Pergamon

Tetrahedron Letters, Vol. 38, No. 36, pp. 6379-6382, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01468-8

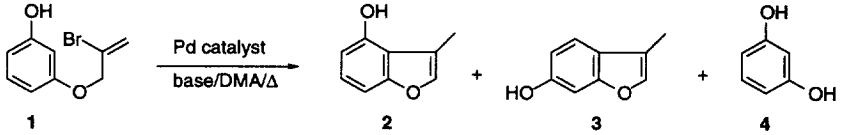
Anion-Accelerated Palladium-Mediated Intramolecular Cyclizations: Synthesis of Benzofurans, Indoles, and a Benzopyran

D. David Hennings, Seiji Iwasa, and Viresh H. Rawal*
Department of Chemistry, The University of Chicago, Chicago, Illinois 60637

Abstract: Substituted benzo-fused heterocycles such as indoles, benzofurans, and a benzopyran were obtained using an intramolecular cross-coupling of vinyl halides with phenols. This transformation represents a new route to these heterocycles and is accomplished using a palladacyclic catalyst under anionic conditions. © 1997 Elsevier Science Ltd.

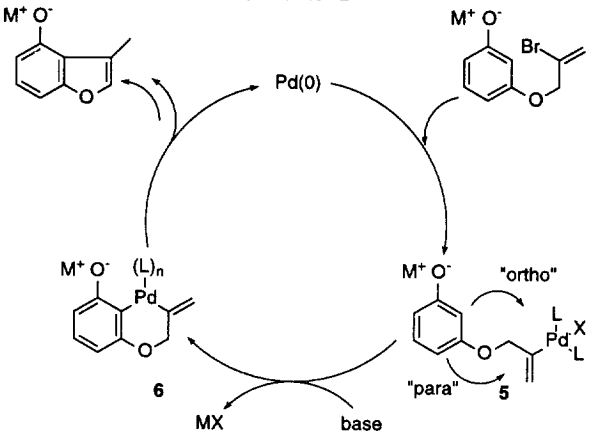
The widespread occurrence of benzo-fused heterocycles such as indoles and benzofurans has stimulated considerable research directed toward their syntheses.[1,2] Recently we reported a mild and selective procedure for the palladium-catalyzed intramolecular coupling of aryl halides with phenols.[3] The rate of this cyclization was significantly accelerated in the presence of bases, presumably because the phenolate anion formed under the reaction conditions is much more reactive as a soft nucleophile than phenol. In an effort to expand the scope of this coupling, we have examined the palladium-mediated cyclizations of phenols containing various vinyl halide side chains and report here their successful cyclizations leading to substituted benzofurans, indoles, and a benzopyran derivative.

The general strategy is illustrated through the cyclization of vinyl bromide **1** (Eq 1). Heating a mixture of bromide **1**[4] and Cs_2CO_3 in dimethylacetamide (DMA) in the presence of a catalytic amount of Herrmann's palladacyclic catalyst (HC)[5,6] promoted cyclization to the "ortho" and "para" benzofurans **2** and **3**, which were formed in a 1:1 ratio along with a small amount of resorcinol (**4**). The mechanism of this coupling reaction is depicted in Scheme 1, and is analogous to that suggested for the aryl coupling reaction. Oxidative addition of a Pd(0) species[7] to the vinyl halide is followed by nucleophilic attack of the ambident phenolate anion on σ-palladium intermediate **5** to afford, after rearomatization of the presumed cyclohexadienone intermediate, aryl-vinyl palladium species **6**. Reductive elimination of palladium followed by isomerization of the exocyclic double bond affords the observed products. The main side product of this reaction, which was not observed in the aryl coupling process,[3] is resorcinol. The exact mechanism for this side chain elimination is not clear, although the reaction of allyl phenyl ethers with Pd(0) to afford a π-allyl palladium species and a phenolate ion is well precedented.[8-10]



1 **2** **3** **4** (Eq. 1)

Scheme 1



We briefly examined the effect of reaction parameters on the extent of resorcinol formation and on the "ortho" vs. "para" selectivity for the cyclization of **1** (Table 1). The extent of side chain elimination appears to be dependent on the reaction temperature and is minimal at 70 °C using HC (entries 1-3). Lowering the temperature further slows down the reaction so as to make it impractical. Typical palladium catalysts also promote cyclization, although not as well as HC. Thus, when the cyclization of **1** was carried out using $Pd(PPh_3)_4$ at 90 °C only resorcinol was isolated. The cyclized product was formed at lower temperature but was accompanied by a large amount of resorcinol (entry 5). The cyclization was also effective using a 1:1 ratio of Pd/phosphine, which should generate in situ a palladium species similar to HC (entry 6). Optimum results were obtained by carrying out the reaction using HC at 70 °C.

Table 1: Optimization of Conditions for the Cyclization of 1.

Entry	Catalyst (mol %)	Temp (°C)	Time (days)	2 + 3 (ratio)	Yield (%)	Resorcinol (%)
1	HC (5)	95	1	1 : 1	44	30
2	HC (5)	70	1	1 : 1	78	---[a]
3	HC (5)	70	3	1 : 1	82	15
4	HC (5)	55	5	1 : 1	58	18
5	$Pd(PPh_3)_4$ (5)	70	2	2 : 3	32	42
6	$Pd(OAc)_2$ (5) $P(o\text{-tolyl})_3$ (5)	70	2	3 : 5	43	37

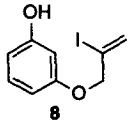
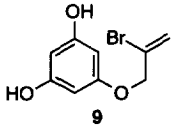
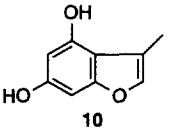
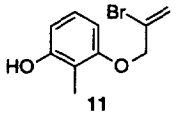
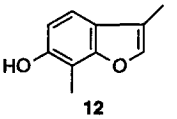
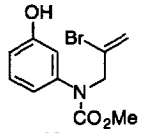
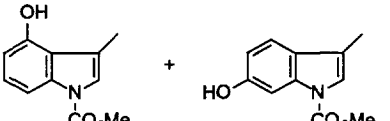
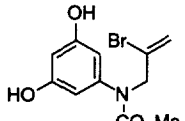
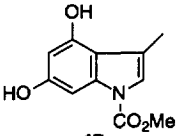
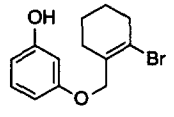
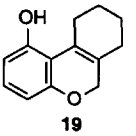
[a]Resorcinol was observed but not isolated.

The cyclization procedure developed here appears to be general and can be used for the synthesis of a variety of different heterocyclic products (Table 2).[11] Entry 1 shows that a vinyl iodide also undergoes cyclization and gives slight selectivity for the "para" product. The issue of "ortho" vs. "para" selectivity is avoided either by using a symmetrical phenol (entry 2) or by blocking one of the cyclizable positions (entry 3). Entries 4 and 5 show that substituted indoles can also be synthesized using this strategy.[4] With the indole forming reactions, prolonged

reaction times gave side-products resulting from the hydrolysis of the indole carbamate. Six-membered rings can also be synthesized by this methodology, as illustrated by the benzopyran formation (entry 6). Interestingly, this cyclization gave predominantly the "ortho" cyclization product. The phenolic group present in these cyclization products provides a useful handle for further functionalization. For example, the corresponding triflates would be well set up for Stille couplings.

Overall, the intramolecular coupling of phenols with vinyl halides described here provides a simple, direct method for the synthesis of substituted heterocycles.

Table 2: Synthesis of Benzo-heterocycles via Palladium Mediated Cyclizations.

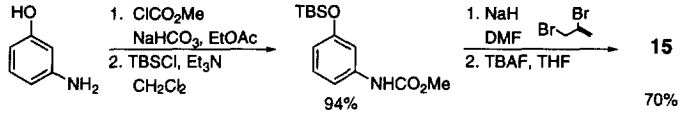
Entry[a]	Substrate	Rxn Temp (°C)	Time (d)	Products (ratio)	Yield
1	 **8**	70	2	**2** + **3** (1 : 2.2)	54[b]
2	 **9**	65	3	 **10**	77[b]
3	 **11**	70	1.5	 **12**	61[b]
4	 **13**	78	1	 **14** (1 : 1) **15**	79[b]
5	 **16**	70	1	 **17**	71
6	 **18**	70	2	 **19**	55[b]

[a]See reference 10 for a general procedure. [b]Starting material consumed, major side product is the phenol corresponding to elimination of the allylic side chain.

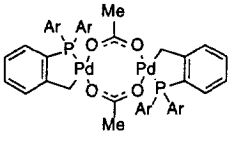
Acknowledgments: We thank the University of Chicago for partial support of this work and the Department of Education for a GAANN Fellowship to D.D.H. Pfizer Inc. and Merck & Co. are thanked for generous financial assistance, in the form of faculty awards to V.H.R.

References and Notes

1. Reviews on indole syntheses: (a) *Indoles*, Sundberg, R.J. Academic Press: San Diego, 1996 (b) Saxton, J.E. *Indoles*; Wiley-Interscience: New York, 1983; Part 4.
2. Review on benzofurans: Röhrkasten, R.; Konrad, M. *Methoden der Organischen Chemie (Houben-Weyl); Heteroarenes I, Part 2*; 4th ed.; Kreher, R.P., Ed.; Georg Thieme Verlag: Stuttgart, 1994; Vol. E6b, p. 33-162.
3. Hennings, D. D.; Iwasa, S.; Rawal, V. H. *J. Org. Chem.* **1997**, *62*, 2-3.
4. Compounds **1**, **8**, **9**, **11**, and **13** were prepared by simple allylation of the corresponding phenol with the appropriate allylic bromide in DMF with K_2CO_3. Compounds **15** and **18** were prepared from the corresponding amino-phenols in four steps, as shown below.



5. Herrmann, W. A.; Brossmer, C.; Öfele, K.; Reisinger, C. P.; Priermeier, T.; Beller, M.; Fischer, H. *Angew. Chem. Int. Ed. Eng.* **1995**, *34*, 1844-1848.
6. Herrmann's catalyst (HC) is the dimeric palladacycle shown below.



HC

7. Louie, J.; Hartwig, J.F. *Angew. Chem. Int. Ed. Eng.* **1996**, *35*, 2359-2361. These authors report a pathway for the palladacycle to be converted into a Pd(0) species in the presence of alkyl amines and an aryl stannane. It is likely that the present cyclization also involves a Pd(0) catalyst, although a mechanism involving a Pd(II) species cannot be ruled out. However, it is unclear how the Pd(0) is being formed in the process described here. One possibility is a nucleophile mediated cleavage of the Pd-C bond.
8. Hata, G.; Takahashi, K.; Miyake, A. *J. Chem. Soc., Chem. Commun.* **1970**, 1392-1393.
9. Tsuji, J.; Kobayashi, Y.; Kataoka, H.; Takahashi, T. *Tetrahedron Lett.* **1980**, *21*, 1475-1478.
10. It should be noted that attempted cyclization of the O-methyl derivative of **1** gave only the side chain elimination product, 3-methoxyphenol.
11. *General Procedure:* To a mixture of 3-(2-bromoallyloxy)-phenol **1** (0.2917 g, 1.279 mmol), Cs_2CO_3 (1.24 g, 3.81 mmol) and Herrmann's catalyst[5,6] (28.9 mg, 0.0617 mmol) was added 13.0 mL of N,N-dimethylacetamide (DMA). The mixture was blanketed with N_2 and then evacuated under vacuum. This process was repeated twice. The mixture was then heated at 70 °C for 3 days, cooled to room temperature, and quenched with saturated aqueous NH_4Cl (5 mL) and H_2O (25 mL). After extraction with diethyl ether (3x25 mL) the combined organic phase was washed with brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (elution with 20% ether in hexanes) to give 75.3 mg (40%) of **2** and 72.2 mg (38%) of **3.**
Data for **2**: mp 108-110 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.40 (d, J = 1.3 Hz, 3H), 4.94 (s, 1H), 6.52 (dd, J = 7.1, 1.4 Hz, 1H), 7.05 (m, 2H), 7.27 (q, J = 1.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.8, 104.7, 107.6, 115.1, 117.4, 124.7, 140.2, 150.6, 157.3; IR (Nujol, cm^{-1}) 3200, 1625, 1606, 1582, 1377, 1243, 1093, 1026; HRMS calcd for $C_9H_8O_2$ [M^+]: 148.0524, found 148.0540.
Data for **3**: mp 92-94 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.20 (d, J = 1.3 Hz, 3H), 4.71 (s, 1H), 6.78 (dd, J = 8.2, 2.2 Hz, 1H), 6.93 (d, J = 2.2 Hz, 1H), 7.30 (q, J = 1.2 Hz, 1H), 7.33 (d, J = 8.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.9, 98.3, 111.2, 115.0, 115.5, 119.6, 140.6, 153.4, 156.1; IR (neat, cm^{-1}) 3400, 1627, 1489, 1444, 1301, 1223, 1128, 1068, 942; HRMS calcd for $C_9H_8O_2$ [M^+]: 148.0524, found 148.0525.

(*Received in USA* 27 *May* 1997; *accepted* 8 *July* 1997)