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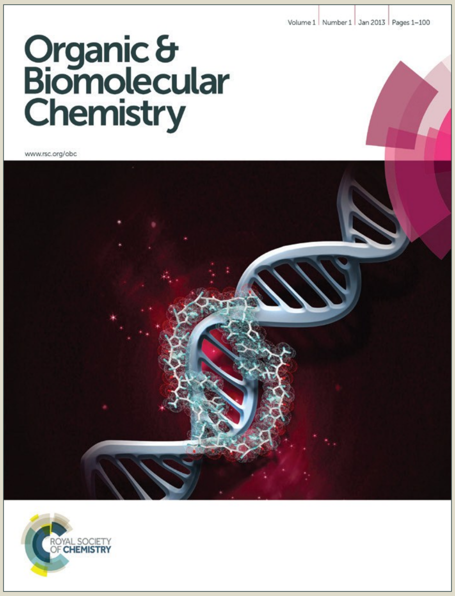

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An efficient indenyl-derived phosphine ligand for the Suzuki-Miyaura coupling of sterically hindered aryl halides

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Abstract

An air-stable aryl substituted indenyl phosphine used in combination with $Pd(OAc)_2$ provides a highly efficient catalyst for the Suzuki-Miyaura cross-coupling reaction of sterically hindered aryl halides with aryl boronic acids. In addition, a catalyst loading down to 0.025 mol% can be achieved.

Introduction

Sterically hindered biaryl structures exist in many biologically important natural products and also serve as pivotal frameworks for efficient ligands in homogenous catalysis.[1,2] Their synthesis has attracted a great deal of interest. The use of the palladium-catalyzed Suzuki-Miyaura cross-coupling reaction to construct biaryl compounds is particularly attractive owing to its versatility and compatibility with various functional groups.[3,4] However, the Suzuki–Miyaura coupling reaction of sterically demanding substrates remains a synthetic challenge. Only a limited number of methods are available for the synthesis of tetra-*ortho*-substituted biaryl compounds. An efficient catalyst for the synthesis of highly sterically hindered biaryls was reported by Buchwald and co-workers in 2002.[5] Since then, the groups of Snieckus,[6] Kwong,[7] Hagiwara,[8] Ackermann,[9] Tang,[10] and others have reported their progress (Figure 1).[11] N-heterocyclic carbene ligands have also shown efficiency in the

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Suzuki-Miyaura coupling reaction of sterically hindered substrates.[12] Despite these advances, limitations remain. For example, previously reported catalyst loadings for this transformation were often higher (>1mol%) than those required to make the large-scale synthesis of pharmaceutical intermediates or other bulk fine chemicals economical.[13] These factors have limited the use of the Suzuki-Miyaura coupling reaction of arylboronic acids with aryl halides to produce low cost, sterically hindered biaryls and commodity building blocks. Therefore, the development of efficient catalytic system towards the synthesis of sterically hindered biaryls using lower catalyst loadings remains a very challenging and important goal. The cyclopentadienyl phosphine ligand developed by Plenio have demonstrated a broad substrate scope in Suzuki-Miyaura, Sonogashira, and Buchwald-Hartwig cross-coupling reaction.[14] In addition, the indenyl phosphine ligands developed by our group have been widely used in cross-coupling reaction (Figure 2).[15] Herein, we report a novel aryl substituted indenyl monophosphine ligand, We expected that this ligand would afford excellent reactivity for the syntheses of sterically hindered biaryls using the Suzuki-Miyaura coupling reaction with low-catalyst loadings and therefore be complementary to existing catalytic system.

Results and discussion

The Synthesis of ligand **2** was accomplished in two steps, which could be prepared on a gram scale from 2-bromoindene. A palladium-catalyzed Suzuki-Miyaura coupling reaction of 2-bromoindene and 2, 6-dimethoxyphenyl boronic acid provided **1** in 90% yield. Straightforward deprotonation of **1** using *n*BuLi followed by reaction of the lithiated intermediate with dicyclohexyl phosphine chloride (Cy_2PCl) gave the air-stable monophosphine ligand **2** in 70% yield (Scheme 1).

We initially investigated the reaction of 2-bromomesityl with naphthenylboronic acid to establish the performance of ligand **2** in the Suzuki-Miyaura coupling reaction and to optimize the reaction conditions (Table 1). First, the reaction was conducted without any base and/or phosphine ligand and no product was obtained (Table 1, entries 1–3). Then, 2.0 mol% of phosphine ligand **2** and 3.0 equivalent *t*BuONa were

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used to give the coupling product in 81% yield (Table 1, entry 4). Whereas low conversions were generally observed in this challenging cross-coupling reaction with indenyl phosphine ligands such **13**, **14** and **15** (Table 1, entries 5–7). The use of base was found to be crucial for a high yield in the reaction. While strong bases (such as *t*BuOK) provided almost no desired product (Table 1, entry 8), the use of weak bases (such as Cs_2CO_3 and CsF) gave excellent yields (Table 1, entries 9, 10). Among the various bases employed, K_3PO_4 proved to be most efficient and provided the desired coupling product in 99% yield (Table 1, entry 11). Studies to determine the efficiency of the catalyst showed that the reaction occurred to completion after 3 h at 110 ºC in 99% yield with 0.1 mol% of catalyst (Table 1, entry 12). The reaction conducted with 0.05 mol% of $Pd(OAc)_2$ and 0.10 mol% of ligand **2** gave 98% conversion at 110 ºC after 3 h (Table 1, entry 13). Also, the reaction occur to almost full completion in 98% yield after 3 h at 110 ºC with 0.025 mol% of catalyst (Table 1, entry 14) and to 36% conversion with only 0.01 mol% catalyst (Table 1, entry 15). For comparison, several commercially available phosphine ligands, such as CyJohnPhos, RuPhos and BrettPhos provided low to moderate conversions (Table 1, entries 16–18). To further expand the application of ligand **2**, the optimized reaction conditions were established using $Pd(OAc)_2$ (0.05 mol%)/**2** (0.10 mol%) as the catalyst, K_3PO_4 as the base and toluene (2.0 mL) as the solvent at 110 ºC for 3 h.

Using the optimized reaction conditions, we then looked into the substrate scope of the catalytic system using $Pd(OAc)_2$/**2** in the Suzuki-Miyaura coupling reaction of sterically demanding substrates. As illustrated in Table 2, aryl bromides bearing electron-donating substituents such as $–CH_3$ and $–OCH_3$ in the *ortho* position were coupled with 1-naphthylboronic acid to afford the corresponding biaryl products in very high yield (Table 2, entries 1, 2). Various di-*ortho*-substituted aryl halides such as 2, 6-dimethoxyiodobenzene and 9-bromoanthracene were coupled with 1-naphthylboronic acid to provide tri-*ortho*-substituted biaryl products in excellent yield (Table 2, entries 3, 4). Extremely hindered 1-bromo-2, 4, 6-triisopropylbenzene also gave the desired coupling product in 83% yield (Table 2, entry 5). To further

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extend the scope of the reaction using our catalytic system, we investigated the cross-coupling reaction of aryl chlorides. For example, the reaction of 1-naphthylboronic acid with 2-chlorotoluene gave the desired product in 71% yield (Table 2, entry 6). Aryl chlorides bearing electron-withdrawing groups such as –CHO, $–NO_2$, –Cl in the *ortho* position were also tolerated in the cross-coupling reaction with 1-naphthylboronic acid and gave the desired products in moderate to high yield (Table 2, entries 7-9). Heteroaryl substrates, such as quinolone was compatible (Table 2, entry 10).

Besides its excellent reactivity in the coupling reaction of sterically hindered 1-naphthylboronic acid, ligand **2** was also used for the coupling of sterically congested aryl halides (Table 3). For example, 2-methoxyphenylboronic acid underwent coupling reactions with 2-bromomesitylene in excellent yield under the optimized conditions (Table 3, entries 1). In addition, sterically demanding 2,6-dimethoxyphenylboronic acid could also react efficiently with 2-bromomesitylene to afford the corresponding tetra-*ortho*-substituted biaryl products in good yield (Table 3, entry 2). The reaction of 2,6-dimethylphenylboronic acid with 1-iodo-2,6-dimethoxybenzene also gave the tetra-*ortho*-substituted biaryl product in 90% yield (Table 3, entry 3). Moreover, we investigated the coupling reaction of 9-bromoanthracene with *ortho*-substituted phenylboronic acids with high yields being obtained in the case of 2-methylphenylboronic acid and 2-methoxyphenylboronic acid (Table 3, entries 4, 5).

The catalytic system using $Pd(OAc)_2$/**2** was also applicable for the coupling of sterically congested 2-chloro-2,6-*m*-xylene (Table 4). For example, the reaction of 2-chloro-2, 6-*m*-xylene with 1-naphthylboronic acid gave the desired product in almost quantitative yield (Table 4, entry 1). The reaction of 2-chloro-2, 6-*m*-xylene with aryl boronic acids bearing electron-donating substituents such as $–OCH_3$ and $–CH_3$ in the *para* position gave the corresponding tri-*ortho*-substituted biaryl products in moderate yield (Table 4, entries 2, 3). Phenyl boronic acid bearing the electron-withdrawing group $–CF_3$ in the *ortho* position was also tolerated in the

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reaction with 2-chloro-2, 6-*m*-xylene and gave the desired product in 66% yield (Table 4, entry 4).

Conclusion

In summary, we have demonstrated a highly efficient method to perform the Suzuki-Miyaura coupling reaction of sterically demanding substrates using $Pd(OAc)_2$/**2**. The $Pd(OAc)_2$/**2** catalyst system is efficient for the synthesis of functionalized tri- and tetra-*ortho*-substituted biaryls using a low catalyst loading. This catalytic system has also enabled the synthesis of sterically hindered heteroaryls using the Suzuki-Miyaura coupling reaction. Work on further applications of this catalyst system is currently ongoing in our laboratory.

Acknowledgements

The authors would like to thank the National Natural Science Foundation of China (Nos. 21472060, 21072071 and 21272088), self-determined research funds of CCNU from the colleges' basic research and operation of MOE (Nos. CCNU15KFY001, CCNU15A02012).

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Figure Legends

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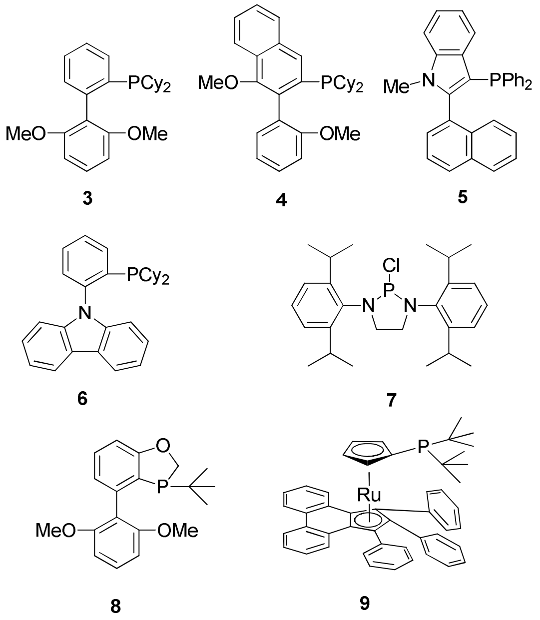

Figure 1 Some effective ligands for the Suzuki-Miyaura cross-coupling reaction.

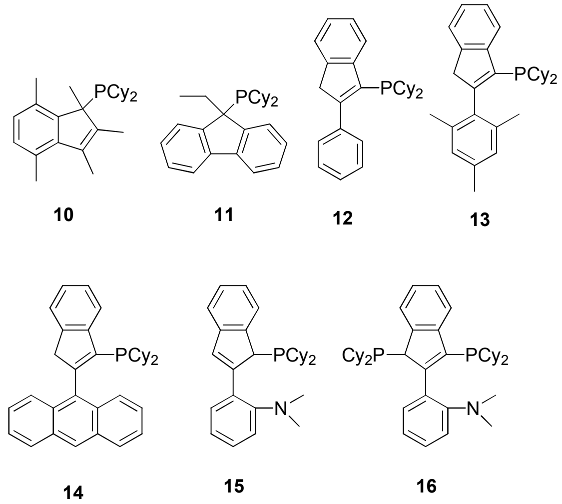

Figure 2 Some indenyl phosphine ligands for the cross-coupling reaction.

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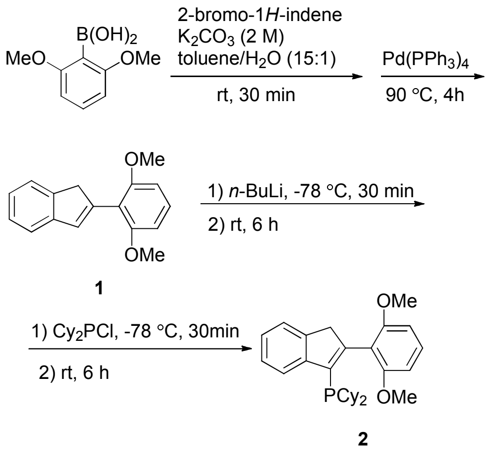

Scheme 1 Syntheses of Phosphine ligand **2**.

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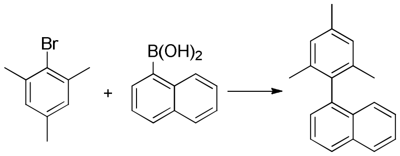
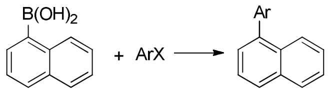
Table 1 Initial screening of Suzuki-Miyaura cross-coupling of 2-bromomesityl with naphthenylboronic acid[a]



entry	$Pd(OAc)_2$ (mol%)	Ligand (mol%)	base	yield (%)[b]
1	1.0	-	-	0
2	1.0	-	*t*BuONa	0
3	1.0	**2** (2.00)	-	0
4	1.0	**2** (2.00)	*t*BuONa	81
5	1.0	**13** (2.00)	*t*BuONa	<5
6	1.0	**14** (2.00)	*t*BuONa	15
7	1.0	**15** (2.00)	*t*BuONa	15
8	1.0	**2** (2.00)	*t*BuOK	<5
9	1.0	**2** (2.00)	CsF	97
10	1.0	**2** (2.00)	Cs_2CO_3	96
11	1.0	**2** (2.00)	K_3PO_4	99
12	0.1	**2** (0.20)	K_3PO_4	99
13	0.05	**2** (0.10)	K_3PO_4	98
14	0.025	**2** (0.05)	K_3PO_4	98
15	0.01	**2** (0.02)	K_3PO_4	36
16	0.025	**CyJohnPhos** (0.05)	K_3PO_4	68
17	0.025	**RuPhos** (0.05)	K_3PO_4	75
18	0.025	**BrettPhos** (0.05)	K_3PO_4	0

[a] Reaction conditions: naphthenylboronic acid (1.5 mmol), 2-bromomesityl (1.0 mmol), $Pd(OAc)_2$, ligand **2**, base (3.0 equiv), toluene (1.5 mL), 110 °C, 3 h. [b] Isolated yield.

Table 2 Suzuki-Miyaura cross-coupling reactions of naphthenyl boronic acid with aryl halides[a]



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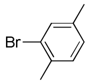
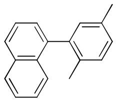
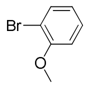
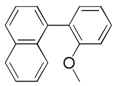
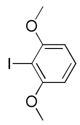
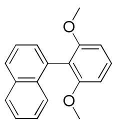
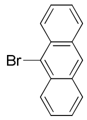
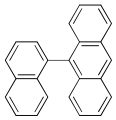
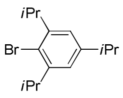
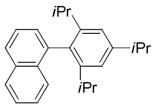
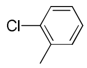
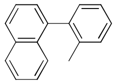
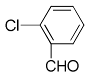
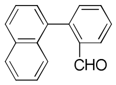
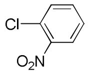
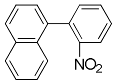
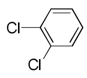
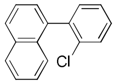
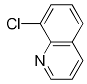
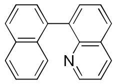
1			97
2			95
3			92
4			94
5			83
6			71
7			85
8			95
9			94
10			86

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[a]Reaction conditions: naphthenylboronic acid (1.5 mmol), 2-bromomesityl (1.0 mmol), $Pd(OAc)_2$ (0.05 mol %), ligand **2** (0.10 mol %), K_3PO_4 (3.0 equiv), toluene (1.5 mL), 110 °C, 3 h. [b]Isolated yield.

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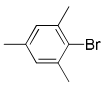
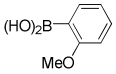
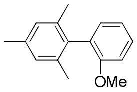
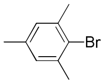
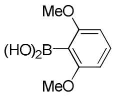
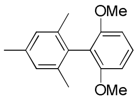
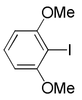
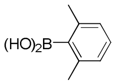
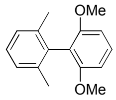
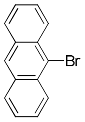
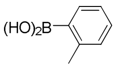
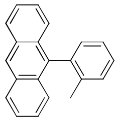
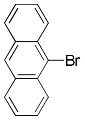
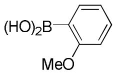
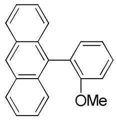
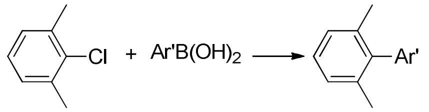
Table 3 Suzuki-Miyaura cross-coupling reactions of sterically hindered aryl bromides and aryl iodides[a]

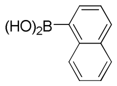
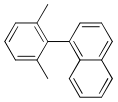
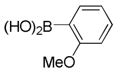
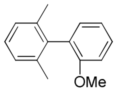
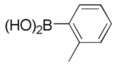
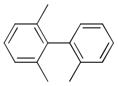
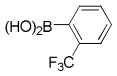
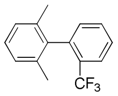
$$ArX + Ar'B(OH)_2 \longrightarrow Ar{-}Ar'$$

entry	ArX	Ar'B(OH)$_2$	product	yield (%)[b]
1				98
2				81
3				90
4				94
5				88

[a] Reaction conditions: arylboronic acid (1.5 mmol), aryl bromides or aryl iodies (1.0 mmol), Pd(OAc)$_2$ (0.05 mol %), ligand **2** (0.10 mol %), K_3PO_4 (3.0 mmol), toluene (1.5 mL), 110 °C, 3 h. [b] Isolated yield.

Table 4 Suzuki-Miyaura cross-coupling reactions of 2-chloro-2, 6-*m*-xylene with aryl boronic acids[a]



entry	Ar	product	yield (%)[b]
1			99
2			65
3			82
4			66

[a] Reaction conditions: 2-chloro-1,3-dimethyl benzene(1.0 mmol), arylboronic acid (1.5 mmol), $Pd(OAc)_2$ (1.0 mol %), ligand **2** (2.0 mol %), K_3PO_4 (3.0 equiv) in toluene at 110 °C for 24 h.[b] Isolated yields.