Synthetic Methods

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Direct Assembly of 3,4-Difunctionalized Benzofurans and Polycyclic Benzofurans by Phenol Dearomatization and Palladium-Catalyzed Domino Reaction**

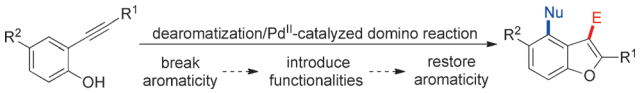
Zhaomeng Han, Liang Zhang, Zhiming Li, and Renhua Fan**

Dedicated to Professor Li-Xin Dai on the occasion of his 90th birthday

Abstract: *A method to directly convert 2-alkynylphenols to 3,4-difunctionalized benzofurans and polycyclic benzofurans was developed. This protocol involves a hypervalent-iodine-mediated oxidative dearomatization to break the aromaticity of 2-alkynylphenols, and a palladium-catalyzed domino reaction to install two functional groups at the C3 and the C4 positions and restore the aromaticity of benzofurans.*

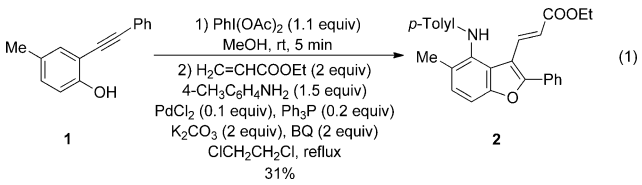
The dearomatization of aromatic compounds provides numerous possibilities for the construction of complex molecules.[1] The main advantage of the dearomatization is the possibility of converting an aromatic ring into a three-dimensional molecule. Moreover, since dearomatization offers unique strategic opportunities to circumvent the inherent *ortho*/*para* selectivity of electron-rich aromatic systems, the dearomatization strategy can also be used in the synthesis of multi-functionalized aromatic compounds that are difficult to prepare by electrophilic substitution reactions.

Among the family of benzofurans, 3,4-difunctionalized benzofurans are attractive synthetic targets because of their remarkable biological activities.[2] The synthetic challenge is the selective functionalization of the C4 position of benzofurans, which is not a preferred site for electrophilic substitution reactions. 2-Alkynylphenols are the most commonly used precursors to prepare benzofurans. A number of cyclization or cascade cyclization/cross-coupling reactions of 2-alkynylphenols have been developed.[3–12] However, these elegant methods only enable the synthesis of benzofurans with diverse substitutions on the five-membered ring. Herein, we report a method that directly converts 2-alkynylphenols to 3,4-difunctionalized benzofurans (Scheme 1). This protocol involves an oxidative dearomatization to break the aromaticity of 2-alkynylphenols, a palladium-catalyzed domino reaction to simultaneously install two functional groups at the C3 and the C4 positions, and an aromatization to restore the aromaticity.



Scheme 1. Preparation of 3,4-difunctionalized benzofurans from 2-alkynylphenols.

(Diacetoxyiodo)benzene facilitated oxidative dearomatization of 4-methyl-2-(2-phenylethynyl)phenol **1** in methanol. The deleterious cyclization or oxidation of the sensitive alkynyl group was not observed. The crude dearomatization product was directly used to test the palladium-catalyzed domino reaction with *p*-toluidine and ethyl acrylate. When 0.1 equivalents of $PdCl_2$ were used together with 0.2 equivalents of Ph_3P, 4-amino-substituted 3-alkenylbenzofuran **2** was obtained in 7% yield. Its structure was confirmed by single-crystal diffraction analysis.[13] A screening of solvents, temperatures, and bases did not improve the yield beyond 10%, thus indicating that the reaction with palladium was stoichiometric. Therefore, various oxidants were added to promote the regeneration of catalytic Pd^{II} from Pd^0 formed in the Heck coupling. While the addition of 2 equivalents of benzoquinone (BQ) improved the yield to 31% [Eq. (1)],



compound **2** was not formed when $Cu(OAc)_2$, $CuCl_2$, AgOAc, *meta*-chloroperbenzoic acid (*m*-CPBA), or $PhI(OAc)_2$ were added. The product formation was further optimized by examining a variety of palladium salts and phosphine ligands. When $PdBr_2$ was used together with trifuran-2-ylphosphine, the yield of compound **2** increased to 76%.[14]

After establishing the optimized reaction conditions, the scope of this transformation was investigated (Table 1). For a range of 2-alkynylphenols, the reactions proceeded smoothly, leading to the corresponding 3,4-difunctionalized benzofurans in moderate to good yields. In some cases, TsOH was added to promote the aromatization, and $PdCl_2$ was used

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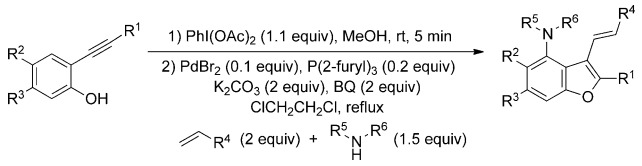
Table 1: Dearomatization and palladium-catalyzed domino reaction.



Entry	Product		Yield[a]
1		**2**: R^1 = Ph	76
2[b]		**3**: R^1 = 4-MeC_6H_4	61
3		**4**: R^1 = 4-ClC_6H_4	74
4[c]		**5**: R^1 = *n*Bu	65
5		**6**: R^1 = *t*Bu	76
6		**7**: R^1 = cyclopropyl	60
7[b,c]		**8**: R^1 = TMS	71
8[b,c]		**9**: R^2 = *n*Bu	55
9		**10**: R^2 = Ph	0
10		**11**: R^2 = OMe	65
11[b]		**12**: R^3 = Me	78
12		**13**: R^4 = CN	63
13		**14**: R^4 = $CON(Me)_2$	62
14		**15**: R^4 = Ph	0
15[b]		**16**: R^5 = Ph	61
16[b,c]		**17**: R^5 = 4-*i*PrC_6H_4	72
17		**18**: R^5 = 4-*n*BuC_6H_4	72
18		**19**: R^5 = 4-$MeOC_6H_4$	82
19[b,c]		**20**: R^5 = 3-$MeOC_6H_4$	42
20		**21**: R^5 = 4-FC_6H_4	61
21[b,c]		**22**: R^5 = 4-ClC_6H_4	65
22[b,c]		**23**: R^5 = 4-BrC_6H_4	71
23[b,c]		**24**: R^5 = 2-IC_6H_4	60
24		**25**: R^5 = Bn	0
25		**26**: R^5 = *n*Bu	0
26		**27**: R^6 = Me	64

[a] Reported yields are of the isolated products. [b] 4-Methylbenzenesulfonic acid (4 equiv) was added after 12 h. [c] $PdCl_2$ was used instead of $PdBr_2$. Bn = benzyl, TMS = trimethylsilyl.

instead of $PdBr_2$ to improve product yields. Electron-deficient alkenes, such as acrylonitrile and *N*,*N*-dimethylacrylamide, were also suitable reaction partners. When styrene was used, the reaction only afforded 4-amino-substituted benzofuran **28**. Various aromatic amines, including a secondary amine, could be used as nucleophile to be introduced at the C4 position of benzofuran. When benzylamine or butan-1-amine was used, no desired product was obtained, but a 4-methoxy-substituted 3-alkenylbenzofuran **29** was isolated. This compound was also the major product when diethyl malonate, phenol, or thiophenol were used as nucleophile. Interestingly, compound **29** was formed in a 63% yield in the absence of an added nucleophile. When 1 equivalent of CD_3OD was added as nucleophile, the incorporation of the OCD_3 group into compound **29** was not observed. This result indicated that compound **29** might be formed through a [1,2] transfer of the methoxy group.

To understand the formation of product **2**, 4-amino-substituted benzofuran **28** was treated with ethyl acrylate under the standard conditions. The formation of compound **2** was not observed. Meanwhile, the isolated non-aromatized product **30** was completely converted to compound **2** when it was treated with $PdBr_2$ in $ClCH_2CH_2Cl$ at reflux.

To gain more insight into the reaction, B3LYP density functional theory (DFT) calculations were performed with the Gaussian 09 software package.[15] We initially evaluated the role of the palladium catalyst. Palladium(II) might work as a Lewis acid to coordinate with the carbonyl group of the dearomatization product by a monodentate coordination mode or with the carbonyl group and the triple bond by a bidentate mode. Palladium(II) might also work as a π acid to coordinate with the triple bond by a monodentate mode. This activation might induce a cyclization to generate a furan-like intermediate (see Scheme S1 in the Supporting Information).[16] The computational results indicated that the furan-like intermediate **A** is the most stable intermediate (Figure 1).

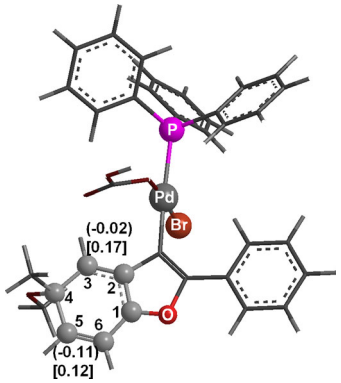


Figure 1. Optimized structures of intermediate **A**. The numbers in parenthesis are the NBO charges on atoms and the numbers in square brackets are the condensed Fukui functions.

It is more than 5 kcal mol^{-1} more stable than other intermediates. Therefore, palladium(II) acts as a π acid in the initial step. Moreover, although there are two possible reaction sites (C3 and C5) for the nucleophilic attack in the structure of intermediate **A**, the natural bond orbital (NBO) analysis showed that the C3 position is more positively charged (−0.02) compared to the C5 position(−0.11). The condensed Fukui function also predicted that the nucleophilic attack will occur at the C3 position. These results are in line with our experimental results.

We identified two possible reaction pathways from intermediate **A** to the non-aromatized product to understand the domino sequence. For clarity, only main stationary points are shown in Figure 2, and the relative free energies are based on the total free energy of intermediate **A**, *p*-toluidine, and methyl acrylate. In one pathway (in black), intermediate **A** is trapped by the electron-poor double bond of acrylate through

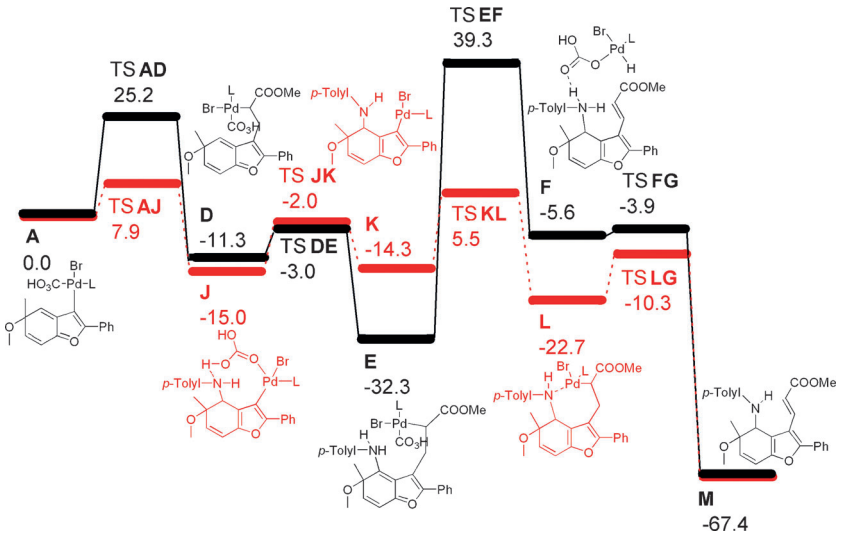
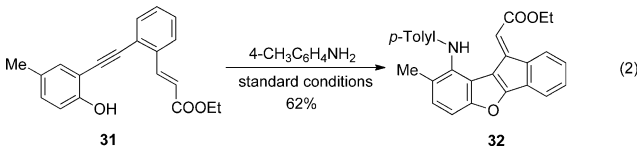


Figure 2. Free-energy reaction profile (kcal mol^{-1}) from intermediate **A** to the non-aromatized product, calculated at the PCM(DCE) B3LYP/6-31G(d,p) with LANL2DZ (for Pd and Br) level. TS = transition state.

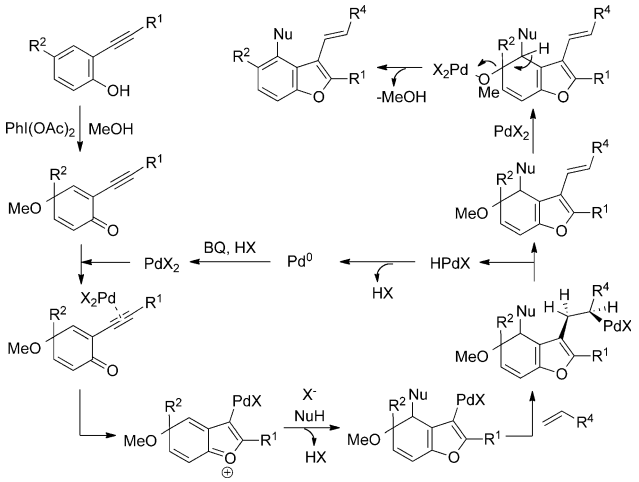
syn insertion, thus affording intermediate **D**. Intermolecular nucleophilic attack of the nitrogen of toluidine on the C3 position forms intermediate **E**. Subsequent *syn* β-H elimination gives rise to the non-aromatized product and releases H_2CO_3 and HPdBr. In the alternative pathway (in red), intermolecular nucleophilic attack occurs before the insertion, thus leading to intermediate **J**. After releasing H_2CO_3, intermediate **K** reacts with acrylate through insertion, followed by β-H elimination to afford the non-aromatized product and generate HPdBr. The potential energy surfaces indicate that the rate-determining step for the first pathway is the β-H elimination step (TS **EF**). For the second pathway, the nucleophilic attack of *p*-toluidine is the rate-determining step (TS **AJ**). The overall barrier for the first pathway is 39.3 kcal mol^{-1}, while it is only 7.9 kcal mol^{-1} for the second one. This means that the domino reaction favors the second pathway to a large extent. On the basis of these results, a plausible mechanism is depicted in Scheme 2. Palladium might play three roles in the domino reaction: 1) as a π acid to activate the triple bond of 2-alkynyl cyclohexadienones to induce the cyclization, 2) as an organopalladium intermediate to react with alkenes through carbopalladation and β-H elimination, and 3) as a Lewis acid to promote the aromatization.

When the electron-deficient alkene was linked to the alkynyl group of the substrate, this strategy could be used to construct polycyclic benzofurans. For example, under the standard conditions, compound **31** was converted to tetracyclic benzofuran **32** in a 62 % yield [Eq. (2)]. An intramolecular conjugated addition took place instead of the Heck coupling, when the acrylate moiety was changed to a vinyl ketone or a 2-methylenemalonate moiety (Scheme 3). It was supposed that a Pd^{II} O-bound enolate might be formed after

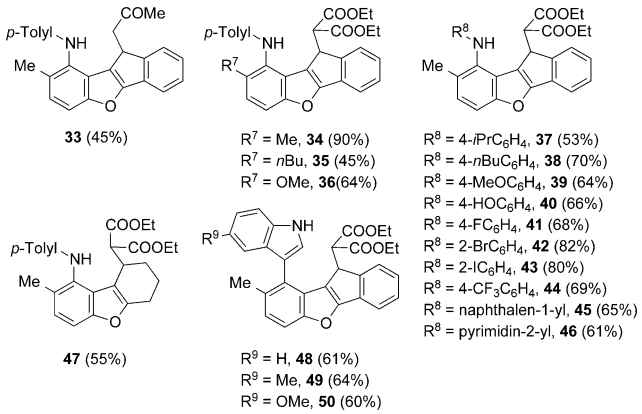


(2)

the intramolecular insertion of organopalladium to the double bond of vinyl ketone or 2-methylenemalonate. The protonolysis of this intermediate might be more favorable than the β-hydride elimination to give a conjugate addition product.[17] In these palladium(II)-catalyzed reactions, the addition of benzoquinone was not required. For most cases, polycyclic benzofurans were produced in moderate to good yields. The linkage between the alkynyl and the alkenyl group could be a benzene ring or an alkyl chain. The reaction of aromatic amines was found to tolerate a range of substituents with different electronic demands on the aromatic rings, involving electron-withdrawing and electron-donating groups. When an unprotected aminophenol was employed,



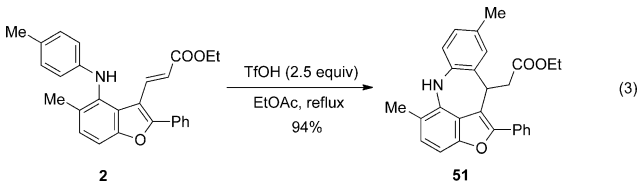
Scheme 2. Plausible mechanism.



Scheme 3. Construction of polycyclic benzofuran derivatives.

the reaction only afforded the *N*-arylated product. The electron-rich indoles could serve as suitable reaction partners in this process. With respect to other electron-rich aromatic compounds, such as *N*,*N*-dimethylaniline, 1,2-dimethoxybenzene, and thiophene, the reactions were complex and the desired products were not obtained.

With the aid of trifluoromethanesulfonic acid, compound **2** could be converted to compound **51** through an intramolecular Friedel–Crafts alkylation in a 94% yield [Eq. (3)]. Compound **51** has a dibenz[*b*,*f*]azepine core, which exists in



(3)

many natural products and medicinal compounds, such as carbazepine and trileptal.[18]

In conclusion, we have developed a method to convert 2-alkynylphenols into 3,4-difunctionalized benzofurans and polycyclic benzofurans. This protocol involves a hypervalent-iodine-mediated oxidative dearomatization and a palladium-catalyzed domino reaction. The application of this strategy to the synthesis of natural products and investigations on a more detailed mechanism are currently underway in our laboratory.

Experimental Section

Representative procedure: $PhI(OAc)_2$ (0.22 mmol) was added to a solution of 4-methyl-2-(2-phenylethynyl)phenol **1** (0.2 mmol) in MeOH (2.0 mL) at 25 °C. After 5 min, the reaction mixture was concentrated in vacuo. The resulting crude product was mixed with ethyl acrylate (0.4 mmol), *p*-toluidine (0.3 mmol), $PdCl_2$ (0.02 mmol), trifuran-2-ylphosphine (0.04 mmol), benzoquinone (0.4 mmol), and K_2CO_3 (0.4 mmol) in $ClCH_2CH_2Cl$ (2 mL). The reaction was stirred under reflux. After the substrate was completely consumed (monitored by TLC analysis), the reaction mixture was passed through a short column of silica gel and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: petroleum ether/ethyl acetate) to furnish the desired compound **2**.

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