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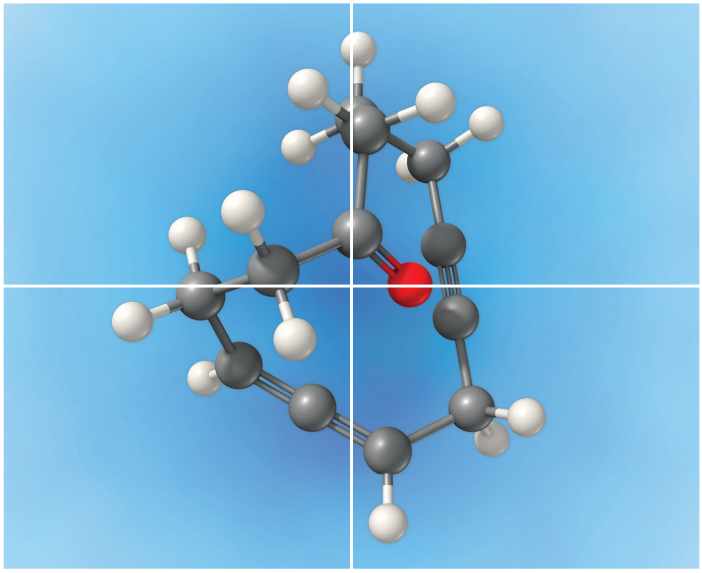

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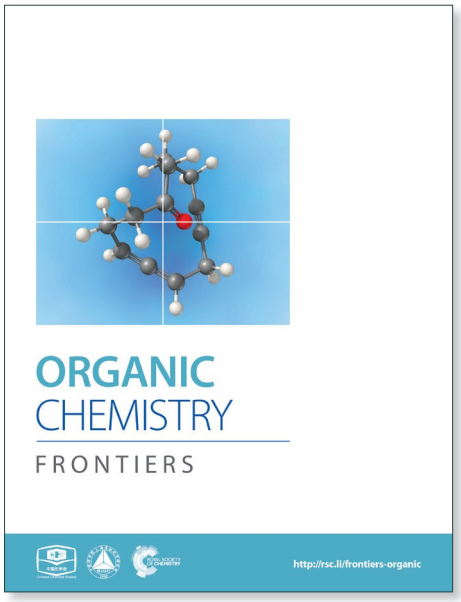

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ARTICLE

A benzo[*c*]carbazolyl-based phosphine ligand for Pd-catalyzed tetra-*ortho*-substituted biaryl syntheses

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A new benzo[*c*]carbazolyl-based phosphine ligand has been designed and synthesized. This newly developed ligand efficiently facilitates the Pd-catalyzed tetra-*ortho*-substituted biaryl syntheses via Suzuki-Miyaura cross-coupling. With 1 mol% of the $Pd(OAc)_2$/**L6** catalyst, sterically congested biaryls were afforded in good-to-excellent yields. In particular, the mild reaction conditions exhibited good compatibility of heterocycles and functional groups including esters and nitrile. **L6** was structurally characterized by X-ray crystallographic analysis.

Palladium-catalyzed cross-coupling has become one of the most powerful methodologies for carbon-carbon bond-forming processes and biaryl constructions.[1] Recent developments have been focused on the development of novel ancillary ligands equipped with different electronic and steric profiles for improving catalytic proficiency and enable more challenging catalytic transformations.[2] While *ortho*-substituted biaryl motif are attractive scaffolds in biologically active compounds and pharmaceutical intermediates,[3] preparation of sterically demanding tetra-*ortho*-substituted biaryls was found to be a persistent challenge.[2a,2b,4] The first successful report of such a difficult reaction can be dated back to Buchwald's work in 2002.[5] Following this pioneering work, a limited number of metal complexes employing phosphine or *N*-heterocyclic carbene (NHC) by Organ,[6] Ackermann,[7] Tang,[8] Nolan,[9] Tu[10] and others[11] were also shown to be effective in promoting the tetra-*ortho*-substituted biaryl cross-couplings (Fig. 1). Despite these tremendous advances, most protocols have drawbacks of high catalyst loadings and limited substrate scope while the synthetic pathways of the ancillary ligands are often lengthy or involve the use of sophisticated organic building blocks. To further the chemistry of this area for the organic and synthetic community, it is desirable to develop a more easily accessible and general catalyst with high efficiency. Furthermore, the relationship between ligand characteristics and catalytic performance of this reaction is rather elusive. As part of our efforts in establishing efficient sterically demanding biaryl preparation processes, we describe herein a new benzo[*c*]carbazolyl-based phosphine ligand

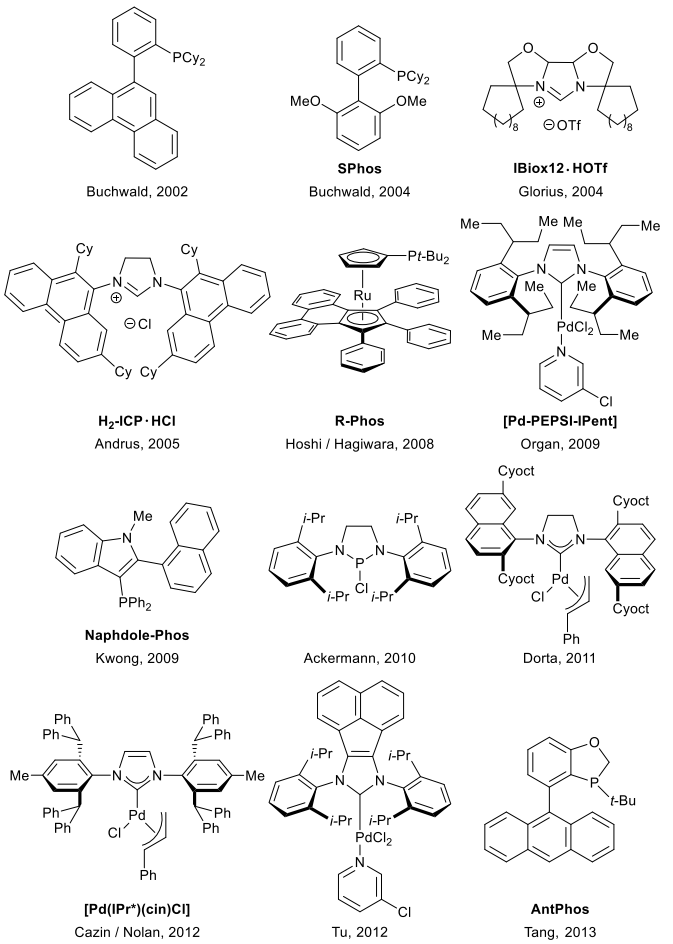

Fig. 1 Palladium catalysts and ancillary ligands used in tetra-*ortho*-substituted biaryl syntheses.

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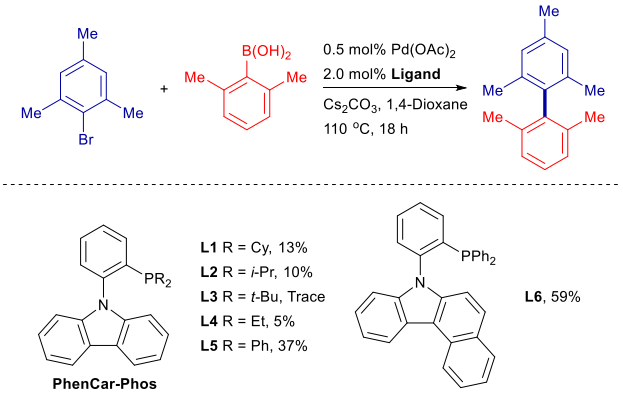
specifically useful for the tetra-*ortho*-substituted biaryl Suzuki coupling.

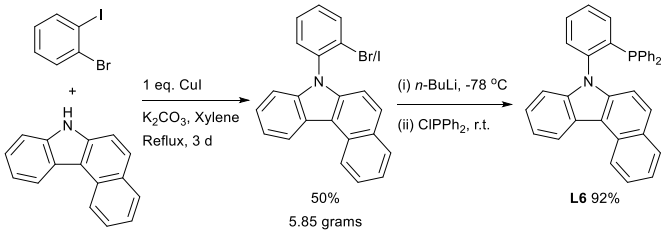
In 2011, we reported PhenCar-Phos (Scheme 1) as an excellent ligand for the Pd-catalyzed tri-*ortho*-substituted biaryl coupling, in which a flattened carbazole ring facilitates the reductive elimination process and a flexible sp^3-N-Pd coordination provides catalyst longevity.[12] Owing to the initial success of PhenCar-Phos in the preparation of hindered tri-*ortho*-substituted biaryls, we were intrigued if the scaffold can be optimized to enable the tetra-*ortho*-substituted biaryl coupling. Whereas highly electron-rich and sterically congested ligands were demonstrated to promote the hindered biaryl synthesis, we envision the success of the catalysis might not depend on the overwhelming electron richness and steric bulkiness, but the balance between these two factors. We have previously demonstrated that the optimal combination of these two aspects is the key of success for a particular catalytic reaction.[13] To investigate our postulation, a series of carbazolyl-ligand bearing different dialkyl and diphenyl phosphino groups was evaluated by the model reaction between 2-bromomesitylene and 2,6-dimethylphenylboronic acid (Scheme 1). Intriguingly, PCy_2-PhenCar-Phos (**L1**), which was successful in promoting tri-*ortho*-substituted biaryl synthesis,[12] along with other electron-rich and bulky dialkylphosphine counterparts (**L2-L4**), were ineffective in this model reaction but **L5** (which embodied only $-PPh_2$ moiety) was found to provide a modest product yield of 37%. It is well-recognized in the lore of the field that electron-rich dialkyl phosphines were able to promote demanding oxidative additions with Ar–Cl or even Ar–OMs bonds.[14] As suggested, these results indicated that the reaction with **L1-L4** might proceed with a facile oxidative addition followed by subsequent demanding transmetalation or reductive elimination. Taking the PhenCar-Phos ligand skeleton into account, we envisaged that the less steric bulkiness of the $-PPh_2$ moiety in **L5** could satisfy the transmetalation of the sterically congested 2,6-dimethylphenylboronic acid intermediate while facilitating a more effective reductive elimination than **L4** in our system. In view of the demanding reductive elimination, we embarked to extend the carbazolyl framework in postulation to overcome this process and thus prepared the benzo[*c*]carbazolyl-based ligand **L6**. To our delight, the product yield was significantly increased to 59% with the use of the newly developed **L6**.

Scheme 1 Ligand effect of carbazolyl-derived phosphines[a]



[a]Reaction conditions: $Pd(OAc)_2$ (0.5 mol%), ligand (2.0 mol%), 2-bromomesitylene (0.3 mmol), 2,6-dimethylphenyl boronic acid (0.45 mmol), Cs_2CO_3 (0.9 mmol), 1,4-Dioxane (0.3 M, 1.0 mL) were stirred for 18 h at 110 °C under nitrogen. Calibrated GC yields were reported.

The ligand **L6** was prepared by a straightforward and convenient ligand-free Cu-catalyzed C-N bond formation process between 1-bromo-2-iodobenzene and 7*H*-benzo[*c*]carbazole (Scheme 2), followed by phosphination with chlorodiphenylphosphine to give the final phosphine ligand in excellent yield. Notably, the synthetic procedure was amenable for multi-gram scaleup and the phosphino building block $ClPPh_2$ is vastly cost-efficient.[15] Single crystals of **L6** suitable for X-ray diffraction were grown by liquid-liquid diffusion of hexane into a chloroform solution containing **L6**, and was fully characterized by crystallographic analysis (Fig. 2).



Scheme 2 The synthesis of benzo[*c*]carbazolyl-based phosphine ligand **L6**.

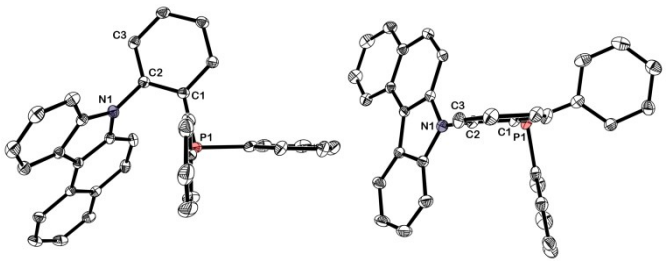
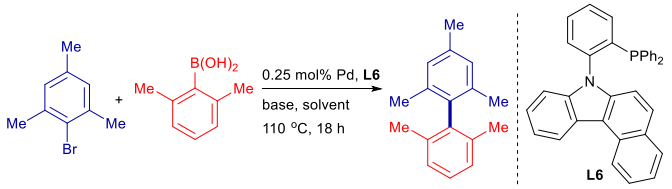


Fig. 2 OPTEP diagrams of **L6**. All hydrogen atoms have been omitted for clarity.

Having the lead ligand candidate, we next carried on the optimization of reaction conditions to ensure the effectiveness of the Pd/**L6** catalytic system (Table 1). Among an array of bases

surveyed, K_3PO_4 was found to be a better base than Cs_2CO_3 while other inorganic and organic bases were inferior (entry 3 *vs.* 1-2 and 4-9). The presence of water equivalents in $K_3PO_4 \cdot H_2O$ led to a decrease in product yield to 35% (entry 4 *vs.* 3). It is noteworthy that the mild basic conditions with K_3PO_4 provided ample functional group tolerance, while ester or nitrile groups might not remain intact with the use of strong bases such as NaO*t*-Bu or KOH in some of the systems. With regard to solvent screening, 1,4-dioxane was found to be a more promising solvent than THF and the others (entry 3 *vs.* 10-13). When other palladium sources were used, the product yields experienced a significant drop of ~20-40% (entry 3 *vs.* 14-17). The best metal to ligand ratio was identified to be 1:4 (entry 3 *vs.* 18-20).

Table 1 Reaction condition screening of Pd/**L6** catalyst system[a]

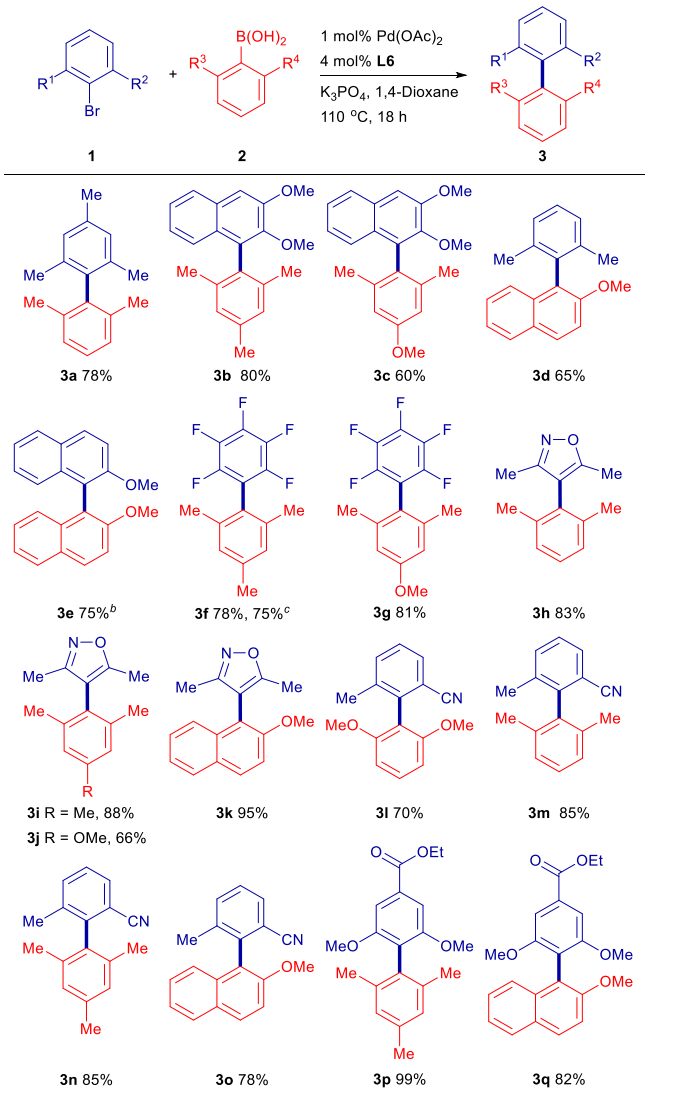


Entry	Solvent	Base	Pd source[b]	Yield
1	1,4-Dioxane	Cs_2CO_3	$Pd(OAc)_2$	53
2	1,4-Dioxane	K_2CO_3	$Pd(OAc)_2$	16
3	1,4-Dioxane	K_3PO_4	$Pd(OAc)_2$	64
4	1,4-Dioxane	$K_3PO_4 \cdot H_2O$	$Pd(OAc)_2$	35
5	1,4-Dioxane	Na_3PO_4	$Pd(OAc)_2$	4
6	1,4-Dioxane	CsF	$Pd(OAc)_2$	2
7	1,4-Dioxane	KOH	$Pd(OAc)_2$	15
8	1,4-Dioxane	NEt_3	$Pd(OAc)_2$	0
9	1,4-Dioxane	DABCO	$Pd(OAc)_2$	0
10	Hexane	K_3PO_4	$Pd(OAc)_2$	2
11	THF	K_3PO_4	$Pd(OAc)_2$	57
12	Toluene	K_3PO_4	$Pd(OAc)_2$	51
13	*t*-BuOH	K_3PO_4	$Pd(OAc)_2$	32
14	1,4-Dioxane	K_3PO_4	$Pd(dba)_2$	30
15	1,4-Dioxane	K_3PO_4	$Pd_2(dba)_3$	22
16	1,4-Dioxane	K_3PO_4	$PdCl_2(ACN)_2$	46
17	1,4-Dioxane	K_3PO_4	$[PdCl(cinnamyl)]_2$	40
18	1,4-Dioxane	K_3PO_4	$Pd(OAc)_2$	62[c]
19	1,4-Dioxane	K_3PO_4	$Pd(OAc)_2$	55[d]
20	1,4-Dioxane	K_3PO_4	$Pd(OAc)_2$	30[e]

[a]Reaction conditions: Pd source(0.25 mol%), Pd:**L6** = 1:4, 2-bromomesitylene (0.3 mmol), 2,6-dimethylphenyl boronic acid (0.45 mmol), base (0.9 mmol), solvent (0.3 M, 1.0 mL) were stirred for 18 h at 110 °C under nitrogen. Calibrated GC yields were reported. [b]Mol% of Pd monomer with respect to 2-bromomesitylene. [c]$Pd(OAc)_2$:**L6** = 1:3. [d]$Pd(OAc)_2$:**L6** = 1:2. [e]$Pd(OAc)_2$:**L6** = 1:1.

With these promising results in hand, we next evaluated the scope of Pd(OAc)2/L6 system in the cross-coupling of a variety of sterically hindered substrates (Table 2). Indeed, only 1 mol% of Pd/L6 catalyst was enough to promote the reactions smoothly with full conversion of aryl halides. Sterically hindered aryl and naphthyl halides coupled well with 2,6-disubstitutedphenyl or 2-methoxynaphthyl boronic acids and gave good product yields (60-80%, entry **3a**-**3e**). Highly electron-deficient halopentafluoro benzene reacted smoothly (entry **3f**-**3g**) and we found that the use of aryl chloride did not affect the catalytic performance in this entry. Sterically hindered heterocycles were also found to be applicable substrates in our system with satisfying yields (66-95%, entry **3h**-**3k**). In particular, it is worthy to note that ester and nitrile groups in entries **3l**-**3q** were compatible under these reaction conditions and desired products were furnished in good-to-excellent yields (70-99%).

Table 2 $Pd(OAc)_2$/**L6**-catalyzed sterically hindered Suzuki-Miyaura biaryl coupling[a]



[a]Reaction conditions: $Pd(OAc)_2$ (1.0 mol%), **L6** (4.0 mol%), aryl halide (0.3 mmol), aryl boronic acid (0.45 mmol), K_3PO_4 (0.9 mmol), 1,4-Dioxane (0.3 M, 1.0 mL) were stirred for 18 h at 110 °C under nitrogen. Isolated yields were reported. [b]Homocoupling of 2-methoxynaphthylboronic acid was not observed when it was used in other entries. [c]Chloropentafluorobenzene was used instead.

Conclusions

In conclusion, the newly developed $Pd(OAc)_2$/**L6** catalyst proved to be efficient in promoting the tetra-*ortho*-substituted biaryl

synthesis using hindered aryl halides and arylboronic acids. We have demonstrated the optimization of an ineffective ligand to fit for such a challenging reaction while ligands bearing electron-rich and bulky dialkyl phosphino groups (**L1-L4**) were inferior. The ligand skeleton of **L6** can be prepared by a simple ligand-free Cu-catalyzed amination with easily accessible materials and was amenable for multigram-scale synthesis. We believe these ligands' characteristics offer an important note for future phosphine ligand design in Pd-catalyzed sterically hindered biaryl synthesis. We envisaged ligand **L6** possesses axial chirality and future efforts will be focused on the resolution of ligand for enantioselective catalysis.

Acknowledgements

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