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Palladium-Catalyzed Cross-Coupling of Unsaturated Phenols with Vinylic Halides and Triflates

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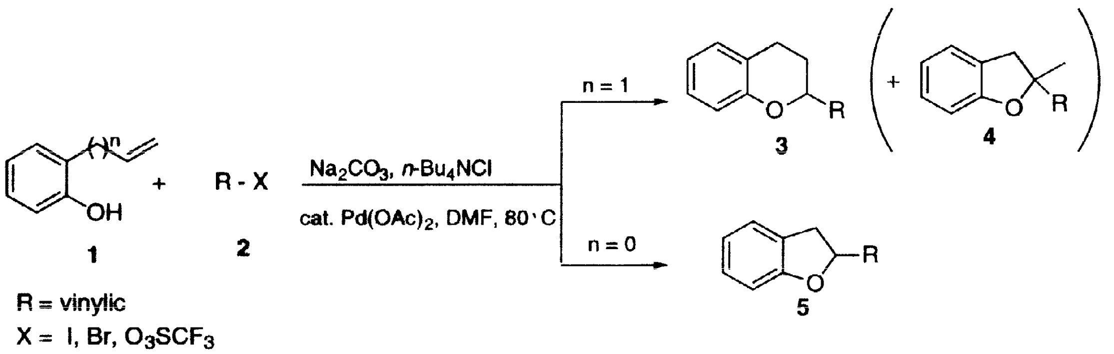
Abstract: The palladium-catalyzed cross-coupling of *o*-allylic and *o*-vinylic phenols with vinylic halides and triflates produces substituted dihydrobenzopyrans and dihydrobenzofurans respectively in good to high yields. © 1997 Elsevier Science Ltd. All rights reserved.

The development of general cross-coupling strategies for the construction of heterocycles possessing variable substitution patterns is a considerable challenge in organic synthesis. Many syntheses have recently taken advantage of the ability of palladium to form π-allyl complexes, which undergo subsequent intramolecular nucleophilic substitution.[1] For example, we and others have recently reported the palladium-catalyzed cross-coupling of vinylic halides and triflates with alkenoic acids[2] and unsaturated sulfonamides[3] to form lactones and cyclic sulfonamides via π-allylpalladium intermediates. Now we wish to report a conceptually related palladium-catalyzed coupling of vinylic halides and triflates with *o*-allylic and vinylic phenols, which provides a convenient, general route to dihydrobenzopyrans (**3**) and dihydrobenzofurans (**5**) respectively (Scheme 1).

Scheme 1



We initially focused our attention on the palladium-catalyzed coupling of vinylic halides with *o*-allylphenol (**1a**), choosing the reaction with β-bromostyrene as a model system. After screening a variety of reaction

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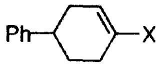
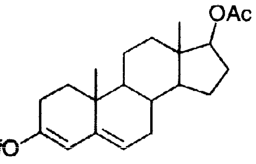
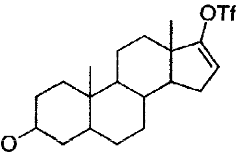
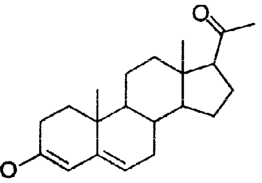
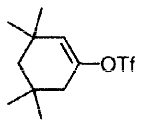
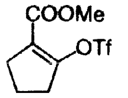
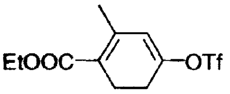
conditions, we settled on a procedure which involved heating 1 equiv of vinylic substrate (0.25 mmol), 2 equiv of phenol, 3.5 equiv of Na_2CO_3, 1.1 equiv of *n*-Bu_4NCl and 5 mol % $Pd(OAc)_2$ in 1.5 mL of DMF at 80 °C for 24 h. Using this procedure, we have been able to obtain the desired 3,4-dihydro-2[(*E*)-β-styryl]-2H-1-benzopyran (**3**), together with 2,3-dihydro-2-methyl-2-[(*E*)-β-styryl]benzofuran (**4**), as a 91:9 inseparable mixture in 90% overall yield (Table 1, entry 1).[4] This procedure worked well on a variety of other vinylic halides, as well as triflates (see entries 2-13). We next examined the cross-coupling of a number of more substituted *o*-allylic phenols, including *o*-methallylphenol (**1b**) and *o*-crotylphenol (**1c**). While the reactions of vinylic halides with *o*-methallylphenol (**1b**) gave the expected cross-coupling products in good to high yields (entries 14-17) with none of the five-membered ring ether being formed, with *o*-crotylphenol (**1c**) the yields were lower as expected for the addition to the more hindered double bond (entries 18 and 19). Unfortunately, in a lot of the reactions examined, vinylic halides gave the annulation products as a mixture of dihydrobenzopyran (**3**) and dihydrobenzofuran (**4**). Formation of the five-membered ring is undoubtedly due to vinylic addition to the internal carbon of the carbon-carbon double bond of the allylic moiety, as observed previously.[5] The greater regioselectivity observed with vinylic triflates is most probably related to the increased steric bulk of the vinylic unit (all the triflates tested are cyclic compounds), since it can reasonably be presumed that the nature of the anion of the organopalladium intermediate does not affect the regiochemical course of the reaction to a large extent. This hypothesis is supported by the nearly identical results obtained in the reactions of 4-phenyl-cyclohex-1-enyl triflate and 4-phenyl-cyclohex-1-enyl iodide with *o*-allylphenol (**1a**) (compare entries 6 and 7).

We next turned our attention to the analogous cross-coupling of *o*-vinylic phenols and vinylic halides or triflates. Taking into account our results with *o*-allylic phenols, we used the same reaction conditions in the reaction of β-bromostyrene with *o*-vinylphenol (**1d**) (entry 20). This reaction afforded the expected product, 2,3-dihydro-2-[(*E*)-β-styryl]benzofuran (**5**), together with a small amount of 2-benzyl-2H-1-benzopyran (91:9 ratio), in a 61% overall yield. It is not clear how the six-membered ring product is formed. Mixed results were obtained with other vinylic halides and triflates. (*E*)-1-Bromo-3,3-dimethyl-1-butene gave the desired product in 40% yield (entry 22), while the 3,3,5,5,-tetramethylcyclohex-1-enyl triflate afforded only a 20% yield of the corresponding dihydrobenzofuran and 77% of the 1,3-diene product. (*E*)-1-Iodo-1-hexene didn't give any recognizable product. Attempts were then made to improve the yields for the reactions of *o*-vinylic phenols and after a systematic examination of the influence of solvents and bases, we have been able to arrive at improved conditions (3.5 equiv of K_2CO_3, 1.1 equiv of *n*-Bu_4NCl, 5 mol % of $Pd(OAc)_2$ at 80°C in acetonitrile as solvent), which in a few cases gave us better results (compare entries 22 and 23). However, further attempts to extend the reaction to more substituted *o*-vinylic phenols gave disappointing results. With *o*-[(*E*)-1-propenyl]phenol only low yields of products were obtained in all cases examined. Reactions with *o*-isopropenylphenol also met with failure.

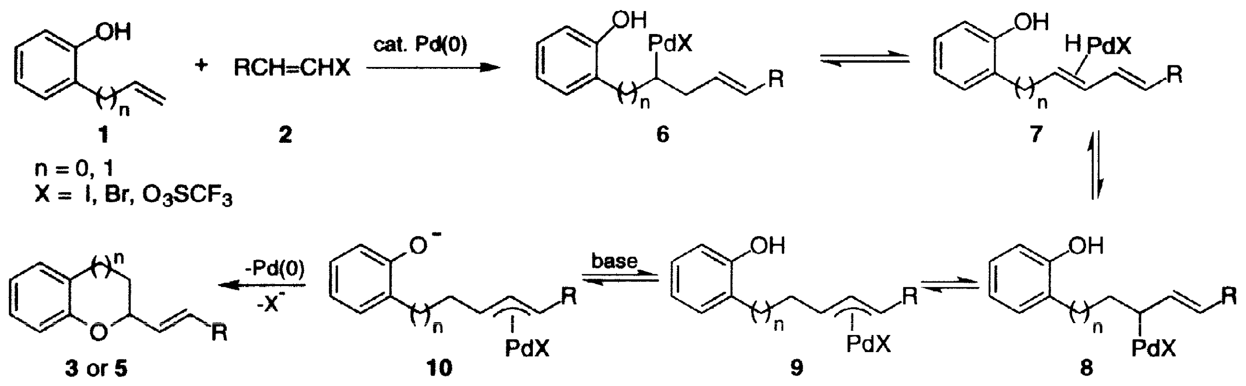
Mechanistically, the present synthesis of 2-vinylic-3,4-dihydrobenzopyrans and dihydrobenzofurans likely proceeds according to the pathway illustrated in Scheme 2. Addition of a σ-vinylpalladium intermediate to the carbon-carbon double bond, followed by migration of palladium along the carbon chain, results in the formation of a π-allylpalladium complex, which subsequently undergoes nucleophilic attack by the anionic oxygen. Elimination of the palladium-hydride from the η^2-complex (**7**), is no doubt responsible for formation of the vinylic substitution side products observed in this process.

Table 1. Pd-Catalyzed Cross-Coupling of Unsaturated Phenols with Vinylic Halides and Triflates.[a]

entry	Phenol (1)	Vinylic halide or triflate (2)	Time (h)	Product yield % [b,c]
1	o-$HOC_6H_4CH_2CH{=}CH_2$ (**1a**)	(*E*)-$PhCH{=}CHBr$	24	82 (8)
2		(*E*)-$PhCH{=}CHI$	48	76 (8)
3		(*E*)-*n*-$BuCH{=}CHI$	36	62 (10)
4		$(CH_3)_2C{=}CHI$	36	68 (7)
5		*n*-$BuCI{=}CH_2$	24	57 (6)
6		 X = I	6	55
7		X = OTf	8	53
8			5	56
9			24	50
10			1.5	59[d]
11			3	76
12			1.0	63[d]
13			1	58[d]
14	o-$HOC_6H_4CH_2C(CH_3){=}CH_2$ (**1b**)	(*E*)-$PhCH{=}CHBr$	24	75[e]
15		(*E*)-$PhCH{=}CHI$	24	75[f]
16		(*E*)-*t*-$BuCH{=}CHBr$	24	83[g]
17		$(CH_3)_2C{=}CHI$	24	60[h]
18	o-$HOC_6H_4CH_2CH{=}CHCH_3$ (**1c**)	(*E*)-$PhCH{=}CHBr$	72	56 (11)
19		$(CH_3)_2C{=}CHI$	24	49 (4)[i]
20	o-$HOC_6H_4CH{=}CH_2$ (**1d**)	(*E*)-$PhCH{=}CHBr$	24	56 (5)[j]
21		(*E*)-$PhCH{=}CHI$	24	54 (18)[j]
22		(*E*)-*t*-$BuCH{=}CHBr$	24	40
23			48	53[k]

[a] Unless otherwise stated, reactions were carried out under an argon atmosphere at 80°C in DMF for an appropriate time interval using the following molar ratios: **1**: **2**: Na_2CO_3: *n*-Bu_4NCl: $Pd(OAc)_2$ = 2 : 1 : 3.5 : 1.1 : 0.05. [b] Figures in parentheses refer to the yield of **4** in the mixture, calculated by ^1H NMR analysis. [c] All products were fully characterized by ^1H NMR, ^{13}C NMR, IR and HRMS analysis. [d] Reaction was carried out using $KHCO_3$ (3.5 equiv) as the base and MeCN as the solvent. [e] *cis/trans* Ratio is 77:23 (see ref. 6) . [f] *cis/trans* Ratio is 71:29 (see ref. 6). [g] *cis/trans* Ratio is 70:30 (see ref. 6). [h] *cis/trans* Ratio is 50:50 (see ref. 6). [i] 5 Equiv of **1c** were used. [j] The number in parenthesis refers to the yield of 2-benzyl-2H-1-benzopyran, calculated by ^1H NMR analysis. [k] Reaction was carried out using K_2CO_3 (3.5 equiv) as the base and MeCN as the solvent.

Scheme 2



We are presently examining analogous reactions using a variety of other heteroatom-containing nucleophiles, since this process holds promise as a useful tool for the construction of a wide variety of heterocyclic compounds. We will report those results shortly.

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3. (a) Harris, G. D., Jr.; Herr, R. J.; Weinreb, S. M. *J. Org. Chem.* **1992**, *57*, 2528. (b) Harris, G. D., Jr.; Herr, R. J.; Weinreb, S. M. *J. Org. Chem.* **1993**, *58*, 5452. (c) Larock, R. C.; Yang, H.; Weinreb, S. M.; Herr, R. J. *J. Org. Chem.* **1994**, *59*, 4172.
4. Selected spectral data for 3,4-dihydro-2-[(*E*)-β-styryl]-2H-1-benzopyran are: ^{1}H NMR ($CDCl_3$) δ 1.88-2.01 (m, 1 H), 2.01-2.18 (m, 1 H), 2.76-2.96 (m, 2 H), 4.68-4.75 (m, 1H), 6.34 (dd, J = 15.9 Hz, J = 6.0 Hz, 1 H), 6.71 (d, J = 15.9 Hz, 1 H), 6.82-6.89 (m, 2 H), 7.05-7.16 (m, 2 H), 7.22-7.43 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 24.4, 28.0, 76.2, 116.9, 120.2, 121.8, 126.6, 127.3, 127.8, 128.5, 128.7, 130.0, 131.5, 136.5, 154.5; IR (KBr) 2952, 1608, 1229 cm^{-1}; HRMS 236.1199 (Calcd. 236.1201 for $C_{17}H_{16}O$). The presence of 2,3-dihydro-2-methyl-2-[(*E*)-β-styryl]benzofuran was revealed in the ^{1}H NMR spectra by the following signals: δ 1.65 (s), 3.14 (d, J = 15.3 Hz), 3.27 (d, J = 15.3 Hz).
5. (a) Larock, R. C.; Leung, W. Y.; Stolz-Dunn, S. *Tetrahedron Lett.* **1989**, *30*, 6629. (b) Larock, R. C.; Leung, W. Y. *J. Org. Chem.* **1990**, *55*, 6244.
6. The ratio of the stereoisomers was determined on the basis of the following references: (a) Kraus, G. A.; Molina, M. T.; Walling, J. A. *J. Chem. Soc., Chem. Commun.* **1986**, 1568. (b) Kraus, G. A.; Molina, M. T.; Walling, J. A. *J. Org. Chem.* **1987**, *52*, 1273. (c) Rao, T. S.; Trivedi, G. K. *Heterocycles* **1987**, *26*, 2117.