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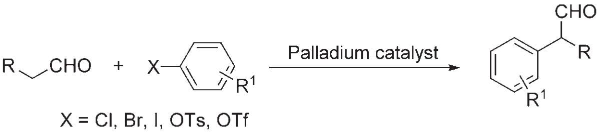
α-Arylation of Aldehydes

# Palladium-Catalyzed α-Arylation of Aldehydes with Bromo- and Chloroarenes Catalyzed by [{Pd(allyl)Cl}$_2$] and dppf or Q-phos**

*Giang D. Vo and John F. Hartwig**

α-Aryl carbonyl compounds are precursors to many important synthetic intermediates bearing alcohol, imine, amine, olefin, and nitrile functional groups.[1–5] The palladium-catalyzed α-arylation of carbonyl compounds has evolved into one of the more important methods for the preparation of compounds.[6,7] The α-arylation process now encompasses the couplings of ketones,[8–10] amides,[11–13] esters,[12,14] malonates,[9,15] and cyanoacetates[15,16] with a broad range of aryl halides and sulfonates. The α-arylation of aldehydes [Eq. (1)], however, has been challenging to develop because of competing aldol condensations under the cross-coupling reaction conditions. Accordingly, only three reports on the α-arylation of aldehydes have been published. The first examples were reported by Miura and co-workers in 2002.[17] Miura's protocols employed high temperatures and high catalyst loadings to give modest yields of the coupled products, and the substrate scope was limited. In 2005 Bertrand and co-workers described the α-arylation of isobutanal with 2-chlorotoluene in the presence of a palladium(II) catalyst ligated by a cyclic(amino)alkyl carbene.[18] Recently, Martín and Buchwald described improved protocols for the α-arylation of aldehydes, but most examples in this work involved the coupling of electron-poor aryl halides; few reactions of haloarenes that could be considered to be electron-neutral or electron-rich were reported, and the one example of the reaction of an electron-rich haloarene was sterically biased.[19]

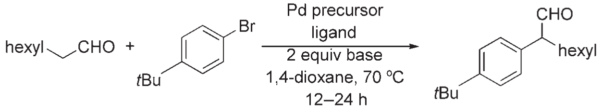


(1)

Herein we report a more general system for palladium-catalyzed coupling of aldehydes with electron-poor and electron-rich aryl bromides. The coupling of linear aldehydes with electron-poor or electron-neutral bromoarenes occurred in good yield when catalyzed by complexes having a bisphosphine ligand. The coupling of branched aldehydes with bromo- and chloroarenes occurred in high yield when catalyzed by complexes bearing monophosphine 1,2,3,4,5-pentaphenyl-1′-(di-*tert*-butylphosphino)ferrocene (Q-phos) that was developed in our laboratory.[20] One factor that leads to the efficiency of this process is the use of these ligands in combination with a palladium precursor that is known[21] to undergo facile generation of active [L$_n$Pd$^0$] species.

Our initial study focused on the identification of a catalyst for α-arylation that reacted with rates that were faster than those of the competing aldol condensations. We examined various combinations of palladium precursors and ligands for the coupling of octanal with 1-bromo-4-*tert*-butylbenzene in the presence of various bases, and the results of this study are summarized in Table 1. Reactions conducted with either [Pd(dba)$_2$] (dba = *trans*,*trans*-dibenzylideneacetone) or Pd(OAc)$_2$ as a catalyst precursor and cesium carbonate as a base formed the coupled product in modest yields. Catalysts generated from [Pd(dba)$_2$] or Pd(OAc)$_2$ and bisphosphine ligands bis[2-(diphenylphosphino)phenyl]ether (dpephos), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (xant-

***Table 1:*** Effects of catalyst components on the coupling of octanal with 1-bromo-4-*tert*-butylbenzene.[a]



| Entry | Pd precursor ([mol%]) | Ligand ([mol%]) | Base | Yield [%][b] |
|---|---|---|---|---|
| 1 | [Pd(dba)$_2$] (5) | dpephos (5) | Cs$_2$CO$_3$ | 40 |
| 2 | [Pd(dba)$_2$] (5) | xantphos (5) | Cs$_2$CO$_3$ | 60 |
| 3 | [Pd(dba)$_2$] (5) | dppf (5) | Cs$_2$CO$_3$ | 68 |
| 4 | [Pd(dba)$_2$] (5) | *rac*-binap (5) | Cs$_2$CO$_3$ | 66 |
| 5 | [Pd(dba)$_2$] (5) | dpephos (5) | Cs$_2$CO$_3$ | 49 |
| 6 | [Pd(dba)$_2$] (5) | P(*t*Bu)$_3$ (5) | Cs$_2$CO$_3$ | 65 |
| 7 | [Pd(dba)$_2$] (5) | Q-phos (5) | Cs$_2$CO$_3$ | 60 |
| 8 | [{PdBr[P(*t*Bu)$_3$]}$_2$] (2.5) | – | Cs$_2$CO$_3$ | 30 |
| 9 | APC (2.5) | dppf (5) | Cs$_2$CO$_3$ | 24 |
| 10 | APC (2.5) | dppf (10) | Cs$_2$CO$_3$ | 94 |
| 11 | APC (2.5) | dppf (10) | K$_2$CO$_3$ | 61 |
| 12 | APC (2.5) | dppf (10) | K$_3$PO$_4$ | 72 |
| 13 | APC (2.5) | xantphos (5) | Cs$_2$CO$_3$ | 88 |
| 14 | APC (2.5) | *rac*-binap (10) | Cs$_2$CO$_3$ | 32 |
| 15 | APC (2.5) | P(*t*Bu)$_3$ (10) | Cs$_2$CO$_3$ | 66 |
| 16 | APC (2.5) | Q-phos (10) | Cs$_2$CO$_3$ | 82 |

[a] Reaction conditions: octanal (0.24 mmol), 1-bromo-4-*tert*-butylbenzene (0.20 mmol), base (0.40 mmol), 1,4-dioxane (1.0 mL). [b] Yields were determined by GC with dodecane as an internal standard.

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[**] We are grateful to the NIH (GM-58108) for support of this work and Johnson-Matthey for gifts of palladium. dppf = 1,1′-bis(diphenylphosphino)ferrocene; Q-phos = 1,2,3,4,5-pentaphenyl-1′-(di-*tert*-butylphosphino)ferrocene.

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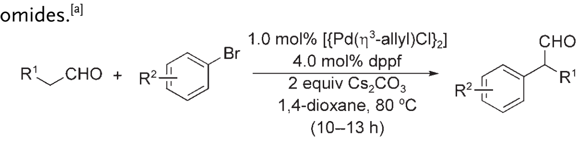
phos), 1,1′-bis(diphenylphosphino)ferrocene (dppf), and 2,2′-bis(diphenylphosphino)-1,1′-binapthyl (*rac*-binap) did not allow complete conversion of the bromoarene after 24 hours. This slow rate led to aldol condensation products in more than 20 % yield (Table 1, entries 1–5). Although catalysts generated from monophosphine ligands Q-phos and $P(tBu)_3$ exhibited higher rates of conversion of the aryl bromide, about 15–20 % of *tert*-butylbenzene was formed from hydrodebromination of the 1-bromo-4-*tert*-butylbenzene (Table 1, entries 6 and 7).

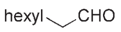
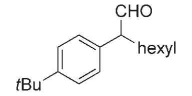
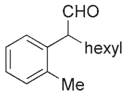
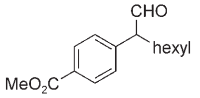
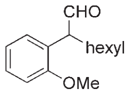
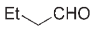
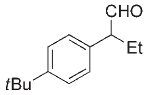
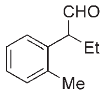
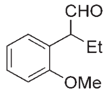
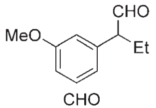
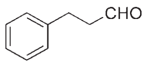
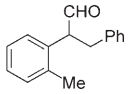
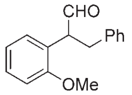
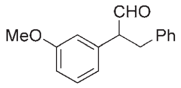
Since the efficiency of generating active catalysts from precursors could affect rates of the coupling reactions, several palladium precursors that are known to undergo facile reduction to the active $[L_nPd^0]$ species were examined.[22] The reaction conducted with 1.0 mol % of allylpalladium-chloride ($[\{Pd(\eta^3\text{-allyl})Cl\}_2]$; APC) proceeded with complete conversion of the bromoarene after 14 hours. Of the catalysts generated from APC, a combination of 2.5 mol % of the APC dimer and 10 mol % of dppf in the presence of $Cs_2CO_3$ formed the coupled product in the highest yield (Table 1, entry 10). The same coupling reactions conducted with either $K_3PO_4$ or $K_2CO_3$ as a base occurred in lower yields (Table 1, entries 11 and 12), and reactions catalyzed by complexes bearing other bisphosphine and monophosphine ligands formed the coupled product in lower yields (Table 1, entries 13–16). Additional experimentation with the combination of APC and dppf showed that reactions conducted with 1 mol % of APC, 4 mol % of dppf, 2 equivalents of $Cs_2CO_3$, 0.25 M bromoarene, and 0.30 M aldehyde in dioxane formed the coupled product in the highest yields.

We evaluated the scope of the coupling of linear aldehydes with various aryl bromides by using the optimized reaction conditions, and the results are summarized in Table 2. The scope of this process encompassed electron-neutral, electron-poor, and in one case electron-rich bromoarenes. Octanal coupled with electron-neutral 1-bromo-4-*tert*-butylbenzene and 2-bromotoluene in excellent yields (Table 2, entries 1 and 2), and reactions with the electron-poor methyl 4-bromobenzoate formed the coupled product in good yield (Table 2, entry 3). The steric properties of the bromoarene favorably affected the yield of the coupled product; for example, the electron-rich 2-bromoanisole formed the coupled product in high yield (Table 2, entry 4), whereas the less hindered electron-rich 4-bromoanisole formed the coupled product in about 30 % yield.

Coupling reactions of *n*-butyraldehyde occurred in good yields, albeit slightly lower than those reported with octanal. Reactions of butyraldehyde with 1-bromo-4-*tert*-butylbenzene and 2-bromotoluene occurred in 67 and 75 % yield, respectively (Table 2, entries 5 and 6). Although subtle, we attribute this difference in yields to the difference in steric bulk of the aldehydes (e.g. Table 2, entry 1 versus entry 5). Presumably the increased bulk leads to faster reductive elimination of the coupled products from the arylpalladium complexes of the octanal enolate than from complexes of the butyraldehyde enolate. Again, the steric properties of the bromoarene affected the yield; electron-rich 2-bromoanisole and 3-bromoanisole coupled with butyraldehyde in good yields (Table 2, entry 7 and 8). Reactions of *ortho*- and *meta*-substituted bromoarenes with the aromatic linear hydrocinnamyl aldehyde formed the coupled products in good yields (Table 2, entries 9–11). In contrast, reactions of the linear aldehydes with chloroarenes and bromopyridines resulted in low conversions and yields after 24 hours at 80 °C.

***Table 2:*** Palladium-catalyzed α-arylation of linear aldehydes with aryl bromides.[a]



| Entry | Aldehyde | Product | Yield [%][b] |
|---|---|---|---|
| 1 |  |  | 83 |
| 2 | |  | 93 |
| 3 | |  | 67 |
| 4 | |  | 77 |
| 5 |  |  | 67 |
| 6 | |  | 75 |
| 7 | |  | 70 |
| 8 | |  | 70 |
| 9 |  |  | 67 |
| 10 | |  | 76 |
| 11 | |  | 61 |

[a] Reaction conditions: aldehyde (1.0–1.2 mmol), aryl halide (1.0 mmol), $Cs_2CO_3$ (2.00 mmol), 1,4-dioxane (4 mL). [b] Yield of isolated product (average of two runs).

Reactions of branched aldehydes in the presence of APC and dppf occurred in substantially lower yields than did those of linear aldehydes. However, additional studies showed that high yields could be obtained when the reactions were catalyzed by combinations of APC and monophosphines. In particular, reactions conducted with APC (0.5 mol %), Q-phos (1 mol %), $Cs_2CO_3$ (2 equivalents), bromoarene (0.50 M), and aldehyde (0.60 M) in THF formed the coupled product in the highest yields. Chloroarenes also reacted with branched aldehydes under these conditions to give high yields of coupled products, albeit with higher catalyst loadings (1 mol% of APC and 2 mol% of Q-phos).

The scope of the reactions of the branched aldehydes is illustrated in Table 3. Electron-rich, electron-poor, and electron-neutral aryl bromides reacted with α-branched 2-methylbutyraldehyde to give α-aryl aldehydes bearing a quaternary center at the α position in high yields (Table 3, entries 1–4, 6 and 8). Both *ortho*- and *meta*-subtituted aryl bromides coupled with this aldehyde in high yields (Table 3, entries 9 and 10), whereas aryl chlorides such as methyl 4-chorobenzoate, 4-chlorobenzonitrile, and 3-chloroanisole reacted with 2-methylbutyraldehyde to give the corresponding α-aryl aldehydes in good yields (Table 3, entries 5, 7, and 11).

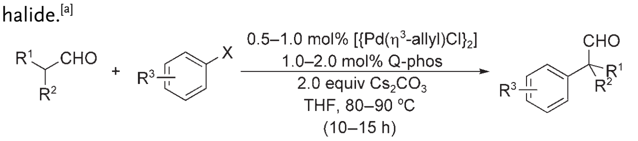
Under the conditions used for reactions of α-branched aldehydes, β-branched isovaleraldehyde reacted with bromoarenes to form coupled products in good yields. The scope of the reaction with respect to the aryl bromide is broad; electron-neutral (Table 3, entry 12), electron-rich (Table 3, entries 13 and 14), and electron-poor (Table 3, entry 15) bromoarenes formed the β-branched, α-aryl aldehydes in good yields. In some cases, reactions of β-branched aldehydes occurred under the conditions used for reactions of linear aldehydes. For example, the reaction between 1-bromo-4-(trimethylsilyl)benzene and β-branched isovaleraldehyde formed the coupled product in good yield when catalyzed by APC with dppf (Table 3, entry 16).

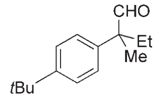
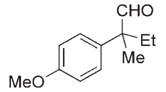
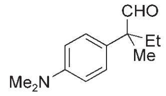
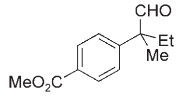
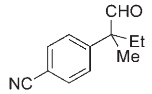
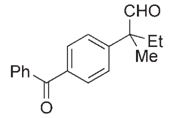
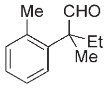
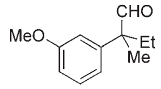
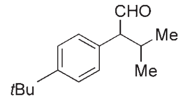
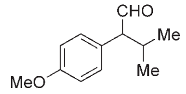
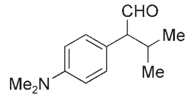
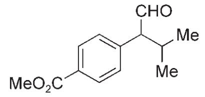
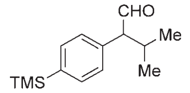
During our investigation of the direct α-arylation of aldehydes, Martín and Buchwald described the use of 2 mol% $Pd(OAc)_2$ and 3 mol% *rac*-binap for the α-arylations of linear aldehydes and 3 mol% of 2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl (S-phos) for the α-arylations of branched aldehydes (see above).[19] Table 4 provides a comparison of the reactions of electron-neutral bromoarenes with linear aldehydes and electron-rich bromoarenes with α-branched aldehydes catalyzed under the conditions of the previous work (conditions A) and under the conditions reported herein (conditions B).[23]

The coupling of both *n*-butanal and *n*-octanal with the electron-neutral 1-bromo-4-*tert*-butylbenzene occurred in substantially lower yields with $Pd(OAc)_2$ and *rac*-binap as the catalyst than with APC and dppf. Likewise, the reactions of 2-methylbutyraldehyde with electron-rich 4-bromo-*N*,*N*-dimethylaniline and 4-bromoanisole formed the coupled products in much higher yields with the catalyst generated from APC and Q-phos than with the catalyst generated from $Pd(OAc)_2$ and S-phos.

We attribute this difference in yields to both the palladium precursor and the ligand. The beneficial effect of the precursor is shown by reactions of octanal conducted with both dppf and *rac*-binap (Table 5). The catalyst generated from 4.5 mol% $[Pd(dba)_2]$ and 9.0 mol% dppf formed the coupled product in lower yield than the catalyst generated from 1 mol% APC and 4 mol% dppf. The catalyst generated from 10 mol% *rac*-binap and 2.5 mol% APC formed the coupled product in higher yield than that generated from 2 mol% $Pd(OAc)_2$ and 3 mol% *rac*-binap. However, the yield from the reaction catalyzed by APC and *rac*-binap remained low, and a comparison of the reactions (Table 5) in which APC and dppf or binap are used shows that dppf contributes significantly to the high yield of coupled product.

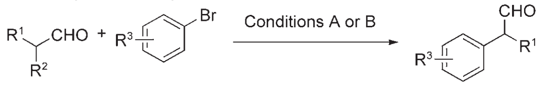
***Table 3:*** Palladium-catalyzed α-arylation of branched aldehydes with aryl halide.[a]



| Entry | Product | | Yield [%][b] |
|---|---|---|---|
| 1 |  | X = Br | 91 |
| 2 |  | X = Br | 81 |
| 3 |  | X = Br | 86 |
| 4 |  | X = Br | 81 |
| 5 | | X = Cl | 77 |
| 6 |  | X = Br | 80 |
| 7 | | X = Cl | 67 |
| 8 |  | X = Br | 79 |
| 9 |  | X = Br | 71 |
| 10 |  | X = Br | 83 |
| 11 | | X = Cl | 76 |
| 12 |  | X = Br | 80 |
| 13 |  | X = Br | 73 |
| 14 |  | X = Br | 67 |
| 15 |  | X = Br | 67 |
| 16[c] |  | X = Br | 85 |

[a] Reaction conditions: aldehyde (1.2 mmol), aryl halide (1.0 mmol), $Cs_2CO_3$ (2.00 mmol). For X = Br: APC (0.005 mmol), Q-phos (0.01 mmol), THF (2 mL), 80 °C; for X = Cl: APC (0.01 mmol), Q-phos (0.02 mmol), THF (4 mL), 90 °C. [b] Yield of isolated product (average of two runs). [c] Reaction conducted with 1.0 mol% APC, 4.0 mol% dppf in 1,4-dioxane.

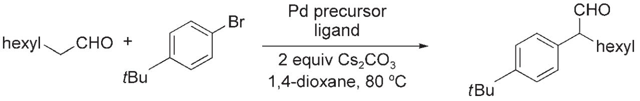
**Table 4:** Comparison of protocols.



| Entry | | Yield [%] Conditions A[a] | Conditions B[b] |
|---|---|---|---|
| 1 | $R^1 = Et$, $R^2 = H$<br>$R^3 = p\text{-}t\text{Bu}$ | 10 | 67 |
| 2 | $R^1 = n\text{C}_6\text{H}_{13}$, $R^2 = H$<br>$R^3 = p\text{-}t\text{Bu}$ | 10 | 83 |
| 3 | $R^1 = Et$, $R^2 = Me$<br>$R^3 = p\text{-NMe}_2$ | 65 | 86 |
| 4 | $R^1 = Et$, $R^2 = Me$<br>$R^3 = p\text{-OMe}$ | 44 | 81 |

[a] Reaction conditions A for entries 1 and 2: aldehyde (1.2 mmol), bromoarene (1.0 mmol), $Cs_2CO_3$ (1.2 mmol), $Pd(OAc)_2$ (0.020 mmol), *rac*-binap (0.030 mmol), 1,4-dioxane (4 mL), 14 h. For entries 3 and 4; S-phos (0.030 mmol) was used for reaction time of 16.5 h. Yields were determined by GC methods. [b] Reaction conditions B for entries 1 and 2: aldehyde (1.0–1.2 mmol), bromoarene (1.0 mmol), $Cs_2CO_3$ (2.0 mmol), APC (0.010 mmol), dppf (0.04 mmol), 1,4-dioxane (4 mL). For entries 3 and 4: APC (0.005 mmol), Q-phos (0.010 mmol), and THF (2 mL) was used instead. Yields of isolated products.

**Table 5:** Effects of the Pd precursor and the ligand.[a]



| Ligand = dppf[b] | | | Ligand = *rac*-binap | | |
|---|---|---|---|---|---|
| Precursor | Conv. | Yield | Precursor | Conv. | Yield |
| 4.5 mol% [Pd(dba)$_2$] | 81% | 60% | 2 mol% Pd(OAc)$_2$[d] | 52% | 10% |
| 1 mol% APC | 100% | 83%[c] | 2.5 mol% APC[e] | 85% | 32% |

[a] Conversions and yields were determined by GC with dodecane as an internal standard. [b] A ratio of 2:1 of dppf to palladium was used. [c] Isolated yield of coupled product. [d] Used 3 mol% of *rac*-binap. [e] Used 10 mol% of *rac*-binap.

In conclusion, we have developed an improved method for the palladium-catalyzed α-arylation of aldehydes. The scope of the arylation of linear aldehydes encompasses electron-poor and electron-neutral aryl bromides, whereas the scope of the arylation of branched aldehydes encompasses electron-rich, electron-neutral, and electron-poor aryl halides. One key to this broad substrate scope includes the use of a palladium precursor that can be easily reduced to an active $[L_nPd^0]$ species. Studies on improving the scope and the understanding of the mechanism for this process are ongoing in our laboratories.

## Experimental Section

General procedure for the α-arylation of linear aldehydes (Table 2): Outside the drybox, $[\{Pd(\eta^3\text{-allyl})Cl\}_2]$ (3.7 mg, 0.010 mmol), dppf (22.2 mg, 0.0400 mmol), $Cs_2CO_3$ (0.652 g, 2.00 mmol), and an aryl halide (if it is a solid) (1.00 mmol) were added to a 25-mL Schlenk flask that contained a magnetic stir bar. The flask was evacuated and back-filled with nitrogen three times. A solution of a linear aldehyde (1.00–1.10 mmol) and an aryl halide (if it is a liquid) (1.00 mmol) in 1,4-dioxane (4 mL) was then added by a gas-tight syringe. The flask was placed in an oil bath at 80 °C for 10–13 h. The reaction mixture was diluted with ethyl acetate (10 mL) and filtered through a pad of celite. The filtrate was concentrated in vacuo, and the crude product was purified using flash column chromatography on silica gel (hexanes/diethyl ether) to give the α-aryl aldehyde.

Procedure for reactions assembled inside the drybox: all reagents as described in the procedure above were added to a 5-dram scintillation vial containing a magnetic stir bar and sealed by a cap lined with teflon. The vial was removed from the drybox and placed in an oil bath at 80 °C.

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[23] Using conditions reported by Martín and Buchwald, we were able to obtain 72% yield of the isolated coupled product from the coupling of butyraldehyde with 2-bromoanisole. This result is consistent with that reported by Buchwald.