Homogeneous Catalysis

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A General Method for the Direct α-Arylation of Aldehydes with Aryl Bromides and Chlorides**

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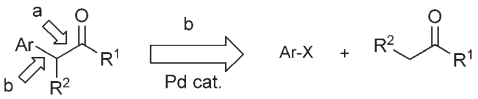
Dedicated to Süd-Chemie on the occasion of its 150th anniversary

The α-aryl carbonyl unit is an important constituent of many pharmaceuticals and bioactive natural compounds.[1] Over the last decade, the development of widely applicable protocols for the transition-metal-catalyzed α-arylation of carbonyl and related compounds has received a great deal of attention (approach b, Scheme 1).[2–5] Surprisingly, however, the α-arylation of aldehydes ($R^1 = H$, Scheme 1), which provides perhaps among the most versatile and useful synthons in organic synthesis, has remained less unexplored.[6]



Scheme 1. Pd-catalyzed α-arylation of carbonyl compounds.

In 2002, Miura and co-workers reported the only Pd-catalyzed protocol for the α-arylation of aldehydes with aryl halides.[7] Despite its importance, the procedure, however, had several drawbacks: 1) the yields were generally modest, 2) high catalyst loadings and temperatures were required, 3) substrate scope was low in both coupling counterparts, 4) the method was restricted to aryl bromides, and 5) a twofold excess of aldehyde was needed. Furthermore, no examples including functionalized or *ortho*-substituted substrates were described.[8] Consequently, as highlighted in a recent review,[9] an improved arylation of aldehydes with a broad scope should be extremely valuable for the synthetic organic chemistry community. Herein, we describe our initial studies on the direct Pd-catalyzed intermolecular α-arylation of linear and α-branched aldehydes with either aryl bromides or chlorides. The protocol allows for the synthesis of highly functionalized compounds and operates under mild conditions.

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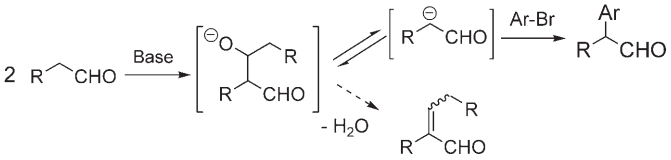
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

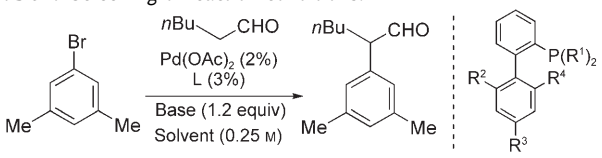
Since aldol condensation of aldehydes takes place under basic conditions, we decided to explore conditions in which the aldol reaction would be reversible,[10] hence masking the reactive enolate and avoiding decomposition pathways, such as dehydration of the aldol products (Scheme 2).



Scheme 2. Reversibility of the aldol reaction.

In a model reaction, we studied the combination of 5-bromo-*m*-xylene and hexanal (1.20 equiv) in the presence of various palladium precatalysts, bases, and solvents (Table 1). When the reaction was carried out at room temperature, the formation of only a small amount of product was observed. At

Table 1: Screening of reaction conditions.[a]



R^1=Cy, R^2=R^3=R^4=*i*Pr, L^1
R^1=Cy, R^2=R^4=OMe, R^3=H, L^2

Entry	L	Base	Solvent	*T* [°C]	Yield [%][b]
1	PPh_3	Cs_2CO_3	dioxane	25	1
2	$PtBu_3$	Cs_2CO_3	dioxane	25	4
3	L^1	Cs_2CO_3	dioxane	25	8
4	L^2	Cs_2CO_3	dioxane	25	13
5	*rac*-binap	Cs_2CO_3	dioxane	25	25
6	*rac*-binap	Cs_2CO_3	dioxane	100	34
7	*rac*-binap	Cs_2CO_3	dioxane	80	93
8	*rac*-binap	K_2CO_3	dioxane	80	74
9	*rac*-binap	K_3PO_4	dioxane	80	81
10	*rac*-binap	NatOBu	dioxane	80	39
11	*rac*-binap	Cs_2CO_3	toluene	80	53
12	*rac*-binap	Cs_2CO_3	MeOH	80	31
13	*rac*-binap	Cs_2CO_3	DME	80	79
14	*rac*-binap	Cs_2CO_3	THE	80	74
15	*rac*-binap	Cs_2CO_3	dioxane	80	3[c]
16	*rac*-binap	Cs_2CO_3	dioxane	80	84[d]

[a] Aryl bromide (1 mmol) and aldehyde (1.20 mmol). [b] GC yields using dodecane as an internal standard. [c] In the presence of 4-Å molecular sieves. [d] 10% water was added.

100 °C, the major product was that resulting from aldol condensation/dehydration of the starting aldehyde. After some experimentation, it was found that a catalyst composed of *rac*-binap and $Pd(OAc)_2$ in dioxane (0.25 M) at 80 °C provided the best results, affording the desired α-aryl aldehyde in excellent yield (Table 1, entry 7). Substitution of Cs_2CO_3 with other bases (Table 1, entries 8–10) or dioxane with other solvents (entries 11–14) resulted in lower yields of product.[11] The inclusion of molecular sieves in the reaction mixture had a deleterious effect, affording exclusively products derived from dehydration of the aldol products (Table 1, entry 15). In contrast, the addition of water (10 mol %) resulted in the formation of the desired α-aryl aldehyde in 84 % yield (Table 1, entry 16).[12] On the basis of these results, we believe that the key to the success of the reaction was determining conditions under which the aldol product can form rapidly, in a reversible manner (further evidence is provided below in Scheme 3).

Encouraged by these initial findings, we decided to examine the reaction with the less reactive aryl chlorides, which are more abundant as well as less expensive than their corresponding iodides, bromides, or fluorides (Figure 1). Based on our own experience in cross-coupling reactions, a bulkier and more electron-rich biaryl ligand was expected to be crucial by using aryl chlorides as coupling partners. Indeed, ligands L^1–L^3 were found to be particularly effective while L^8–L^{10} provided only trace amounts of the desired cross-coupling product. The use of bidentate ligands, such as xantphos (L^{11}) or *rac*-binap (L^{12}), afforded the desired product only in moderate yield. The best results were finally obtained by using L^5 [13] at 100 °C, with 1.5 equivalents of aldehyde under otherwise similar reaction conditions for the corresponding aryl bromides.

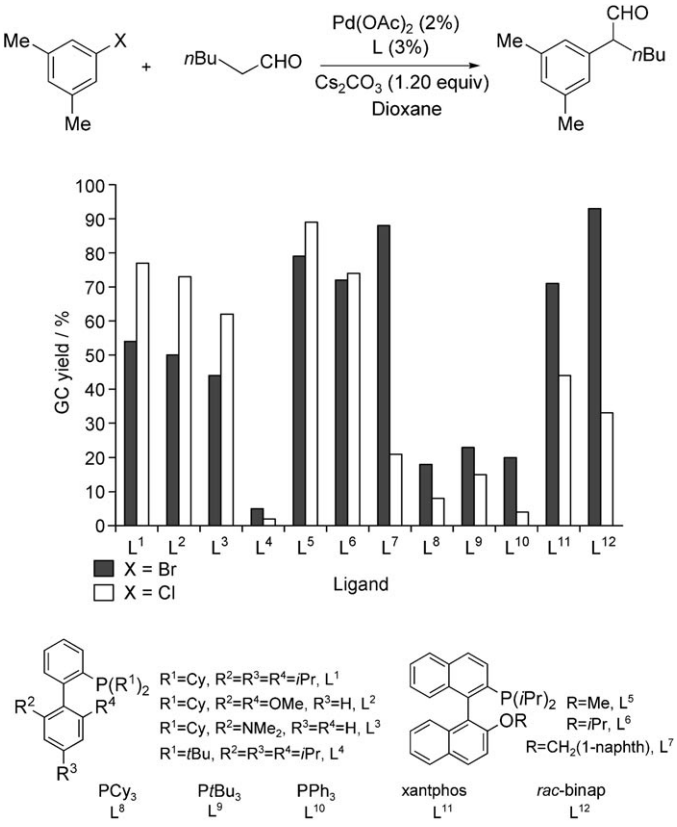


Figure 1. Screening the effect of ligands on the α-arylation of hexanal with aryl halides. For GC yields dodecane was used as internal standard. X = Br: aldehyde (1.20 equiv) in dioxane (0.25 M) at 80 °C for 3 h; X = Cl: aldehyde (1.50 equiv) in dioxane (0.125 M) at 100 °C for 8 h.

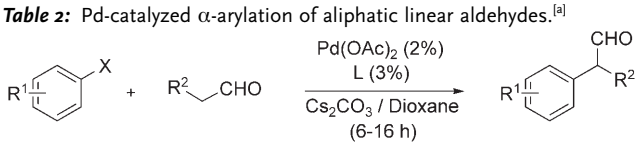
With the optimal reaction conditions established for the Pd-catalyzed α-arylation of aliphatic linear aldehydes, we turned our attention to the scope of this reaction (Table 2). With regard to the aryl halide, both electron-rich and electron-deficient aryl halides were equally efficient. A variety of functional groups were tolerated in either coupling partner, including silyl groups (Table 2, entries 1 and 4), esters (entries 2 and 4), ethers (entries 2, 3, and 6), acetals (entries 1, 5, and 10), alkenes (entry 9), aryl halides (entries 5 and 7), and heterocyclic moieties (entries 8, 9, and 10). Although β-substituents on the aldehyde (Table 2, entry 7) or *ortho* substituents in the aryl moiety (entries 5 and 6) did not hinder the reaction, these substrates required a longer reaction time. While the use of aryl bromides proved to be general, the coupling of 3-chloro-pyridine (Table 2, entry 9) or *ortho*-chlorofluorobenzene (entry 5) was unsuccessful, leading to decomposition. At present we do not have an explanation for this result.

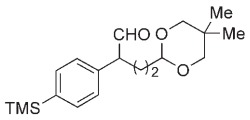
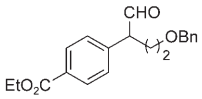
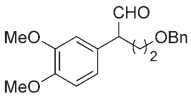
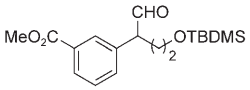
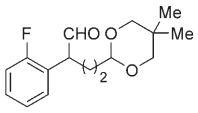
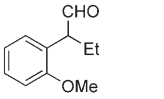
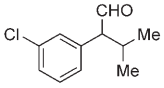
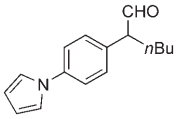
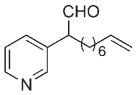
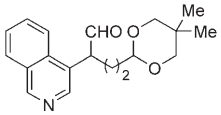
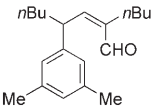
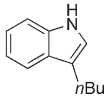
An interesting reaction outcome was observed when changing the solvent to DMF (Table 2, entries 11 and 12). In the first case, the product presumably arises from an aldol dimerization–dehydration, followed by a selective γ-arylation.[14] In contrast, the reaction of 2-bromoaniline did not afford the α-arylation nor the γ-arylation product, but the 3-substituted indole derivative in excellent yield (Table 2, entry 12).[15,16] In a process closely related to the Merck indole synthesis,[17] we believe that this reaction proceeds through the intermediacy of an aldimine, which tautomerizes to the enamine and undergoes an intramolecular arylation and subsequent isomerization to afford the 3-substituted indole.[18,19] Although not yet investigated in detail, α-arylations also occurred with lower catalyst loadings (Table 2, entries 1 and 12).

The formation of all-carbon quaternary centers remains a great challenge in organic synthesis.[20] To further extend the scope of our methodology, the α-arylation of α-branched aldehydes was evaluated (Table 3). While the reaction conditions were essentially identical to those described for Figure 1, the use of L^2 [21] provided superior results when using aryl bromides. As with unbranched aldehydes, the process shows a high degree of functional-group compatibility, leaving silyl groups (Table 3, entry 1), esters (entries 2 and 5), alkenes (entries 5 and 6), acetals (entry 6), aryl tosylates (entry 3), ketones (entry 4), ethers (entry 7), and heterocycles intact (entry 8).

To lend support for our hypothesis of a reversible aldol process, we independently prepared the aldol product **I** (as a mixture of diastereomers) from the self-condensation of hexanal (4:1 *anti*/*syn*).[22] The reaction of **I** (0.60 equiv) with methyl 3-bromobenzoate provided the α-arylated compound in a similar yield and took place at essentially the same rate as the corresponding reaction with hexanal

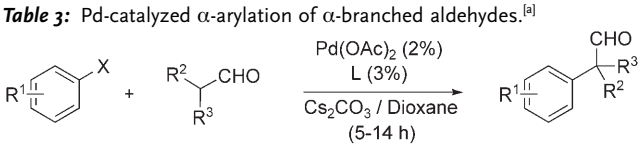
Table 2: Pd-catalyzed α-arylation of aliphatic linear aldehydes.[a]

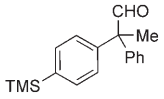
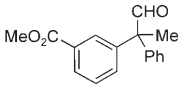
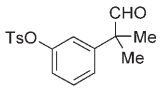
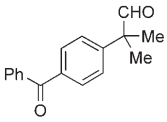
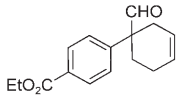
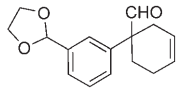
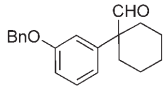
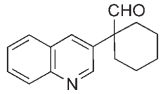


Entry	Product	X	Yield [%][b]
1		Br Cl	85, 74[c] 83
2		Br Cl	72 73
3		Br Cl	80 75
4		Br Cl	84 78
5		Br	66
6		Br Cl	76 64
7		Br	78
8		Br Cl	86 84
9		Br	75
10		Br	66
11		Br Cl	81[d] 83[d]
12		Br Cl	78[d] 84,[d] 72[c,d]

[a] X = Br: aryl bromide (1.0 mmol), $Pd(OAc)_2$ (2%), *rac*-binap (3%), aldehyde (1.20 mmol), Cs_2CO_3 (1.20 mmol) in dioxane (0.25 M) at 80 °C under argon; X = Cl: aryl chloride (1.0 mmol), $Pd(OAc)_2$ (2%), L^5 (3%), aldehyde (1.50 mmol), Cs_2CO_3 (1.20 mmol) in dioxane (0.125 M) at 100 °C under argon. [b] Yields of isolated product are an average of two runs. [c] $Pd(OAc)_2$ (1%) and L (1.5%) were used. [d] Aldehyde (2 equiv) and Cs_2CO_3 (2.40 equiv) were used in DMF (0.25 M) as the solvent. TBDMS = *t*BuMe$_2$Si.

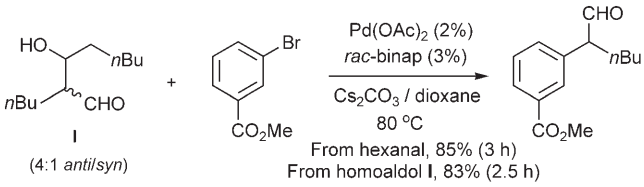
Table 3: Pd-catalyzed α-arylation of α-branched aldehydes.[a]



Entry	Product	X	Yield [%][b]
1		Br Cl	78 76
2		Br Cl	74 73
3		Br Cl	85 51[c]
4		Br Cl	86 57[c]
5		Br Cl	79 81
6		Br Cl	83 78
7		Br Cl	88 89
8		Br	84

[a] X = Br: as in Figure 1, but using L^2 (3%); X = Cl: as in Figure 1. [b] Yields of isolated product are an average of two runs. [c] Two equivalents of aldehyde were used at 80 °C.

(Scheme 3). This result supports a mechanistic pathway in which a reversible aldol reaction takes place under our catalytic reaction conditions, and indicates that aldol products are *both* chemically and kinetically competent as intermediates.



Scheme 3. Demonstration of the aldol product as a chemically and kinetically competent intermediate.

In summary, we have developed an efficient and general protocol for the α-arylation of linear and α-branched aldehydes using aryl bromides and even less reactive chlorides. The generality, ready availability of the starting materi-

als, and functional-group tolerance render this method attractive for organic synthesis. The high yields achieved as well as the versatility of aldehydes as synthons in organic synthesis make both processes useful for further synthetic applications. Further investigations into this reaction and the development of enantioselective protocols are currently underway in our laboratories.

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Keywords: aldehydes · arylation · homogeneous catalysis · P ligands · palladium

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[11] For experimental details, see the Supporting Information.

[12] Presumably the water inhibits dehydration of the aldol product.

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[17] C-Y. Chen, R. D. Larsen, *Org. Synth.* **2002**, *78*, 36 – 39.

[18] This explanation is supported by the fact that neither 3- nor 4-bromoaniline provided α-arylated or γ-arylated compounds by reaction with hexanal.

[19] At present, the available mechanistic information does not allow us to rule alternative pathways out. Thus, an intramolecular Heck reaction from the enamine intermediate could also be considered: J. Barluenga, M. A. Fernández, F. Aznar, C. Valdés, *Chem. Eur. J.* **2005**, *11*, 2276 – 2283.

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