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Palladium *N*-Heterocyclic-Carbene-Catalyzed ortho-Arylation of Benzaldehyde Derivatives

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ABSTRACT: *New, sterically demanding 1,3-dialkylbenzimidazolium salts (**2a–c**) as N-heterocyclic-carbene precursors have been synthesized and characterized. The ortho position of aromatic aldehydes was directly and selectively arylated with aryl chlorides in the presence of a catalytic system prepared in situ from $Pd(OAc)_2$, 1,3-dialkylbenzimidazolium chlorides (**2a–c**), and Cs_2CO_3.* © 2008 Wiley Periodicals, Inc. Heteroatom Chem 19:569–574, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20479

INTRODUCTION

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]. The selective functionalization of C—H bonds has attracted a substantial interest owing to potential shortening of synthetic sequences [5]. At the present, development of the methods for sp^2 C—H bond functionalization in directing group containing arenas and electron-rich heterocycles has received the most attention. For a number of directing group containing substances, the conversion of aromatic ortho-C—H bonds to C—C bonds has been demonstrated. Compounds containing amide-, pyridine-, oxazoline-, imine-, ketone-, and phenol-directing groups have been ortho-arylated or alkylated under palladium, ruthenium, or rhodium catalysis [6]. 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 because 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 [7].

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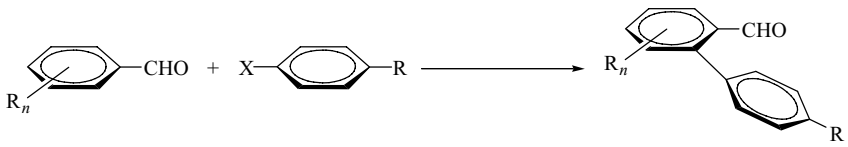


SCHEME 1

Thus, some highly active palladium systems with monodentate carbene ligands have been developed for the activation of aryl chlorides [8].

We have previously reported the use of in situ formed imidazolidin-2-ylidene, tetrahydropyrimidin-2-ylidene, tetrahydrodiazepin-2-ylidene, and benzimidazol-2-ylidene palladium(II) systems that exhibit high activity for various coupling reactions of aryl bromides and aryl chlorides [9]. Recently, we report that the in situ generation of catalysts, from $[RuCl_2(p\text{-cymene})]_2$ and pyrimidinium or benzimidazolium salt in the presence of Cs_2CO_3, selectively promote the diarylation of 2-pyridylbenzene with aryl bromides [10].

The nature of the NHC ligand has a tremendous influence on the rate of catalyzed reactions. To find more efficient palladium catalysts, we have prepared a series of new bulky or functional 1,3-dialkylbenzimidazolium chlorides (LHCl = **2a–c**), containing a benzimidazole ring and herein, we report a mild, practical use of the in situ generated catalytic system composed of commercially available and stable reagents, the $Pd(OAc)_2$ as palladium source, 1,3-dialkylbenzimidazolium chloride (**2a–c**) as a carbene precursor, and Cs_2CO_3 as a base for Miaura coupling of aryl chlorides (Scheme 1).

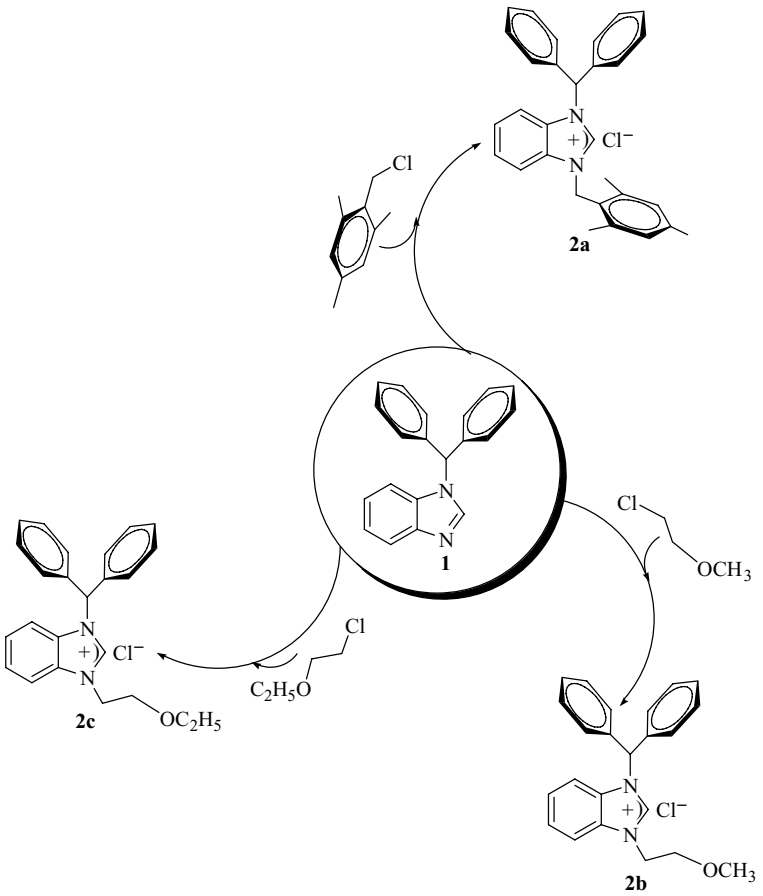
RESULTS AND DISCUSSION

Dialkylbenzimidazolium salts, (**2a–c**) are conventional NHC precursors. The functionalized or bulky benzimidazolium salts, **2a–c**, were synthesized by consecutive alkylation of 1-benzhydrylbenzimidazole (**1**) with alkyl halides (Scheme 2).

According to Scheme 2, the salts (**2a–c)** were obtained in almost quantitative yield by quarternazition of 1-benzhydrylbenzimidazole (**1**) in DMF with alkyl halides [11, 12]. The salts are air- and moisture stable both in the solid state and in the solution. The structures of **2a–c** were determined by their characteristic spectroscopic data and elemental analyses. ^{13}C NMR chemical shifts were consistent with the proposed structure, the imino carbon appeared as a typical singlet in the ^1H-decoupled mode in the 142.4, 142.7, and 142.6 ppm, respectively for benzimidazolium chlorides **2a–c**. The ^1H NMR spectra of the benzimidazolium salts further supported the assigned structures; the resonances for C(2)–H were observed as sharp singlets in the 9.43, 10.16, and 9.95 ppm, respectively for **2a–c**. The IR data for benzimidazolium salts **2a–c** clearly indicate the presence of the —C=N— group with a ν(C=N) vibration at 1543, 1544, and 1557 cm^{-1}, respectively for **2a–c**. The NMR values are similar to those found for other 1,3-dialkylbenzimidazolium salts [12].

It is worth noting that in situ formation of the NHC complex by deprotonation of the azol(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 coworkers [13–16] 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-dialkylbenzimidazolium chlorides (LHCl, **2a–c**, Scheme 2) as the NHC ligand precursors, Cs_2CO_3 as the base, and DMF as the solvent. Our initial exploration of the reaction conditions for the Pd-catalyzed arylation of aldehydes focused on the coupling of benzaldehyde and 4-chloroacetophenone (Table 1, entries 1–3). The best results for mono-ortho-arylation of benzaldehydes using 4-chloroacetophenone were obtained at 100°C in DMF using Cs_2CO_3 as base, and a catalyst system generated in situ from 1% mmol of $Pd(OAc)_2$ and 2% mmol of LHCl (**2a–c**).

Table 1 summarizes representative results from screening of the three benzimidazolium salts (LHCl), for a variety of substrates that undergo ortho-arylation. Several trends are readily apparent: The use of NHC ligand precursors **2a–c** allowed lower reaction temperatures (100°C) and shorter reaction times. The procedure is simple and does not require induction periods. All complexes led to good conversions (78–97%) at low-catalyst concentration (1.0 mmol %). Although not dramatic, consistent differences in yields were observed in the reactions according to the ligand precursors **2a–c**. Presumably, the bulkier ligands derived from **2a–c** are



SCHEME 2 Synthesis of 1,3-dialkylbenzimidazolium chlorides (LHCl).

more effective in stabilizing 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. 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 [17].

The palladium-catalyzed arylation of carbonyl compounds or phenols, reported by Miura, is considered to proceed via coordination between the phenolate or enolate oxygen of the substrates and the arylpalladium intermediate [13]. Consequently, one may expect that oxygen from the aldehyde may function as phenolate oxygen.

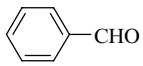
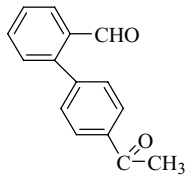
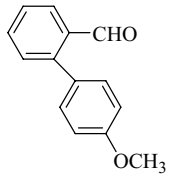
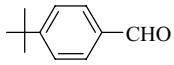
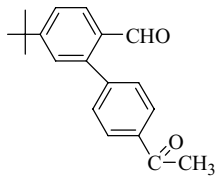
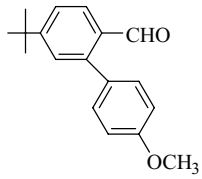
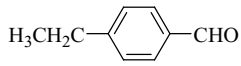
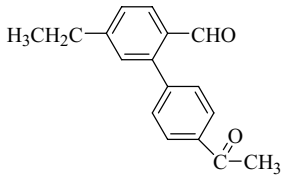
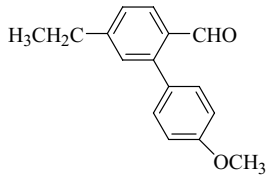
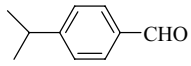
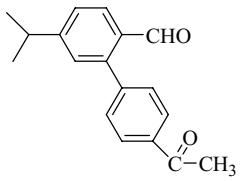
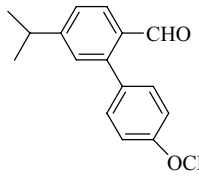
CONCLUSION

Bulky, electron-rich NHC ligand precursors with a benzimidazoline backbone, when combined with $Pd(OAc)_2$, afford a highly active catalyst for the ortho-arylation of benzaldehyde derivatives. The ligand precursors **2a–c** are particularly effective, and with 1.0 mmol % Pd, a variety of aryl halides and benzaldehydes react efficiently and with high selectivity. Detailed investigations, focusing on benzimidazolin-2-ylidene substituent effects, functional group tolerance, and catalytic activity in this and other coupling reactions are in progress.

EXPERIMENTAL

All reactions for the preparation of 1,3-dialkylbenzimidazolium salts (**2a–c**) were carried out under argon using standard Schkenk-type flasks. All reagents were purchased from Aldrich Chemical Co. (Ankara, Turkey). The solvents, Et_2O over Na, DMF over BaO, EtOH over Mg, were distilled prior to use. All ^1H and ^{13}C-NMR were performed in DMSO-d_6. ^1H NMR and ^{13}C NMR spectra were recorded using a Bruker AC300P FT spectrometer operating at 300.13 MHz (^1H) and 75.47 MHz (^{13}C), respectively. Chemical shifts (δ) are given in ppm relative to TMS,

TABLE 1 Arylation of Benzaldehyde Derivatives by Ru–NHC Complexes

Entry	*LHCl*	*R*	*Aromatic Aldehyde*	*Product*	*Yield*[a,b] *(%)*
1	**2a**	$COCH_3$			84
2	**2b**	$COCH_3$			86
3	**2c**	$COCH_3$			83
4	**2a**	OCH_3			92
5	**2b**	OCH_3			96
6	**2c**	OCH_3			81
7	**2a**	$COCH_3$			86
8	**2b**	$COCH_3$			95
9	**2c**	$COCH_3$			83
10	**2a**	OCH_3			80
11	**2b**	OCH_3			83
12	**2c**	OCH_3			78
13	**2a**	$COCH_3$			87
14	**2b**	$COCH_3$			91
15	**2c**	$COCH_3$			84
16	**2a**	OCH_3			96
17	**2b**	OCH_3			97
18	**2c**	OCH_3			85
19	**2a**	$COCH_3$			86
20	**2b**	$COCH_3$			89
21	**2c**	$COCH_3$			85
22	**2a**	OCH_3			83
23	**2b**	OCH_3			82
24	**2c**	OCH_3			79

[a]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-dialkyl benzimidazolium salt, DMF (3 mL), 100°C, 15 h.
[b]Yield determined by NMR, GC, purity of compounds was checked by NMR and yields are based on the aldehyde.

coupling constants (J) in hertz. Melting points were measured in open capillary tubes with an Electrothermal-9200 melting point apparatus and uncorrected. Elemental analyses were performed by TUBITAK Microlab (Ankara, Turkey).

*1-(Benzhydryl)-3-(2,4,6-trimethylbenzyl)-benzimidazolium Chloride (**2a**)*

To a solution of 1-(benzhydryl)benzimidazole (2.0 g, 7.04 mmol) in DMF (3 mL), 2,4,6-trimethylbenzylchloride (1.30 g, 7.70 mmol) was added; the resulting solution was stirred for 1 h at room temperature and heated for 12 h at 80°C. Et_2O (10 mL) was added to the reaction mixture. A white solid was precipitated in this period. The precipitate was then crystallized from $EtOH/Et_2O$ (1:2). Yield: 3.07 g, 93%, mp 204–205°C. IR, ν: 1543 cm^{-1} (C=N). ^1H NMR (DMSO) δ: 2.25 (s, 3H, $CH_2C_6H_2(CH_3)_3$-4), 2.27 (s, 6H, $CH_2C_6H_2(CH_3)_3$-2,6), 5.81 (s, 2H, CH_2-(C_6H_2)-$(CH_3)_3$), 6.97 (s, 2H, CH_2-(C_6H_2)-$(CH_3)_3$), 7.54 (s, 1H, $CH(C_6H_5)_2$), 7.38–7.73 (m, 14H, Ar), 9.43 (s,1H,2-CH). ^{13}C NMR (DMSO) δ: 19.9 ($CH_2C_6H_2(CH_3)_3$-4), 21.1 ($CH_2C_6H_2(CH_3)_3$-2,6), 64.7 (CH_2-(C_6H_2)-$(CH_3)_3$-2,4,6), 131.2 ($CH(C_6H_5)_2$), 114.5, 115.2, 126.4, 127.3, 127.5, 128.8, 128.9, 129.6, 129.7, 130.1, 132.2, 136.5, 138.5, 139.1 (Ar), 142.4 (2-CH). Found: C, 79.41; H, 4.57; N, 6.21%. Calcd for $C_{30}H_{29}N_2Cl$: C, 79.54; H, 4.65; N, 6.18%.

*1-(Benzhydryl))-3-(methoxyethyl)-benzimidazolium Chloride (**2b**)*

This compound was prepared from 1-(benzhydryl)benzimidazole (2 g, 7.04 mmol) and 2-methoxyethyl chloride (0.73 g, 7.74 mmol) in DMF (3 mL). Yield: 2.51 g, 92%, mp 217–218°C. IR, ν: 1544 cm^{-1} (C=N). ^1H NMR ($CDCl_3$) δ: 3.24 (s, 3H, OCH_3), 3.84 (t, 2H, $J = 4.8$ Hz, NCH_2CH_2O), 4.91 (t, 2H, $J = 4.8$ Hz, NCH_2CH_2O), 7.41 (s, 1H, $CH(C_6H_5)_2$), 7.26–7.97 (m, 14H, Ar), 10.16 (s, 1H, 2-CH). ^{13}C NMR ($CDCl_3$) δ: 59.2 (OCH_3), 66.7 (NCH_2CH_2O), 70.2 (NCH_2CH_2O), 131.2 ($CH(C_6H_5)_2$), 114.6, 114.8, 127.3, 127.4, 128.7, 129.68, 129.7, 132.7, 135.4 (Ar), 142.7 (2-CH). Found: C, 72.87; H, 6.21; N, 7.43%. Calcd for $C_{23}H_{23}N_2OCl$: C, 72.91; H, 6.12; N, 7.39%.

*1-(Benzhydryl)-3-(ethoxyethyl)benzimidazolium Chloride (**2c**)*

This compound was prepared from 1-(benzhydryl)benzimidazole (2 g, 7.04 mmol) and 2-ethoxyethyl chloride (0.84 g, 7.74 mmol) in DMF (3 mL). Yield: 2.69 g, 95%, mp 179–180°C. IR, ν: 1557 cm^{-1} (C=N). ^1H NMR ($CDCl_3$) δ: 0.95 (t, 3H, $J = 7.2$ Hz, OCH_2CH_3), 3.39 (q, 2H, $J = 6.8$ Hz, OCH_2CH_3), 3.85 (t, 2H,$J = 4.4$ Hz, NCH_2CH_2O), 4.90 (t, 2H, $J = 4.8$ Hz, CH_2CH_2O), 7.39 (s, 1H, $CH(C_6H_5)_2$, 7.33–7.95 (m, 14H, Ar), 9.95 (1H, 2-CH). ^{13}C NMR ($CDCl_3$) δ: 15.1 (OCH_2CH_3), 58.3 (OCH_2CH_3), 66.6 (NCH_2CH_2O), 67.9 (NCH_2CH_2O), 131.2 ($CH(C_6H_5)_2$), 114.6, 114.7, 127.2, 127.3, 128.7, 129.8, 129.7, 132.6, 135.4 (Ar), 142.6 (2-CH). Found: C, 73.55; H, 6.81; N, 7.09%. Calcd for $C_{24}H_{25}N_2OCl$: C, 73.36; H, 6.41; N, 7.13%.

General Procedure for Arylation of Benzaldehyde Derivatives

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), benzimidazolium chloride (0.02 mmol), Cs_2CO_3 (2.0 mmol), and DMF (3 mL). After stirring at 100°C for 15 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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