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1,4,5,6-TETRAHYDROPYRIMIDINIUM HALIDES LIGANDS FOR SUZUKI-MIYAURA CROSS-COUPPLING OF UNACTIVATED ARYL CHLORIDES

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Abstract- Four functionalized bis(1,4,5,6-tetrahydropyrimidinium) salts (**2a-d**) have been prepared and characterized by conventional spectroscopic methods and elemental analyses. A highly effective, easy to handle and environmentally benign process for palladium mediated Suzuki cross-coupling was developed. The *in situ* prepared three component system Pd(OAc)₂ / bis(1,4,5,6-tetrahydropyrimidinium) bromides (**2a-d**) and Cs₂CO₃ catalyses quantitatively the Suzuki cross-coupling of deactivated aryl chloride.

INTRODUCTION

Suzuki coupling reaction¹ has, over the past decade or so, established itself as a powerful method for the formation of carbon-carbon bonds. The coupling of two sp²-centered carbons remains an important goal as well as a challenge for synthetic organic chemists. Chloroarenes are generally readily available and inexpensive and, therefore the productive activation of C-Cl bonds in chloroarenes is of significant industrial interest. Traditionally, however, the C-Cl bond in chloroarenes has been found to be comparatively inert.² For along time, the use of unactivated aryl chlorides as substrates in Suzuki-Miyaura cross-coupling was not feasible. Instead, more costly and less readily available aryl iodides and aryl bromides had to be used. Buchwald³ and Fu⁴ were the first to independently developed catalyst systems based on electron-rich, sterically demanding phosphine ligands, which allow the Suzuki-Miyaura cross-coupling of many unactivated aryl chlorides. 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.⁵ The application of *N*-heterocyclic carbene (NHC)⁶ ligands in the reaction was first reported by Herrmann in 1998.⁷

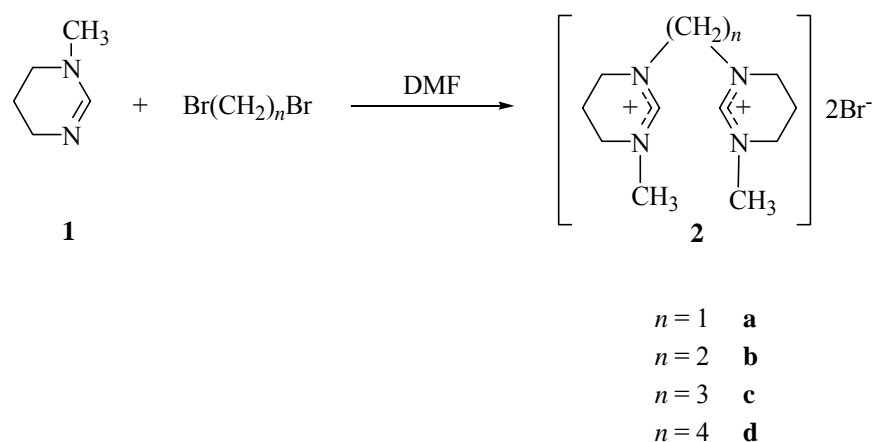
The NHC complexes are cost efficient to prepare, insensitive to air and moisture and are thermally stable in both the solid state and in solution; the carbenes are non-dissociative ligands. However, the development of new ligands or the application of existing ligands in these reactions, particularly 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 and benzimidazolium salts.⁸

Although the nature of the NHC ligand on complexes has a tremendous influence on the rate of catalyzed reactions, the use of 1,4,5,6-tetrahydropyrimidinium ligands in coupling reactions is a neglected area. In order to find more efficient palladium catalysts we have prepared a series of new bis(1,4,5,6-tetrahydropyrimidinium) bromides LHX (**2**) (Scheme 1). We now report the use of the *in situ* generated catalytic system composed of commercially available and stable reagents, the Pd(OAc)₂ as palladium source, bis(1,4,5,6-tetrahydropyrimidinium) (**2a-d**) as a carbene precursor and Cs₂CO₃ as a base for cross coupling of aryl chlorides with phenylboronic acid.

RESULTS AND DISCUSSION

Bis(1,4,5,6-tetrahydropyrimidinium) bromides (**2a-d**) are conventional NHC precursors. According to Scheme 1, the salts (**2a-d**) were obtained in almost quantitative yield by quaternization of 1-alkyl(1,4,5,6-tetrahydropyrimidine)⁹ in DMF with alkyl bromides.⁸



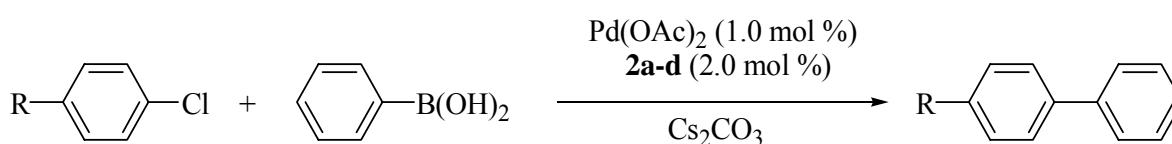
Scheme 1

The structures of **2** were determined by their characteristic spectroscopic data and elemental analyses (EXPERIMENTAL). ¹³C NMR chemical shifts were consistent with the proposed structure; the imino carbon appeared as a typical singlet in the ¹H-decoupled mode in the 154.8, 154.4, 150.5 and 153.5 ppm respectively for pyrimidinium salts **2a-d**. The ¹H NMR spectra of the pyrimidinium salts further supported the assigned structures; the resonances for C(2)-H were observed as sharp singlets in the 8.7, 8.5, 8.4 and 8.3 ppm respectively for **2a-d**. The IR spectral data for pyrimidinium salts (**2a-d**) clearly indicate the presence of the –C=N– group with a ν(C=N) vibration at 1697, 1694, 1690 and 1699 cm⁻¹ respectively for **2a-d**.

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. To find optimum conditions a series of

experiments has been performed with 4-chloroanisole and phenylboronic acid as model compounds. As a base, Cs₂CO₃ 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 C₆H₅B(OH)₂ with various *p*-substituted aryl chlorides. The results were summarized in Table 1.

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



Entry	R	LHX	Yield ^{a-d} (%)
1	COCH ₃	2a	93
2	COCH ₃	2b	95
3	COCH ₃	2c	89
4	COCH ₃	2d	87
5	CH ₃	2a	80
6	CH ₃	2b	84
7	CH ₃	2c	76
8	CH ₃	2d	73
9	CHO	2a	94
10	CHO	2b	96
11	CHO	2c	91
12	CHO	2d	89
13	OCH ₃	2a	80
14	OCH ₃	2b	86
15	OCH ₃	2c	84
16	OCH ₃	2d	81
17	H	2a	90
18	H	2b	93
19	H	2c	86
20	H	2d	82

^a Reaction conditions: 1.0 mmol of R-C₆H₄Cl-*p*, 1.5 mmol of phenylboronic acid, 2 mmol Cs₂CO₃, 1 mmol % Pd(OAc)₂, 2 mmol % **2**, dioxane (3 mL), ^b Purity of compounds is checked by NMR spectrum and yields are based on aryl chloride. ^c All reactions were monitored by TLC, ^d temperature 80 °C, 2 h.

Under those conditions, *p*-chloroacetophenone, *p*-chlorotoluene, *p*-chlorobenzaldehyde, *p*-chloroanisole and chlorobenzene react very cleanly with phenylboronic acid in goods yields (Table 1, Entries 2, 6, 10, 14 and 18).

Table 1 summarizes our results from the screening of four pyrimidinium salts, for Suzuki cross-coupling reaction. Several trends are readily apparent. First, the procedure is simple and does not require induction periods. Second, the scope of this reaction is broad and includes aryl chlorides that are activated or

deactivated. Third, all complexes led to good conversions at low catalyst concentration (1 mmol %). It is evident that the NHC precursors that contain pyrimidinium (**2a-d**) are the most effective of the salts examined.

In conclusion, we have developed a new type of easily prepared bis(1,4,5,6-tetrahydropyrimidinium) salts LHX (**2a-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 C₆H₅B(OH)₂ in the presence of Cs₂CO₃. The procedure is simple and efficient towards various aryl halides and does not require induction periods.

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 (Et₂O, dioxane). ¹H NMR and ¹³C NMR spectra were recorded using a Bruker AC300P FT spectrometer operating at 300.13 MHz (¹H), 75.47 MHz (¹³C). FT-IR spectra were recorded on a Mattson 1000 spectrophotometer. Elemental analyses were performed by TUBITAK Microlab.

Preparation of 3,3'-dimethyl-1,1'-methylenedi(1,4,5,6-tetrahydropyrimidinium) diibromide (**2a**)

To a solution of 1-methyl-1,4,5,6-tetrahydropyrimidine (0.98 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. Ether (15 mL) was added to obtain a white crystalline solid which was filtered off. The solid was washed with ether (3x15 mL), dried under vacuum and the crude product was recrystallized from ethanole / ether. Yield: 1.65 g, 89 %. mp 197-198 °C, IR (KBr) $\nu = 1697 \text{ cm}^{-1}$ (-CH=N-). ¹H NMR (DMSO-d₆) δ : 2.2 (4H, quintet, $J = 5.9 \text{ Hz}$, H-5), 3.3 (6H, s, NCH₃); 3.5 (4H, t, $J = 6.0 \text{ Hz}$, H-6), 3.6 (4H, t, $J = 5.8 \text{ Hz}$, H-4); 5.2 (2H, s, H-bridge); 8.7 (2H, s, 2-H). ¹³C NMR (DMSO-d₆) δ : 18.5 (NCH₃); 42.3 (C-5), 45.6 (C-6), 46.8 (C-4), 71.2 (C-bridge), 154.8 (C-2). Anal. Calcd for C₁₁H₂₂N₄Br₂: C, 35.70; H, 5.99; N, 15.14. Found: C, 35.66; H, 5.89; N 15.11.

Preparation of 3,3'-dimethyl-1,1'-ethylenedi(1,4,5,6-tetrahydropyrimidinium) dibromide (**2b**)

Compound (**2b**) was prepared in the same way as **2a** from 1-methyl-1,4,5,6-tetrahydropyrimidine (0.98 g, 10 mmol) and 1,2-dibromoethane (0.94 g, 5 mmol) to give white crystals of **2b**. The crude product was recrystallized from ethanole / ether. Yield: 1.75 g, 91 %. mp 242-243 °C, IR $\nu = 1696 \text{ cm}^{-1}$ (-CH=N-). ¹H NMR (DMSO-d₆) δ : 2.2 (4H, quintet, $J = 5.8 \text{ Hz}$, H-5), 3.3 (6H, s, NCH₃), 3.5 (4H, t, $J = 6.0 \text{ Hz}$, H-6), 3.6 (4H, t, $J = 5.9 \text{ Hz}$, H-4), 3.9 (4H, s, NCH₂CH₂N), 8.5 (2H, s, H-2). ¹³C NMR (DMSO-d₆) δ : 18.9 (NCH₃),

41.8 (C-5), 43.2 (C-6), 45.1 (C-4), 52.2 (C-bridge) 154.4 (C-2). Anal. Calcd for $C_{12}H_{24}N_4Br_2$: C, 37.52; H, 6.30; N, 14.58. Found: C, 37.39; H, 6.21; N, 14.21.

Preparation of 3,3'-dimethyl-1,1'-propylenedi(1,4,5,6-tetrahydropyrimidinium) dibromide (2c)

Compound (**2c**) was prepared in the same way as **2a** from 1-methyl-1,4,5,6-tetrahydropyrimidine (0.98 g, 10 mmol) and 1,3-dibromopropane (1.01 g, 5 mmol) to give white crystals of **2c**. The crude product was recrystallized from ethanole / ether. Yield: 1.80 g, 91 %. mp 120-121°C, IR $\nu=1690\text{ cm}^{-1}$ (-CH=N-). ^1H NMR (DMSO- d_6) δ : 2.2 (4H, quintet, $J=6.1$ Hz, H-5); 3.3 (6H, s, NCH_3); 3.5 (12H, m, H-6 and bridge $\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$), 3.6 (4H, t, $J=7.3$ Hz, H-4), 8.4 (2H, s, H-2). ^{13}C NMR (DMSO- d_6) δ : 8.9 (NCH_3), 25.8 (bridge, - $\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}=\text{N}$), 41.4 (C-5), 42.68 (C-6), 44.9 (C-4), 52.03 (bridge - $\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$ -), 150.5 (C-2). Anal. Calcd for $C_{13}H_{26}N_4Br_2$: C, 39.21; H, 6.58; N, 14.07. Found: C, 39.15; H, 6.51; N, 13.98.

Preparation of 3,3'-dimethyl-1,1'-buthylenedi(1,4,5,6-tetrahydropyrimidinium) dibromide (2d)

Compound (**2d**) was prepared in the same way as **2a** from 1-methyl-1,4,5,6-tetrahydropyrimidine (0.98 g, 10 mmol) and 1,4-dibromobutane (1.08 g, 5 mmol) to give white crystals of **2d**. The crude product was recrystallized from ethanole / ether. Yield: 1.92 g, 93 %. mp 138-139°C, IR $\nu=1699\text{ cm}^{-1}$ (-CH=N-). ^1H NMR (DMSO- d_6) δ : 1.7-1.8 (4H, m, bridge - $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 2.2 (4H, quintet, $J=5.8$ Hz, H-5), 3.3 (6H, s, NCH_3), 3.3-3.4 (12H, m, ring H-4,-6 and bridge- $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 8.3 (2H, s, H-2). ^{13}C NMR (DMSO- d_6) δ : 18.9 (NCH_3), 24.5 (bridge - $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ -), 41.4 (C-5), 42.6 (C-6), 44.9 (C-4), 54.6 (bridge - $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ -), 153.5 (C-2). Anal. Calcd for $C_{14}H_{28}N_4Br_2$: C, 40.79; H, 6.85; N, 13.59. Found: C, 40.64; H, 6.49; N, 13.89.

General Procedure for the Suzuki Type Coupling reactions. $\text{Pd}(\text{OAc})_2$ (1 mmol %), bis(tetrahydropyrimidinium) bromides (**2a-d**) (2 mmol %), aryl chloride (1.0 mmol), phenylboronic acid (122 mg; 1.5 mmol), Cs_2CO_3 (652 mg; 2 mmol) dioxane (3 mL) were added in a small Schlenk tube under argon and the mixture was heated at 80 °C for 2 h. At the conclusion of the reaction mixture was cooled, extracted with ether, filtered through a pad of silicagel with copious washings, concentrated and purified by flash chromatography on silicagel. Purity of compounds is checked by NMR spectrum and yields are based on aryl chloride.

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