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Application of quinoxaline based diimidazolium salt in palladium catalyzed cross-coupling reactions

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Abstract. The reaction of 2,3-bis(bromomethyl)quinoxaline with imidazole afforded the quinoxaline bridged diimidazolium salt (**1**) in good yield. Diimidazolium salt (**1**) in conjunction with $Pd(OAc)_2$ was employed as a catalyst for C–C cross-coupling reactions. The diimidazolium salt was found to be efficient in catalyzing Suzuki-Miyaura cross-coupling reaction in ethanol under ambient conditions. Moderate to good selectivity of the *trans* product was observed in the Heck cross-coupling reaction. The molecular structure of **1** was confirmed by single crystal X-ray diffraction study.

Keywords. Carbene; Imidazolium salt; Suzuki-Miyaura coupling; Mizoroki-Heck coupling; Palladium (II).

1. Introduction

Transition metal catalyzed cross-coupling reactions have emerged as the most efficient and versatile methods in academic research as well as in industry for the synthesis of natural products, pharmaceutical drugs, fine chemicals and advanced materials.[1] Palladium catalyzed Suzuki-Miyaura and Mizoroki-Heck are the most powerful C–C bond formation reactions available to synthetic chemists due to the broad tolerance of functional groups and relatively mild reaction conditions.[2] Apart from the well-known $[Pd(PPh_3)_4]$ as a catalyst, a vast number of palladium complexes containing bulky as well as electron rich phosphines have been designed and successfully employed in different cross-coupling reactions.[3] However, phosphine-based auxiliary catalysts are expensive, toxic, necessitate a tedious method to prepare and require inert atmosphere and often mild reaction conditions. For a catalyst to be attractive or popular in the industrial sector, the ligands have to be cheaper, stable to moisture, readily available or involve simple methods of preparation. In this context, several phosphine-free catalytic systems with nitrogen as donor ligands such as amines,[4a] imines[4b] and oxazolines[4c] as well as NHCs[4d–h] have been designed and employed in various catalytic reactions.

Similar to phosphines, functionalized NHCs are becoming popular in recent years.[5,6] NHC ligands having extra donor sites or pendant donor arms: for example, tridentate pincer ligand with two carbene arms (**I**), hybrid pincer ligands with amine (**II**) or phosphine (**III**) donor arms[7] or heteroatom functionalized dicarbene ligands with aromatic heterocyclic bridging units have been documented in the literature (chart 1).[8] The strong σ-donor ability of NHC ligands in comparison with phosphines results in stronger metal-ligand bonding, thereby stabilizing the metal centre during the catalytic process by neutralizing the charge deficit at the metal centre.[9,10] The dicarbene ligands of the type (**IV**) lead to dinuclear complexes with metal centres located in close proximity. Contrary to this, the dicarbene ligands of the type (**V**) places the metal centres in remote positions which can be seen as the dinuclear version of the picoline or benzoimidazoline functionalized carbene complexes (**VI**).[11] As a part of our continuous efforts towards designing novel and cheap catalysts for cross-coupling reactions,[12a–e] we recently reported the diamino-diol based palladium catalysts for Suzuki-Miyaura cross coupling reaction.[12f] Herein, we describe the synthesis of quinoxaline bridged imidazolium salt and its *in situ* generated palladium catalyst in Suzuki-Miyaura and Mizoroki-Heck coupling reactions.

2. Experimental

1-methyl Imidazole, bromo compounds, phenyl boronic acid and styrene were purchased from Aldrich. Anhydrous K_2CO_3 was purchased from S.D. Fine chemicals,

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and used as received without further purification. All other reagents were used as received. The ^{1}H and ^{13}C NMR spectra were taken in DMSO-d_6 with reference to TMS. GC analyses were conducted using an Agilent Gas Chromatograph 6890 Series, Hewlett Packard equipped with an HP5-MS capillary column (30 m × 0.25 mm × 0.25 μm) and an FID detector. All GCMS analyses were done by Agilent 7890A GC system connected with 5975C inert XL EI/CI MSD (with triple axis detector).

2.1 *Synthesis of 2,3-bis(imidazolylmethyl)quinoxalium bromide (**1**)*

A mixture of 1-methyl imidazole (0.26 g, 3.11 mmol) and 2,3-bis(bromomethyl)quinoxaline (0.5 g, 1.58 mmol) in acetonitrile was refluxed over night at 80°C. The solution was filtered under *reduced pressure* to obtain a brown precipitate, which was washed with petroleum ether and the residue obtained was recrystallized from ethanol to give colourless crystals of **1**. Yield: 75%. M.p.: 265–268°C (dec). IR (KBr) υ_{max} (cm^{-1}): 3408, 3046, 1567, 1174, 860, 776. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 4.0 (s, 6H, CH_3), 6.17 (s, 4H, CH_2), 7.85–7.87 (m, 4H, *Ar*), 7.92–7.95 (m, 4H, *Ar*), 9.42 (s, 2H, NC*H*N). ^{13}C-NMR (400 MHz, DMSO-d_6): δ 36.03 (imidazolium-NCH_3), 50.39 (quinoxaline-CH_2N), 123.54, 123.71 (imidazolium-*C*), 128.50, 130.91 (quinoxaline-*C*), 137.94 (imidazolium-NC*N*), 140.08, 147.93 (quinoxaline-*C*). ESI-MS:m/z 399.0954 [M−Br]$^{+}$.

2.2 *General method for Suzuki cross-coupling reaction*

In a two-neck round-bottomv flask, a mixture of palladium acetate (1 mol%), **1** (1 mol%), K_2CO_3 (1 mmol), aryl bromide (0.5 mmol), and phenyl boronic acid (0.75 mmol) were allowed to reflux in ethanol at 78°C. The course of reaction was monitored by GC analysis. Ethanol was removed under reduced pressure and the residue was dissolved in dichloromethane and passed through celite. An aliquot was taken with a syringe and subjected to GC analysis. Yields were calculated with aryl halides as internal standards.

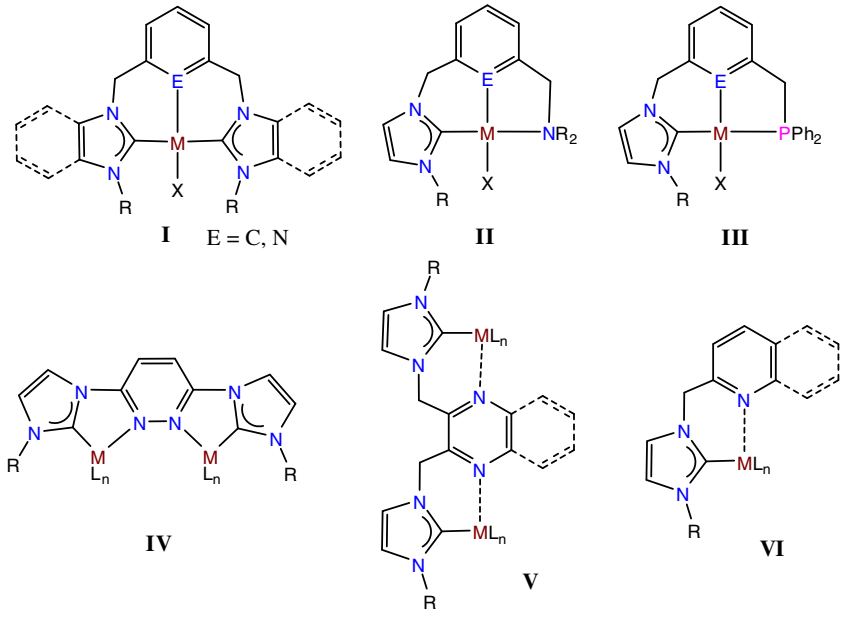
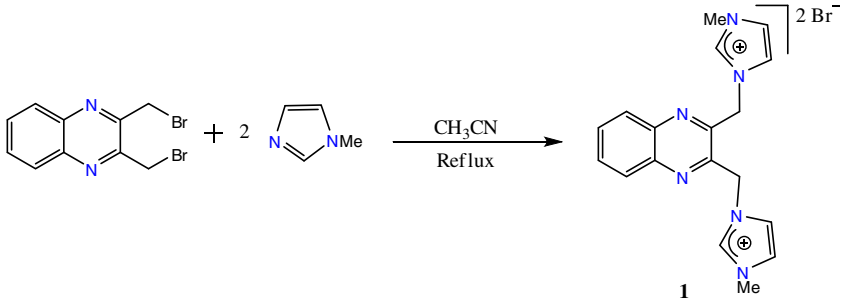


Chart 1. Different coordination modes.



Scheme 1. Preparation of *2,3-bis*(imidazolylmethyl)quinoxalium bromide (**1**).

2.3 *General method for Heck cross-coupling reaction*

Heck coupling reactions were carried out using aryl bromides (1.0 mmol), styrene (1.4 mmol), and K_2CO_3 as base (2 mmol) dissolved in 5 mL of N,N-dimethylformamide (DMF). An appropriate amount of **1** (1.0 mol%) and palladium acetate (2.0 mol%) were added to this reaction mixture. The reaction mixture was heated to 130°C for the selected reaction time. Coupling product yields were calculated from GC data relative to the residual aryl halide. The product identity was confirmed by GC–MS.

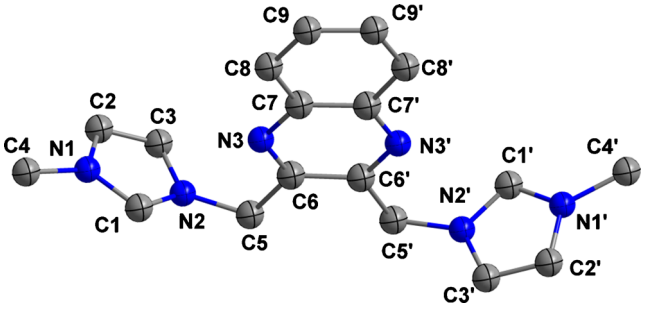


Figure 1. Molecular structure of 2,3 bis-(imidazolylmethyl) quinoxilium bromide (**1**). Hydrogen atoms and the bromide counterions have been omitted for clarity; thermal ellipsoids are drawn at 50% probability level. Selected bond angles (Å) and bond distances (°): C1–N1 = 1.323(4) Å, C1–N2 = 1.332(4), C2–N1 = 1.373(4), C4–N1 = 1.477(5); N1–C1–N2 = 108.0(3), C1–N1–C2 = 108.6(3), C3–N2–C5 = 124.5(3).

2.4 *X-ray structure determination of **1***

Diffraction data for **1** was obtained on a Rigaku Saturn724+ (4 x 4 bin mode) diffractometer equipped with a rotating anode using Mo Kα radiation (λ = 0.7107 Å). The diffraction data were measured at 293 K in the range $3.30 < 2\theta < 24.99$. Structure solution and refinement were achieved with standard Patterson and Fourier techniques. All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were added to the structure models at calculated positions.

Selected crystallographic details for 1

Mol. Formula = $C_{18}H_{20}Br_2N_6$, Colourless crystals, M = 480.22, Tetragonal, space group $P4_32_12$, a = 11.969(3), b = 11.969(3), c = 14.415(4) Å, $a = \beta = \gamma = 90°$, V = 2065.05 Å^3, Z = 4, Dc = 1.544 g cm^{-3}, μ(Mo Kα) = 3.939 mm^{-1}, F(000) = 960, T = 293 K, GoF = 0.98, final R_1 = 0.0282 and wR_2 = 0.0642 for $I > 2\sigma(I)$, R_1 = 0.0707, wR_2 = 0.0965 for all data. CCDC Number: 1035187.

3. Results and Discussion

The reaction of 2,3-bis(bromomethyl)quinoxaline with two equivalents of 1-methyl imidazole in acetonitrile under reflux conditions afforded 2,3 bis-(imidazolylmethyl)quinoxaline (**1**) as brown colour solid (scheme 1). The crude product was purified by recrystallization from ethanol to get colourless crystals in 75% yield.[13] The

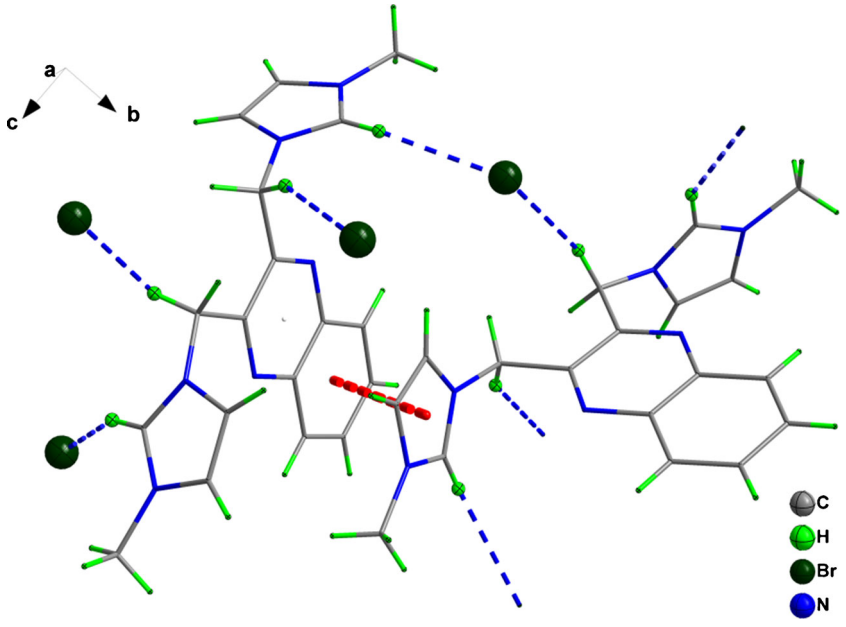
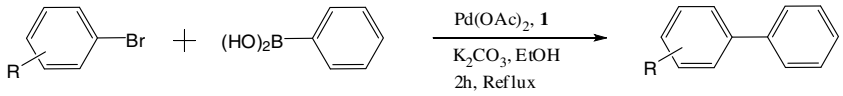
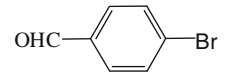
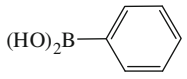
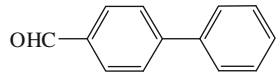
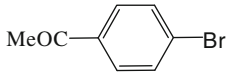
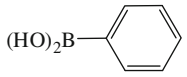
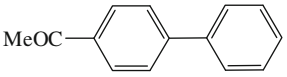
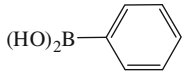
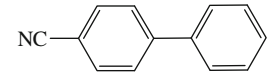
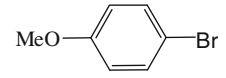
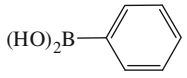
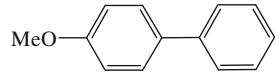
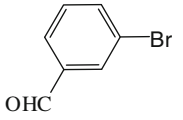
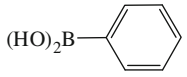
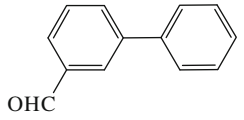
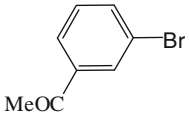
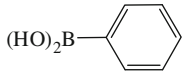
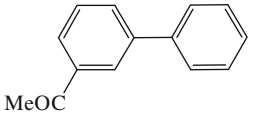
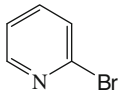
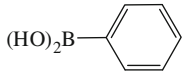
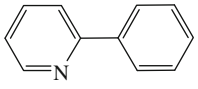
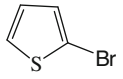
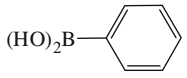
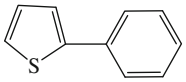


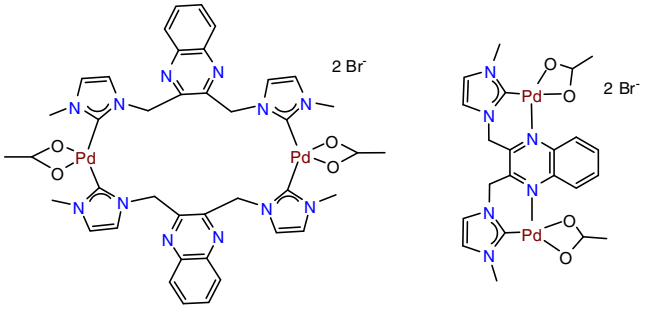
Figure 2. Intermolecular hydrogen bonding (2.71 Å) and π–π stacking (3.69 Å) interactions leading to polymeric structure in the crystal lattice of **1**.



Scheme 2. Suzuki-Miyaura cross-coupling reaction.

Table 1. Suzuki–Miyaura reaction of phenylboronic acid with aryl halides.

Entry	Aryl halide	Arylboronic acid	Product	Conversion
1				96%
2				90%
3				93%
4				85%
5				82%
6				80%
7				65%
8				58%



VII **VIII**

Figure 3. Proposed structures for complexes **VII** and **VIII**.

^{1}H NMR spectrum of the diimidazolium salt **1** showed the signal for NCHN protons at 9.42 ppm, which is in the range of NCHN protons of imidazolium and benzoimidazolium salts. The resonances for N-Methyl and methylene protons appear as singlets at 4.00 ppm and 6.17 ppm, respectively (figure 1).

The compound **1** crystallizes in tetragonal crystal system with $P4_32_12$ space group. The two imidazolyl rings are almost perpendicular to the plane of the quinoxaline ring. The carbene carbon (NCHN) of both the imidazolyl groups are aligned in opposite direction to each other as observed in pyrazine based diimidazolium salts. The C1–N1 [1.323(4) Å] and C1–N2 [1.332(4) Å] bond distances as well as the N1–C1–N2 bond angle [108.0(3)°] are comparable with the same observed in arene bridged diimidazolium salts.[11]

The crystal structure of **1** shows interesting (C–H)$^+$···· Br$^-$ ionic hydrogen bonding. The imidazolium moiety of the ligand is involved in hydrogen bonding with the bromide ion with the bromide ion with C1–H1···· Br1 = 2.716 Å and C1–H1–Br1 = 150.2°. The bromide ion is further involved in hydrogen bonding with one of the hydrogen of the methylene group [C5–H5···· Br1 = 2.839 Å, < C5–H5···Br1 = 152.9°]. As both the imidazolyl groups are pointing in opposite directions, the H-bonding leads to the formation of a polymeric structure in the solid state. Furthermore, intermolecular π-π stacking interaction is observed between one of the imidazoles and quinoxaline ring as shown in figure 2 (distance = 3.69 Å).

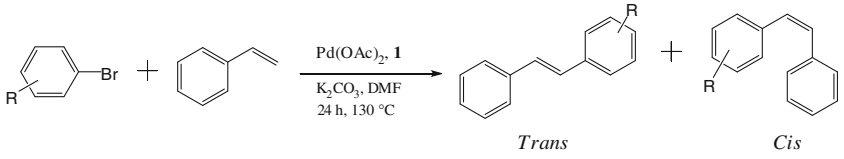
3.1 *Suzuki-Miyaura cross coupling reaction*

Attempts to isolate the Pd-complex of quinoxaline-imidazolium salt by transmetallation method using Ag_2O and by also direct deprotection method have been unsuccessful. Thus, a mixture of diimidazolium salt **1** and $Pd(OAc)_2$ was employed as the catalytic system for Suzuki-Miyaura and Mizoroki-Heck coupling reactions. The Pd-catalyzed Suzuki-Miyaura coupling reaction of *para*-bromo benzaldehyde and other aryl bromides with phenyl boronic acid has been carried out (scheme 2). All the reactions were carried out under reflux conditions in air by using environmentally benign EtOH as solvent and K_2CO_3 as base. Chromatographic analysis of the reaction mixture revealed 96% conversion in 2 h under reflux conditions.

To expand the scope of catalytic investigation, several *meta* and *para* substituted aryl bromides with phenyl boronic acid as the coupling partner were employed under the given reaction conditions. Good to excellent conversions were observed for the desired biphenyl product with conversion ranging from 80–93% (table 1, entry 2–6). Moderate to good conversions were also observed for heteroaromatic bromides such as 2-bromo pyridine and 2-bromo thiophene (table 1, entry 7–8). Homo-coupling product was not observed in all the cases. The *in situ* generated catalyst in this cross-coupling reaction is proposed to be **VII** (figure 3), a dimeric complex where two Pd centres are bridging between two imidazolyl-carbene ligands, as observed in the case of benzmidazolium derivative.[14]

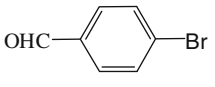
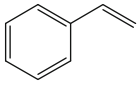
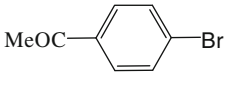
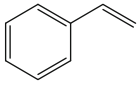
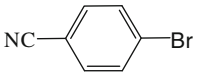
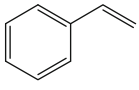
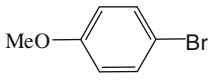
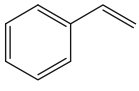
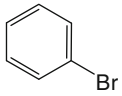
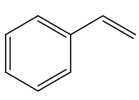
3.2 *Mizoroki-Heck cross-coupling reaction*

Heck coupling reactions were carried out with a 1:2 mixture of diimidazolium salt **1** and palladium acetate as catalyst precursor by choosing 4−bromo benzaldehyde and styrene as the cross-coupling partners (scheme 3). Under the optimized conditions (1.0 mol% of diimidazolium salt **1**, 2.0 mol% of $[Pd(OAc)_2]$ and 2.0 mmol of K_2CO_3 in dimethylformamide at 130°C over a reaction period of 24 h, almost quantitative conversions were achieved. Electron withdrawing aryl bromides showed better conversions. However moderate conversions were obtained with electron donating aryl halides. In all the cases moderate to good selectivity towards the *trans* product was observed (table 2). The *in situ* generated catalyst in the Heck cross-coupling reaction is proposed to be **VIII** (figure 3), where the Pd centres are coordinated to (C, N) hetero-donor carbene ligand. The metal centres in this case are in remote positions which can be seen as the dinuclear version of the picoline or benzoimidazoline functionalized carbene complexes.



Scheme 3. Mizoroki-Heck cross-coupling reaction.

Table 2. Mizoroki–Heck reaction of styrene with various aryl halides.

Entry	Aryl halide	Olefin	*Trans*	*Cis*	Conversion (%)
1			89.5	10.5	100
2			70	30	99
3			54	46	84
4			66	37	70
5			85	15	81

The catalytic activity in Suzuki-Miyaura cross coupling reactions is moderate in comparison to Pd-phosphine based ligand systems.[12b,c] The catalytic activity for the Heck cross-coupling reaction is lower than those found for well-defined palladium complexes with mixed carbene/phosphine, pincer-type ligands which exhibit better conversion rates for shorter reaction times, even with low catalyst loading.[15]

4. Conclusions

We have demonstrated the use of *in situ* prepared palladium catalyst with quinoxaline bridged diimidazolium salt (**1**) in Suzuki as well as Heck cross-coupling reactions. This is a versatile catalytic system which effectively catalyses Suzuki cross-coupling reactions at ambient conditions for a wide range of substrates using environmentally benign ethanol as solvent. Moderate to good selectivity towards the *trans*-product was observed in Mizoroki-Heck reactions. The coordination chemistry and further exploration of the catalytic activity of diimidazolium salt is under active investigation.

Supplementary Information

^{1}H, ^{13}C NMR and ESI-MS Spectral data for **1** are provided. The electronic supplementary information can be seen at www.ias.ac.in/chemsci. Crystallographic data for **1** has been deposited at the Cambridge Crystallographic Data Centre with CCDC no. 1035187. This data can be obtained free of charge at www.ccdc.cam.ac.ul/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033; E-mail: deposit@ccdc.cam.ac.uk +44(0)1223-3360].

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