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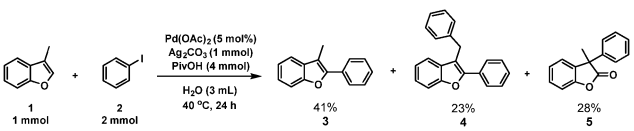
Palladium-catalyzed bisarylation of 3-alkylbenzofurans to 3-arylalkyl-2-arylbenzofurans on water: tandem C(sp^3)–H and C(sp^2)–H activation reactions of 3-alkylbenzofurans†

Beom Shin Cho and Young Keun Chung*

A protocol involving facile sequential C(sp^3)–H and C(sp^2)–H activation reactions of 3-alkylbenzofurans catalyzed by $Pd(OAc)_2$ in the presence of pivalic acid, silver salt, and tricyclohexylphosphine 'on water' was developed. Aryl iodides were used as substrates in a tandem bisarylation reaction to generate 3-arylalkyl-2-arylbenzofurans in moderate to high yields at room temperature. The reaction revealed in this study is a rare example of consecutive C(sp^3)–H and C(sp^2)–H bond activation under mild reaction conditions.

Benzo[*b*]furan derivatives are an important class of biologically active oxygen-containing heterocyclic compounds.[1] The 2-phenyl-3-alkylbenzofuran moiety is found in biologically active natural products exhibiting a broad range of biological and pharmacological activities.[2–4] Natural products represent a significant source of inspiration for the design of structural analogues with improved pharmacological profiles.[5] Thus, this desirable biological activity of naturally occurring 2-phenyl-3-alkylbenzofurans stimulated our interest in the synthesis of 2-aryl-3-alkylbenzofurans. Various synthetically viable procedures have been used for the construction of 2,3-disubstituted benzofurans.[6–10] The most common strategies utilized are transition-metal-catalyzed intra/intermolecular annulations[6] and modification of pre-functionalized benzofurans.[7] Direct arylation of 2- or 3-substituted benzofurans with aryl halides[8,9] and oxidative dehydrogenative cross-coupling reactions of benzofuran with benzene derivatives[10] have also been documented. Conceptually, 2-aryl-3-alkylbenzofurans can be obtained from 2-arylbenzofurans. However, C3-alkylation of 2-arylbenzofurans has not yet been reported. Moreover, no systematic study of the direct C2 arylation of 3-alkylbenzofurans with aryl halides has been presented to date. Thus, we evaluated the direct C2 arylation of 3-alkylbenzofurans and discovered the sequential C(sp^3)–H and C(sp^2)–H activation (or a double C–H activation) of 3-alkylbenzofurans in the presence of a palladium catalyst in (on) water to give 3-arylalkyl-2-arylbenzofurans. Achieving the selective activation of a C(sp^3)–H bond in the presence of a competitive C(sp^2)–H bond is considered to be a formidable challenge. To the best of our knowledge, the present study represents the first example of a metal-catalyzed difunctionalization (bisarylation) of benzofuran *via* the activation of a C(sp^3)–H bond and an aryl C(sp^2)–H bond. Preliminary data for this novel finding are presented herein, where double activation of unactivated C(sp^3)–H and C(sp^2)–H bonds in a single step is achieved on water. Thus, a mild and eco-friendly reaction for the bisarylation of 3-alkylbenzofuranes was discovered.



(1)

Initially, the reaction of 3-methylbenzofuran (**1**) with iodobenzene (**2**) to afford the C-2 arylated product, 3-methyl-2-phenylbenzofuran (**3**), "on water" was chosen as the model reaction in the presence of $Pd(OAc)_2$ (5 mol%), Ag_2CO_3 (1 mmol), and PivOH (4 mmol) at 40 °C (eqn (1)).[11] However, the reaction of **1** with **2** afforded a mixture of 3-methyl-2-phenylbenzofuran (**3**), 3-benzyl-2-phenylbenzofuran (**4**),[12] and 3-methyl-3-phenylbenzofuran-2(3*H*)-one (**5**)[13] in 41%, 23%, and 28% yields, respectively. Although the expected product **3** was obtained in 41% yield, a bisarylation product **4** was also isolated in 23% yield. Moreover, furanone **5**, another unexpected compound, was obtained in 28% yield. The observed formation of the bisarylation product **4** was very unusual because a tandem C(sp^3)–H and C(sp^2)–H activation reaction is rare. Several years ago, tandem (sequential) sp^3 C–H and sp^2 C–H activations were reported by Sames and coworkers and by White and coworkers.[14] Encouraged by the above observation, the reaction conditions for the bisarylation of benzofurans were optimized. Screening of the amount of PivOH, Ag_2CO_3, $Pd(OAc)_2$, and iodobenzene was utilized to maximize the yield of **4** (see Table S1 in the ESI†). From these optimization studies, a mixture of 1 mmol of

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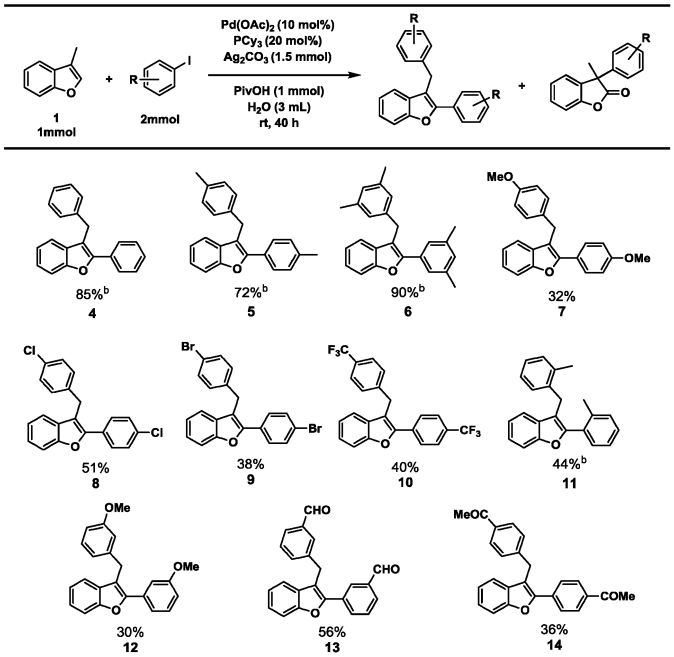
Table 1 Scope of iodobenzenes[a]



[a] **1** (1 mmol), iodobenzene (2 mmol), $Pd(OAc)_2$ (10 mol%), PCy_3 (20 mol%), Ag_2CO_3 (1.5 mmol), PivOH (1 mmol), and H_2O (3 mL) at room temperature for 40 h. Yields are of isolated products. [b] Isolated yields of a pre-stirred solution. PCy_3 = tricyclohexylphosphine. PivOH = pivalic acid.

3-methylbenzofuran, 2 mmol iodobenzene, 10 mol% $Pd(OAc)_2$, 20 mol% PCy_3, 1.5 mmol Ag_2CO_3, and 1 mmol PivOH at room temperature, and 40 h of reaction time provided the maximum yield of **4** of 85% yield (a pre-stirred solution of $Pd(OAc)_2$ and PCy_3 was used as the catalyst). To confirm the advantages of this catalyst system, $Pd(OAc)_2$ was used as a homogeneous catalyst under the same conditions in different organic solvents, such as DMF (**4**: 2%; **5**: 5%), dichloromethane (**4**: 29%; **5**: 3%), toluene (**4**: 21%; **5**: 5%), THF (**4**: 8%; **5**: trace), and MeOH (**4**: 58%, **5**: 3%). Thus, the activation of the C–H bond by the Pd catalyst system was less efficient in organic solvents than on water under the optimized conditions.

After optimization of the reaction conditions, the substrate scope of the reaction was examined (Table 1). 3-Methylbenzofuran was found to react smoothly with iodobenzene derivatives to afford the bisarylated products in moderate to excellent yields. For the reaction with iodobenzene (**4**), 1-iodo-4-methylbenzene (**5**), or 1-iodo-3,5-dimethylbenzene (**6**), a pre-stirred solution of $Pd(OAc)_2$ and PCy_3 was used as catalyst system, resulting in high yields (85%, 72%, and 90% yield, respectively) of the bisarylated products. However, the use of the pre-stirred catalytic solution did not produce the best yield for other aryl iodides (see the ESI†). Gratifyingly, a broad functional compatibility was observed among the aryl iodides. Br and Cl substitutions (**8**, **9**) were both tolerated. *p*-Bromo(iodo)benzene was selectively phenylated at the iodo moiety. Electron-donating (**5**, **6**, **7**, **11**, **12**) as well as electron-withdrawing substituents (**8**, **9**, **10**, **13**, **14**) were tolerated under the given reaction conditions. The yield of the reaction was not significantly affected by the electronic effects of the iodobenzene

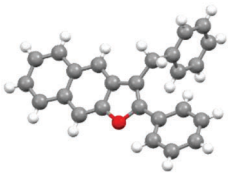
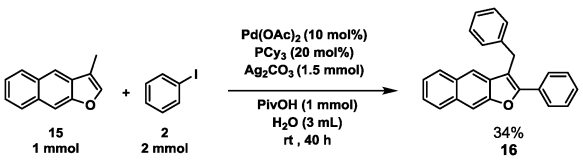


Fig. 1 X-ray structure of **16**.

derivatives. However, a steric effect was observed in the reaction with 2-tolyl iodides (**11**). In the case of 3-iodobenzonitrile, a mono-arylation (C-2 arylated) product was observed predominantly.

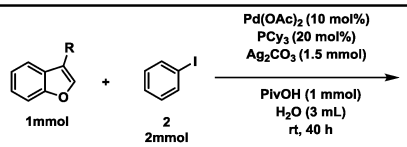
The reaction can be extended to a naphtho[2,3-*b*]furan (**15**) although the yield (34%) of bisarylation products was not high (eqn (2)). The formation of a bisarylated product was confirmed by an X-ray diffraction study (Fig. 1).[15]

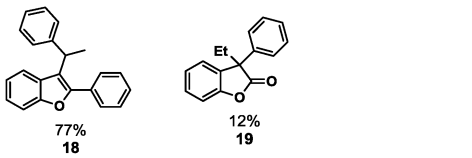
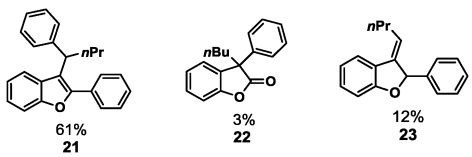
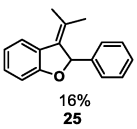
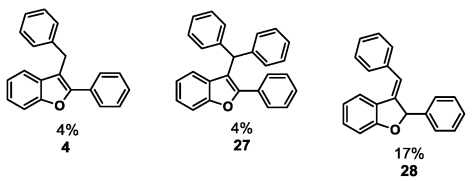


(2)

Although cascade C–H activation reactions of simple aliphatic substrates leading to complexity have rarely been observed,[16] the sequential sp^3 and sp^2 double C–H activation reactions of 3-methylbenzofuran with iodobenzene derivatives were quite common under the present reaction conditions. The bisarylation of other 3-alkylbenzofurans with iodobenzene was also investigated (Table 2). The reaction of 3-ethylbenzofuran yielded 2-phenyl-3-(1-phenylethyl)benzofuran (**18**) and 3-ethyl-3-phenylbenzofuran-2(3*H*)-one (**19**) in 77% and 12% yields, respectively. Compared to the case of 3-methylbenzofuran, the yield of the product derived from the sequential C(sp^3)–H activation and C(sp^2)–H activation reactions declined slightly, presumably due to the steric hindrance. This reaction also exhibited excellent site selectivity for the methylene group over the methyl group. Interestingly, the site selectivity observed herein was quite different from that in alkyl arenes reported by Curto and Kozlowski.[17] In the reaction of 3-*n*-butylbenzofuran with iodobenzene, 2-phenyl-3-(1-phenylbutyl)benzofuran (**21**), 3-*n*-butyl-3-phenylbenzofuran-2(3*H*)-one (**22**), and 3-butylidene-2,3-dihydrobenzofuran (**23**) were isolated in 61%, 3%, and 12% yields, respectively. The 3-benzylidene-2,3-dihydrobenzofuran skeleton was previously reported in the base-mediated cyclization of *o*-alkynylphenyl ether.[18,19] The appearance of the dihydrobenzofuran derivative may possibly be due to the steric congestion at the butyl group. In contrast, the reaction of 3-isopropylbenzofuran with iodobenzene yielded neither a doubly arylated product nor a lactone. Instead, 3-(dimethylmethylene)-2-phenyl-2,3-dihydrofuran (**25**) was isolated in 16% yield. The bisarylated product was not formed, presumably due to the steric congestion at the isopropyl group. In the reaction of 3-benzylbenzofuran with iodobenzene, 3-benzylidene-2-phenyl-2,3-dihydrobenzofuran (**28**) was isolated in 17% yield as one of the major isolable products. Moreover, 3-benzyl-2-phenylbenzofuran (**4**) and 3-benzhydryl-2-phenylbenzofuran (**27**) were both obtained in 4% yield. 3-Benzylidene-2-phenyl-2,3-dihydrobenzofuran and

Table 2 Bisarylation of 3-alkylbenzofuran derivatives[a]

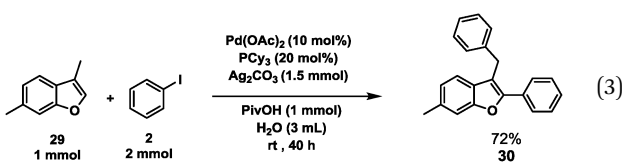


Starting material	Products
R = Et (**17**)	
R = *n*Bu (**20**)	
R = iPr (**24**)	
R = Bn (**26**)	

[a] 3-Alkylbenzofuran (1 mmol), **2** (2 mmol), $Pd(OAc)_2$ (10 mol%), PCy_3 (20 mol%), Ag_2CO_3 (1.5 mmol), PivOH (1 mmol), H_2O (3 mL) at room temperature for 40 h. Yields are of isolated products.

3-benzyl-2-phenylbenzofuran were both derived from monoarylation. 3-Benzhydryl-2-phenylbenzofuran was derived from C(sp^3)–H activation of the benzyl group and C(sp^2)–H activation of the furan moiety, although activation of methylene C(sp^3)–H bonds is quite rare.[20] In addition to these products, several intractable side-products were also formed. No lactone formation was observed.

Thus, when the 3-position of benzofuran was substituted with Me, Et, or *n*Bu, the corresponding bisarylated product was isolated as the major product, whereas substitution of this position with iPr or Bn predominantly yielded the monoarylated product. The differences in the reactivities may be related to the feasibility of generating a π-allyl intermediate.

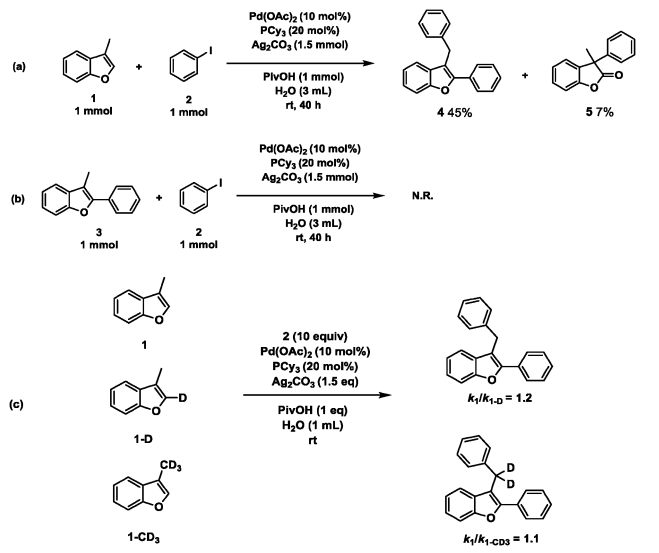


(3)

We studied the bisarylation of substituted 3-methylbenzofuran under the optimized reaction conditions (eqn (3)). When a 3,6-dimethylbenzofuran (**29**) was utilized, the corresponding bisarylated product (**30**) was isolated in 72% yield. However, the use of 6-methoxy-3-methylbenzofurans failed to give the bisarylated product (not shown here). Thus, the bisarylation was highly sensitive to the electronic effect of the substituent on the 6-position.

Control experiments were performed to gain insight into the reaction mechanism (Scheme 1). When 3-methylbenzofuran was reacted with 1 equiv. of iodobenzene, **4** was isolated in 45% yield based on 3-methylbenzofuran (90% based on iodobenzene) and **5** was isolated in 7% yield (Scheme 1a). Neither 3-benzylbenzofuran nor 3-methyl-2-phenylbenzofuran was observed. Thus, it appears that the two reactions, the arylation reactions *via* C(sp^3)–H activation and C(sp^2)–H activation, may occur almost simultaneously. No reaction was observed for the use of 3-methyl-2-phenylbenzofuran (**3**) (Scheme 1b). These observations suggested that the formation of 3-benzyl-2-phenylbenzofuran from 3-methylbenzofuran did not occur *via* 3-methyl-2-phenylbenzofuran. Moreover, the C–H activations appeared to proceed by a sequence initiated by C(sp^3)–H activation and followed by C(sp^2)–H activation. Selective activation of the C(sp^3)–H bond over the C(sp^2)–H bond was reported by Takemoto *et al.*,[21] whereas in the Pd-catalyzed C(sp^3)–H activation/amidation reaction of carbamoyl chloride precursors, they observed selective benzylic C(sp^3)–H activation despite the presence of the C(sp^2)–H bond of naphthalene in the substrate. According to Fu's mechanistic study,[22] the selective C(sp^3)–H activation was due to the higher acidity of the benzylic C(sp^2)–H group in comparison to that of the naphthalene C(sp^2)-H group. Two deuterated compounds (**1-D** and **1-CD$_3$**) were prepared and their kinetic isotope effects (KIEs) were measured (Scheme 1c): the KIE values for $k_1/k_{\mathbf{1\text{-}D}}$ and $k_1/k_{\mathbf{1\text{-}CD_3}}$ were 1.2 and 1.1, respectively, suggesting that the C–H bond breaking event was not rate-limiting.[17,23] Moreover, a parallel experiment with **1** and **1-CD$_3$** revealed that the deuterated analogue proceeded 1.5 times slower, indicating that the C–H activation step might be reversible (see the ESI†).

In conclusion, we have demonstrated that a consecutive bisarylation of 3-alkylbenzofurans occurs in the presence of $Pd(OAc)_2$, Ag_2CO_3, and PivOH on water at room temperature. The reaction



Scheme 1 Control experiments.

revealed in the study is a rare example of consecutive C(sp^3)–H and C(sp^2)–H bond activation under mild reaction conditions. The mild reaction conditions permit a broad set of functionalities in the aryl iodide unit to be tolerated, and a variety of novel compounds were successfully prepared in good yields. Thus, the one-pot, mild, and eco-friendly process may provide a powerful synthetic tool to access the synthesis of 3-arylalkyl-2-arylbenzofurans.

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