Heterocycle Synthesis

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Palladium-Catalyzed Synthesis of Benzofurans and Coumarins from Phenols and Olefins**

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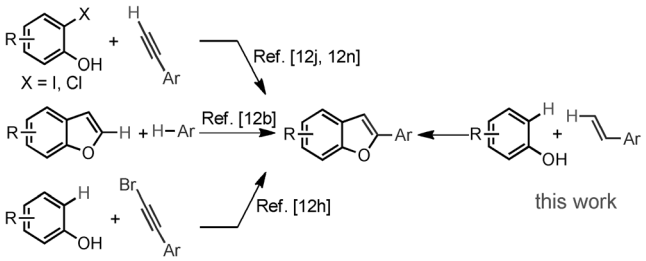
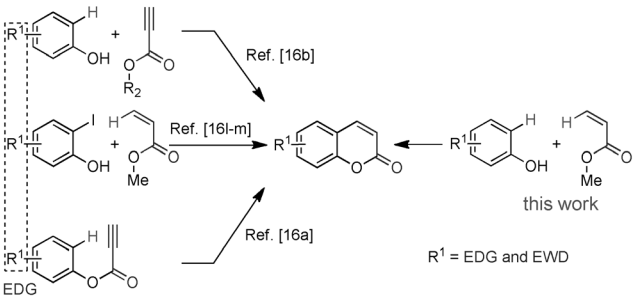
Benzofuran derivatives are ubiquitous in natural products,[1] agrochemicals,[2] pharmaceuticals,[3,4] and organic materials.[5] Particularly, 2-arylbenzofurans are widely distributed in nature,[6] and possess a number of biological activities.[4b,7] Over the years, several effective strategies involving transition-metal-catalyzed[8] inter[9]/intramolecular[10] heteroannulation reactions have been reported for synthesizing benzofuran scaffolds.[11] However, synthesis of 2-substituted benzofuran[12] by simply reacting phenol and an unactivated olefin has yet to be reported (Scheme 1).



Scheme 1. Synthesis of 2-arylbenzofurans via C–H activation (select examples).

Another "privileged scaffold",[13] coumarin, possesses various interesting biological activities.[14] The most common approach for their synthesis is the Pechmann condensation wherein phenol is reacted with a β-ketoester or acid under strongly acidic conditions.[15] Despite having a number of effective alternative methods (mainly for electron-rich phenols),[16] the synthesis of coumarins from phenol and methyl acrylate remains attractive (Scheme 2). Herein, we report a palladium-catalyzed C–O/C–C bond formation sequence between phenol and an olefin for the convenient synthesis of benzofurans and coumarins.

Initial studies revealed that the benzofuran moiety can be synthesized efficiently (94%) from 4-nitrophenol and styrene by a palladium-catalyzed method involving $Pd(OAc)_2$ (10 mol%), 1,10-phenanthroline (20 mol%), $Cu(OAc)_2$ (1 equiv), and NaOAc (3 equiv) in $ClCH_2CH_2Cl$ at 110°C for 24 hours.[17,18] Without NaOAc, the yield of the benzofuran decreases to 43%. First we tested electron-deficient phenols since the synthesis of 2-arylbenzofurans bearing strong-electron withdrawing groups, such as NO_2, CN, CHO, and $COCH_3$, on the benzenoid portion remain intangible.[12a–l] Styrenes having either a *meta* or *para* substituent reacted successfully with 4-nitrophenol to produce the desired product in 55–92% yield (**3a–d**; Table 1). Switching to 4-cyanophenol from 4-nitrophenol did not affect the outcome of the reaction (**3e–j**), and sterically demanding *ortho*-substituted styrenes also produced the expected product in synthetically useful yields (**3f** and **3o**). Halogen-substituted phenols or styrene gave the benzofuran derivative in good yield without any dehalogenation (**3d**, **3h**, **3j**, and **3n**), and carbonyl groups, such as CHO and $COCH_3$, on either coupling partner remained intact under the reaction conditions (**3i, 3k**, and **3l**). Unfortunately, only 30% yield of 2-phenylbenzofuran (**3m**) was obtained under the optimized reaction conditions. In the case of 3-chloro and 3-trifloromethylphenol two regioisomers were formed (**3q** and **3r**). A derivative of vitamin E was also converted into the desired benzofuran product **3zb**. A gram-scale reaction was carried out successfully in 85% yield (**3a**).[17]



Scheme 2. Synthesis of coumarins by C–H functionalization (select examples). EDG = electron-donating group, EWG = electron-withdrawing group.

Next, we focused on the synthesis of naphthofuran since they are found in natural products and in pharmacologically relevant molecules.[19] As expected, 6-bromo-2-phenylnaphthofuran (**3z**; 89%, Table 1) was obtained in excellent yield from the corresponding 6-bromo-2-naphthol. 2-Naphthol also provided naphthofuran in high yield (**3za**; 82%). In spite of possibility of forming regioisomers in both these cases, only one product was exclusively generated.

After evaluating the scope with styrene derivatives, different terminal and internal aliphatic olefins were tested

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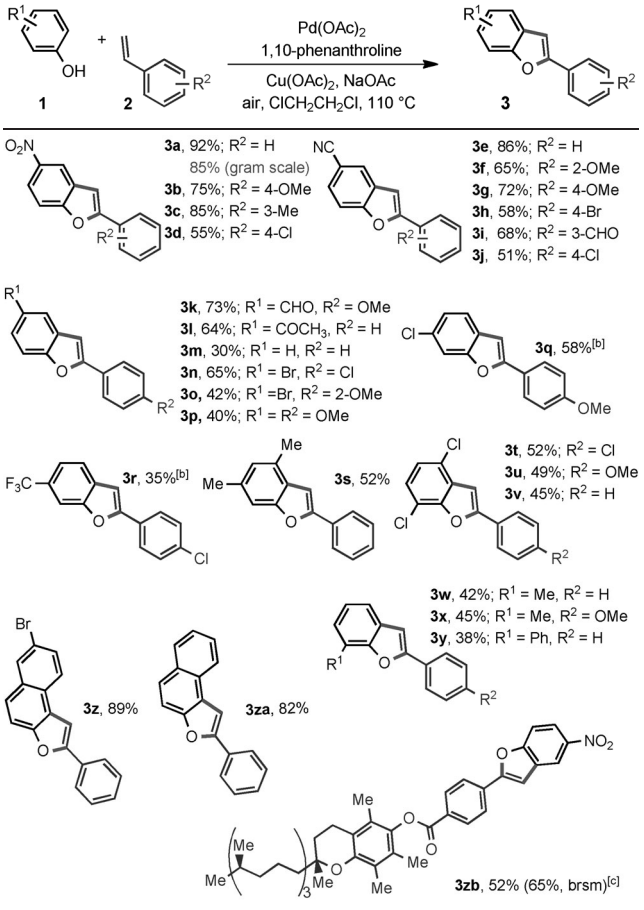
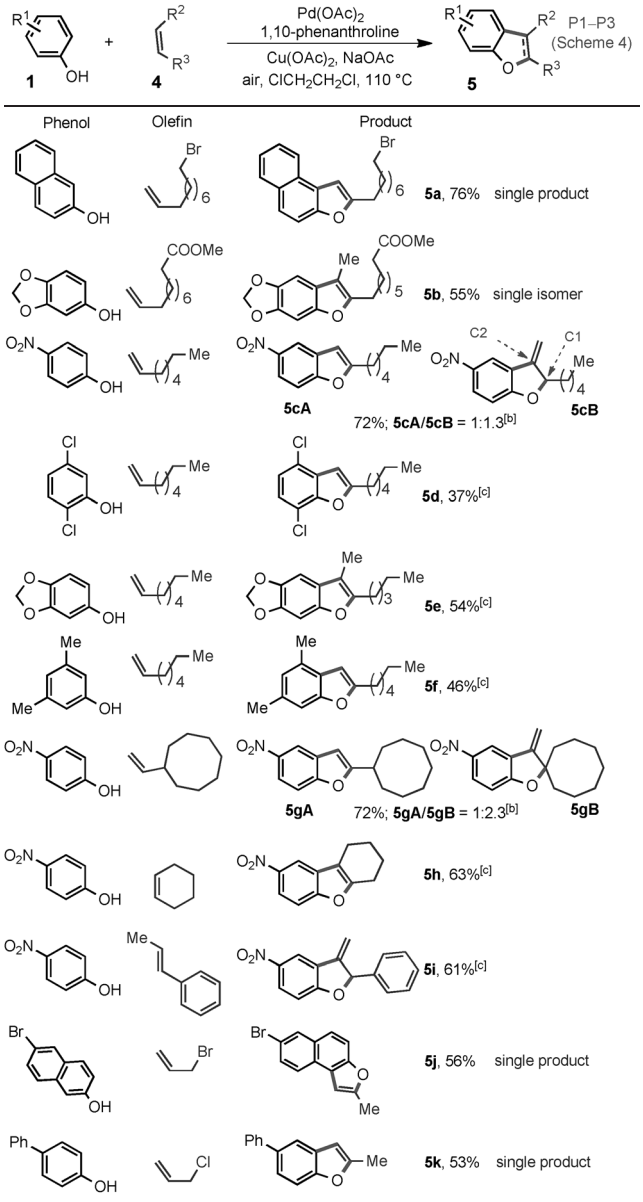
Table 1: Reactions of phenols and styrenes.[a],[17]



[a] Reaction conditions: **1** (1 mmol, 2 equiv), **2** (0.5 mmol, 1 equiv), $Pd(OAc)_2$ (0.05 mmol, 0.1 equiv), 1,10-phenanthroline (0.1 mmol, 0.2 equiv), $Cu(OAc)_2$ (0.5 mmol, 1 equiv), NaOAc (1.5 mmol, 3 equiv), 4 Å molecular sieves (130 mg), $ClCH_2CH_2Cl$ (4 mL), 110 °C for 24 h. Yields are those of the isolated products. [b] Yield of one isolated isomer. Other regioisomer was detected by GC/GC-MS but could not be isolated in pure form. [c] brsm = based on recovered starting material.

Table 2: Reactions of phenols and either terminal or internal olefins.[a],[17]

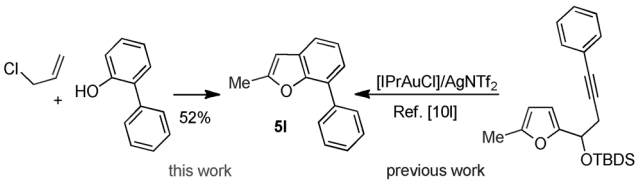


[a] Reaction conditions: **1** (1 mmol, 2 equiv), **4** (0.5 mmol, 1 equiv), $Pd(OAc)_2$(0.05 mmol, 0.1 equiv), 1,10-phenanthroline (0.1 mmol, 0.2 equiv), $Cu(OAc)_2$ (0.5 mmol, 1 equiv), NaOAc (1.5 mmol, 3 equiv), 4 Å molecular sieves (130 mg), $ClCH_2CH_2Cl$ (4 mL), 110 °C for 24 h. Yields are those of the isolated products. [b] **A**/**B** ratio was determined on the basis of GC-MS analysis of the reaction mixture. Isolated compounds were characterized by HRMS, 1D (^{1}H NMR, ^{13}C NMR, and DEPT) and 2D NMR (HSQC, HMBC, COSY, and NOESY) spectroscopy. [c] Other products could not be isolated in pure form.[17]

under optimal reaction conditions (Table 2). Reaction of 10-bromodec-1-ene with 2-naphthol regioselectively provided a single product (**5a**). In the case of simple terminal olefins, for example 1-octene, a 2-substituted benzofuran having an exocyclic double bond at C2 (**5cB**) was observed along with the desired **5cA** (**5cA**/**5cB** = 1:1.3). Similarly, vinylcyclooctane produced the 2-substituted products (**5gA** and **5gB**). In this case **5gB** comprised a spirocyclic compound with an exocyclic double bond at C2. Such spirocyclic compounds are of synthetic and biological interest.[20] A cyclic olefin also resulted in the formation of desired benzofuran product (**5h**). In the case of β-methylstyrene, a compound having an exocyclic double bond was observed as the major product (**5i**). *Ortho*- and *meta*-substituted phenols also resulted in the formation of the desired benzofuran product (**5d** and **5f**). Surprisingly, reaction of sesamol with methyl-10-undecanoate resulted in the 3-methylsubstituted product **5b** exclusively, and a similar 3-methylsubstituted product (**5e**) was also observed with a simple terminal olefin. Note that the present method in conjunction with a previous report[21] will therefore allow the synthesis of unsymmetrical 2,3-disubstitutedbenzofurans.

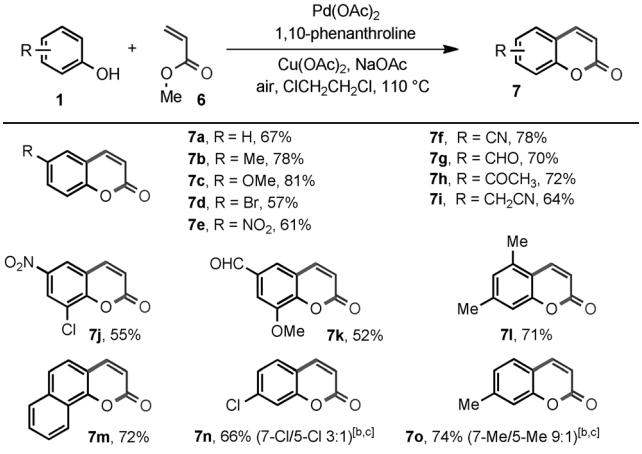
Interestingly, when allyl chloride was treated with 2-phenylphenol, 2-methyl-7-arylbenzofuran was obtained (**5l**; Scheme 3). Such a 7-arylbenzofuran unit is present in a number of biologically active molecules and their direct synthesis from ArOH has previously not been reported.[10l]

Next, we used the optimal reaction conditions in the synthesis of coumarin derivatives by reacting phenol and



Scheme 3. Synthesis of 2-methyl-7-arylbenzofuran. TBDS = *tert*-butyldiphenylsilyl, Tf = trifluoromethanesulfonyl.

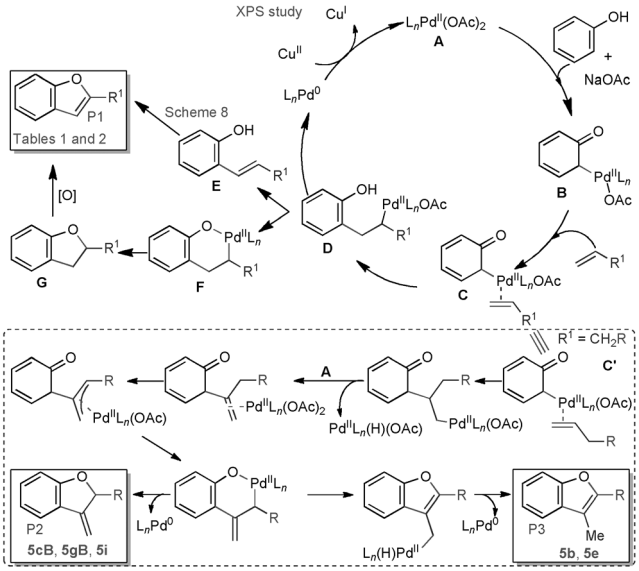
Table 3: Synthesis of coumarins.[a],[17]



[a] Reaction conditions: **1** (1 mmol, 2 equiv), **6** (0.5 mmol, 1 equiv), $Pd(OAc)_2$(0.05 mmol, 0.1 equiv), 1,10-phenanthroline (0.1 mmol, 0.2 equiv),$Cu(OAc)_2$ (0.5 mmol, 1 equiv), NaOAc (1.5 mmol, 3 equiv), 4 Å molecular sieves (130 mg), $ClCH_2CH_2Cl$ (4 mL), 110 °C for 24 h. Yields are those of the isolated products. [b] Ratio was determined on the basis of GC-MS analysis of the reaction mixture. [c] From 3-chlorophenol. [d] From 3-methylphenol.

methyl acrylate (or ethyl acrylate; Table 3). Substituents such as CH_3, OCH_3, Cl, and Br at either the *ortho*, *meta*, or *para* position on a phenol ring produced the corresponding coumarins in good yields (**7b-d, 7i, 7m**, and **7n**). Note that a palladium-catalyzed reaction with alkynoates failed to produce coumarin from both 4-methoxyphenol and 3-methylphenol.[16b] The most important finding of the current catalytic method is the tolerance of various electron-withdrawing functional groups, such as NO_2, CN, CHO, $COCH_3$, and CH_2CN, thus producing the corresponding coumarins in preparatively useful yields (**7e–j**). A disubstituted phenol such as 2-chloro-4-nitrophenol and the natural product vanillin also produced the corresponding coumarins (**7j** and **7k**) under the present reaction conditions. 3,5-Dimethyl phenol was also successfully employed for coumarin synthesis (**7l**), and in the case of unsymmetrical phenols, a regioisomer corresponding to cyclization at the sterically less hindered position is favored (**7n** and **7o**).[12f,22] The current method is also applicable for the synthesis of naphthocoumarin (**7m**) with complete regioselectivity.

Although the exact mechanism is yet to be established, a plausible mechanism is provided in Scheme 4. The *ortho* palladation of phenol can provide the quinone-type moiety **B**.[23] Interaction with an olefin can lead to the species **C** and subsequently **D**, which can undergo reductive elimination to provide 2-hydroxystilbene (**E**).[24] This intermediate **E** may be

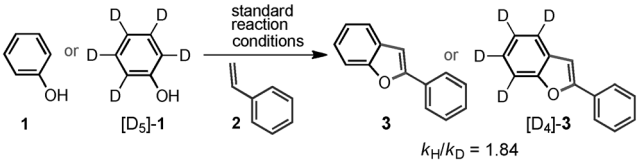


Scheme 4. Plausible mechanism.

converted into the final product (P1, see Tables 1 and 2) under the reaction conditions.[16b] Alternatively, the final product can be produced via **F**. Plausible pathways leading to P2 and P3 (see Table 2) are also depicted in Scheme 4. At present, we cannot explain the reason behind different modes of product formation involving aliphatic olefins (Table 2). Further investigation is planned for a detailed understanding.

The partial order with respect to both 4-nitrophenol and styrene were determined ($k = 8.3 \times 10^{-6}\,M^{0.38}\,s^{-1}$). The reaction is first order in 4-nitrophenol.[17] However, a negative order (−0.38) was established with respect to styrene.[17] Therefore, a side reaction involving styrene is likely to be competing with the desired pathway. The formation of a copper(I) species from $Cu(OAc)_2$ under the reaction conditions was confirmed by X-ray photoelectron spectroscopy (Scheme 4).[17]

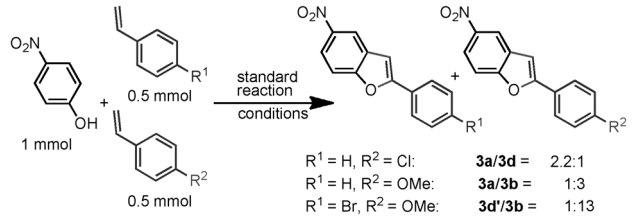
To obtain further insights into the mechanism, rates with PhOH and [D_5]PhOH were studied. A kinetic isotope effect (KIE, k_H/k_D) value of 1.84 was obtained (Scheme 5), thus



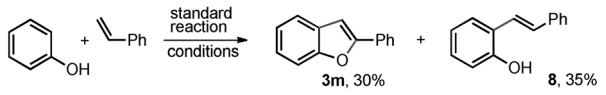
Scheme 5. Kinetic isotope effect.

indicating the probable involvement of the breaking of a phenol C–H bond in the rate-determining step.[17,25,26] Competition experiments with 4-nitrophenol revealed that electron-rich styrenes are favored over neutral and electron-deficient styrenes (Scheme 6).

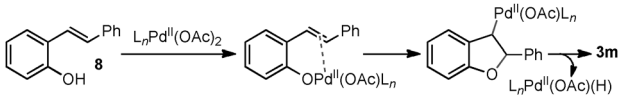
2-Hydroxystilbene (**8**) was isolated from the reaction of phenol and styrene (Scheme 7) in 35% yield along with 2-phenylbenzofuran (**3m**; 30%). Under standard reaction conditions, **3m** was obtained from **8** in 33% yield (Scheme 8). Unfortunately, only 4% yield of 2-phenylbenzo-



Scheme 6. Competition experiments.



Scheme 7. Mechanistic investigations.



Scheme 8. Formation of 2-phenylbenzofuran (**3m**) from **8**.

furan was observed with sodium phenolate as compared to 30% with phenol/NaOAc.[17] A likely pathway for the formation of **3m** from **8** is shown in Scheme 8.[27,28]

In summary, a versatile catalytic method for the synthesis of 2-substituted benzofuran through palladium-catalyzed intermolecular annulation of phenols and olefins have been disclosed.[29] The catalytic method was also applied successfully for the synthesis of various substituted coumarins starting from the corresponding phenols and methyl acrylate. Extension of the present reaction to the synthesis of related heterocyclic moieties and detailed mechanistic studies are ongoing in our laboratory.

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[29] A provisional patent on this work has been filed: IPA No. 2012/Mum/2013.

