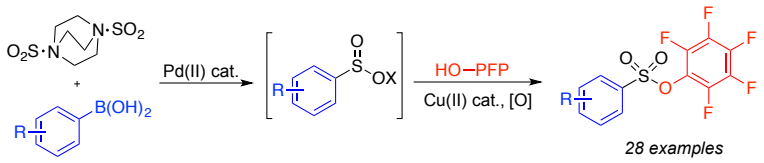
Copper-Catalyzed Synthesis of Activated Sulfonate Esters from Boronic Acids, DABSO and Pentafluorophenol

Vincent Vedovato,[a] Eric P. A. Talbot[b] and Michael C. Willis[a,*]

[a]Department of Chemistry, University of Oxford, Chemistry Research Laboratory, Mansfield Road, Oxford, OX1 3TA, United Kingdom. [b]GlaxoSmithKline Medicines Research Centre, Gunnels Wood Road, Stevenage, SG1 2NY, United Kingdom.

Supporting Information Placeholder

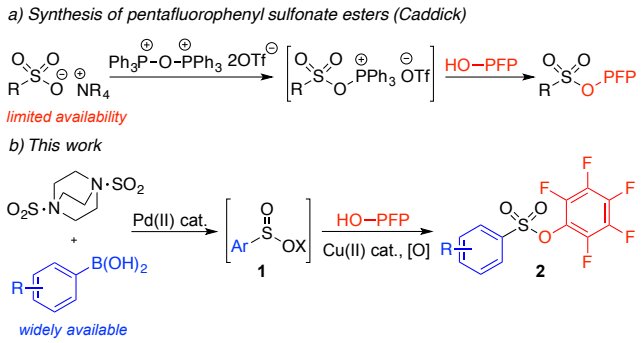


ABSTRACT: The synthesis of pentafluorophenyl (PFP) sulfonate esters based on the Pd-catalyzed sulfination of aryl and heteroaryl boronic acids is reported. The sulfinate intermediates are converted in situ to the corresponding sulfonate esters using a copper-catalysed oxidative process, providing a broad range of PFP-esters in good yields.

Sulfonyl-derived functional groups, such as sulfones, sulfonamides and sulfonate esters, are of proven value in organic chemistry, and feature as intermediates or as final compounds in a wide variety of applications.[1] A common method to prepare these molecules is to combine an electrophilic sulfonyl-derivative with an appropriate nucleophilic component. Sulfonyl chlorides are often the electrophile of choice for these reactions, and they benefit from wide commercial availability and high reactivity.[2] High chemical reactivity can also lead to disadvantages, and can make the synthesis and purification of sulfonyl chlorides challenging, and can also limit stability to long-term storage.[3] Efforts to overcome these limitations include the in situ generation of sulfonyl chlorides,[4] as well as the identification of alternative electrophilic species.[3,5] Pentafluorophenyl (PFP) sulfonate esters have emerged as effective sulfonyl chloride mimics and generally enjoy the benefits of high crystallinity and bench stability, while maintaining useful electrophilicity.[6] A significant disadvantage of aryl PFP sulfonate esters is that their synthesis usually requires a sulfonic acid, or related salt, as starting material, and these have limited commercial availability (Scheme 1a).[6c]

We envisaged an alternative route to PFP sulfonate esters that employed boronic acids – one of the most diverse sets of monomers available for discovery chemistry – as the starting material, in combination with catalytic sulfinylation methods using a sulfur dioxide surrogate (Scheme 1b).[7,8] We, and others, have reported a variety of catalysts and sulfur dioxide sources for the formation of sulfinates (1) from boronic acids,[9] and so the challenge was to identify reaction conditions that would allow the in situ conversion of the sulfinate intermediates into the required pentafluorophenyl sulfonate esters (**1** → **2**).

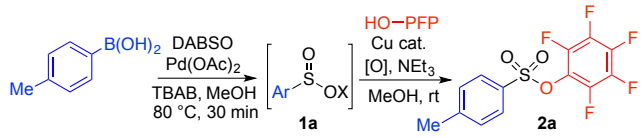
Scheme 1. The preparation of pentafluorophenyl sulfonate esters.



To assess the viability of our proposed route we studied the conversion of 4-tolylboronic acid into PFP sulfonate ester **2a** (Table 1). We used our reported procedure for sulfinate formation,[9a] employing $Pd(OAc)_2$ as a catalyst and DABSO as the SO_2 source to generate sulfinate **1a**, and then explored a variety of conditions to convert the sulfinate into the required PFP sulfonate ester. Initial reactions employing I_2 or NBS in combination with pentafluorophenol were not effective (entries 1 and 2);[10] however, the addition of $Cu(OAc)_2$ as a catalyst significantly improved these yields (entries 3 and 4). Following evaluation of several oxidants and copper salts, we found that the use of $K_2S_2O_8$ as the oxidant, $CuBr_2$ as the catalyst, and the addition of molecular sieves provided sulfonate ester **2a** in good yield (entries 5-10). The addition of NaBr was found to further increase the yield, allowing the sulfonate

ester to be isolated in 86% yield (entry 11). The requirement for the use of a copper catalyst was confirmed (entry 12).

Table 1. Reaction optimization for the formation of pentafluorophenyl sulfonate ester 2a.[a]

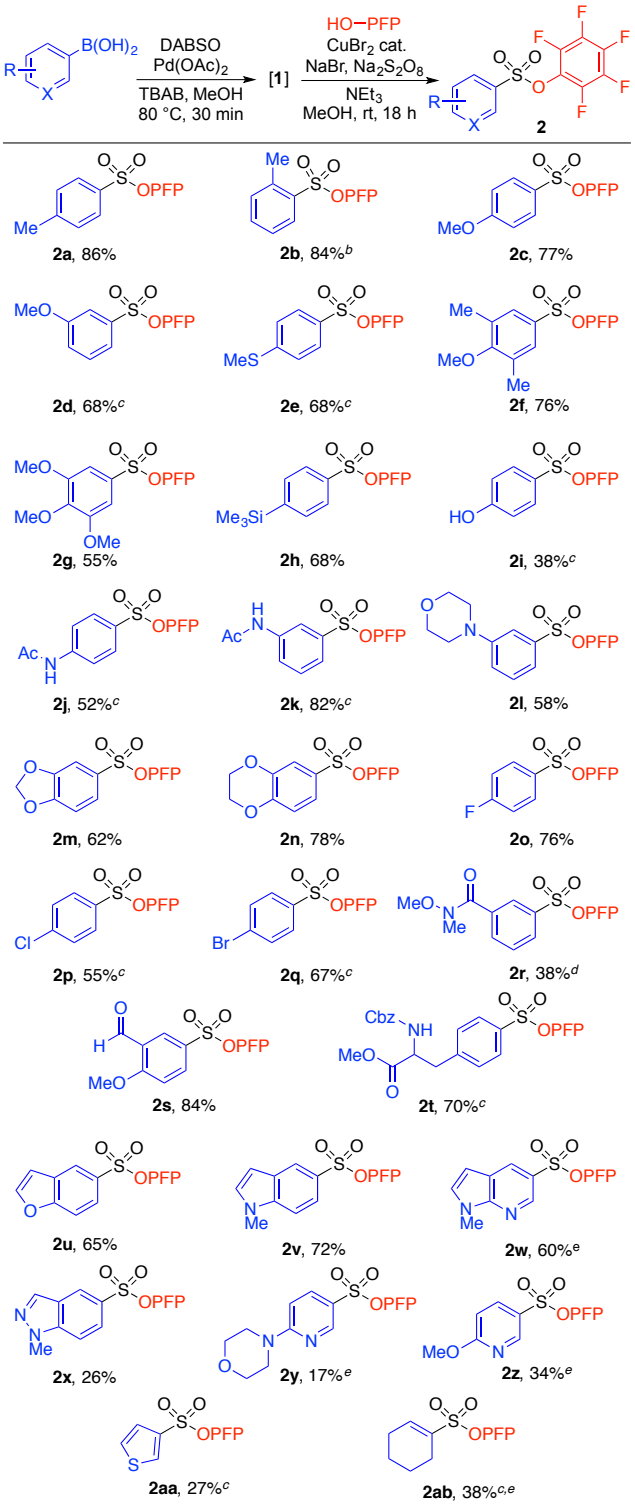


entry	catalyst	[O]	additive	yield (%)[b]
1	-	I_2	-	<2%
2	-	NBS	-	0
3	$Cu(OAc)_2$	I_2	-	13
4	$Cu(OAc)_2$	NBS	-	37
5	$Cu(OAc)_2$	$K_2S_2O_8$	-	42
6	$Cu(OTf)_2$	$K_2S_2O_8$	-	30
7	$Cu(acac)_2$	$K_2S_2O_8$	-	34
8	$Cu(OAc)_2$	$Na_2S_2O_8$	-	65
9	$Cu(OAc)_2$	$Na_2S_2O_8$	3 Å MS	69
10	$CuBr_2$	$Na_2S_2O_8$	3 Å MS	75
11	$CuBr_2$	$Na_2S_2O_8$	3 Å MS + NaBr	92 (86)
12	-	$Na_2S_2O_8$	3 Å MS + NaBr	0

[a] Reaction conditions: i) boronic acid (0.5 mmol), DABSO (0.5 mmol), TBAB (0.15 mmol), $Pd(OAc)_2$ (0.025 mmol), MeOH [0.16 M]; then pentafluorophenol (0.25 mmol), $Na_2S_2O_8$ (0.5 mmol), $CuBr_2$ (0.05 mmol), NaBr (0.15 mmol), NEt_3 (1.0 mmol), 3 Å MS, rt, 18 h. [b] Determined by ^{19}F NMR spectroscopy using fluorobenzene as an internal standard. Isolated yield in parentheses.

With the optimal reaction conditions in hand, we then examined the scope of this transformation with respect to the boronic acid substrate. As shown in Scheme 2, a wide range of boronic acids were found to be suitable substrates for this transformation. Boronic acids bearing substituents at all positions of the aromatic ring, including a variety of electron-donating substituents, delivered the expected sulfonates esters in good yields (**2a**-**n**). Notable examples included the use of a free phenol (**2i**), as well as amido (**2j**,**k**) and amino groups (**2l**). Benzodioxane (**2n**) and methylenedioxyphenyl boronic acid (**2m**) provided sulfonate esters in high yields. Boronic acids featuring electron-withdrawing substituents (**2o**-**r**) were also tolerated, although the isolated yields were slightly reduced relative to the electron-donating examples. 4-Bromophenylsulfonate ester (**2q**) was produced on multigram scale from a 10 mmol reaction. More complex products, such as tri-substituted example **2s**, and tyrosine-derived **2t**, were obtained in good yields. We then turned our attention to heteroaromatic boronic acids. Heterocycles such as benzofuran (**2u**), indole (**2v**) and 7-azaindole (**2w**) afforded the corresponding sulfonate esters in good yields. However, the indazole boronic acid only delivered the desired product in low yield (**2x**). We were pleased to see that pyridine boronic acids could also be tolerated (**2y**,**z**), as well as a thiophene substrate (**2aa**). The final example in scheme 2 shows that alkenyl boronic acids can also be included (**2ab**).

Scheme 2. Evaluation of reaction scope with respect to boronic acid.[a]

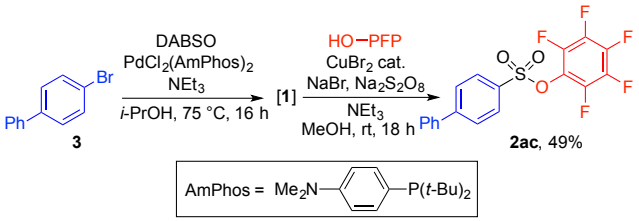


[a] Reaction conditions: boronic acid (0.5 mmol), DABSO (0.5 mmol), $Pd(OAc)_2$ (0.025 mmol), TBAB (0.25 mmol), MeOH [0.16 M], 80 °C, 30 min, then PFPOH (0.25 mmol), $Na_2S_2O_8$ (0.5 mmol), $CuBr_2$ (0.05 mmol), NaBr (0.15 mmol), Et_3N (1.0 mmol), 3 Å MS, rt, 18 h. [b] No TBAB used. [c] Sulfination step 1

hour. [d] Sulfination step 3 hours. [e] MeOH/1,4-dioxane (1:1) [0.16 M] used as solvent.

Although a broad range of boronic acids are widely available, we also wanted to demonstrate that alternative substrate classes could be employed for PFP sulfonate formation. Accordingly, aryl bromide **3** was converted into PFP sulfonate ester **2ac**, using our reported Pd(0)-catalyzed reaction conditions for the first step of the sequence, followed by the optimized copper-catalyzed process (Scheme 3).[11] While this transformation establishes that aryl bromides are viable substrates in this chemistry, the longer reaction times needed to achieve sulfinate formation, relative to the boronic acid examples (16 h *vs* 30 mins), favor the use of the boron-based reagents.

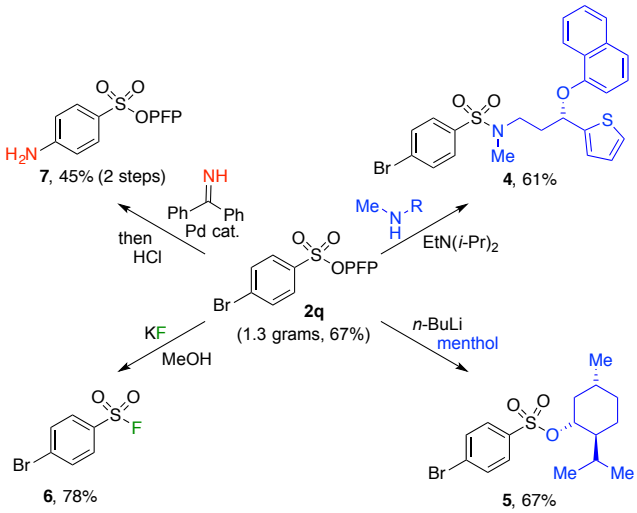
Scheme 3. PFP sulfonate ester synthesis starting from an aryl bromide 3.



To demonstrate the utility of the PFP sulfonate esters produced in this study, we chose to transform the 4-bromophenylsulfonate ester (**2q**) into a range of products of interest (Scheme 4). Treatment of sulfonate **2q** with the indicated secondary amine in the presence of Hünigs base provided sulfonamide **4** in good yield.[6f] The amine used in this example is the anti-anxiety compound Duloxetine.[12] It was also possible to transform pentafluorophenyl sulfonate ester **2q** into other sulfonate esters, for example, we subjected PFP ester **2q** to lithiated menthol, which afforded a menthol sulfonate ester **5** in 67% yield. The importance of sulfonyl fluoride in chemical biology is now well established;[13] treating sulfonate **2q** with a solution of KF in methanol delivered sulfonyl fluoride **6** in 78% yield. Finally, Avitabile and co-workers have previously reported that pentafluorophenyl sulfonate esters are stable to reaction conditions in which other sulfonyl species do not survive.[14] Accordingly, we performed a Pd-catalyzed amination on the aryl bromide group of sulfonate **2q**; coupling with benzophenone imine, followed by acid deprotection, provided primary aniline **7** in 45% yield, with the sulfonate ester remaining intact.

In conclusion, we have developed a one-pot synthesis of pentafluorophenyl sulfonate esters using aryl boronic acids as substrates. Combining the boronic acids with DABSO under Pd(II)-conditions generates a sulfinate intermediate which is subsequently coupled with pentafluorophenol under oxidative copper(II) catalysis. A broad range of aryl and heteroaryl boronic acids can be employed in the process and provide the desired PFP sulfonate esters in generally good yields. We also established that aryl bromides are viable substrates for this chemistry.

Scheme 4. The reactivity of PFP sulfonate esters.



Supporting Information

Experimental procedures and full characterization for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

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

ACKNOWLEDGMENT

We thank GlaxoSmithKine and the University of Oxford for their support of this study.

REFERENCES

(1) a) Aziz, J.; Messaoudi, S.; Alami, M.; Hamze, A. Sulfinate derivatives: dual and versatile partners in organic synthesis, *Org. Biomol. Chem.* **2014**, *12*, 9743; b) Feng, M.; Tang, B.; Liang, S. H.; Jiang, X. Sulfur Containing Scaffolds in Drugs: Synthesis and Application in Medicinal Chemistry, *Curr. Top. Med. Chem.* **2016**, *16*, 1200; c) Scott, K. A.; Njardarson, J. T. Analysis of US FDA-Approved Drugs Containing Sulfur Atoms, *Top Curr. Chem.* **2018**, *376*, 5; d) Simpkins, N. S. Sulfones in Organic Synthesis; Pergamon Press: Oxford, 1993; e) Manolikakes, G.; Liu, N.-W.; Liang, S. Recent Advances in the Synthesis of Sulfones, *Synthesis* **2016**, *48*, 1939.

(2) Ryckebusch, A.; Déprez-Poulain, R.; Debreu-Fontaine, M. A.; Vandaele, R.; Mouray, E.; Grellier, P.; Sergheraert, C. Parallel Synthesis and Anti-Malarial Activity of a Sulfonamide Library, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2595.

(3) Bogolubsky, A. V.; Moroz, Y. S.; Mykhailiuk, P. K.; Pipko, S. E.; Konovets, A. I.; Sadkova, I. V.; Tolmachev, A. Sulfonyl fluorides as alternative to sulfonyl chlorides in parallel synthesis of aliphatic sulfonamides, *ACS Comb. Sci.* **2014**, *16*, 192.

(4) a) DeBergh, J. R.; Niljianskul, N.; Buchwald, S. L. Synthesis of aryl sulfonamides via palladium-catalyzed chlorosulfonylation of arylboronic acids, *J. Am. Chem. Soc.* **2013**, *135*, 10638; b) Bouchez, L. C.; Dubbaka, S. R.; Turks, M.; Vogel, P. Sulfur Dioxide Mediated One-Pot, Three- and Four-Component Syntheses of Polyfunctional Sulfonamides and Sulfonic Esters: Study of the

Stereoselectivity of the Ene Reaction of Sulfur Dioxide, *J. Org. Chem.* **2004**, *69*, 6413.

(5) a) Yan, L.; Bertarelli, D. C. G.; Hayallah, A. M.; Meyer, H.; Klotz, K.-N.; Müller, C. E. A New Synthesis of Sulfonamides by Aminolysis of *p*-Nitrophenylsulfonates Yielding Potent and Selective Adenosine A2B Receptor Antagonists, *J. Med. Chem.* **2006**, *49*, 4384; b) Wilden, J. D.; Geldeard, L.; Lee, C. C.; Judd, D. B.; Caddick, S. Trichlorophenol (TCP) sulfonate esters: a selective alternative to pentafluorophenol (PFP) esters and sulfonyl chlorides for the preparation of sulfonamides, *Chem. Commun*. **2007**, 1074.

(6) a) Caddick, S.; Wilden, J. D.; Bush, H. D.; Judd, D. B. Synthesis of Functionalised Sulfonamides via Microwave Assisted Displacement of PFP-Sulfonates with Amines, *QSAR & Combinatorial Science* **2004**, *23*, 902; b) Caddick, S.; Wilden, J. D.; Bush, H. D.; Wadman, S. N.; Judd, D. B. A New Route to Sulfonamides via Intermolecular Radical Addition to Pentafluorophenyl Vinylsulfonate and Subsequent Aminolysis, *Org. Lett*. **2002**, *4*, 2549; c) Caddick, S.; Wilden, J. D.; Judd, D. B. Direct Synthesis of Sulfonamides and Activated Sulfonate Esters from Sulfonic Acids, *J. Am. Chem. Soc*. **2004**, *126*, 1024; d) Caddick, S.; Wilden, J. D.; Judd, D. B. Observations on the reactivity of pentafluorophenyl sulfonate esters, *Chem. Commun*. **2005**, 2727; e) Wilden, J. D.; Judd, D. B.; Caddick, S. Rate enhancement of PFP sulfonate ester aminolysis by chloride salts in organic and aqueous media, *Tetrahedron Lett*. **2005**, *46*, 7637; f) Bornholdt, J.; Fjære, K. W.; Felding, J.; Kristensen, J. L. Heterocyclic pentafluorophenyl sulfonate esters as shelf stable alternatives to sulfonyl chlorides, *Tetrahedron* **2009**, *65*, 9280.

(7) a) Deeming, A. S.; Emmett, E. J.; Richards-Taylor, C. S.; Willis, M. C. Rediscovering the Chemistry of Sulfur Dioxide: New Developments in Synthesis and Catalysis, *Synthesis* **2014**, *46*, 2701; b) Emmett, E. J.; Willis, M. C. The Development and Application of Sulfur Dioxide Surrogates in Synthetic Organic Chemistry, *Asian. J. Org. Chem*. **2015**, *4*, 602; c) Liu, G.; Fan, C. B.; Wu, J. Fixation of sulfur dioxide into small molecules, *Org. Biomol. Chem.* **2015**, *13*, 1592.

(8) For the copper-catalyzed synthesis of sulfonates esters derived from alkyl alcohols, starting from aryl diazonium salts and DABSO, see: Wang, Y.; Deng, L.; Deng, Y.; Han, J. Copper-Catalyzed Multicomponent Reaction of DABCO.$(SO_2)_2$, Alcohols, and Aryl Diazoniums for the Synthesis of Sulfonic Esters, *J. Org. Chem*. **2018**, *83*, 4674.

(9) a) Deeming, A. S.; Russell, C. J.; Willis, M. C. Palladium(II)-Catalyzed Synthesis of Sulfinates from Boronic Acids and DABSO: A Redox-Neutral, Phosphine-Free Transformation, *Angew. Chem. Int. Ed*. **2016**, *55*, 747; b) Johnson, M. W.; Bagley, S. W.; Mankad, N. P.; Bergman, R. G.; Mascitti, V.; Toste, F. D. Application of fundamental organometallic chemistry to the development of a gold-catalyzed synthesis of sulfinate derivatives, *Angew. Chem. Int. Ed*. **2014**, *53*, 4404; c) Shavnya, A.; Hesp, K. D.; Mascitti, V.; Smith, A. C. Palladium-Catalyzed Synthesis of (Hetero)Aryl Alkyl Sulfones from (Hetero)Aryl Boronic Acids, Unactivated Alkyl Halides, and Potassium Metabisulfite, *Angew. Chem. Int. Ed.* **2015**, *54*, 13571; d) Chen, Y.; Willis, M. C. Copper(I)-catalyzed sulfonylative Suzuki-Miyaura cross-coupling, *Chem. Sci*. **2017**, *8*, 3249; e) Mao, R.; Zheng, D.; Xia, H.; Wu, J. Copper(I)-catalyzed sulfonylation of (2-alkynylaryl)boronic acids with DABSO, *Org. Chem. Front*. **2016**, *3*, 693.

(10) Gao, J.; Pan, X.; Liu, J.; Lai, J.; Chang, L.; Yuan, G. Iodine-induced synthesis of sulfonate esters from sodium sulfinates and phenols under mild conditions, *RSC Adv.* **2015**, *5*, 27439.

(11) a) Davies, A. T.; Curto, J. M.; Bagley, S. W.; Willis, M. C. One-pot palladium-catalyzed synthesis of sulfonyl fluorides from aryl bromides, *Chem. Sci*. **2017**, *8*, 1233; b) Flegeau, E. F.; Harrison, J. M.; Willis, M. C. One-Pot Sulfonamide Synthesis Exploiting the Palladium-Catalyzed Sulfination of Aryl Iodides, *Synlett* **2016**, *27*, 101; c) 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.

(12) Bymaster, F. P.; Beedle, E. E.; Findlay, J.; Gallagher, P. T.; Krushinski, J. H.; Mitchell, S.; Robertson, D. W.; Thompson, D. C.; Wallace, L.; Wong, D. T. Duloxetine (Cymbalta™), a dual inhibitor of serotonin and norepinephrine reuptake, *Bioorg. Med. Chem. Lett*. **2003**, *13*, 4477.

(13) Narayanan, A.; Jones, L. H. Sulfonyl fluorides as privileged warheads in chemical biology, *Chem. Sci*. **2015**, *6*, 2650.

(14) Avitabile, B. G.; Smith, C. A.; Judd, D. B. Pentafluorophenyl Sulfonate Ester as a Protecting Group for the Preparation of Biaryl- and Heterobiaryl Sulfonate Esters, *Org. Lett*. **2005**, *7*, 843.