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Efficient Route to 1,3-Di-*N*-imidazolylbenzene. A Comparison of Monodentate vs Bidentate Carbenes in Pd-Catalyzed Cross Coupling

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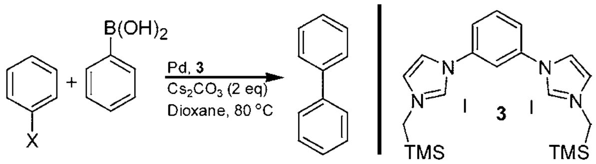
ABSTRACT



A new bis(carbene) ligand architecture has been developed and was evaluated in the Suzuki–Miyaura cross-coupling reaction of various aryl halides with phenylboronic acid. Several new bis(carbene) ligands were tested in different carbene:Pd ratios. Pd(OAc)$_2$ and Pd$_2$(dba)$_3$ were compared for efficiency as a Pd source. It was found that the Pd(OAc)$_2$/bis(carbene) system formed a catalyst for the activation of chlorobenzene.

Due to our interest in preparing stable ligands for selected catalytic processes, we prepared 1,3-bis(imidazolium)-benzene, a precursor to bidentate carbenes. Initial evaluations as ligands for palladium-catalyzed cross coupling reactions are reported. Palladium-catalyzed cross-coupling reactions are one of the most widely used modern methodologies in organic synthesis.[1] N-Heterocyclic carbenes (NHC) have been exploited as ligands for transition metal catalysis. Carbenes have been shown to be effective ligands for ROMP catalysis,[2] RCM catalysis,[3] Pd-catalyzed cross-coupling reactions,[4] and hydrogenation[5] among many.[6] One of the most notable accomplishments achieved with N-heterocyclic carbenes as ligands has been the activation of aryl chlorides under mild conditions with high yields.[4a,7]

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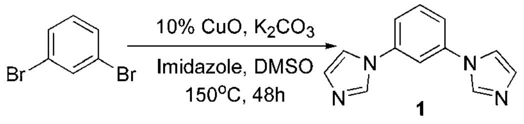
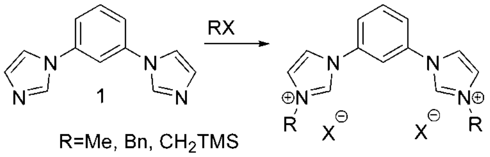
1,3-Di-*N*-imidazolyl benzene was required to prepare the bis(imidazolium) salts, precursors to the desired NHCs. To our knowledge, the best previously reported synthesis of 1,3-di-*N*-imidazolyl benzene involved four steps from 1,3-diaminobenzene for which no yield was reported.[8] We report here a high yielding one-step synthesis from 1,3-dibromobenzene and imidazole (Scheme 1).[9] The reaction is based on precedent from the preparation of the 1,2 analogue.[10] This reaction has been performed on a multigram scale with a 77% unoptimized yield.

Scheme 1. Synthesis of 1,3-Bis(imidazolyl) Benzene



The imidazolium salts were prepared by combining the bis(imidazole) **1** with various alkyl halides and heating as outlined in Scheme 2.[11,12] These facile syntheses provided efficient access to the requisite imidazolium salt[13,14] and is amenable to combinatorial synthesis of carbene ligands.

Scheme 2. Synthesis of Bis(imidazolium) Salts



For purposes of comparison, we have evaluated several ligand precursors, illustrated in Figure 1. The N-heterocyclic carbene precursor **2**, *N*,*N*-bis(mesityl)imidazolium chloride, which has been demonstrated to be highly effective in Pd-catalyzed cross-couplings by Nolan[4a] was chosen for comparison. An analogue of the recently prepared methylene-bridged bis(imidazolium) reported by Crabtree was also evaluated, **5**,[11b] along with three imidazolium salts featuring the 1,3 phenylene architecture **3**, **4**, and **6**.

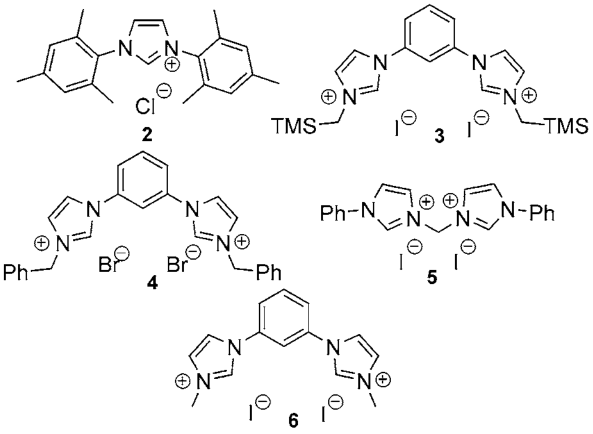


Figure 1. Imidazolium salts evaluated.

Our initial catalytic evaluation of the salts as ligand precursors for Pd followed the protocol developed by Nolan for aryl chlorides.[4a] The carbenes have been implicated as the efficacious ligand derived from combining imidazolium salts with Cs$_2$CO$_3$ under the reaction conditions,[15] which would produce a bis(carbene)Pd complex with ligands **3**−**6**. Presented in Table 1 are the results of evaluating the catalysis

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[7] For a reference to activation of aryl chlorides employing phosphine ligands, see: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387.

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[9] Compound **1** was prepared by combining 1,3-dibromobenzene (2.5 mL, 21 mmol), imidazole (3.5 g, 52 mmol), K$_2$CO$_3$ (7.2 g, 52 mmol), CuO (0.4 g, 5.2 mmol), and DMSO (20 mL). The solution was heated at 150 °C for 48 h. The reaction was cooled, and the DMSO was distilled at low-pressure, yielding an off-white solid. Chromatography on silica gel (25:1) eluting with CH$_2$Cl$_2$/MeOH (10:1) gave a white solid (3.3 g, 77%): ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.92 (pseudo-t, $J = 1.0$ 2 H), 7.67−7.62 (m, 1 H), 7.47 (m, 2 H), 7.44 (m, 1 H), 7.36 (t, $J = 1.5$, 2 H), 7.30 (m, 2 H); ^{13}C (75 MHz, CDCl$_3$) δ 138.6, 135.5, 131.5, 131.0, 120.1, 118.1, 114.5; MS(EI) *m/z* 210.0903 (M$^+$; calcd for C$_{12}$H$_{10}$N$_4$, 210.0905). Anal. Calcd for C$_{12}$H$_{10}$N$_4$: C, 68.56; H, 4.79; N, 26.65. Found: C, 68.23; H, 4.60; N, 26.65.

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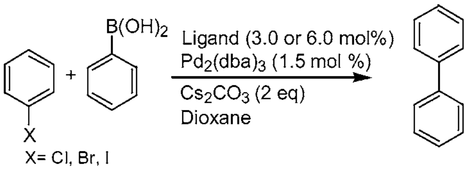
[12] Compounds **3** and **6** were prepared by combining bis(imidazolyl)-benzene (1 equiv) and an alkyl iodide (1.25 equiv) and then heating to 150 °C. The resulting two-phase mixture was cooled to room temperature whereupon the lower layer solidified. The top layer was decanted and the solid washed with CH$_2$Cl$_2$. CH$_2$Cl$_2$ (5 mL) was added and heated on a steam bath until the solid melted, yielding a solution. When the solution was cooled, a white precipitate was formed, which was collected, washed with CH$_2$Cl$_2$/hexane (1:1), and dried under vacuum. Compound **3** (0.32 g, 44%): ^{1}H NMR (300 MHz, DMSO) δ 9.76 (s, 2 H), 8.44 (d, 2 H $J = 10.2$), 7.98 (d, 2 H $J = 6.2$) 4.02 (s, 4 H) 0.15 (s 18H); ^{13}C (75 MHz, CDCl$_3$) δ 138.7, 136.5, 131.0, 124.9, 122.1, 114.5, 110.0, 42.2, −2.3; MS(EI) *m/z* 383.2075 (M$^+$; calcd for C$_{20}$H$_{31}$N$_4$Si$_2$, 383.2087). Compound **6** (0.15 g, 0.71 mmol): ^{1}H NMR (300 MHz, DMSO) δ 9.87 (s, 2 H), 8.15 (s, 2 H) 8.00 (s, 2 H), 7.81 (m, 4 H), 3.98 (s 6 H); ^{13}C (75 MHz, CDCl$_3$) δ 138.8, 136.5, 131.0, 125.2, 121.6, 120.3, 114.4, 37.2; MS(EI) *m/z* 225.1127 (M$^+$; calcd for C$_{13}$H$_{13}$N$_4$, 225.1140).

[13] Compound **4** was prepared by combining 1,3-bis(imidazolyl) benzene (0.2 g, 0.94 mmol), benzyl bromide (0.4 g, 1.2 mmol), and toluene (10 mL) and heating to 120 °C. The precipitate was collected and washed with benzene and then dried under vacuum: yield = 0.2 g, 33%; ^{1}H NMR (300 MHz, DMSO) δ 10.25 (s, 2 H), 8.48 (s, 2 H), 8.41 (s, 1 H), 8.13 (s, 2 H), 8.07−7.94 (m, 3 H), 7.57−7.42 (m, 10 H), 5.56 (s, 4 H); ^{13}C (75 MHz, CDCl3) δ 136.7, 136.4, 135.0, 132.6, 129.7, 129.3, 124.3, 123.5, 122.4, 53.3; MS(EI) *m/z* 391.1909 (M$^+$; calcd for C$_{26}$H$_{23}$N$_4$, 391.1923).

[14] Compound **5** was prepared by combining diiodomethane (0.21 g, 0.8 mmol), 1-phenylimidazol (0.22 g, 1.58 mmol), and toluene (10 mL) and heating to 120 °C. The precipitate was collected and washed with benzene and then dried under vacuum, yielding a white solid (0.13 g, 30%): ^{1}H NMR (300 MHz, DMSO) δ 10.0 (s, 2 H), 8.44 (s, 2 H), 8.25 (s 2 H), 7.81−7.65 (m, 10 H), 6.80 (s, 2 H); ^{13}C (75 MHz, CDCl$_3$) δ 138.0, 136.6, 135.2, 130.8, 124.3, 123.8, 122.8, 59.6; MS(EI) *m/z* 301.1454 (M$^+$; calcd for C$_{19}$H$_{17}$N$_4$, 301.1453).

[15] General catalytic procedure using Pd$_2$(dba)$_3$. Under an atmosphere of Ar, a solution of 1,4-dioxane (3 mL), aryl halide (1 mmol), and PhB(OH)$_2$ (1.5 mmol) was added to a vial charged with a magnetic stir bar, Pd$_2$(dba)$_3$ (1.5 mol %) and Cs$_2$CO$_3$ (2.0 mmol). Imidazolium salt with a 2:1 carbene: palladium ratio: **2**, 6.0 mol %; **3**, 3.0 mol %; **4**, 3.0 mol %; **5**, 3.0 mol %; **6**, 3.0 mol %. Imidazolium salt with a 1:1 carbene:Pd ratio: **2**, 3.0 mol %; **3**, 1.5 mol %; **4**, 1.5 mol %; **5**, 1.5 mol %; **6**, 1.5 mol %. The vial was placed in an 80 °C heating block and stirred for 2 h. An aliquot was analyzed by GC.

Table 1. Carbene:Pd Ratio of 2:1, Comparison of Both Monodentate and Bidentate Ligands with Various Substrates[a]



entry	ligand	X = Cl[b]	X = Br[b]	X = I[b]
1	**2**	46%	47%	87%
2	**3**	0%	54%	82%
3	**4**	0%	69%	90%
4	**5**	0%	19%	95%
5	**6**	0%	70%	100%

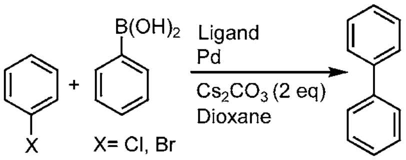
[a] Reaction conditions: aryl halide (1.0 mmol), $PhB(OH)_2$ (1.5 mmol), Cs_2CO_3 (2.0 mmol), $Pd_2(dba)_3$ (1.5 mol %), ligand (3.0 or 6.0 mol %), 1,4-dioxane (3 mL), 80 °C, 2 h. [b] GC yields.

with a carbene:Pd ratio of 2:1 for chlorobenzene, bromobenzene, and iodobenzene.

At a 2:1 carbene:Pd ratio, only the bis(mesitylene) NHC ligand **2** yielded a system that activated chlorobenzene. This system, previously reported by Nolan, was taken as the benchmark catalyst system.[4a] Ligand precursors **3**, **4**, and **6** yielded catalytic systems that were equal to or better than **2** for activating bromobenzene. Methylene-bridged bis(carbene) precursor **5** yielded a system with only poor reactivity toward bromobenzene. All five ligand precursors (**2**−**6**) yielded active catalysts for the reaction of $PhB(OH)_2$ with iodobenzene.

Presented in Table 2 are the catalytic results obtained when evaluating reactivity at a 1:1 carbene:Pd ratio for chlorobenzene and bromobenzene. The Pd source was also varied using $Pd_2(dba)_3$ and $Pd(OAc)_2$ for comparison.[16] With the 1:1 carbene:Pd ratio, bis(mesitylene) NHC precursor **2** produced a highly active catalyst system as Nolan has reported (entry 1, $Pd_2(dba)_3$). Surprisingly, this system was less reactive with bromobenzene than with chlorobenzene (entries 1 and 2). At a 1:1 carbene:Pd ratio, bis(carbene) precursors **3**, **4**, and **6** yielded no reactivity with $Pd_2(dba)_3$. In contrast, when $Pd(OAc)_2$ was the Pd source, ligand precursors **3**, **4**, and **6** showed significantly improved catalytic activity (entries 3, 5, 7, and 9). The catalyst derived from bis(carbene) precursor **5** and $Pd(OAc)_2$ showed only trace activity (5%) with chlorobenzene. All of the catalyst systems showed high reactivity with bromobenzene with $Pd(OAc)_2$ as Pd source except Me-imidazolium **6**. This difference appears to be a result of steric hindrance. With $Pd_2(dba)_3$ the activities of bromobenzene also appear to be influenced by steric factors since the activity increased with increasing steric bulk (**2** > **3** > **4** > **5** > **6**) at the carbene coordination site. The bis(carbene) ligands are comparable to or better than the bis(mesitylene) NHC for activating bromobenzene at a 1:1 carbene:Pd ratio. The 1:1 carbene:Pd system is faster than the 2:1 carbene:Pd systems, which is consistent with a monocarbene Pd complex as the active catalyst.

Table 2. Carbene:Pd Ratio of 1:1, Comparison of $Pd_2(dba)_3$ vs $Pd(OAc)_2$ with Chlorobenzene and Bromobenzene[a]



entry	ligand[b]	X	$Pd_2(dba)_3$[c,d]	$Pd(OAc)_2$[d,e]
1	**2**	Cl	92%	80%
2		Br	56%	84%
3	**3**	Cl	2%	24%[f]
4		Br	42%	80%
5	**4**	Cl	1%	38%[f]
6		Br	24%	92%
7	**5**	Cl	0%	5%[f]
8		Br	15%	95%
9	**6**	Cl	0%	17%[f]
10		Br	11%	15%

[a] Reaction conditions: arly halide (1.0 mmol), $PhB(OH)_2$ (1.5 mmol), Cs_2CO_3 (2 mmol), 1,4-dioxane (3 mL). [b] Ligand **2**: 3.0 mol %. Ligands **3**, **4**, **5** and, **6**: 1.5 mol %, 80 °C, 2 h. [c] $Pd_2(dba)_3$ (1.5 mol %). [d] GC yields. [e] $Pd(OAc)_2$ (3.0 mol %) was used. [f] 18 h.

In conclusion, we report an efficient synthesis of a new carbene ligand architecture and demonstrated its efficiency in Pd-catalyzed cross-coupling reactions. Further study is underway to optimize the reactivity of the bis(NHC) precursors for chlorobenzene activation with $Pd(OAc)_2$, and work is also under way to compare transition metal complexes of Ir, Rh, Ru, and Pd to explore their catalytic activity.

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(16) General catalytic procedure using $Pd(OAc)_2$. Under an atmosphere of Ar, a solution of 1,4-dioxane (1 mL) was added to a vial charged with a magnetic stir bar and $Pd(OAc)_2$ (3.0 mol %), Cs_2CO_3 (2.0 mmol), and imidazolium salt (**2**, 3.0 mol %; **3**, 1.5 mol %; **4**, 1.5 mol % **5**, 1.5 mol %; **6**, 1.5 mol %) with a 1:1 carbene:Pd ratio. The vial was then placed in a 80 °C heating block and stirred for 30 min. The vial was cooled, and a solution of 1,4-dioxane (3 mL), aryl halide (1 mmol), and $PhB(OH)_2$ (1.5 mmol) was then added. The vial was then heated to 80 °C and stirred for 2 h. An aliquot was analyzed by GC.