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

Tim Markovic, ‡ Philip R. D. Murray, ‡ Benjamin N. Rocke, ‡ Andre Shavnya, ‡ David C. Blakemore, ‡ and Michael C. Willis* ‡

†Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford OX1 3TA, U.K.
‡Medicine Design, Pfizer Inc., Eastern Point Road, Groton, Connecticut 06340, United States

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 sulfinates 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, in materials, and in ligands for metal catalysts. The presence of a key C(sp²)−C(sp³) bond joining the two heterocycles results in metal-catalyzed cross-coupling being a popular disconnection for this fragment assembly. 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. These heterocycle boron reagents are difficult to prepare and store and, due to rapid protodeboronation, deliver poor-yielding reactions. To address many of these issues, we recently introduced a variety of heteroarene-derived metal sulfinate reagents and demonstrated that they function as efficient nucleophilic reaction partners in palladium-catalyzed cross-coupling reactions with aryl and heteroaryl halides (Scheme 1a). 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.

Despite the success of heterocyclic 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, have been shown to be tolerant of a series of transformations and aryl MIDA- and DAN-boronates have been used in iterative coupling reactions. Transformations of alkyl and alkenyl boronic esters are also known. 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, 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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coupling. Importantly, our design should not compromise the reactivity of the sulfinic 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. 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 sulfinic acid as a leaving group; 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 sulfinic 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, 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 sulfonylation of a bromopyridine, followed by S-allylation, and is a one-pot, two-step protocol (eq 6). These five complementary routes allowed the preparation of >30 heterocyclic allylsulfones and, importantly, provided flexibility dependent on the class of starting material that was available.

With efficient access to heterocyclic allylsulfones established, we turned to the evaluation of a trial coupling reaction and selected 6-methyl-substituted 2-pyridine allylsulfone 1a and 4-bromotoluene as the reaction components (Table 1). Although the Pd(0)-catalyzed deallylation of benzene-derived allylsulfones has been reported, 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 (PCy3 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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**Scheme 1.** (a) Heterocyclic Sulfinates and (b) Heterocyclic Allylsulfones in Cross-Coupling Reactions

**Scheme 2.** Preparation of Allylsulfones

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See the Supporting Information for individual reaction conditions.
sulfinate reactions we next explored the use of P(t-Bu)$_2$Me as a supporting ligand$^{2b}$ and we 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-Bu)$_2$Me as the ligand, Cs$_2$CO$_3$ 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$_2$CO$_3$ 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,$^{9}$ 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). Pharmacologically relevant trifluoromethyl groups could also be introduced (2m–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-nitro derivatives (2s, 2t). Our investigation of 2-pyridyl examples concluded with the S-hydroxymethyl (2u) and the S-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,$^{3}$ 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.$^{23}$

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 indomethacin (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 was insufficient 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 4).
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.
boronic acid and Pd(PPh₃)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). 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(PPh₃)₄ as a catalyst provided Suzuki product 10, with the aryl chloride and allylsulfone functionalities remaining intact in excellent 75% yield. Deallylative/desulfonylative 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.

Table 3. Scope of the (Hetero)arene Coupling Partner

| Reaction conditions: heteroaromatic allylsulfone (0.6 mmol, 1.5 equiv), aryl halide (0.4 mmol, 1.0 equiv), Cs₂CO₃ (0.8 mmol, 2.0 equiv), Pd(OAc)₂ (5 mol %), P(t-Bu)₂Me.HBF₄ (10 mol %), solvent 0.2 M, 18 h. Isolated yields. | a | Reaction conditions: heteroaromatic allylsulfone (0.6 mmol, 1.5 equiv), aryl halide (0.4 mmol, 1.0 equiv), Cs₂CO₃ (0.8 mmol, 2.0 equiv), Pd(OAc)₂ (5 mol %), P(t-Bu)₂Me.HBF₄ (10 mol %), solvent 0.2 M, 18 h. Isolated yields. |
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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 chemistry 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)

AUTHOR INFORMATION

Corresponding Author

*michael.willis@chem.ox.ac.uk.

ORCID

Philip R. D. Murray: 0000-0001-7873-5232
Michael C. Willis: 0000-0002-0636-6471

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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REFERENCES

(1) (a) Cui, J. J.; Tran-Dubé, M.; Shen, H.; Nambu, M.; Kung, P.-P.; Pairish, M.; Jia, L.; Meng, J.; Funk, L.; Botrous, I.; McCague, M.; Grodsky, N.; Ryan, K.; Padrique, E.; Alton, G.; Timofeevski, S.; Yamanaka, S.; Li, Q.; Zou, H.; Christensen, J.; Mroczkowski, B.; Bender, S.; Kania, R. S.; Edwards, M. P. Structure Based Drug Design of Crizotinib (PF-02341066), a Potent and Selective Dual Inhibitor of Mesenchymal–Epithelial Transition Factor (c-MET) Kinase and Anaplastic Lymphoma Kinase (ALK). J. Med. Chem. 2011, 54, 6342. (b) Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. Synthesis and Biological Evaluation of the 1,3-Diarylpyrazole Class of Cyclooxygenase-2 Inhibitors: Identification of 4-[5-(4-Methylphenyl)-3- (trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide (SC-58635, Celecoxib). J. Med. Chem. 1997, 40, 1347. (c) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals. J. Med.
Catalyzed Aryl-B(OH)2 Protodeboronation Revisited: From Con-
Leach, A. G.; Campbell, A. D.; King, E. J.; Lloyd-Jones, G. C. Base-
2017
-certed Proton Transfer to Liberation of a Transient Aryl Anion. (d) Molander, G. A.; Ribagorda, M. Expanding Organoboron
Chemistry: Epoxidation of Potassium Organotrifluoroborates. J. Am.
Chem. Soc. 2003, 125, 11148. (e) Molander, G. A.; Figueroa, R. cis-
Dihydroxylation of Unsaturated Potassium Allyl- and Aryltriﬁ-
oborates. Org. Lett. 2006, 8, 75. (f) Molander, G. A.; Sandrock, D. L. Orthogonal Reactivity in Boryl-Substituted Organotrifluoroborates. J. Am.
Chem. Soc. 2008, 130, 15792.
(13) Selected examples: (a) Lee, S. J.; Gray, K. C.; Paek, J. S.; Burke, M. D. Simple, Efﬁcient, and Modular Syntheses of Polylene Natural
Products via Iterative Cross-Coupling. J. Am. Chem. Soc. 2008, 130, 466. (b) Gillis, E. P.; Burke, M. D. A Simple and Modular Strategy for Small Molecule Synthesis: Iterative Suzuki–Miyaura Coupling of B-
Protected Haloboronic Acid Building Blocks. J. Am. Chem. Soc. 2007, 129, 6716.
(14) Noguchi, H.; Hojo, K.; Sugino, M. Boron-Masking Strategy for the Selective Synthesis of Oligoarenes via Iterative Suzuki–
Miyaura Coupling. J. Am. Chem. Soc. 2007, 129, 758.
(15) Xu, L.; Zhang, S.; Li, P. Boron-selective reactions as powerful tools for modular synthesis of diverse complex molecules. Chem. Soc.
Res. 2015, 44, 8848.
(16) (a) Matteson, D. S. Functional group compatibilities in boronic ester chemistry. J. Organomet. Chem. 1999, 581, 51. (b) Leonori, D.;
Aggarwal, V. K. Lithiation-borylation methodology and its application in synthesis. Acc. Chem. Res. 2014, 47, 3174. (c) Lovinger, G. J.;
Morken, J. P. Ni-Catalyzed Enantioselective Conjugate Coupling with C(sp3)-Electrophiles: A Radical-Ionic Mechanistic Dichotomy.
J. Am. Chem. Soc. 2017, 139, 17293. (d) Heinrich, M. R.; Sharp, L. A.; Zard, S. Z. A convergent approach to gamma-carbonyl vinyl
boronates. Chem. Commun. 2005, 3077.
(17) Gauthier, D. R., Jr.; Yoshikawa, N. A General, One-Pot Method for the Synthesis of Sulfinic Acids from Methyl Sulfoxones. Org. Lett.
2016, 18, 5994.
(18) For recent examples of sulfoxides as reagents in coupling chemistry, see (a) Merchant, R. R.; Edwards, J. T.; Qin, T.; Kruszyn, M. B.; Bi, C.; Che, G.; Bao, D.-H.; Qiao, W.; Sun, L.; Collins, M. R.; Fadey, O. O.; Gallego, G. M.; Moussseau, J. J.; Nuhant, P.; Baran, P. S. Modular radical cross-coupling with sulfoxides enables access to sp 3
rich ( ﬂ uoro)alkylated scaffolds. Science 2018, 360, 75. (b) Nambo, M.; Crudden, C. M. Modular synthesis of triarylmethanes through palladium-catalyzed sequential arylation of methyl phenyl sulfoxone. Angew. Chem., Int. Ed. 2014, 53, 7942. (c) Yim, J. C.; Nambo, M.;
Crudden, C. M. Pd-Catalyzed Desulfonative Cross-Coupling of Benzyl Sulﬁne Derivatives with 1,3-Oxazoles. Org. Lett. 2017, 19, 3715. (d) Ariki, Z. T.; Maekawa, Y.; Nambo, M.; Crudden, C. M. Preparation of Quaternary Centers via Nickel-Catalyzed Suzuki-
Miyaura Cross-Coupling of Tertiary Sulfones. J. Am. Chem. Soc. 2018, 140, 78.
(19) Poli, G.; Madec, D.; Le Duc, G.; Bernoud, E.; Prestat, G.;
Cacchi, S.; Fabrizi, G.; Iazzetti, A. Palladium-Catalyzed Aromatic Sulfonylation: A New Catalytic Domino Process Exploiting in situ
Generated Sulﬁnate Anions. Synlett 2011, 2011, 2943.
(20) Fier, P. S.; Hartwig, J. F. Synthesis and Late-Stage Functionalization of Complex Molecules through C–H Fluorination and
Nucleophilic Aromatic Substitution. J. Am. Chem. Soc. 2014, 136, 10139.
(21) (a) Emmett, E. J.; Hayter, B. R.; Willis, M. C. Palladium-
Catalyzed Synthesis of Ammonium Sulﬁnates from Aryl Halides and a Sulfur Dioxide Surrogate: A Gas- and Reductant-Free Process. Angew.
Chem., Int. Ed. 2014, 53, 10204. (b) Shavnya, A.; Coffey, S. B.; Smith, A. C.; Mascitti, V. Palladium-Catalyzed Sulﬁnation of Aryl and Heteroaryl Halides: Direct Access to Sulfoxones and Sulfonylamides. Org.
Lett. 2015, 13, 6226.
(22) (a) Sakya, S. M.; Hou, X.; Minich, M. L.; Rast, B.; Shavnya, A.;
DeMello, K. M. L.; Cheng, H.; Li, J.; Jaynes, B. H.; Mann, D. W.; Petras, C. F.; Seibel, S. B.; Haven, M. L. S-Heteroatom substituted
pyrazoles as canine COX-2 inhibitors. Part II: Molecular modeling studies on binding contribution of 1-(5-methylsulfonyl)pyrid-2-yl and
4-nitro. Bioorg. Med. Chem. Lett. 2007, 17, 1067.
(23) Chen, M.; Liu, A.; Ouyang, Y.; Huang, Y.; Chao, X.; Pi, R.
Fasudil and its analogs: a new powerful weapon in the long war
against central nervous system disorders? Expert Opin. Invest. Drugs 2013, 22, 537.

(24) Blakemore, D. C.; Castro, L.; Churcher, L.; Rees, D. C.; Thomas, A. W.; Wilson, D. M.; Wood, A. Organic synthesis provides opportunities to transform drug discovery. Nat. Chem. 2018, 10, 383.

(25) Casimiro-Garcia, A.; Filzen, G. F.; Flynn, D.; Bigge, C. F.; Chen, J.; Davis, J. A.; Dudley, D. A.; Edmunds, J. J.; Esmaeil, N.; Geyer, A.; Heemstra, R. J.; Jalaie, M.; Ohren, J. F.; Ostroski, R.; Ellis, T.; Schaum, R. P.; Stoner, C. Discovery of a series of imidazo[4,5-b]pyridines with dual activity at angiotensin II type 1 receptor and peroxisome proliferator-activated receptor-gamma. J. Med. Chem. 2011, 54, 4219.

(26) McClure, K. F.; Piotrowski, D. W.; Petersen, D.; Wei, L.; Xiao, J.; Londregan, A. T.; Kamlet, A. S.; Dechert-Schmitt, A. M.; Raymer, B.; Ruggeri, R. B.; Canterbury, D.; Limberakis, C.; Liras, S.; DaSilva-Jardine, P.; Dullea, R. G.; Loria, P. M.; Reidich, B.; Salatto, C. T.; Eng, H.; Kimoto, E.; Atkinson, K.; King-Ahmad, A.; Scott, D.; Beaumont, K.; Chabot, J. R.; Bolt, M. W.; Maresca, K.; Dahl, K.; Arakawa, R.; Takano, A.; Halldin, C. Liver-Targeted Small-Molecule Inhibitors of Proprotein Convertase Subtilisin/Kexin Type 9 Synthesis. Angew. Chem., Int. Ed. 2017, 56, 16218.

(27) de Koning, P. D.; McAndrew, D.; Moore, R.; Moses, I. B.; Boyles, D. C.; Kissick, K.; Stanchina, C. L.; Cuthbertson, T.; Kamatani, A.; Rahman, L.; Rodriguez, R.; Urbina, A.; Sandoval, A.; Rose, P. R. Fit-for-Purpose Development of the Enabling Route to Crizotinib (PF-02341066). Org. Process Res. Dev. 2011, 15, 1018.

(28) Davies, I. W.; Marcoux, J.-F.; Corley, E. G.; Journet, M.; Cai, D.-W.; Palucki, M.; Wu, J.; Larsen, R. D.; Rossen, K.; Pye, P. J.; DiMichele, L.; Dormer, P.; Reider, P. J. A Practical Synthesis of a COX-2-Specific Inhibitor. J. Org. Chem. 2000, 65, 8415.