J. Braz. Chem. Soc., Vol. 21, No. 9, 1635-1641, 2010.
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0103 - 5053 $6.00+0.00

Article

Palladium Catalyzed Suzuki Cross-Coupling of 3-Iodo-2-(methylthio)-benzo[*b*]furan Derivatives: Synthesis of 3-Aryl-2-(methylthio)benzo[*b*]furans

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Neste trabalho desenvolvemos um método seletivo e eficiente para a síntese de derivados de 3-aril-2-(tiometil)-benzo[*b*]furanos, *via* reação de acoplamento com ácidos borônicos, catalisada por paládio. As condições reacionais usadas foram brandas e compatíveis com ácidos borônicos contendo substituintes retiradores, doadores de elétrons ou neutros.

A selective and efficient method for the synthesis of 3-aryl-2-(methylthio)benzo[*b*]furans derivatives by palladium catalyzed cross-coupling reaction with boronic acids has been developed. The reaction proceeded cleanly under mild conditions and was performed with aryl boronic acids bearing electron-withdrawing, electron donating and neutral substituents.

Keywords: palladium, Suzuki cross-coupling, benzofuran, boronic acids

Introduction

The construction of benzo[*b*]furans substituted in the 2,3 positions is of great synthetic interest due to the presence of this moiety in many complex compounds, which have potential therapeutic applications.[1] In this context, the preparation of 2,3-disubstituted benzo[*b*] furans represents a synthetic challenge and the palladium-catalyzed Suzuki coupling is one of the most straightforward methodologies to synthesize 3-arylated-benzofurans.[2] The palladium-catalyzed Suzuki cross-coupling reaction of aryl halides with organoboron reagents has become a common and convenient synthetic method in organic chemistry.[3] Many examples of Suzuki coupling reaction of heterocyclic halides with boronic acids have appeared in the literature over the past two decades as a promising synthetic tool.[4] More recently, significant advances have been made in the use of organoboron reagents as coupling partners in a number of palladium-mediated carbon–carbon bond formation. Among them, the use of potassium organotrifluoroborates, as the organoboron coupling partner, has some of these advantages are higher nucleophilicity, air-stability and ready access in comparison to boronic acids and boronic esters.[5]

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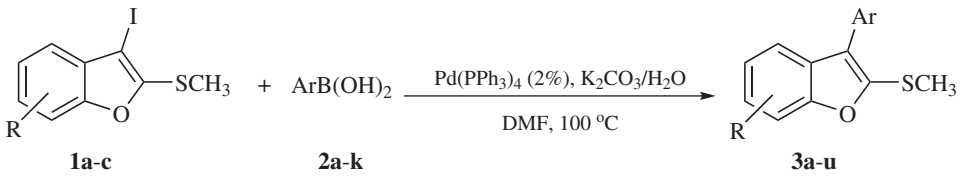
In addition, the presence of a sulfide group at the 2-position of benzo[*b*]furan is significant, since it could be easily oxidized to 2-sulfonylbenzofurans,[6] a class of compounds which has attracted tremendous interest from the pharmaceutical industry. During the course of our research program aiming at structure-activity relationship studies in order to evaluate the pharmacology activity of heterocycles,[7,8] we required the synthesis of benzofurans having an organochalcogen group at the 2-position and a substituted aromatic ring at the 3-position. Since the Suzuki reaction has proven to be successful for the selective arylation of heterocyles,[2] it was of interest to explore this reaction to obtain 3-aryl-2-(methylthio) benzo[*b*]furan derivatives. To our knowledge this methodology has not been explored and we now wish to report the application of 3-iodo-2-(methylthio)benzo[*b*] furans **1a**-**c** as substrates on the cross-coupling reaction with boronic acids **2a**-**k** in the presence of a palladium salt to obtain 3-aryl-2-(methylthio)benzo[*b*]furans **3a**-**u** (Scheme 1).

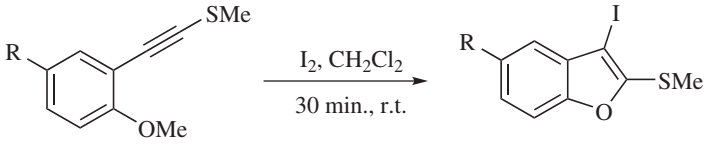
The starting materials **1a**-**c** were readily available by using the electrophilic cyclization protocol[9] of 2-(methylthio)alkynylanisoles (Scheme 2). The treatment of 2-(methylthio)alkynylanisoles with iodine in CH_2Cl_2, at room temperature, led to the formation of **1a**-**c**, isolated in 87-95% yield after purification (Scheme 2).[10]



1a-c **2a-k** **3a-u**

R = H, Me, F;
Ar = C_6H_5, *p*-OMe-C_6H_4, *p*-Me-C_6H_4, *o*-Me-C_6H_4, *p*-Cl-C_6H_4, *p*-Br-C_6H_4, *p*-Me-COC_6H_4, *m*-Me-COC_6H_4, *m*-CF_3-C_6H_4, *m*-NO_2-C_6H_4, naphtyl

Scheme 1.



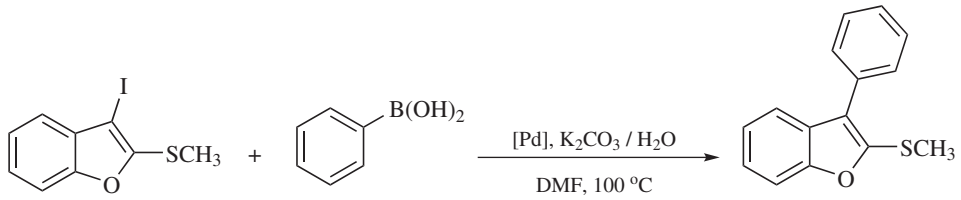
R= H, **1a**- 93%
R= Me, **1b**- 95%
R= F, **1c**- 87%

Scheme 2.

Results and Discussion

Our initial studies on Suzuki cross-coupling focused on the development of an optimum set of reaction conditions. In this way, 3-iodo-2-(methylthio)benzo[*b*]furan **1a** and phenylboronic acid **2a** were used as standard substrates. Thus, the reaction of **1a** (0.5 mmol), boronic acid **2a** (0.75 mmol), and a solution of K_2CO_3 (1.0 mmol) in H_2O (0.4 mL), using DMF (4.0 mL) as solvent, at reflux with different palladium catalysts was tested (Table 1). As shown in Table 1, both Pd(0) and Pd(II) catalysts with different ligands were tested. The best result was obtained using $Pd(PPh_3)_4$ (5 mol%) which gave the desired product **3a** in 97% yield (Table 1; entry 1). It is important to note that when the amount of catalyst was reduced from 5 to 2 mol%, a small decrease in the yield was observed (Table 1; entry 7).

Table 1. Effects of palladium catalysts on reaction of **1a** and **2a**[a]



1a **2a** **3a**

Entry	Catalysts (mol %)	Yield / (%)[b]
1	$Pd(PPh_3)_4$ (5)	97
2	$Pd(acac)_2$ (5)	traces
3	$PdCl_2(PPh_3)_2$ (5)	83
4	$PdCl_2(PhCN)_2$ (5)	traces
5	$PdCl_2$ (5)	nr
6	$Pd(OAc)_2$ (5)	15
7	$Pd(PPh_3)_4$ (2)	93
8	-	nr

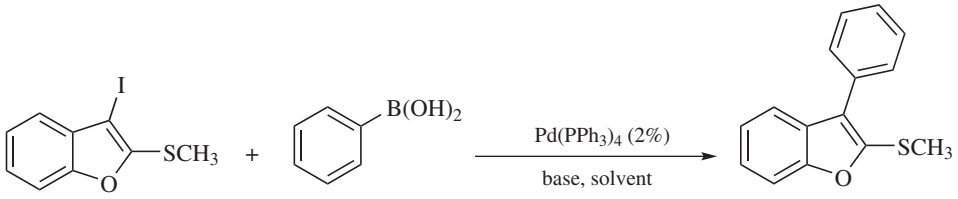
[a]Reactions were performed in the presence of **1a** (0.5 mmol), **2a** (0.75 mmol), K_2CO_3 (1.0 mmol), H_2O (0.4 mL), in DMF (4.0 mL), under 100 °C, during 1h.
[b]Yields are given by GC analysis. nr = no reaction.

Our experiments also showed that in the absence of catalyst the product was not detected, and the starting material was recovered (Table 1; entry 8).

Regarding the influence of solvent, optimal results were achieved using DMF (Table 2, entry 1). By using dioxane, CH_3CN and THF (Table 2, entries 2, 4 and 6) good yields were also obtained, while the use of DME (Table 2, entry 5) did not give the desired product **3a**. We also observed that the nature of the base was critical for the success of the coupling. When the reaction was carried out with an aqueous solution of inorganic bases such as K_3PO_4, Cs_2CO_3 and Na_2CO_3 the coupling product was obtained in good yields (Table 2; entries 7-9), while the use of NaOH (Table 2, entry 10) furnished the desired coupling product in low yield. It is also important to mention that when dry base were used in place of an aqueous solution, only 54% of product was obtained (Table 2; entry 11). Careful analysis of the results revealed that the optimum condition for this coupling reaction was found to be the use of $Pd(PPh_3)_4$ (2 mol%), 3-iodo-2-(methylthio)-benzo[*b*]furan **1a** (0.5 mmol), phenylboronic acid (0.75 mmol) in DMF (4.0 mL) and H_2O (0.4 mL) at room temperature. After that, the base K_3PO_4 (1.0 mmol) was added and the mixture was heated at 100 °C for 1h. Using this reaction condition we were able to prepare 3-aryl-2-(methylthio)-benzo[*b*]furan derivative **3a** in excellent yield.[12]

In order to demonstrate the efficiency of this protocol, we explored the generality of our method extending the conditions to other aryl boronic acids and 3-iodo-2-(methylthio)-benzo[*b*]furan derivatives and the results are summarized in Table 3. Inspection of Table 3 shows that the reaction worked well for a variety of arylboronic acids. A closer inspection of the results revealed that the reaction is sensitive to the electronic effect of the aromatic ring attached in the arylboronic acid. For example, arylboronic acids bearing an electron-donating group, methyl or methoxyl, at the *para* position gave a better yield than the arylboronic acid bearing an electron-withdrawing group, halide and acetyl (Table 3; entries 2, 3 *versus* 4-6). These results are in full agreement with the fact that electron donating groups increase the nucleophilicity of boronic acids. We have found that steric effects had a little influence on the coupling reaction since boronic acids containing 2-methylphenyl or naphtyl group, gave similar yields than arylboronic acids with no substituent, however an increase in the reaction time was required (Table 3; entries 10, 15, 18 and 21). Differentiation in the reactivity between halogen and boron atoms can be seen by coupling showed in the experiments described in Table 1 (enties 4 and 5), which provide only the Suzuki product, without any homo-coupling product. To the best

Table 2. Study of base and solvent effects on cross-coupling reaction[a]

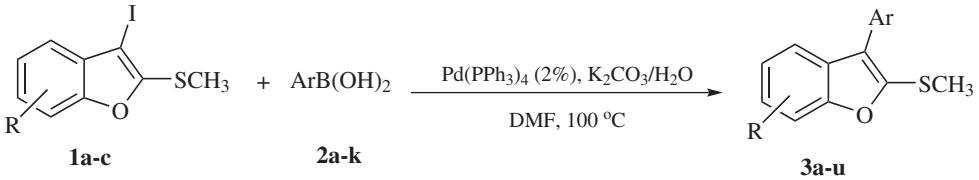


1a **2a** **3a**

Entry	Base	Solvent	Yield **3a** / (%)[b]
1	K_2CO_3	DMF	93
2	K_2CO_3	Dioxane	91
3	K_2CO_3	Toluene	45
4	K_2CO_3	CH_3CN	90
5	K_2CO_3	DME	nr
6	K_2CO_3	THF	70
7	K_3PO_4	DMF	64
8	Na_2CO_3	DMF	60
9	Cs_2CO_3	DMF	73
10	NaOH	DMF	36
11	K_2CO_3	DMF	54[c]

[a] Reactions were performed by using **1a** (0.5 mmol), **2a** (0.75 mmol), $Pd(PPh_3)_4$ (2 mol%), base (1.0 mmol), H_2O (0.4 mL) with different solvents (4.0 mL), under 100 °C. [b] Yields are given by GC analysis. [c] This reaction was carried out using dry base.

Table 3. Coupling products obtained using 3-iodo-2(methylthio)benzo[*b*]furans **1a-c** and boronic acids **2a-k**[a]



1a-c **2a-k** **3a-u**

R = H, Me, F

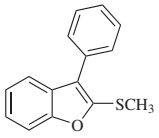
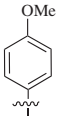
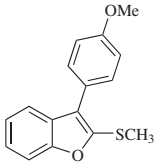
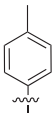
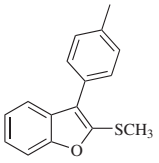
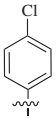
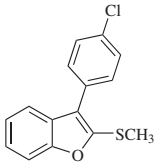
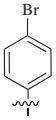
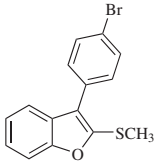
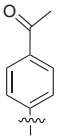
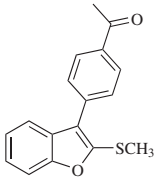
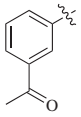
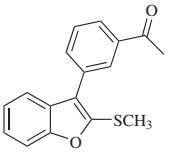
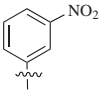
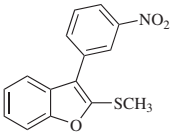
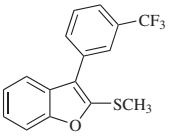
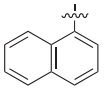
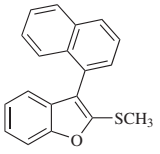
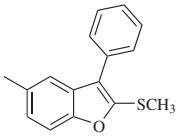
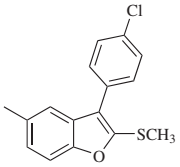
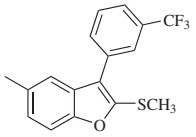
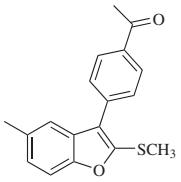
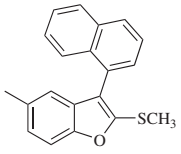
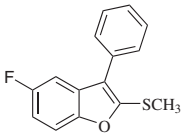
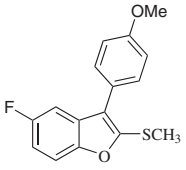
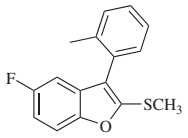
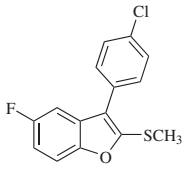
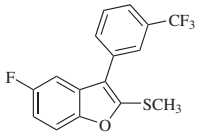
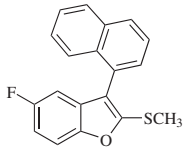
Entry	Substrate	Ar	Yield (%)[c] / Reaction time
1	**1a**	 **2a**	 **3a** 93/1 h[b]
2	**1a**	 **2b**	 **3b** 80/1 h
3	**1a**	 **2c**	 **3c** 92/2 h
4	**1a**	 **2d**	 **3d** 63/1 h
5	**1a**	 **2e**	 **3e** 70/2 h
6	**1a**	 **2f**	 **3f** 70/3 h
7	**1a**	 **2g**	 **3g** 90/1 h
8	**1a**	 **2h**	 **3h** 57/12 h
9	**1a**	 **2i**	 **3i** 89/2 h
10	**1a**	 **2j**	 **3j** 83/6 h
11	**1b**	**2a**	 **3k** 95/1 h
12	**1b**	**2d**	 **3l** 86/2 h

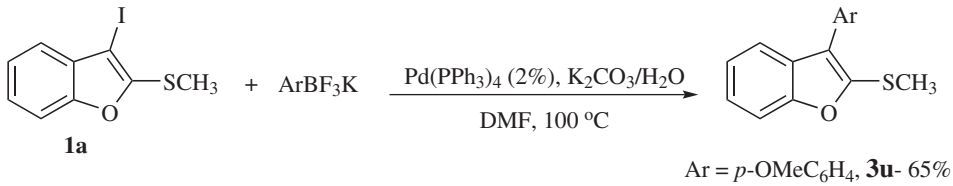
Table 3. continuation

Entry	Substrate	Ar	Yield (%)[c] / Reaction time
13	**1b**	**2i**	 **3m** 82/1 h
14	**1b**	**2f**	 **3n** 60/3 h
15	**1b**	**2j**	 **3o** 92/4 h
16	**1c**	**2a**	 **3p** 80/1 h
17	**1c**	**2b**	 **3q** 90/1 h
18	**1c**	 **2k**	 **3r** 82/3 h
19	**1c**	**2d**	 **3s** 85/1 h
20	**1c**	**2i**	 **3t** 71/2 h
21	**1c**	**2j**	 **3u** 82/2 h

[a] Reactions were performed by using **1a-c** (0.5 mmol), **2a-k** (0.75 mmol), $Pd(PPh_3)_4$ (2 mol%), K_2CO_3 (1.0 mmol), H_2O (0.4 mL) in DMF (4.0 mL), under 100 °C. [b] Yield given by GC analysis. [c] Yields given for isolated products.

of our knowledge, aryl halogen could react with boronic acids in the presence of palladium catalysts to afford biaryl products.[11] In the example reported in this study, the halogen substituent was not affected. In an attempt to broaden the scope of our methodology, the possibility of performing the reaction with other 3-iodo-2-(methylthio)-benzofurans was also investigated. Then substrates **1b** and **1c**, which have methyl and fluoro group in the side chain, were efficiently cross-coupled. Under these conditions, both electron-rich and electron-poor arylboronic acids produced the desired products in good yields (Table 3; entries 11-21).

Alternatively, under the same conditions described to boronic acids, we were able to use other organoboron source, the aryltrifluoroborates (Scheme 3).[5] In this way, 3-iodo-2-(methylthio)-benzofuran **1a** underwent palladium cross-coupling with aryltrifluoroborates furnishing the corresponding 3-aryl-2-(methylthio)benzo[*b*]furan in good yields.



Ar = *p*-$OMeC_6H_4$, **3u**- 65%
p-MeC_6H_4, **3v**- 70%
o-MeC_6H_4, **3w**- 63%
thienyl, **3x**- 60%

Scheme 3.

Conclusions

In summary, we have explored the Suzuki cross-coupling reaction of arylboronic acids with 3-iodo-2-(methylthio)-benzofurans using a catalytic amount of $Pd(PPh_3)_4$. In addition, the same procedure used to aryl boronic acids was efficiently extended to aryltrifluoroborates. The reaction proceeded cleanly under mild reaction conditions, short reaction time and was performed with aryl boronic acids bearing electron withdrawing, electron donating, and neutral substituents. It is important to point out that this route permits an easy and efficient access to highly substituted benzofurans.

Supplementary Information

Supplementary data (Experimental details and caracterization of the compounds) are available free of charge at http://jbcs.sbq.org.br, as PDF file.

Acknowledgments

We are grateful to Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS), for the fellowship and financial support.

References

1. Kirilmis, C.; Ahmedzade, M.; Servi, S.; Koca, M.; Kizirgil, A.; Kazaz, C.; *Eur. J. Med. Chem.* **2008**, *43*, 300; Schultz, D. M.; Prescher, J. A.; Kidd, S.; Marona-Lewicka, D.; Nichols, D. E.; Monte, A.; *Bioorg. Med. Chem.* **2008**, *16*, 6242; Ando, K.; Kawamura, Y.; Akai, Y.; Kunitomo, J.; Yokomizo, T.; Yamashita, M.; Ohta, S.; Ohishi, T.; Ohishi, Y.; *Org. Biomol. Chem.* **2008**, *6*, 296; Sakata, Y.; Kuramoto, M.; Ando, K.; Yamaguchi, M.; Kawasaki, I.; Kunitomo, J-I.; Yokomizo, T.; Ohishi, Y.; *Org. Biomol. Chem*. **2007**, *5*, 3083.
2. Tung, D. T.; Tuan, D. T.; Rasool, N.; Villinger, A.; Reinke, H.; Fischer, C.; Langer, P.; *Adv. Synth. Catal.* **2009**, *351*, 1595; Ullah, I.; Khera, R. A.; Hussain, M.; Villinger, A.; Langer, P.; *Tetrahedron Lett*. **2009**, *50*, 4651; Dang, T. T.; Rasool, N.; Dang, T. T.; Reinke, H.; Langer, P.; *Tetrahedron Lett*. **2007**, *48*, 845; Tuan, D. T.; Tung, D. T.; Langer, P.; *Synlett* **2006**, 2812; Bellur, E.; Langer, P.; *Eur. J. Org. Chem*. **2005**, *22*, 4815.
3. Miyaura, N.; Suzuki, A.; *Chem. Rev.* **1995**, *95*, 2457; Suzuki, A.; *Pure Appl. Chem*. **1994**, *66*, 213; Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J., eds.; Wiley-VHC: Weinheim, 1998; Lloyd-Williams, P.; Giralt, E.; *Chem. Soc. Rev*. **2001**, *30*, 145.
4. Barancelli, D. A.; Alves, D.; Prediger, P.; Stangherlin, E. C.; Nogueira, C. W.; Zeni, G.; *Synlett* **2008**, 119; Stanforth, S. P.; *Tetrahedron* **1998**, *54*, 263; Cailly, T.; Fabis, F.; Legay, R.; Oulyadi, H.; Rault, S.; *Tetrahedron* **2007**, *63*, 71; Sicre, C.; Alonso-Gomez, J. L.; Cid, M. M.; *Tetrahedron* **2006**, *62*, 11063; Schnurch, M.; Flasik, R.; Khan, A. F.; Spina, M.; Mihovilovic, M. D.; Stanetty, P.; *Eur. J. Org. Chem*. **2006**, *15*, 3283.
5. Molander, G. A.; Ellis, N.; *Acc. Chem. Res*. **2007**, *40*, 275; Molander, G. A.; Petrillo, D. E.; Landzberg, N. R.; Rohanna, J. C.; Biolatto, B.; *Synlett* **2005**, 1763; Molander, G. A.; Figueroa, R.; *Aldrichimica Acta* **2005**, *38*, 49; Molander, G. A.; Felix, L. A.; *J. Org. Chem*. **2005**, *70*, 3950; Molander, G. A.; Yun, C. S.; Ribagorda, M.; Biolatto, B.; *J. Org. Chem*. **2003**, *68*, 5534; Molander, G. A.; Biolatto, B.; *J. Org. Chem*. **2003**, *68*, 4302; Molander, G. A.; Katona, B. W.; Machrouhi, F.; *J. Org. Chem*. **2002**, *67*, 8416; Molander, G. A.; Reviro, M. R.; *Org. Lett*. **2002**, *4*, 107.
6. Kakarla, R.; Dulina, R. G.; Hatzenbuhler, N. T.; Hui, Y. W.; Sofia, M. J.; *J. Org. Chem*. **1996**, *61*, 8347.
7. Stein, A. L.; Alves, D.; Rocha, J. T.; Nogueira, C. W.; Zeni, G.; *Org. Lett*. **2008**, *10*, 4983; Alves, D.; Luchese, C.; Nogueira, C. W.; Zeni, G.; *J. Org. Chem*. **2007**, *72*, 6726; Prediger, P.; Moro, A. V.; Nogueira, C. W.; Savegnago, L.; Rocha, J. B. T.; Zeni, G.; *J. Org. Chem*. **2006**, *71*, 3786; Moro, A. V.; Nogueira, C. W.; Barbosa, N. B. V.; Menezes, P. H.; Rocha, J. B. T.; Zeni, G.; *J. Org. Chem*. **2005**, *70*, 5257; Zeni, G.; Stracke, M. P.; Nogueira, C. W.; Braga, A. L.; Menezes, P. H.; Stefani, H. A.; *Org. Lett*. **2004**, *6,* 1135; Zeni, G.; Barros, O. S. D.; Moro, A. V.; Braga, A. L.; Peppe, C.; *Chem. Commun*. **2003**, 1258; Barros, O. S. D.; Lang, E. S.; Peppe, C.; Zeni, G.; *Synlett* **2003**, 1725.

8. Zeni, G.; Ludtke, D. S.; Panatieri, R. B.; Braga, A. L.; *Chem. Rev*. **2006**, *106*, 1032; Zeni, G.; Braga, A. L.; Stefani, H. A.; *Acc. Chem. Res*. **2003**, *36*, 731; Zeni, G.; Panatieri, R. B.; Lissner, E.; Menezes, P. H.; Braga, A. L.; Stefani, H. A.; *Org. Lett*. **2001**, *3*, 819; Alves, D.; Nogueira, C. W.; Zeni, G.; *Tetrahedron Lett*. **2005**, *46*, 8761.
9. Yue, D.; Yao, T.; Larock, R. C.; *J. Org. Chem*. **2006**, *71*, 62; Yue, D.; Larock, R. C.; *J. Org. Chem*. **2002**, *67*, 1905; Kesharwani, T.; Worlikar, S. A.; Larock, R. C.; *J. Org. Chem*. **2006**, *71*, 2307.
10. Manarin, F. G.; Roehrs, J. A.; Gay, R. M.; Brandao, R.; Menezes, P. H.; Nogueira, C. W.; Zeni, G.; *J. Org. Chem*. **2009**, *74*, 2153.
11. Arvela, R. K.; Leadbeater, N. E.; *Org. Lett*. **2005**, *7*, 2101; LeBlond, C. R.; Andrews, A. T.; Sowa, J. R.; Sun, Y.; *Org. Lett*. **2001**, *3*, 1555.
12. *General procedure for the cross-coupling reaction*: To a solution of appropriate 3-iodo-2-(methylthio)Benzo[*b*]furan (0.5 mmol) in DMF (4.0 mL) and H_2O (0.4 mL) was added to $Pd(PPh_3)_4$ (0.011g, 2 mol%) and K_2CO_3 (1 mmol), under argon. After this time, boronic acid (0.75 mmol) was added. The mixture was then heated at 100 °C during 1-4 h, cooled to room temperature, diluted with dichloromethane (20 mL), and washed with brine (2 × 20 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel using hexane/ethyl acetate as eluent. *Selected spectral and analytical data for 2-(methylthio)-3-phenylBenzo[b]furan* ***3a****:* Yield: 0.111 g (93%). ^{1}H NMR: $CDCl_3$, 400 MHz, δ (ppm): 7.61-7.59 (m, 3H), 7.50-7.46 (m, 3H), 7.37 (t, *J* 7.3 Hz, 1H), 7.29 (t, *J* 7.3 Hz, 1H), 7.23 (dd, *J* 7.5 Hz and *J* 2.5 Hz, 1H), 2.52 (s, 3H). ^{13}C NMR: $CDCl_3$, 100 MHz, δ (ppm): 155.9, 147.5, 131.8, 129.1, 128.5, 128.3, 127.4, 124.4, 122.9, 122.5, 119.7, 110.8, 16.9. MS (EI, 70 eV) *m/z* (relative intensity): 238 (26), 222 (17), 194 (100), 163 (23), 151 (10), 76 (8). Anal. (%) Calc. for $C_{15}H_{12}OS$: C 74.97, H 5.03. Found: C 75.15, H 5.39.

Submitted: February 4, 2010
Published online: May 11, 2010