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Palladium-catalyzed cross-coupling reaction of alkenyl aluminums with 2-bromobenzo[*b*]furans†

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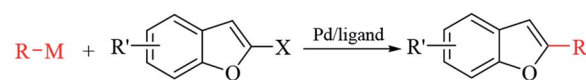
Highly efficient and simple cross-coupling reactions of 2-bromobenzo[*b*]furans with alkenylaluminum reagents for the synthesis of 2-alkenylbenzo[*b*]furan derivatives using PdCl₂ (3 mol%)/XantPhos (6 mol%) as catalyst are reported. Excellent yields (up to 97%) were obtained for a wide range of substrates at 80 °C for 4 h in DCE.

2-Substituted benzo[*b*]furans are important structural scaffolds found in many natural products and pharmaceutical products.¹ Some of these compounds have been known to exhibit anti-inflammatory,² antitumor,³ anticancer,⁴ and anti-fungal,⁵ antiplasmodial,⁶ antioxidant,⁷ anti-HIV,⁸ and estrogenic activities.⁹ In addition, they serve as building blocks for many organic transformations.¹⁰ Thus, their synthesis and applications have attracted considerable attention in the chemical and pharmaceutical industries over the past decades.¹¹ Until now numerous effective synthetic methodologies of synthesis 2-substituted benzo[*b*]furans have been reported.^{12,13} Among these methods hitherto developed, the metal-catalyzed 2-halobenzo[*b*]furans coupling with organometallic nucleophiles is one of the most effective methods (Scheme 1).¹³ However, in most cases generally suffer from one or more drawbacks such as requirement co-catalyst like Cu salts, limited substrate scope, high catalyst loading, high temperature and poor chemoselectivity *etc.* Therefore, the development of more efficient and atom economical approaches for the preparation of 2-substituted benzo[*b*]furans remains as desirable work. Previous studies show that organoaluminum reagents are highly efficient nucleophiles for cross-coupling reactions with aromatic halides¹⁴ or benzylic halides,¹⁵ and the investigations have demonstrated that palladium is a good catalytic metal.¹⁶

At present, a variety of methods have been developed to prepare compounds containing olefin functional groups through hydrocarbon activation of olefins.¹⁷ To continue our effort to develop coupling reactions using reactive organoaluminum reagents,¹⁸ we herein report a palladium(II)-catalyzed, base free cross-coupling reactions of 2-bromo benzo[*b*]furans with alkenylaluminum reagents at 80 °C in short reaction time with good to excellent isolated yields for 2-alkenyl

benzo[*b*]furans. The process was simple and easily performed, and it provides an efficient method for the synthesis of 2-alkenyl benzo[*b*]furans derivatives. Notably, in our procedure palladium is used as the single catalyst and base free.

Our initial studies used 2-bromo-6-methoxybenzo[*b*]furan (**2e**) with diethyl(oct-1-enyl)aluminum (**1a**) as model substrates. Treatment of compound **2e** with the alkenylaluminum (**1a**) using PdCl₂ (3 mol%)/XantPhos (6 mol%) as catalyst in toluene at 60 °C for 4 h, the coupled product 6-methoxy-2-(oct-1-enyl) benzo[*b*]furan (**3ae**) was obtained in 46% isolated yield (Table 1, entry 1). However, when using other palladium catalysts, such as Pd(OAc)₂ and Pd(acac)₂ the yield is lower than that of palladium dichloride (Table 1, entries 2 and 3). Some bases were investigated to further improve the yield of coupled products (**3ae**). When Et₃N was used as a base, the reaction of compound **2e** with alkenylaluminum (**1a**) produced the coupled product (**3ae**) with a 27% isolated yield only (Table 1, entry 4). While, the coupled product (**3ae**) could not obtain when K₂CO₃ and TMEDA were used as base (Table 1, entries 5 and 6). To further understand the nature of this catalysis, we tested the cross-coupling reaction of **1a** with **2e** under various solvents and the results revealed that DCE was the solvent of choice (Table 1, entry 9). In hexane or THF, the isolated yield of the coupled product (**3ae**) was low efficient (Table 1, entries 7 and 8). To our delighted, the isolated yield of the coupled product (**3ae**) increased from 74% to 85% when the reaction temperature was increased from 60 °C to 80 °C (Table 1, entries 9 and 10). Interestingly, the isolated yield of the coupled product (**3ae**) was almost unchanged when the alkenylaluminum loading was decreased from 1.0 mmol to 0.8 mmol (Table 1, entries 10 and



M = Bi, Sn, B; R = (hetero)aryl; X = Br, I.

High catalyst loading, high temperature and limited substrate scope.

Scheme 1 Palladium-catalyzed cross-coupling reactions of 2-halobenzo[*b*]furans derivatives with organometallic nucleophiles.

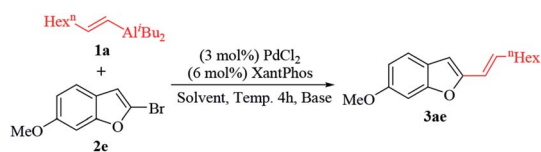
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Table 1 The cross-coupling reaction of diethyl(oct-1-enyl) aluminum (**1a**) with 2-bromo-6-methoxybenzo[*b*]furan (**2e**) catalyzed by palladium^a



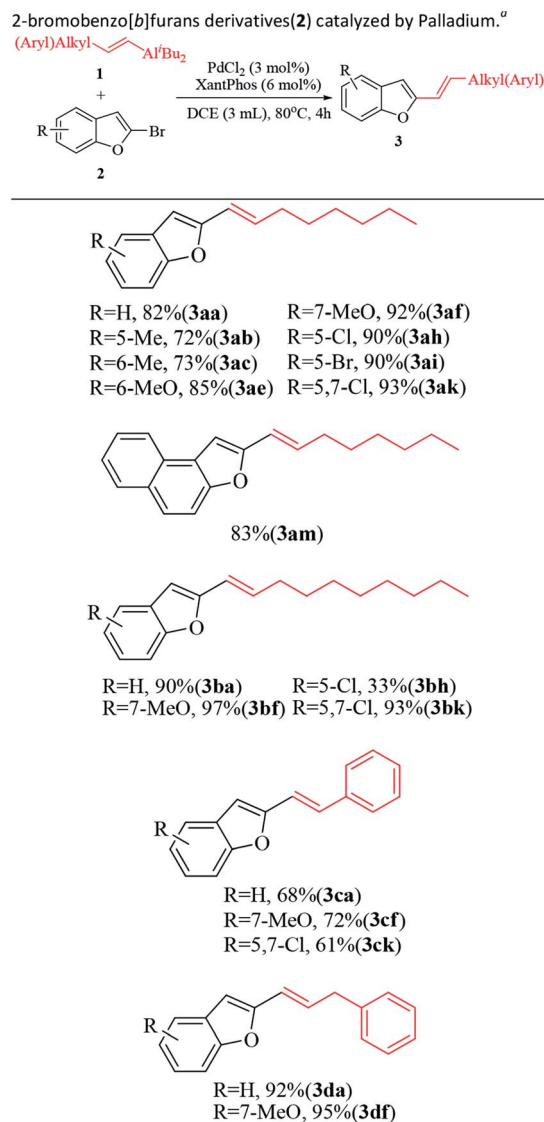
| Entry | Pd salt. | 1a (equiv.) | Base (<i>x</i> equiv.) | Solvent | 3ae ^b yield (%) |
|-------------------|-----------------------|-----------------------|--------------------------------------|---------|--------------------------------------|
| 1 | PdCl ₂ | 1.0 | — | Toluene | 46 |
| 2 | Pd(OAc) ₂ | 1.0 | — | Toluene | 19 |
| 3 | Pd(acac) ₂ | 1.0 | — | Toluene | 10 |
| 4 | PdCl ₂ | 1.0 | Et ₃ N (2.0) | Toluene | 27 |
| 5 | PdCl ₂ | 1.0 | K ₂ CO ₃ (2.0) | Toluene | NR |
| 6 | PdCl ₂ | 1.0 | TMEDA (2.0) | Toluene | NR |
| 7 | PdCl ₂ | 1.0 | — | Hexane | 47 |
| 8 | PdCl ₂ | 1.0 | — | THF | 51 |
| 9 | PdCl ₂ | 1.0 | — | DCE | 74 |
| 10 ^c | PdCl ₂ | 1.0 | — | DCE | 85 |
| 11 ^c | PdCl ₂ | 0.8 | — | DCE | 84 |
| 12 ^c | PdCl ₂ | 0.6 | — | DCE | 53 |
| 13 ^{c,d} | PdCl ₂ | 0.8 | — | DCE | 49 |

^a **1a**/2a/PdCl₂/XantPhos = 1.0/0.5/0.03/0.06 mmol, 60 °C, 3 mL solvent, 4 h, Ar₂. ^b Isolated yield of **3ae**. ^c 80 °C. ^d **1a**/2a/PdCl₂/XantPhos = 0.8/0.5/0.02/0.04 mmol.

11). However, the isolated yield of the coupled product (**3ae**) is 53% only when the alkenylaluminum loading was decreased from 0.8 mmol to 0.6 mmol (Table 1, entries 11 and 12). Further studies indicated that the catalyst loading dramatically influenced the isolated yield of the coupled product (**3ae**). It was found that the most favorable catalyst loading is 3 mol% PdCl₂/6 mol% XantPhos (Table 1, entry 11). Extensive screening showed that the optimized coupling conditions were 3 mol% PdCl₂/6 mol% XantPhos, 0.8 mmol **1a**, 0.5 mmol **2e** in DCE at 80 °C for 4 h (Table 1, entry 11).

Under the optimized conditions, coupling reactions of aliphatic alkenylaluminum reagents, such as di-*sec*-butyl(oct-1-enyl)aluminum (**1a**) and di-*sec*-butyl(dec-1-enyl)aluminum (**1b**), proceed with electron-neutral, electron rich and electron-deficient 2-bromo benzo[*b*]furans derivatives affording the products in good yields (Table 2, **3(ae–ak)**, **3(ba–bk)**). For example, 2-bromobenzo[*b*]furans containing methyl and methoxy affording the corresponding coupled products in 72–97% isolated yields (Table 2, **3(ab–af)**, **3bf**). 2-Bromobenzo[*b*]furans containing chloro and bromo groups affording the corresponding coupled products in 33–95% isolated yields (Table 2, **3(ah–ak)**, **3(bh–bk)**). Interestingly, 5,7-dichloro-2-bromobenzo[*b*]furan affording the corresponding coupled products (**3ak**) and (**3bk**) in 93% and 93% isolated yields, respectively (Table 2). Furthermore, the 2-bromonaphtho[2,3-*b*]furan was also produced the 2-(oct-1-enyl)naphtho[2,1-*b*]furan (**3am**) with isolated yield of 83% (Table 2). Besides aliphatic alkenylaluminums, aromatic alkenyl aluminums such as di-*sec*-butyl(styryl)aluminum (**1c**) and di-*sec*-butyl(3-

Table 2 The cross-coupling reaction of alkenylaluminums (**1**) with 2-bromobenzo[*b*]furans derivatives (**2**) catalyzed by palladium^a

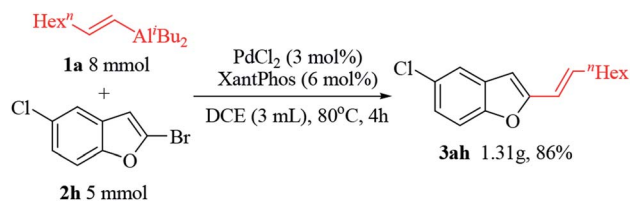


^a **1**/2/PdCl₂/XantPhos = 0.8/0.5/0.03/0.06 mmol, 80 °C, 4 h. Isolated yield of **3**, two runs.

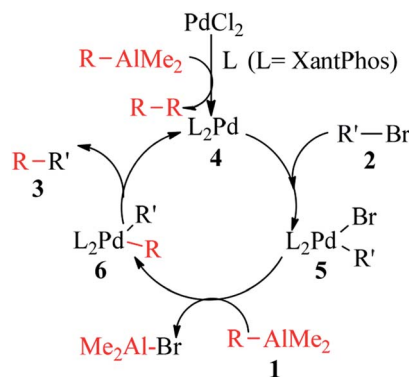
phenylprop-1-enyl)aluminum (**1d**) also reacted smoothly to afford satisfactory isolated yields (61–95%) (Table 2, **3(ca–ck)**, **3(da,df)**). Importantly, the coupling reactions with 2,5-dibromo benzo[*b*]furan, 2-bromo-5-chloro-benzo[*b*]furan and 2-bromo-5,7-dichlorobenzo[*b*]furan reacted regioselectivity at 2-position affording the corresponding 2-nylbenzo[*b*]furans derivatives in 33–95% isolated yields (Table 2, **3(ah–ak)**, **3(bh, bk)**, **3ck**). At the same time, the dehalogenation was not observed in the cross-coupling with 2-bromobenzo[*b*]furans derivatives containing halogen-substituents (Table 2, **3(ah–ak)**, **3(bh, bk)**, **3ck**).

The reaction was also found to be effective in gram-scale synthesis, which indicated its potential for practical





Scheme 2 Preparative scale synthesis of compound 3ah.



Scheme 3 The proposed mechanism for the formation of coupled product 3.

application (Scheme 2). 2-Substituted benzo[*b*]furans derivatives **3ah** was synthesized in 1.31 gram using this methodology.

In order to further explore the reaction mechanism, control experiments were carried out (see the ESI[†]). We performed the reaction between 2-bromobenzo[*b*]furan (**2a**, 0.5 mmol) with di-*sec*-butyl(oct-1-enyl)aluminum (**1a**, 0.8 mmol) in the presence of PdCl₂ (3 mol%)/XantPhos (6 mol%) in DCE at 80 °C for 4 h. The reaction mixture was analyzed by ³¹P NMR, it was found that the characteristic peak of ³¹P NMR appeared around at 22.98 ppm and 30.98 ppm. However, ³¹P NMR peak of pure XantPhos is -18.03 ppm. The results show that XantPhos work as a ligand of the palladium center. Thus, a proposed possible reaction mechanism for the cross-coupling reaction is shown in Scheme 3. The first step is the oxidative addition of 2-bromobenzo[*b*]furans (**2**) to Pd(0) phosphine complex (**4**) (which in turn from PdCl₂ and RAlMe₂ (**1**) reagents) to form the organopalladium(II) bromide intermediate (**5**). Transmetalation of RAlMe₂ (**1**) with complex **5** gives R'Pd(II) intermediate (**6**) and Me₂AlBr. Finally, complex **6** under goes reductive elimination to afford the desired coupling product of 2-alkenylbenzo[*b*]furans (**3**) and regenerate the active Pd(0) species for the next catalytic cycle.

Conclusions

A palladium-catalyzed the cross-coupling reactions of 2-bromobenzo[*b*]furans derivatives with alkenylaluminum reagents is reported. The cross-coupling reactions of aliphatic and aromatic alkenylaluminum reagents proceed with electron-neutral, electron rich and electron-deficient 2-bromobenzo[*b*]furans derivatives affording the coupled products 2-alkenyl benzo[*b*]furans in 33–97% isolated yields. More importantly, the reaction was found to be effective in gram-scale synthesis,

and can be utilized as precursors for the synthesis of important bioactive compounds. The methodology provides useful procedure for the synthesis of 2-alkenylbenzo[*b*]furans derivatives. The coupling reactions with 2-bromo-5,7-dichlorobenzo[*b*]furan reacted regioselectivity at 2-position furnishing the corresponding 2-substituted benzo[*b*]furans derivatives in good yields. Further studies on the application of this catalytic system to synthesis of bioactive compounds are currently under way.

Experimental

Melting points were determined with an XRC-1 micro melting point apparatus and uncorrected. ¹H and ¹³C NMR spectra were recorded using a Varian 400 MHz spectrometer in CDCl₃ with tetramethylsilane as internal standard. HRMS were recorded on a Bruker Micro TOF spectrometer equipped with an ESI ion source. Analytical thin-layer chromatography (TLC) was performed on silica 60F-254 plates. Flash column chromatography was carried out on silica gel (200–400 mesh). All reactions were carried out under an Argon gas atmosphere. The starting material 2-bromo benzo[*b*]furans was prepared according to literature.¹⁹ Alkenylaluminum reagents were prepared according to literature.^{15a} Chemical reagents and solvents were purchased from Adamas-beta, Aldrich and XPKchem, and were used without further purification with the exception of these reagents: THF, hexane and toluene were distilled from sodium in nitrogen, and DCE was distilled from CaH₂. Other reagents were commercially available and used as received.

General producer for cross-coupling of 2-bromobenzo[*b*]furans with alkenylaluminum reagents

Under an atmosphere of Argon gas, PdCl₂ (2.6 mg, 0.015 mmol), XantPhos (17.4 mg, 0.015 mmol), 2-bromobenzo[*b*]furans (98.0 mg, 0.5 mmol) and DCE (3 mL) were mixed in a Schlenk flask. Shortly afterwards, a solution of alkenylaluminums (0.8 mmol) was added with a syringe pump. At the end of the addition, the reaction mixture stirring was continued for 4 h at 80 °C. After completion the reaction, the mixture was diluted with 1 N aqueous HCl solution (10 mL) and extracted with EA (3 × 15 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and evaporated *in vacuo*. The residue was subjected to flash column chromatography on silica gel (hexane gradient) to afford the corresponding products.

(E)-1-(Benzofuran-2-yl)oct-1-en-3-one(3aa).^{12e} Colourless liquid; yield: 0.099 g (82%), ¹H NMR (400 MHz, CDCl₃, ppm) δ: 7.47 (dd, *J* = 7.9, 24.9 Hz, 2H), 7.27–7.17 (m, 2H), 6.56–6.46 (m, 2H), 6.34 (d, *J* = 15.8 Hz, 1H), 2.27 (q, *J* = 7.1 Hz, 2H), 1.57–1.49 (m, 2H), 1.41–1.28 (m, 6H), 0.96–0.89 (m, 3H). ¹³C NMR (101 MHz, CDCl₃, ppm) δ: 155.3, 154.6, 134.0, 129.2, 123.9, 122.6, 120.6, 118.6, 110.7, 102.6, 33.0, 31.7, 29.0, 28.9, 22.6, 14.1.

Conflicts of interest

The authors declare no competing financial interest.



Acknowledgements

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