Palladium-catalyzed Suzuki–Miyaura reaction using saturated *N*-heterocarbene ligands

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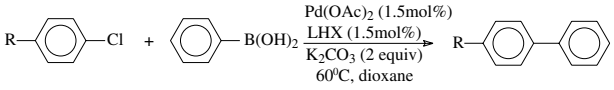
The incorporation of saturated *N*-heterocyclic carbenes into palladium pre-catalysts give high catalyst activity in the Suzuki coupling of deactivated aryl chloride substrates.



The complexes were generated in the presence of $Pd(OAc)_2$ by *in situ* deprotonation of bis(imidazolinium) bromides LHX (**3**) which were characterized by conventional spectroscopic methods and elemental analyses.

KEY WORDS: carbene; Suzuki; palladium; imidazolidin-2-ylidene; aryl chlorides; phenylboronic acid.

1. Introduction

The palladium-catalyzed cross-coupling reaction of aryl halides with arylboronic acids, the so-called Suzuki–Miyaura reaction, is one of the most versatile and powerful methods for C–C bond formation and has attracted much current interest [1,2].

The low reactivity of aryl chlorides in cross-coupling reactions is generally ascribed to their reluctance to oxidatively add to Pd(0) [3]. Current interest focuses on the use of aryl chlorides since they are cheaper and more readily accessible than bromides and iodides [4]. The reaction is normally promoted by a palladium catalyst precursor, a ligand that binds to the palladium center to stabilize the catalyst during the reaction process, and a base that captures the boronic acid moiety. The choice of the right ligand is a pivotal factor in determining the rate of the reaction. Triaryl phosphines are traditionally employed as ligands for the reaction. Recently electron-rich, bulky phosphines [5] and phosphine oxides [6] have been reported to be effective ligands.

However, the major drawback of these is that the phosphine ligands are comparatively difficult to make or rather expensive. Furthermore, tertiary phosphines require air-free handling to prevent their oxidation and are susceptible to P–C bond cleavage at elevated temperatures [7]. On the other hand, palladium complexes of *N*-heterocyclic carbene ligands(NHC's) [8], in particular have proved to be excellent catalysts not only for the Suzuki and Heck reaction, but also for Stille and Sonagashira reactions [9]. Also ruthenium *N*-heterocyclic carbene complexes have been found effective catalysts for the formation of furans, cyclopropanation [10,11] alkene metathesis [12,13] and cycloisomerisation [14].

The NHC complexes are cost efficient to prepare, insensitive to air and moisture and are thermally stable in both the solid state and in solution; the carbenes are non-dissociative ligands. However, the development of new ligands or the application of existing ligands in these reactions, particularly those involving aryl chlorides as substrates, is still of considerable importance. Recently, we have developed improved procedures Heck and Suzuki reactions of aryl chlorides making use of novel ligands 1,3-bis(dialkyl)imidazolium salts [15], 1-alkylimidazoline, α-bis(imine) [16].

Although the nature of the NHC ligand on complexes has a tremendous influence on the rate of catalyzed reactions, the use of saturated NHC ligands in coupling reactions is a neglected area. In order to find more efficient palladium catalysts we have prepared a series of new bis(imidazolinium) bromides LHX, **3** (scheme 1), containing a saturated imidazole ring and we report here *in situ* Pd-carbene based catalytic system for the Suzuki coupling reaction.

2. Experimental

All reactions were performed using Schlenk-type flask under argon and standard high vacuum-line techniques. Solvents were analytical grade and distilled under Ar from sodium benzophenone (Et_2O, dioxane). ^1H NMR

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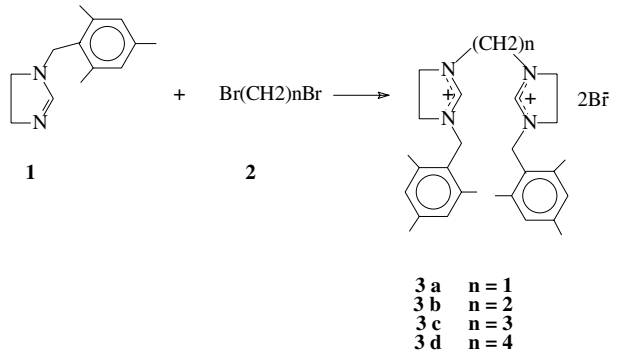

Scheme 1.

and ^{13}C NMR spectra were recorded using a Bruker AC300P FT spectrometer operating at 300.13 MHz (^{1}H), 75.47 MHz (^{13}C). FT-IR spectra were recorded on a Mattson 1000 spectrophotometer. Elemental analyses were performed by TUBITAK Microlab.

2.1. Preparation of 1,1′-bis{3-(2,4,6-trimethylbenzyl) imidazolinium}methane bromide, (**3a**)

To a solution of 1-(2,4,6-trimethylbenzyl)imidazoline (2.02 g, 10 mmol) in DMF (10 mL) was added slowly dibromomethane (0.87 g, 5 mmol) at 25 °C and the resulting mixture was stirred at RT for 6 h. Diethyl ether (15 mL) was added to obtain a white crystalline solid which was filtered off. The solid was washed with diethyl ether (3 × 15 mL), dried under vacuum. mp = 266.0 – 267.0 °C, and the yield was 2.62 g, 91%, $\nu_{(CN)} = 1667$ cm^{-1}.

Anal. Cal. For $C_{27}H_{38}N_4Br_2$; C: 56.06, H: 6.62, N: 9.68; found C: 56.04, H: 6.65, N: 9.70. ^{1}H NMR (δ, $CDCl_3$): 2.31 and 2.25 [s, 18H, 2,4,6-(CH_3)$_3$–$C_6H_2CH_2$]; 4.65 [s, 4H, 2,4,6-$(CH_3)_3$–C_6H_2CH_2]; 6.95 [s, 4H, 2,4,6-$(CH_3)_3$–$C_6H_2CH_2$]; 3.93 [s, 8H, NCH_2CH_2N]; 5.17 [s, 2H,–CH_2–]; 8.56 [s, 2H, NCHN]; ^{13}C{H}NMR (δ, $CDCl_3$): 20.7 and 19.6 [2,4,6-(CH_3)$_3$–$C_6H_2CH_2$]; 49.4 [2,4,6-$(CH_3)_3$–$C_6H_2CH_2$]; 138.3, 138.2, 129.4 and 126.0 [2,4,6-$(CH_3)_3$–$C_6H_2CH_2$]; 47.1 and 45.9 [NCH_2CH_2N]; 58.4 [–CH_2–]; 157.5 [NCHN].

2.2. Preparation of 1, 2-bis{3-(2,4,6-trimethylbenzyl) imidazolinium}ethane bromide, (**3b**)

Compound **3b** was prepared in the same way as **3a** from 1-(2,4,6-trimethylbenzyl)-imidazoline (2.02 g, 10 mmol) and 1,2-dibromoethane (0.94 g, 5 mmol) to give white crystals of **3b** in 2.54 g, 86% yield, mp = 267.5–268.0 °C, $\nu_{(CN)} = 1664$ cm^{-1}.

Anal. Cal. For $C_{28}H_{40}N_4Br_2$; C: 56.76, H: 6.80, N: 9.45; found C: 56.73, H: 6.82, N: 9.43. ^{1}H NMR (δ, $CDCl_3$): 2.25 and 2.17 [s, 18H, 2,4,6-(CH_3)$_3$–$C_6H_2CH_2$]; 4.75 [s, 4H, 2,4,6-$(CH_3)_3$–C_6H_2CH_2]; 6.78 [s, 4H, 2,4,6-$(CH_3)_3$–$C_6H_2CH_2$]; 4.24 and 3.73 [t, $J = 10.5$ Hz, 8H, NCH_2CH_2N]; 4.02 [s, 4H,–CH_2CH_2–]; 10.03 [s, 2H, NCHN]; ^{13}C{H}NMR (δ, $CDCl_3$): 21.5 and 20.5 [2,4,6-(CH_3)$_3$–$C_6H_2CH_2$]; 49.4 [2,4,6-$(CH_3)_3$–C_6H_2CH_2]; 139.3, 138.3, 130.2 and 125.6 [2,4,6-$(CH_3)_3$–$C_6H_2CH_2$]; 46.6 and 45.6 [NCH_2CH_2N]; 48.2 [–CH_2CH_2–]; 159.2 [NCHN].

2.3. Preparation of 1,3-bis{3-(2,4,6-trimethylbenzyl) imidazolinium}propane bromide, (**3c**)

Compound **3c** was prepared in the same way as **3a** from 1-(2,4,6-trimethylbenzyl)imidazoline (2.02 g, 10 mmol) and 1,3-dibromopropane (1.01 g, 5 mmol) to give white crystals of **3c** in 2.45 g, 81% yield, mp = 172.5–173.0 °C , $\nu_{(CN)} = 1665$ cm^{-1}.

Anal. Cal. For $C_{29}H_{42}N_4Br_2$; C: 57.43, H: 6.98, N: 9.24; found C: 57.41, H: 6.95, N: 9.23. ^{1}H NMR (δ, $CDCl_3$): 2.29 and 2.18 [s, 18H, 2,4,6-(CH_3)$_3$–$C_6H_2CH_2$]; 4.76 [s, 4H, 2,4,6-$(CH_3)_3$–C_6H_2CH_2]; 6.80 [s, 4H, 2,4,6-$(CH_3)_3$–$C_6H_2CH_2$]; 3.98 and 3.76 [t, $J = 9.95$ Hz, 8H, NCH_2CH_2N]; 4.01 [t, $J = 7.7$ Hz, 4H,–CH_2CH$_2$CH_2–]; 2.07 [m, 2H,–CH$_2$CH_2CH$_2$–]; 9.96 [s, 2H, NCHN]; ^{13}C{H}NMR (δ, $CDCl_3$): 21.3 and 20.5 [2,4,6-(CH_3)$_3$–$C_6H_2CH_2$]; 48.5 [2,4,6-$(CH_3)_3$–C_6H_2CH_2]; 139.2, 138.3, 130.3 and 125.8 [2,4,6-$(CH_3)_3$–$C_6H_2CH_2$]; 48.1 and 46.7 [NCH_2CH_2N]; 44.7 [–CH_2CH$_2$CH_2–]; 24.3 [–CH$_2$CH_2CH$_2$–]; 162.8 [NCHN].

2.4. Preparation of 1, 4-bis{3-(2,4,6-trimethylbenzyl) imidazolinium}butane bromide, (**3d**)

Compound **3d** was prepared in the same way as **3a** from 1-(2,4,6-trimethylbenzyl)imidazoline (2.02 g, 10 mmol) and 1,4-dibromobutane (1.08 g, 5 mmol) to give white crystals of **4d** in 2.94 g, 95% yield, mp = 296.0–297.0 °C, $\nu_{(CN)} = 1659$ cm^{-1}.

Anal. Cal. For $C_{30}H_{44}N_4Br_2$; C: 58.07, H: 7.15, N: 9.03; found C: 58.10, H: 7.17, N: 9.00. ^{1}H NMR (δ, $CDCl_3$): 2.29 and 2.19 [s, 18H, 2,4,6-(CH_3)$_3$–$C_6H_2CH_2$]; 4.80 [s, 4H, 2,4,6-$(CH_3)_3$–C_6H_2CH_2]; 6.81 [s, 4H, 2,4,6-$(CH_3)_3$–$C_6H_2CH_2$]; 4.05 and 3.73 [t, $J = 11.28$ Hz, 8H, NCH_2CH_2N]; 3.64 [t, $J = 7.0$ Hz, 4H,–CH_2CH$_2$CH$_2$CH_2–]; 1.92 [m, 4H,–CH$_2$CH_2CH_2CH$_2$–]; 9.68 [s, 2H, NCHN]; ^{13}C{H}NMR (δ, $CDCl_3$): 21.3 and 20.6 [2,4,6-(CH_3)$_3$–$C_6H_2CH_2$]; 49.2 [2,4,6-$(CH_3)_3$–C_6H_2CH_2]; 139.3, 138.2, 130.1 and 125.7 [2,4,6-$(CH_3)_3$–$C_6H_2CH_2$]; 48.1 and 47.6 [NCH_2CH_2N]; 46.6 [–CH_2CH$_2$CH$_2$CH_2–]; 24.4 [–CH$_2$CH_2CH_2CH$_2$–]; 158.0 [NCHN].

3. Results and discussion

Dialkylimidazolinium salts, LHX (**3**) are conventional NHC precursors. According to Scheme 1, the salts (**3a–d**) were obtained in almost quantitative yield by quarternazition of 1-alkyl-2-imidazoline in DMF with alkyl bromides. The salts are air- and moisture-stable both in the solid state and in solution. The structures of **3** were determined by their characteristic spectroscopic data and elemental analyses (Section 2).

^{13}C NMR chemical shifts were consistent with the proposed structure, the imino carbon appeared as a typical singlet in the ^{1}H-decoupled mode in the 157.5, 159.2, 162.8 and 158.0 ppm, respectively for imidazolinium salts **3a**–**d**. The ^{1}H NMR spectra of the imidazolinium salts further supported the assigned structures; the resonances for C(2)–H were observed as sharp singlets in the 8.56, 10.03, 9.96 and 9.68 ppm, respectively for **3a**–**d**. The IR data for imidazolinium salts **3a**–**d** clearly indicate the presence of the —C=N— group with a ν(C=N) vibration at 1667, 1664, 1665 and 1659 cm^{-1} respectively for **3a**–**d**. The NMR and IR values are similar to those found for other 1,3-dialkylimidazo-linium salts [15].

It has been found that the *in situ* formation of the ligand by deprotonation of the bis(imidazolinium) bromides, lead to significantly better results than use of the preformed carbene [17].

The palladium-catalyzed cross-coupling of arylboronic acids with aryl halides has been shown to proceed under a variety of conditions: A wide range of bases and solvents, as well as catalysts, have been employed with varying degrees of success according to the substrates [1]. To find optimum conditions a series of experiments has been performed with 4-chloroanisole and phenylboronic acid as model compounds. As a base, K_2CO_3 was the best choice and as a solvent dioxane was found to be better than other solvents. After having established the optimised coupling reaction conditions, the scope of the reaction and efficiencies of the salts were evaluated by investigating the coupling of $C_6H_5B(OH)_2$ with various *p*-substituted aryl chlorides.The results were summarized in table 1.

Under those conditions, chlorobenzene, *p*-chlorotoluene, *p*-chloroanisole, 4-chloroacetophenone, and *p*-chlorobenzaldehyde react very cleanly with phenylboronic acid in goods yields (table 1, entry 1, 8, 12, 13 and 18).

Previous researchers have reported induction periods for Suzuki reactions promoted by $Pd(OAc)_2$/imidazolium salts. It was proposed that during these induction periods Pd(II)/NHC complexes were formed and were then slowly reduced to catalytically active Pd(0)/NHC complexes [18]. It is important to note that these induction periods could be avoided with the present catalyst system.

Table 1
The Suzuki coupling reaction of aryl chlorides with phenylboronic acid

Entry	R	LHX	Time (h)	Yield[a,b,c,d] (%)
1	H	**3a**	5.0	97
2	H	**3b**	5.0	76
3	H	**3c**	5.0	95
4	H	**3d**	5.0	80
5	CH_3	**3a**	2.0	86
6	CH_3	**3b**	2.0	74
7	CH_3	**3c**	2.0	83
8	CH_3	**3d**	1.0	91
9	OCH_3	**3a**	2.0	84
10	OCH_3	**3b**	2.0	82
11	OCH_3	**3c**	2.0	90
12	OCH_3	**3d**	2.0	95
13	$COCH_3$	**3a**	2.0	89
14	$COCH_3$	**3b**	1.0	70
15	$COCH_3$	**3c**	1.0	74
16	$COCH_3$	**3d**	2.0	85
17	CHO	**3a**	2.0	90
18	CHO	**3b**	2.0	92
19	CHO	**3c**	2.0	83
20	CHO	**3d**	2.0	98

[a] *Reaction conditions*: 1.0 mmol of R-C_6H_4Cl-*p*, 1.5 mmol of phenylboronic acid, 2 mmol K_2CO_3, 1.50 mol% $Pd(OAc)_2$, 1.50 mol% LHX, dioxane (3 mL).
[b] purity of compounds is checked by NMR and yields are based on arylchloride.
[c] All reactions were monitered by TLC.
[d] temperature 60 °C.

4. Conclusion

We have developed a new type of easily prepared dialkylimidazolinium salts LHX (**3a**–**d**) ligands in the Suzuki–Miyaura coupling reaction. Through the use of LHX and $Pd(OAc)_2$ as a pre-catalyst mixture, aryl halides undergo efficient coupling reactions with $C_6H_5B(OH)_2$ in the presence of K_2CO_3. The procedure is simple and efficient towards various aryl halides and does not require induction periods. Investigations focusing on the reactivity profile of **3** and related imidazolinium and benzimidazolinium salts, their efficacy as catalysts in cross-coupling reactions are under progress in our laboratory.

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