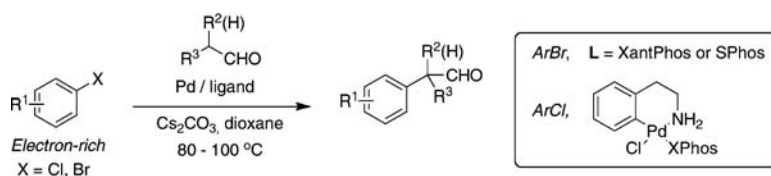


An Improved Protocol for the Pd-Catalyzed #-Arylation of Aldehydes with Aryl Halides

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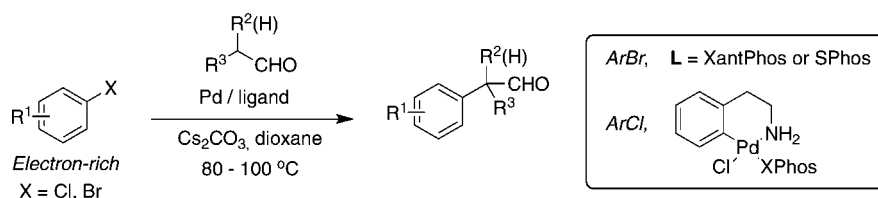
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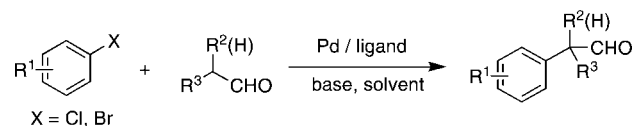
ABSTRACT



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 has 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

Scheme 1. α -Arylation of Aldehydes with Aryl Halides

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

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(3) (a) First intermolecular α -arylation of aldehydes: Terao, Y.; Fukuoka, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **2002**, *43*, 101. (b) Intramolecular version: Muratake, H.; Natsume, M.; Nakai, H. *Tetrahedron* **2004**, *60*, 11783. (c) For an example using 2-chlorotoluene, see: Lavallo, V.; Canac, Y.; Prasang, C.; Donnadiou, B.; Bertrand, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 5705.

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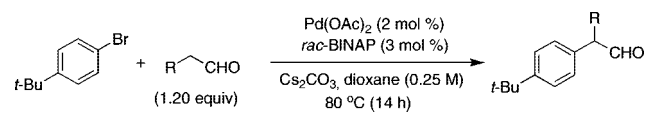
(5) Martín, R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 7236.

(6) Vo, G. D.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2008**, *47*, 2127.

(7) According to the known $-I$ effect of a methoxy group in the meta position ($\sigma_{\text{meta}} = +0.12$), 3-chloroanisole cannot be considered electron-neutral: Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *97*, 165.

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

Table 1. Role of Water in Aldehyde α -Arylation Reactions



entry	R	additive	H ₂ O in dioxane ^a (ppm)	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	(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.

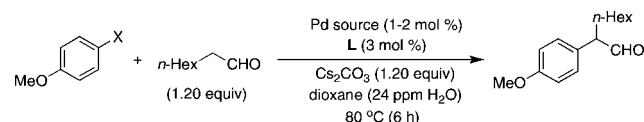
loss of catalytic activity (entry 1). Additionally, the use of flame-dried Cs₂CO₃ (entry 2)⁸ and/or a rigorously anhydrous solvent (entry 3)^{8,9} resulted in very low conversions of octanal to the desired α -aryl aldehyde. The yields of these reactions are comparable with those recently reported in 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” 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 6–8) 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 dppf 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.

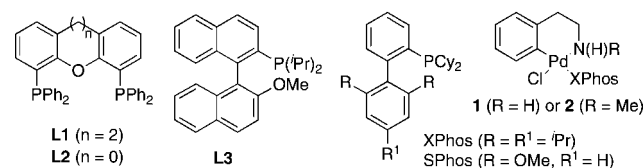
We initially studied the reaction of octanal with 4-bromoanisole using various palladium sources, ligands, bases, and solvents (Table 2). Although several bases and solvents

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}

^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.



were examined, the combination of Cs₂CO₃ and dioxane (24 ppm water content) gave the best results. Entries 1–3 show that the previously reported best ligands, *rac*-BINAP⁵ (entry 1), dppf⁶ (entry 3), and QPhos⁶ (entry 2), afforded low yields of the desired product. It is well recognized that the bite

(8) The reaction was set up in the glovebox.

(9) Dioxane was freshly distilled and dried over 4 Å molecular sieves. (10) (a) Fors, B. P.; Krattiger, P.; Strieter, E.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 3505. (b) Amatore, C.; Jutand, A.; Khalil, F. *Arkivoc* **2006**, *4*, 38. (c) Ozawa, F.; Kubo, A.; Hayashi, T. *Chem. Lett.* **1992**, 2177.

(11) *Cross-Coupling Reactions. A Practical Guide*; Miyaura, N., Ed.; Topics in Current Chemistry; Springer: Berlin, 2002.

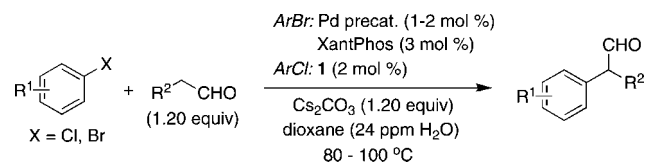
angle of bidentate phosphines may play a crucial role in the reaction outcome of catalytic reactions,¹² with wider bite angles facilitating reductive elimination.¹³ In line with this notion, we found that the use of XantPhos, which has a wider bite angle than BINAP or dppf, afforded the desired α -aryl 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 dppb (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

Table 3. Pd-Catalyzed α -Arylation of Linear Aldehydes



entry	product	X ^a	yield (%) ^b
1		Br	70 ^c
		Cl	65
2		Br	73 ^c
		Cl	58
3		Br	64 ^d
		Cl	51
4		Br	66 ^e
		Cl	60
5		Br	74 ^e
		Cl	58
6		Br	65 ^d
		Cl	61
7		Br	56 ^d
		Cl	51
8		Br	65 ^e
		Cl	45
9		Br	58 ^d
		Cl	50
10		Br	84 ^d
		Cl	62
11		Br	73 ^d
		Cl	57
12		Br	56 ^e
		Cl	50

^a X = Br: aryl bromide (1.0 mmol), Pd precatalyst (1–2 mol %), XantPhos (3 mol %), Cs₂CO₃ (1.20 mmol) in dioxane (0.25 M) at 80 °C under argon; X = Cl: Aryl chloride (1.0 mmol), **1** (2 mol %), Cs₂CO₃ (1.20 mmol) in dioxane (0.25 M) at 100 °C under argon. ^b Yields of isolated products are an average of two runs. ^c [Pd(allyl)Cl]₂ (1 mol %). ^d Pd(OAc)₂ (2 mol %). ^e [Pd(cinnamyl)Cl]₂.

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 reaction conditions identical to those using unbranched aldehydes. The results

(20) The use of QPhos as the ligand gave comparable results.

(21) Selected total synthesis of (±)-sporochinol: (a) Alibés, R.; Busqué, F.; Bardají, G. G.; de March, P.; Figueredo, M.; Font, J. *Tetrahedron: Asymmetry* **2006**, *17*, 2632. (b) Ávila-Zárraga, J. G.; Barroso, M.; Covarrubias-Zúñiga, A.; Romero-Ortega, M. *Synth. Commun.* **2005**, *35*, 389. (c) Shan, S.; Ha, C. *Synth. Commun.* **2005**, *34*, 4005. (d) Ohira, S.; Kuboki, A.; Hasegawa, T.; Kikuchi, T.; Kutsukake, T.; Nomura, M. *Tetrahedron Lett.* **2002**, *43*, 4641.

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(13) Brown, J. M.; Guiry, P. J. *Inorg. Chem. Acta* **1994**, *220*, 249.

(14) Similar results were obtained when the Pd/L ratio was 1:2 or 1:3.

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(18) In any case, products derived from the ring-opening of the epoxide could not be detected by NMR of the crude reaction mixtures.

(19) For recent cross-coupling reactions in the presence of epoxides: (a) Fürstner, A.; Martín, R.; Krause, H.; Seidel, G.; Goddard, R.; Lehmann, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 8773. (b) Cattoën, X.; Pericàs, M. A. *J. Org. Chem.* **2007**, *72*, 3253.

Table 4. Pd-catalyzed α -Arylation of α -Branched Aldehydes

ArBr: Pd(OAc)_2 (2 mol %)
 SPhos (3 mol %)
 ArCl: 1 (2 mol %)
 Cs_2CO_3 (1.20 equiv)
dioxane (24 ppm H_2O)
80 - 100 °C

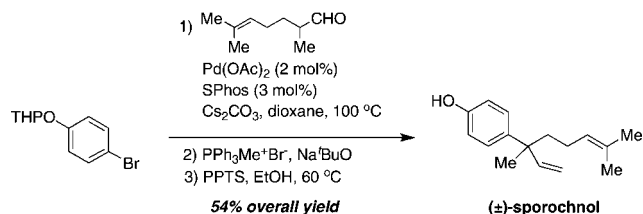
entry	product	X ^a	yield (%) ^b
1		Br	63
		Cl	60
2		Br	54
		Cl	51
3		Br	65
		Cl	54
4		Br	67
		Cl	59
5		Br	68
		Cl	55
6		Br	56
		Cl	52

^a X = Br, as in Table 2, but using Pd(OAc) (2 mol %) and SPhos (3 mol %); X = Cl, as in Table 2. ^b Yields of isolated products are an average of two runs.

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)-sporochinol,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

Scheme 2. Total Synthesis of (\pm)-Sporochinol

reaction followed by deprotection of the aryl ether provided (\pm)-sporochinol in 54% overall yield over three 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.

Acknowledgment. We thank the National Institutes of Health (GM 46059) for support of this work. Chemetall and BASF are acknowledged for a generous gift of Cs₂CO₃ and Pd(OAc)₂, respectively. We are also indebted to Merck, Amgen, and Boehringer-Ingelheim for unrestricted support. The Varian 300 MHz used in this work was purchased with funding from the National Institutes of Health (GM 1S10RR-13886-01).

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>. OL8017775