A General Chemoselective Suzuki-Miyaura Coupling of Polyhalogenated Aryl Triflates Enabled by an Alkyl-Heteroaryl-Based Phosphine Ligand

Chau Ming So,[*,†,‡] On Ying Yuen,[†] Shan Shan Ng,[†] and Zicong Chen[†]*

[†] State Key Laboratory of Chemical Biology and Drug Discovery and Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong SAR, China

[‡] The Hong Kong Polytechnic University Shenzhen Research Institute, Shenzhen 518057, Guangdong Province, China

KEYWORDS: palladium, phosphine, chemoselectivity, Suzuki-Miyaura coupling, polyhalogenated aryl triflates

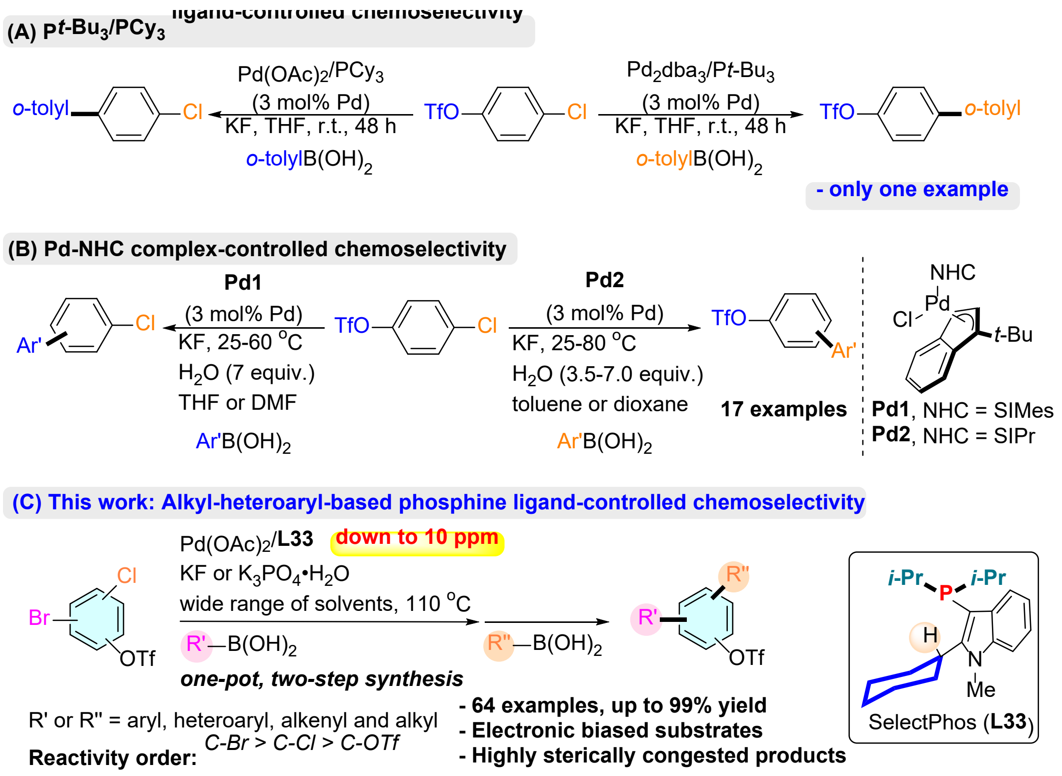
ABSTRACT: This study describes a general chemoselective Suzuki-Miyaura coupling of polyhalogenated aryl triflates with the reactivity order of C−Cl > C−OTf using Pd/**L33** catalyst. The methine hydrogen and the steric hindrance offered by the alkyl bottom ring of **L33** were found to be key factors in reactivity and chemoselectivity. With Pd/**L33** catalyst, a wide range of polyhalogenated (hetero)aryl triflates, which were independent of the substrates and of the relative positioning of the competing reaction sites, were well coupled with (hetero)aryl, alkenyl, and alkylboronic acids to obtain the corresponding products with good chemoselectivity and yields. The chemoselective reaction can easily be scaled up to gram scale, and the use of parts per million levels of Pd catalyst (as low as 10 ppm Pd) was achieved.

Palladium-catalyzed cross-coupling reactions are an extremely versatile tool in organic synthesis for connecting electrophilic and organometallic fragments.[1] Among the electrophiles, aryl bromides, chlorides, and triflates are still the most widely used electrophiles in the pharmaceutical, industry, and routine synthesis despite the recent discovery of more attractive alternatives.[2] Although the actual chemoselectivity of Pd-catalyzed cross-coupling reactions with a given multiple(pseudo)halides can be affected by multiple factors, the approximate reactivity order of C−I >> C−Br ≈ C−OTf >> C−Cl is commonly accepted and used as a general guideline to predict the chemoselectivity.[3] However, it would be extremely attractive to easily alternate the reactivity order by changing ligands to align with the ideal synthetic pathways.

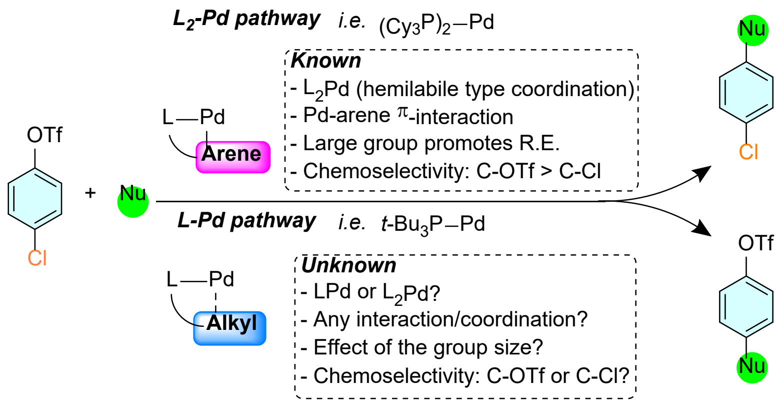
Fu reported a single example in the Suzuki coupling of 4-chlorophenyl triflate with *o*-tolylboronic acid, which the reactivity order between C−Cl and C−OTf could be alternated by the ligands, where P*t*-Bu$_3$ favors a reaction at C−Cl over C−OTf, but where PCy$_3$ favors a reaction at C−OTf over C−Cl (Scheme 1A).[4] Further investigations by Schoenebeck,[4b] Houk,[5] and Sigma[6] revealed that the palladium ligation state (LPd or L$_2$Pd) with the phosphine ligand during the oxidative addition significantly affects the preference for the oxidative addition of C−Cl or C−OTf. More recently, Neufeldt reported that the use of carbene Pd−complexes, which was presynthesized from (η^3-1-t-Bu-indenyl)$_2$(μ-Cl)$_2$Pd$_2$, SIMes and SIPr, can allow the chemoselective Suzuki coupling of chloroaryl triflates (Scheme 1B).[7] However, in general, there are still significant problems remain unresolve, such as the limitation of the 1) chemoselectivity of the electronically-biased chloroaryl triflates, 2) chemoselectivity of the highly sterically congested product formation, 3) high catalyst loading, 4) origin of the different chemoselectivity generated by the catalysts (i.e., the sets of Pd carbene complexes)[7] as well as the factors of ligand design influence on the chemoselectivity.

A previous study suggested that even though the extremely bulky biaryl mono-phosphine ligand is usually found to have a ratio of Pd:L of 1:1, the hemilabile Pd-arene interaction offered by the aryl bottom ring makes it a "bidentate" ligand and prefers the oxidative addition of C−OTf over C−Cl (Scheme 2).[6] In contrast to the phosphine ligands bearing the aryl structure, the use of the alkyl group as the bottom ring in the ligand design has received less attention and is underexplored in coupling reactions. We envision that using the alkyl group as the bottom may offer different interaction and coordination modes, which may alternate the chemoselectivity. Herein, we attempted to design and develop a new type of phosphine ligand with an alkyl bottom group for chemoselectivity reactions (Scheme 1C).

Scheme 1. Chemoselective Suzuki-Miyaura cross-coupling reaction of polyhalogenated aryl triflates

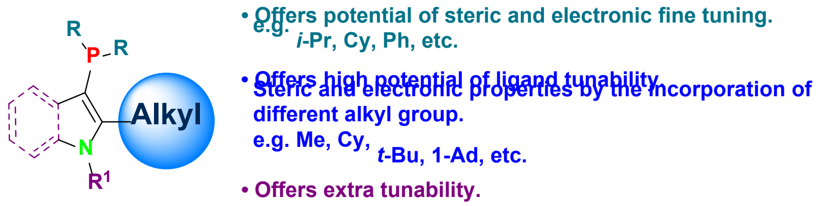


Scheme 2. Chemoselectivity related to the palladium ligation state



In this study, we chose indole as the heterocyclic moiety for the ligand skeleton, which can offer several advantages: (1) the easy installation of a different alkyl group at the specific position; (2) the electronic-biased C3-position allows the rapid regioselective bromination and phosphination; (3) the first and second advantages can offer an excellent ligand diversity for the structure-activity relationship investigations; (4) 2-arylindole-type phosphines have been proven to be effective ligands in Pd-catalyzed cross-coupling reactions,[8] which can offer a direct and sophisticated reference to evaluate the effectiveness and the chemoselectivity of the new type of alkyl-based phosphine ligands (Scheme 3).

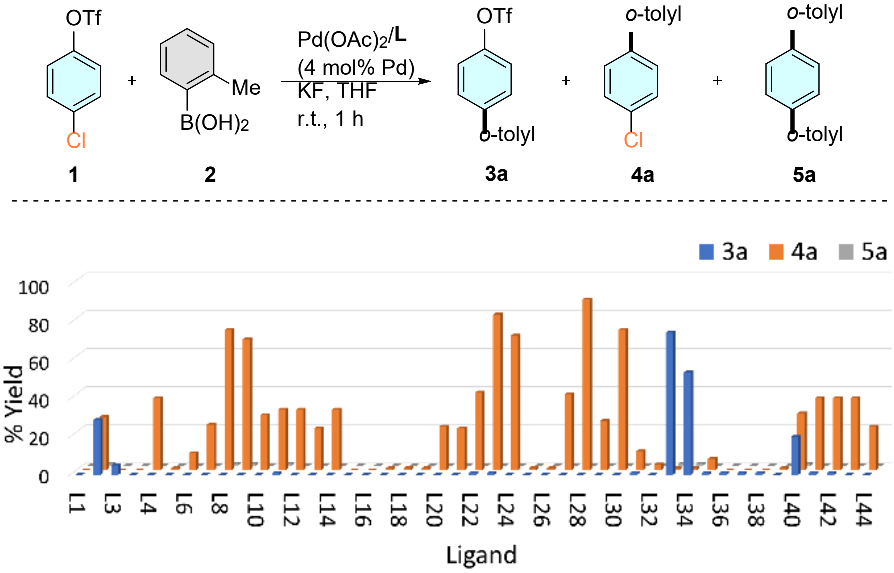
Scheme 3. Proposed alkyl-based phosphine ligand design with high potential for tunability



Our initial investigation of the chemoselective Suzuki coupling of polyhalogenated aryl triflates employed 4-chlorophenyl triflates and *o*-tolylboronic acid as the model substrates with a typical reaction condition (Table 1 and see SI, Table S1 for detail).[4] Among the classical phosphine ligands tested (**L1−L5**), only P*t*-Bu$_3$ (**L3**) resulted in selective C−Cl activation, yet a poor yield was obtained. *t*-Bu$_3$P-Pd(I)-I dimer (**L3'**) was found to be inactive in this reaction. PCy$_3$ (**L2**) offered a better overall yield but showed a low selectivity between the **3a**/**4a**. Buchwald biaryl type ligands (**L6−L11**) showed chemoselective C−OTf activation. The increase in the *ortho*-steric bulkiness of the bottom aryl ring (**L6** vs. **L8−L9**) further promoted the C−OTf reaction. Moreover, heterocyclic-based phosphine with a phenyl bottom ring (**L12−L13**) and bidentate ligands

(**L14–L30**) also exhibited C–OTf chemoselectivity. The direct usage of IMes·HCl (**L31**) and IPr·HCl (**L32**) showed a low reactivity and C–OTf chemoselectivity. We were delighted to observe that the newly developed phosphine ligands (**L33**) with a cyclohexyl bottom ring provided an inversion of the common selectivity order of OTf > Cl for the Suzuki reaction in both intra- and inter-molecular coupling reactions (See SI, Scheme S5 for detail). A series of ligands with different alkyl bottom groups and substitution groups on the phosphorous atom were prepared to probe the structural effect on the reactivity and chemoselectivity.

Table 1. Ligand screening of chemoselective C–Cl (over C–OTf) Suzuki coupling at room temperature[a]



L1, PPh_3
L2, PCy_3
L3, P*t*-Bu_3
L3', (P*t*-Bu_3-Pd-I)$_2$
L4, P(*p*-tolyl)$_3$
L5, P(*o*-tolyl)$_3$

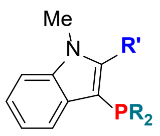
L6, JohnPhos
L7, DavePhos
L8, SPhos
L9, RuPhos
L10, XPhos
L11, BrettPhos

L12, cataCXium®PCy
L13, cataCXium®PInCy
L14, CM-Phos
L15, PhMezole-Phos
L16, MorDalphos

L17, dppm
L18, dppe
L19, dppp
L20, dppb
L21, dcype

L22, dppf
L23, dippf
L24, dcypf
L25, BINAP
L26, dppBz

L27, DPEPhos
L28, XantPhos
L29, CyXantPhos
L30, NiXantPhos
L31, IMes•HCl
L32, IPr•HCl



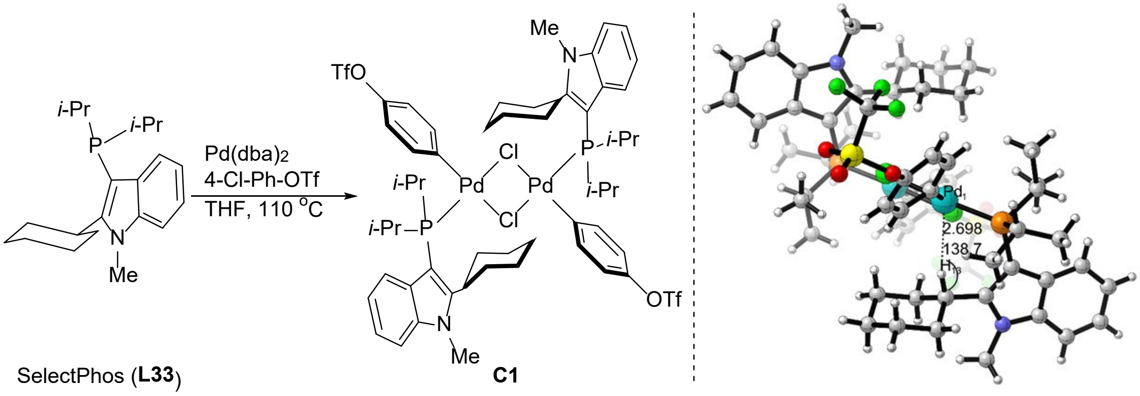
L33, R=*i*-Pr, R'=Cy (SelectPhos)
L34, R=Cy, R'=Cy (CySelectPhos)
L35, R=Ph, R'=Cy (PhSelectPhos)
L36, R=Cy, R'=*t*-Bu
L37, R=Cy, R'=Ad
L38, R=*i*-Pr, R'=Ad
L39, R=Ph, R'=Ad
L40, R=Cy, R'=Me
L41, R=*i*-Pr, R'=Ph
L42, R=Cy, R'=Ph
L43, R=Cy, R'=*o*-anisole
L44, R=Cy, R'=2,6-dimethoxylbenzene

[a]Reaction conditions: **1** (0.20 mmol), *o*-tolylboronic acid (0.20 mmol), $Pd(OAc)_2$ (4 mol%), **L** (4 mol%), KF (0.60 mmol), and THF (0.60 mL) were stirred at r.t. for 1 h. Calibrated GC yields were reported using dodecane as an internal standard.

Ligands bearing a more electron-rich dialkyl phosphines group (**L33−L34**), which may facilitate the oxidative addition process, offered better activity toward the coupling reaction than the $-PPh_2$ group (**L35**). The ligand with the secondary alkyl group (**L33−L34**) offered the best reactivity and chemoselectivity to give product **3a**. The poor chemoselectivity offered by the ligand with a small methyl group (**L40**) may result from the lack of *ortho*-steric hindrance to prevent the formation of L_2Pd species. Surprisingly, ligands (**L36−L39**) with tertiary alkyl bottom groups, which were intended to further increase the steric hindrance, were found to be inferior in this reaction. Further increase in the steric with adamantyl group or changing the phosphine group offered no improvement on the reactivity, which is uncommon[9] and implies that the methine hydrogen may play a critical role in the catalyst reactivity. As a direct comparison, the ligands with an aryl bottom ring (**L41−L44**) showed only the C−OTf selectivity, irrespective of the substitution group on the aryl bottom ring.

To investigate the origin of ligand effects on reactivity and chemoselectivity. The palladium oxidative addition complex **C1** was individually prepared[10] (Scheme 4), which displayed essentially the same reactivity and chemoselectivity in the reaction (See SI, Scheme S4 for detail). The crystallographic analysis of the single crystal of **C1** showed that it was a chloride bridged dimeric Pd(II) complex with a Pd−L ratio of 1:1. The most interesting feature of **C1** was the interaction between the methine hydrogen on the cyclohexyl bottom ring and the Pd center C13−H12···Pd1. The methine hydrogen was in close proximity to the vacant axial position around the Pd1 center. The distances (2.698Å) and angles (138.7°) of the atoms, which lie within a standard range of 2.3-2.9Å and 110-170° with downfield shift (5.73 ppm) of the methine hydrogen, indicate this C−H···Pd interaction as anagostic/preagostic interactions.[11]

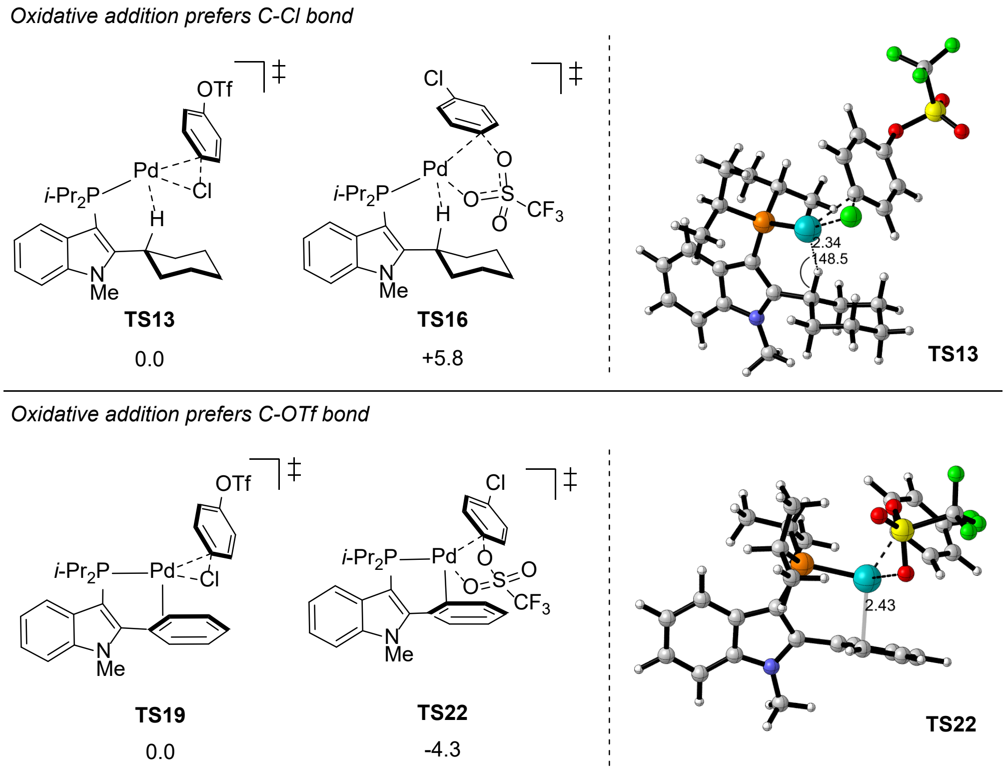
Scheme 4. Preparation and C−H···Pd interaction of **C1**



To further investigate ligand effects on chemoselectivity, we performed a density functional theory (DFT) study of the oxidative addition process for Pd/**L33** and Pd/**L41** catalytic systems. The calculations were performed at SMD(THF) B3PW91-D3(BJ)/6-31G*//B2PLYP-D3(BJ)/ Def2-TZVP level of theory (see SI for details). The monoligated Pd−**L33** react with 4-chlorophenyl triflate was used for the oxidative addition study. The DFT result showed that Pd−**L33** was more favorable in reacting with the C−Cl bond (**TS13**) than the C−OTf bond (**TS16**) with a difference of 5.8 kcal mol^{-1}, which is consistent with the experimental results (Scheme 5). The calculation results also suggested the existence of anagostic/preagostic interaction between the palladium center and the methine hydrogen of the cyclohexyl ring across the oxidative addition process. A preliminary study of the nature of the C–H···Pd interaction using the quantum theory of atoms in molecules (QTAIM) analysis for **TS13** indicated a bond path and associated BCP for the Pd···H separation; the Laplacian of the electron density at the BCP was positive [$\nabla^2\varrho(\mathrm{BCP})$ = 0.0614 e/bohr^5] and the energy density was negative [H(BCP) = -0.0026 e/bohr^3], which have been used previously as the basis for the preagostic interaction.[11b, 12] The natural bond orbital (NBO) analysis showed that the Pd to antibonding sp^3 C−H backdonation at 3.24 kcal mol^{-1} of the second-order perturbation energy, which can be regarded as an attractive component in terms of electron donation.[13] Since anagostic interaction involving only repulsive electrostatics, the Pd···H separation in the complexes should be described as preagostic interaction.[13] A recent study suggested that the anagostic/preagostic interaction might assist the stabilization of the unsaturated complexes in the catalytic cycle.[14] We also performed the calculation for the monoligated Pd−**L41**, in which the phenyl group was in place of the cyclohexyl group, to evaluate the effect of the bottom ring on the chemoselectivity. Consistent with the experimental results, Pd−**L41** favored undergoing the oxidative addition of C−OTf (**TS22**) then C−Cl (**TS19**) by 4.3 kcal mol^{-1} (Scheme 5). The phenyl bottom ring had a π-arene hemilabile interaction/coordination with the palladium center[15] and it agrees with the previous finding that the bis-coordinated palladium complex prefers the C−OTf bond activation.[6]

Based on the above observations and studies, we posit that the methine hydrogen and the steric hindrance offered by the alkyl bottom group of the ligands might be the key factors accounting for the reactivity and chemoselectivity. The preagostic interaction between methine hydrogen and the palladium center may play a role in stabilizing and affecting the activity of the unsaturated palladium complex during the course of the oxidative addition. The steric effect induced by the cyclohexyl bottom ring may account for the prevention of the second coordination of the phosphine ligand and the formation of the L_2Pd species.

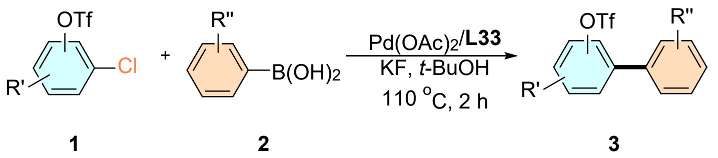
Scheme 5. Calculated transition structures of the oxidative addition step for Pd/**L33** and Pd/**L41**

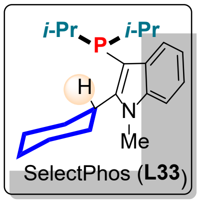


We then optimized the reaction conditions using alkyl-indolyl-based ligand SelectPhos **L33** for the Suzuki reaction (see SI, Table S2 for detail). A series of palladium sources were screened (Table S2, entries 1-4). $Pd(OAc)_2$ was found to be the best palladium source in this reaction (Table S2, entry 1). We attempted to reduce the catalyst loading from 4 to 0.02 mol% $Pd(OAc)_2$ and increase the temperature to 110 °C. The desired product yield **3** was only decreased slightly (Table S2, entry 6). Efforts were taken to change the ligand ratio (Table S2, entries 6-9). Delightfully, the Pd-to-ligand ratio being 1:2 resulted in a 99% product yield (Table S2, entry 7). Among an array of inorganic bases surveyed, KF was found to be the best base (Table S2, entries 7 vs. 10-15). The presence of water equivalents in $K_3PO_4 \cdot H_2O$ led to an increase in product yield compared with K_3PO_4 (Table S2, entries 13 and 12). With regard to solvent screening, *t*-BuOH was found to be a more effective solvent than THF and the others (Table S2, entries 20 vs. 16-20). Hence, Pd(OAc)$_2$/**L33** with KF as the base and *t*-BuOH as the solvent gave the best result, in which the catalyst loading could be lowered to 0.02 mol% Pd at 110 ºC. The reaction rate experiment showed that Pd(OAc)$_2$/**L33** system provided a much higher catalytic activity than the reported Pd−SIPr system, which was suspected to suffer from catalyst deactivation at low catalyst loading (see SI, Scheme S1 for detail).

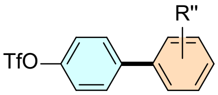
In general, in the presence of the 0.02 mol% Pd/**L33** catalyst, most of the chloroaryl triflates were completed within 2 h and displayed excellent chloro-selectivity (Table 2). A wide range of arylboronic acids was examined. Electron-neutral (H, Me, and *t*-Bu), -deficient (F and CF$_3$), and -rich (OMe) arylboronic acids were coupled smoothly with 4-chlorophenyltriflate in excellent yields (**3a**-**3i** and **3l**). Meanwhile, sterically congested arylboronic acids were found to be feasible cross-coupling partners (**3h**-**3j** and **3k**). The use of heteroarylboronic acids was successful for the first time, which gave the corresponding products an excellent yield (**3o-3r**). Apart from arylboronic acids, alkenylboronic acids were found to be applicable substrates (**3s** and **3t**). 1-Pyreneboronic acid and 9-phenanthracenyl boronic acid containing functional material properties were also feasible cross-coupling partners (**3u**, **3y**, and **3z**).

Table 2. Palladium-catalyzed chemoselective C−Cl (over C−OTf) Suzuki-Miyaura coupling[a]



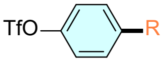


SelectPhos (**L33**)



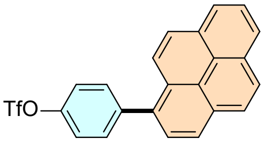
3a, R"=2-Me, 0.02 mol% Pd, 90%
3b, R"=H, 0.02 mol% Pd, 96%
3c, R"=4-Me, 0.02 mol% Pd, 90%
3d, R"=4-*t*-Bu, 0.02 mol% Pd, 92%
3e, R"=4-F, 0.02 mol% Pd, 90%[b]
3f, R"=3,5-di-F, 0.02 mol% Pd, 82%
3g, R"=4-CF_3, 0.05 mol% Pd, 81%

3h, R"=2-CF_3, 0.05 mol% Pd, 70%[c]
3i, R"=2-OMe, 0.05 mol% Pd, 82%[d]
3j, R"=2-Ph, 0.02 mol% Pd, 85%
3l, R"=4-OMe, 0.02 mol% Pd, 86%
3m, R"=3-Ac, 0.02 mol% Pd, 88%
3n, R"=4-COOMe, 0.1 mol% Pd, 85%

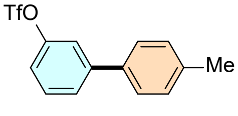


3k, R=1-Naphthyl, 0.02 mol% Pd, 86%
3o, R=4-dibenzofuranyl, 0.03 mol% Pd, 89%
3p, R=4-dibenzothiophenyl, 0.05 mol% Pd, 84%
3q, R=3-benzothiophenyl, 0.2 mol% Pd, 66%

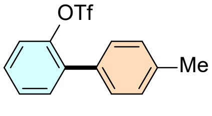
3r, R=2-benzothiophenyl, 0.5 mol% Pd, 80%[c]
3s, R=1-cyclopentenyl, 0.05 mol% Pd, 81%[d]
3t, R=1-cyclohexenyl, 0.05 mol% Pd, 87%[d]



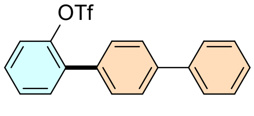
3u
88%
(0.2 mol% Pd)[g]



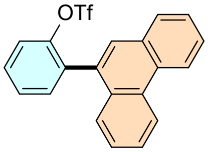
3v
90%
(0.05 mol% Pd)



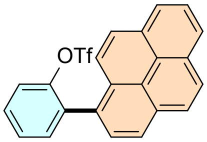
3w
70%
(0.05 mol% Pd)



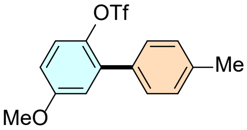
3x
98%
(0.2 mol% Pd)[e,g]



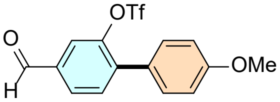
3y
94%
(0.2 mol% Pd)[e,g]



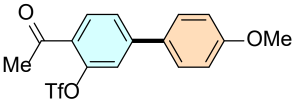
3z
99%
(0.2 mol% Pd)[e,g]



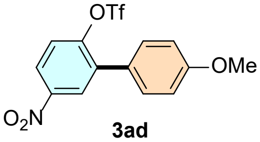
3aa
92%
(0.05 mol% Pd)



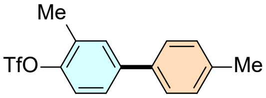
3ab
60%
(0.05 mol% Pd)[b,c,h]



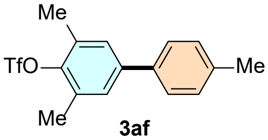
3ac
95%
(0.2 mol% Pd)[c,i]



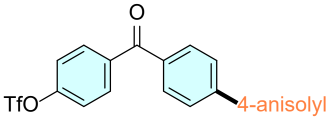
3ad
87%
(0.25 mol% Pd)[e,f]



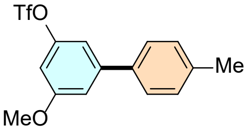
3ae
92%
(0.05 mol% Pd)



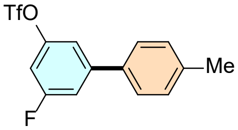
3af
92%
(0.05 mol% Pd)



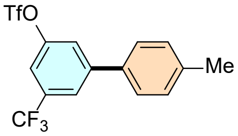
3ag
82%
(0.1 mol% Pd)[c,h]



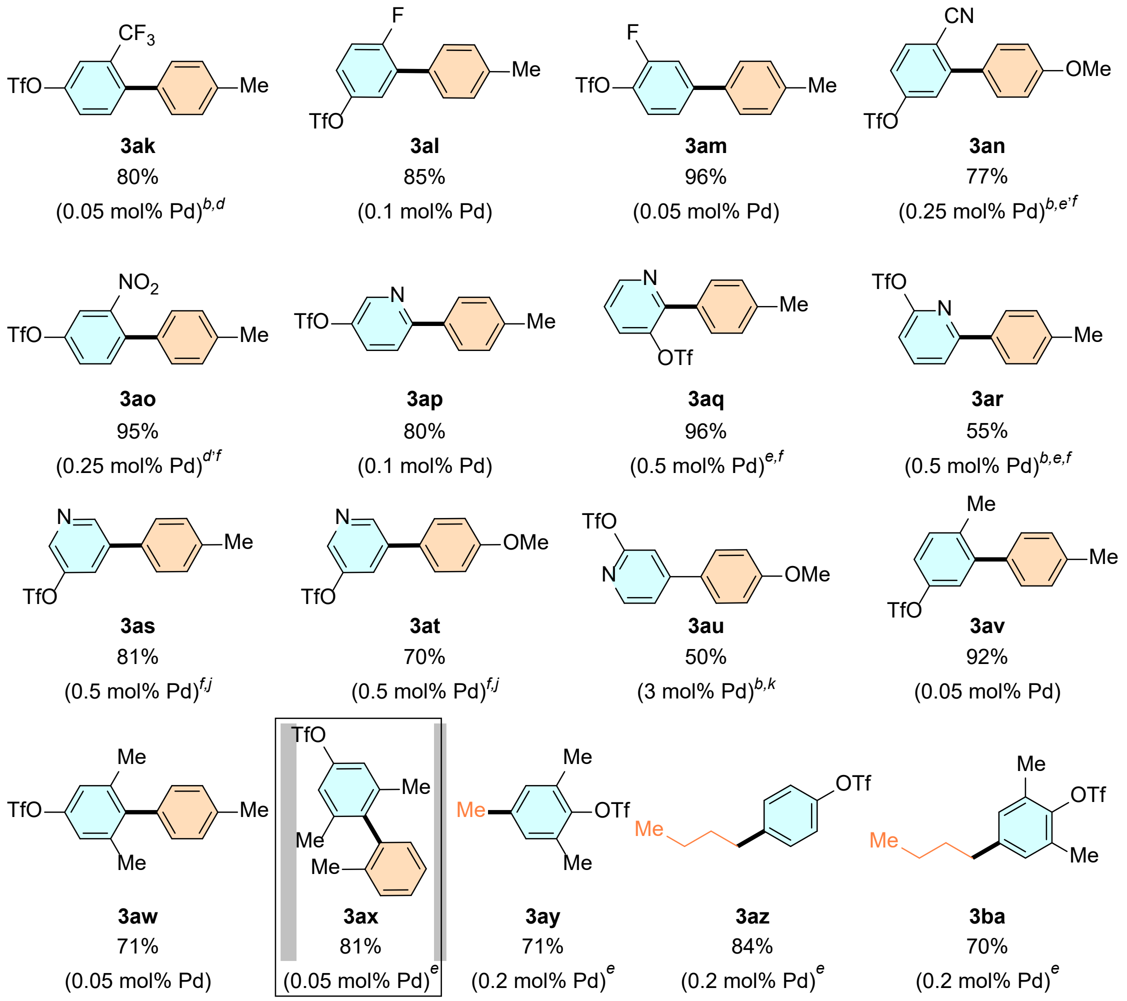
3ah
82%
(0.05 mol% Pd)



3ai
90%
(0.2 mol% Pd)[g]



3aj
82%
(0.2 mol% Pd)[g]



3ak 80% (0.05 mol% Pd)[b,d]

3al 85% (0.1 mol% Pd)

3am 96% (0.05 mol% Pd)

3an 77% (0.25 mol% Pd)[b,e'f]

3ao 95% (0.25 mol% Pd)[d'f]

3ap 80% (0.1 mol% Pd)

3aq 96% (0.5 mol% Pd)[e,f]

3ar 55% (0.5 mol% Pd)[b,e,f]

3as 81% (0.5 mol% Pd)[f,j]

3at 70% (0.5 mol% Pd)[f,j]

3au 50% (3 mol% Pd)[b,k]

3av 92% (0.05 mol% Pd)

3aw 71% (0.05 mol% Pd)

3ax 81% (0.05 mol% Pd)[e]

3ay 71% (0.2 mol% Pd)[e]

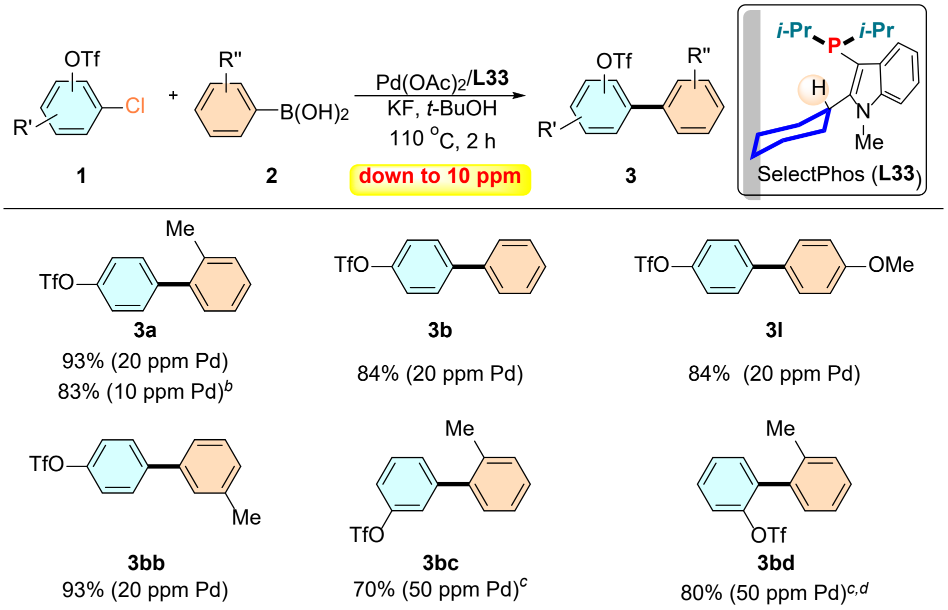
3az 84% (0.2 mol% Pd)[e]

3ba 70% (0.2 mol% Pd)[e]

[a]Reaction conditions: **1** (0.20 mmol), Ar'B(OH)$_2$ (0.20 mmol), Pd(OAc)$_2$:**L33** = 1:2, KF (0.60 mmol), and *t*-BuOH (0.60 mL) were stirred at 110 °C for 2 h under a nitrogen atmosphere. Isolated yields were reported. 95-100% selectivity observed throughout all compounds, and the conversion and selectivity ratio of each compound were provided in SI. [b]<95% selectivity observed. [c]1.2 equiv. Ar'B(OH)$_2$ was used. [d]1.1 equiv. Ar'B(OH)$_2$ was used. [e]1.5 equiv. Ar'B(OH)$_2$ was used. [f]Toluene was used, and the reaction time was 4 h. [g]Toluene:*t*-BuOH = 1:1 (total 0.60 mL) was used, and the reaction time was 4 h. [h]The reaction was conducted for 1 h. [i]Toluene was used, and the reaction time was 3 h. [j]**1** (0.30 mmol) and Ar'B(OH)$_2$ (0.20 mmol) were used. [k]3.0 equiv. Ar'B(OH)$_2$ and toluene were used, and the reaction time was 30 min.

Particularly noteworthy is that we were able to perform selective arylation, regardless of whether the C−Cl and C−OTf bonds were positioned *ortho* (**3w**-**3ab** and **3ad**), *meta* (**3v**, **3ac**, **3ah**, **3ai**, **3aj**, **3al**, and **3an**), or *para* (**3ae**, **3af**, **3ag**, **3ak**, **3am**, and **3ao**) to each other and whether additional steric hinderances or functional groups were present. Methoxy (**3aa** and **3ah**), ester (**3n**), aldehyde (**3ab**), nitro (**3ad** and **3ao**), ketone (**3m**, **3ac**, and **3ag**), fluoro (**3ai**-**3am**), and nitrile (**3an**) moieties were well tolerated. Chloropyridyl triflates were also feasible cross-coupling partners and produced the corresponding products smoothly (**3ap-3au**). The reactivity of pyridine C−X bonds toward Pd(0) generally follows the order C2 > C4 > C3/C5.[3a] Cross-coupling at C−Cl, regardless of the position, occurred preferentially over reaction at C−OTf. The incomplete conversion of chloropyridyl triflates and the decomposition of starting materials/products accounts for the moderate yield of compounds **3ar** and **3au**. Notably, cross-coupling at C4−Cl occurred favorably over reaction at C2−OTf (**3au**) using our Pd/**L33** catalyst system, a clear distinction from Neufeldt's work.[7]

Table 3. Palladium-catalyzed chemoselective C−Cl (over C−OTf) Suzuki-Miyaura coupling at ppm levels[a]



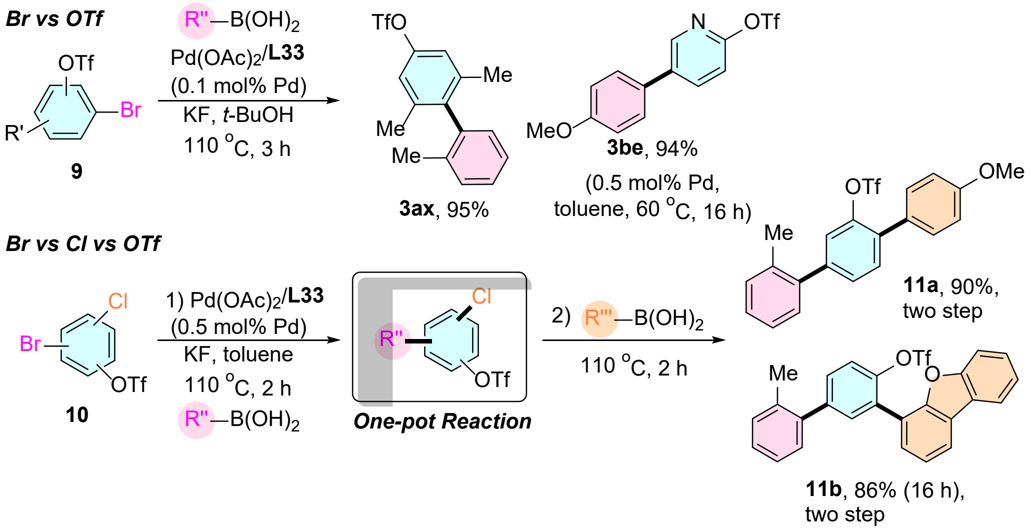
[a]Reaction conditions: **1** (0.20 mmol), Ar'B(OH)$_2$ (0.20 mmol), Pd(OAc)$_2$:**L33** = 1:2, KF (0.60 mmol), and *t*-BuOH (0.60 mL) were stirred at 110 °C for 2 h under a nitrogen atmosphere. Isolated yields were reported. 95-100% selectivity observed throughout all compounds, and the conversion and selectivity ratio of each compound were shown in SI. [b]18 h. [c]<95% selectivity observed. [d]1.5 equiv. Ar'B(OH)$_2$ was used.

Sterically hindered chloroaryl triflates furnished the coupling products in good yields (**3av**-**3ax**). Pd/**L33** catalyst also demonstrated high Cl/OTf chemoselectivity toward the highly challenging tri-*ortho*-substituted biaryl synthesis, as with the first example in Suzuki-Miyaura coupling (**3ax**). Notably, we achieved catalyst loading as low as 0.05 mol% Pd. The challenging alkylboronic acids were also selectively coupled with 4-chloro-2,6-dimethylphenyl triflate, and 4-chlorophenyl triflate was coupled with methylboronic acid and *n*-butylboronic acid as the first chemoselective alkylation of C−Cl bonds in the presence of C−OTf bonds with good yields (**3ay**-**3ba**).

To further investigate the effectiveness of Pd/**L33** catalytic system, we attempted to lower the catalyst loading to the ppm level of Pd. This system effectively converted the substrates into corresponding products with excellent yields and chemoselectivity at 20-50 ppm Pd catalyst (Table 3). Remarkably, the catalyst loading reached up to 10 ppm Pd without a significant drop in catalytic activity (**3a**).

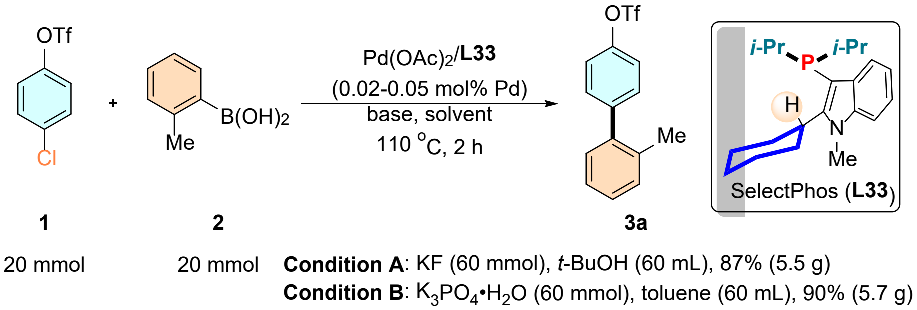
As expected, Pd/**L33** catalyzed the coupling of polyhalogenated aryl triflates with high Br/OTf and Br/Cl selectivities (Scheme 6). This highly chemoselective one-pot sequential method can offer a highly convenient method to access the novel phenylene triflates building block to construct structurally new PAHs for optoelectronic devices and materials.[16]

Scheme 6. Sequential functionalization of polyhalogenated aryl triflates



This reaction can also be directly scaled up 100 times to produce the coupling product without diminishing the yield and chemoselectivity. The use of $K_3PO_4{\cdot}H_2O$ and toluene, which is one of the most common conditions in the Suzuki-Miyaura coupling reaction, also works well to successfully synthesize product **3a** (Scheme 7).

Scheme 7. Large-scale chemoselective Suzuki reaction



In summary, we have designed and developed a conceptually new type of phosphine ligand with an alkyl group as the bottom ring for chemoselective coupling reactions. This type of ligand showed high chemoselectivity for Suzuki-Miyaura coupling of chloroaryl triflates toward a wide range of substrates, with an inversion of the common reactivity order of C−Cl > C−OTf in all cases. The excellent reactivity was also demonstrated, for the first time, by its scale-up ability and achieved the chemoselective reaction at parts per million levels of palladium catalyst.

ASSOCIATED CONTENT

Supporting Information

This material is available free of charge via the Internet at http://pubs.acs.org.

^{1}H, ^{13}C, ^{19}F, and ^{31}P NMR and HRMS spectra and characterization data of the compounds and crystallographic data of complex **C1**, and experimental and computational details (PDF)

X-ray crystal structure data for complex **C1** (CIF)

Accession Codes

CCDC 2074310 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Author

Chau Ming So – *State Key Laboratory of Chemical Biology and Drug Discovery and Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom,* *Kowloon, Hong Kong SAR, China; The Hong Kong Polytechnic University Shenzhen Research Institute, Shenzhen 518057, Guangdong Province, China*; orcid.org/0000-0001-6268-651X; Email: chau.ming.so@polyu.edu.hk

Authors

On Ying Yuen – *State Key Laboratory of Chemical Biology and Drug Discovery and Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong SAR, China*

Shan Shan Ng – *State Key Laboratory of Chemical Biology and Drug Discovery and Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong SAR, China*

Zicong Chen – *State Key Laboratory of Chemical Biology and Drug Discovery and Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong SAR, China*

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We would like to thank the National Natural Science Foundation of China (21972122), the Research Grants Council of Hong Kong, Early Career Scheme (ECS 25301819) and General

Research Fund (GRF 15300220), and the Science, Technology and Innovation Commission of Shenzhen Municipality (JCYJ20180306173843318) for financial support. We are grateful to Prof. Tamio Hayashi (NTHU) for the helpful discussion of this manuscript and Mr. Junyu Wu for preparing some of the polyhalogenated aryl triflates.

REFERENCES

---

(1) (a) Molnár, Á. *Palladium-Catalyzed Coupling Reactions: Practical Aspects and Future Development*; Wiley-VCH: Weinheim, 2013. (b) de Meijere, A.; Bräse, S.; Oestreich, M. *Metal-Catalyzed Cross-Coupling Reactions and More*, Vol. 1-3; Wiley-VCH: Weinheim, 2014. (c) Calacot, T. J. *New Trends in Cross-Coupling: Theory and Applications*; RSC: Cambridge, 2015. (d) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. Palladium-Catalyzed Cross-Coupling: A Historical Contextual Perspective to the 2010 Nobel Prize. *Angew. Chem. Int. Ed.* **2012**, *51*, 5062-5085. (e) Campeau, L.-C.; Hazari, N. Cross-Coupling and Related Reactions: Connecting Past Success to the Development of New Reactions for the Future. *Organometallics* **2019**, *38*, 3-35.

(2) (a) Nguyen, H. N.; Huang, X.; Buchwald, S. L. The First General Palladium Catalyst for the Suzuki-Miyaura and Carbonyl Enolate Coupling of Aryl Arenesulfonates. *J. Am. Chem. Soc.* **2003**, *125*, 11818-11819. (b) Zhang, L.; Wu, J. Palladium-Catalyzed Hiyama Cross-Couplings of Aryl Arenesulfonates with Arylsilanes. *J. Am. Chem. Soc.* **2008**, *130*, 12250-12251. (c) So, C. M.; Kwong, F. Y. Palladium-Catalyzed Cross-Coupling Reactions of Aryl Mesylates. *Chem. Soc. Rev.* **2011**, *40*, 4963-4972. (d) Chen, X.; Chen, Z.; So, C. M. Exploration of Aryl Phosphates in Palladium-Catalyzed Mono-α-arylation of Aryl and Heteroaryl Ketones. *J. Org. Chem.* **2019**, *84*, 6337-6346. (e) Chen, Z.; Chen, X.; So, C. M. Palladium-Catalyzed C(sp^2)-N Bond Cross-Coupling

---

with Triaryl Phosphates. *J. Org. Chem.* **2019**, *84*, 6366-6376. (f) Kamikawa, T.; Hayashi, T. Palladium Catalysts for Cross-Coupling of Ortho-Substituted Aryl Triflates with Grignard Reagents. *Synlett* **1997**, 163-164. (g) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. Highly Active Palladium Catalysts for Suzuki Coupling Reactions. *J. Am. Chem. Soc.* **1999**, *121*, 9550-9561. (h) Littke, A. F.; Fu, G. C. Palladium-Catalyzed Coupling Reactions of Aryl Chlorides. *Angew. Chem. Int. Ed.* **2002**, *41*, 4176-4211. (i) Riggleman, S.; DeShong, P. Application of Silicon-Based Cross-Coupling Technology to Triflates. *J. Org. Chem.* **2003**, *68*, 8106-8109.

(3) (a) Almond-Thynne, J.; Blakemore, D. C.; Pryde, D. C.; Spivey, A. C. Site-Selective Suzuki-Miyaura Coupling of Heteroaryl Halides – Understanding the Trends for Pharmaceutically Important Classes. *Chem. Sci.* **2017**, *8*, 40-62. (b) Fairlamb, I. J. S. Regioselective (Site-Selective) Functionalisation of Unsaturated Halogenated Nitrogen, Oxygen and Sulfur Heterocycles by Pd-Catalysed Cross-Couplings and Direct Arylation Processes. *Chem. Soc. Rev.* **2007**, *36*, 1036-1045. (c) Schröter, S.; Stock, C.; Bach, T. Regioselective Cross-Coupling Reactions of Multiple Halogenated Nitrogen-, Oxygen-, and Sulfur-Containing Heterocycles. *Tetrahedron* **2005**, *61*, 2245-2267. (d) Kalvet, I.; Magnin, G.; Schoenebeck, F. Rapid Room-Temperature, Chemoselective Csp^2–Csp^2 Coupling of Poly(pseudo)halogenated Arenes Enabled by Palladium(I) Catalysis in Air. *Angew. Chem. Int. Ed.* **2017**, *56*, 1581-1585. (e) Kalvet, I.; Sperger, T.; Scattolin, T.; Magnin, G.; Schoenebeck, F. Palladium(I) Dimer Enabled Extremely Rapid and Chemoselective Alkylation of Aryl Bromides over Triflates and Chlorides in Air. *Angew. Chem. Int. Ed.* **2017**, *56*, 7078-7082. (f) Kundu, G.; Sperger, T.; Rissanen, K.; Schoenebeck, F. A Next-Generation Air-Stable Palladium(I) Dimer Enables Olefin Migration and Selective C–C Coupling in Air. *Angew. Chem. Int. Ed.* **2020**, *59*, 21930-21934.

---

(4) (a) Littke, A. F.; Dai, C.; Fu, G. C. Versatile Catalysts for the Suzuki Cross-Coupling of Arylboronic Acids with Aryl and Vinyl Halides and Triflates under Mild Conditions. *J. Am. Chem. Soc.* **2000**, *122*, 4020-4028. (b) However, the use of other chloroaryl triflates or boronic acids only leads to poor yields and selectivity. For a reference, see: Keaveney, S. T.; Kundu, G.; Schoenebeck, F. Modular Functionalization of Arenes in a Triply Selective Sequence: Rapid C(sp^2) and C(sp^3) Coupling of C−Br, C−OTf, and C−Cl Bonds Enabled by a Single Palladium(I) Dimer. *Angew. Chem. Int. Ed.* **2018**, *57*, 12573-12577.

(5) Schoenebeck, F.; Houk, K. N. Ligand-Controlled Regioselectivity in Palladium-Catalyzed Cross Coupling Reactions. *J. Am. Chem. Soc.* **2010**, *132*, 2496-2497.

(6) Niemeyer, Z. L.; Milo, A.; Hickey, D. P.; Sigman, M. S. Parameterization of Phosphine Ligands Reveals Mechanistic Pathways and Predicts Reaction Outcomes. *Nat. Chem.* **2016**, *8*, 610-617.

(7) (a) Reeves, E. K.; Humke, J. N.; Neufeldt, S. R. N-Heterocyclic Carbene Ligand-Controlled Chemodivergent Suzuki-Miyaura Cross Coupling. *J. Org. Chem.* **2019**, *84*, 11799-11812. (b) For nickel-catalyzed chemoselective Suzuki-Miyaura reaction of chloroaryl tosylates, see: Entz, E. D.; Ryssell, J. E. A.; Hooker, L. V.; Neufeldt, S. R. Small Phosphine Ligands Enable Selective Oxidative Addition of Ar−O over Ar−Cl Bonds at Nickel(0). *J. Am. Chem. Soc.* **2020**, *142*, 15454-15463.

(8) (a) So, C. M.; Zhou, Z.; Lau, C. P.; Kwong, F. Y. Palladium-Catalyzed Amination of Aryl Mesylates. *Angew. Chem. Int. Ed.* **2008**, *47*, 6402-6406. (b) Fu, W. C.; So, C. M.; Chow, W. K.; Yuen, O. Y.; Kwong, F. Y. Design of an Indolylphosphine Ligand for Reductive Elimination-Demanding Monoarylation of Acetone Using Aryl Chlorides. *Org. Lett.* **2015**, *7*, 4612-4615. (c)

Lee, H. W.; So, C. M.; Yuen, O. Y.; Wong, W. T.; Kwong, F. Y. Palladium-Catalyzed Cross-Coupling of (Hetero)aryl or Alkenyl Sulfonates with Aryl Titanium as the Multi-functional Reagent. *Org. Chem. Front.* **2020**, *7*, 926-932.

(9) Bulky substituents generally promote reductive elimination and increase catalyst stability by preventing cyclometalation. For a reference, see: Surry, D. S.; Buchwald, S. L. Dialkylbiaryl Phosphines in Pd-Catalyzed Amination: A User's Guide. *Chem. Sci.* **2011**, *2*, 27-50.

(10) An initial attempt of preparation of the palladium oxidative addition complex with **L38** was not successful.

(11) (a) Brookhart, M.; Green, M. L. H.; Parkin, G. Agostic Interactions in Transition Metal Compounds. *PNAS* **2007**, *104*, 6908-6914. (b) Scherer, W.; Dunbar, A. C.; Barquera-Lozada, J. E.; Schmitz, D.; Eickerling, G.; Kratzert, D.; Stalke, D.; Lanza, A.; Macchi, P.; Casati, N. P. M.; Ebad-Allah, J.; Kuntscher, C. Anagostic Interactions under Pressure: Attractive or Repulsive? *Angew. Chem. Int. Ed.* **2015**, *54*, 2505-2509. (c) Lepetit, C.; Poater, J.; Alikhani, M. E.; Silvi, B.; Canac, Y.; Contreras-García, J.; Solà, M.; Chauvin, R. The Missing Entry in the Agostic–Anagostic Series: Rh(I)-η^1-C Interactions in P(CH)P Pincer Complexes. *Inorg. Chem.* **2015**, *54*, 2960-2969. (d) Sundquist, W. I.; Bancroft, D. P.; Lippard, S. J. Synthesis, Characterization, and Biological Activity of Cis-diammineplatinum(II) Complexes of the DNA Intercalators 9-Aminoacridine and Chloroquine. *J. Am. Chem. Soc.* **1990**, *112*, 1590-1596. (e) Taubmann, C.; Öfele, K.; Herdtweck, E.; Herrmann, W. A. Complexation of (5*H*)-Dibenzo[*a*,*d*]cyclohepten-5-ylidene to Palladium(II) via the Diazo Route and Evidence of C−H···Pd Interactions. *Organometallics* **2009**, *28*, 4254-4257.

(12) (a) Zhang, Y.; Lewis, J. C.; Bergman, R. G.; Ellman, J. A.; Oldfield, E. NMR Shifts, Orbitals, and M···H−X Bonding in d^8 Square Planar Metal Complexes. *Organometallics* **2006**, *25*, 3515-3519. (b) Braga, D.; Grepioni, F.; Tedesco, E.; Biradha, K.; Desiraju, G. R. Hydrogen Bonding in Organometallic Crystals. 6.† X−H---M Hydrogen Bonds and M---(H−X) Pseudo-Agostic Bonds. *Organometallics* **1997**, *16*, 1846-1856.

(13) Nielson, A. J.; Harrison, J. A.; Sajjad, M. A.; Schwerdtfeger, P. Electronic and Steric Manipulation of the Preagostic Interaction in Isoquinoline Compleses of Rh^{I}. *Eur. J. Inorg. Chem.* **2017**, 2255-2264.

(14) Cao, H.-J.; Zhao, Q.; Zhang, Q.-F.; Li, J.; Hamilton, E. J. M.; Zhang, J.; Wang, L.-S.; Chen, X. Catalyst Design Based on Agostic Interactions: Synthesis, Characterization, and Catalytic Activity of Bis(pyrazolyl)borate Copper Complexes. *Dalton Trans.* **2016**, *45*, 10194-10199.

(15) Surry, D. S.; Buchwald, S. L. Biaryl Phosphane Ligands in Palladium-Catalyzed Amination. *Angew. Chem. Int. Ed.* **2008**, *47*, 6338-6361.

(16) Uryu, M.; Hiraga, T.; Koga, Y.; Saito, Y.; Murakami, K.; Itami, K. Synthesis of Polybenzoacenes: Annulative Dimerization of Phenylene Triflate by Twofold C−H Activation. *Angew. Chem. Int. Ed.* **2020**, *59*, 6551-6554.

TOC