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Tetrahedron Letters 46 (2005) 2273–2277

Tetrahedron Letters

Selective palladium-catalyzed arylation(s) of benzaldehyde derivatives by *N*-heterocarbene ligands

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Received 3 December 2004; revised 27 January 2005; accepted 2 February 2005

Abstract—The 2- or 2,6-position(s) of aromatic aldehydes were directly and selectively arylated with aryl chlorides or bromides in the presence of a catalytic system prepared in situ from $Pd(OAc)_2$, imidazolinium chlorides (**1**–**5**) and Cs_2CO_3.

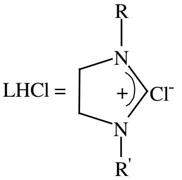
Biaryls are important structural units frequently found in pharmaceuticals, polymers, liquid crystals, new materials and ligands for homogeneous transition metal catalysts.[1] Among the most commonly employed catalytic methods in biaryl synthesis are Suzuki or Stille cross-coupling reactions, which invariably proceed using either nickel or palladium catalysts. Typically, these synthetic operations are carried out with the aid of functional groups such as boronic acid/esters or triorganotin fragments, respectively.[2,3] Therefore, the ability to couple an aryl halide directly at the unreactive C–H position of an arene without the need for a sacrificial electrophilic boron or tin fragment would be highly desirable.[4]

In this context, palladium/PR_3 catalyzed aryl–aryl coupling via C–H bond cleavage has recently been developed by Miura and co-workers;[5] for example, 2-phenylphenols,[6] alkyl aryl ketones,[7] benzyl phenyl ketones[8] and benzylanilides[9] were polyarylated with aryl bromides or triflates above 110 °C. However, aryl chlorides were rarely used, despite the fact that chlorinated arenes are cheaper to manufacture and therefore play a vital role as intermediates in the chemical industry. Presumably this is due to the fact that the chlorides were generally found to be unreactive under the conditions employed to couple bromides, iodides and triflates.

Recently it has been shown that palladium complexes of *N*-heterocyclic carbene (NHC) ligands offer distinct advantages as possible alternatives for Pd/phosphine systems in C–C coupling reactions.[10] Thus, some highly active palladium systems with monodentate carbene ligands have been developed for the activation of aryl chlorides.[11]

It is worth noting that in situ formation of the NHC complex by deprotonation of the imidazol(in)ium salt led to significantly better results than the use of the preformed complex.

The success of these processes as well as the recent reports by Miura and co-workers[5–9] prompted us to examine whether in situ generated NHC complexes could be used for the direct arylation of the arene rings of aromatic aldehydes. Formyl groups are synthetically very useful because they can be converted to many other functional groups. Herein, we report a mild, practical, Pd-catalyzed arylation of benzaldehydes using air-stable $Pd(OAc)_2$ as the catalyst, 1,3-bis(alkyl) imidazolinium halides (LHCl, **1**–**5**, Scheme 1) as the NHC ligand precursors, Cs_2CO_3 as the base and dioxane as the solvent



1 $R = R' = 2,4,6\text{-}(CH_3)_3\text{-}C_6H_2$
2 $R = R' = 2,4,6\text{-}(OCH_3)_3\text{-}C_6H_2$
3 $R = R' = 3,4,5\text{-}(OCH_3)_3\text{-}C_6H_2$
4 $R = 2,4,6\text{-}(OCH_3)_3\text{-}C_6H_2$; $R' = CH_2CH_2OCH_3$
5 $R = 2,4,6\text{-}(OCH_3)_3\text{-}C_6H_2$; $R' = CH_2CH_2OC_2H_5$

Scheme 1. The imidazolinium salts (LHCl) used.

Keywords: C–H activation; Arylations; Pd-catalysis; Aldehydes.

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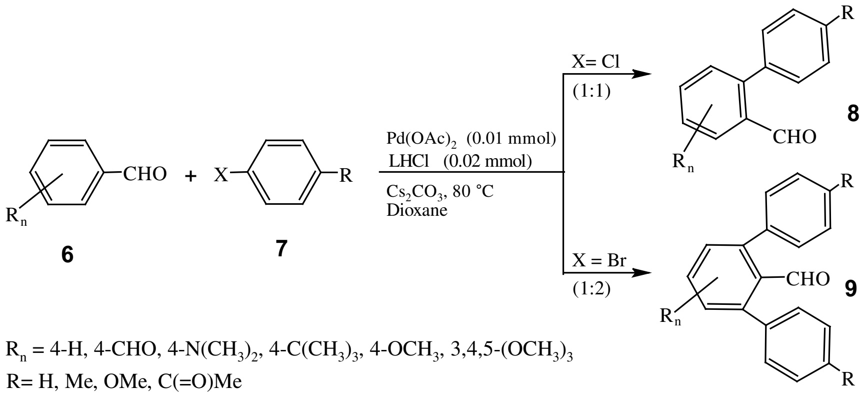
doi:10.1016/j.tetlet.2005.02.023



R_n = 4-H, 4-CHO, 4-N(CH$_3$)$_2$, 4-C(CH$_3$)$_3$, 4-OCH$_3$, 3,4,5-(OCH$_3$)$_3$
R= H, Me, OMe, C(=O)Me

Scheme 2.

Table 1. Arylation of benzaldehyde derivatives

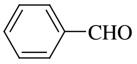
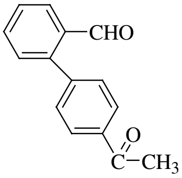
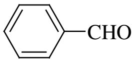
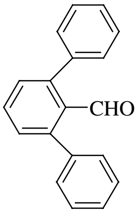
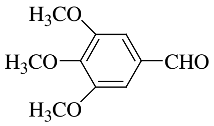
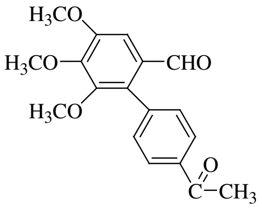
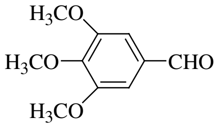
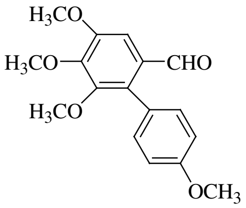
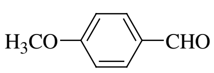
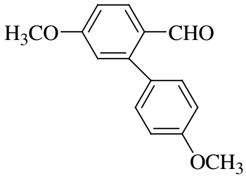
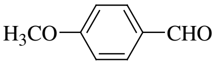
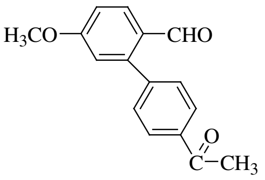
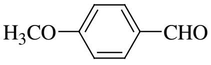
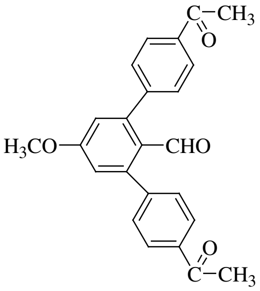
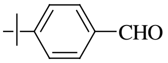
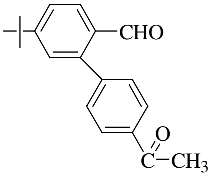
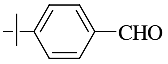
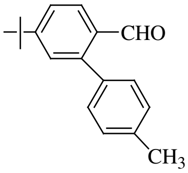
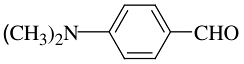
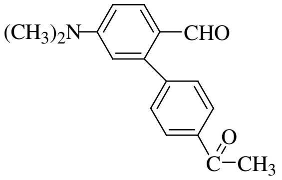
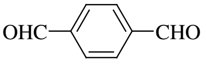
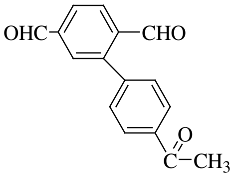
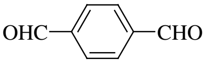
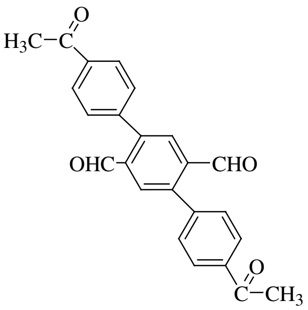
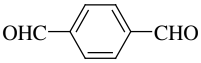
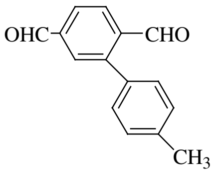
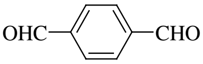
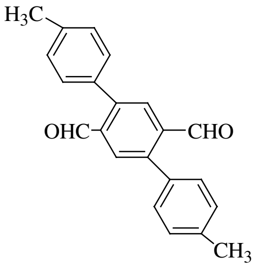
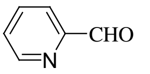
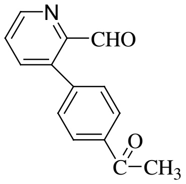
Entry	LHCl	R[a]	Aromatic aldehyde	Product	Yield[b,c,d] (%)
1	**1**	COCH$_3$			92
2	**2**	COCH$_3$			90
3	**3**	COCH$_3$			83
4	**4**	COCH$_3$			81
5	**5**	COCH$_3$			78
6	**1**	H			85
7	**1**	COCH$_3$			94
8	**2**	COCH$_3$			89
9	**3**	COCH$_3$			84
10	**4**	COCH$_3$			82
11	**5**	COCH$_3$			80
12	**1**	OCH$_3$			95
13	**2**	OCH$_3$			94
14	**3**	OCH$_3$			94
15	**4**	OCH$_3$			81
16	**5**	OCH$_3$			90
17	**1**	OCH$_3$			91
18	**2**	OCH$_3$			94
19	**3**	OCH$_3$			79
20	**4**	OCH$_3$			76
21	**5**	OCH$_3$			78

Table 1 (*continued*)

Entry	LHCl	R[a]	Aromatic aldehyde	Product	Yield[b,c,d] (%)
22	**1**	$COCH_3$			95
23	**2**	$COCH_3$			97
24	**3**	$COCH_3$			82
25	**4**	$COCH_3$			81
26	**5**	$COCH_3$			85
27	**1**	$COCH_3$			87
28	**1**	$COCH_3$			83
29	**1**	CH_3			56
30	**1**	$COCH_3$			92
31	**1**	$COCH_3$			76
32	**1**	$COCH_3$			81

(*continued on next page*)

Table 1 (*continued*)

Entry	LHCl	R[a]	Aromatic aldehyde	Product	Yield[b,c,d] (%)
33	**1**	CH_3			65
34	**1**	CH_3			93
35	**1**	$COCH_3$			88

[a] For entries 6 and 27, aryl bromides (2 equiv) were used as aryl halide. In all other cases aryl chlorides were used.

[b] Reactions conditions: 1.0 mmol of R–C_6H_4Cl-*p*, 1.0 mmol of aldehyde, 2 mmol Cs_2CO_3, 1.0 mmol % $Pd(OAc)_2$, 2 mmol % 1,3-dialkylimidazolinium salt, dioxane (3 mL), 80 °C, 16 h.

[c] Purity of compounds was checked by NMR and yields are based on the aldehyde.

[d] All reactions were monitored by TLC.

(Scheme 2). 1,3-Bis(alkyl)imidazolinium chlorides, LHCl, were prepared according to the literature.[12]

Our initial exploration of the reaction conditions[13] for the palladium catalyzed arylation of aldehydes focused on the coupling of benzaldehyde and 4-chloroacetophenone (Table 1, entries 1–5). After screening imidazolinium salts **1**–**5**, the more bulky **1** and **2** were found to be particularly effective ligands, whilst **3**–**5** also provided good yields of the cross-coupled product. The best results for mono *ortho*-arylation of benzaldehydes using 4-chloroacetophenone were obtained at 80 °C in dioxane using Cs_2CO_3 as base, and a catalyst system generated in situ from 1 mmol % of $Pd(OAc)_2$ and 2 mmol % of LHX (**1**–**5**). However, depending on the nature of the substrate haloarene, either mono- or diarylation can take place. Thus, when benzaldehyde or 4-methoxybenzaldehyde (1.0 mmol) were treated with 2 equiv of the bromoarene under similar reaction conditions, the corresponding 2,6-diphenylated product was obtained in 85% and 87% yield, respectively (entries 6 and 27). Thus, bromoarenes and chloroarenes are interesting substrates for discriminating di- and monoarylation reactions of benzaldehydes under these conditions.

Table 1 summarizes representative results from screening the five imidazolinium salts LHCl, for a variety of substrates that undergo *ortho*-arylation. Several trends are readily apparent: The use of saturated NHC ligand precursors **1**–**5** allowed lower reaction temperatures (80 °C), and shorter reaction times. The procedure is simple and does not require induction periods. The scope of this reaction is broad and includes aryl chlorides and bromides that are activated or deactivated. All complexes led to good conversions (56–97%) at low catalyst concentration (1.0 mmol%). Although not dramatic, consistent differences in yields were observed in the reactions according to the ligand precursors **1**–**5**. Presumably, the bulkier ligands derived from **1** and **2** are more effective in stablizing the palladium complex.

This new method was compatible with the presence of both electron-withdrawing and electron-donating groups in the *para* position of the halobenzene. Table 1 also shows that a diverse group of aromatic aldehydes can be coupled. For instance, the reaction of pyridine-2-carboxaldehyde with *p*-chloroacetophenone in the presence of $Pd(OAc)_2$/**1**/Cs_2CO_3 gave the coupling product in 88% yield (entry 35).

Control experiments showed that in the absence of either $Pd(OAc)_2$ or LHCl, no reaction was observed. It is worth noting that, in contrast to our findings, arylation of benzaldehyde with 4-bromoanisole in the presence of $Ni(dppe)Br_2$/Zn has been reported to give diaryl carbinols.[14] The palladium-catalyzed arylation of carbonyl compounds or phenols, reported by Miura and co-workers is considered to proceed via coordination between the phenolate or enolate oxygen of the substrates and the arylpalladium intermediate.[5] Consequently, one may expect that oxygen from the aldehyde may function as a phenolate oxygen.

In conclusion, bulky, electron-rich NHC ligand precursors with an imidazolidine backbone, when combined with $Pd(OAc)_2$, afford a highly active catalyst for the *ortho*-arylation of benzaldehyde derivatives. The ligand precursors **1** and **2** are particularly effective, and with 1.0 mmol % Pd, a variety of aryl halides and benzaldehydes react efficiently and with high selectivity. Furthermore, it was demonstrated that by changing the halide atom in the arylating substrate (X = Cl–Br), it was possible to produce two totally different reaction products with very little cross-contamination.

Detailed investigations, focusing on imidazolin-2-ylidene and benzimidazolin-2-ylidene substituent effects, functional group tolerance and catalytic activity in this and other coupling reactions are ongoing.

Acknowledgements

We thank the Technological and Scientific Research Council of Türkiye TÜBİTAK [TÜBİTAK COST D17 and TBAG-2474 (104T085)] and Inönü University Research Fund for financial support of this work.

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13. *Typical procedure*: A dried Schlenk flask equipped with a magnetic stirring bar was charged with the aldehyde (1.0 mmol), aryl chloride (1.0 mmol), $Pd(OAc)_2$ (0.01 mmol), imidazolinium chloride (0.02 mmol), Cs_2CO_3 (2.0 mmol) and, dioxane (3 mL). After stirring at 80 °C for 16 h the mixture was cooled to room temperature and then quenched by addition of aqueous 1 N HCl and extracted with diethyl ether. The isolated organic layer was dried over $MgSO_4$, filtered, concentrated in vacuo and purified by column chromatography on silica gel eluting with ethyl acetate/hexane (1:5). Analysis of the reaction product was carried out by NMR and GC–MS.
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