Communications

Anion-Accelerated Palladium-Catalyzed Intramolecular Coupling of Phenols with Aryl Halides

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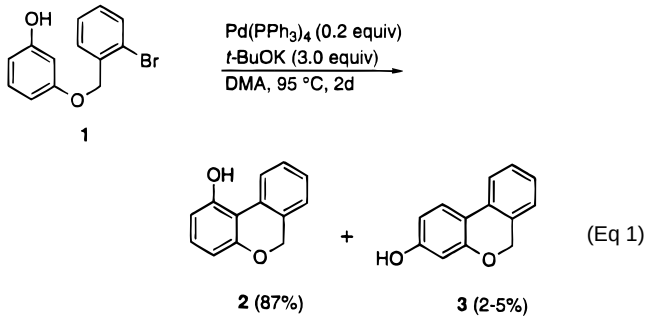
The aryl−aryl linkage is found in a wide range of compounds, from natural products such as vancomycin[1] and aporphine alkaloids[2] to important unnatural compounds such as 1,1′-bi-2-naphthol[3] and BINAP.[4] Although several procedures have been developed for the coupling of aryl moieties, many of them have limited applicability due to the harshness or functional group intolerance of the conditions required.[5] In connection with our interest in asymmetric synthesis of biaryls,[6] we have examined several different procedures for constructing the aryl−aryl linkage. We report here a mild, selective procedure for the palladium-catayzed intramolecular coupling of phenols with aryl halides.

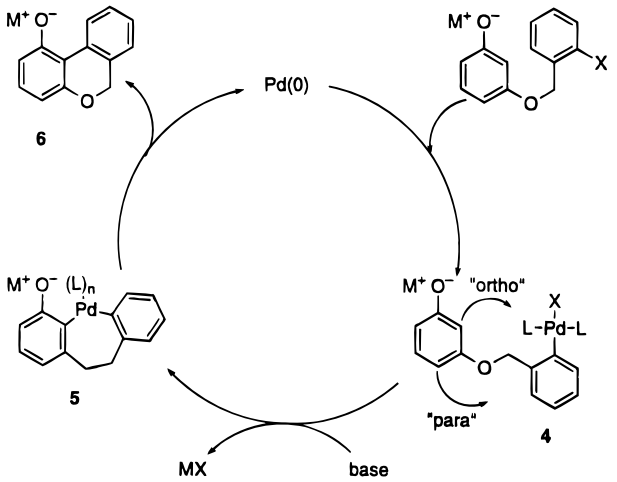
The coupling of carbon nucleophiles with aryl halides has been accomplished with palladium catalysis.[7] The reaction is believed to proceed via attack of the nucleophile to a σ-bound palladium species, followed by reductive elimination of palladium to give the coupled product.[8] Carbon nucleophiles that have been used successfully include enolates, particularly those derived from β-dicarbonyl compounds.[9,10] Aromatic rings are also effective as nucleophiles, although high temperatures are generally required for the reaction. We have found, however, that when the aryl unit has a hydroxyl group attached, then the ambident nature of the corresponding phenolate anion renders the aryl ring more electron-rich and, hence, more reactive in the coupling reaction.[11]

The initial studies were carried out on bromide **1** using $Pd(PPh_3)_4$ as the catalyst (eq 1). On treatment



(Eq 1)

Scheme 1



with *t*-BuOK (3 equiv) and $Pd(PPh_3)_4$ (0.2 equiv) in dimethylacetamide (DMA) at 95 °C (bath), bromide **1** smoothly cyclized to predominently the "ortho" product **2**, isolated in 87% yield. The reaction is expected to proceed by the pathway shown in Scheme 1. Oxidative addition of palladium to the aryl bromide would give σ-aryl palladium intermediate **4**. Nucleophilic attack of the phenolate on the palladium would yield, after tautomerization, diaryl palladium species **5**, which on reductive elimination of the palladium would give the observed product**.**

Experiments were performed to exclude the possibility of a benzyne intermediate and to confirm that the cyclization is palladium catalyzed (Table 1). When the above reaction was carried out using the weaker base K_2CO_3, which is unlikely to produce benzyne under the conditions used, the same results were obtained (entry 2). With *t*-BuOK as the base and with no palladium catalyst, the starting material was slowly consumed, but gave none of the cyclized product, thus ruling out the benzyne mechanism (entry 3). The cyclization also did not take place if base was omitted from the reaction mixture, supporting the notion that the reaction is accelerated using the phenolate as the nucleophile (entry 4). DMA was the solvent of choice for this transformation. In other solvents that were examined (e.g., DME, THF, CH_3CN, toluene), the yield of the cyclized product was lower and included a higher percentage of the "para" product **3**. Interestingly, reduction of the halide, to afford 3-(benzyloxy)phenol (**7**), was by far the major pathway when the reaction was carried out in DMF (entry 5).[12]

Of the other commonly used palladium catalysts that were examined (e.g., $Pd(OAc)_2$, $Pd_2(dba)_3$, $PdCl_2$), none were as effective as $Pd(PPh_3)_4$ for this cyclization. Herrmann recently reported a robust, discrete palladacycle

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(11) Wiegand, S.; Schafer, H. J. *Tetrahedron* **1995**, *51*, 5341−5350.
(12) Zask, A.; Helquist, P. *J. Org. Chem.* **1978**, *43*, 1619−1620. The authors have reported the reduction of aryl bromides in DMF in the presence of $Pd(PPh_3)_4$ and $NaOCH_3$. They proposed that the reducing hydrogen arises from palladium-mediated decomposition of the methoxide to formaldehyde, a process which cannot take place in the present example. It is likely that in the present case saponification of DMF yields a formate ion, the decomposition of which to PdH, which provides the reducing hydrogen, and CO_2 has ample precedent.

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Table 1

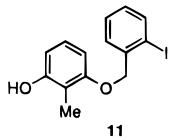
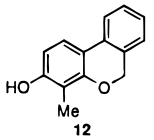
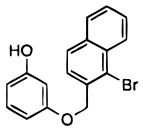
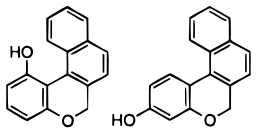
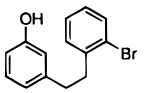
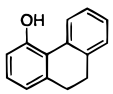
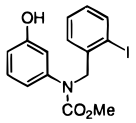
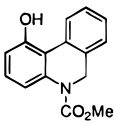
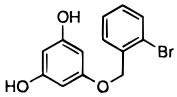
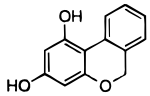
entry	substrate	base (3 equiv)	catalyst (mol %)	solvent	temp (°C)	time (days)	yield cyclized product
1	**1**	*t*-BuOK	$Pd(PPh_3)_4$ (20)	DMA	95	2	87[a]
2	**1**	K_2CO_3	$Pd(PPh_3)_4$ (10)	DMA	95	2	88[a]
3	**1**	*t*-BuOK	none	DMA	95	2	0 (56% recovered **1**)
4	**1**	none	$Pd(PPh_3)_4$ (10)	DMA	95	2	0 (77% recovered **1**)
5	**1**	*t*-BuOK	$Pd(PPh_3)_4$ (20)	DMA	95	2	0 (77% reduction product **7**)
6	**9**	Cs_2CO_3	HC, **8**, (5)	DMA	80	1	97
7	**10**	Cs_2CO_3	HC, **8**, (5)	DMA	80	1	10 (90% recovered **10**)
8	**9**	Cs_2CO_3	$Pd(OAc)_2$ (5) $(o\text{-tolyl})_3P$ (5)	DMA	84	1	94

[a] A small amount (<5%) of the para product **3** was also observed.

(**8**),[13] formed in high yield from $Pd(OAc)_2$ and P(*o*-tolyl)$_3$. Herrmann's catalyst (HC) has been shown to efficiently catalyze the Heck[14] and Suzuki[15] cross-coupling reactions. We have found HC to be as good or better than other catalysts and have utilized it for all subsequent cyclizations (Table 1). Unlike $Pd(PPh_3)_4$, HC can be stored and handled without taking special precautions. The cyclization of iodide **9**[13] proceeded in high yield at 75−80 °C using just 5 mol % of HC (entry 6). The reaction was faster with Cs_2CO_3 than with K_2CO_3 as the base.[16] Whereas bromide **1** and iodide **9** reacted at comparable rates,[17] the corresponding aryl chloride was much less reactive under the same conditions. It should be noted that other than being convenient to use there appears to be nothing special about using preformed catalyst **8** for this reaction. Subjection of iodide **9** to the standard reaction conditions using a 1:1 ratio of $Pd(OAc)_2$ and P(*o*-tolyl)$_3$ gave the cyclization product in about the same yield as using the preformed catalyst. This observation differs from Herrmann's, who found the preformed catalyst to be "more active and productive than a conventional 'in situ catalyst'" for the Heck reaction.[14] The main disadvantage with the in situ catalyst is that the 1:1 stoichiometry of the two components needs to be maintained. The reaction was found to be significantly slower when $Pd(OAc)_2$ and the phosphine were used in a 1:2 ratio. The accelerating effect of the phenolate anion is evident from entry 7. Under the same conditions used for the cyclization of phenol **9**, the corresponding methyl ether **10**[13] gave primarily recovered starting material, along with the "para" cyclized product in 10% yield.

This anion-accelerated cyclization procedure using HC appears to be general (Table 2). When the ortho position is blocked, as in **11**, the substrate was forced to cyclize at the "para" position to yield **12**. Cyclization of naphthyl bromide **13** required longer reaction time but proceeded in excellent yield to afford a mixture of the "ortho" and "para" products. An additional heteroatom on the phenolic component is not necessary for successful cyclization, although it may accelerate the reaction. The deoxy-analog of **1**, dihydrostilbenoid **16**, required a higher temperature for the cyclization and gave the corresponding dihydrophenanthranol, **17**, in 75% yield (96% based on recovered starting material), with good "ortho" selectivity. The ability to use nitrogen-containing compounds opens up this methodology to applications in alkaloid synthesis. The cyclization of iodide **18** gave the "ortho" cyclization product, dihydrophenanthridine derivative **19**. None of the cyclized product was isolated from reaction of the corresponding free amine of **18**. Presumably, the intermediate aryl palladium species is tied up through coordination with the amine.

Table 2[a]

Entry	Substrate	Rxn Temp (° C), Time (h)	Products(ratio)	% Yield
1	 **11**	95, 24	 **12**	80
2	 **13**	115, 48	 **14** (1:2) **15**	96
3	 **16**	115, 48	 **17**	75(96)[b]
4	 **18**	90, 60	 **19**	76
5	 **20**	95, 48	 **21**	84

[a] Conditions: All reactions done with 5 mol % of palladacycle and 3 equiv of Cs_2CO_3 in DMA. [b] Based on recovered starting material.

In conclusion, the intramolecular coupling of phenols with aryl halides is efficiently promoted under basic conditions with palladium catalysts, particularly Herrmann's catalyst. Extension of this coupling protocol to natural product synthesis is currently under investigation.

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Supporting Information Available: Experimental procedure for the cyclization of compound **1**, and spectral data, including copies of ^{1}H NMR and ^{13}C NMR spectra, for compounds **1**−**3** and **9**−**21** (35 pages).

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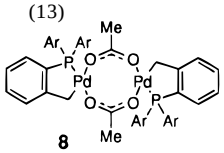
(13)



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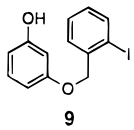

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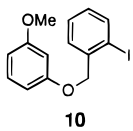

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(16) Little or no cyclization product was observed with Na_2CO_3 or Li_2CO_3. Presumably, the larger cations are better solvated, resulting in a more nucleophilic, "naked" phenolate anion.

(17) On the basis of the available data, it seems that the rate-determining step for aryl bromides and iodides is not the oxidative addition but the nucleophilic attack of the phenolate on the transient palladium species **3**.