ChemComm

Cite this: *Chem. Commun.*, 2011, **47**, 5079–5081

www.rsc.org/chemcomm

COMMUNICATION

Highly efficient carbazolyl-derived phosphine ligands: application to sterically hindered biaryl couplings†

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Received 6th February 2011, Accepted 10th March 2011
DOI: 10.1039/c1cc10708a

A new family of phosphine ligands bearing a bulky carbazolyl scaffold is described. With the combination of ligand 2a and $Pd(OAc)_2$, difficult tri-*ortho*-substituted biaryl couplings are accomplished smoothly. In particular, the catalyst loading as low as 0.02 mol% of Pd for non-activated 2,6-disubstituted aryl chloride coupling can be achieved.

Palladium-catalyzed cross-coupling reactions have been successful in constructing various aromatic carbon–carbon bonds.[1] In particular, Suzuki–Miyaura coupling has captured considerable attention in a variety of material and pharmaceutical intermediate syntheses.[2] In fact, a plethora of evolutional phosphine ligands have been designed to give milder coupling reaction conditions, as well as vastly expand the substrate scope for these reactions. For instance, Buchwald's biaryl-based monophosphines[3] and Beller's heterobiaryl phosphines[4] have been shown as excellent phosphine ligands for palladium-catalyzed aromatic carbon–carbon and carbon–heteroatom bond-forming processes. Interestingly, even though these biaryl-type monophosphines are generally regarded as monodentate ligands, the X-ray crystallographic data unambiguously showed that the non-phosphine containing arene ring binds to the palladium center to a certain extent (*via ipso*-carbon coordination).[5] This coordination has been suggested as a key feature to enhance the oxidative addition step in cross-coupling reactions.[6]

Numerous phosphines are found to be effective in the Suzuki–Miyaura coupling reaction. The effectiveness of these ligands is usually screened by the model reaction with sterically non-hindered coupling partners. The sterically encumbered tri-*ortho*-substituted biaryl examples are not always reported in general using stated reaction conditions, but usually require higher catalyst loading or elevated reaction temperature.[7] To the best of our knowledge, there have been only a few reports disclosing the general tri-*ortho*-substituted biaryl synthesis from aryl chlorides, especially in using low Pd loading.[8] In fact, there are many pharmaceutically attractive organic molecules bearing tri-*ortho*-substituted biaryl motifs, such as vancomycin,[9] steganacin[10] and an $\alpha_{2/3}$-selective $GABA_A$ agonist candidate.[11] In view of this difficult but valuable method, we are attracted to explore a ligand structure which can effectively handle the sterically congested coupling reaction from aryl chlorides. Herein, we report a new series of carbazolyl-derived phosphine ligands and their applications in sterically hindered tri-*ortho*-substituted biaryl synthesis, using low palladium loading.

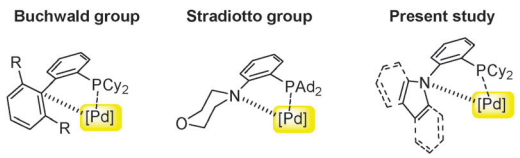
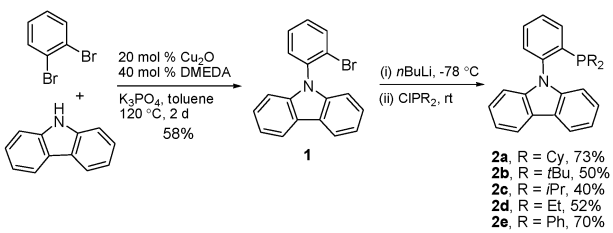


Fig. 1 Previous ligand structures/coordinations and our present attempted investigation.

Inspired by the interesting *ipso*-carbon-Pd coordination[12] and Stradiotto's morpholinyl P,N-type ligand structure[13] (with a flexible bottom ring and sp^3-N-Pd coordination) (Fig. 1), we were interested in exploring carbazolyl ligands with all-aromaticity in the heteroaromatic ligand scaffold. The flattened carbazolyl bottom ring takes advantage to provide an extended flat-wall-like rigidity for facilitating the reductive elimination process, while the sp^2-N would offer a weak coordination to the palladium center whenever needed during the catalytic cycle to potentially increase the catalyst longevity.

We embarked to prepare the carbazolyl-derived ligand series by using the Cu-catalyzed C–N bond coupling of 1,2-dibromobenzene and carbazole (Scheme 1).[14] In our ligand synthesis optimization, Cu_2O salt was found to be more effective than CuI in this *N*-arylation. The single X-ray crystal structure was obtained from the reaction of $PdCl_2(CH_3CN)_2$ and **2a** (Fig. 2). The palladium dimer complex showed that the two ligands were *trans* to each other. The proximity of the



Scheme 1 The synthesis of carbazolyl-derived phosphines.

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c1cc10708a

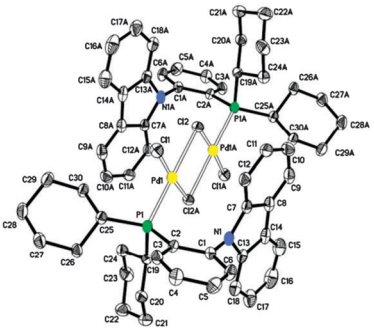
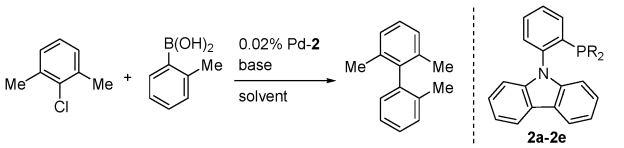


Fig. 2 ORTEP drawing of the Pd–**2a** complex.

Table 1 An evaluation of carbazolyl-derived phosphine ligands **2**[a]



Entry	Ligand **2**	Base	Solvent	Yield%[b]
1	**2a**	$K_3PO_4·H_2O$	Dioxane	98 (95)[c]
2	**2b**	$K_3PO_4·H_2O$	Dioxane	20
3	**2c**	$K_3PO_4·H_2O$	Dioxane	89
4	**2d**	$K_3PO_4·H_2O$	Dioxane	11
5	**2e**	$K_3PO_4·H_2O$	Dioxane	9

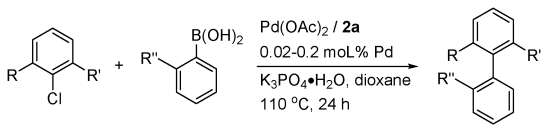
[a] Reaction conditions: $Pd(OAc)_2$ (0.02 mol%), ligand 2 (0.06 mol%), ArCl (1.0 mmol), $Ar'B(OH)_2$ (1.5 mmol), $PhB(OH)_2$ (1 mg), base (3.0 mmol), solvent (3.0 mL) were stirred for 24 h at 110 °C under nitrogen. [b] Calibrated GC yields were reported. [c] Isolated yield in parenthesis.

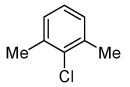
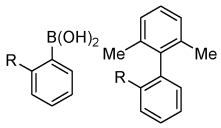
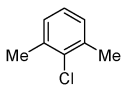
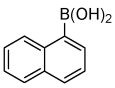
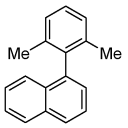
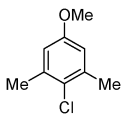
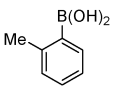
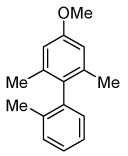
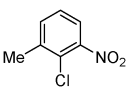
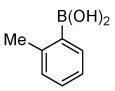
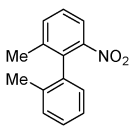
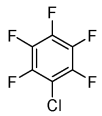
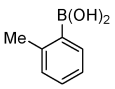
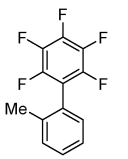
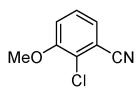
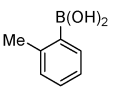
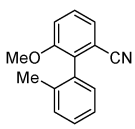
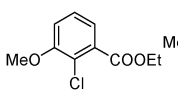
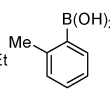
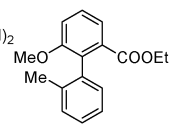
nitrogen atom on the carbazole ring to the palladium center was 3.3 Å. The stiff and bulky carbazole plane hindered one side of the palladium complex.

To test the effectiveness of the new family of ligand, we avoided the use of "privileged" phenylboronic acid as the nucleophile. Thus, difficult 2-chloro-*m*-xylene and 2-tolylboronic acid were chosen in our model investigations (Table 1). Ligand **2a** and **2c** bearing Cy and *i*Pr groups, respectively, gave superior results (entries 1 and 3). It is noteworthy that this tri-*ortho*-substituted biaryl coupling is highly sensitive to the steric bulkiness of the ligand. The incorporation of the sterically more hindered $–PtBu_2$ group or sterically less congested $–PEt_2$ group to the ligand scaffold (**2b** and **2d**, respectively) provided significantly inferior results (entries 2 and 4). The ligand **2e** with the $–PPh_2$ moiety gave 9% yield (entry 5). Solvents and bases were screened (see ESI†).

With the optimized reaction conditions in hand, we next probed the substrate scope of this new catalyst system (Table 2). The coupling of sterically more hindered 2-ethylphenylboronic acid with 2-chloro-*m*-xylene was successfully achieved using 0.02 mol% of palladium loading (entry 2). This represents the *lowest* catalyst loading achieved so far for tri-*ortho*-substituted biaryl synthesis where the *ortho*-substituted group is bigger than a methyl moiety. In general, the tri-*ortho*-substituted biaryl syntheses could be accomplished within the range of 0.02–0.2 mol% of catalyst. Functional groups such as nitro, cyano, ester, *etc*. were well tolerated (Table 2). In particular

Table 2 Palladium-catalyzed Suzuki–Miyaura coupling of di-*ortho*-substituted aryl chlorides[a]



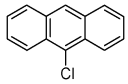
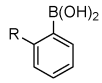
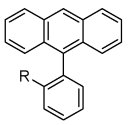
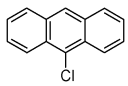
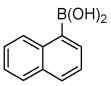
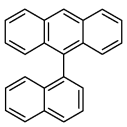
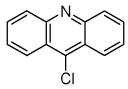
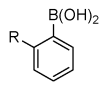
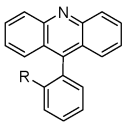
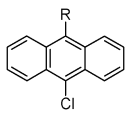
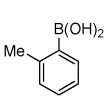
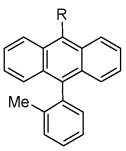
Entry	Ar′Cl	$Ar'B(OH)_2$	Product		Pd loading	% Yield[b]
1				R = Me	0.02%	98
2				R = Et	0.02%	96
3				R = OMe	0.1%	86
4				R = Ph	0.2%	99
5				R = F	0.2%	70
6					0.1%	82
7					0.1%	86
8					0.2%	95
9					0.1%	76
10					0.2%	99
11					0.1%	85

[a] Reaction conditions: ArCl (1.0 mmol), $ArB(OH)_2$ (1.5 mmol), $Pd(OAc)_2$ (mol% as indicated), ligand (Pd/**2a**, 1 : 3), $PhB(OH)_2$ (1 mg), $K_3PO_4·H_2O$ (3.0 mmol), dioxane (3.0 mL) were stirred for 24 h (reaction time for each substrate is not optimized) at 110 °C under nitrogen. [b] Isolated yields.

the even more challenging substrate, both deactivated and sterically hindered aryl chloride, could be successfully coupled (entry 7).

The newly developed catalyst system was further extended to the coupling of anthracene derivatives (Table 3). 9-Chloroanthracene was coupled with a series of *ortho*-substituted arylboronic acids in excellent yields (entries 1–4). Acridine was also a feasible coupling partner (entries 6–7). The aldehyde group was compatible under these reaction conditions (entry 10).

Table 3 Palladium-catalyzed Suzuki–Miyaura coupling of anthracene-based aryl chlorides[a]

Entry	ArCl	$Ar'B(OH)_2$	Product		Pd loading	% Yield[b]
1				R = Me	0.05%	97
2				R = Et	0.1%	98
3				R = OMe	0.1%	84
4				R = Ph	0.05%	98
5					0.1%	95
6				R = Me	0.1%	92
7				R = Et	0.1%	92
8				R = Me	0.1%	94
9				R = Ph	0.1%	91
10				R = CHO	0.1%	90

[a] Reaction conditions: ArCl (1.0 mmol), $ArB(OH)_2$ (1.5 mmol), $Pd(OAc)_2$ (mol% as indicated), ligand (Pd/**2a**, 1 : 3), $PhB(OH)_2$ (1 mg), $K_3PO_4 \cdot H_2O$ (3.0 mmol), dioxane (3.0 mL) were stirred for 24 h at 110 °C under N_2. [b] Isolated yields.

The palladium-catalyzed coupling of 2,6-disubstituted arylboronic acids with hindered aryl chlorides was feasible (see ESI Table†). Chloropyridine and chlorothiophene coupled with 2-*m*-xylylboronic acid smoothly (entries 4–5). In general, the coupling of sterically hindered arylboronic acid leading to the same tri-*ortho*-substituted biaryl requires higher catalyst loading (*cf*. ESI Table†, entry 1 *vs*. Table 2, entry 1). Presumably the transmetallation of the bulky organoboron nucleophile is not efficient.

In summary, we have reported a new family of highly effective carbazolyl-derived phosphine ligands. We found that the tri-*ortho*-substituted biaryl coupling is highly sensitive to the ligand bulkiness. Ligands bearing either the more hindered $-PtBu_2$ group or less hindered $-PEt_2$ moiety did not benefit to the reaction, while moderate bulkiness $-PCy_2$ and $-PiPr_2$ groups favored this catalysis. This information may provide an important note for future ligand design aimed towards challenging and difficult coupling processes. With the aid of the new Pd–**2a** complex, a general system for tri-*ortho*-substituted biaryl synthesis is established and particularly noteworthy is that the catalyst loading can be as low as 0.02 mol% Pd for non-activated aryl chlorides. We believe these new ligand systems are highly versatile for handling other difficult coupling reactions.

We thank the Research Grants Council of Hong Kong (GRF: PolyU5014/10P) and PolyU Internal Grant (A-PG13) for support. UGC special equipment grant (SEG PolyU01) is acknowledged. Prof. Z. Zhou is thanked for X-ray support.

Notes and references

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