Palladium(II)-Catalyzed Synthesis of Sulfinates from Boronic Acids and DABSO: A Redox-Neutral, Phosphine-Free Transformation

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Abstract: A redox-neutral palladium(II)-catalyzed conversion of aryl, heteroaryl, and alkenyl boronic acids into sulfinate intermediates, and onwards to sulfonyl and sulfonamides, has been realized. A simple Pd(OAc)_2 catalyst, in combination with the sulfur dioxide surrogate 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) (DABSO), is sufficient to achieve rapid and high-yielding conversion of the boronic acids into the corresponding sulfinates. Addition of C- or N-based electrophiles then allows conversion into sulfonyl and sulfonamides, respectively, in a one-pot, two-step process.

The sulfonyl group, which is embedded in sulphones, sulfonamides, sulfonate esters, and sulfinic acids, is a structural motif with numerous uses. These important functional groups contribute significant physiochemical properties,[1] as well as varied synthetic utility,[2] and a wide range of pharmaceutical and agrochemical applications are known.[3,4]

Sulones and sulfonamides are the most prominent sulfonyl-containing molecules, and general and simple methods for their construction are in high demand. Classical syntheses which are commonly employed include sulfide oxidation[5] and sulfonyl chloride-amine coupling,[6] to access sulones and sulfonamides, respectively. Limitations of such strategies include the use of odorous thiols and functional-group-restricting oxidative conditions in the sulphone synthesis, and harsh acidic treatment of arenes to access sulfonyl chloride precursors by electrophilic aromatic sulfonation. In addition, electrophilic substitution processes impose constraints on the substitution patterns which can be readily prepared.

Alternative routes to a variety of sulfonyl derivatives can be achieved from the direct insertion of sulfur dioxide into suitably functionalized substrates. For example, the SO_2 surrogate DABSO,[7] DABCO(SO_2) (DABCO = 1,4-

diazabicyclo[2.2.2]octane), has been combined with preformed organometallic reagents to generate metal sulfinates which can then undergo in situ conversion into sulones[8] and sulfonamides.[9-11] A palladium-catalyzed preparation of ammonium sulfinates has also been reported by our laboratory, and allows (hetero)aryl iodides and DABSO to be efficiently combined using a palladium(0) catalyst and iPrOH as reductant (Scheme 1a).[12] A similar transformation was developed by Shavnya and co-workers with the formation of sulfinates from aryl halides using K_2S_2O_5 as the sulfur dioxide source and formate as the reductant (Scheme 1b).[13] While these processes serve as effective means of accessing sulfonyl-containing compounds, they suffer from either the use of specialized and expensive phosphine ligands or high catalyst and ligand loadings, and are also slow reactions (typically 16–18 h). The need for supporting ligands presumably arises from the operation of a Pd^II cycle.

To address these shortcomings we targeted the development of a palladium(II) catalytic system employing boronic acids as substrates in combination with DABSO. Such a process would be redox-neutral, should allow greater functional-group tolerance, and should avoid the requirement for specialized, often costly, phosphine ligands. Toste and co-workers recently disclosed a process for the conversion of aryl boronic acids into sulfinates using K_2S_2O_5 and gold(I) catalysis.[14] This elegant study demonstrates the viability of a redox-neutral sulinate synthesis, albeit in a gold(I) manifold, but suffers from the use of high catalyst loadings and limited onwards sulinate reactivity with products obtained in moderate yields. Herein, we outline the successful develop-
ment of a one-pot, redox-neutral palladium(II)-catalyzed preparation of sulfinate derivatives from boronic acid substrates. A phosphine-free catalyst allows the rapid conversion of boronic acids into the corresponding sulfinates, and then onwards to a variety of sulfones and sulfonamides (Scheme 1c).[15–17]

Initial investigations quickly revealed that the union of p-tert-butylphenylboronic acid, DABSO, and tert-butyl bromoacetate could be achieved by the use of Pd(OAc)$_2$ as the catalyst with Et$_3$N as the base in a 1,4-dioxane/MeOH solvent mixture. The addition of TBAFI resulted in a small increase in yield, thus allowing isolation of the sulfone 1a in 83% (Scheme 2a). A brief assessment of the scope of boronic acids and electrophiles compatible with this one-pot, one-step process was carried out (Scheme 2b). Aryl boronic acids bearing electron-donating and electron-withdrawing substituents proved to be effective substrates (1a–e), and simple heteroaromatic variants were also well tolerated (1f). Alkenyl boronic acids were found to be lower yielding (1g). Aromatic BF$_3$K salts were compatible with this system (1e).

In terms of suitable electrophiles, only activated alkyl halides (1a–h–j) proved to be effective in this process with simple alkyl halides affording none of the desired products (e.g., butyl bromide). A further limitation with this one-step format, was that the solvent for the sulfinate functionalization was confined to 1,4-dioxane/MeOH, thus resulting in the incompatibility of more elaborate electrophiles such as epoxides and $O$-hydroxylaminesulfonic acid. Such couplings generally require water as a solvent.[18]

To achieve a more general process we were motivated to pursue the proposed synthesis of sulfinate derivatives with subsequent in situ trapping in a two-step format. We postulated that the palladium sulfinate generated after Pd–C$_2$O$_2$ insertion was responsible for the observed low reactivity with simple electrophiles, and that a Lewis acid or ligand could aid Pd–O(S) bond cleavage to release an alternative metal sulfinate and turnover the palladium(II) catalyst. While initial attempts were unsuccessful, upon introducing a Brønsted acid in the form of TFA into the reaction [p-tolylboronlic acid with DABSO and Pd(OAc)$_2$, without Et$_3$N, the sulfinic acid 2b (for structure see Scheme 3) was observed in 75% yield (HPLC). When performing the same transformation in the absence of both TFA and Et$_3$N, 2b was formed in 92% yield, thus translating into a 88% yield of the sulfone 1b after base treatment and alklylation (Scheme 3).

With this key observation that the desired boronic acid sulfination could be achieved by simple treatment with Pd(OAc)$_2$, and DABSO in a short reaction time (30 min), further assessment of the reaction conditions revealed that lower palladium(II) loadings could effect this transformation and that MeOH was integral as a cosolvent (see the Supporting Information for details). On examination of the boronic acid scope of the reaction, using these optimized reaction conditions, it was quickly established that varying the electronics of the aryl boronic acid was detrimental to reactivity. Substrates bearing p-fluoro and p-tert-butyl functionalities resulted in immediate biphenyl and palladium(0) formation. This side-reaction could be suppressed by employing TBAB as an additive in a low loading (0.25 equiv). A full examination of the reaction scope was then conducted, and by employing triethylamine and tert-butyldimethylacetate, as the electrophilic trap, a range of sulfones could be accessed (Table 1).[19] Substrates bearing electron-donating and electron-withdrawing groups, as well as ortho-, meta-, and para-substitution patterns were all well tolerated in this system. Pleasingly, sensitive functional groups such as phenol (1m), amide (1n), amine (1p), and indole (1u) moieties were compatible with sulfones obtained in good yields.

The incorporation of the methythio-substituted boronic acid (1I) promotes the use of this chemistry over traditional sulfide oxidation strategies, where access to such mixed oxidation-state $S$ products would not be possible. Pleasingly, a variety of heteroaromatic groups were well tolerated in this reaction, with thiophene and furan substrates delivering the corresponding products in acceptable yields (1f and 1s), while examples incorporating pyridine (1r), benzodioxane...
Alkenyl boronic acids could be employed as substrates, with styryl and straight-chain alkenyl variants giving products in modest yields (1v, w), and the cyclohexenyl boronic acid afforded the corresponding sulfone in high yield (1x).

We next looked to expand the scope of sulfonyl-containing products beyond those accessible with the one-step procedure (Scheme 2), and were pleased to find that a variety of C-based electrophiles could be employed (Table 2). Alkylations could be achieved by maintaining 1,4-dioxane/MeOH as the solvent and simple alkyl iodides were found to perform well (1y, z). Diaryl sulfones were accessible using either an aryl iodonium salt (1aa) or through SNAr chemistry (1ab and 1ac).[21]

Modification of the reaction conditions for the derivatization of the sulfinic acid derivatives allowed the chemistry to be extended to epoxide ring opening. For example, use of cyclohexene oxide delivered the sulfone 1ad in good yield. The β-hydroxy sulfone 1ae was prepared using this one-pot process in moderate yield, and is significant as it corresponds to the methyl ester derivative of the anti-androgen pharmaceutical Casodex.[22]

Finally, we were able to demonstrate the application of this one-pot sulfone synthesis on a preparative scale. Using a 1 mol% catalyst loading and a slightly extended sulfination reaction time, the sulfone 1b was isolated in 90% yield on a 3.5 gram scale (Scheme 4). Importantly, this larger scale reaction was performed open to air.

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**Table 1:** Scope with respect to the boronic acid in the one-pot, two-step palladium(II)-catalyzed sulfone synthesis.[4]

| Reaction conditions: 1) Boronic acid (0.25 mmol, 1 equiv), Pd(OAc)2 (5 mol%), DABSO (1 equiv), TBAB (0.25 equiv), 1,4-dioxane/MeOH (1:1) [0.16 m], 80 °C. 2) Et3N (2 equiv) RT, 1 min then tert-butyl bromoacetate (3 equiv), 80 °C, 30 min. [b] Without TBAB. [c] Sulfination step for 3 h. [d] Sulfination step for 1 h. |

| Compound | Yield |
|----------|-------|
| 1c       | 78%   |
| 1d       | 83%   |
| 1e       | 91%   |
| 1f       | 82%   |
| 1g       | 68%   |
| 1h       | 58%   |
| 1i       | 52%   |
| 1j       | 59%   |
| 1k       | 48%   |
| 1l       | 72%   |
| 1m       | 62%   |
| 1n       | 77%   |
| 1o       | 65%   |
| 1p       | 52%   |
| 1q       | 59%   |
| 1r       | 64%   |
| 1s       | 65%   |
| 1t       | 72%   |
| 1u       | 62%   |
| 1v       | 45%   |
| 1w       | 37%   |
| 1x       | 92%   |

[a] Reaction conditions: 1) Boronic acid (0.25 mmol, 1 equiv), Pd(OAc)2 (5 mol%), DABSO (1 equiv), TBAB (0.25 equiv), 1,4-dioxane/MeOH (1:1) [0.16 m], 80 °C. 2) Et3N (2 equiv) RT, 1 min then tert-butyl bromoacetate (3 equiv), 80 °C, 30 min. [b] Without TBAB. [c] Sulfination step for 3 h. [d] Sulfination step for 1 h.

**Table 2:** Scope with respect to the C-electrophile in the one-pot, two-step palladium(II)-catalyzed sulfone synthesis.[4]

| Compound | Yield |
|----------|-------|
| 1y       | 77%   |
| 1z       | 52%   |
| 1aa      | 81%   |
| 1ab      | 60%   |
| 1ac      | 41%   |
| 1ad      | 69%   |
| 1ae      | 58%   |

[a] Reaction conditions for sulfinate derivatization step: E+ (3 equiv), 1,4-dioxane/MeOH, 80 °C, 1 h. [b] Ph2I+Cl− (3 equiv), 1,4-dioxane/MeOH, 80 °C, 6 h. [c] E− (2 equiv), DMAc, 100 °C, 1 h. [d] E− (3 equiv), DMSO, 80 °C, 2 h. [e] Epoxide (5 equiv), H2O, 90 °C, 6 h. DMAc = N,N-dimethylacetamide, DMSO = dimethylsulfoxide.

**Table 3:** The use of N-electrophiles to access sulfonamides.[23]

| Reaction conditions for sulfinate derivatization step: Et3N, RT then H2NSO3H (2 equiv), H2O, RT, 2 h or R2NH (5 equiv), NaOCl (3 equiv), H2O, RT, 16 h. |

| Compound | Yield |
|----------|-------|
| 3a       | 82%   |
| 3b       | 56%   |
| 3c       | 82%   |
| 3d       | 87%   |
| 3e       | 56%   |
| 3f       | 67%   |

Sulfinate derivatization step: [a] Et3N, RT then H2NSO3H (2 equiv), H2O, RT, 2 h or R2NH (5 equiv), NaOCl (3 equiv), H2O, RT, 16 h.

The methodology could be extended to allow the use of N-electrophiles. Both primary and substituted sulfonamides could be prepared by combining the in situ generated sulfinites with either O-hydroxylaminesulfonic acid or N-chloroamines (also generated in situ; Table 3).[23a]
In summary, we have developed a one-pot, redox-neutral and ligand-free synthesis of sulfinic acid derivatives. By simply treating boronic acid substrates with DABSO and low loadings of Pd(OAc)$_2$, sulfinic acid intermediates were formed and subsequently coupled with a variety of electrophiles in situ, to access a broad range of sulfones and sulfonylamides. In addition to this, a one-step reaction was also developed, thus allowing preparation of sulfones using activated alkyl halides.

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**Keywords:** electrophiles - oxidation - palladium - sulfur - synthetic methods

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