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New pyrazole-tethered Schiffs bases as ligands for the Suzuki reaction

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Abstract—Pyrazole-tethered Schiffs base ligands **2** promote Suzuki coupling of aryl bromides and chlorides with phenylboronic acid efficiently under mild conditions.

Transition metal catalyzed cross-coupling reactions are useful tools in organic synthesis for constructing C–C bonds.[1] Among these, the coupling of an aryl halide with an organoboron reagent, the Suzuki reaction has emerged a favourite because of its mild conditions.[1c] Pd–phosphine complexes[2,3] have been the most commonly employed catalysts for the Suzuki reaction. The high price associated with bulky tertiary phosphines and difficulties associated with separation of the ligands and their degradation products, phosphine oxides, etc., from coupling products have encouraged researchers to explore alternative ligands. Recently a few nonphosphine ligands such as *N*-heterocyclic carbenes (NHCs),[4] imidazol-2-ylidenes[5] and diazabutadienes[6] have been used in Suzuki coupling reactions.

Recent developments in this area suggest that an electron rich metal center (possibly aided by a σ-donor ligand) facilitates oxidative addition and steric congestion around the metal accelerates the reductive elimination step. Accordingly, we designed ligand systems depicted in Figure 1. There are two types of nitrogen donor atoms in these potentially bidentate ligands. The pyrazole is expected to act as a hemilabile ligand[7] while the Schiffs base nitrogen acts as the principal donor. For comparison, an *ortho*-NMe_2 group (as in **1**) instead of CH=N was also examined.[8a]

Ligand **1** did not catalyze the Suzuki coupling reaction at all. Deposition of Pd black commences after 1 h at room temperature and within a few minutes at 65–70 °C. This result indicates that a low valent Pd(0) complex cannot be stabilized by a hard donor like NMe_2. The use of ligands **2a**–**d**, on the other hand, effected efficient coupling. The preparation of ligands **2** is depicted in Scheme 2.[8b,c] The relative efficiency of the ligands **2a**–**d** was assessed by reference to results of the Suzuki coupling between 4-bromoanisole and phenylboronic acid (Table 1).

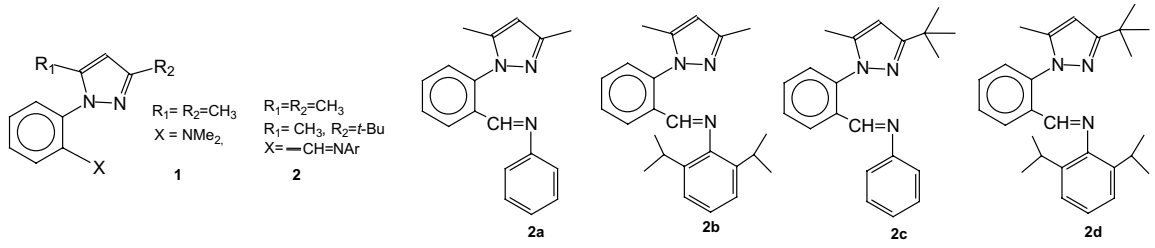

Figure 1.

Keywords: Pyrazole; Schiffs base; *N*,*N*-donor system; Suzuki coupling; Pd.
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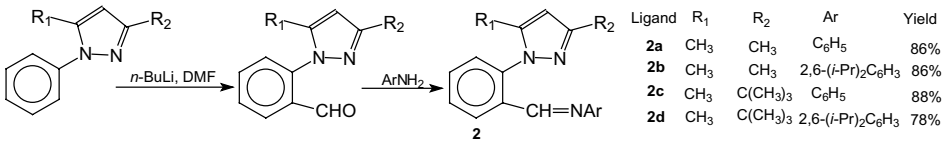
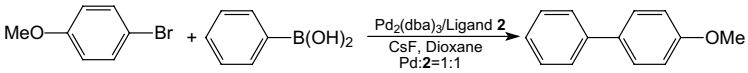


Scheme 2.

Table 1. Influence of ligands **2** on the palladium-catalyzed Suzuki coupling of 4-bromoanisole with phenyl boronic acid[a]



Entry	Ligand	Temp (°C)	Time (h)	Yield (%)[b]
1	**2a**	45	7	68 (71)
2	**2b**	rt	10	77 (47)
3	**2b**	45	3	78 (49)
4	**2c**	45	7	71 (71)
5	**2d**	rt	10	78 (31)
6	**2d**	45	3	81 (49)

[a] Reaction conditions: $Pd_2(dba)_3$: 1 mol%, Ligand **2**: 2 mol%, Pd:**2** = 1:1, Dioxane: 3 mL, CsF: 3 mmol, Time: 3–10 h.
[b] Yield in parentheses refer to ratio of Pd:ligand **2** = 1:2. Results are based upon isolated material, average of two runs.

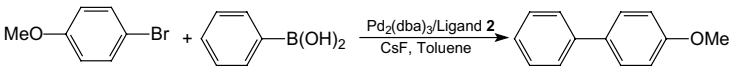
Coupling was observed at room temperature when the ligands **2b** or **2d** were used (Table 2, entries 2 and 5). At 45 °C the reaction was complete within 3 h and the yield was improved. Neither ligand **2a** nor **2c** promoted coupling at room temperature. This trend in reactivity is in agreement with the stronger donating ability of the *t*-butyl group of the pyrazole ring and the *iso*-propyl group on the benzene ring, making the ligands **2b** and **2d** more electron rich. Sensitivity to the Pd:ligand ratio was observed for the sterically demanding ligands **2b** and **2d** but not with **2a** and **2c** (see Table 1). Dioxane was found to be superior to toluene as solvent (Table 2). Both CsF and Cs_2CO_3 gave comparable yield of products.[9]

All the ligands **2a**–**d** appear to be useful in the reactions of aryl bromides. However, with an activated aryl chloride, only ligands **2b** and **2d** were effective (Table 3).

As is evident from Table 3, the Pd-catalyzed Suzuki coupling reactions with the ligands **2** proceeded extremely well. In case of a neutral aryl bromide (Table 3, entry 2), the reaction can be performed at room temperature, though it required a longer time. *ortho*-Substituted and sterically congested substrates also led to excellent yields in the presence of ligands **2b** and **2d** (Table 3, entries 5–8). Activated and neutral aryl chlorides in the presence of ligands **2b** and **2d** afforded good yields of the desired products (Table 3, entries 10–13), whereas attempts to couple the electron rich 4-chloroanisole were not successful.

In summary, we have developed a new and efficient catalyst system for Suzuki coupling reactions. To the best of our knowledge this is the first report of pyrazole-tethered nonphosphine ligands being explored for catalysis of Suzuki reactions.[10,11] We have shown that the catalytic activity depends considerably on the donor atoms and the steric environment around the metal present in the ligand system. These nonphosphine ligands constitute interesting alternatives to traditional phosphine ligands. Schiffs base structures also promote the ready

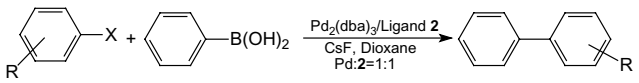
Table 2. Effect of solvent on the $Pd_2(dba)_3$/ligand **2**-catalyzed cross-coupling reaction of 4-bromoanisole with phenylboronic acid[a]



Entry	Ligand	Solvent	Yield (%)
1	**2a**	Toluene	53
2	**2a**	Dioxane	68
3	**2b**	Toluene	61
4	**2b**	Dioxane	78
5	**2c**	Toluene	31
6	**2c**	Dioxane	71
7	**2d**	Toluene	63
8	**2d**	Dioxane	81

[a] Reaction conditions: Aryl bromide: 1 mmol, Phenyl boronic acid: 1.5 mmol, CsF: 3 mmol, $Pd_2(dba)_3$: 1 mol%, Ligand **2:** 2 mol%, Toluene: 3 mL, Temp: 45 °C. Results are based upon isolated material, average of two runs.

Table 3. $Pd_2(dba)_3$/ligand **2** catalyzed coupling of aryl halides with phenyl boronic acid[a]



Entry	Ligand	Aryl halide	Time (h)	Product	Yield (%)
1	**2a**	4-Bromotoluene	7	4-Methylbiphenyl	79
2	**2b**	4-Bromotoluene	3	4-Methylbiphenyl	88 (81)[b]
3	**2c**	4-Bromotoluene	7	4-Methylbiphenyl	81
4	**2d**	4-Bromotoluene	2	4-Methylbiphenyl	95
5	**2b**	2-Bromotoluene	3	2-Methylbiphenyl	87
6	**2d**	2-Bromotoluene	3	2-Methylbiphenyl	91
7	**2b**	2-Bromoacetophenone	5	2-Acetylbiphenyl	89
8	**2b**	2-Bromomesitylene	10	2,4,6-Trimethylbiphenyl	73[c]
9	**2b**	4-Bromoacetophenone	1	4-Acetylbiphenyl	93 (91)[d]
10	**2b**	4-Chlorotoluene	10	4-Methylbiphenyl	69[e]
11	**2d**	4-Chlorotoluene	10	4-Methylbiphenyl	67
12	**2b**	4-Chloroacetophenone	8	4-Acetylbiphenyl	75
13	**2d**	4-Chloroacetophenone	8	4-Acetylbiphenyl	79
14	**2b**	4-Chloroanisole	12	4-Methoxybiphenyl	0

[a] Reaction conditions: Aryl halide (1 mmol), Phenyl boronic acid (1.5 mmol), $Pd_2(dba)_3$: 1 mol%, Ligand **2**: 2 mol%, Base: CsF (for aryl bromide), K_3PO_4 (for aryl chloride): 3 mmol. Dioxane: 3 mL, Temp: 45–55 °C.
[b] Reaction was performed at room temperature for 12 h.
[c] Temp: 55 °C.
[d] Reaction was performed at room temperature for 2 h.
[e] For chloro substrate the temperature was fixed at 55 °C.

synthesis of a large number of enantiopure chiral ligands. The utility of the $Pd_2(dba)_3$/ligand **2** catalysts in other coupling reactions such as Heck, Sonogashira and amination is being explored in our laboratory.

Acknowledgements

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8. (a) When 4-bromoanisole and phenylboronic acid were treated with *N*-phenylpyrazole as the ligand instead of ligand **2**, below 65 °C, no coupling was observed. Above 65 °C rapid precipitation of Pd-black was observed.; (b) *General procedure for synthesizing ligands* **2**: the pyrazole-tethered aldehyde (1 equiv) and aromatic amine (1 equiv) in dry ethanol were refluxed in the presence of one drop of acetic acid until the starting material was completely consumed (monitored by TLC). After removal of solvent, the product was obtained either as a solid or a semi-solid, which was purified by crystallization using hot ethanol. (c) *Spectral and analytical data for ligands* **1** *and* **2a**–**d**: ligand **1**: (Liquid). Yield: 66%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.28–7.19 (2H, m, PhH), 6.94–6.89 (2H, m, PhH) 5.91 (1H, s, PzH), 2.46 (6H, s, $N(CH_3)_2$), 2.26 (3H, s, CH_3), 2.06 (3H, s, CH_3). ^{13}C NMR (50.32 MHz, $CDCl_3$) δ: 148.5, 140.9, 130.6, 129.4, 128.9, 120.2, 117.3, 105.0, 41.5, 13.3, 10.8. Microanalysis: $C_{13}H_{17}N_3$ (215): calcd: C: 72.56%, H: 7.91%, N: 19.53%. Found: C: 72.44%, H: 7.88%, N: 19.43%.
Ligand **2a**: (Yellow solid). Mp: 65–67 °C. IR (KBr, cm^{-1}): 1552, 1496. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.40–8.37 (1H, m, CH=N), 8.05 (1H, s, PhH), 7.54–7.52 (3H, m, PhH), 7.37–7.31 (3H, m, PhH), 7.14–7.12 (2H, m, PhH), 6.02 (1H, s, PzH), 2.32 (3H, s, CH_3), 2.11 (3H, s, CH_3). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 156.3, 151.7, 149.3, 141.4, 140.1, 133.3, 131.5, 129.0, 128.2, 127.8, 127.6, 120.9, 106.1, 13.5, 11.6. Microanalysis: $C_{18}H_{17}N_3$ (275): calcd: C: 78.54%, H: 6.18%, N: 15.27%. Found: C: 78.29%, H: 5.91, N: 15.25%.
Ligand **2b**: (Yellow solid). Mp: 104–107 °C. IR (KBr, cm^{-1}): 1552, 1498. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.45–8.41 (1H, m, CH=N), 7.72 (1H, s, PhH), 7.63–7.59 (2H, m, PhH), 7.39–7.34 (1H, m, PhH), 7.13 (3H, bs, PhH), 5.94 (1H, s, PzH), 3.00–2.87 (2H, m, $CH(CH_3)_2$), 2.22 (3H, s, CH_3). 2.12 (3H, s, CH_3), 1.14 (12H, d, J = 6 Hz, $CH(CH_3)_2$).^{13}C NMR (50.32 MHz, $CDCl_3$): 159.7, 158.4, 149.1, 140.8, 140.3, 137.6, 133.9, 131.4, 129.2, 128.1, 127.6,

124.2, 123.0, 105.9, 27.8, 23.4, 13.3, 11.3. Microanalysis: $C_{24}H_{29}N_3$ (359): calcd: C: 80.22%, H: 8.07%, N: 11.69%. Found: C: 80.12%, H: 8.03%, N: 11.59%.

Ligand **2c**: (Yellow semi-solid). IR (Neat, cm^{-1}): 1550, 1480. ^1H NMR (300 MHz, $CDCl_3$): δ 8.39–8.37 (1H, m, CH=N), 7.99 (1H, s, PhH), 7.57–7.53 (2H, m, PhH), 7.40–7.35 (3H, m, PhH), 7.23–7.12 (2H, m, PhH), 6.08 (1H, s, PzH), 2.14 (3H, s, CH_3), 1.35 (9H, s, $C(CH_3)_3$). ^{13}C NMR (75.47 MHz, $CDCl_3$): 162.5, 157.1, 151.9, 140.9, 140.3, 134.1, 133.5, 131.4, 129.0, 126.9, 127.8, 127.7, 126.1, 120.9, 102.9, 32.0, 30.5, 11.7. Microanalysis: $C_{21}H_{23}N_3$ (317): calcd: C: 79.49%, H: 7.25%, N: 13.25%. Found: C: 79.31%, H: 7.38%, N: 13.20%.

Ligand **2d**: (Yellow semi-solid). IR (Neat, cm^{-1}): 1552, 1496. ^1H NMR (300 MHz, $CDCl_3$):δ 8.46–8.42 (1H, m, CH=N), 7.73 (1H, s, PhH), 7.62–7.58 (2H, m, PhH), 7.40–7.38 (1H, m, PhH), 7.15–7.06 (3H, m, PhH), 6.00 (1H, s, PzH), 3.03–2.86 (2H, m, $CH(CH_3)_2$), 2.09 (3H, s, CH_3), 1.26 (9H, s, $C(CH_3)_3$), 1.10 (12H, d, $J = 6$ Hz, $CH(CH_3)_2$). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 162.3, 158.1, 149.0, 140.4, 137.3, 133.6, 131.6, 129.3, 128.5, 127.3, 124.1, 122.9, 102.5, 30.4, 27.8, 23.4, 22.4, 11.4. Microanalysis: $C_{27}H_{35}N_3$ (401): calcd: C: 80.79%, H: 8.72%, N: 10.47%. Found: C: 81.41%, H: 8.90%, N: 10.33%.

9. (a) $Pd_2(dba)_3$ is a better catalyst precursor than $Pd(OAc)_2$ for this reaction. (b) *General procedure for Suzuki coupling*: an oven dried round bottomed flask was cooled under argon and charged with $Pd_2(dba)_3.CHCl_3$ (1 mol%), ligand **2** (2 mol%), phenyl boronic acid (1.5 mmol) and base (3 mmol). The flask was evacuated and flushed with argon once again. Aryl halide (1 mmol) and dioxane (3 mL) were added to the reaction mixture by a syringe. The reaction mixture was heated (45–55 °C) with stirring for the specified time. Reaction was monitored by TLC. The reaction mixture was then cooled to room temperature, filtered through Celite and washed with dichloromethane. The crude material was purified by flash chromatography. The identity of every product was confirmed by comparison with literature spectroscopic data: 4-methoxybiphenyl,[12a] 2-methylbiphenyl,[12b] 2,4,6-trimethylbiphenyl,[12c] 4-methylbiphenyl,[2a] and 4-acetylbiphenyl.[12d]
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