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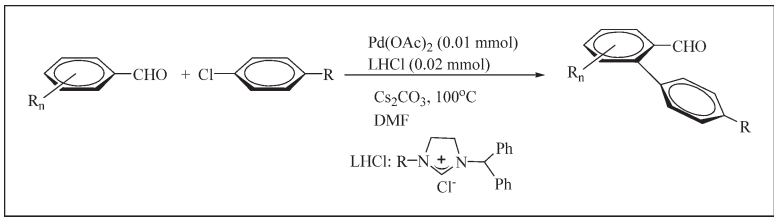

Novel functionalized 1,3-dialkylimidazolinium salts (LHCl) as NHC precursors have been prepared and successfully applied in palladium-catalyzed arylation of benzaldehydes. The ortho position of aromatic aldehydes was directly and selectively arylated with aryl chlorides in the presence of a catalytic system prepared *in situ* from $Pd(OAc)_2$, 1,3-dialkylimidazolinium chlorides (**2a–c**), and Cs_2CO_3.

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INTRODUCTION

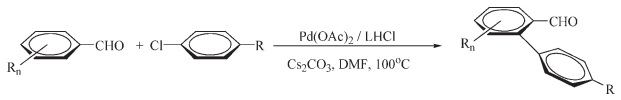
The functionalization of aryl compounds is of major importance in the field of modern arene chemistry because of the ubiquity of aromatic and heteroaromatic units in fine chemical intermediates, pharmaceutical, agrochemicals, polymers, liquid crystals, new materials [1], and ligands for homogeneous transition metal catalysts [1]. Among the different aromatic functionalization reactions, palladium-catalyzed coupling processes such as the Heck [2], Suzuki [3], Kumada [4], Sonogashira [5], Buchwald-Hartwig amination [6], and other C—C and C—O bond forming reactions offer elegant possibilities for the synthesis of substituted arenas. The main advantages of the coupling processes are based on the ready availability of starting materials, the simplicity and generality of the methods, and the broad tolerance of palladium catalysts toward various functional groups. 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 [7]. The selective functionalization of C—H bonds has attracted substantial interest due to potential shortening of synthetic sequences [8]. At present, development of 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 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 [9]. 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].

We have previously reported the use of an *in situ* formed imidazolidin-2-ylidene, tetrahydropyrimidin-2-ylidene and tetrahydrodiazepin-2-ylidene, benzimidazol-2-ylidene palladium(II) systems that exhibit high activity for various coupling reactions of aryl bromides and aryl chlorides [12]. 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 [13].

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-dialkylimidazolinium (**2a–c**), containing imidazoline ring. Herein, we report a Miaura coupling of aryl chlorides (Scheme 1) using a

Scheme 1



mild practical *in situ* generated catalytic system composed of commercially available and stable reagents, $Pd(OAc)_2$ as the palladium source, 1,3-dialkylimidazolinium chloride (**2a–c**) as a carbene precursor, and Cs_2CO_3 as a base.

RESULTS AND DISCUSSION

1,3-Dialkylimidazolinium chlorides (**2a–c**) are conventional NHC precursors. The functionalized or bulky imidazolinium salts, **2a–c**, were synthesized by consecutive alkylation of 1-benzhydrylimidazoline (**1**) with alkyl halides (Scheme 2).

According to Scheme 2, the salts (**2a–c**) were obtained in almost quantitative yield by quarternization of 1-benzhydrylimidazoline [1] in DMF with alkyl halides [14,15]. The salts are air- and moisture-stable both in the solid state and in solution. The structures of **2a–c** were determined by their characteristic spectroscopic data and elemental analyses. ^{13}C NMR chemical shifts are consistent with the proposed structure; the imino carbon resonance appeared as a typical singlet in the ^1H-decoupled mode at 157.8, 158.6, and 157.7 ppm, respectively, for imidazolinium chlorides **2a–c**. The ^1H NMR spectra of the imidazolinium salts further supported the assigned structures; the resonances for C[2]-H were observed as sharp singlets in the 8.75, 8.58, and 8.31 ppm, respectively, for **2a–c**. The IR data for imidazolinium salts **2a–c** clearly indicate the presence of the —C=N— group with a ν(C=N) vibration at 1636, 1650, and 1645 cm^{-1}, respectively, for **2a–c**. The NMR values are similar to those found for other 1,3-dialkylimidazolinium salts [15].

It is worth noting that *in situ* formation of the NHC complex by deprotonation of the imidazolinium 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 [16–19] 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-dialkylimidazolinium 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 palladium-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 the three imidazolinium 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 (79 to 95%) 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 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

Scheme 2. Synthesis of 1,3-dialkylimidazolinium chlorides (LHCl).

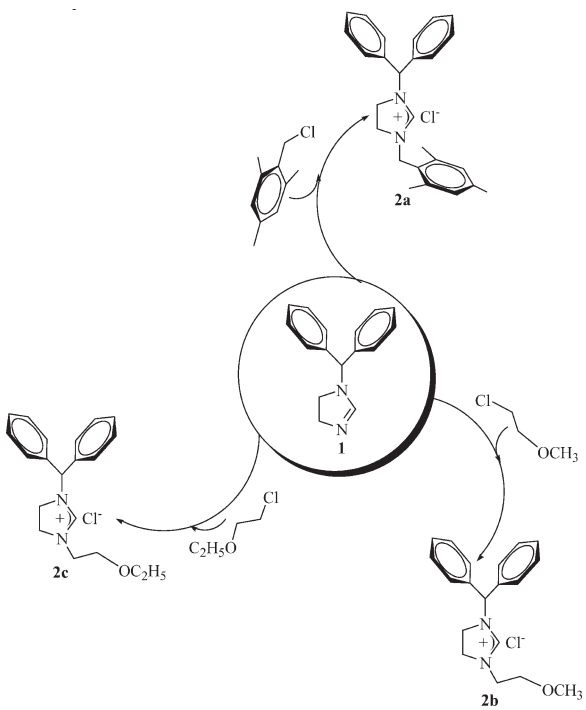
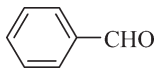
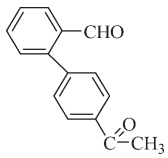
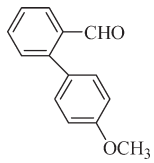
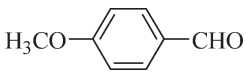
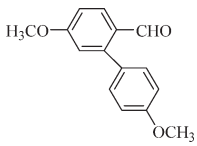
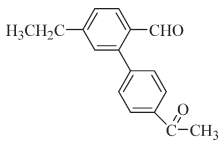
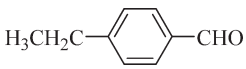
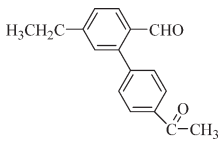
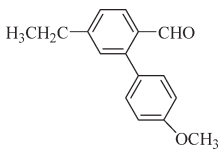
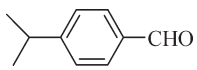
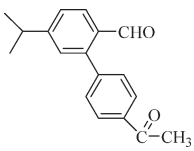
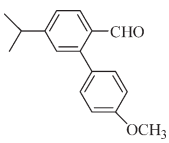


Table 1

Arylation of benzaldehyde derivatives by Pd-NHC complexes.

Entry	LHCl	R	Aromatic aldehyde	Product	Yield[a,b] (%)
1	**2a**	$COCH_3$			84
2	**2b**	$COCH_3$			87
3	**2c**	$COCH_3$			89
4	**2a**	OCH_3			83
5	**2b**	OCH_3			88
6	**2c**	OCH_3			90
7	**2a**	$COCH_3$			89
8	**2b**	$COCH_3$			95
9	**2c**	$COCH_3$			92
10	**2a**	OCH_3			79
11	**2b**	OCH_3			82
12	**2c**	OCH_3			83
13	**2a**	$COCH_3$			92
14	**2b**	$COCH_3$			94
15	**2c**	$COCH_3$			92
16	**2a**	OCH_3			84
17	**2b**	OCH_3			91
18	**2c**	OCH_3			89
19	**2a**	$COCH_3$			82
20	**2b**	$COCH_3$			87
21	**2c**	$COCH_3$			85
22	**2a**	OCH_3			80
23	**2b**	OCH_3			79
24	**2c**	OCH_3			80

[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-dialkylimidazolinium salt, DMF (3 mL), 100°C, 15 h.

[b] Yield determined by NMR and GC, purity of compounds was checked by NMR and yields are based on the aldehyde.

findings, arylation of benzaldehyde with 4-bromoanisole in the presence of Ni(dppe)Br_2/Zn has been reported to give diaryl carbinols [20].

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 [16]. Consequently, one may expect that oxygen from the aldehyde may function as a phenolate oxygen.

EXPERIMENTAL

All reactions for the preparation of 1,3-dialkylimidazolinium salts [2a–c] were carried out under argon using standard Schlenk-type flasks. All reagents were purchased from Aldrich Chemical (Istanbul). The solvents, Et_2O over Na, DMF over BaO, EtOH over Mg were distilled before use. All ^1H and ^{13}C NMR experiments were performed in $CDCl_3$. ^1H NMR and ^{13}C NMR spectra were recorded using a Bruker AC300P FT spectrometer operating at 300.13 MHz (^1H), 75.47 MHz (^{13}C). Chemical shifts (δ) are given in ppm relative to TMS, coupling constants (*J*) in Hz. Melting points were measures in open capillary tubes with an Electrothermal-9200 melting point apparatus and are uncorrected. Elemental analyses were performed by TUBITAK (Ankara, Turkey) Microlab.

Preparation of 1-benzhydryl-3-(2,4,6-trimethylbenzyl)-imidazolinium chloride (2a). To a solution of 1-(benzhydryl) imidazolin (2.0 g, 9.6 mmol) in DMF (3 mL), 2,4,6-tri-methylbenzylchloride (1.78 g, 10.5 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 precipitated during this period. The precipitate was then crystallized from EtOH/Et_2O (1:2). Yield: 3.12 g (86%), mp 209–210°C; ir: 1636 cm^{-1} (C=N). ^1H NMR (δ, $CDCl_3$): 2.19 (3H, $CH_2C_6H_2(CH_3)_3$-4), 2.26 (s, 6H, $CH_2C_6H_2(CH_3)_3$-2,6), 3.88 (s, 4H, NCH_2CH_2N), 5.79 (s, 2H, CH_2—(C_6H_2)—$(CH_3)_3$-2,4,6), 6.80 (s, 2H, CH_2—(C_6H_2)—$(CH_3)_3$), 6.45 (s, 1H, $CH(C_6H_5)_2$), 7.26–7.37 (m, 10H, Ar), 8.75 (s,1H, 2—CH). ^{13}C NMR (δ, $CDCl_3$): 21.1 ($CH_2C_6H_2(CH_3)_3$-4), 20.3 ($CH_2C_6H_2(CH_3)_3$-2,6), 47.1 (CH_2—(C_6H_2)—$(CH_3)_3$-2,4,6), 48.0 and 48.7 (NCH_2CH_2N), 65.9 ($CH(C_6H_5)_2$), 125.5, 128.6, 129.1, 129.5, 139.9, 135.9, 139.0, and 139.3 (Ar), 157.8 (2—CH). Anal. Calcd. for $C_{26}H_{29}N_2Cl$: C, 72.54; H, 7.23; N, 6.59. Found: C, 72.56; H, 7.28; N, 6.55.

Preparation of 1-benzhydryl-3-(methoxyethyl)-imidazolinium chloride (2b). This compound was prepared from 1-(benzhydryl)imidazolin (2 g, 9.6 mmol) and 2-methoxyethyl chloride (1.0 g, 10.5 mmol) in DMF (3 mL). Yield:2.65 g (91%), mp 144–145°C; ir: 1650 cm^{-1} (C=N). ^1H NMR (δ, $CDCl_3$): 3.25 (s, 3H, OCH_3), 3.57 (t, 2H, J = 4.4 Hz, NCH_2CH_2O), 3.78 (t, 2H, J = 4.4 Hz, NCH_2CH_2O), 3.89 and 4.13 (m, 4H, NCH_2CH_2N), 6.37 (s, 1H, $CH(C_6H_5)_2$), 7.32 (m, 10H, Ar); 8.58 (s, 1H, 2—CH). ^{13}C NMR (δ, $CDCl_3$): 48.3 and 48.8 (NCH_2CH_2N), 59.3 (OCH_3), 66.1 (NCH_2CH_2O), 50.3 (NCH_2CH_2O), 69.0 ($CH(C_6H_5)_2$), 128.9, 129.3, 129.7, and 136.1 (Ar), 158.6 (2—CH). Anal. Calcd. for $C_{19}H_{23}N_2OCl$: C, 68.97; H, 7.01; N, 8.47. Found: C, 68.93; H, 6.98; N, 8.50.

Preparation of 1-benzhydryl-3-(ethoxyethyl)imidazolinium chloride (2c). This compound was prepared from 1-(benzhydryl)imidazolin (2 g, 9.6 mmol) and 2-ethoxyethyl chloride (1.15 g, 10.5 mmol) in DMF (3 mL). Yield: 2.70 g (89%), ir: 1645 cm^{-1} (C=N). ^1H NMR (δ, $CDCl_3$): 0.89 (t, 3H, J = 5.7 Hz, OCH_2CH_3), 3.31 (q, 2H, J = 5.7 Hz, OCH_2CH_3), 3.46 (t, 2H, J = 4.2 Hz, NCH_2CH_2O), 3.58 (t, 2H, J = 3.9 Hz, CH_2CH_2O), 3.73 and 4.04 (m, 4H, NCH_2CH_2N), 6.26 (s, 1H, $CH(C_6H_5)_2$), 6.96–7.59 (m, 10H, Ar), 8.31 (s, 1H, 2—CH). ^{13}C NMR (δ, $CDCl_3$): 14.9 (OCH_2CH_3), 47.8 (OCH_2CH_3), 65.5 (NCH_2CH_2O), 66.2 (NCH_2CH_2O), 48.3 and 49.9 (NCH_2CH_2N); 66.4 ($CH(C_6H_5)_2$); 128.3, 128.8, 129.2, and 135.7 (Ar), 157.8 (2—CH). Anal. Calcd. for $C_{20}H_{25}N_2OCl$: C, 69.65; H, 7.31; N, 8.12. Found: C, 69.66; H, 7.29; N, 8.11.

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), imidazolinium 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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