

Robust Acenaphthoimidazolylidene Palladium Complexes: Highly Efficient Catalysts for Suzuki–Miyaura Couplings with Sterically Hindered Substrates

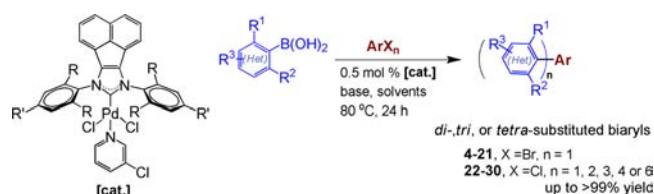
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ABSTRACT



Robust acenaphthoimidazolylidene palladium complexes have been demonstrated as highly efficient and general catalysts for the sterically hindered Suzuki–Miyaura cross-coupling reactions in excellent yields even with low catalyst loadings under mild reaction conditions. The high catalytic activity of these complexes highlights that, besides the “flexible steric bulky” concept, σ -donor properties of the NHC ligands are also crucial to accelerate the transformations.

Sterically hindered biaryls are vital substructures found in various biologically active compounds,¹ functional materials,² and many useful ligands (such as Buchwald’s biaryl-based monophosphines **1a–c**, Figure 1).³ Therefore, considerable attention has been focused toward the field of sterically congested biaryl synthesis. Although, Suzuki–Miyaura coupling reactions constitute one of the most powerful, attractive, and practical protocols for C–C bond formation,⁴ the transformation with sterically demanding boronic acids and aryl halides to construct di-, tri-, and even tetra-*ortho*-substituted biaryls remains an

extremely challenging task, especially under mild reaction conditions.⁵

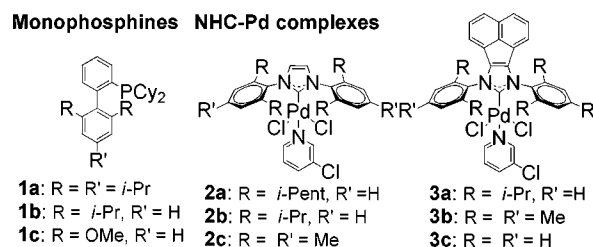


Figure 1. A selection of ligands and complexes applied in Pd-catalyzed sterically hindered cross-coupling reactions.

Inspired by recent advances in the development of novel catalysts, research efforts have focused on coupling reactions with sterically hindered substrates. A variety of palladium catalysts derived from sterically congested monodentate

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phosphines have been designed and prepared for this purpose, and some of them demonstrated a broad substrate scope and good functional group tolerance.^{3a,6} Furthermore, N-heterocyclic carbenes (NHCs) represent a class of environmentally friendly ligands and have exhibited promising potential in these transformations.^{5a,7} In general, the steric and electronic properties of ligands play a crucial role in enhancing the coupling efficiency. Influenced by the “flexible steric bulky” concept proposed by Glorius and co-workers,⁸ currently, a number of research groups have focused on increasing catalytic activity by using the bulkier NHC ligands. For example, among NHC palladium complexes **2** developed by Organ and co-workers, the *i*-Pent carbene complex exhibited higher activity than its *i*-Pr analogues.^{7c,9} However, much less attention has been given to the variation of the electronic properties of NHC ligands to accelerate the coupling process. Furthermore, the existing protocols are still hampered: (1) a high catalyst loading (usually 2–10 mol %) is required to achieve a reasonable conversion; (2) some ligand syntheses are often time-consuming; (3) the general catalyst, which has the ability to satisfy the diverse requirements of the coupling reactions with various substrates, is still under investigation.

During our recent research on the synthesis of metal complexes and their potential applications in catalysis and soft matter aspects,^{10,11} we found that ylidenes derived from benzimidazolium or other π -extended imidazolium salts show better catalytic activity than their imidazolium analogues, which may arise from their stronger σ -donor and weaker π -acceptor properties. Therefore, a novel robust palladium NHC complex **3a** was recently synthesized from

commercially available starting materials by our group and revealed high catalytic activity in the amination of (hetero)aryl chlorides.^{11a} Herein, we now extend this study and explore the catalytic potential of this new type of catalysts **3a–c** toward sterically hindered biaryl coupling reactions.

To evaluate the efficiency of Pd-NHC complexes **3a–c** in highly sterically congested aryl formation reactions, 2-methoxynaphthalene bromide and 2,6-dimethylphenyl boronic acid were selected as substrates to optimize the reaction conditions (Table 1). To our delight, with only 0.5 mol % of **3a**, the tetra-*ortho*-substituted biaryl **4a** was formed almost in a quantitative yield when the reaction was carried with *t*-BuOK and dioxane at 80 °C within 24 h (Table 1, entry 1). However, when less bulky catalysts **3b** and **3c** were applied, very unsatisfying results were observed (Table 1, entries 2 and 3). In general, 4 Å molecular sieves (M.S.) are required in the coupling reactions in order to avoid phenol formation.¹² However, there is no difference the yields with or without 4 Å M.S. even when *t*-BuOK and *t*-BuOH were applied with **3a**. Further increasing the catalyst loading to 1 mol % resulted in a similar isolated yield (96% vs 97%, Table 1, entries 4–5). When toluene was utilized, the coupling process still works well and a 95% yield was obtained (Table 1, entry 6). When other organic solvents were screened, however, no desired product could be detected (see the Supporting Information). In addition, only a 70% isolated yield was observed when *t*-BuONa was applied instead of its potassium analogue. Therefore, other potassium bases were selected for further optimization. The strong base KOH afforded a moderate yield, whereas weak bases such as K₂CO₃ and K₃PO₄ even suppressed the transformation (Table 1, entries 8, 9, and 11). By varying bases to Cs₂CO₃ or CsF, or using xylene instead of dioxane, 75%, 55%, and 42% yields were observed (Table 1, entries 10, 12, and 13), respectively. Additionally, no reactions occurred when selected organic bases were tested (see the Supporting Information). In contrast to the blank test, upon decreasing the catalyst loading to 0.1 or 0.05 mol %, 94% and 77% yields were still obtained (Table 1, entries 14–16), which further confirmed the catalyst efficiency.

As illustrated in Scheme 1, Pd-NHC complex **3a** exhibits high catalytic activity to form sterically hindered di-, tri-, and tetra-*ortho*-substituted biaryls. Even with a 0.5 mol % catalyst loading, the protocol well tolerated a number of substituted arylboronic acids to form tetra-*ortho*-substituted biaryl products in good to quantitative yields (**4–6**). The electronic properties of the *ortho*-substituted groups affected the coupling process slightly more strongly than the additional substituted groups in the *para*-position of arylboronic acids (**4b** and **6a–b** vs **5a–c**); in the later case all substrates result in similar excellent yields (**5a–c**, 98–>99%). When Cs₂CO₃ and *t*-BuOH

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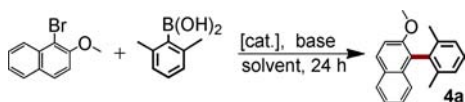
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Table 1. Optimization of the Sterically Encumbered Suzuki–Miyaura Couplings with Pd–NHC Complexes **3a–c**^a



entry	[cat.] (mol %)	base	solvent	yield (%) ^b
1	3a : 0.5	<i>t</i> -BuOK	dioxane	>99
2	3b : 0.5	<i>t</i> -BuOK	dioxane	5
3	3c : 0.5	<i>t</i> -BuOK	dioxane	0
4	3a : 0.5	<i>t</i> -BuOK	<i>t</i> -BuOH	96/96 ^c
5	3a : 1	<i>t</i> -BuOK	<i>t</i> -BuOH	97
6	3a : 1	<i>t</i> -BuOK	toluene	95
7	3a : 1	<i>t</i> -BuONa	dioxane	70
8	3a : 1	KOH	dioxane	77
9	3a : 1	K ₂ CO ₃	dioxane	NR
10	3a : 1	Cs ₂ CO ₃	dioxane	75
11	3a : 1	K ₃ PO ₄	dioxane	NR
12	3a : 1	K ₃ PO ₄	xylene	42
13	3a : 1	CsF	dioxane	55
14	3a : 0.1	<i>t</i> -BuOK	dioxane	94
15	3a : 0.05	<i>t</i> -BuOK	dioxane	77
16	–	<i>t</i> -BuOK	dioxane	NR

^a Reactions were carried out at 80 °C in 2 mL of solvent for 24 h with bromoarene (0.5 mmol), aryl boronic acid (1 mmol), and base (1.5 mmol). ^b Isolated yield. ^c With 4 Å M.S.

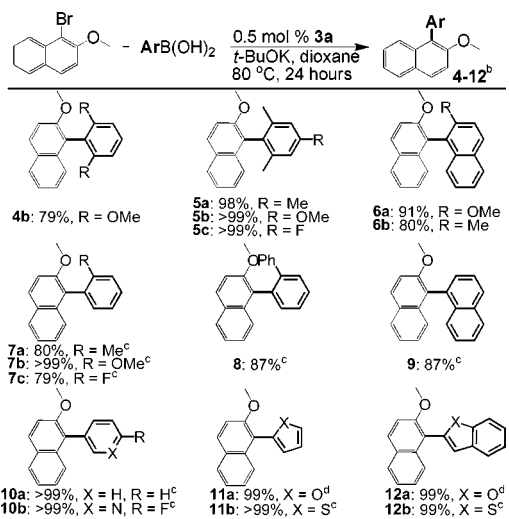
were applied, the protocol was also successfully extended to produce the tri-*ortho*-substituted biaryls.^{6a,14} Again, the electronic properties of the *ortho*-substituted group influenced the coupling transformation, and the boronic acids with an electron-donating group resulted in higher yields (**7a–b** vs **7c**). Identical yields were observed with **8** and **9**, when bulky (1,1'-biphenyl)-2-ylboronic acid and naphthalen-1-ylboronic acid were applied. Furthermore, less sterically hindered phenyl and heterocyclic arylboronic acids were also well accommodated to synthesize di-*ortho*-substituted heterocyclic biaryls even with a 0.5 mol % catalyst loading (**10–12**).

Delighted by the high efficiency and tolerance of Pd–NHC **3a** presented in the sterically hindered coupling reactions with various (hetero-)aryl boronic acids, we turned our attention to study the protocol accommodation ability for a broad range of aryl and heteroaryl bromides; the results are compiled in Scheme 2. With the standard reaction conditions, the relative positions, electronic properties, and bulkiness of the functional groups were well tolerated, and almost all di-, tri-, and tetra-*ortho*-substituted biaryls (**13–21**) were formed in quantitative yields (91–>99%), even with heteroaryl substrates possessing strong coordination abilities, which further demonstrated the powerful applicability of complex **3a**.

To our delight, regardless of the electronic effects and bulkiness of the functional groups, sluggish chloroarenes¹⁵ reacted with various arylboronic acids efficiently to afford the desired di-, tri-, and tetra-*ortho*-substituted

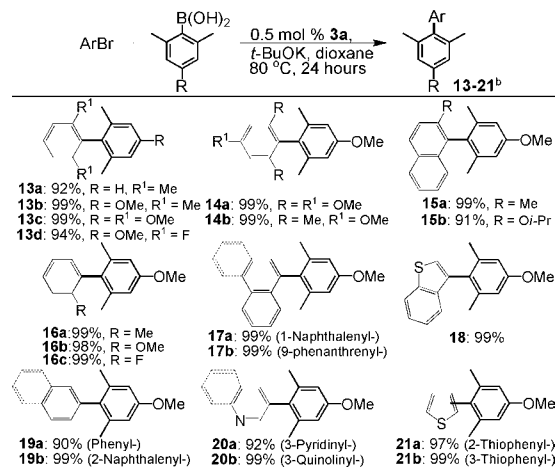
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Scheme 1. Sterically Encumbered Suzuki–Miyaura Couplings with Various Arylboronic Acids^a



^a 0.5 mmol scale at 80 °C for 24 h. ^b Isolated yield. ^c With Cs₂CO₃ and *t*-BuOH. ^d With CsF and *t*-BuOH.

Scheme 2. Sterically Encumbered Suzuki–Miyaura Couplings with Various Aryl Boronides^a

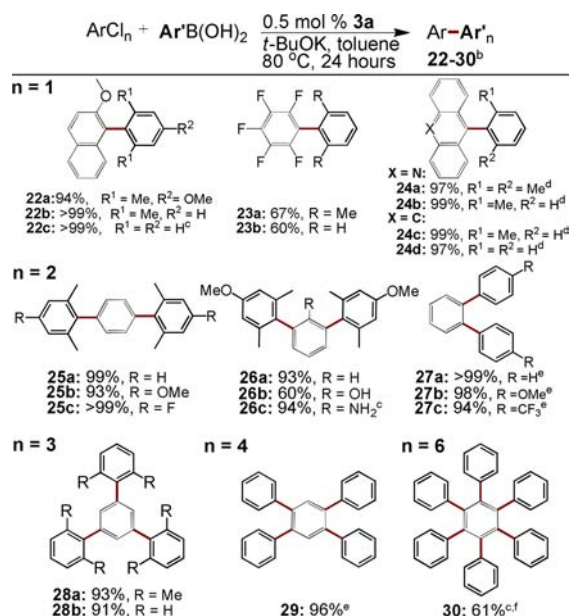


^a 0.5 mmol scale at 80 °C for 24 h. ^b Isolated yield.

(hetero)biaryls in good to quantitative yields (**22–24**, Scheme 3). Due to polyarylbenzenes having played a crucial role in organic optical and electronic sensors,¹⁶ synthesizing them is still regarded as an intriguing task especially by one-pot multiple couplings. Decoupled coupling reactions were performed, and products (**25–27**) were isolated in excellent yields (93–99%) without mono-coupled adducts. Particularly, the protocol successfully

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Scheme 3. Sterically Encumbered Suzuki–Miyaura Couplings with Various Aryl Chlorides^a



^a0.5 mmol scale at 80 °C for 24 h. ^bIsolated yield. ^cWith CsF and toluene. ^dWith K₃PO₄ and xylene. ^eWith Cs₂CO₃ and *t*-BuOH. ^fWith CsF and toluene at 80 °C for 6 days or assisted with microwave irradiation at 110 °C for 60 min.

accommodated free hydroxyl and amino groups without additional protection procedures. And this concept was readily extended to triple and quadruple couplings to produce the corresponding polyarylbenzenes (**28–29**) in excellent isolated yields (91–96%). As precursors of hexabenzocoronene (HBC) derivatives, hexaphenylbenzene (HPB, **30**) and its analogues have wide application in synthetic chemistry and material sciences.¹⁷ To the best of our knowledge, there is only one coupling example with perbromobenzene resulting in a very low yield.¹⁸ However, even with a lower catalyst loading, our protocol successfully produced HPB (**30**) in a 61% yield. Moreover, the transformation can dramatically be expedited by microwave irradiation.






With potential application in the synthesis of functional materials such as HPB, we further extended this protocol to construct other di-, tri-, and tetra-*ortho*-substituted functional molecules such as useful ligands (**31–32**, Table 2, entries 1–2) and biologically active compounds (**33–35**, Table 2, entries 3–5), which all resulted in good to

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quantitative yields. To our delight, in the synthesis of Lamotrigine analogue **34**, two chloro-substituted groups are well tolerated.

Table 2. Functionalized Molecules Synthesized by Suzuki–Miyaura Coupling Reactions Using Pd–NHC Complex **3a**^a

entry	3a (mol %)	base	product	yield (%) ^b
1	0.5	<i>t</i> -BuOK	 31	72
2	1	<i>t</i> -BuOK	 32	99
3	1	<i>t</i> -BuOK	 33	85
4	1	CsF	 34	68
5	0.5	<i>t</i> -BuOK	 35	>99

^a0.5 mmol scale at 80 °C for 24 h. ^bIsolated yield.

In summary, our newly developed robust acenaphthoimidazolylidene palladium complexes have been demonstrated as highly efficient and general catalysts for the Suzuki–Miyaura cross-coupling of sterically hindered (hetero)aryl bromides/chlorides with various aryl boronic acids to form di-, tri-, and tetra-*ortho*-substituted (hetero)biaryls in excellent yields under mild reaction conditions. Furthermore, the protocol was successfully extended not only to prepare polyarylbenzenes from sterically hindered and unreactive polychloroarenes but also to construct various useful functional molecules. In contrast to its imidazolylidene analogues **2a–c**, the high activity of Pd–NHC **3a** exhibited even with a low catalyst loading revealed that, besides the “flexible steric bulky” environment around the catalytic center, σ -donor properties of the ligands are also crucial in order to increase the activity of the catalyst.

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Supporting Information Available. Experimental details, NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.