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DOI: 10.1039/C7CC05851A

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COMMUNICATION

Pd(NHC)-Catalyzed Alkylsulfonylation of Boronic Acids: A General and Efficient Approach for Sulfone Synthesis†

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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Robust N-heterocyclic carbene palladium complexes are highly efficient catalysts for direct alkylsulfonylation of (hetero)aryl- or alkenyl- boronic acids with potassium metabisulfite and (hetero)alkyl-halides. Among them, acenaphthoimidazolylidene palladium(II) complexes exhibited the highest activities, and up to quantitative yields were obtained for diverse structurally distinct sulfones under very mild reaction conditions.

As a versatile protocol to construct C-C and C-X bonds, Pd(0)-catalyzed cross-coupling reactions constitute one of best options in organic synthesis,[1] especially with readily available and low-toxicity aryl boronic acids.[2] Benefiting from the development of ligand design, the feasibility of such protocols has been demonstrated in the classic cross-coupling reactions, and also exhibited high selectivity in the related carbonylation tranformations.[3] In contrast with intensively investigated air-sensitive phosphines, robust N-heterocyclic carbene (NHC) ligands sometimes exhibited better catalytic activity for such kinds of transformations.[4,5] One possible explanation is the strong σ-donor property of NHCs, which can improve retain Pd centre during the transformation. Consequently, well-defined Pd(NHC) species can deliver longer lifetimes and consistent efficiency.[5]

Sulfone groups are present in numerous functional molecules of agrochemical, pharmaceutical or material significances.[6] The success of the Pd-catalyzed carbonylation reactions[7] has been extended to the analogous sulfonylative cross-coupling reaction due to their similar electronic and coordination properties between carbon monoxide and sulfur dioxide.[8] In contrast to conventional oxidative methods, the Pd-catalyzed sulfonylation of aryl boronic acids with *C*-electrophiles is compatible with sensitive functional groups.[9] However, there is only one recent report that indicates that the *C*-electrophile could be added at the start of the reaction along with other substances,[10] where a 10 mol% catalyst loading was required. Despite these achievements, the development of general and direct sulfones synthesis from diverse readily available boronic acids at low catalyst loading with excellent yields and selectivity under mild reaction conditions is still highly desirable. To the best of our knowledge, there is no example of a Pd(NHC) catalyzed sulfonylation reaction. Building on our recent study that demonstrated acenaphthoimidazolylidene palladium complexes exhibit extremely high catalytic activity toward sterically hindered cross-coupling reactions[11] and direct carbonylation reactions,[12] herein we report a robust and general catalytic protocol for direct alkylsulfonylation of aryl- and alkenyl- boronic acids with $K_2S_2O_5$ and diverse *C*-electrophiles with low catalyst loadings of acenaphthoimidazolylidene palladium complexes..

Direct alkylsulfonylation of 4-tolylboronic acid by *tert*-butyl bromoacetate was selected as a model reaction to evaluate the catalytic activity of Pd(NHC) complexes **1a-c** and **2**, which were synthesized according to the reported procedures.[11,13] In the presence of 5 mol% of allylic Pd(NHC) complex **1a** and tetrabutylammonium bromide (TBAB) in DCE at 100 °C after 24 hours, produced **3a** was in a yield of 20% (Table 1, entry 1). However, the yield dramatically increased to 71% when nonpolar toluene was used (Table 1, entry 2). Quantitative transformation was achieved with dioxane as a solvent (Table 1, entry 3). Other polar and nonpolar solvents resulted in inferior results (See ESI†) and no product was detected when the reaction was carried out in methanol or DMSO. Besides allylic ligands, other "throw away" ligands[14] anchored on the Pd(NHC) complexes **1b** and **1c** only showed slightly impact on the transformation (Table 1, entries 3 and 4). In the case of catalyst containing 3-chloro pyridine (**1c**), a 90% yield of **3a** was obtained under in dioxane at 100 °C after 24 hours. However, the allylic catalyst derived from imidazolium analogue (**2**), which has been proven as a highly active catalyst

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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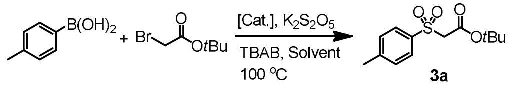
DOI: 10.1039/C7CC05851A

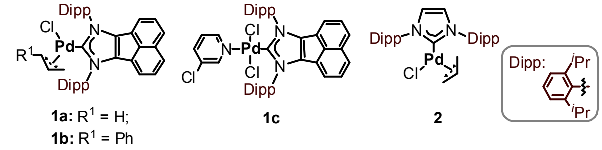
in a number of coupling reactions,[15] was applied, the yield decreased into 85% (Table 1, entry 6 vs entry 3). This result is consistent with our previous observation that ylidenes derived from acenaphtho-imidazolyium salts exhibit higher catalytic activity than their imidazolium analogues due to the stronger σ-donor and weaker π-acceptor properties.[11,12]

Table 1. Optimization of the reaction conditions[a]



Entry	[Cat.]/mol%	Solvent	Yield (%)[b]
1	**1a** /5	DCE	20
2	**1a** /5	Toluene	71
3	**1a** /5	Dioxane	>99
4	**1b**/5	Dioxane	98
5	**1c**/5	Dioxane	90
6	**2**/5	Dioxane	85
7	$PdCl_2$/5	Dioxane	74
8	$PdCl_2/PPh_3$/5	Dioxane	85
9	$Pd(OAc)_2$/5	Dioxane	62
10	$Pd_2(dba)_3$/5	Dioxane	15
11	**1a**/2	Dioxane	80
12	**1a**/1	Dioxane	47
13	/	Dioxane	NR

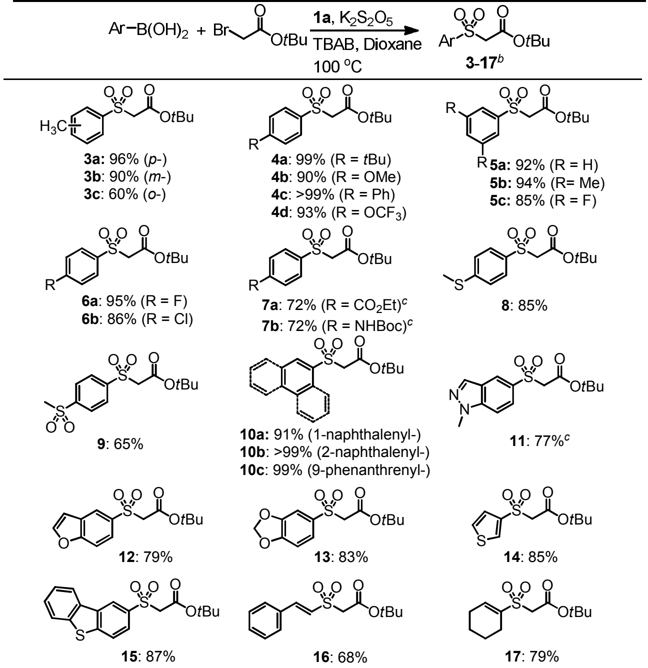
[a] Reaction was carried with 5 mol% catalyst, 4-Methylphenylboronic acid (0.5 mmol), $K_2S_2O_5$ (2.0 equiv.), TBAB (1.1 equiv.), and *tert*-butyl bromoacetate (2.0 equiv.) in 2 mL solvent at 100 °C for 24 hours. [b] Isolated yield.



The NHC ligand is crucial for the alkylsulfonylation process. When palladium salts such as $PdCl_2$ and $Pd(OAc)_2$ were applied directly, moderate to good yields were achieved (74% and 62%, Table 1, entries 7 and 9), whereas, Pd(0) precatalyst like $Pd_2(dba)_3$ resulted in even worse outcomes (15%, Table 1, entry 1), indicating that the Pd(II) species and redox-neutral pathway may be responsible for this transformation. When 5 mol% triphenylphosphine was added along with $PdCl_2$, a compatible yield with complex **2** could be observed (85%, Table 1, entry 8), supporting the role of the ligands. The yields decreased when lower catalyst loadings of Pd(NHC) complex **1a** was applied (80% and 47%, entries 11 and 12, respectively). As expected, no reaction took place in when no palladium was added under the optimized reaction conditions (entry 13, Table 1).

We next tested the feasibility of the protocol with a variety of (hetero)aryl and alkenyl boronic acids, and the results are summarized in Table 2. Both electron-rich and electron-deficient substituents on the phenyl ring of boronic acids were well tolerated (Table 2, **3**-**9**) under the optimized reaction conditions, however, the position of the methyl group of tolylboronic acid partially affected the transformation efficiency. In contrast to *p*-tolylboronic acid that 96% yield of sulfone **3a** was obtained, products **3b** and **3c** were produced with yields of 90% and 60%, respectively, from the corresponding *meta*- and *ortho*- isomers. Other *mono*- and *di*-electron-neutral, rich and poor substitutes were all compatible (**4**-**7**), and up to quantitative yields were obtained. Halo-substituted boronic acids were also fully tolerated. Remarkably, in the case of chlorinated substrate, no direct Suzuki-coupling products was formed, although complex **1a** is efficient catalyst for both transformations.[11b] Sulfone **6b** was produced in a 86% yield, which not only provided the opportunity for further transformation, but also highlighted the chemoselectivity of the newly developed catalytic system.

Table 2. Reaction of *tert*-butyl bromoacetate with various hetero(aryl)boronic acids[a]



[a] Reaction was carried with 5 mol% **1a**, 4-Methylphenylboronic acid (0.5 mmol), $K_2S_2O_5$ (2.0 equiv.), TBAB (1.1 equiv.), and *tert*-butyl bromoacetate (2.0 equiv.) in 2 mL dioxane at 100 °C for 24 hours. [b] Isolated yield. [c] With 5 mol% of Pd(NHC) complex **1c**.

We further expanded the substrate scope to the ester and amide groups by using **1c**, which produced the desired products **7a** and **7b** in good yields (72%). In the case of challenging substrate containing sulfide group, 4-thiomethylphenylboronic acid, an unexpected excellent yield was obtained for the production of sulfide-sulfone **8** (85%), a product usually difficult to prepared using the conventional oxidative or other coupling methodologies. 4-(Methylsulfonyl)-phenylboronic acid with a strong electron-withdrawing group was also good substrate to produce sulfone **9** in a 65% yield. Although, *ortho*-tolylboronic acid resulted in a moderate yield (**3c**), aryl boronic acids with extended conjugated system were all converted to the corresponding products in excellent to quantitative yields (**10a-c**, 91->99%). Similar outcomes were also observed from the reactions with heterocyclic substrates,

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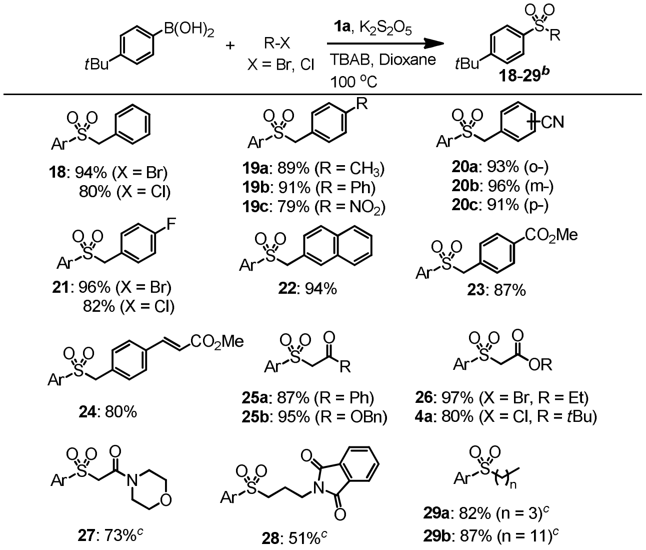
and the challenging hetero-arylboronic acids containing N, O, S atoms were all well accommodated, and good yields were obtained for the corresponding sulfones (**11-13**). As sulfide-sulfones are difficult to access by conventional oxidation approaches, 3-thiophene and dibenzo[*b,d*]thiophen-2-yl boronic acids were also studied, and good yields were obtained even considering strong coordination ability of this substrates to Pd (**14** and **15**, 85% and 87%, respectively). Challenging alkenyl boronic acids were also considered as suitable substrates for this protocol, and *E*-phenylethenylboronic acid and the 1-cyclohexenylboronic acid were converted to the corresponding alkenyl-alkyl products in good yields (**16** and **17**, 68% and 79%, respectively).

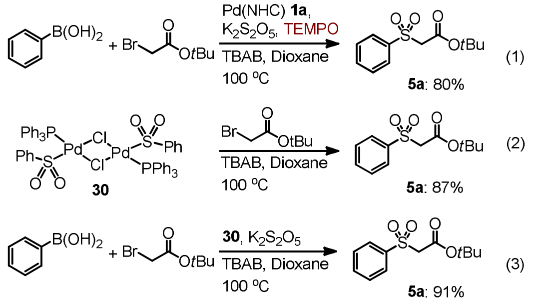
Table 3. Reaction scope with various *C*-electrophiles[a]



18: 94% (X = Br)
80% (X = Cl)
19a: 89% (R = CH_3)
19b: 91% (R = Ph)
19c: 79% (R = NO_2)
20a: 93% (o-)
20b: 96% (m-)
20c: 91% (p-)
21: 96% (X = Br)
82% (X = Cl)
22: 94%
23: 87%
24: 80%
25a: 87% (R = Ph)
25b: 95% (R = OBn)
26: 97% (X = Br, R = Et)
4a: 80% (X = Cl, R = *t*Bu)
27: 73%[c]
28: 51%[c]
29a: 82% (n = 3)[c]
29b: 87% (n = 11)[c]

[a] Reaction was carried with 5 mol% **1a**, 4-*tert*-butylphenylboronic acid (0.5 mmol), $K_2S_2O_5$ (2.0 equiv.), TBAB (1.1 equiv.), and electrophile (2.0 equiv.) in 2 mL Dioxane at 100 °C for 24 hours. [b] Isolated yield. [c] With 10 mol% of Pd(NHC) complex **1c**.

Inspired by the excellent outcomes obtained with a range of (hetero)-aryl and alkenyl boronic acids, we then focused on the scope of *C*-electrophiles (Table 3). This investigation showed that beside reactive α-bromoacetates, less active benzyl bromide and benzyl chloride were all competent substrates to access sulfone **18** (94% and 80%, respectively). Various electronic-donating and electronic-withdrawing substitutes on the phenyl ring of benzyl bromides were also well tolerated, and good to excellent yields were provided (79-99%, **19-21**). Among these the electron-withdrawing substrates containing -NO_2, -CN or -F substitutes were more active (79-96%, **19c-21**). The relative position of substituents of the electrophiles did not hamper the catalytic efficiency, and only slightly different yields were found with *ortho*-, *meta*-, *para*-isomers (**20a-c**, 91-96%). Good yield was still provided with inactive 4-fluorobenzyl chloride (**21**, 82%). When electron-rich and bulky 2-(bromomethyl)naphthalene was investigated, sulfone **22** was obtained in a 94% yield. In the case of active methyl 4-(bromomethyl)benzoate and methyl 3-(4-bromomethyl)-cinnamate, which have both ester and alkenyl groups, good to excellent yields were attained (**23** and **24**, 87% and 80%, respectively). Primary alkyl bromides, 2-bromoacetophenone, benzyl 2-bromoacetate and ethyl 2-bromoacetate were all suitable electrophiles to afford the sulfone products (**25a-b**, **26**, 87%, 95% and 97%, respectively). An 80% yield (**4a**) was reached with inactive *tert*-butyl 2-chloroacetate, further highlighting the protocol efficiency. Amide groups were also well tolerated where active or inactive electrophiles were involved (**27** and **28**). Using the standard reaction conditions for inert *n*-alkyl bromides, good yields for the desired aryl alkyl sulfone were observed (**29a-b**, 82% and 87%) in the presence of 10 mol% catalyst loading.



Scheme 1. Control experiments for plausible mechanism investigation.

To investigate the plausible reaction mechanism, several control experiments were carried out (Scheme 1). When TEMPO, a radical scavenger, was added into the reaction mixture containing Pd(NHC) **1a**, phenyl boronic acid and *tert*-butyl bromoacetate under the standard reaction conditions, sulfone **5a** was still obtained in an 80% yield (Eq. 1, Scheme 1). Combining the outcomes from Pd salts (Table 1, entries 7, 9 and 10), the Pd(II) species may be a true active intermediate. However, extensive efforts aiming to isolate the possible intermediates from the reaction mixture with stoichiometric amount of Pd(NHC) complex **1a**, **1c** or **2** have been proved to be unsuccessful. When less bulky PPh_3 was applied instead of NHC ligands, dimeric Pd(II) complex **30** was isolated. With this complex in hand, a stoichiometric reaction with *tert*-butyl bromoacetate was carried out under the standard reaction conditions; sulfone **5a** was produced in a yield of 87% after 12 hours (Eq. 2, Scheme 1). Unlike previous Pd-catalyzed alkylsulfonylation with phosphine ligands,[9] no possible routine sulfinates were detected in this stoichiometric reaction. When 5 mol% dimeric complex **30** was used as a catalyst without additional ligands, a yield of 91% for sulfone **5** was obtained (Eq. 3, Scheme 1), highlighting this dimeric species may be the true active species in the catalytic cycle.

Single crystals suitable for X-ray diffraction analysis were obtained by slow diffusion of ether to the solution of dimeric Pd(II) complex **30** in CH_2Cl_2 (Fig. 1), which may help us to better understand the mechanism. The Pd-S bond length is relative long (2.2516(17) Å), and 0.116 Å longer than the corresponding Pd-S bond in the known anionic dimeric Pd(II) complex,[10] suggesting this intermediate is more reactive in the presence of electrophile. Interestingly, although phosphine ligands are bulky, the phenyl group attached in S atom keep in same side with phosphine

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resulting the torsion angle between two Cl-Pd-Cl planes is 129.6°, due to C-H···π interactions (the shortest one is 2.495 Å). This data suggests the reactive dimeric complex is liable to dissociate, which makes the electrophile trapping more easy (blue arrows in Fig. 1b). With these two crucial information in hand, we propose that the congested dimeric Pd(II) intermediate may be released after the alkylation, which accelerate the conversion process leading to the sulfone formation in good yields.[2b]

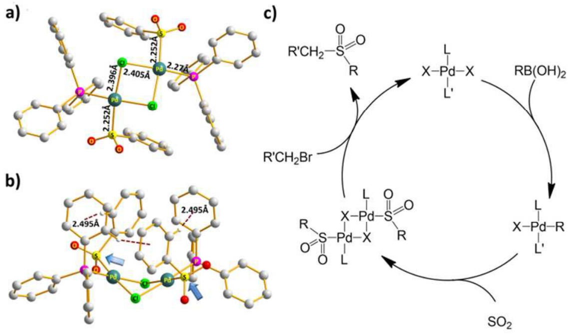

Fig. 1. a) Top view and b) side view of X-ray crystal structure of complex **30** (Ellipsoids set at 50% probability, and the hydrogen atoms are omitted for clarity); c) the plausible mechanism for the Pd(II)-catalyzed alkylsulfonylation of boronic acids.

Based on these results, a new plausible transformation route is proposed (Fig. 1c). Initially, transmetalation takes place between Pd(II) species and boronic acid,[2b] and follows by the insertion of SO_2 into the Pd-C bond[16] to generate a dimeric Pd(II) intermediate complex **30**. Due to the bulky and electronic rich properties of ligand, the long and accessible Pd-S bond is easily attacked by *C*-electrophiles in the presence of TBAB. Along with the corresponding sulfone product formation, the ligated Pd(II) catalyst is regenerated. Combining the result of Eq. 2 and the previous study,[10] there may be two plausible roles of TBAB in the transformation: 1) increasing the solubility of the inorganic salt in dioxane and 2) accelerating the transformation of dimeric Pd(II) intermediate like **30** into sulfinate leading to the corresponding sulfone formation.

In conclusion, robust Pd(NHC) complexes have been demonstrated for the first time as highly efficient catalysts in the direct alkylsulfonylation of readily available (hetero)aryl- or alkenyl-boronic acids with potassium metabisulfite and diverse alkylhalides. Remarkably, acenaphthoimidazolylidene palladium complexes exhibited the highest activity, and up to quantitative yields could be obtained even at low catalyst loading. Although it is difficult to isolate the intermediate derived from the Pd(NHC) complexes, the crystal structure of a dimeric Pd(II) analogue helps us to propose plausible mechanism for this challenging transformation, in which routine sulfinate intermediates may not be involved. This first Pd(NHC)-catalyzed redox-neutral protocol presented a direct, general, and efficient approach to access diverse (hetero)aryl-alkyl and alkenyl-alkyl sulfones.

Financial support from the National Key R&D Program of China (2016YFA0202902), National Natural Science Foundation of China (No. 21572036, 81670810 and 91127041), the Shanghai International Cooperation Program (14230710600), and Department of Chemistry, Fudan University is gratefully acknowledged.

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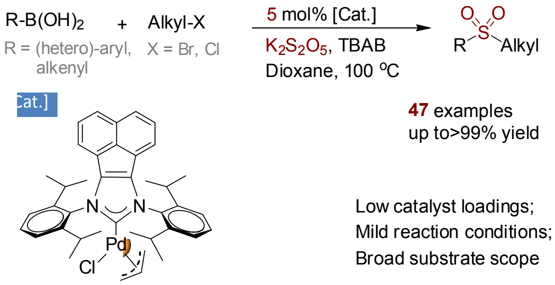

The first Pd(NHC) catalyzed direct alkylsulfonylation of boronic acids with $K_2S_2O_5$ and alkyl halides has been successfully developed to afford various functional sulfones under very mild reaction conditions at low catalyst loadings.