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Influence of Biaryl Phosphine Structure on C−N and C−C Bond Formation

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Abstract: In order to understand how electronic and other structural characteristics of biphenyl phosphine ligands affect Pd-catalyzed C−N and C−C bond-forming reactions, a new ligand, 2-(dicyclohexylphosphino)-4′-(*N*,*N*-dimethylamino)-1,1′-biphenyl, was synthesized. This compound is isomeric with the commercially available 2-(dicyclohexylphosphino)-2′-(*N*,*N*-dimethylamino)-1,1′-biphenyl that has been useful in C−N bond-forming reactions of nucleosides. The new *p*-dimethylamino biphenyl ligand bears electronic similarities to the *o*-dimethylamino isomer, but it also possesses structural similarities to 2-(dicyclohexylphosphino)biphenyl, such as the unsubstituted ortho positions in the non-phosphine ring. Whereas 2-(dicyclohexylphosphino)-biphenyl can support catalysts for C−C bond formation, it was not effective in promoting aryl amination of a nucleoside substrate. However, the new ligand proved to be effective in promoting *both* aryl amination *and* C−C bond-forming reactions of nucleoside substrates, with some reactions even occurring at room temperature. Thus, the composite structural elements of this new ligand are thought to be criteria for reactivity of the catalytic system derived from it. We have probed the structures of the isomeric *N*,*N*-dimethylamino biphenyl ligands by X-ray crystallographic analysis. Interactions of the two ligands with $Pd(OAc)_2$ have been investigated by ^{31}P NMR, and they show substantial stoichiometry-dependent differences. These results have been compared to the interactions of $Pd(OAc)_2$ with 2-(dicyclohexylphosphino)biphenyl as well as 2-(di-*tert*-butylphosphino)biphenyl, and they reveal marked differences as well. In this process, three cyclopalladated biaryl derivatives have been isolated and characterized by X-ray analysis.

Introduction

Methodological advances in Pd-catalyzed amination[1] and cross-coupling with boronic acids[2] have contributed significantly to contemporary organic synthesis. In the context of generating biomolecular diversity, we have sought to understand and develop applications of Pd catalysis for modifying the biologically venerable nucleosides via C−N (aryl amination)[3−10] and C−C (Suzuki−Miyaura)[3,6,9,11−13] bond-forming reactions. In

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(5) Lagisetty, P.; Russon, L. M.; Lakshman, M. K. *Angew. Chem., Int. Ed.* **2006**, *45*, 3660–3663.

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(7) Ngassa, F. N.; DeKorver, K. A.; Melistas, T. S.; Yeh, E. A.-H.; Lakshman, M. K. *Org. Lett.* **2006**, *8*, 4613–4616.

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(9) Lakshman, M. K.; Hilmer, J. H.; Martin, J. Q.; Keeler, J. C.; Dinh, Y. Q. V.; Ngassa, F. N.; Russon, L. M. *J. Am. Chem. Soc.* **2001**, *123*, 7779–7787.

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(12) Lakshman, M K.; Gunda, P.; Pradhan, P. *J. Org. Chem.* **2005**, *70*, 10329–10335.

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 10.1021/ja902679b CCC: $40.75

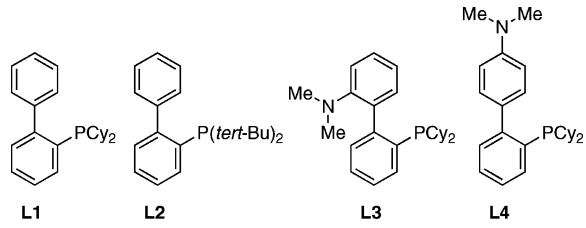
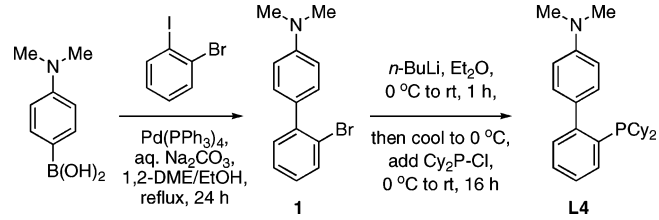


Figure 1. Biaryl phosphine ligands that have been studied for nucleoside modification.

our work[3−13] as well as those of other groups,[14−16] finding effective catalysts for transformations of complex nucleoside substrates has been an important consideration. From our studies, among the cyclohexyl and *tert*-butyl biaryl phosphine ligands **L1-L3**, unsubstituted **L1** (Figure 1) was observed to yield a highly efficient catalyst for C−C bond formation in conjunction with a Pd source.[6,9,11−13] On the other hand, combinations of **L3** and Pd provided effective amination catalysts.[6,8−10] However, in some preliminary experiments, **L1** had not produced an effective amination catalyst, and **L2** has thus far not been effective for reactions involving nucleosides.

On the basis of our prior results, we wanted to investigate the structure−reactivity properties of these ligands, and we queried whether combining the structural features of **L1** and **L3** would produce a more general ligand useful for both C−N and C−C bond-forming reactions of nucleosides. In this event, comparison of the new ligand to commercially available **L3** would also be possible. We reasoned that **L4**, with the *p*-dimethylamino group, would have the electronic components of **L3** needed for C−N bond formation (e.g., the increased electron density in the aromatic ring) while incorporating other structural features of **L1** that may be needed for C−C cross-coupling, such as the unsubstituted ortho positions in the nonphosphine ring. This paper reports the synthesis and evaluation of this new ligand **L4** for C−N and C−C cross-coupling reactions. In addition, we compare the interactions of these ligands with $Pd(OAc)_2$ and report the X-ray crystal structures of **L3** and **L4** as well as palladated complexes of **L1**, **L2**, and **L4**.

Scheme 1. Synthesis of 2-(Dicyclohexylphosphino)-4′-(*N*,*N*-dimethylamino)-1,1′-biphenyl (**L4**)



Results and Dicussion

From a synthetic standpoint, **L4** can be readily prepared in two steps from commercially available *p*-(dimethylamino)phenylboronic acid (Scheme 1) by methods that parallel the synthesis of **L3**.[17] With **L4** in hand, initial studies were directed at first ascertaining whether it was capable of enabling C−N and C−C bond formation among simpler substrates and second comparing the efficiency of catalysts derived from **L4** to those derived from **L3**. For this, we chose to primarily evaluate aryl chlorides that are typically difficult substrates. The results from these reactions are shown in Table 1 (in each case, the conditions used parallel those reported,[17] except that **L4** was used in place of **L3**).

From these experiments, it became clear that **L4**-supported catalysts were active and that their productivity was generally comparable to those derived from **L3** for the reactions of the aryl halides assessed. We next chose to examine the efficiency of catalysts supported by **L4** in comparison to **L3** with nucleoside substrates that generally possess more complex reactivities. For this we selected the O^6-(4-methylphenyl)sulfonyl derivative of 2′-deoxyguanosine (**2**),[18] a system we have previously studied.[6,12] The results from the aryl amination of **2** are shown in Table 2.

We first ascertained that, in these reactions, S_NAr displacement was not competitive with a catalyzed reaction, and as anticipated no product formation was observed in the absence of $Pd(OAc)_2$. In the reaction involving **L1** (devoid of the dimethylamino group), no product formation was observed (entries 1 and 8), consistent with our preliminary observations. However, in each case **L3** and **L4** yielded catalysts that led to successful amination. From these results it appears that, for an effective amination catalyst, the *electronic influence* of the dimethylamino group on the ligand is important but its *location* is less critical. Under these reaction conditions and in side-by-side comparisons, **L4** emerged as at least comparable to, and in some instances superior to **L3**. Thus, subtle differences in the reactivities of catalysts derived from **L1**, **L3**, and **L4** become clearer in the reactions of the more complex substrate **2**.

We then became interested in studying the effectiveness of **L3** and **L4** in C−C bond-forming reactions with arylboronic acids. For this two substrates were selected, the 6-bromo nucleoside **4** and the O^6-(2,4,6-trimethylphenyl)sulfonyl derivative of 2′-deoxyguanosine **5**. We have previously shown that **L1**/$Pd(OAc)_2$ yields a highly effective catalytic complex, capable of C−C bond-forming reactions with **5** under mild conditions

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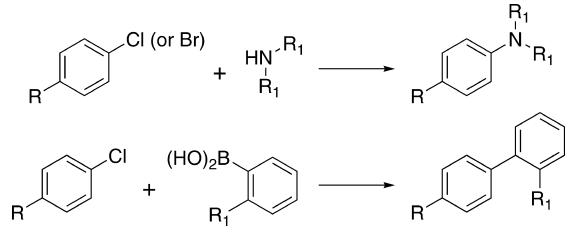
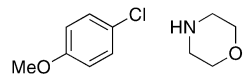
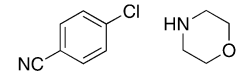
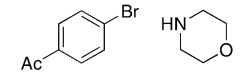
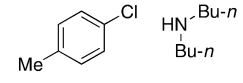
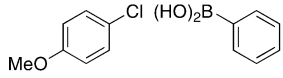
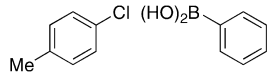
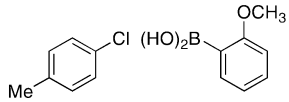
(16) For examples on Pd-catalyzed Suzuki−Miyaura reactions of nucleosides, see: (a) Jacobsen, M. F.; Ferapontova, E. E.; Gothelf, K. V. *Org. Biomol. Chem.* **2009**, *7*, 905–908. (b) Hobley, G.; Gubala, V.; Del, C.; Rivera-Sánchez, M.; Rivera, J. M. *Synlett* **2008**, 1510–1514. (c) Čapek, P.; Hocek, M. *Synlett* **2005**, 3005–3007. (d) Hocek, M.; Nauš, P.; Pohl, R.; Votruba, I.; Furman, P. A.; Tharnish, P. M.; Otto, M. J. *J. Med. Chem.* **2005**, *48*, 5869–5873. (e) Fernández, F.; García-Mera, X.; Morales, M.; Vilariño, L.; Caamaño, O.; De Clercq, E. *Tetrahedron* **2004**, *60*, 9245–9253. (f) Western, E. C.; Daft, J. R.; Johnson, E. M., II; Gannett, P. M.; Shaughnessy, K. H. *J. Org. Chem.* **2003**, *68*, 6767–6774. (g) Amann, N.; Wagenknecht, H.-A. *Synlett* **2002**, 687–691. (h) Hocek, M.; Holý, A.; Votruba, I.; Dvořáková, H. *J. Med. Chem.* **2000**, *43*, 1817–1825. (i) Havelková, M.; Hocek, M.; Česnek, M.; Dvořák, D. *Synlett* **1999**, 1145–1147.

(17) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722–9723.

(18) (a) Nagatsugi, F.; Uemura, K.; Nakashima, S.; Maeda, M.; Sasaki, S. *Tetrahedron* **1997**, *53*, 3035–3044. (b) Hayakawa, Y.; Hirose, M.; Noyori, R. *J. Org. Chem.* **1993**, *58*, 5551–5555.

Table 1. Comparison of C−N as well as C−C Bond Formation Using Catalysts Derived from **L3** and **L4**[a]



entry	coupling partners	temp	yield using **L3**	yield using **L4**[b]
1		100 °C	91%[c]	91%
2		rt	96%[c]	quant[d]
3		100 °C	88%[b] 94%[c]	quant
4		rt	75%[b]	66%
5		100 °C	93%[c]	quant
6		100 °C	96%[c]	98%
7		80 °C	82%[c]	93%

[a] Reactions were conducted under conditions previously reported,[17] except that **L4** was used in place of **L3**. [b] Yields reported are of isolated and purified products. [c] Yield reported in ref 17 using **L3**. [d] A comparable result was obtained at 100 °C.

and at room temperature.[11,12] On the other hand, reactions of **4** at room temperature have not been evaluated. The results from the experiments on these two substrates are shown in Table 3.

As can be seen from Table 3, in reactions of bromo nucleoside **4**, catalysts derived from both **L3** and **L4** perform well at elevated temperatures. However, **L4** performs admirably in room-temperature reactions (entries 2, 7, and 11). In comparison to bromo nucleoside **4**, the nucleoside aryl sulfonate **5** appears to be a more difficult substrate for C−C bond formation, requiring elevated temperature for complete reactions (incomplete reactions of $PhB(OH)_2$ were observed with **L3** and **L4** over 24 h at room temperature). We have previously shown that 2:1 **L1**/$Pd(OAc)_2$ is excellent for reactions of **5** at room temperature.[12] In the current analysis, the presence of the dimethylamino group, even at the para position, was found to diminish catalytic efficiency. Nevertheless, in every reaction involving substrate **5**, **L4**, which bears two vacant ortho positions like **L1**, was superior to **L3** under the conditions utilized, and these reactions include the electron-deficient (entry 17) as well as the ortho-substituted arylboronic acids (entry 19).

X-ray Crystal Structures of L3 and L4. In order to compare the structures of **L3** and **L4**, we have obtained X-ray crystallographic data (Figure 2).[20] In the solid state, the angle between the two aryl rings is about 66° in **L3**, whereas in **L4** this angle is smaller, about 55°. In both cases the phosphorus lone pair is directed toward the amino group-substituted aromatic ring, as reported for other biaryl phosphines.[21] A planarization at the nitrogen atom in **L4** is observed, indicating conjugation of its electron pair with the aromatic ring. If greater electron density is important for the catalytic efficiency in amination reactions, then **L4** has this advantage over **L3**.

$^{31}P\{^1H\}$ NMR Experiments with the Ligands. In comparing the ^{31}P chemical shifts of the four ligands shown in Figure 1, in toluene-d_8 the resonance of **L1** appears at −13.4 ppm, **L2** at 18.0 ppm, **L3** at −8.5 ppm, and **L4** at −12.6 ppm.[22] In this comparison, **L4** is more similar to **L1** than to **L3**. We next undertook $^{31}P\{^1H\}$ NMR experiments to evaluate the interactions of $Pd(OAc)_2$ with **L3** and **L4**.

Within 15 min of combining **L3**/$Pd(OAc)_2$ in a 2:1 molar ratio in toluene-d_8 at room temperature, five new resonances [δ ppm: 48.9, 43.9, 43.7, 31.0, and 29.3] were observed (see

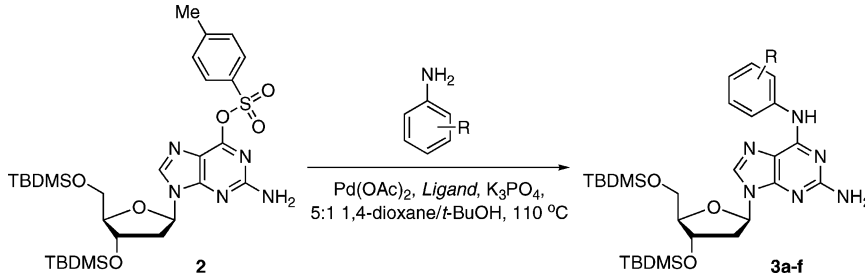
(19) A similar type of reaction has been observed in the cross-coupling of Grignard reagents with an O^6-aryl sulfonate of 2′-deoxyguanosine: Nagatsugi, F.; Ogata, Y.; Imoto, S.; Sasaki, S. *Heterocycles* **2007**, *73*, 493–501.

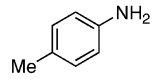
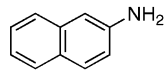
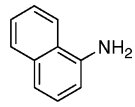
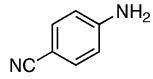
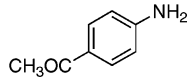
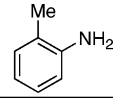
(20) CCDC depositions 689629 and 689630 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

(21) Barder, T. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 5096–5101.

(22) ^{31}P resonances (202 MHz, C_6D_6): **L1** = −14.1 ppm, **L2** = 17.9 ppm, **L3** = −9.7 ppm, and **L4** = −13.7 ppm.

Table 2. Aryl Amination Reactions of 3′,5′-Di-*O*-(*tert*-butyldimethylsilyl)-*O*^{6}-[(4-methylphenyl)sulfonyl]-2′-deoxyguanosine (**2**) Using Biaryl Phosphines **L1**, **L3**, and **L4**[a]



entry	amine	ligand	time (min)[b]	yield[c]
1		**L1**	30	no reaction
2		**L3**	30	**3a:** 55%
3		**L4**	30	**3a:** 77%
4		**L3**	80	**3b:** 78%
5		**L4**	80	**3b:** 83%
6		**L3**	90	**3c:** 66%[d]
7		**L4**	90	**3c:** 60%[d]
8		**L1**	80	no reaction
9		**L3**	80	**3d:** 88%
10		**L4**	80	**3d:** 98%
11		**L3**	30	**3e:** 87%
12		**L4**	30	**3e:** 98%
13		**L3**	80	**3f:** 69%[d]
14		**L4**	80	**3f:** 69%[d]

[a] Reactions were conducted at 0.1 M concentration of **2** in the solvent mixture (5:1 1,4-dioxane/*t*-BuOH) using 10 mol % $Pd(OAc)_2$, 20 mol % ligand, 2 molar equiv K_3PO_4, and 2 molar equiv amine. [b] Reactions were monitored by TLC for completion. [c] Yields reported are of isolated and purified products. [d] Average of two reactions.

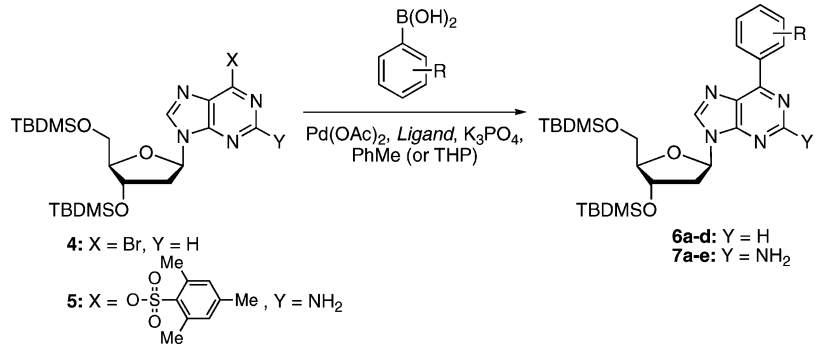
Figure 1 in the Supporting Information). Rapid appearance of a broad singlet at 48.9 ppm was observed, even at 15 min, that persisted and increased with time, and a substantial amount of unligated **L3** was observed after 1 h (Figure 3A). Upon changing this stoichiometry to 1:1 **L3**/$Pd(OAc)_2$, no major difference was observed in the pattern of resonances, although some differences emerged at 24 h (Figure 3B and Figure 2 in the Supporting Information). These data indicate largely similar interactions of **L3** with $Pd(OAc)_2$ under 2:1 or 1:1 stoichiometry.

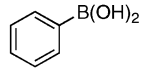
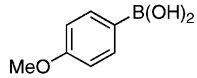
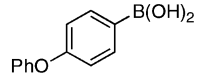
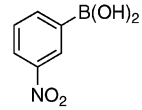
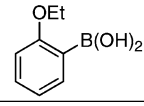
In marked contrast to the behavior of **L3**, a 2:1 combination of **L4** and $Pd(OAc)_2$ in toluene-d_8 at room temperature produced a major $AB_{quartet}$ pattern within 15 min, centered at 27.9 ppm (doublets at 29.8 and 26.0 ppm, $J_{A,B} \sim 370$ Hz; Figure 3 in the Supporting Information), with some residual **L4**. The species producing the $AB_{quartet}$ pattern was stable to storage in solution for 4 weeks at −5 °C. On the basis of the *J* value, it may be inferred that the two phosphines are trans ligated to the metal and are nonequivalent in the predominant species produced here. There is broadening of the ligand resonance at −13.6 ppm that may indicate a dynamic exchange process with the species producing the $AB_{quartet}$.

At a 1:1 **L4**/$Pd(OAc)_2$ stoichiometry, three major resonances were observed within 15 min [δ ppm: 47.3, 42.8, and an $AB_{quartet}$ centered at 27.8; Figure 4 in the Supporting Information]. Other than for the $AB_{quartet}$, the remaining resonances appear similar to those produced in interaction between **L3** and $Pd(OAc)_2$ described above. Thus, the interaction of **L4** with $Pd(OAc)_2$ varies substantially with stoichiometry (Figure 3C,D). The broad resonance at 47.3 ppm persisted and increased with time (Figure 4 in the Supporting Information).

The broad resonances produced at 47−49 ppm in the interactions of **L3** with $Pd(OAc)_2$ as well as in the 1:1 complex of **L4** and $Pd(OAc)_2$ are reminiscent of the interaction of **L1** and $Pd(OAc)_2$ at a 1:1 stoichiometry.[12] Since both **L1** and **L4** have similar stoichiometry-dependent behavior, we were curious to compare the influence of additional ligand subsequent to formation of the major species under the 1:1 stoichiometry. For this reason, 1:1 complexes of **L1** and **L4** with $Pd(OAc)_2$ were prepared in toluene-d_8 and allowed to age for 24 h (Figure 5 in the Supporting Information). After 24 h, in the case of **L1** there was clear formation of a broad resonance as the major species at 47.4 ppm (ca. 75%), and in the case of **L4** the broad resonance at 47.3 ppm was formed almost exclusively. At that time an additional equivalent of the appropriate ligand was added to each solution, and in each case rapid formation of an $AB_{quartet}$ was observed. This indicates that association of a second ligand occurs to an

Table 3. C−C Bond-Forming Reactions of Bromo Nucleoside **4** and Nucleoside Aryl Sulfonate **5** Using Biaryl Ligands **L3** and **L4**[a]



entry	Ar-B(OH)$_2$	substrate	ligand	temp, time,[b] solvent	yield[c]
1		**4**	**L3**	rt, 20 h, PhMe	**6a:** 82%[d]
2		**4**	**L4**	rt, 20 h, PhMe	**6a:** 98%[d]
3		**5**	**L3**	80°C, 1.5 h, PhMe	**7a:** 58%[d]
4		**5**	**L4**	80°C, 1.5 h, PhMe	**7a:** 68%[d]
5		**4**	**L3**	100°C, 1 h, PhMe	**6b:** 95%[e]
6		**4**	**L4**	100°C, 1 h, PhMe	**6b:** 97%[e]
7		**4**	**L4**	rt, 20 h, PhMe	**6b:** 93%[d]
8		**5**	**L3**	80°C, 1.5 h, PhMe	**7b:** 29%[d,f]
9		**5**	**L4**	80°C, 1.5 h, PhMe	**7b:** 53%[d,f]
10		**4**	**L3**	35°C, 24 h, PhMe	**6c:** 45%[d,g]
11		**4**	**L4**	rt, 20 h, PhMe	**6c:** 91%[d,h]
12		**5**	**L3**	80°C, 1.5 h, PhMe	**7c:** 60%[d]
13		**5**	**L4**	80°C, 1.5 h, PhMe	**7c:** 66%[d]
14		**4**	**L3**	100°C, 1 h, THP	**6d:** 60%[d]
15		**4**	**L4**	100°C, 1 h, THP	**6d:** 55%[d]
16		**5**	**L3**	80°C, 2 h, THP	**7d:** 43%[d,f,h]
17		**5**	**L4**	80°C, 2 h, THP	**7d:** 65%[d,f,h]
18		**5**	**L3**	80°C, 1 h, PhMe	**7e:** 60%[d]
19		**5**	**L4**	80°C, 1 h, PhMe	**7e:** 77%[d]

[a] Reactions with **4** and **5** were conducted at 0.1 M nucleoside concentration, using 2 molar equiv K_3PO_4 and 2 molar equiv of $ArB(OH)_2$, with $Pd(OAc)_2$ and ligand stoichiometry as indicated. [b] Reactions were monitored by TLC for completion. [c] Yields reported are of isolated and purified products. [d] Reaction using 10 mol % $Pd(OAc)_2$/20 mol % ligand. [e] Reaction using 5 mol % $Pd(OAc)_2$/10 mol % ligand. [f] In these cases, formation of an unsymmetrical dimer was observed; see ref 19. [g] This reaction was incomplete at room temperature as well as at 35 °C. [h] Average of two reactions.

initially formed 1:1 ligand−Pd species. This experiment again shows similar solution behavior of **L1** and **L4**.

In order to compare this entire set of ligands, we also conducted $^{31}P\{^1H\}$ experiments with **L2** (Figures 6 and 7 in the Supporting Information). Interestingly, at either a 2:1 or a 1:1 **L2**/$Pd(OAc)_2$ stoichiometry, no $AB_{quartet}$ pattern is observed with this ligand. Instead, in each case only the same species that produced a resonance at δ 70.0 ppm was seen to form.

A cyclopalladated species resulting from **L2** has been reported,[23] indicating cyclopalladation to be a facile process with the biaryl phosphine ligands when appropriate unsubstituted carbons are present on the non-phosphine ring. Thus, we attempted crystallization of the various 1:1 and 2:1 Pd−ligand complexes. So far we have not been successful at isolating any 2:1 complex or a 1:1 complex of **L3**. However, crystals of 1:1 complexes from the unsubstituted biphenyls **L1**[24] and **L2**[23,25] were obtained, yielding the X-ray structures shown in Figure 4. The cyclopalladated complex from **L1** (complex 1) is a dimeric species with two bridging acetates, whereas that from **L2** (complex 2) is monomeric with a single ligated acetate. A plausible basis for these differences resides in the relative steric congestion at the phosphorus atoms in each ligand. Consistent with this notion, two **L1**'s can be accommodated at the Pd center under the 2:1 ligand/$Pd(OAc)_2$ stoichiometry, which can then lead to the observed $AB_{quartet}$ if the two phosphorus atoms are nonequivalent. On the other hand, the lack of such a pattern with **L2** could be due to the increased steric demand at the phosphine.

In order to evaluate the effect of additional ligand on the cyclopalladated complexes 1 and 2, we conducted several more $^{31}P\{^1H\}$ NMR experiments (Figure 5, also see Figures 8 and 9 in the Supporting Information). To complex 1 was added a stoichiometric amount of **L1**. The resonance at 47.6 ppm corresponding to complex 1 disappeared almost immediately upon addition of **L1** and resulted in a broad signal at about 28 ppm. This resonance remained unchanged at room

Figure 2. X-ray crystal structures of **L3** (left) and **L4** (right).

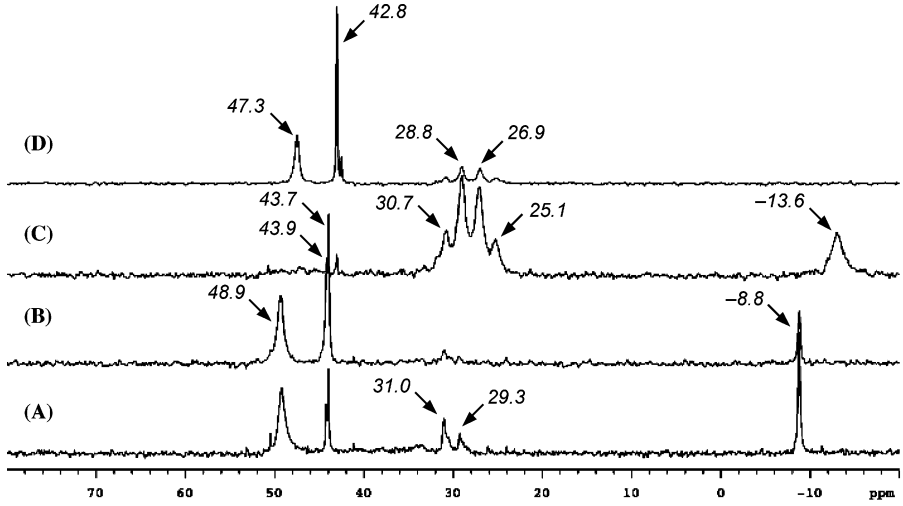


Figure 3. $^{31}P\{^{1}H\}$ NMR spectra of solutions of **L3** or **L4** and $Pd(OAc)_2$ in toluene-d_8 after 1 h at room temperature: (A) 2:1 **L3**/$Pd(OAc)_2$; (B) 1:1 **L3**/$Pd(OAc)_2$; (C) 2:1 **L4**/$Pd(OAc)_2$; and (D) 1:1 **L4**/$Pd(OAc)_2$.

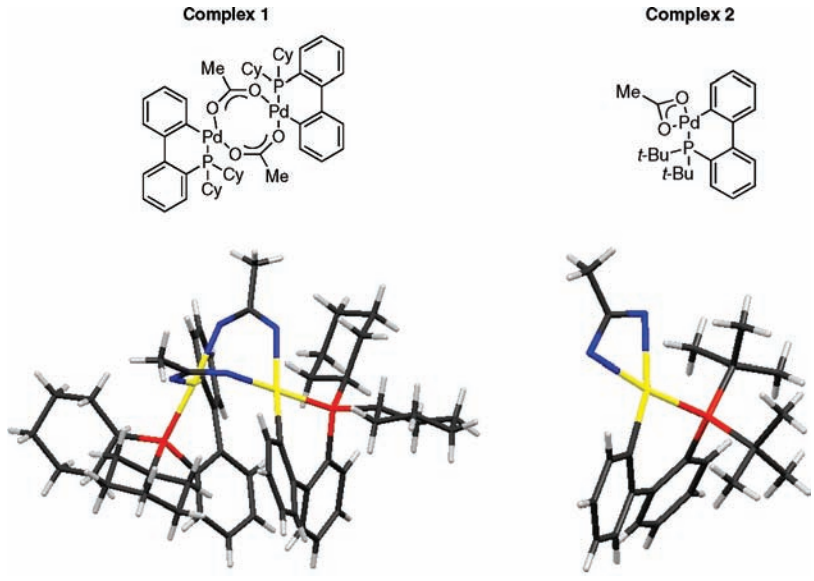


Figure 4. X-ray crystal structures of cyclopalladated complexes derived from **L1** (complex 1) and **L2** (complex 2).

temperature over 24 h (Figure 5A and Figure 8 in the Supporting Information). Upon cooling this NMR sample to 0 °C, the broad resonance resolved into a sharp $AB_{quartet}$ ($J_{A,B}$ ∼ 370 Hz, Figure 5B). Notably, the resonance of unligated **L1**, which was also broadened at room temperature, sharpened upon cooling, indicating a possible dynamic exchange process. Warming this sample back to room temperature again produced the broad resonance. However, upon addition of 1 molar equiv of acetic acid to this sample, the $AB_{quartet}$ pattern was restored at room temperature almost immediately (Figure 5C).

From these experiments the following inferences may be drawn. As shown to the left in Scheme 2, addition of **L1** to complex 1 (R = H) most likely produces a 2:1 ligand−Pd

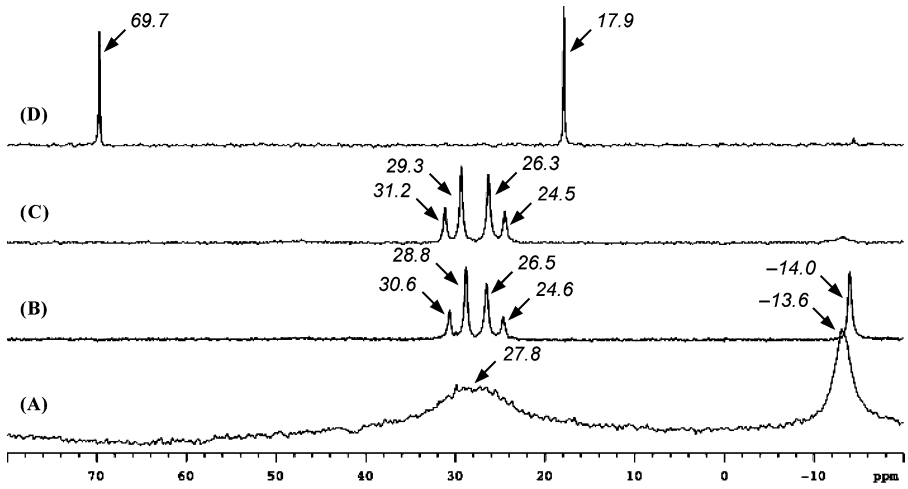
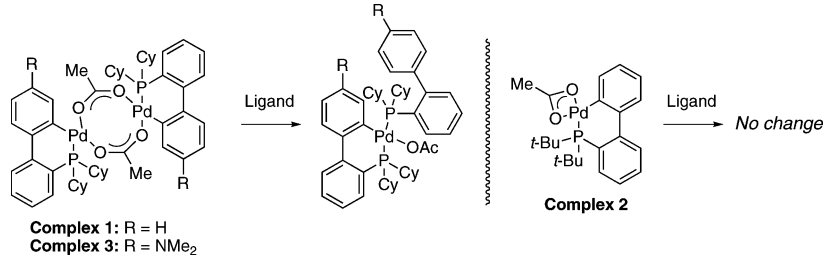


Figure 5. $^{31}P\{^{1}H\}$ NMR experiments with complexes 1 and 2 in toluene-d_8: (A) 24 h after addition of a molar equiv of **L1** to complex 1; (B) same sample as in panel A but data acquired at 0 °C; (C) data acquired at room temperature immediately after addition of 1 molar equiv of acetic acid to the sample; (D) 24 h after addition of a molar equiv of **L2** to complex 2.

Scheme 2. Possible Interaction of Additional Ligand with the Cyclopalladated Complexes



species. In this case, the two phosphorus atoms are nonequivalent and can result in an $AB_{quartet}$ in the $^{31}P\{^{1}H\}$ NMR. On the basis of the foregoing, at the 1:1 ligand/$Pd(OAc)_2$ stoichiometry, cyclopallation appears to be predominant, but when this stoichiometry is changed to 2:1, it is likely that the cyclopalladated species undergoes ligation with a second **L1**, resulting in the observed $AB_{quartet}$. However, in this case, the presence of acetic acid resulting from the cyclopalladation yields the $AB_{quartet}$ at room temperature (for reasons not known currently). When complex 1 is isolated, free of acetic acid, and exposed to additional **L1**, the $AB_{quartet}$ is observable only at low temperature. Addition of acetic acid then produces the $AB_{quartet}$ at room temperature, comparable to the solution results. In marked departure from the behavior of complex 1, addition of a stoichiometric amount of **L2** to complex 2 produced no observable change in the resonance at 69.7 ppm (Figure 9 in the Supporting Information), and this did not alter even after 24 h (Figure 5D). Thus, in the case of **L2**, it appears that the cyclopalladated species, which is also formed quite readily, does not undergo ligation with a second **L2**.

We have obtained the crystal structure of a 1:1 complex of **L4** and $Pd(OAc)_2$ (complex 3, Figure 6). This structure shares similarities to complex 1 obtained from **L1**, in that it is dimeric with two bridging acetates. The nitrogen atom is quite planarized due to conjugation with the aromatic ring. Overall, **L1** and **L4** share common features in the solid state. On the basis of the previously described NMR experiments, **L4** demonstrates solution behavior quite similar to that of **L1**, and Scheme 2 ($R = NMe_2$) illustrates this. However, the position of the dimethylamino group in the non-phosphine ring seems to be responsible for the different interactions of **L3** and **L4** with the metal.

At this time, it is intriguing as to how the ligand−metal interactions of **L4** influence amination reactions of nucleosides that do not otherwise proceed with **L1**. This may be related to the higher electron density of the non-phosphine aryl ring in **L4**, but independent of the location of the dimethyl amino group. One important consideration related to this moiety could be the

(23) Zim, D.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 2413–2415.

(24) Complex 1: ^{1}H NMR (500 MHz, C_6D_6): δ 8.48 (d, 1H, Ar−H, J = 7.8), 7.52 (d, 1H, Ar−H, J = 4.9), 7.32 (d, 1H, Ar−H, J = 7.3), 7.13−6.98 (m, 4H, Ar−H), 6.94 (app t, 1H, Ar−H, J = 7.8), 2.07 (s, 3H, OAc), 1.87−1.71 (m, 4H), 1.63−1.60 (m, 2H), 1.50−1.47 (m, 4H), 1.42−1.38 (m, 4H), 1.26−1.17 (m, 1H), 1.03−0.84 (m, 6H), 0.67−0.63 (m, 1H). ^{31}P NMR (202 MHz, toluene-d_8): δ 47.6. This complex appears to be somewhat more labile compared to complex 3 during routine operations.

(25) Complex 2: ^{1}H NMR (500 MHz, C_6D_6): δ 8.30 (d, 1H, Ar−H, J = 6.3), 7.67 (app t, 1H, Ar−H, J = 7.8), 7.54 (dd, 1H, Ar−H, J = 3.4, 7.8), 7.16−7.11 (m, 2H, Ar−H), 6.99−6.92 (m, 3H, Ar−H), 1.96 (s, 3H, OAc), 1.16 (s, 9H, *t*-Bu), 1.13 (s, 9H, *t*-Bu). ^{31}P NMR (202 MHz, toluene-d_8): δ 69.7.

(26) Complex 3: ^{1}H NMR (500 MHz, C_6D_6): δ 7.87 (s, 1H, Ar−H), 7.67−7.65 (m, 1H, Ar−H), 7.44 (d, 1H, Ar−H, J = 8.3), 7.21−7.16 (m, 2H, Ar−H), 6.96−6.94 (m, 1H, Ar−H), 6.47 (d, 1H, Ar−H, J = 9.3), 2.61 (s, 6H, NCH_3), 2.06 (s, 3H, OAc), 1.98−1.92 (m, 2H), 1.83−1.79 (m, 2H), 1.70−1.68 (m, 2H), 1.59−1.48 (m, 6H), 1.40−1.37 (m, 2H), 1.24−1.20 (m, 1H), 1.09−1.04 (m, 2H), 0.97−0.83 (m, 4H), 0.46−0.43 (m, 1H). ^{31}P NMR (202 MHz, toluene-d_8): δ 47.4.

(27) (a) Christmann, U.; Pantazis, D A.; Benet-Buchholz, J.; McGrady, J. E.; Maseras, F.; Vilar, R. *J. Am. Chem. Soc.* **2006**, *128*, 6376–6390. (b) Faller, J. W.; Sarantopoulos, N. *Organometallics* **2004**, *23*, 2008–2014. (c) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew, Chem., Int. Ed.* **2004**, *43*, 1871–1876. (d) Christmann, U.; Vilar, R.; White, A. J. P.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **2004**, 1294–1295. (e) Yin, J.; Rainka, M. P.; Zhang, X.-X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162–1163.

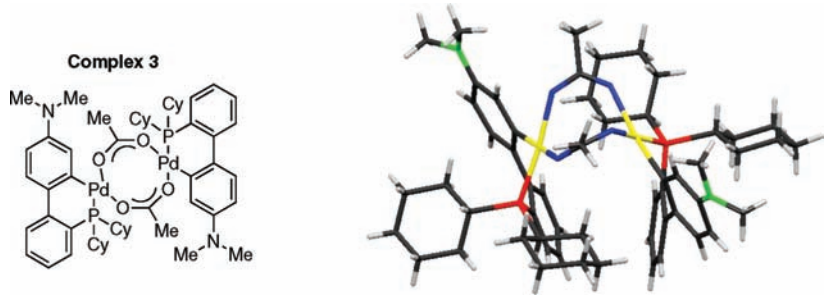


Figure 6. X-ray structure of complex 3 obtained from **L4** and $Pd(OAc)_2$.

increased electron density in the non-phosphine ring. In this context, some unusual coordination modes of biaryl ligands with Pd are known. For example, Pd complexes with biphenyl phosphines,[27] MAP,[28] and MeO-MOP[29] have all been shown to display arene−Pd interactions with the non-phosphine ring. Thus, it is plausible that **L4** with the para dimethylamino group could yield similar arene−Pd interactions as well, and this may be assisted by the greater conjugation of the amino group with the aryl ring. If, on the other hand, formation of biaryl palladacycles is a relatively facile process in these ligand−$Pd(OAc)_2$ interactions, then the efficiency with which the palladacycles catalyze reactions could be dependent on how easily they are converted to active catalyst.[30,31] In this context, it is noteworthy that a C−C bond-forming reaction between **4** and $PhB(OH)_2$ using 20 mol % **L2**/10 mol % $Pd(OAc)_2$ at room temperature resulted in only 50% product formation after 24 h, with no additional progress beyond that time. Thus, subtle factors in structures of these ligands play a critical role in the formation of active catalyst and the catalytic efficiency of each. We were curious to evaluate whether another Pd(II) source would yield similar interactions with **L1**. However, solutions of $(CH_3CN)_2PdCl_2$ and **L1** did not display any of the NMR characteristics observed with $Pd(OAc)_2$ (see Figure 10 in the Supporting Information). Nevertheless, unusual arene−Pd interactions have been reported between Pd halide salts and **L2** as well as related ligands.[27a,d]

Finally, we were interested in qualitatively assessing the relative efficiencies of Pd complexes derived from **L3** and **L4** in the room-temperature C−C bond-forming reactions. Since the anomeric H-1′ resonances of **4** and **6a** are well separated, they can be used for monitoring reactions by NMR. Four separate cross-coupling experiments of **4** and $PhB(OH)_2$ were performed using 1:1 as well as 2:1 ligand (**L3** and **L4**)/$Pd(OAc)_2$ stoichiometry. After mixing all components at room temperature, the reactions were monitored every 15 min, with the first sampling at 2 min after mixing (Figure 7). Notably, all three reactions had commenced within 2 min with noticeable product formation. The absence of any induction period indicated that

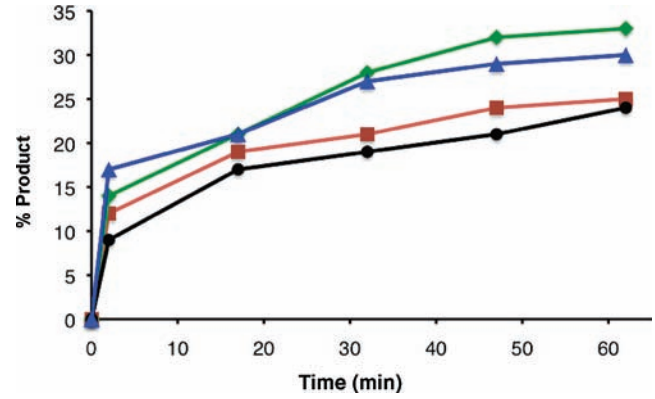


Figure 7. Monitoring the amount of product (**6a**) formed as a function of time: (◆) reaction catalyzed by 2:1 **L4**/$Pd(OAc)_2$; (▲) reaction catalyzed by 1:1 **L4**/$Pd(OAc)_2$; (■) reaction catalyzed by 2:1 **L3**/$Pd(OAc)_2$; and (●) reaction catalyzed by 1:1 **L3**/$Pd(OAc)_2$.

active catalyst was generated rapidly in each case.[32] Continued sampling showed that the **L4**-based catalysts tended to yield product faster than those from **L3** (◆ and ▲ compared to ■ and ● in Figure 7). However, the 1:1 **L4**/$Pd(OAc)_2$ reaction, which was initiated quite rapidly, appeared to be retarded as time progressed (▲). Thus, from this experiment as well as the ^{31}P NMR results, a plausible conclusion that emerges is that the second equivalent of **L4** may not be a bystander but appears to have a role in the reaction. In contrast, the ^{31}P NMR results with **L3** indicate that the interaction of the metal with the ligand is quite independent of stoichiometry, and the reactions appear comparable in the initial hour of observation.

A separate experiment was conducted in which the reactions catalyzed by 2:1 **L3**/$Pd(OAc)_2$ and **L4**/$Pd(OAc)_2$ were monitored until no starting material was detectable by NMR. Although both reactions appeared complete at 20 h by NMR, the **L4**-derived catalyst showed faster product formation (see Figure 11 in the Supporting Information) and an overall better product yield (Table 3, entries 1 and 2). In this context, it should be recognized that the behavior of nucleosides can be markedly different from that of simpler systems, and often data obtained from the reactions of simpler systems are not always directly applicable to these more complex substrates. The reactivity properties of nucleosides have offered the possibility to probe ligand-based differences of catalytic activities.

Conclusions

We have studied the utility of a new ligand, 2-(dicyclohexylphosphino)-4′-(*N*,*N*-dimethylamino)-1,1′-biphenyl, for C−C and

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(29) (a) Dotta, P.; Kumar, P. G. A.; Pregosin, P. S.; Albinati, A.; Rizzato, S. *Organometallics* **2004**, *23*, 4247–4254. (b) Dotta, P.; Kumar, P. G. A.; Pregosin, P. S. *Helv. Chim. Acta* **2004**, *87*, 272–278. (c) Dotta, P.; Kumar, P. G. A.; Pregosin, P. S.; Albinati, A.; Rizzato, S. *Organometallics* **2003**, *22*, 5345–5349.
(30) Dupont, J.; Consorti, C. S.; Spencer, J. *Chem. Rev.* **2005**, *105*, 2527–2571.
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C−N bond formation. This ligand, which is readily synthesized from commercially available compounds, catalyzes *both* aryl amination *and* Suzuki−Miyaura cross-coupling of nucleosides. In contrast, **L1**, which lacks the dimethylamino moiety, catalyzes the latter but not the former. Therefore, it appears that, by balancing the structure and electronic properties of the biaryl phosphines, more generally applicable ligands can be obtained. We have also compared the interactions of these ligands with $Pd(OAc)_2$, and there are substantial differences. Whereas **L3** demonstrates a generally stoichiometry-independent behavior, **L4** produces stoichiometry-dependent intermediates, and this appears to be borne out in the relative efficiencies of the reactions. The behavior of **L4** parallels that of **L1**, but **L2**, which has bulkier substituents on the phosphorus atom, demonstrates only a single type of interaction with $Pd(OAc)_2$, namely cyclopalladation. During the course of these investigations, we have obtained X-ray crystallographic structures of cyclopalladated complexes derived from **L1**, **L2**, and **L4**. In comparing these, the complex obtained from **L1** exhibits a dimeric structure, whereas that from **L2** is monomeric. The cyclopalladated species derived from **L1** likely forms a bis-ligated Pd complex upon exposure to additional **L1**, but the formation of such a species in solution by mixing **L1** and $Pd(OAc)_2$ in a 2:1 molar ratio appears to be quite facile. On the basis of data obtained in solution as well as in the solid state, the behavior of **L4** is similar to that of **L1**. By contrast, the cyclopalladated compound derived from **L2** seems to remain a monoligated complex upon exposure to additional **L2**. It is conceivable that the effectiveness of these ligands in catalyzing transformations is dependent upon the ability of the various cyclopalladated species produced to yield active catalyst in a reaction medium, and this is tuned by subtle structural features of the various biaryl ligands.

Experimental Section

General Experimental Considerations. Thin-layer chromatography was performed on 250 μm silica plates and column chromatographic purifications were performed on 200−300 mesh silica gel. The ligands and $Pd(OAc)_2$ were purchased from commercial suppliers. All other reagents were obtained from commercial sources and used without further purification. 1,4-Dioxane was distilled over $LiAlH_4$ and was freshly distilled over Na prior to use. Toluene and Et_2O were distilled over Na. Nucleoside substrates were prepared as described previously. ^{1}H NMR spectra were recorded at 500 MHz and ^{13}C NMR spectra at 125 MHz in the solvents indicated (when $CDCl_3$ was used, it was deacidified by percolating the solvent through a bed of solid $NaHCO_3$ and basic alumina). All proton spectra are referenced to residual protonated solvent resonance, and carbon spectra are referenced to the solvent resonance. ^{31}P NMR spectra were recorded at 202 MHz in the solvents indicated, using 85% H_3PO_4 as external standard. No attempt has been made to ascertain the position of the aryl amino proton (−N*H*−Ar) in the products. Therefore, this and the aromatic protons are collectively assigned as Ar−H. The sugar protons are numbered 1′−5′ beginning at the anomeric carbon and proceeding via the carbon chain to the primary carbinol carbon.

Synthesis of Ligand L4. Step 1: Synthesis of 2-Bromo-*N*,*N*-(dimethylamino)-1,1′-biphenyl (1). A solution of 4-(*N*,*N*-dimethylamino)phenylboronic acid (736 mg, 4.46 mmol) in EtOH (5 mL) was added to a round-bottomed flask containing a solution of $Pd(PPh_3)_4$ (260 mg, 5 mol %) and 2-bromoiodobenzene (728 μL, 5.68 mmol) in DME (40 mL) under nitrogen gas. A solution of Na_2CO_3 (2.00 g, 19.04 mmol) in degassed water (15 mL) was added to the reaction mixture, and the mixture was heated at reflux for 24 h. The reaction mixture was then cooled to room temperature, diluted with Et_2O (100 mL), and transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 100 mL). The aqueous layer was discarded, and the combined organic layer was then extracted with 1 M aqueous NaOH (100 mL). Subsequently, the organic layer was extracted with 1 M aqueous HCl (4 × 100 mL) and discarded. The aqueous acid layer was basified to pH 14 with 6 M aqueous NaOH and then extracted with Et_2O (4 × 100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material thus obtained was purified by flash chromatography on silica gel using 20% CH_2Cl_2 in hexanes to yield 0.91 g (74%) of the bromo biphenyl **1** as a white, crystalline solid, R_f (1:1 CH_2Cl_2 in hexanes) = 0.66. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, 1H, Ar−H, J = 7.8), 7.36−7.32 (m, 4H, Ar−H), 7.17−7.14 (m, 1H, Ar−H), 6.80 (d, 2H, Ar−H, J = 8.7), 3.02 (s, 6H, $N(CH_3)_2$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.1, 142.9, 133.4, 131.6, 130.4, 129.3, 128.1, 127.6, 123.3, 111.9, 40.7. HRMS: calcd for $C_{14}H_{15}BrN$ $[M + H]^+$ 276.0382, found 276.0388.

Step 2: Synthesis of 2-(Dicyclohexylphosphino)-4′-*N*,*N*-(dimethylamino)-1,1′-biphenyl (L4). An oven-dried, three-neck round-bottomed flask, equipped with a stirring bar, was charged with 2-bromo-*N*,*N*-(dimethylamino)-1,1′-biphenyl (552 mg, 2 mmol) under a nitrogen atmosphere. The flask was then evacuated, held under vacuum, and filled with nitrogen gas. Anhydrous Et_2O (15 mL) was transferred via syringe, and the solution was cooled to 0 °C. *n*-BuLi (1.87 mL of 1.6 M solution in hexanes, 3 mmol) was added dropwise to this stirred mixture, and the mixture was warmed to room temperature and allowed to stir for 1 h. The reaction mixture was then cooled to 0 °C, and Cl-PCy_2 (788 mg, 3.4 mmol) was added dropwise. The reaction mixture was again warmed to room temperature and allowed to stir for 16 h. The mixture was filtered through Celite, and the residue was washed with Et_2O. The solvent was evaporated under reduced pressure, and crude product was purified by recrystallization from hot, degassed ethanol under a nitrogen atmosphere to afford 526 mg (67%) of **L4** as a white solid, R_f (CH_2Cl_2) = 0.47. ^{1}H NMR (500 MHz, C_6D_6): δ 7.57 (d, 1H, Ar−H, J = 7.1), 7.48 (d, 2H, Ar−H, J = 8.1), 7.46−7.45 (m, 1H, Ar−H), 7.22−7.17 (m, 2H, Ar−H), 6.69 (d, 2H, Ar−H, J = 8.5), 2.53 (s, 6H, $N(CH_3)_2$), 1.88−1.81 (m, 4H), 1.72−1.53 (m, 8H), 1.26−1.13 (m, 8H), 1.11−1.03 (m, 2H). ^{13}C NMR (125 MHz, C_6D_6): δ 151.3 (d, J = 28.6), 149.4, 134.7 (d, J = 22.3), 132.8 (d, J = 2.7), 131.8 (d, J = 4.8), 131.3 (d, J = 6.0), 130.7 (d, J = 5.0), 128.2, 125.8, 111.6, 39.9, 35.1 (d, J = 16.9), 30.8 (d, J = 18.5), 29.6 (d, J = 9.6), 27.2, 27.1 (d, J = 4.8), 26.5. ^{31}P NMR (202 MHz, C_6D_6): δ −13.7. HRMS: calcd for $C_{26}H_{37}NP$ $[M + H]^+$ 394.2658, found 394.2661.

Cross-Coupling Reactions Shown in Table 1. In each case the reaction was conducted using identical amounts of reagents, under identical stoichiometry, solvent, and conditions as those reported in ref 17, using **L3** or **L4**.

Typical Procedure for C−N Bond-Forming Reactions of Nucleoside Aryl Sulfonate 2. In an oven-dried screw-cap vial, equipped with a stirring bar, were placed $Pd(OAc)_2$ (1.4 mg, 6.2 μmol), **L3** or **L4** (4.8 mg, 12.3 μmol), K_3PO_4 (26.0 mg, 0.123 mmol), nucleoside sulfonate **2** (40 mg, 0.615 mmol), and aryl amine (0.123 mmol). A mixture of 5:1 anhydrous 1,4-dioxane and *t*-BuOH (0.6 mL) was added, the vial was flushed with nitrogen gas and sealed with a Teflon-lined cap, and the mixture was allowed to stir at 110 °C in a pre-equilibrated oil bath. Upon completion, the reaction mixture was filtered through Celite, and the residue was washed with CH_2Cl_2. Evaporation of the filtrate provided the crude mixture that was purified by column chromatography on silica gel using 3% acetone in CH_2Cl_2 as eluent. Data for all compounds except **3b** have been reported previously.[6]

2,6-Diamino-*N*^{6}-(2-naphthyl)-9-[3,5-di-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-β-D-ribofuranosyl]purine (3b). The eluting solvent for chromatography was CH_2Cl_2, followed by 3% acetone in CH_2Cl_2. Colorless oil, R_f (5% acetone in CH_2Cl_2) = 0.25. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.37 (s, 1H, Ar−H), 7.89 (s superimposed on br s, 2H, Ar−H), 7.79−7.77 (m, 3H, Ar−H), 7.74−7.72 (m, 1H, Ar−H), 7.46−7.43 (m, 1H, Ar−H), 7.38−7.35 (m, 1H, Ar−H),

6.34 (t, 1H, H-1′, J = 6.6), 4.91 (br s, 2H, NH_2), 4.62−4.60 (m, 1H, H-3′), 4.01 (app q, 1H, H-4′, $J \sim 3.4$), 3.85 (dd, 1H, H-5′, J = 4.1, 11.1), 3.77 (dd, 1H, H-5′, J = 3.2, 11.1), 2.62 (app quint, 1H, H-2′, $J_{app} \sim 6.1$), 2.38 (ddd, 1H, H-2′, J = 3.8, 6.0, 13.0), 0.93 and 0.92 (2s, 18H, *t*-Bu), 0.11 and 0.10 (2s, 12H, Si−CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.6, 152.4, 151.0, 136.5, 136.3, 134.0, 130.1, 128.5, 127.6, 127.4, 126.3, 124.5, 120.8, 116.2, 115.2, 87.7, 83.7, 71.9, 62.8, 41.0, 26.0, 25.8, 18.4, 18.0, −4.7, −4.8, −5.4, −5.5. HRMS: calcd for $C_{32}H_{49}N_6O_3Si_2$ $[M + H]^+$ 621.3399, found 621.3399.

General Procedure for C−C Bond-Forming Reactions of Bromo Nucleoside 4 at Room Temperature. In an oven-dried, screw-cap vial equipped with a stirring bar were placed $Pd(OAc)_2$ (1.6 mg, 7.0 μmol), **L3** or **L4** (5.5 mg, 14.0 μmol), the boronic acid (2 molar equiv), and K_3PO_4 (29.5 mg, 0.14 mmol). Finally, bromo nucleoside **4** (38 mg, 0.070 mmol) was added, followed by the addition of dry toluene (0.7 mL). The vial was flushed with nitrogen gas and sealed with a Teflon-lined cap, and the mixture was allowed to stir at room temperature. Reactions were monitored by TLC. Upon completion, the mixtures were filtered through Celite, the residue was washed with CH_2Cl_2, and the filtrate was evaporated to dryness. The products were purified by column chromatography on silica gel using appropriate solvents.

General Procedure for C−C Bond-Forming Reactions of Bromo Nucleoside 4 at Elevated Temperature. These reactions were carried out as described for the ones at room temperature with some differences. Specifically, the reaction of *p*-methoxyphenylboronic acid was conducted using a lower catalyst loading, $Pd(OAc)_2$ (0.8 mg, 3.5 μmol) and **L3** or **L4** (2.8 mg, 7.0 μmol), and THP was used as solvent for the reaction of *m*-nitrophenylboronic acid. The reactions were conducted in an oil bath that was maintained at 100−102 °C.

Purification and characterization data for **6a**, **6b**, and **6d** have been described previously.[9]

9-[3,5-Di-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-β-D-ribofuranosyl]-6-(4-phenoxyphenyl)purine (6c). The eluting solvent for chromatography was CH_2Cl_2, followed by 3% acetone in CH_2Cl_2. Colorless oil, R_f (5% acetone in CH_2Cl_2) = 0.73. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.98 (s, 1H, Ar−H), 8.80 (d, 2H, Ar−H, J = 8.9), 8.42 (s, 1H, Ar−H), 7.40−7.37 (m, 2H, Ar−H), 7.18−7.15 (m, 3H, Ar−H), 7.11−7.10 (m, 2H, Ar−H), 6.56 (t, 1H, H-1′, J = 6.4), 4.66−4.64 (m, 1H, H-3′), 4.06 (app q, 1H, H-4′, $J \sim 3.5$), 3.89 (dd, 1H, H-5′, J = 3.9, 11.2), 3.79 (dd, 1H, H-5′, J = 3.0, 11.2), 2.70 (app quint, 1H, H-2′, $J_{app} \sim 6.6$), 2.50 (ddd, 1H, H-2′, J = 3.9, 5.9, 13.2), 0.93 and 0.91 (2s, 18H, *t*-Bu), 0.12, 0.09, and 0.08 (3s, 12H, Si−CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.3, 156.6, 154.4, 152.5, 152.1, 142.8, 131.9, 131.5, 130.6, 130.1, 124.2, 123.2, 119.9, 118.5, 88.3, 84.7, 72.3, 63.1, 41.5, 26.2, 26.0, 18.7, 18.3, −4.4, −4,5, −5.1, −5.2. HRMS: calcd for $C_{34}H_{49}N_4O_4Si_2$ $[M + H]^+$ 633.3287, found, 633.3285.

Typical Procedure for C−C Bond-Forming Reactions of Nucleoside Aryl Sulfonate 5. In an oven-dried, screw-cap vial equipped with a stirring bar were placed $Pd(OAc)_2$ (1.3 mg, 5.9 μmol), **L3** or **L4** (4.6 mg, 11.8 μmol), K_3PO_4 (25 mg, 0.118 mmol), nucleoside arylsulfonate **5** (40 mg, 0.059 mmol), and the arylboronic acid (2 molar equiv). PhMe or THP (0.6 mL) as appropriate was added, the vial was flushed with nitrogen gas and sealed with a Teflon-lined cap, and the mixture was allowed to stir at 80 °C in an oil bath. Upon completion, the reaction mixture was filtered through Celite, and the residue was washed with CH_2Cl_2. Evaporation of the filtrate yielded the crude mixture that was purified by column chromatography on silica gel using 3% acetone in CH_2Cl_2 as eluent. Characterization data for **7a**, **7b**, **7d**, and **7e** have been described previously.[33]

2-Amino-9-[3,5-di-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-β-D-ribofuranosyl]-6-(4-phenoxyphenyl)purine (7c). The eluting solvent was CH_2Cl_2 followed by 3% acetone in CH_2Cl_2. Colorless oil, R_f (5% acetone in CH_2Cl_2) = 0.25. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.69 (d, 2H, Ar−H, J = 8.8), 8.08 (s, 1H, Ar−H), 7.39−7.36 (m, 2H, Ar−H), 7.17−7.12 (m, 3H, Ar−H), 7.09−7.08 (m, 2H, Ar−H), 6.39 (t, 1H, H-1′, J = 6.4), 5.12 (br s, 2H, NH_2), 4.63−4.60 (m, 1H, H-3′), 4.01 (app q, 1H, H-4′, $J \sim 3.4$), 3.82 (dd, 1H, H-5′, J = 4.4, 11.2), 3.77 (dd, 1H, H-5′, J = 3.4, 11.2), 2.62 (app quint, 1H, H-2′, $J_{app} \sim 6.1$), 2.40 (ddd, 1H, H-2′, J = 3.4, 6.7, 13.0), 0.93 and 0.91 (2s, 18H, *t*-Bu), 0.12, 0.09, and 0.08 (3s, 12H, Si−CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.7, 159.3, 156.5, 154.9, 153.9, 139.8, 131.4, 130.6, 129.8, 125.8, 123.7, 119.5, 118.3, 87.7, 83.6, 72.1, 62.9, 40.7, 25.9, 25.8, 18.4, 18.1, −4.7, −4.8, −5.4, −5.5. HRMS: calcd for $C_{34}H_{50}N_5O_4Si_2$ $[M + H]^+$ 648.3396, found 648.3395.

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Supporting Information Available: $^{31}P\{^1H\}$ NMR analysis of 2:1 and 1:1 ligand/$Pd(OAc)_2$ combinations involving ligands **L2**, **L3**, and **L4**; $^{31}P\{^1H\}$ NMR analysis of the effect of additional **L1** and **L4** on initially formed 1:1 complexes in solution; $^{31}P\{^1H\}$ NMR analysis of the effect of additional **L1** and **L2** on cylopalladated complexes derived from each; $^{31}P\{^1H\}$ NMR analysis of **L2**/$(MeCN)_2PdCl_2$ at 2:1 and 1:1 stoichiometry; analysis of a reaction between **4** and $PhB(OH)_2$ over 20 h using catalytic complexes derived from **L3** and **L4**; ^{1}H NMR spectra of **1**, **L4**, all products in Table 1, **3a**−**f**, **6a**−**d**, and **7a**−**e**; ^{13}C NMR spectra of **1**, **L4**, **3c**, **6c**, and **7c**; $^{31}P\{^1H\}$ and HMQC spectra of **L4**; ^{1}H and $^{31}P\{^1H\}$ NMR spectra for complexes 1−3; additional X-ray (ORTEP) structures of **L3**, **L4**, and complexes 1−3; and CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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