Cross-Coupling

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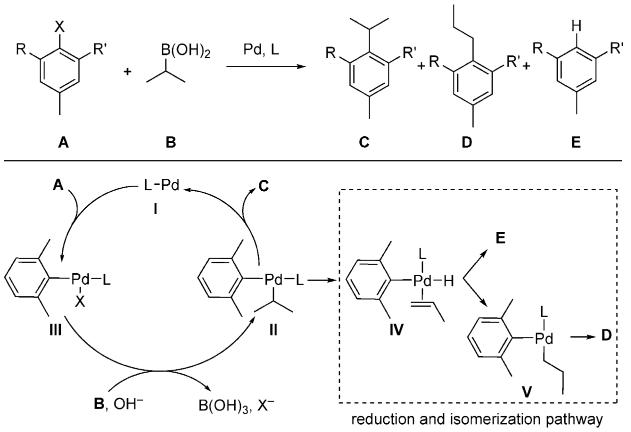
Efficient Synthesis of Sterically Hindered Arenes Bearing Acyclic Secondary Alkyl Groups by Suzuki–Miyaura Cross-Couplings**

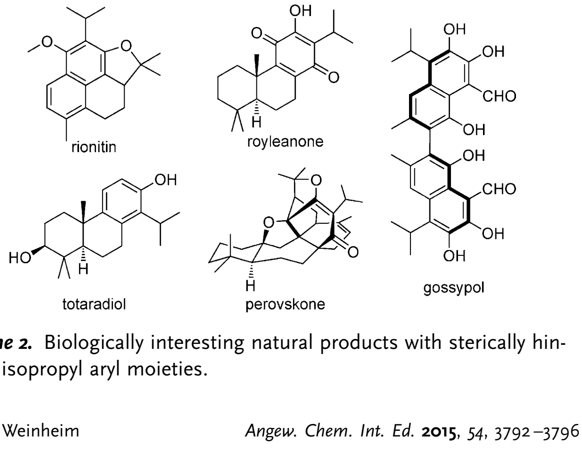
*Chengxi Li, Tianyu Chen, Bowen Li, Guolan Xiao, and Wenjun Tang**

Abstract: *Bulky P,P=O ligands were designed to inhibit isomerization and reduction side reactions during the cross coupling between sterically hindered aryl halides and alkylboronic acids. Suzuki–Miyaura cross-couplings between di-ortho-substituted aryl bromides and acyclic secondary alkylboronic acids have been achieved with high yields. The method has also enabled the preparation of ortho-alkoxy di-ortho-substituted arenes bearing isopropyl groups in excellent yields. The utility of the synthetic method has been demonstrated in a late-stage modification of estrone and in the application to a new synthetic route toward gossypol.*



Scheme 1. Reduction and isomerization in Suzuki–Miyaura cross-couplings of sterically hindered aryl halides and acyclic secondary alkylboronic acids.

The cross-coupling of aryl halides with alkyl substrates[1–5] has become an important method for the formation of substituted aryls and complements the traditional Friedel–Crafts alkylation. In particular, aryl–alkyl Suzuki–Miyaura cross-couplings are increasingly employed in the total synthesis of complex natural products and drug molecules.[1i] Despite their growing synthetic relevance, aryl–alkyl Suzuki–Miyaura cross-couplings are often complicated by reduction and/or isomerization side reactions as a result of the presence of β-hydrogen atoms in the alkyl group.[3a] These issues become severe in cross-couplings between sterically hindered aryl halides and acyclic secondary alkylboronic acids, as isomerization and reduction products **D** and **E** often become the major products (Scheme 1). The high-yielding synthesis of di-*ortho*-substituted arenes bearing acyclic secondary alkyl groups is thus particularly challenging by cross-coupling reactions. Buchwald[3g] reported a high-yielding method for an aryl–isopropyl Negishi cross-coupling that was used in the highly selective transformation of a series of mono-*ortho*-substituted halides. Organ et al.[3l] reported high selectivities in aryl–isopropyl Negishi cross-coupling of nonhindered substrates by employing a palladium catalyst with a bulky N-heterocyclic carbene (NHC) ligand. Excellent selectivity was reported by Biscoe and co-workers[3r] in the aryl–isopropyl Stille cross-coupling and Suzuki–Miyaura cross-coupling[3s] of nonhindered substrates. Feringa et al.[3t] showed an efficient aryl–isopropyl coupling method with organolithium reagents at room temperature that was also applicable to the reaction of several di-*ortho*-substituted aryl halides with Q-Phos as the ligand. In contrast, significant isomerization and low yields were observed in aryl–isopropyl Suzuki–Miyaura couplings of *ortho*-substituted aryl halides in particular.[3d] High yields and selectivities remained to be achieved for the Suzuki–Miyaura coupling between di-*ortho*-substituted aryl halides and acyclic secondary alkylboronic acids. An efficient method for the coupling of *ortho*-alkoxy di-*ortho*-substituted aryl halides with isopropylboronic acids is not available that might be applicable to the synthesis of biologically interesting natural products[6] (Scheme 2). We herein present the design and development of bulky P,P=O ligands **L3** and **L4** and their efficient utilization in aryl–alkyl cross-couplings. These ligands effectively inhibited isomer-



Scheme 2. Biologically interesting natural products with sterically hindered isopropyl aryl moieties.

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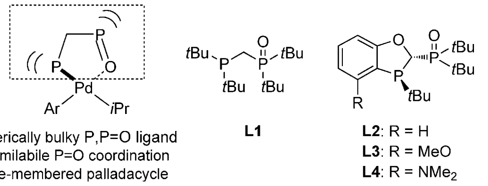
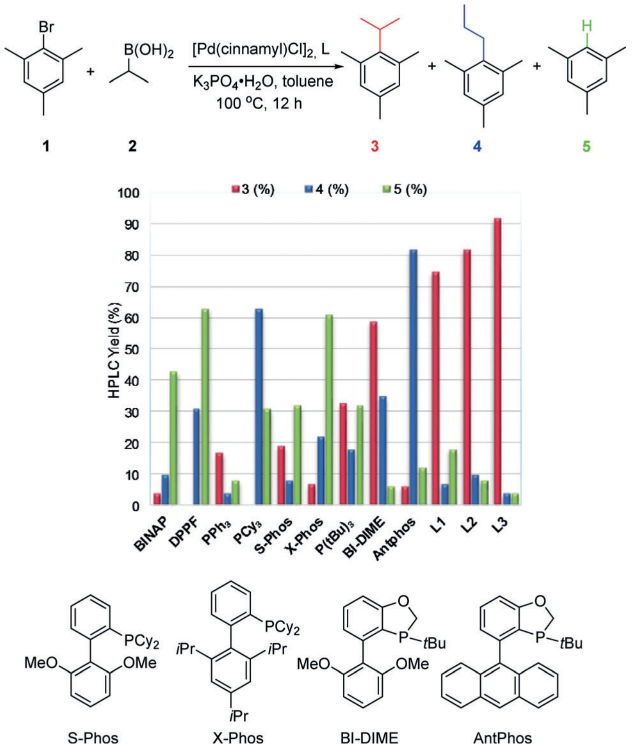
ization and reduction side reactions and enabled the formation of cross-coupling products between di-*ortho*-substituted aryl halides with acyclic secondary alkylboronic acids in high yields. The method has also allowed the preparation of *ortho*-alkoxy di-*ortho*-substituted isopropyl arenes in excellent yields by cross-couplings. Its synthetic utility has been successfully demonstrated in the late-stage modification of estrone and the application to a new synthetic route toward gossypol.



Scheme 3. Design of bulky P,P=O ligands for the Suzuki–Miyaura coupling of sterically hindered aryl halides with acyclic secondary alkylboronic acids.



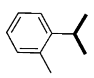
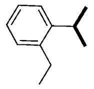
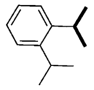
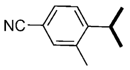
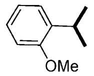
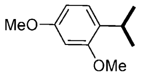
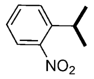
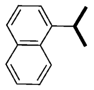
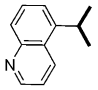
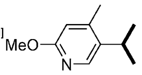
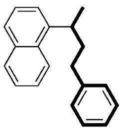
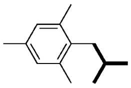
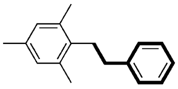
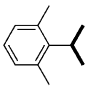
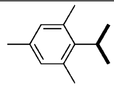
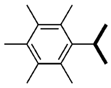
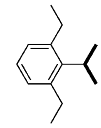
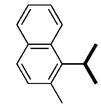
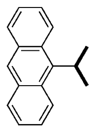
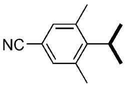
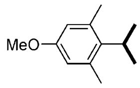
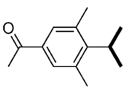
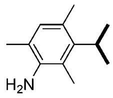
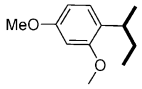
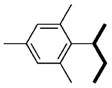
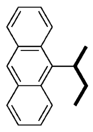
Scheme 4. Cross-coupling between 2-bromo-1,3,5-trimethylbenzene (**1**) and isopropylboronic acid (**2**): ligand study.

It is well-known that ligands can exert significant influence on reactivity and selectivity of transition-metal-catalyzed cross-couplings.[7] We hypothesized that the design of a bulky P,P=O ligand[8] could be beneficial for the coupling of aryl halides with acyclic secondary alkylboronic acids under the following conditions (Scheme 3): 1) The hemilabile coordination[7d] of the P=O group can block an empty coordination site at the palladium center, but does not lower the required rates of transmetallation and reductive elimination in the cross-coupling of sterically hindered aryl halides with alkylboronic acids. 2) The formation of a five-membered palladacycle from the ligand can ensure this hemilabile coordination. 3) The P,P=O ligand should be sufficiently bulky to promote facile reductive elimination,[9] and effectively block other open coordination sites around the Pd center to inhibit β-hydride elimination, isomerization, and reduction. 4) A well-defined and tunable P,P=O ligand skeleton should help to shape the required structure systematically. Toward this end, we designed a bis(di-*tert*-butylphosphinyl)methane monooxide (**L1**) and three bulky P,P=O ligands (**L2–4**) on the basis of a 2,3-dihydrobenzo[*d*][1,3]oxaphosphole framework developed in our laboratory.[10] It is noteworthy that all these ligands can be prepared in five steps in gram quantities.

The Suzuki–Miyaura cross-coupling between 2-bromo-1,3,5-trimethylbenzene (**1**) and isopropylboronic acid (**2**) was studied (Scheme 4). Various commercially available phosphorus ligands were also tested for comparison. The reactions were performed in toluene under nitrogen atmosphere at 100 °C for 12 h in the presence of 0.5 mol% [{Pd(cinnamyl)Cl}$_2$] and 2 mol% ligand with $K_3PO_4 \cdot H_2O$ (3 equiv) as the base. As shown in Scheme 4, different phosphorus ligands provided very different results. Diphosphines, such as BINAP and DPPF, gave the isomerization product **4** and the reduction product **5** as the major products, with little formation of the desired product **3**. A low conversion and selectivity was also observed with PPh_3 as the ligand. The formation of **3** was not observed when the monophosphorus ligand PCy_3 was employed. Significant isomerization and reduction occurred when S-Phos, X-Phos, P(tBu)$_3$, BI-DIME,[10] or AntPhos[11] were employed as the ligand. Among them, BI-DIME showed slightly better selectivity and **3** was formed in 59% yield. Although the screened monophosphorus ligands did not provide satisfactory yields, the newly developed P,P=O ligands **L1–3** were highly efficient. Excitingly, the use of ligand **L1** resulted in the formation of **3** in more than 70% yield. The use of the conformationally more rigid P,P=O ligand **L2** gave **3** in over 80% yield. An excellent yield (92%) was achieved when **L3** was employed and the side products **4** and **5** were both formed in only 4% yield, thus providing one of the highest selectivities in cross-couplings between di-*ortho*-substituted aryl halides and aliphatic secondary alkyl substrates to date.

Next, a series of mono- or di-*ortho*-substituted aryl bromides were cross-coupled with acyclic primary or secondary alkyl substrates in excellent yields and selectivities through the Suzuki–Miyaura cross-coupling with **L3** as the ligand (Table 1). High yields (90–99%) were achieved for a range of mono-*ortho*-substituted isopropyl arenes (entries 1–9). The *ortho* substituents were not limited to methyl, ethyl, and isopropyl groups. Functional groups such as methoxy, nitro, cyano, quinoline, and pyridine moieties were well tolerated. A series of di-*ortho*-substituted arenes bearing acyclic primary or secondary alkyl groups and various substituents and functionalities were successfully formed in high yields and selectivities (entries 12–26). Functional groups, such as methoxy, cyano, carbonyl, and amino groups

Table 1: Cross-coupling of sterically hindered aryl halides and acyclic secondary alkylboronic acids.

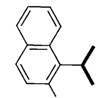
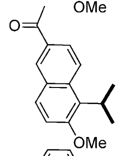
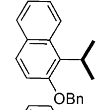
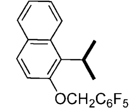
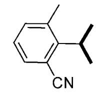
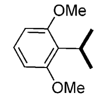
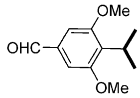
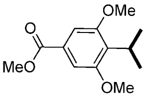
Entry[a]	Product	Yield (%)[b]	*i*Pr/*n*Pr ratio[c]
1		99	99:1
2		94	94:1
3		94	94:1
4		99	99:1
5		90	45:1
6		95	19:1
7		91	10:1
8		90	45:1
9		97	32:1
10[d]		88	10:1
11		97	97:1
12		96	99:1
13		98	99:1
14		96	96:1
15		92	23:1
16		93	23:1
17		94	94:1
18		90	45:1
19		96	48:1
20		96	24:1
21		93	23:1
22		94	94:1
23		96	48:1
24		88	22:1
25		94	47:1
26		94	94:1

[a] Reaction conditions, unless otherwise specified: aryl bromide (0.25 mmol), 1.5 equiv of isopropylboronic acid (**2**), 0.5 mol% [Pd-(cinnamyl)Cl]$_2$, 2 mol% of **L3**, 3.0 equiv of $K_3PO_4 \cdot H_2O$, toluene, 100 °C, 12 h. [b] Yields of isolated *i*Pr–Ar. [c] *i*Pr/*n*Pr ratios were determined by HPLC on a C18 reverse-phase column or by ^{1}H NMR spectroscopy. [d] Ligand **L4** was employed.

were compatible with the reaction, which thus provides advantages over the corresponding Negishi and Kumada aryl–alkyl cross-couplings.[3] Various acyclic primary or secondary alkylboronic acids were also successfully employed to form the corresponding alkyl arenes in high yields and selectivities (entries 11–13 and 24–26).

The aryl–isopropyl cross-coupling of *ortho*-alkoxy di-*ortho*-substituted arenes with isopropylboronic acids may serve as an important method for the synthesis of isopropyl arene natural products. However, excellent yields (> 90%) and selectivities have not yet been achieved. We reasoned that the coordinating ability of the *ortho*-alkoxy group to the palladium catalyst led to a slower rate of reductive elimination, allowing the formation of isomerization and reduction side products. Indeed, the coupling between 1-bromo-2-methoxynaphathalene and isopropylboronic acid with **L2** provided the isopropyl arene in only 16% yield with a 0.2:1 ratio of *i*Pr/*n*Pr substituents (Table 2, entry 1). Encouragingly, use of the bulkier ligand **L3** led the desired product in an improved yield (51%) with a 1.3:1 ratio of *i*Pr/*n*Pr substituents (entry 2). Excitingly, the cross-coupling with ligand **L4** led to the desired coupling product with a 31/1 ratio of *i*Pr/*n*Pr products, providing the *ortho*-alkoxy di-*ortho*-substituted isopropyl arenes in the best yield achieved to date by cross-coupling (94%, entry 3). Thus, a series of *ortho*-alkoxy di-*ortho*-substituted isopropyl arenes were efficiently synthesized in excellent yields and selectivities. Functionalities such as ketone, aldehyde, nitrile, and ester moieties were well tolerated (entries 4–10). According to a kinetic study monitored by React-IR, the coupling of 4-bromo-3,5-dimethoxybenzaldehyde (entry 9) proceeded completely within 4 h at a Pd catalyst loading of 0.5 mol%.[12]

Table 2: Cross-couplings between sterically hindered *ortho*-alkoxy di-*ortho*-substituted aryl halides and isopropylboronic acids.

Entry[a]	Product	Yield (%)[b]	*i*Pr/*n*Pr ratio[c]
1[d]		16	0.2:1
2[e]		51	1.3:1
3		94	31:1
4		92	12:1
5		90	18:1
6		91	23:1
7		96	24:1
8		96	24:1
9		99	99:1
10		95	19:1

[a] Reaction conditions, unless otherwise specified: aryl bromide (0.25 mmol), 1.5 equiv of isopropylboronic acid (**2**), 0.5 mol% [{Pd-(cinnamyl)Cl}$_2$], 2 mol% of **L4**, 3.0 equiv of $K_3PO_4 \cdot H_2O$, toluene, 100 °C, 12 h. [b] Yields of isolated *i*Pr–Ar. [c] *i*Pr/*n*Pr ratios were determined by HPLC on a C18 reverse-phase column or by ^{1}H NMR spectroscopy. [d] **L2** was employed as the ligand. [e] **L3** was employed as the ligand.

In order to investigate the remarkable efficiency of **L3**/**L4**-mediated cross-couplings toward sterically hindered isopropyl arenes, both [Pd(**L3**)Cl$_2$] and [Pd(**L4**)Cl$_2$] complexes were prepared with [(COD)PdCl$_2$] as the Pd source.[12] Notably, both Pd complexes were applicable as catalysts for the cross-couplings. The X-ray structures[13] showed the steric bulk and chelating nature through both P and P=O coordination in the

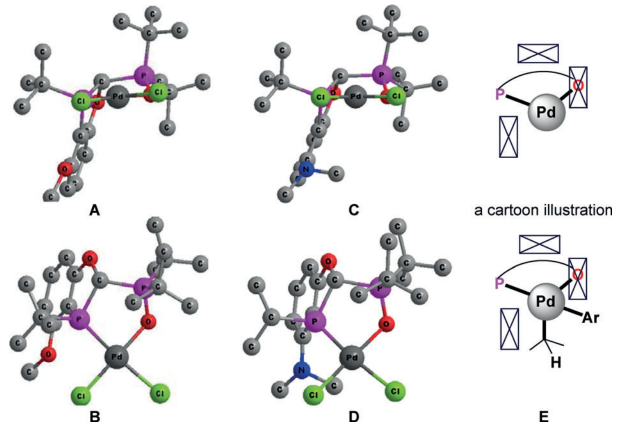
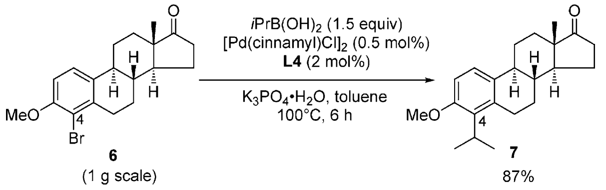


Figure 1. X-ray structure of [Pd(**L3**)Cl$_2$] and [Pd(**L4**)Cl$_2$]. A,B) front and top view of [Pd(**L3**)Cl$_2$]; C,D) front and top view of [Pd(**L4**)Cl$_2$]; E) Model of Pd(**L3**/**L4**)Ar(*i*Pr) during the reductive elimination step (hydrogen atoms and a dichloromethane molecule were omitted for clarity).

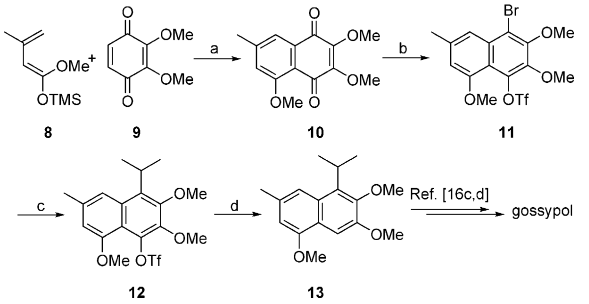
solid state (Figure 1). We considered that the hemilabile P=O coordination contributes to the steric bulk at the right rear side of the Pd center and also allows a fast reductive elimination. Both **L3** and **L4** effectively block coordination from the top and front left sides of the palladium center and leave limited space for β-hydrogen elimination and isomerization pathways. In comparison, **L4** is even bulkier than **L3** because of its dimethylamino moiety, which further facilitates the reductive elimination[9,14] and allows the synthesis of *ortho*-alkoxy di-*ortho*-substituted isopropyl arenes with excellent selectivities and yields. Coordination between the dimethylamino group of **L4** and the palladium center was not observed.

To demonstrate the synthetic utility of this method, the coupling of sterically hindered aryl bromides with isopropyl substrates was employed in a late-stage modification of estrone (Scheme 5). Bromide **6**[15] was readily synthesized from estrone in two steps. Direct cross-coupling between **6** and isopropylboronic acid with Pd-**L4** as the catalyst provided the 4-isopropyl-substituted isolated estrone derivative **7** in 87% yield on a 1-gram scale, thus demonstrating the applicability of this method.



Scheme 5. Synthesis of 4-isopropyl-substituted estrone **7**.

The cross-coupling was further applied in a new synthetic route toward gossypol, a male antifertility agent and PAF antagonist (Scheme 6).[16] A Diels–Alder reaction between diene **8** and dimethoxyquinone **9** provided benzoquinone **10** in 82% yield. Reduction of **10** using HSiEt$_3$/PBr$_3$, followed by bromination and triflate formation provided **11** in 50% overall yield in three steps. Cross-coupling of **11** with isopropylboronic acid with Pd-**L4** as the catalyst provided compound **12** in 86% yield with a 9.6:1 ratio of *i*Pr/*n*Pr substitution. Removal of the triflate group in **12** using Pd/C/H$_2$ provided compound **13**, a key intermediate in the synthesis of gossypol,[16] in 99% yield.



Scheme 6. Synthesis of gossypol intermediate **13** by employing the aryl–alkyl cross-coupling strategy. a) AcOH, DCM, RT, 82%; b) 1. Et$_3$SiH, PBr$_3$, DCM; 2. NBS, THF; 3. Tf$_2$O, Et$_3$N, DCM; 50% (3 steps); c) *i*PrB(OH)$_2$, [Pd(cinnamyl)Cl]$_2$ (0.5 mol%), **L4** (2 mol%), 86%, (*i*Pr/*n*Pr = 9.6:1); d) Pd/C, H$_2$, Et$_3$N, MeOH, 99%.

In summary, we have designed and developed bulky P,P=O ligands that successfully inhibit the isomerization and reduction side reactions in Suzuki–Miyaura cross-couplings between sterically hindered aryl halides and alkylboronic acids. Ligands **L3** and **L4** have enabled Suzuki–Miyaura cross-couplings between di-*ortho*-substituted aryl bromides and acyclic secondary alkylboronic acids to the corresponding products in high yields. The method has also enabled the preparation of *ortho*-alkoxy di-*ortho*-substituted isopropyl arenes in excellent yields by cross-couplings. Its synthetic utility has been demonstrated in a late-stage modification of estrone and the application to a new synthetic route toward gossypol. Further development of efficient aryl–alkyl or alkyl–alkyl cross-couplings are currently ongoing in our group and progress will be reported in due course.

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[12] See the Supporting Information for details.

[13] CCDC 1026685 ([Pd(**L3**)Cl$_2$]), 1036101 ([Pd(**L4**)Cl$_2$]), and 1029789 (**11**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[14] Conjugation between the Me$_2$N group and the phenyl ring in **L4** was not observed in the crystal structure. In this case, the Me$_2$N group might serve as an electron-withdrawing group, as mentioned by Buchwald in reference [3h], thus further facilitating the reductive elimination.

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