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An Improved Protocol for the Pd-catalyzed α -Arylation of Aldehydes with Aryl Halides

Rubén Martín and Stephen L. Buchwald*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts

Abstract

An improved protocol for the Pd-catalyzed α -arylation of aldehydes with aryl halides has been developed. The new catalytic system allows for the coupling of an array of substrates including challenging electron-rich aryl bromides and less reactive aryl chlorides. The utility of this method has been demonstrated in a new total synthesis of ($\pm$)-sporochinol.

The potential utility of α -aryl carbonyl compounds have prompted organic chemists to look for alternatives to their classical syntheses.¹ In recent years, the metal-catalyzed α -arylation of carbonyl compounds has gained considerable attention due to the ready availability of the starting materials and the mild reaction conditions that are needed.² Despite the advances realized, the high sensitivity of aldehydes and their propensity to undergo aldol condensation in basic media make them particularly challenging substrates for α -arylation reactions (Scheme 1).^{3,4}

In 2007, our research group reported a protocol for the α -arylation of aldehydes with both aryl bromides and aryl chlorides under mild reaction conditions.⁵ More recently, a similar α -arylation reaction has been described with aryl bromides and a limited set of activated aryl chlorides using dppf and QPhos as the ligands, respectively.^{6,7} Despite these improvements, however, the coupling of electron-rich aryl bromides or their less reactive counterparts, aryl chlorides, with linear aldehydes still remains a challenge.

Although we previously suggested that water content may be important in these α -arylation reactions,⁵ our early experiments did not completely establish its significance. We began our new investigation by studying the effects of water in our Pd(OAc)₂/BINAP catalytic system. As shown in Table 1, the addition of molecular sieves resulted in the complete loss of catalytic activity (entry 1). Additionally, the use of flame-dried Cs₂CO₃ (entry 2)⁸ and/or a rigorously anhydrous solvent (entry 3)^{8,9} resulted in very low conversions of octanal to the desired α -aryl aldehyde. The yields of these reactions are comparable with those recently reported in the literature in which poor catalytic performance was found when using the Pd(OAc)₂/BINAP system.⁶ In contrast, yields could substantially be improved by using regular “anhydrous”

sbuchwal@mit.edu.

Supporting Information Available: Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

solvents with higher water content (entries 4 and 5). These results indicate that water might be promoting the reduction of Pd(OAc)₂ to the active L_nPd(0) species.¹⁰ In accordance with this hypothesis, a faster reaction rate was observed either by adding water (entries 6, 7, and 8) or by using our recently developed water-mediated preactivation protocol (entry 9).^{10a}

Next, we set out to explore the reaction of electron-rich aryl halides in the α -arylation of linear aldehydes. Because the elementary steps, oxidative addition, transmetalation and reductive elimination are relatively slow, such substrates are more challenging than electron-neutral ones in cross-coupling reactions.¹¹ Recently, it has been demonstrated that both electronic and steric effects might play a crucial role in the Pd-catalyzed α -arylation of linear aldehydes.⁶ Indeed, while the coupling of linear aldehydes with 2-bromoanisole using dppe as the ligand proceeded efficiently, the reaction of the less sterically encumbered, electron-rich 4-bromoanisole resulted in very low yields.⁶ In light of these precedents, we present herein an improved protocol for the direct Pd-catalyzed α -arylation of linear and α -branched aldehydes with challenging electron-rich aryl bromides and the less reactive aryl chlorides under mild conditions.

We initially studied the reaction of octanal with 4-bromoanisole using various palladium sources, ligands, bases, and solvents (Table 2). Although several bases and solvents were examined, the combination of Cs₂CO₃ and dioxane (24 ppm water content) gave the best results. Entries 1 to 3 show that the previously reported best ligands, *rac*-BINAP⁵ (entry 1), dppe⁶ (entry 2) and QPhos⁶ (entry 3) afforded low yields of the desired product. It is well recognized that the bite angle of bidentate phosphines may play a crucial role in the reaction outcome of catalytic reactions,¹² with wider bite angles facilitating reductive elimination.¹³ In line with this notion, we found that the use of XantPhos, which has a wider bite angle than BINAP or dppe, afforded the desired α -aryl aldehyde in 70% yield after 6 h (entry 4).¹⁴ Consistent with the previous results shown in Table 1, while no conversion was observed in the presence of molecular sieves (entry 4) similar yields were obtained when using a water-mediated preactivation protocol (entry 5).^{10a} It is worth mentioning, however, that ligands with wider bite angles than XantPhos, such as **L2**¹⁵ (entry 9) or dppe (entry 10) resulted in lower yields, thus illustrating the subtleties of the system. Finally, catalysts generated from [Pd(allyl)Cl]₂⁶ or [Pd(cinnamyl)Cl]₂¹⁶ turned out to be slightly more efficient than Pd(OAc)₂ (entry 4 vs entries 6 and 7).

Encouraged by these results, we turned our attention to the α -arylation of 4-chloroanisole since there are no previous reports on the effective coupling of electron-rich aryl chlorides with linear aldehydes. We found, however, that low yields could be achieved when using our previous catalytic system based on **L3**⁵ (Table 2, entry 12). After optimization, we found that our recently developed one-component XPhos precatalyst (**1**)¹⁷ afforded the corresponding α -aryl aldehyde in 69% yield (Table 2, entry 17). These differences might be due to the ability of **1** to generate the active L_nPd(0) species efficiently within the catalytic cycle.

The scope of the Pd-catalyzed α -arylation of linear aldehydes with electron-rich aryl bromides and chlorides is shown in Table 3. The more challenging electron-rich chloroarenes could all be successfully coupled albeit in moderate yields. The process is compatible with several functional groups in both coupling counterparts, including those bearing ethers, amines, sulfides, alkenes, esters, carbamates or acetals. In line with our previous findings, the coupling of isovaleraldehyde required a longer reaction time (entries 3, 6, 7 and 9). Particularly significant is the compatibility of the new protocol toward labile substrates such as epoxides (entry 7),¹⁸ which have not been thoroughly investigated in the context of cross-coupling methods,¹⁹ and *N*-Boc-protected groups (entry 12). Furthermore, the method exhibited an excellent chemoselectivity for aldehyde α -arylation over ester α -arylation (entry 8).

Next, we set out to probe whether electron-rich aryl halides were amenable to couple with α -branched aldehydes (Table 4). While the coupling of electron-rich aryl bromides was better performed with SPhos and Pd(OAc)₂ as the palladium precursor,²⁰ the Xphos precatalyst **1** was found to be optimal for electron-rich aryl chlorides under identical reaction conditions to those using unbranched aldehydes. The results summarized in Table 4 indicate that the coupling of non sterically biased 4-oxygen-, 4-sulfur- as well as 4-nitrogen-substituted aryl halides behaved similarly well. Notably, epoxides could again be tolerated under these reaction conditions, thus affording the corresponding α -aryl aldehyde in moderate yield (entry 2).

The utility of this method is further illustrated in the short total synthesis of ($\pm$)-sporochnol,²¹ a natural product that is a fish deterrent, by using the α -arylation of an α -branched aldehyde as the key step (Scheme 2). Subsequent Wittig reaction followed by deprotection of the aryl ether provided ($\pm$)-sporochnol in 54% overall yield over 3 steps from commercially available starting materials.

In summary, we have shown that subtle ligand changes can lead to a dramatic increase in the catalytic activity of aldehyde α -arylation reactions. The transformation is distinguished by its scope, including the coupling of challenging electron-rich aryl bromides and aryl chlorides under mild reaction conditions. The combination of these results with those previously reported in the literature^{5,6} provide a fairly general means for the α -arylation of aldehydes. Further studies on this transformation as well as the development of enantioselective protocols are currently underway.

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Scheme 1.
 α -Arylation of Aldehydes with Aryl Halides

Scheme 2.
Total synthesis of (±)-sporochinol

Table 1Role of Water in Aldehyde α -Arylation Reactions

entry	R	additive	H ₂ O in dioxane (ppm) ^a	yield (%) ^b
1	<i>n</i> -Hexyl	+ 4 Å sieves	24	0
2	<i>n</i> -Hexyl	None	24	33 ^c
3	<i>n</i> -Hexyl	None	2	24
4	<i>n</i> -Hexyl	None	24	64
5	<i>n</i> -Hexyl	None	51	67
6	<i>n</i> -Hexyl	+ H ₂ O (5 mol %)	24	67 ^d
7	<i>n</i> -Hexyl	+ H ₂ O (10 mol %)	24	66 ^d
8	<i>n</i> -Hexyl	+ H ₂ O (20 mol %)	24	51 ^d
9	<i>n</i> -Hexyl	+ H ₂ O (4 mol %)	24	66 ^e
10	Ethyl	None	24	55

^a Determined by Karl Fisher titration.^b GC yields using dodecane as internal standard.^c Freshly flame-dried Cs₂CO₃ was used.^d After 8 h reaction time.^e Water-mediated preactivation, according to ref. 10a.

Table 2 α -Arylation of Octanal with Electron-rich Aryl Halides^a

entry	X	Pd source	L	yield (%) ^b
1	Br	Pd(OAc) ₂	<i>rac</i> -BINAP	32
2	Br	[Pd(allyl)Cl] ₂	QPhos	19 ^c
3	Br	[Pd(allyl)Cl] ₂	dppf	39
4	Br	Pd(OAc) ₂	XantPhos	70, 0 ^d
5	Br	Pd(OAc) ₂	XantPhos	71 ^e
6	Br	[Pd(cinnamyl)Cl] ₂	XantPhos	73
7	Br	[Pd(allyl)Cl] ₂	XantPhos	76
8	Br	[Pd(allyl)Cl] ₂	DPEPhos	21
9	Br	[Pd(allyl)Cl] ₂	L1	68
10	Br	[Pd(allyl)Cl] ₂	L2	34
11	Br	[Pd(allyl)Cl] ₂	dppb	21
12	Cl	Pd(OAc) ₂	L3	34 ^f
13	Cl	[Pd(allyl)Cl] ₂	L3	33 ^f
14	Cl	[Pd(allyl)Cl] ₂	QPhos	0 ^{f,g}
15	Cl	Pd(OAc) ₂	XPhos	55 ^f
16	Cl	Pd(OAc) ₂	SPhos	41 ^f
17	Cl	1	-	69 ^{f,h}
18	Cl	2	-	58 ^{f,h}

L1 (n = 2)**L2** (n = 0) **L3** XPhos (R = R¹ = *i*Pr)
SPhos (R = OMe, R¹ = H) **1** (R = H) or **2** (R = Me)

^a Reaction conditions: aryl bromide (1.0 mmol), aldehyde (1.20 mmol), Pd precatalyst (2 mol %, 1 mol % if dimer was used), ligand (3 mol %), Cs₂CO₃ (1.20 mmol) and dioxane (0.25 M) at 80 °C for 6 h.

^b GC yields using dodecane as internal standard.

^c According to ref. ⁶: [Pd(allyl)Cl]₂ (0.50 mol %), QPhos (1 mol %), Cs₂CO₃ (2.0 mmol) and THF (0.50 M).

^d With 4 Å molecular sieves.

^e Water-mediated preactivation, according to ref. ^{10a}.

^f Reaction conducted at 100 °C.

^g According to ref. ⁶: [Pd(allyl)Cl]₂ (1 mol %), QPhos (2 mol %), Cs₂CO₃ (2.0 mmol) and THF (0.25 M) at 90 °C.

^h Pd-precatalyst (2 mol %) was used.

Table 3

Pd-catalyzed α -Arylation of Linear Aldehydes

$ \begin{array}{c} \text{ArBr: Pd precat. (1-2 mol \%)} \\ \text{XantPhos (3 mol \%)} \\ \text{ArCl: } \mathbf{1} \text{ (2 mol \%)} \\ \text{Cs}_2\text{CO}_3 \text{ (1.20 equiv)} \\ \text{dioxane (24 ppm H}_2\text{O)} \\ 80 - 100\text{ }^\circ\text{C} \end{array} $		
entry	product	X ^a
1		Br Cl
2		Br Cl
3		Br Cl
4		Br Cl
5		Br Cl
6		Br Cl

entry

product

 X^a

7

Br
Cl

8

Br
Cl

entry

product

 X^a

9

Br
Cl

entry

product

X^a

10

Br
Cl

11

Br
Cl

entry

product

 X^a

12

Br
Cl

^a $\text{X}=\text{Br}$: Aryl bromide (1.0 mmol), Pd precatalyst (1-2 mol %), XantPhos (3 mol %), Cs_2CO_3 (1.20 mmol) in dioxane (0.25 M) at 80 °C under argon;
 $\text{X}=\text{Cl}$: Aryl chloride (1.0 mmol), **1** (2 mol %), Cs_2CO_3 (1.20 mmol) in dioxane (0.25 M) at 100 °C under argon.

^bYields of isolated products are an average of two runs.

^c $[\text{Pd}(\text{allyl})\text{Cl}]_2$ (1 mol %).

^d $\text{Pd}(\text{OAc})_2$ (2 mol %).

^e $[\text{Pd}(\text{cinnamyl})\text{Cl}]_2$.

Table 4

Pd-catalyzed α -Arylation of α -Branched Aldehydes

entry

product

 X^a

1

Br
Cl

2

Br
Cl

entry

product

 X^a

3

Br
Cl

entry

product

 X^a

4

Br
Cl

entry

product

 X^a

5

Br
Cl

6

Br
Cl

^aX=Br, as in Table 2, but using Pd(OAc) (2 mol %) and SPhos (3 mol %); X=Cl, as in Table 2.

^bYields of isolated products are an average of two runs.