Cite this: Chem. Commun., 2012, 48, 7753-7755

## COMMUNICATION

## A palladium-catalyzed three-component coupling of arylboronic acids, sulfur dioxide and hydrazines<sup>†</sup>

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*Received 24th May 2012, Accepted 11th June 2012* DOI: 10.1039/c2cc33725h

A novel and efficient route to aryl *N*-aminosulfonamides *via* a palladium-catalyzed three-component coupling of arylboronic acids, sulfur dioxide and hydrazines in the presence of a balloon of dioxygen is reported. The reaction proceeded smoothly under mild conditions and DABCO· $(SO_2)_2$  was used as the source of sulfur dioxide.

Due to the enormous scale of annual sulfur dioxide production, applications of sulfur dioxide in organic synthesis are of high interest.1 So far, various transformations, including cycloaddition reactions, nucleophilic additions and ene reactions, using sulfur dioxide as a reagent have been reported.<sup>2,3</sup> Additionally, the coordination of sulfur dioxide with metal centers is common.<sup>4</sup> Transition metal-catalyzed insertion reactions of sulfur dioxide are rare,<sup>5</sup> although organic sulfonic acids could be prepared through a reaction of sulfur trioxide with different nucleophilic organometallic reagents.<sup>6</sup> Recently, Willis and co-workers described an interesting result using DABCObis(sulfur dioxide) as a sulfur dioxide equivalent in several organic transformations.<sup>7</sup> Since the limitation of sulfur dioxide application in organic synthesis is mainly due to the difficulties associated with the handling and use of a toxic gaseous reagent,<sup>8</sup> this bench-stable solid as a replacement for gaseous sulfur dioxide would open a new window to introduce sulfur dioxide into simple organic molecules.

Due to their easy handling and long shelf life, arylboronic acids have been widely used in organic synthesis.<sup>9</sup> Encouraged by the advantages of DABCO-bis(sulfur dioxide) and the chemistry of arylboronic acids, we conceived that the sulfonyl group could be incorporated *via* a palladium-catalyzed three-component reaction of arylboronic acids and DABCO-bis(sulfur dioxide) with nucleophiles (Scheme 1). We anticipated that the sulfonyl derivatives would be generated through an efficient and environmentally benign process.

Due to the importance of sulfonamides in medicinal chemistry and pharmaceuticals, the initial studies were performed for the reaction of *p*-methylphenylboronic acid 1a, DABCO-bis(sulfur dioxide) and morpholin-4-amine 2a (Table 1). At the outset, the reaction was catalyzed by palladium acetate (5 mol%) with  $P^{t}Bu_{3}$ (10 mol%) in the presence of DABCO and O<sub>2</sub> (balloon) in 1,4-dioxane at 90 °C (Table 1, entry 1). However, the result was poor with a trace amount of the desired product 3a detected. A similar outcome was achieved when the base was changed to cesium carbonate (Table 1, entry 2). To our delight, the expected 4-methyl-N-morpholinobenzenesulfonamide 3a was generated in 33% yield when the base was replaced by potassium carbonate (Table 1, entry 3). The reactions all failed when other bases were employed (Table 1, entries 4-9: K<sub>3</sub>PO<sub>4</sub>, Na<sub>2</sub>CO<sub>3</sub>, NaHCO<sub>3</sub>, CsF, KF, KOAc). Further exploration found that the yield was increased to 40% when TBAB (tetrabutylammonium bromide) was utilized as the base (Table 1, entry 10). Screening of reaction temperature revealed that the transformation worked efficiently at 80 °C, affording the desired product, 3a, in 56% yield (Table 1, entries 11-15). The yield was lower when the reaction occurred in air (Table 1, entry 16). A control experiment indicated that the palladium catalyst was essential for the successful conversion (Table 1, entry 17). Gratifyingly, the yield was increased to 90% in the absence of the phosphine ligand (Table 1, entry 18). A similar result was furnished when the amount of palladium catalyst was increased to 10 mol% (Table 1, entry 19). However, a lower reactivity was observed when 2 mol% of Pd(OAc)<sub>2</sub> was utilized (Table 1, entry 20). Other palladium sources were then screened and no better results were obtained (Table 1, entries 21–24). Further examination of solvents demonstrated that 1,4-dioxane was the best choice (Table 1, entries 25-29).

With the optimized reaction condition in hand, we set out to explore the scope of this palladium-catalyzed three-component reaction of arylboronic acids **1** and DABCO-bis(sulfur dioxide) with hydrazines **2**. The results are presented in Table 2. The conditions are mild, and the reaction proceeds smoothly in the



**Scheme 1** A proposed synthetic route for the generation of sulfonyl derivatives *via* a palladium-catalyzed reaction of arylboronic acids and DABCO-bis(sulfur dioxide) with nucleophiles.

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<sup>†</sup> Electronic supplementary information (ESI) available: Experimental procedure, characterization data, <sup>1</sup>H and <sup>13</sup>C NMR spectra of compound 3. See DOI: 10.1039/c2cc33725h

**Table 1** Initial studies for the palladium-catalyzed reaction of *p*-methylphenylboronic acid **1a**, DABCO-bis(sulfur dioxide) and morpholin-4-amine  $2a^{a}$ 

		SCO)•(SO <sub>2</sub> )	2 [Pd] (cat.) ligand, O <sub>2</sub> base, solve temp.	nt	}—so₂ HN−N	$\bigcirc$
1a 2a 3a						
			Base/			Yield <sup>t</sup>
Entry	[Pd]	Ligand	additive	Solvent	Temp	(%)
1	Pd(OAc) <sub>2</sub>	P'Bu <sub>3</sub>	DABCO	Dioxane	90	Trace
2	$Pd(OAc)_2$	$P'Bu_3$	$Cs_2CO_3$	Dioxane	90	Trace
3	$Pd(OAc)_2$	$P'Bu_3$	$K_2CO_3$	Dioxane	90	33
4	$Pd(OAc)_2$	$P'Bu_3$	K <sub>3</sub> PO <sub>4</sub>	Dioxane	90	Trace
5	$Pd(OAc)_2$	$P'Bu_3$	Na <sub>2</sub> CO <sub>3</sub>	Dioxane	90	Trace
6	$Pd(OAc)_2$	$P'Bu_3$	NaHCO <sub>3</sub>	Dioxane	90	Trace
7	$Pd(OAc)_2$	$P'Bu_3$	CsF	Dioxane	90	Trace
8	$Pd(OAc)_2$	$P'Bu_3$	KF	Dioxane	90	Trace
9	$Pd(OAc)_2$	$P'Bu_3$	KOAc	Dioxane	90	Trace
10	$Pd(OAc)_2$	$P'Bu_3$	TBAB	Dioxane	90	40
11	$Pd(OAc)_2$	$P'Bu_3$	TBAB	Dioxane	100	39
12	$Pd(OAc)_2$	$P'Bu_3$	TBAB	Dioxane	80	56
13	$Pd(OAc)_2$	$P'Bu_3$	TBAB	Dioxane	70	43
14	$Pd(OAc)_2$	$P'Bu_3$	TBAB	Dioxane	50	Trace
15	$Pd(OAc)_2$	$P'Bu_3$	TBAB	Dioxane	30	Trace
16 <sup>c</sup>	$Pd(OAc)_2$	$P'Bu_3$	TBAB	Dioxane	80	45
17	_	$P'Bu_3$	TBAB	Dioxane	80	nr
18	$Pd(OAc)_2$	_	TBAB	Dioxane	80	90
19 <sup>d</sup>	$Pd(OAc)_2$		TBAB	Dioxane	80	89
$20^e$	$Pd(OAc)_2$		TBAB	Dioxane	80	58
21	PdCl <sub>2</sub>		TBAB	Dioxane	80	75
22	$Pd_2(dba)_3$		TBAB	Dioxane	80	66
23	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub>		TBAB	Dioxane	80	59
24	$Pd(PhCN)_2Cl_2$		TBAB	Dioxane	80	64
25	$Pd(OAc)_2$		TBAB	toluene	80	67
26	$Pd(OAc)_2$		TBAB	DMF	80	64
27	$Pd(OAc)_2$	_	TBAB	MeCN	80	63
28	$Pd(OAc)_2$	_	TBAB	DCE	80	62
29	$Pd(OAc)_2$	_	TBAB	<sup>t</sup> BuOH	80	81

<sup>*a*</sup> *Reaction conditions: p*-methylphenylboronic acid **1a** (1.0 mmol), morpholin-4-amine **2a** (0.5 mmol), DABCO·(SO<sub>2</sub>)<sub>2</sub> (1.0 mmol), palladium catalyst (5 mol%), ligand (10 mol%), base (1.5 equiv.), solvent (2.0 mL), O<sub>2</sub> (balloon). <sup>*b*</sup> Isolated yield based on morpholin-4-amine **2a**. <sup>*c*</sup> The reaction was performed in air. <sup>*d*</sup> In the presence of Pd(OAc)<sub>2</sub> (10 mol%). <sup>*e*</sup> In the presence of Pd(OAc)<sub>2</sub> (2 mol%). TBAB: tetrabutylammonium bromide.

presence of dioxygen (balloon) at 80 °C. A range of arylboronic acids and amines were examined under the standard conditions. For most cases, the expected products 3 were formed in good to excellent yields. For instance, 2-methylphenylboronic acid or 4-methoxyphenylboronic acid reacted with DABCO-bis(sulfur dioxide) and morpholin-4-amine 2a leading to the corresponding aryl N-aminosulfonamide 3b or 3c in almost quantitative yields. 4-tert-Butylphenylboronic acid or naphthalenylboronic acid were good reactants as well in the reaction of DABCO-bis(sulfur dioxide) and morpholin-4-amine 2a. However, the results were inferior when arylboronic acids 1 with electron-withdrawing groups attached on the aromatic ring were examined. For example, a moderate yield was afforded when 4-halophenylboronic acid was employed in the palladium-catalyzed, threecomponent reaction. Interestingly, the free hydroxyl and amino groups could be tolerated under the conditions, and the expected products 3k or 3l were generated in 75% and 50% yields, respectively. However, 3-pyridinylboronic acid was not a good partner in the reaction. Reaction of (E)-styrylboronic acid and

Table 2Palladium-catalyzed three-component reaction of arylboronicacids 1 and DABCO-bis(sulfur dioxide) with amines  $2^a$ 



DABCO-bis(sulfur dioxide) with morpholin-4-amine **2a** was examined in the meantime, which gave rise to the desired product **3m** in 50% yield. Palladium-catalyzed reactions of piperidin-1-amine or 1-methyl-1-phenylhydrazine were explored, and all reactions worked well to produce the corresponding aryl *N*-aminosulfonamides in good yields. However, no reaction took place when piperidine or *p*-toluidine were employed in the transformation under the optimal conditions, which was similar to the results reported by Willis.<sup>7</sup> This might be due to the difference of nucleophilicity and basicity between amines and hydrazines.

A possible catalytic cycle is presented in Scheme 2. We hypothesized that a transmetallation of Pd(II) with arylboronic acid 1 would occur first to generate a Pd(II) species **A**. The subsequent coordination and insertion of sulfur dioxide<sup>4</sup> would result in the formation of intermediate **B**. Then a nucleophilic attack of hydrazine would take place to produce the coupling product **3** and Pd(0). The latter would be oxidized in the presence of dioxygen to afford Pd(II), which would re-enter the catalytic cycle.

In summary, we have developed a novel and efficient route to aryl *N*-aminosulfonamides *via* a palladium-catalyzed threecomponent coupling of arylboronic acids, sulfur dioxide and hydrazines in the presence of a balloon of dioxygen.



**Scheme 2** A possible mechanism for the palladium-catalyzed reaction of arylboronic acids, DABCO-bis(sulfur dioxide), with hydrazines.

The reaction proceeded smoothly under mild conditions and DABCO $(SO_2)_2$  was used as the source of sulfur dioxide. Employing DABCO-bis(sulfur dioxide) in other coupling reactions is under investigation currently, and the results will be reported in due course.

Financial support from the National Natural Science Foundation of China (Nos. 21032007, 21172038) is gratefully acknowledged.

## Notes and references

- (a) S. D. Burke, in Encylopedia of Reagents for Organic Synthesis, ed. L. A. Paquette, Wiley, Chichester, 1995, vol. 7, p. 4688;
   (b) Z. Florjańczyk and D. Raducha, Pol. J. Chem., 1995, 69, 481;
   (c) P. Vogel, M. Turks, L. Bouchez, D. Markovic, A. Varela-Álvarez and J. A. Sordo, Acc. Chem. Res., 2007, 40, 931;
   (d) Ullmann's Encyclopedia of Industrial Chemistry, ed. B.Elvers, S. Hawkins and W. Russey, VCH, Weinheim, Germany, 5th edn 1994, vol. A25.
- 2 (a) P. Vogel and J. A. Sordo, *Curr. Org. Chem.*, 2006, 10, 2007;
   (b) R. V. Hoffmann, *Org. Synth.*, 1981, 60, 121; (c) C. P. Tsonis, in *Polymeric Materials Encyclopedia*, ed. J.C. Salamone, CRC Press, NewYork, 1996, vol. 9, p. 6866.
- 3 (a) G. D. Laubach, E. C. Schreiber, E. J. Agnello and K. J. Brunings, J. Am. Chem. Soc., 1956, **78**, 4743; (b) M. M. Rogic and D. Masilamani, J. Am. Chem. Soc., 1977, **99**, 5219; (c) T. Hamada and O. Yonemitsu, Synthesis, 1986, 852; (d) J.-P. Wu, J. Emeigh and

X.-P. Su, Org. Lett., 2005, 7, 1223; (e) L. C. Bouchez, S. R. Dubbaka,
M. Turks and P. Vogel, J. Org. Chem., 2004, 69, 6413;
(f) L. C. Bouchez, M. Turks, S. Reddy Dubbaka, F. Fonquerne,
C. Craita, S. Laclef and P. Vogel, Tetrahedron, 2005, 61, 11473;
(g) V. Narkevitch, K. Schenk and P. Vogel, Angew. Chem., Int. Ed., 2000, 39, 1806.

- 4 (a) G. J. Kubas, Acc. Chem. Res., 1994, 27, 183; (b) W. A. Schenk, Angew. Chem., Int. Ed. Engl., 1987, 26, 98; (c) G. J. Kubas, Inorg. Chem., 1979, 18, 182; (d) D. M. P. Mingos, Transition Met. Chem., 1978, 3, 1; (e) A. Wojcicki, Adv. Organomet. Chem., 1974, 12, 31; (f) W. Kitching and C. W. Fong, Organomet. Chem. Rev. A, 1970, 5, 281; (g) A. Wojcicki, Acc. Chem. Res., 1971, 4, 344.
- 5 (a) H. S. Klein, Chem. Commun., 1968, 377; (b) J. Herwig and W. Keim, J. Chem. Soc., Chem. Commun., 1993, 1592; (c) J. Herwig and W. Keim, Inorg. Chim. Acta, 1994, 222, 381; (d) W. Keim, J. Herwig and G. Pelzer, J. Org. Chem., 1997, 62, 422; (e) G. Pelzer and W. Keim, J. Mol. Catal. A: Chem., 1999, 139, 235; (f) L. M. Wojcinski, M. T. Boyer and A. Sen, Inorg. Chim. Acta, 1998, 270, 8; (g) U. M. Dzhemilev and R. V. Kunakova, J. Organomet. Chem., 1993, 455, 1; (h) G. Pelzer, J. Herwig, W. Keim and R. Goddard, Russ. Chem. Bull., 1998, 47, 904.
- 6 (a) E. E. Gilbert, Chem. Rev., 1962, 62, 549; (b) C. Eaborn and T. Hashimoto, Chem. Ind., 1961, 1081; (c) R. W. Bott, C. Eaborn and T. Hashimoto, J. Chem. Soc., 1963, 3906; (d) R. W. Bott, C. Eaborn and T. Hashimoto, J. Organomet. Chem., 1965, 3, 442; (e) H. Schmibaur, L. Sechser and M. Schmidt, J. Organomet. Chem., 1968, 15, 77; (f) J. Dubac and P. Mazerolles, J. Organomet. Chem., 1969, 20, 5; (g) W. Kitching and C. W. Fong, Organomet. Chem. Rev. Sect. A, 1970, 5, 281; (h) K. A. R. Salib and J. B. Senior, J. Chem. Soc., Chem. Commun., 1970, 1259; (i) K. Smith and D. Hou, J. Org. Chem., 1996, 61, 1530.
- 7 (a) B. Nguyen, E. J. Emmett and M. C. Willis, J. Am. Chem. Soc., 2010, 132, 16372; (b) H. Woolven, C. González-Rodríguez, I. Marco, A. L. Thompson and M. C. Willis, Org. Lett., 2011, 13, 4876; (c) E. J. Emmett, C. S. Richards-Taylor, B. Nguyen, A. Garcia-Rubia, B. R. Hayter and M. C. Willis, Org. Biomol. Chem., 2012, 10, 4007.
- 8 W. J. Mahn, Academic Laboratory Chemical Hazards Guidebook; Van Norstrand Reinhold, New York, 1991, p. 264.
- 9 For reviews: (a) N. Miyaura, Top. Curr. Chem., 2002, 219, 11; (b) A. Suzuki, J. Organomet. Chem., 1999, 576, 147; (c) A. F. Littke and G. C. Fu, Angew. Chem., Int. Ed., 2002, 41, 4176; (d) K. Fagnou and M. Lautens, Chem. Rev., 2003, 103, 169; (e) T. Hayashi and K. Yamasaki, Chem. Rev., 2003, 103, 2829.