ORGANOMETALLICS

Article

Cite This: *Organometallics* XXXX, XXX, XXX−XXX

pubs.acs.org/Organometallics

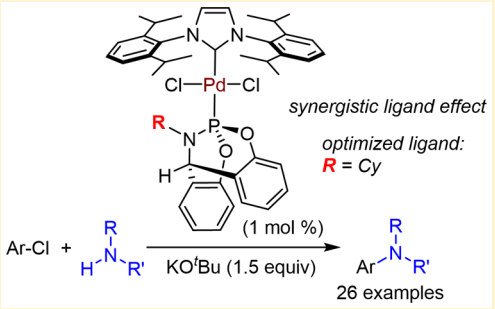
Synergistic Ligand Effect between N-Heterocyclic Carbene (NHC) and Bicyclic Phosphoramidite (Briphos) Ligands in Pd-Catalyzed Amination

Miji Kim, Taeil Shin, Ansoo Lee, and Hyunwoo Kim*

Department of Chemistry, Korea Advanced Institute of Science and Technology (KAIST), Daejeon 34141, Korea

Supporting Information

ABSTRACT: A synergistic ligand effect between NHC and phosphorus ligands in Pd-catalyzed Buchwald−Hartwig amination reactions was demonstrated with tunable π-acceptor bicyclic bridgehead phosphoramidite (briphos) ligands. The catalytic activity of NHC-Pd-**L** (**L** = phosphorus ligand) precatalysts depends on the electronic properties of **L**. A NHC-Pd-**L** catalyst with an *N*-cyclohexyl-substituted briphos ligand was found to be highly efficient. A series of C−N bond coupling reactions between primary or secondary amines and aryl chlorides were performed with high yields under mild reaction conditions.



INTRODUCTION

The catalytic performance of transition metals highly depends on the character of the ligands that bind to the central metal atoms. Thus, the investigation of ligand effects has been one of the major research topics in the field of transition-metal catalysis. In recent years, *N*-heterocyclic carbenes (NHC) have emerged as privileged ligands for transition-metal catalysis due to their unique electronic and steric properties.[1] The strong σ-donor property of NHCs is reported to facilitate the oxidative addition processes found to be rate determining in many transition-metal catalysis.[1,2] With this excellent ligand platform, there has been much effort to improve the catalytic performance of the NHC-based catalysts. In this context, the cooperative ligand effect between NHC and additive ligands is proposed to modulate the reactivity and selectivity of the transition-metal catalysts.[3] Organ and co-workers have introduced pyridine-enhanced precatalyst preparation stabilization and inhibition (PEPPSI) (Figure 1a).[4] A significant improvement in the catalytic performance has been achieved in Pd-PEPPSI-catalyzed cross-coupling reactions even at ambient temperature.[4,5] In addition to the pyridine ligands, other ligands with coordination atoms such as C, N, and P have been used to develop NHC-Pd^{II} precatalysts for cross-coupling reactions.[6]

Among several types of ligands, phosphorus ligands caught our attention because these classical ligands are suitable for the electronic and steric tuning of ligand properties as well as mechanistic investigation by ^{31}P NMR spectroscopy (Figure 1b). Herrmann and Cazin prepared NHC-Pd-**L** complexes (**L** = phosphines or phosphites), which are efficient precatalysts in several cross-coupling reactions including the Suzuki−Miyaura,[7] Mizoroki−Heck,[8] and Migita−Kosugi−Stille[8] couplings. In addition, we wanted to systematically investigate the cooperative ligand effect between NHC and phosphorus ligands in the same ligand platform. To perform this research, we used bicyclic bridgehead phosphoramidite (briphos) ligands, new types of tunable π-acceptor ligands (Figure 1c).[9] Here we demonstrate the cooperative ligand effect of

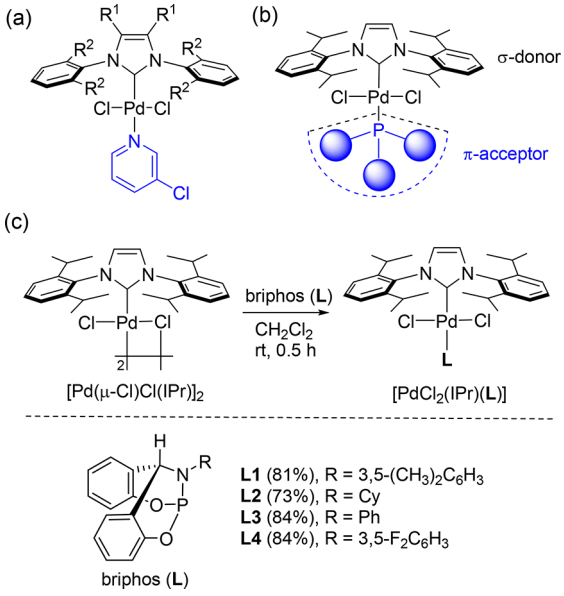


Figure 1. (a) Pd-PEPPSI precatalyst, (b) Pd complex with IPr and a phosphorus ligand, and (C) preparation of [PdCl$_2$(IPr)**L**] (**L** = briphos).

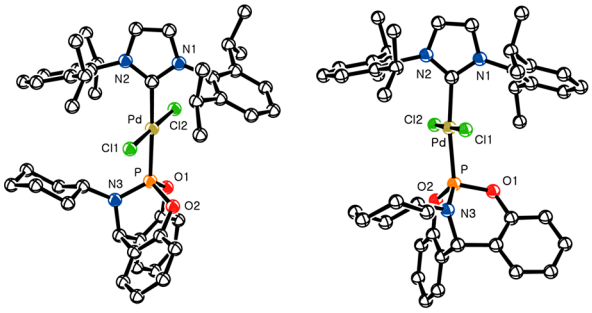
Received: June 15, 2018

DOI: 10.1021/acs.organomet.8b00413
Organometallics XXXX, XXX, XXX−XXX

NHC-Pd-briphos complexes and their applications to Buchwald−Hartwig amination reactions.

RESULTS AND DISCUSSION

Synthesis and Characterization of [$PdCl_2$(IPr)-(briphos)]. A series of NHC-Pd-briphos complexes were prepared from a reaction between $[Pd(\mu\text{-}Cl)Cl(IPr)]_2$ (IPr = 1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene) and briphos ligands with various substituents. According to the reported procedure[7b] for the preparation of $[PdCl_2(IPr)L]$ (**L** = PPh_3, $P(OR)_3$), $[PdCl_2(IPr)(briphos)]$ complexes were successfully prepared in 73−84% yields (Figure 1c). The structure of $[PdCl_2(IPr)(\mathbf{L2})]$ was determined by X-ray crystallographic analysis, as shown in Figure 2.[10] Two



Pd-1 **Pd-2**

Figure 2. ORTEP representation of $[PdCl_2(IPr)(\mathbf{L2})]$ with 50% probability ellipsoids. The two conformationally different structures **Pd-1** and **Pd-2** were found in the unit cell. Hydrogen atoms are omitted for clarity.

conformationally different structures, **Pd-1** and **Pd-2**, were identified, and their structural parameters are given in Table 1.

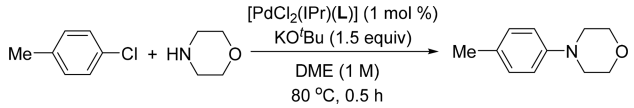
Table 1. $\%V_{bur}$ Values and Selected Bond Lengths (Å) and Bond Angles (deg) for Pd-1 and Pd-2

	Pd-1	Pd-2
$\%V_{bur}$ of IPr	37.0	36.2
$\%V_{bur}$ of **L2**	24.2	23.6
Φ_1	86.3	75.3
Φ_2	74.7	83.0
$90° - \Phi_{av}$	9.5	10.9
Pd−C	2.020(3)	2.021(3)
Pd−P	2.2667(8)	2.2655(8)
Pd−Cl(1)	2.2887(8)	2.2898(8)
Pd−Cl(2)	2.2961(8)	2.2939(8)
C−Pd−P	176.58(8)	172.36(9)
C−Pd−Cl(1)	90.33(8)	89.90(8)
C−Pd−Cl(2)	89.35(8)	89.06(8)
P−Pd−Cl(1)	86.36(3)	89.17(3)
P−Pd−Cl(2)	93.98(3)	91.82(3)
Cl(1)−Pd−Cl(2)	178.50(3)	178.90(3)

Consistent with the previous structures, IPr and briphos ligands are coordinated to the Pd center in a trans fashion. However, the C−Pd−P bonds are slightly bent: the C−Pd−P bond angles in **Pd-1** and **Pd-2** were found to be 176.58(8) and 172.36(9)°, respectively. These bent structures may be attributed to the highly rigid and unsymmetrical nature of the briphos ligand. Indeed, the briphos ligand **L2** enables one of the 2,6-diisopropylphenyl groups in IPr to rotate by about 15° from an orthogonal orientation relative to the NHC plane (Φ_2 = 74.7° for **Pd-1** and Φ_1 = 75.3° for **Pd-2** in Table 1). The rotation of the NHC N substitutents results in a significant increase in the $\%V_{bur}$ value (37.0 for **Pd-1** and 36.2 for **Pd-2** in Table 1) in comparison with the calculated $\%V_{bur}$ value of IPr (31.3 for $[IrCl(IPr)(CO)_2]$). Cazin and co-workers reported that the $[PdCl_2(IPr)\{P(OMe)_3\}]$ precatalyst with the highest $\%V_{bur}$ value of 36.3 exhibited an excellent reactivity for the Suzuki−Miyaura reaction among several $[PdCl_2(IPr)\{P(OR)_3\}]$ precatalysts.[7b] Thus, $[PdCl_2(IPr)(briphos)]$ complexes have some beneficial structural features that make them effective cross-coupling catalytsts.

Ligand Effect for C−N Bond Coupling Reactions. To investigate the synergistic ligand effect between IPr and briphos ligands, we carried out a coupling reaction between 4-chlorotoluene and morpholine[11] with several $[PdCl_2(IPr)(\mathbf{L})]$ (**L** = PCy_3, PPh_3, $P(OPh)_3$, briphos **L1**−**L4**, 3-chloropyridine (3-ClPy)) and $[PdCl(IPr)(\eta^3\text{-cinnamyl})]$ complexes (Table 2). The coupling reactions were performed at 80 °C for 30 min

Table 2. Catalyst Screening with the $[PdCl_2(IPr)(L)]$ Complexes[a]



entry	L	R in briphos	yield (%)[b]
1	PCy_3		3
2	PPh_3		28
3	$P(OPh)_3$		66
4	**L1**	3,5-$(CH_3)_2C_6H_3$	99
5	**L2**	Cy	99
6	**L3**	Ph	99
7	**L4**	3,5-$F_2C_6H_3$	97
8	3-ClPy		99
9	η^3-cinnamyl[c]		83

[a]Conditions unless specified otherwise: 4-chlorotoluene (0.250 mmol), morpholine (0.275 mmol), KO^{t}Bu (0.375 mmol), and $[PdCl_2(IPr)(\mathbf{L})]$ (1 mol %) were stirred in 1,2-dimethoxyethane (DME, 0.25 mL) at 80 °C for 0.5 h. [b]Yield of the isolated product. [c]$[PdCl(IPr)(\mathbf{L})]$.

in the presence of 1 mol % of the Pd complex and 1.5 equiv of KO^{t}Bu. In the cases where **L** is PCy_3, PPh_3, or $P(OPh)_3$, the reaction with $P(OPh)_3$ had a better conversion in comparison to that with PCy_3 or PPh_3, indicating that a more π accepting phosphorus ligand provides a beneficial catalytic activity (entries 1−3, Table 2). Indeed, such a favorable ligand effect between the σ-donating NHC ligands and π-accepting phosphorus ligands has also been found in several cross-coupling reactions such as Suzuki coupling,[12] a coupling between alkenes and aldehydes,[13] and a coupling of aryl diarylboronic acids or anhydrides with aryl halides.[14] Because we developed the briphos ligands as tunable π-accepting phosphorus ligands, $[PdCl_2(IPr)(briphos)]$ complexes were tested for Buchwald−Hartwig amination reactions. As shown in Table 2, all of the NHC-Pd-briphos complexes showed an excellent yield (>97%) and were found to be as efficient as a PEPPSI catalyst (entries 4−8, Table 2). The complex $[PdCl(IPr)(\eta^3\text{-cinnamyl})]$ showed a reduced yield of 83% (entry 9, Table 2). To closely compare the ligand effects, we

DOI: 10.1021/acs.organomet.8b00413
Organometallics XXXX, XXX, XXX−XXX

then did the coupling reaction with 0.1 mol % of Pd precatalysts. As shown in Figure 3, the experimental results

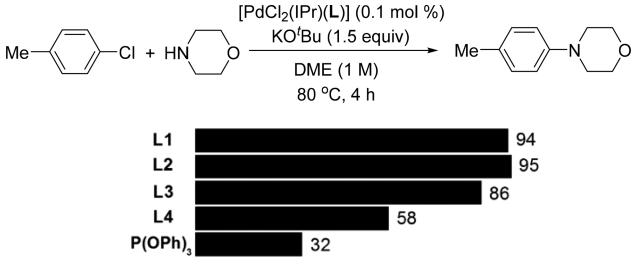


Figure 3. Conversion for the C−N bond formation with a 0.1 mol % catalyst loading (isolated yields are given).

indicated that the briphos ligands substituted with the 3,5-dimethylphenyl (**L1**) and cyclohexyl (**L2**) groups were slightly more efficient than **L3**, **L4**, or $P(OPh)_3$. When 0.05 mol % of Pd precatalysts were used, **L2** was found to be more efficient than the other briphos ligands **L1**, **L3**, and **L4** because the conversions with **L1**−**L4** were measured to be 26, 58, 21, and 29%, respectively (Figure S1 in the Supporting Information). According to the literature and our previous studies on the electronic properties of ligands,[9e,15] the order of the π-accepting ligand property can be given as **L4** > **L3** > **L2** = $P(OPh)_3$ > **L1** > PPh_3 > PCy_3. Thus, efficient NHC-Pd-**L** precatalysts for Buchwald−Hartwig amination reactions can be developed by optimizing the π-accepting ability of the phosphorus ligands. Moreover, additional ligand properties such as a steric effect related to the $\%V_{bur}$ value can be considered because **L2** ($\%V_{bur}$ = 36.2, 37.0)[16] is more efficient than $P(OPh)_3$ ($\%V_{bur}$ = 34.3),[7b] albeit with the same π-accepting property.

Our experimental results show a synergistic ligand effect between NHC and phosphorus ligands in the NHC-Pd-**L** complexes. To understand the role of the additional ligand **L**, we monitored a stoichiometric reaction by following the $^{31}P\{^1H\}$ NMR spectra. When [$PdCl_2$(IPr)(briphos)] was mixed with the starting materials at ambient temperature, the ^{31}P NMR spectra showed that the briphos ligand was completely dissociated from the complex, indicating the generation of the NHC-Pd(0) complex which has been proposed as the active catalytic species.[1−3] Although the synthesis of the NHC-Pd^0-PPh_3 complex has been reported,[17] we were unable to synthesize the NHC-Pd^0-briphos complex probably due to its instability. We then proposed that the binding ability of the phosphorus ligands may be related to the catalytic activity because the easily removable ligand would provide the active NHC-Pd^0 species more efficiently. Thus, we did a competition experiment to determine the relative binding ability of the phosphorus ligands. Our competition experiment showed that the order of the ligand binding ability was found to be PPh_3 > **L2** > $P(OPh)_3$ > **L3** > **L1** = **L4**. Because **L1** and **L2** were found to be highly efficient, the binding strength is not directly correlated to the catalyst activity (see the Supporting Information). Thus, the electronic property of the ligand, not its binding ability, is the major factor that determines the catalytic activity of the NHC-Pd-P precatalysts.

On the basis of our experimental results, we propose a catalytic cycle, as shown in Figure 4. Closely related to the Organ model,[18] the NHC-Pd^0 species generated from the NHC-Pd-**L** precursors is the active catalyst, which reacts with

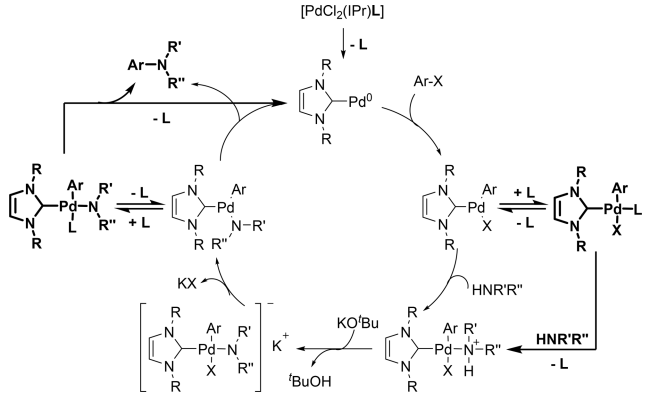


Figure 4. Proposed catalytic cycle.

aryl chloride to form a Pd(II) intermediate. Then, subsequent processes such as the coordination of amine, deprotonation, and reductive elimination occur to give the desired cross-coupled product and NHC-Pd^0 catalyst. In this catalytic cycle, we propose that phosphorus ligand **L** can associate with the Pd intermediates and dissociate to complete the catalytic reaction. The role of the briphos ligands would be the stabilization of the Pd intermediates to maintain the catalytic activity of the Pd catalyst.

Reaction Scope for the C−N Bond Coupling Reactions. Our results of the catalyst screening suggest that [$PdCl_2$(IPr)(**L2**)] is the most efficient among the NHC-Pd-**L** catalysts. With this highly efficient catalyst [$PdCl_2$(IPr)(**L2**)], we have expanded the reaction scope to achieve several types of C−N bond formations. Under our optimized reaction conditions, 1.1 equiv of primary or secondary amine, 1.0 equiv of aryl chloride, and 1 mol % of [$PdCl_2$(IPr)(**L2**)] were mixed in 1,2-dimethoxyethane (DME, 1 M) at 80 °C for 1 h. As shown in Figure 5, most of the reactions proceeded to completion to afford the desired coupled products in good yields. In the case of morpholine (**1**−**11**), aryl chlorides with various substituents such as methyl, methoxy, trifuloromethyl, and cyano groups were used to provide the desired *N*-aryl morpholines in good yields (87−99%) except for 2-(fluorophenyl)morpholine (**11**, 53% yield). Other secondary amines such as *N*-methylpiperazine, pyrrolidine, piperidine, and diisooctylamine were successfully coupled with aryl chlorides in good to excellent yields (80−96%) (**12**−**17**). In addition, primary alkyl amines (**18** and **19**), 2,4,6-trimethylaniline (**20**−**22**), and 2,6-diisopropylaniline (**23**) gave the desired products in good yields (76−99%). Particularly, more challenging reactions using aniline (**24** and **25**) and 4-fluoroaniline (**26**) with aryl chlorides[19] proceeded with high yields, although an increased reaction time of 24 h and temperature of 100 °C were required.

We have demonstrated that π-acceptor briphos ligands can be combined with the NHC ligand in Pd-catalyzed Buchwald−Hartwig amination reactions to develop highly efficient catalysts. These types of synergistic ligand effects can be applied to other Pd-catalyzed cross coupling reactions. As shown in Figure 6, we compared the catalytic activities of the NHC-Pd-**L** complexes in both the Buchwald−Hartwig reaction and Suzuki−Miyaura reaction. In both reactions, 4-chlorotoluene was used as the substrate. Interestingly, the catalyst [$PdCl_2$(IPr)(**L**)] showed quite different reaction outcomes. While the catalyst [$PdCl_2$(IPr)(**L1**)] was highly efficient in both reactions, the catalyst [$PdCl_2$(IPr)(**L2**)] or [$PdCl_2$(IPr)-

DOI: 10.1021/acs.organomet.8b00413
Organometallics XXXX, XXX, XXX−XXX

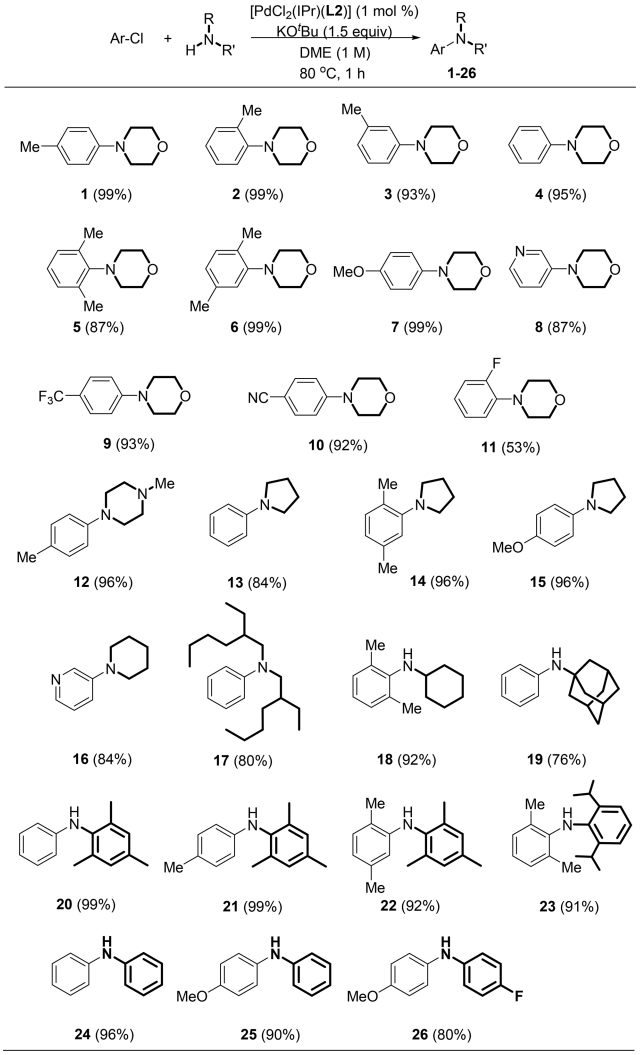


Figure 5. Scope for the $[PdCl_2(IPr)(\mathbf{L2})]$-catalyzed C−N bond formation. Conditions: aryl chloride (0.250 mmol), amine (0.275 mmol), KO^{t}Bu (0.375 mmol), and $[PdCl_2(IPr)(\mathbf{L2})]$ (1 mol %) were stirred in DME (0.250 mL) at 80 °C for 1 h. For the synthesis of **11** and **24**−**26**, the reaction was performed in 1,4-dioxane (0.250 mL) at 100 °C for 24 h. Isolated yields are shown.

$\{P(OPh)_3\}]$ was efficient only in the Buchwald−Hartwig amination or Suzuki−Miyaura reaction, respectively.

CONCLUSIONS

We have demonstrated a synergistic ligand effect between NHC and briphos ligands in Pd-catalyzed Buchwald−Hartwig amination reactions. In our reaction screening, the optimal π-accepting ligand **L2** was found to be the most efficient among the phosphorus ligands tested. The catalytic performance of the NHC-Pd-**L** precatalysts for Buchwald−Hartwig amination reactions depends on the steric and electronic properties of the phosphorus ligand (**L**), not on the binding ability of the ligand. We have shown that $[PdCl_2(IPr)(\mathbf{L2})]$ is a highly efficient precatalyst for the coupling of primary or secondary amines with aryl chlorides with high yields under mild reaction conditions. Moreover, $[PdCl_2(IPr)(\mathbf{L1})]$ is found to be only effective for both C−N and C−C bond forming cross couplings. The reaction mechanism was proposed on the basis of in situ $^{31}P\{^1H\}$ NMR analysis and competition experiments.

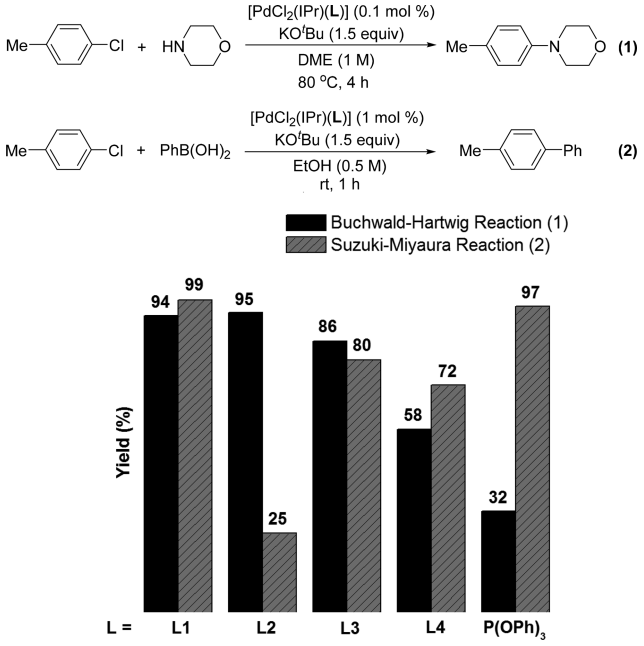


Figure 6. Reactivity comparison of the $[PdCl_2(IPr)(\mathbf{L})]$ complexes. Suzuki−Miyaura reaction conditions: 4-chlorotoluene (0.250 mmol), phenylboronic acid (0.262 mmol), KO^{t}Bu (0.375 mmol), and $[PdCl_2(IPr)(\mathbf{L})]$ (1 mol %) were stirred in ethanol (EtOH, 0.500 mL) at room temperature for 1 h. The GC yields were calculated from the averages of three runs.

The briphos ligand is an excellent ligand platform to systematically investigate the synergistic ligand effect with NHC ligand because the steric and electronic properties of briphos can be readily modified and the reaction intermediates can be identified by $^{31}P\{^1H\}$ NMR analysis. The concept of the synergistic ligand effect may be applied to transition-metal-catalyzed reactions, and thus briphos and NHC can be a useful combination to develop highly efficient transition-metal catalysts.

EXPERIMENTAL SECTION

General Information. Commercially available compounds were used without further purification or drying. The ^1H NMR (400 MHz), ^{13}C NMR (100 MHz), ^{19}F NMR (376 MHz), and ^{31}P NMR (162 MHz) spectra were recorded on a Bruker Ascend 400 or a Bruker Advance III HD spectrometer. The high-resolution mass spectra (EA) were obtained on a Thermo Scientific FLASH 2000 series. GC analysis was performed on an Agilent 7890A instrument using an HP-5 column (length 30 m, diameter 0.320 mm, film 0.25 μm).

Procedure for Synthesis of $[PdCl_2(IPr)\{briphos(R)\}]$. To a stirred solution of $[Pd(\mu\text{-}Cl)Cl(IPr)]_2$[20] (0.29 mmol) in CH_2Cl_2 (6 mL) was added briphos(R)[9] (0.58 mmol). The resulting solution was stirred for 30 min at room temperature under a nitrogen atmosphere and then concentrated in vacuo. Addition of pentane led to a precipitate, which was filtered and dried under vacuum to afford the desired product as a pale yellow powder (73−84%).

*$[PdCl_2(IPr)(\mathbf{L1})]$, **L1** = briphos(3,5-$(CH_3)_2C_6H_3$).* Pale yellow powder (81% yield). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.46 (m, 2H), 7.26 (m, 4H), 7.11 (m, 2H), 7.00 (m, 6H), 6.90 (m, 2H), 6.63 (m, 1H), 6.55 (m, 2H), 5.15 (d, J = 8.6 Hz, 1H), 3.03 (m, 4H), 2.04 (s, 6H), 1.32 (d, J = 6.6 Hz, 12H), 1.05 (d, J = 6.9 Hz, 12H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 169.2, 166.3, 149.8, 149.7, 146.6, 142.2, 142.1, 138.5, 135.0, 130.2, 129.1, 128.4, 127.0, 126.9, 126.6, 125.2, 125.1, 124.8, 124.7, 123.9, 123.2, 119.4, 119.3, 61.7, 28.7, 26.4, 23.2, 21.4. $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ (ppm) 81.0. Anal.

DOI: 10.1021/acs.organomet.8b00413
Organometallics XXXX, XXX, XXX−XXX

Calcd for $C_{48}H_{54}Cl_2N_3O_2PPd$: C, 63.13; H, 5.96; N, 4.60. Found: C, 62.89; H, 6.03; N, 4.44.

*[PdCl$_2$(IPr)(**L2**)]*, ***L2*** = *briphos(Cy)*. Pale yellow powder (73% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.49 (m, 2H), 7.36 (m, 4H), 7.10 (m, 2H), 7.05 (m, 4H), 6.89 (m, 4H), 4.99 (d, J = 9.7 Hz, 1H), 3.52 (m, 1H), 3.16 (m, 4H), 1.48−1.39 (m, 5H), 1.45 (d, J = 6.7 Hz, 12H), 1.16−1.07 (m, 2H), 1.12 (d, J = 6.9 Hz, 12H), 0.87 (m, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 170.1, 167.2, 150.5, 150.4, 146.8, 135.3, 130.2, 128.8, 128.2, 128.1, 126.0, 124.7, 124.7, 124.2, 123.0, 119.4, 119.3, 58.1, 58.0, 51.7, 32.4, 32.3, 28.8, 26.4, 25.3, 23.4. ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ (ppm) 87.3. Anal. Calcd for $C_{46}H_{56}Cl_2N_3O_2PPd$: C, 61.99; H, 6.33; N, 4.71. Found: C, 61.63; H, 6.26; N, 4.59.

*[PdCl$_2$(IPr)(**L3**)]*, ***L3*** = *briphos(Ph)*. Pale yellow powder (84% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.54 (m, 2H), 7.34 (m, 4H), 7.14−6.81 (m, 15H), 5.39 (d, J = 8.3 Hz, 1H), 3.07 (m, 4H), 1.33 (d, J = 6.6 Hz, 12H), 1.06 (d, J = 6.9 Hz, 12H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 168.9, 166.0, 149.9, 149.8, 146.8, 142.7, 142.6, 135.2, 130.2, 129.2, 129.2, 127.0, 126.9, 126.4, 125.0, 124.9, 124.8, 124.7, 124.6, 124.2, 123.5, 119.4, 119.4, 60.5, 28.7, 26.4, 23.3. ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ (ppm) 80.8. Anal. Calcd for $C_{46}H_{50}Cl_2N_3O_2PPd$: C, 62.41; H, 5.69; N, 4.75. Found: C, 62.13; H, 5.56; N, 4.58.

*[PdCl$_2$(IPr)(**L4**)]*, ***L4*** = *briphos(3,5-F$_2$C$_6$H$_3$)*. Pale yellow powder (84% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.49 (m, 2H), 7.31 (m, 4H), 7.15 (m, 2H), 7.06−6.93 (m, 8H), 6.55 (m, 2H), 6.44 (m, 1H), 5.26 (d, J = 7.8 Hz, 1H), 3.05 (m, 4H), 1.37 (d, J = 6.6 Hz, 12H), 1.08 (d, J = 6.9 Hz, 12H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 168.2, 165.3, 163.8, 161.5, 161.3, 149.6, 149.4, 146.5, 145.2, 134.8, 130.3, 129.5, 126.5, 126.3, 126.2, 124.9, 124.8, 124.0, 123.8, 119.5, 119.4, 110.0, 109.9, 109.7, 102.1, 101.9, 61.3, 28.7, 26.4, 23.2. ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ (ppm) 80.0. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ (ppm) −107.5. Anal. Calcd for $C_{46}H_{48}Cl_2F_2N_3O_2PPd$: C, 59.98; H, 5.25; N, 4.56. Found: C, 59.78; H, 5.38; N, 4.38.

General Procedure for the Amination of Aryl Chlorides. In a nitrogen-filled glovebox, a mixture of [PdCl$_2$(IPr)(**L2**)] (0.0025 mmol, 1 mol %), aryl chloride (0.250 mmol), and 1,2-dimethoxyethane (DME, 0.250 mL) was placed in a screw-capped glass tube containing a magnetic stirring bar. After the solution was stirred for 5 min, amine (0.275 mmol) and KO^{t}Bu (0.375 mmol) were added successively. The tube was sealed and removed from the glovebox. The resulting mixture was stirred at 80 °C for 1 h. After the mixture was cooled to room temperature, the volatiles were evaporated under reduced pressure. Purification by flash column chromatography on silica gel with diethyl ether/pentane (1/50 to 1/10) as eluent gave the desired products (**1**−**26**). For the synthesis of **11** and **24**−**26**, 1,4-dioxane was used as the solvent and the mixture was stirred at 100 °C for 24 h. Compounds **1**−**26** have all been reported (see the Supporting Information).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.8b00413.

Experimental and spectroscopic data and crystallographic details (PDF)

Accession Codes

CCDC 1539245 contains the supplementary crystallographic data for this paper. These 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

*E-mail for H.K.: hwkim@kaist.edu.

ORCID

Hyunwoo Kim: 0000-0001-5030-9610

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors are grateful for the financial support provided by the C1 Gas Refinery Program (2016M3D3A1A01913256) and the National Research Foundation of Korea (2017R1A2B4002650). The authors thank Dr. Alan J. Lough (University of Toronto) for his X-ray analysis.

■ REFERENCES

(1) For selected reviews, see: (a) Zhao, D.; Candish, L.; Paul, D.; Glorius, F. N-Heterocyclic Carbenes in Asymmetric Hydrogenation. *ACS Catal.* **2016**, *6*, 5978−5988. (b) Clavier, H.; Nolan, S. P. Percent Buried Volume for Phosphine and N-heterocyclic Carbene Ligands: Steric Properties in Organometallic Chemistry. *Chem. Commun.* **2010**, *46*, 841−861. (c) Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. Palladium Complexes of N-Heterocyclic Carbenes as Catalysts for Cross-Coupling Reactions—A Synthetic Chemists Perspective. *Angew. Chem., Int. Ed.* **2007**, *46*, 2768−2813.

(2) (a) Szilvási, T.; Veszprémi, T. Internal Catalytic Effect of Bulky NHC Ligands in Suzuki−Miyaura Cross-Coupling Reaction. *ACS Catal.* **2013**, *3*, 1984−1991. (b) Lewis, A. K. de K.; Caddick, S.; Cloke, F. G. N.; Billingham, N. C.; Hitchcock, P. B.; Leonard, J. Synthetic, Structural, and Mechanistic Studies on the Oxidative Addition of Aromatic Chlorides to a Palladium (N-Heterocyclic Carbene) Complex: Relevance to Catalytic Amination. *J. Am. Chem. Soc.* **2003**, *125*, 10066−10073.

(3) (a) Takeda, Y.; Ikeda, Y.; Kuroda, A.; Tanaka, S.; Minakata, S. Pd/NHC-Catalyzed Enantiospecific and Regioselective Suzuki−Miyaura Arylation of 2-Arylaziridines: Synthesis of Enantioenriched 2-Arylphenethylamine Derivatives. *J. Am. Chem. Soc.* **2014**, *136*, 8544−8547. (b) Pompeo, M.; Farmer, J. L.; Froese, R. D. J.; Organ, M. G. Room-Temperature Amination of Deactivated Aniline and Aryl Halide Partners with Carbonate Base Using a Pd-PEPPSI-IPent^{Cl}-o-Picoline Catalyst. *Angew. Chem., Int. Ed.* **2014**, *53*, 3223−3226. (c) Di Giuseppe, A.; Castarlenas, R.; Pérez-Torrente, J. J.; Crucianelli, M.; Polo, V.; Sancho, R.; Lahoz, F. J.; Oro, L. A. Ligand-Controlled Regioselectivity in the Hydrothiolation of Alkynes by Rhodium N-Heterocyclic Carbene Catalysts. *J. Am. Chem. Soc.* **2012**, *134*, 8171−8183. (d) Marion, N.; Nolan, S. P. Well-Defined N-Heterocyclic Carbenes-Palladium(II) Precatalysts for Cross-Coupling Reactions. *Acc. Chem. Res.* **2008**, *41*, 1440−1449.

(4) (a) Froese, R. D. J.; Lombardi, C.; Pompeo, M.; Rucker, R. P.; Organ, M. G. Designing Pd−N-Heterocyclic Carbene Complexes for High Reactivity and Selectivity for Cross-Coupling Applications. *Acc. Chem. Res.* **2017**, *50*, 2244−2253. (b) Valente, C.; Çalimsiz, S.; Hoi, K. H.; Mallik, D.; Sayah, M.; Organ, M. G. The Development of Bulky Palladium NHC Complexes for the Most-Challenging Cross-Coupling Reactions. *Angew. Chem., Int. Ed.* **2012**, *51*, 3314−3332.

(5) Atwater, B.; Chandrasoma, N.; Mitchell, D.; Rodriguez, M. J.; Pompeo, M.; Froese, R. D. J.; Organ, M. G. The Selective Cross-Coupling of Secondary Alkyl Zinc Reagents to Five-Membered-Ring Heterocycles Using Pd-PEPPSI-IHept^{Cl}. *Angew. Chem.* **2015**, *127*, 9638−9642.

(6) For recent examples, see: (a) Balcells, D.; Nova, A. Designing Pd and Ni Catalysts for Cross-Coupling Reactions by Minimizing Off-Cycle Species. *ACS Catal.* **2018**, *8*, 3499−3515. (b) Yin, S.-C.; Zhou, Q.; Zhao, X.-Y.; Shao, L.-X. N-Heterocyclic Carbene-Palladium(II)-1-Methylimidazole Complex Catalyzed Direct C−H Bond Arylation of Benzo[b]furans with Aryl Chlorides. *J. Org. Chem.* **2015**, *80*, 8916−

DOI: 10.1021/acs.organomet.8b00413
Organometallics XXXX, XXX, XXX−XXX

8921. (c) Arnold, P. L.; Sanford, M. S.; Pearson, S. M. Chelating N-Heterocyclic Carbene Alkoxide as a Supporting Ligand for $Pd^{II/IV}$ C-H Bond Functionalization Catalysis. *J. Am. Chem. Soc.* **2009**, *131*, 13912−13913.

(7) (a) Schmid, T. E.; Jones, D. C.; Songis, O.; Diebolt, O.; Furst, M. R. L.; Slawin, A. M. Z.; Cazin, C. S. J. Mixed Phosphine/N-Heterocyclic Carbene Palladium Complexes: Synthesis, Characterization and Catalytic Use in Aqueous Suzuki−Miyaura Reactions. *Dalton Trans* **2013**, *42*, 7345−7353. (b) Diebolt, O.; Jurcik, V.; Correa da Costa, R.; Braunstein, P.; Cavallo, L.; Nolan, S. P.; Slawin, A. M. Z.; Cazin, C. S. J. Mixed Phosphite/N-Heterocyclic Carbene Complexes: Synthesis, Characterization and Catalytic Studies. *Organometallics* **2010**, *29*, 1443−2450.

(8) Herrmann, W. A.; Böhm, V. P. W.; Gstöttmayr, C. W. K.; Grosche, M.; Reisinger, C.-P.; Weskamp, T. Synthesis, structure and catalytic application of palladium(II) complexes bearing N-heterocyclic carbenes and phosphines. *J. Organomet. Chem.* **2001**, *617−618*, 616−628.

(9) (a) Jung, H.; Lee, A.; Kim, J.; Kim, H.; Baik, M.-H. Regiodivergent Conjugate Addition Controlled by Rhodium(I) and Palladium(II) Catalysts: A Combined Computational and Experimental Study. *Adv. Synth. Catal.* **2017**, *359*, 3160−3175. (b) Lee, A.; Kim, H. Chiral Bicyclic Bridgehead Phosphoramidite (Briphos) Ligands for Asymmetric Rhodium-Catalyzed 1,2- and 1,4-Addition. *J. Org. Chem.* **2016**, *81*, 3520−3527. (c) Kang, K.; Kim, J.; Lee, A.; Kim, W. Y.; Kim, H. Palladium-Catalyzed Dehydrative Cross-Coupling of Allylic Alcohols and N-Heterocycles Promoted by a Bicyclic Bridgehead Phosphoramidite Ligand and an Acid Additive. *Org. Lett.* **2016**, *18*, 616−619. (d) Lee, A.; Kim, H. Rhodium-Catalyzed Asymmetric 1,4-Addition of *α,β,*-Unsaturated Imino Esters Using Chiral Bicyclic Bridgehead Phosphoramidite Ligands. *J. Am. Chem. Soc.* **2015**, *137*, 11250−11253. (e) Lee, A.; Ahn, S.; Kang, K.; Seo, M.-S.; Kim, Y.; Kim, W. Y.; Kim, H. Bicyclic Bridgehead Phosphoramidite (Briphos) Ligands with Tunable *π*-Acceptor Ability and Catalytic Activity in the Rhodium-Catalyzed Conjugate Additions. *Org. Lett.* **2014**, *16*, 5490−5493.

(10) CCDC 1539245 contains the supplementary crystallographic data. See the Supporting Information for X-ray data details.

(11) Chartoire, A.; Frogneux, X.; Boreux, A.; Slawin, A. M. Z.; Nolan, S. P. Pd(IPr*)(3-Cl-pyridinyl)Cl_2]: A Novel and Efficient PEPPSI Precatalyst. *Organometallics* **2012**, *31*, 6947−6951.

(12) Ke, H.; Chen, X.; Zou, G. N-Heterocyclic carbene/phosphite synergistically assisted Pd/C-catalyzed Suzuki coupling of aryl chlorides. *Appl. Organomet. Chem.* **2014**, *28*, 54−60.

(13) Ho, C.-Y.; Jamison, T. F. Highly Selective Coupling of Alkenes and Aldehydes Catalyzed by [Ni(NHC){$P(OPh)_3$}]: Synergy between a Strong *σ* Donor and a Strong *π* Acceptor. *Angew. Chem., Int. Ed.* **2007**, *46*, 782−785.

(14) Chen, X.; Ke, H.; Chen, Y.; Guan, C.; Zou, G. Cross-Coupling of Diarylborinic Acids and Anhydrides with Aryl-halides Catalyzed by a Phosphite/N-Heterocyclic Carbene Co-supported Palladium Catalyst System. *J. Org. Chem.* **2012**, *77*, 7572−7578.

(15) Tolman, C. A. Steric Effects of Phosphorus Ligands in Organometallic Chemistry and Homogeneous Catalysis. *Chem. Rev.* **1977**, *77*, 313−348.

(16) %V_{bur} values of Pd-**1** and Pd-**2** were calculated.

(17) Henwood, A. F.; Lesieur, M.; Bansal, A. K.; Lemaur, V.; Beljonne, D.; Thompson, D. G.; Graham, D.; Slawin, A. M. Z.; Samuel, I. D. W.; Cazin, C. S. J.; Zysman-Colman, E. Palladium(0) NHC Complexes: a New Avenue to Highly Efficient Phosphorescence. *Chem. Sci.* **2015**, *6*, 3248−3261. (b) Fantasia, S.; Nolan, S. P. A General Synthetic Route to Mixed NHC−Phosphane Palladium(0) Complexes (NHC = N-Heterocyclic Carbene). *Chem. - Eur. J.* **2008**, *14*, 6987−6993.

(18) O'Brien, C. J.; Kantchev, E. A. B.; Valente, C.; Hadei, N.; Chass, G. A.; Lough, A.; Hopkinson, A. C.; Organ, M. G. Easily Prepared Air- and Moisture-Stable Pd−NHC (NHC = N-Heterocyclic Carbene) Complexes: A Reliable, User-Friendly, Highly Active Palladium Precatalyst for the Suzuki−Miyaura Reaction. *Chem. - Eur. J.* **2006**, *12*, 4743−4748.

(19) (a) Bastug, G.; Nolan, S. P. [Pd(IPr*^{OMe})(cin)Cl] (cin = Cinnamyl): A Versatile Catalyst for C−N and C−C Bond Formation. *Organometallics* **2014**, *33*, 1253−1258. (b) Fors, B. P.; Krattiger, P.; Strieter, E.; Buchwald, S. L. Water-Mediated Catalyst Preactivation: An Efficient Protocol for C−N Cross-Coupling Reactions. *Org. Lett.* **2008**, *10*, 3505−3508.

(20) (a) Furst, M. R. L.; Cazin, C. S. J. Copper N-Heterocyclic Carbene (NHC) Complexes as Carbene Transfer Reagents. *Chem. Commun.* **2010**, *46*, 6924−6925. (b) Jensen, D. R.; Sigman, M. S. Palladium Catalysts for Aerobic Oxidative Kinetic Resolution of Secondary Alcohols Based on Mechanistic Insight. *Org. Lett.* **2003**, *5*, 63−65.

DOI: 10.1021/acs.organomet.8b00413
Organometallics XXXX, XXX, XXX−XXX