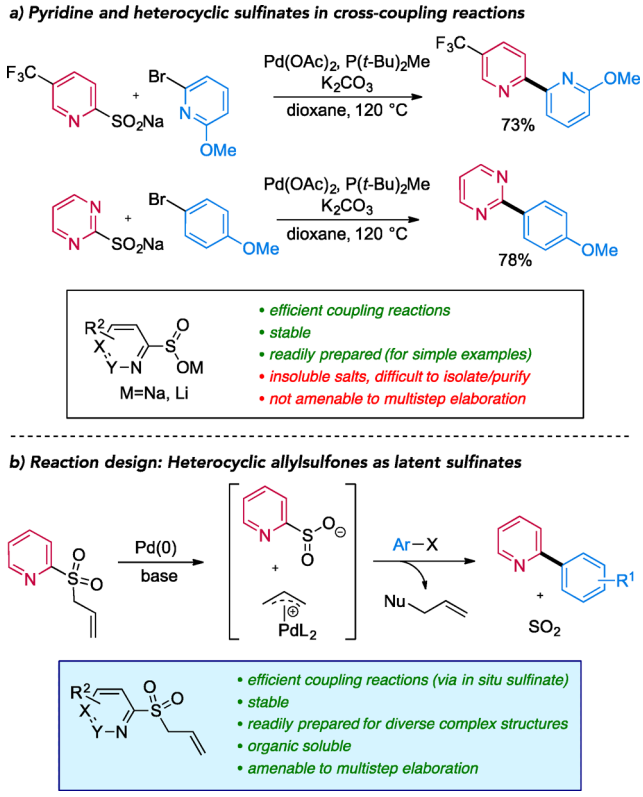
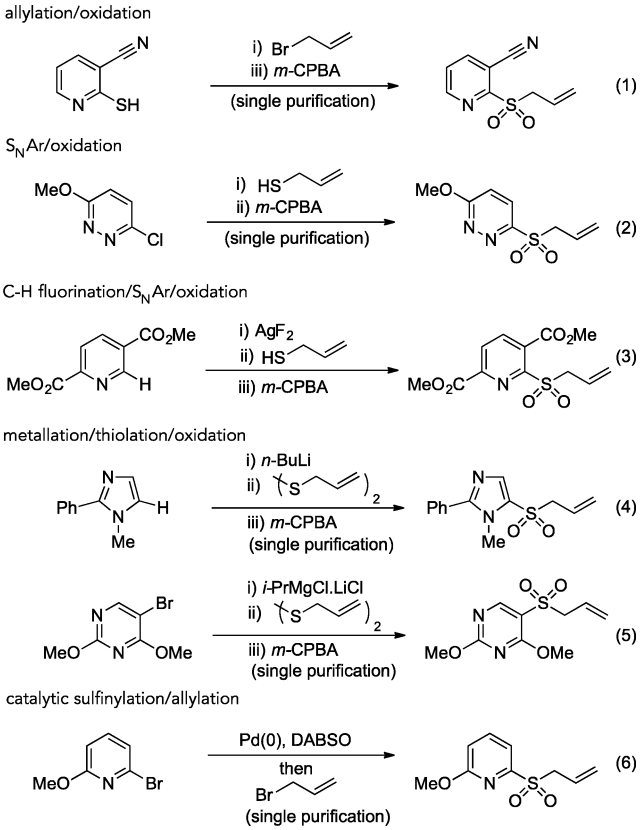
Scheme 1. (a) Heterocyclic Sulfinates and (b) Heterocyclic Allylsulfones in Cross-Coupling Reactions



Scheme 2. Preparation of Allylsulfones[a]



[a]See the Supporting Information for individual reaction conditions.

coupling. Importantly, our design should not compromise the reactivity of the sulfinate reagent in cross-coupling. We settled on the use of heterocycle-derived allylsulfones as potential coupling partners, and our reaction plan is shown in Scheme 1b.[18] Allylsulfones are accessible by a number of routes, and as neutral organic molecules, purification should not be problematic. The allylsulfone units ought also to be stable to a broad range of reaction conditions, therefore allowing the manipulation of additional functional groups and the installation of the sulfone unit at the start of a synthesis sequence. Crucially, under the Pd(0) reaction conditions, fragmentation of the allylsulfone would generate a π-allyl-Pd intermediate while releasing the sulfinate as a leaving group;[19] interception of the π-allyl-Pd intermediate with a nucleophile would regenerate Pd(0) and allow cross-coupling to proceed. In this contribution, we report the realization of this concept and show that heterocycle-derived allylsulfones function as latent sulfinates and are broadly effective nucleophilic coupling partners in Pd-catalyzed cross-coupling reactions.

RESULTS AND DISCUSSION

We were able to access diverse heterocyclic allylsulfones featuring a variety of functional groups from a range of readily available distinct starting materials. Scheme 2 shows representative syntheses, starting from four different monomer sets (thiols, S_NAr suitable heterocyclic halides, miscellaneous heterocyclic halides, and unfunctionalized heterocycles) and employing five different approaches. Thiols could be alkylated with allyl bromide and, after S-oxidation of the sulfide intermediate, provide the required sulfones (eq 1). For small-scale preparations, *m*-CPBA was routinely used as the oxidant, but for larger-scale reactions, hydrogen peroxide in combination with catalytic tungstate was employed. Halogen derivatives appropriate for S_NAr chemistry could be treated with allyl thiol, with subsequent oxidation of the intermediate sulfide, which again required only a single purification (eq 2). We exploited the silver-promoted 2-fluorination of pyridines, described by Hartwig,[20] to access 2-fluoropyridines, which were then subjected to S_NAr chemistry (eq 3). Appropriate five-membered heterocycles could be directly deprotonated, or alternatively, halogen derivatives could be subjected to metal−halogen exchange conditions, typically using *i*-PrMgCl·LiCl or *n*-BuLi, and the trapping of the metalated heterocycles with allyl disulfide, followed by oxidation, provided the desired sulfones (eqs 4 and 5). The final example is redox-neutral and involves the Pd-catalyzed sulfinylation of a bromopyridine,[21] followed by S-allylation, and is a one-pot, two-step protocol (eq 6). These five complementary routes allowed the preparation of >30 heterocyclic allysulfones and, importantly, provided flexibility dependent on the class of starting material that was available.

With efficient access to heterocycle allylsulfones established, we turned to the evaluation of a trial coupling reaction and selected 6-methyl-substituted 2-pyridine allysulfone **1a** and 4-bromotoluene as the reaction components (Table 1). Although the Pd(0)-catalyzed deallylation of benzene-derived allylsulfones has been reported,[19] no examples of heterocycles undergoing this transformation are known, nor are examples of combining deallylation with desilfonylative coupling. Therefore, we were encouraged to find that using reaction conditions developed for our original sulfinate couplings[9a] (PCy_3 as a ligand in dioxane at 150 °C) delivered desired biaryl **2a** in 10% yield (entry 1). Again, guided by our earlier

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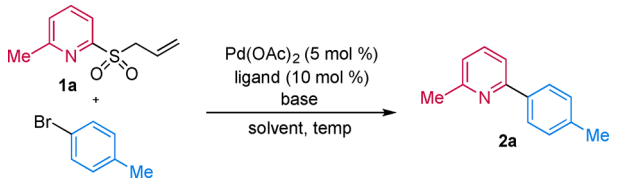
Table 1. Optimization of Conditions for the Preparation of Coupled Pyridine 2a[a]



entry	ligand	base	solvent	temp	yield[b]
1	PCy_3	K_2CO_3	dioxane	150 °C	10%
2	$P(t\text{-Bu})_2Me$	K_2CO_3	dioxane	150 °C	76%
3	$P(t\text{-Bu})_2Me$	Cs_2CO_3	dioxane	150 °C	83%
4	$P(t\text{-Bu})_2Me$	Cs_2CO_3	dioxane	110 °C	65%
5	$P(t\text{-Bu})_2Me$	Cs_2CO_3	toluene	150 °C	<5%
6	$P(t\text{-Bu})_2Me$	Cs_2CO_3	NMP	150 °C	12%
7	$P(t\text{-Bu})_2Me$	Cs_2CO_3	DMSO	150 °C	17%
8	$P(t\text{-Bu})_2Me$	Cs_2CO_3	DMF	150 °C	88%
9	$P(t\text{-Bu})_2Me$	K_2CO_3	DMF	120 °C	78%
10	$P(t\text{-Bu})_2Me$	Cs_2CO_3	DMF	120 °C	82%

[a]Reaction conditions: 2-pyridyl allylsulfone (0.6 mmol, 1.5 equiv), base (0.8 mmol, 2.0 equiv), 4-bromotoluene (0.4 mmol, 1.0 equiv), $Pd(OAc)_2$ (5 mol %), ligand (10 mol %), and solvent (0.2 M). [b]Determined by HPLC using 4,4′-dimethylbiphenyl as an internal standard.

sulfinate reactions we next explored the use of $P(t\text{-Bu})_2Me$ as a supporting ligand[9b] and were pleased to observe a significant increase in reaction efficiency (entry 2). After a brief investigation of the choices of base, solvent, and temperature (entries 2−9), we settled on $P(t\text{-Bu})_2Me$ as the ligand, Cs_2CO_3 as the base, and DMF as the solvent at 120 °C as optimal conditions (entry 10). We also noted that the variation of the base to K_2CO_3 was effective (entry 9) and that dioxane can be used as an alternative solvent (entries 2 and 3). The addition of exogenous nucleophiles to trap the presumed π-allyl-Pd intermediate was not necessary. It should also be noted that the formation of sulfone products, originating from S-arylation of the sulfinate intermediates, was never observed.[19]

We next explored the scope with respect to the variation of the sulfone coupling partner, using simple aryl halides as the second reaction component (Table 2). Given the prevalence of 2-substituted pyridines in pharmaceuticals and agrochemicals,[1c] in addition to the well-documented challenges associated with the use of 2-pyridine boronic acids and related reagents,[5] we chose to explore a wide range of 2-pyridine-based allylsulfones. The parent 2-pyridine allylsulfone, which can be readily prepared on a 50 mmol scale, delivered the coupled product in 76% yield (**2b**). Simple alkyl substituents were tolerated at all positions of the pyridine core (**2c**−**2g**). A selection of electron-donating substituents was introduced, including 6-methoxy (**2i**) and 5-anilino (**2j**), as well as a primary amino group at the 5-position (**2k**). Pharmaceutically relevant trifluoromethyl groups could also be introduced (**2l**−**2n**), as could a 5-chloro-substituent (**2o**). A variety of carbonyl derivatives, including methyl esters and a primary amide, could be incorporated (**2p**−**2r**), along with 3- and 6-nitrile derivatives (**2s**, **2t**). Our investigation of 2-pyridyl examples concluded with the 5-hydroxylmethyl (**2u**) and the 5-nitro-derivatives (**2v**). A broad range of allylsulfones based on alternative heterocycles could also be successfully used. Diazenes, in general, represent a further class of heterocycles for which Suzuki−Miyaura couplings are challenging,[5] and as such, we were pleased to observe efficient coupling reactions with allylsulfones featuring pyridazine (**2w**), 2- and 5-substituted pyrimidines (**2x**, **2y**), and pyrazine (**2z**) cores. Reactions employing quinoline and quinoxaline-derived allylsulfones proceeded smoothly (**2aa**, **2ab**). As a rule, five-membered heterocyclic nucleophiles are challenging substrates for cross-coupling reactions; however, we were able to successfully employ allylsulfones derived from 4- and 5-substituted pyrazoles (**2ac**, **2ad**), imidazole (**2ae**), and isoxazole (**2af**). We also prepared allylsulfone derivatives of two heterocyclic cores of medicinal agents: pyrazole **2ag** contains the core structure of known COX-2 inhibitors[22] and represents a considerable achievement in delivering a tetra-substituted five-membered heterocycle, while isoquinoline **2ah** features the core structure of the Rho kinase inhibitor fasudil.[23] These last two examples further highlight the functional group tolerance of the process, with nitrile, sulfone, sulfonamide, trifluoromethyl, and carbamate groups remaining intact during the coupling reactions, providing new opportunities for parallel medicinal chemistry of complex molecules.

To explore the scope with respect to the aryl halide coupling partner, we focused on using heteroaryl halides and medicinally relevant substrates[24] in combination with a selection of heterocyclic allylsulfones as the reaction partners (Table 3). Bipyridines with varied linkages and substitution patterns could be prepared in good yields (**3a**−**3d**). An imidazole−pyridine coupling (**3e**) was possible, and bis-pyrazole **3f** was obtained in an excellent 72% yield. We then explored the use of a series of halogenated druglike intermediates and were pleased to find that in the majority of cases the coupled products were obtained in good yields. Included in this selection are examples of tri- and tetra-substituted pyrimidines (**3g**, **3h**), with the latter bearing both a free amine and hydroxyl functionalities, although in this case a temperature of 150 °C was needed to achieve full conversion. Derivatives of fasudil (**3i**), the corresponding allylsulfone of which was used to prepare isoquinoline **2ah**, sildenafil (**3j**), celecoxib (**3k**), estrone (**3l**), loratidine (**3m**), and indomethacine (**3n**), all delivered coupled products in good yields. The arene fragment incorporating imidazopyridine **3o** is a derivative of an angiotensin II type 1 receptor antagonist and a partial PPARγ agonist,[25] while molecules incorporating the piperidine-substituted core of arene **3p** inhibit PCSK9 synthesis;[26] brominated derivatives of both of these complex arenes were effectively coupled with heterocyclic allylsulfones, reinforcing the excellent functional group compatibility of the developed chemistry.

The primary utility of the chemistry reported here is expected to be the coupling of heterocyclic allylsulfones; however, we wanted to establish that aryl allylsulfones were also compatible. Accordingly, sulfone **1aj**, derived from the arene core of celecoxib, was coupled with a bromopyridine to provide benzene derivative **3q** in 59% yield (Scheme 3). It is important to note that an increased temperature of 150 °C was needed to achieve this yield, as reaction at 130 °C, sufficient for the majority of heterocyclic allylsulfone examples, returned only a 42% yield.

One of our key design criteria was that the latent sulfinate coupling partners should be stable to varied reaction conditions so that secondary functional groups present in the molecules could be manipulated in a chemoselective manner. Accordingly, we explored a variety of common synthetic transformations on a series of pyridyl-2-allylsulfones (Scheme

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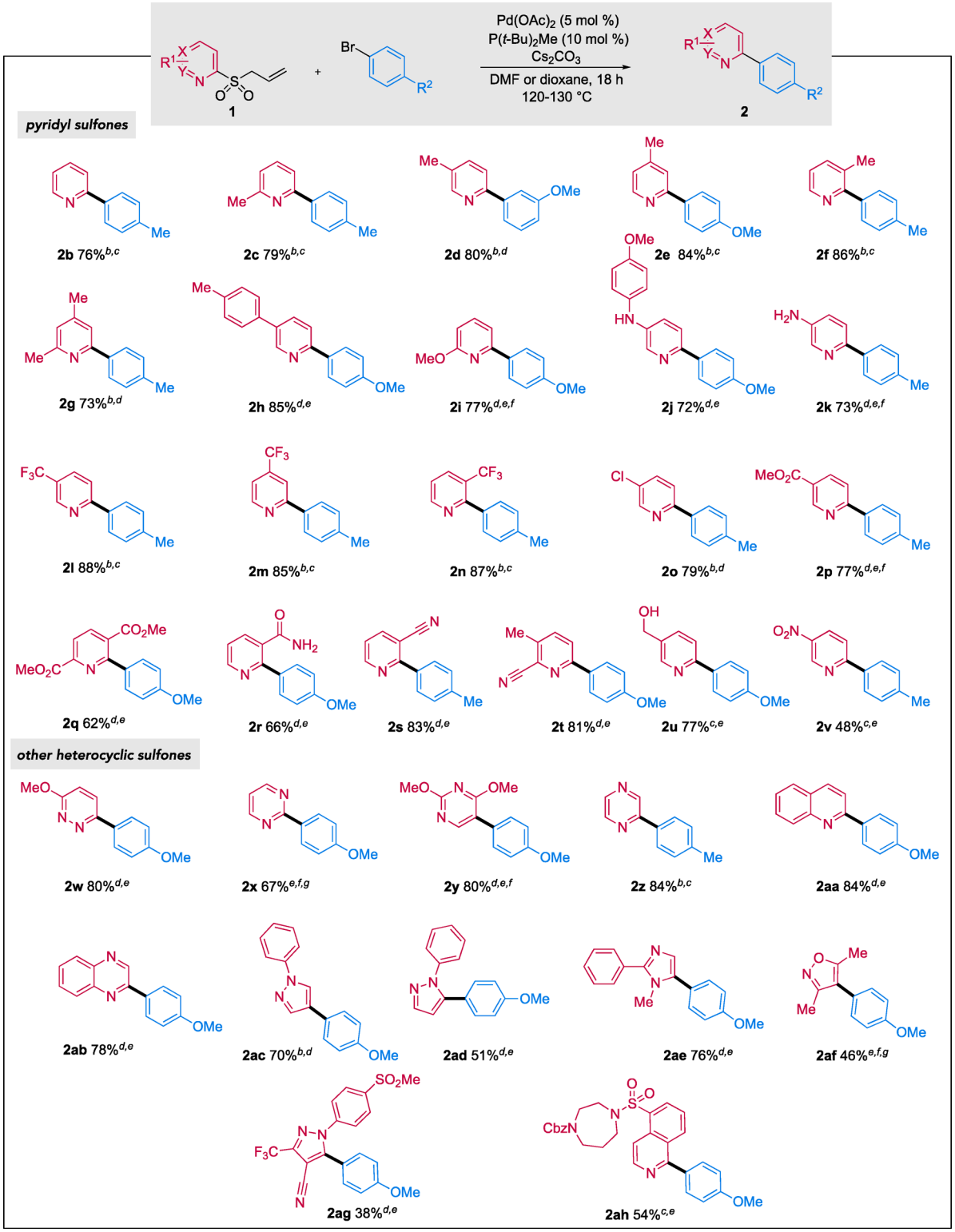
Table 2. Scope of the Allylsulfone Coupling Partner[a,b]



[a]Reaction conditions: heteroaromatic allylsulfone (0.6 mmol, 1.5 equiv), aryl halide (0.4 mmol, 1.0 equiv), Cs_2CO_3 (0.8 mmol, 2.0 equiv), $Pd(OAc)_2$ (5 mol %), $P(t\text{-}Bu)_2Me{\cdot}HBF_4$ (10 mol %), solvent 0.2 M, 18 h. Isolated yields [b]Footnotes in the table: [b]DMF used as a solvent; [c]130 °C; [d]120 °C; [e]1,4-dioxane used as a solvent; [f]K_2CO_3 used in place of Cs_2CO_3; [g]150 °C.

4). Ester-substituted pyridylsulfone **1p** was reduced with DIBAL-H to the corresponding alcohol (**4a**) in 88% yield. In a second reductive transformation, the nitro group in sulfone **1v** was converted to the amine (**4b**) using iron and acetic acid in 95% yield. Base-mediated hydrolysis of nitrile **1s** smoothly produced amide **4c** in 81% yield. Orthogonal palladium-catalyzed coupling was achieved when pyridylsulfone **1ak**, featuring a 5-bromo substituent, was reacted with *p*-tolyl

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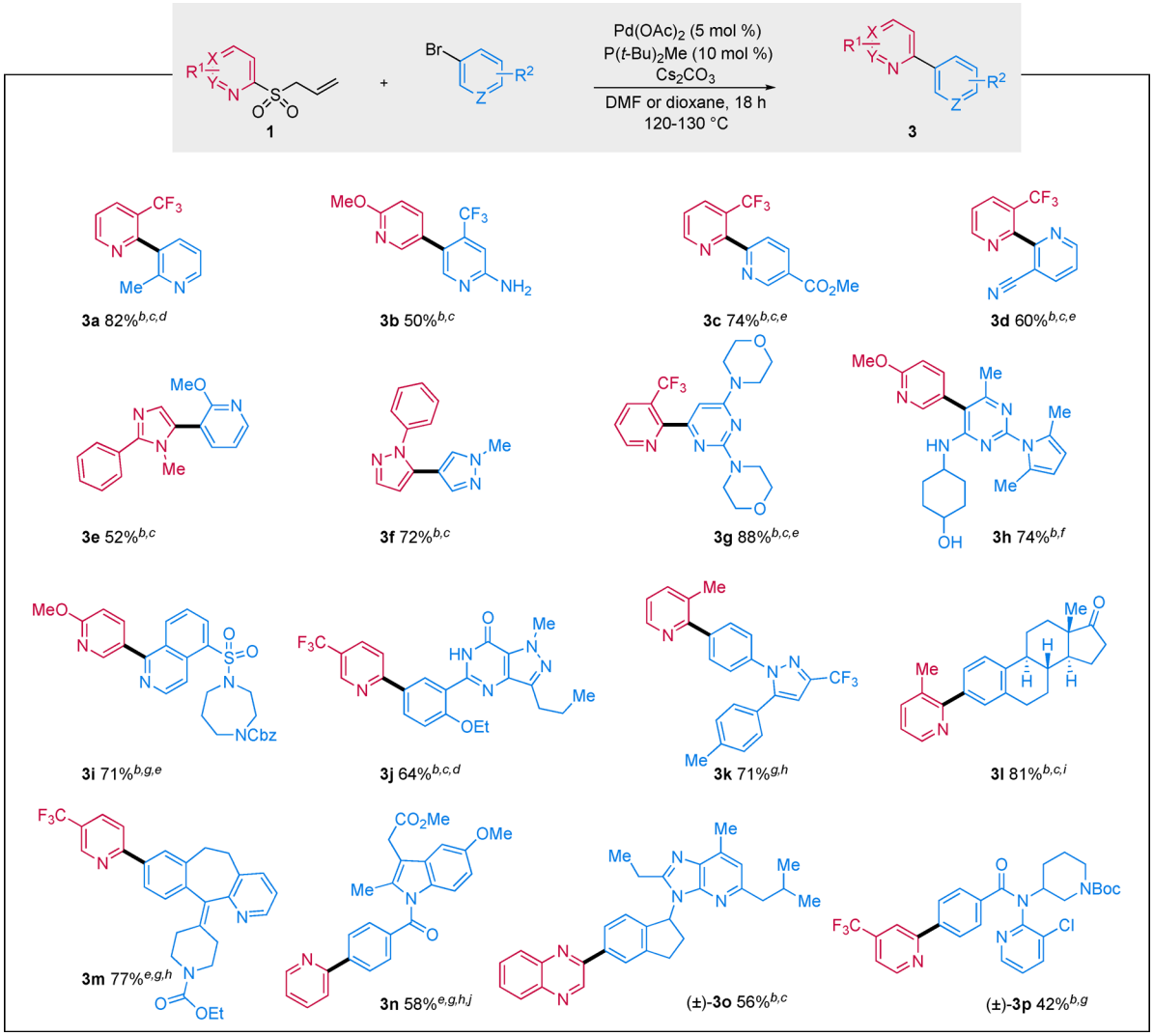
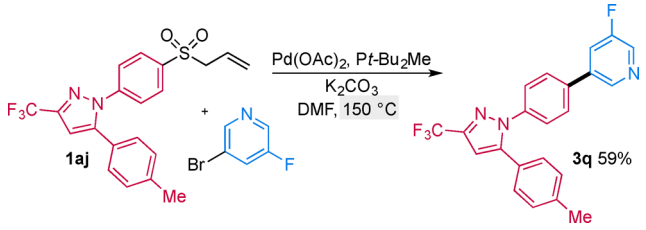
Table 3. Scope of the (Hetero)arene Coupling Partner[a,b]



[a]Reaction conditions: heteroaromatic allylsulfone (0.6 mmol, 1.5 equiv), aryl halide (0.4 mmol, 1.0 equiv), Cs_2CO_3 (0.8 mmol, 2.0 equiv), $Pd(OAc)_2$ (5 mol %), $P(t\text{-}Bu)_2Me.HBF_4$ (10 mol %), solvent 0.2 M, 18 h. Isolated yields [b]Footnotes used in the table: [b]1,4-dioxane used as a solvent; [c]120 °C; [d]K_2CO_3 used in place of Cs_2CO_3; [e]aryl chloride used as a coupling partner; [f]150 °C; [g]130 °C; [h]DMF used as a solvent; [i]aryl triflate used as a coupling partner; [j]2.0 equiv of sulfone used.

Scheme 3. Coupling of Arylallylsulfone 1aj



boronic acid and $Pd(PPh_3)_4$ at 90 °C, providing the Suzuki product (**4d**) in 70% yield. We used amino-substituted pyridylsulfone **4b** to explore a variety of methods to achieve catalytic N-arylation: Chan-Lam coupling employing 4-methoxyphenyl boronic acid and stoichiometric $Cu(OAc)_2$ provided the coupled product (**4e**) in 76% yield; copper(I)-catalyzed arylation using an aryl iodide as the coupling partner generated the same coupled material in 53% yield; and a palladium(0)-catalyzed transformation using the corresponding aryl bromide as the aryl fragment produced the coupled product in 70% yield.

In order to further demonstrate the utility of heterocyclic allylsulfones as effective coupling partners, we explored their application in the synthesis of two active pharmaceutical ingredients (APIs). The coupling between pyrazole allylsulfone **5** and pyridyl bromide **6** provided the *N*-Boc-derivative of the Pfizer lung cancer drug crizotinib (**7**) in a respectable 52% yield, demonstrating the tolerance of the chemistry toward a multiply halogenated arene, carbamate, and primary amino groups (Scheme 5).[27] The second synthesis provides an additional example of an orthogonal cross-coupling; the combination of 3-Br-5-Cl-2-pyridine allylsulfone **8** and sulfonyl boronic acid **9** using $Pd(PPh_3)_4$ as a catalyst provided Suzuki product **10**, with the aryl chloride and allylsulfone functionalities remaining intact in excellent 75% yield. Deallylative/desuilfonylative coupling between sulfone **10** and 3-Br-6-Me-pyridine, using our standard reaction conditions, delivered the COX-2 inhibitor etoricoxib (**11**) in 69% yield.[28]

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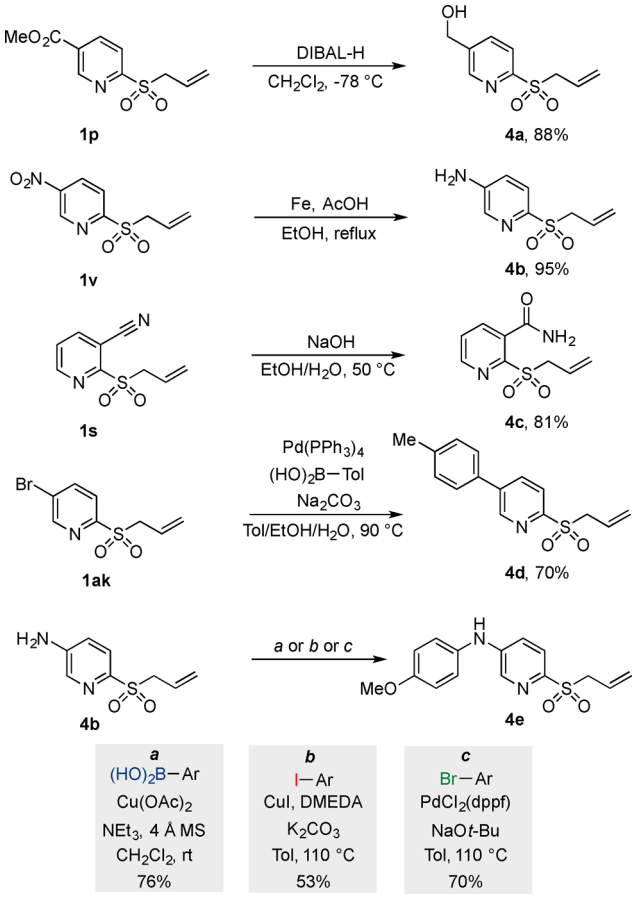
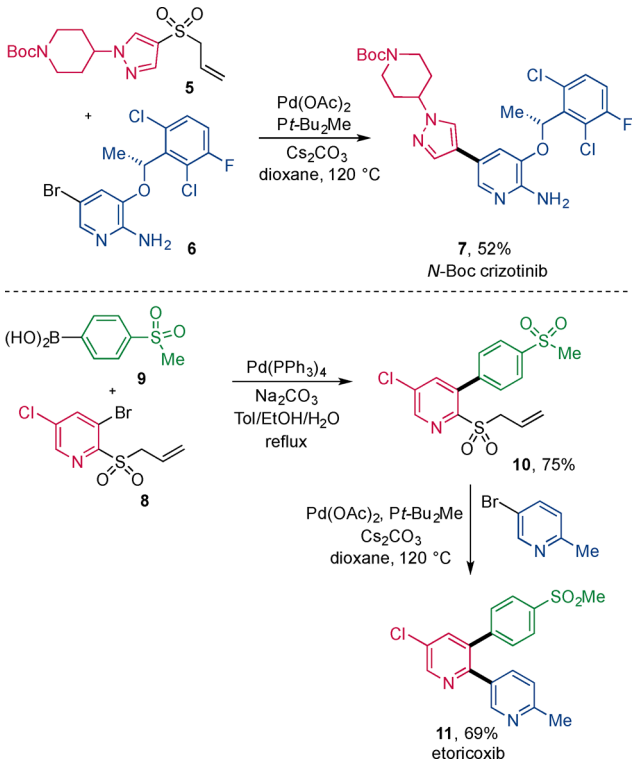
Scheme 4. Functional Group Interconversions[a]



[a]See the Supporting Information for individual reaction conditions.

Scheme 5. Syntheses of Active Pharmaceutical Ingredients



CONCLUSIONS

We have demonstrated that heterocyclic allylsulfones act as latent sulfinate reagents and that under palladium(0) catalysis they undergo efficient coupling reactions with a wide range of aryl and heteroaryl halides. The allylsulfones can be prepared from four readily available monomer sets and are stable to a variety of common synthetic transformations, including several transition-metal-catalyzed processes, allowing the chemoselective manipulation of secondary functional groups. The coupling reactions are broad in scope, with both coupling partners tolerating varied functionalities and substitution patterns, allowing the preparation of challenging linked heteroaryl-(hetero)aryl products. Finally, we demonstrated the potential utility of these new coupling partners with short syntheses of marketed pharmaceuticals crizotinib and etoricoxib and with the late-stage functionalization of established pharmacophores. Given these attributes and the importance of functionalized heterocycles in medicinal chemistrty and other life sciences, we anticipate that the developed methods will find wide application.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b09595.

Experimental procedures and supporting characterization data and spectra (PDF)

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Notes

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

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