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Homogeneous Catalysis

A General Palladium-Catalyzed Suzuki–Miyaura Coupling of Aryl Mesylates**

*Chau Ming So, Chak Po Lau, and Fuk Yee Kwong**

Palladium-catalyzed cross-coupling reactions have become an extremely versatile tool in organic synthesis for the connection of electrophilic and organometallic fragments by the formation of either carbon–carbon or carbon–heteroatom bonds.[1] In particular, the Suzuki–Miyaura reaction, employing organoboron nucleophiles, represents an effective method for the construction of $C(sp^2){-}C(sp^2)$ linkages, and has numerous applications in pharmaceutical, material, and agricultural chemistry.[2] In addition to aryl iodides, bromides, and, more recently, chlorides,[3] aryl and vinyl sulfonates, such as triflates, nonaflates, and tosylates, are useful alternative electrophiles for palladium-catalyzed cross-coupling reactions[4,5] and are readily available from phenols and ketones, respectively. Recently, a plethora of ligands have been investigated to tackle difficult palladium-catalyzed aryl tosylate couplings.[6,7] Buchwald's X-Phos displays excellent reactivity in Suzuki–Miyaura, Buchwald–Hartwig, and Sonogashira reactions of aryl arenesulfonates (Figure 1).[6a,f,h] Ackermann's PinP(O)H enables the highly efficient Kumada cross-coupling of aryl tosylates (Figure 1).[6e] It is interesting to note that Josiphos-type ligands(Figure 1).[8] are effective for Kumada coupling of aryl tosylates,[6d] yet are inferior in Suzuki-type coupling of aryl tosylates.[6a] Ligand structure seems to be crucial in successfully achieving specific catalytic reactions.

In general, aryl mesylates are considerably more inert than the corresponding aryl arenesulfonates (e.g. benzenesulfonate or *p*-toluenesulfonate) in coupling reactions.[9] Although nickel-catalyzed mesylate couplings have been reported, precedents for a general palladium system capable of coupling aryl mesylates remain scarce.[10] To date, only two publications report palladium-catalyzed mesylate couplings. Buchwald and co-workers reported C−C bond formation (carbonylation) in the presence of palladium acetate and the bidentate phosphane ligand $Cy_2P(CH_2)_3PCy_2{\cdot}HBF_4$,[6j] whereas our group reported C−N bond formation (amination) in the presence of Pd/**L2** (see Scheme 1).[11] Aryl mesylates are an attractive substrate, based on their ease of preparation, as well as a higher degree of atom economy for coupling reactions than those employing the corresponding aryl tosylates.[12] We report herein, to our knowledge, the first general palladium catalyst system for Suzuki–Miyaura coupling of unactivated mesylates. The indolyl phosphane ligand displays excellent reactivity in coupling aryl and heteroaryl mesylates with various organoboron nucleophiles including arylboronic acids, pinacolboronic esters, and trifluoroborate salts.

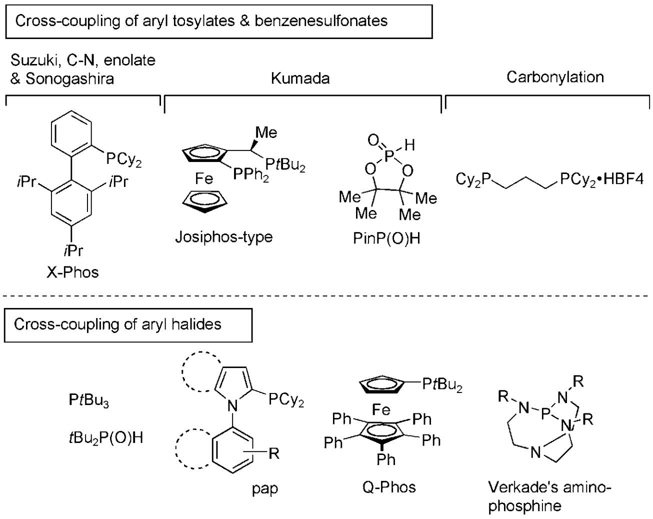
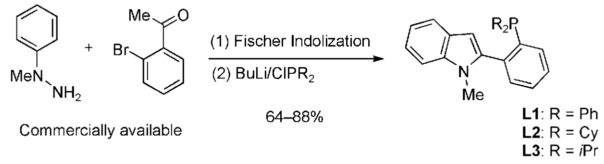


Figure 1. Selected examples of effective phosphane ligands. pap = phosphino-substituted *N*-aryl pyrrole.

In 2007, we reported aminophosphane ligands with indole templates.[13] Similar pap-type ligands containing an indole scaffold (see Figure 1, pap ligand, pap = phosphino-substituted *N*-aryl pyrrole) were also reported by Beller and co-workers for the cross-coupling of aryl halides.[14] We report herein the results of investigations using phosphane (C−P) ligands incorporating an indole moiety. The ligand skeleton can be obtained in good yield from commercially available *N*-methylphenylhydrazine and bromoacetophenone by straightforward Fischer indole synthesis (Scheme 1).[15] The steric and



Scheme 1. Preparation of indolyl-phosphane ligands **L1**–**L3**.

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[*] C. M. So, Prof. Dr. C. P. Lau, Prof. Dr. F. Y. Kwong
Open Laboratory of Chirotechnology, The Institute of Molecular Technology for Drug Discovery and Synthesis
Department of Applied Biology and Chemical Technology, Hong Kong Polytechnic University
Hung Hom, Kowloon, Hong Kong (Hong Kong)
Fax: (+852) 2364-9932
E-mail: bcfyk@inet.polyu.edu.hk

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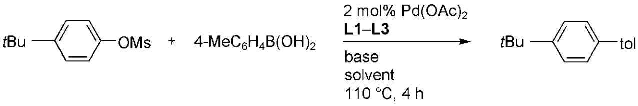
electronic effects of the ligand framework can be simply modified by a random matching of arylhydrazines and substituted acetophenones (Scheme 1). Moreover, ligands **L1**–**L3** can be directly purified by a single crystallization and are highly air-stable in both solid and solution states.[16]

Palladium-catalyzed Suzuki–Miyaura couplings of unactivated aryl mesylates have, to date, not been reported. This area remains highly challenging, as aryl mesylate electrophiles are proposed to be less susceptible to oxidative addition than the corresponding aryl arenesulfonates.[9] In addition, the reactivity of aryl mesylates (ArOMs) was at least fivefold lower in general than the corresponding aryl tosylates (ArOTs) under the same reaction conditions.[17] With a series of indolylphosphane ligands, the feasibility on Suzuki-type couplings of aryl mesylates was investigated. Electronically neutral 4-*tert*-butylphenyl mesylate and 4-tolylboronic acid were used as the prototypical substrates in our reaction (Table 1). Ligand **L1** (with a diphenylphosphano moiety) apparently provided no conversion. However, the dicyclohexylphosphano **L2** and diisopropylphosphano **L3** analogues showed good to excellent catalytic activity (Table 1, entries 1–3). Among the solvents surveyed (*t*BuOH, toluene, DMF, and THF), *t*BuOH provided the best product yield (Table 1, entries 2 and 5–7). Screening of commonly used inorganic bases indicated that CsF and K_3PO_4 were suitable bases for the aryl mesylate coupling reaction (Table 1, entries 11 and 12). When potassium *tert*-butoxide was applied as a base in this reaction, a significant amount of phenolic side products (from the hydrolysis of sulfonate) were formed (Table 1, entry 10).

Table 1: Initial screening of Suzuki–Miyaura coupling of unactivated ArOMs.[a]



Entry	Ligand	Solvent	Base	Yield [%][b]
1	**L1**	*t*BuOH	$K_3PO_4\cdot H_2O$	< 1
2	**L2**	*t*BuOH	$K_3PO_4\cdot H_2O$	89
3	**L3**	*t*BuOH	$K_3PO_4\cdot H_2O$	84
4	none	*t*BuOH	$K_3PO_4\cdot H_2O$	< 1
5	**L2**	toluene	$K_3PO_4\cdot H_2O$	42
6	**L2**	DMF	$K_3PO_4\cdot H_2O$	50
7	**L2**	THF	$K_3PO_4\cdot H_2O$	33
8	**L2**	*t*BuOH	Cs_2CO_3	83
9	**L2**	*t*BuOH	K_2CO_3	79
10	**L2**	*t*BuOH	KO*t*Bu	< 1
11	**L2**	*t*BuOH	CsF	93
12	**L2**	*t*BuOH	K_3PO_4	97

[a] Reaction conditions: ArOMs (1.0 mmol), Ar′B(OH)$_2$ (2.0 mmol), base (3.0 mmol), Pd(OAc)$_2$ (2 mol%), ligand (**L1**–**L3**; 0.04 mmol), solvent (3.0 mL), at 110 °C under N_2 for 4 h (see Supporting Information for experimental details). [b] Yields were calculated using calibrated GC with dodecane as the internal standard. tol = *p*-tolyl.

To test the effectiveness of the Pd/**L2** catalytic system, a range of aryl mesylates (prepared from substituted phenols with methanesulfonyl chloride) was examined using the preliminary optimized reaction conditions (Table 2). In general, complete conversion was detected within 3 h when 2 mol% of Pd were used. No homocoupled side-products were detected by GC-MS analysis. Notably, the coupling of unactivated aryl mesylates was achieved with 0.5 mol% of Pd (Table 2, entry 2). A variety of common functional groups were compatible under these mild reaction conditions, including keto, aldehyde, ester, and nitrile (Table 2, entries 6–12). Moreover, deactivated *p*-methoxyphenyl mesylate was discovered to be a feasible coupling partner in this reaction (Table 2, entry 14).

Besides functionalized aryl mesylates, the scope of the Pd/**L2** catalytic system can be extended to heteroaryl mesylates (Table 3). Sterically congested arylboronic acids were efficiently coupled with quinolyl mesylate in excellent yields (Table 3, entries 1–3). Particularly noteworthy was that the extremely hindered 2,4-di-*tert*-butyl-6-methoxyphenylboronic acid was found to be a capable coupling partner in this reaction (Table 3, entry 3). Benzothiazolyl and pyridyl mesylates can be coupled with arylboronic acids to afford the corresponding desired product in good yields (Table 3, entries 4–6).

In addition to arylboronic acids, which are widely used as coupling partners in Suzuki–Miyaura reactions, other boronic acid surrogates are highly attractive.[18] The new palladium catalyst system demonstrated the versatility of aryl mesylates in Suzuki-type coupling reactions using other organoboron nucleophiles. Aryl trifluoroborate salts and a pinacol boronate ester were successfully coupled in good yields with aryl mesylates using the Pd/**L2** catalytic system (Scheme 2).

Within the past decade, isolated palladium precatalysts have received increasing levels of attention.[19] In addition to their convenience in handling, they display comparative (or sometimes even greater) activity with respect to in situ generated catalysts in cross-coupling reactions. We applied the isolated dimeric palladacyclic complex to the Suzuki–Miyaura coupling of aryl mesylates (Scheme 3). This air-stable palladium complex **5** with twice the amount of additional **L2** displayed essentially the same reactivity as in the in situ generated catalyst (Scheme 3 vs. Table 1, entry 2).

In conclusion, we have succeeded in showing the first Suzuki–Miyaura coupling of unactivated aryl mesylates. The Pd/**L2** catalyst system is active with a range of mesylate substrates with various common functional groups. Moreover, the scope of the organoboron nucleophile can be extended beyonded boronic acids to aryltrifluoroborate salts and boronate esters. In view of the simplicity of the ligand synthesis as well as the easy modification of the ligand skeleton, we anticipate that further enhancements in reactivity and versatility of the ligand series will be attainable.

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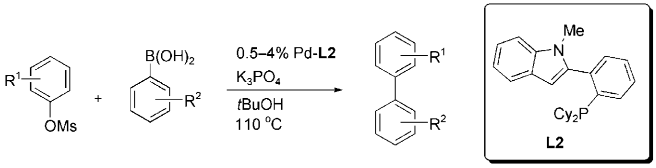
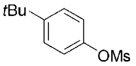
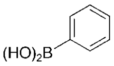
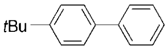
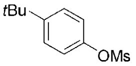
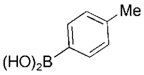
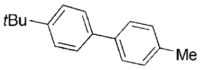
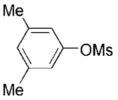
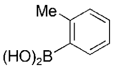
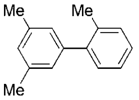
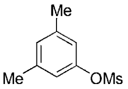
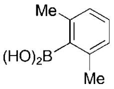
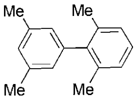
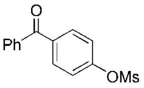
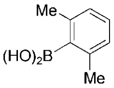
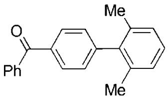
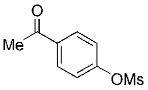
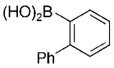
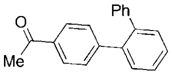
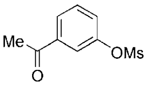
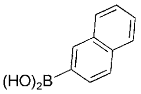
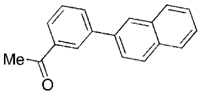
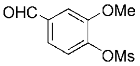
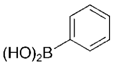
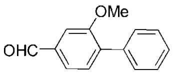
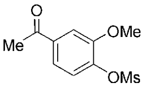
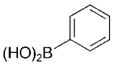
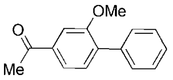
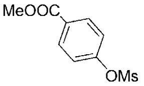
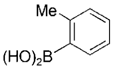
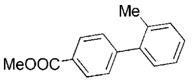
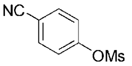
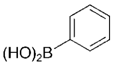
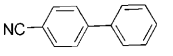
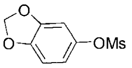
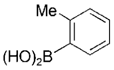
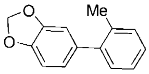
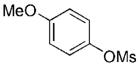
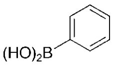
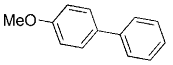
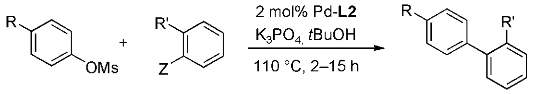
Table 2: Palladium-catalyzed Suzuki–Miyaura coupling of ArOMs with Ar′B(OH)$_2$.[a]



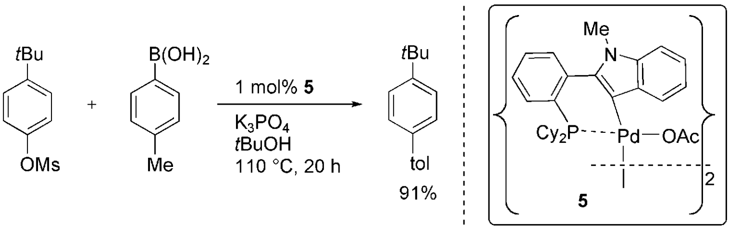
Entry	ArOMs	Ar′B(OH)$_2$	Product	Pd [mol%]	t [h]	Yield [%][b]
1				1	19	91
2				0.5	24	88
3				1	19	90
4				3	8	97
5				4	8	70
6				2	3	93
7				2	3	92
8				2	3	94
9				2	3	81
10				2	3	95
11				2	3	97
12				2	3	95
13				2	3	89
14				4	8	89

[a] Reaction conditions: ArOMs (1.0 mmol), Ar′B(OH)$_2$ (2.0 mmol), K$_3$PO$_4$ (3.0 mmol), Pd(OAc)$_2$/**L2** (mol% as indicated), tBuOH (3.0 mL), at 110°C under N$_2$ for indicated period of time (see Supporting Information for experimental details). [b] Yields of isolated product.



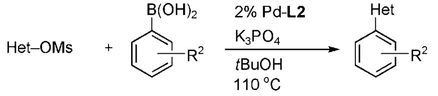
R = tBu, R' = H, Z = BF$_3$K, 15 h, 85%
R = PhC(O), R' = Me, Z = BF$_3$K, 2 h, 86%
R = PhC(O), R' = H, Z = BPin, 6 h, 83%

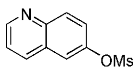
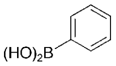
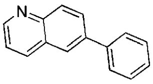
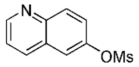
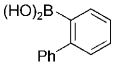
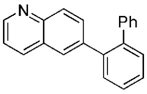
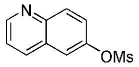
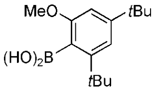
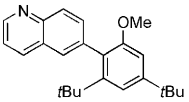
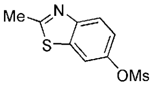
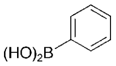
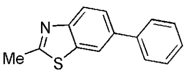
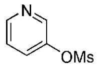
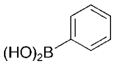
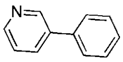
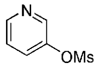
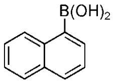
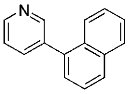
Scheme 2. Palladium-catalyzed Suzuki-type coupling of ArOMs with Ar′BF$_3$K and Ar′BPin. ArOMs = aryl mesylate, BPin = pinacolboronate.



Scheme 3. Application of dimeric palladacyclic complex **5** in Suzuki–Miyaura coupling of ArOMs.

Table 3: Palladium-catalyzed Suzuki–Miyaura coupling of Het-OMs with Ar'B(OH)$_2$.[a]



Entry	Het–OMs	Ar'B(OH)$_2$	Product	Pd [mol %]	*t* [h]	Yield [%][b]
1				2	3	97
2				2	3	91
3				2	3	77
4				2	3	91
5				2	3	84
6				2	3	85

[a] Reaction conditions: Het-OMs (1.0 mmol), Ar'B(OH)$_2$ (2.0 mmol), K$_3$PO$_4$ (3.0 mmol), Pd(OAc)$_2$/**L2** (mol % as indicated), *t*BuOH (3.0 mL), at 110°C under N$_2$. [b] Yields of isolated product. Het-OMs = heteroaryl mesylate.

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[17] A series of competitive test experiments were performed to show ArOMs is a less reactive substrate than ArOTs for coupling reactions. In reaction with 0.2 mol% of Pd/**L2** at 110 °C for 20 h, over 99% conversion of $t\mathrm{BuC_6H_4OTs}$ and only 18% conversion of $t\mathrm{BuC_6H_4OMs}$ were detected, as compared by GC-FID and GC-MS analyses.

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