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Triazole-Based Monophosphine Ligands for Palladium-Catalyzed Cross-Coupling Reactions of Aryl Chlorides

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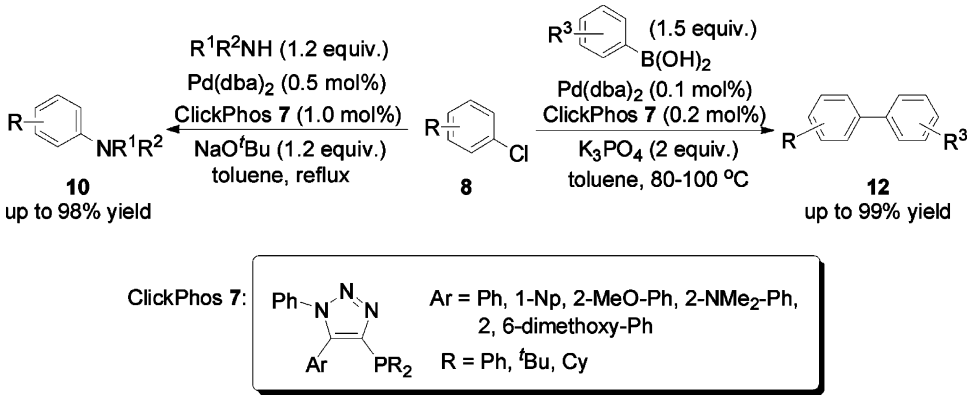

A variety of triazole-based monophosphines (ClickPhos) have been prepared via efficient 1,3-dipolar cycloaddition of readily available azides and acetylenes. Their palladium complexes provided excellent yields in the amination reactions and Suzuki−Miyaura coupling reactions of unactivated aryl chlorides. Ligand **7i**, which has a 2,6-dimethoxybenzene moiety, provided good results in Suzuki−Miyaura reaction to form hindered biaryls. A CAChe model for the Pd/**7i** complex shows that the likelihood of a Pd−arene interaction might be a rationale for its high catalytic reactivity.

Introduction

Transition metal catalyzed cross-coupling reactions to form C−C, C−N, C−O, and C−S bonds are among the most powerful organometallic transformations in organic chemistry.[1] For instance, Pd-catalyzed amination of aryl halides is a principle method for the synthesis of aniline derivatives.[2] Employing readily available aryl chlorides in this transformation has been a recent focus. Since the initial findings reported by Kosugi,[3] numerous ligands have been developed for this type of transformation (Figure 1). P(*o*-tolyl)$_3$ was originally used; however, poor yields were obtained for the reaction of primary amines with aryl halides.[4] A second generation of chelating bisphosphine ligands (**1**, **2**) was introduced to solve this problem, but these ligands were not effective for the reaction of unactivated aryl chlorides.[5] In the late 1990s, Buchwald and co-workers reported a series of monophosphine ligands **3** which are very effective for the room-temperature amination reactions.[6] More recently, Beller and co-workers reported the synthesis of ligand **4** for the coupling of sterically hindered amines[7] and

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(4) (a) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609. (b) Guram, A. S.; Rennel, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348. (c) Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901.

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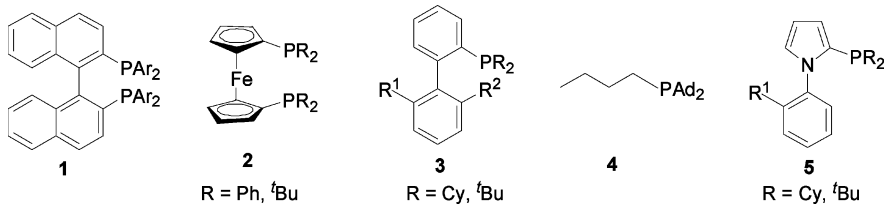

FIGURE 1. Examples of ligands for Pd-catalyzed amination reactions.

ligand **5** with excellent reactivity for a wide variety of substrates.[8a,b]

Pd-catalyzed Suzuki−Miyaura coupling reaction is one of the most attractive methods for the preparation of biaryl compounds due to the advantages of the wide functional group tolerance and the use of stable and nontoxic organoborane reagents.[9] Some of the recent progresses in this reaction have been focused on the use of aryl chlorides as coupling partners in view of their low cost and readily available diversity.[10] A number of reports have shown that Pd complexes derived from sterically hindered and electron-rich phosphines are effective catalysts for this transformation.[11] Some of the notable examples include the use of bulky trialkylphosphines (i.e., P^tBu_3) by Fu,[12] dialkylbiphenylphosphines (i.e., **3**) by Buchwald,[6a−c,13] and dialkyl heteroaromatic phosphines (i.e., **5**) by Beller.[8a,c] Other strategies such as using sterically hindered *N*-heterocyclic carbenes (NHCs) as ligands,[14] and palladacycles as the pre-catalysts,[15] also provide efficient catalytic systems.

It has been well recognized that ligands employed in these processes have significant impact on the outcome of the reactions. Therefore, designing ligands with appropriate natures and great diversity is crucial for dealing with the challenging substrates in this area. Our previous work on the Pd-catalyzed Suzuki−Miyaura coupling reaction has demonstrated that the triazole monophosphines, ClickPhos, are excellent ligands for this transformation with turnovers of up to 9300.[16] These ligands can be obtained by a Grignard reagent mediated 1,3-dipolar addition to form a triazole compound, followed by deprotonation and reaction with different phosphine chlorides. Herein, we wish to report a more detailed study on ligand preparation and their applications to the amination reactions of unactivated aryl chlorides and Suzuki−Miyaura coupling reactions of a variety of substrates, including ortho-substituted aryl chlorides to form hindered biaryls.

Results and Discussion

Although various new ligands have been reported, rapid assembling of structurally diverse ligand systems via efficient synthetic methods is still important for the development of effective catalysts for the widespread applications of coupling reactions. Recently, Sharpless and co-workers have reported elegant chemistry for the formations of 1,4- and 1,5-disubstituted triazole compounds. The unique properties such as modularity, wide reaction scope, mild reaction conditions, high yields, and regioselectivity make these reactions excellent examples of click chemistry.[17] Following the general procedure reported by Sharpless,[17c] a straightforward two-step synthesis of ClickPhos has been developed (Scheme 1). 1,5-Disubstituted triazoles **6a**−**e** were obtained in good yields from phenyl azide[18a] and various aryl acetylenes, which can be easily prepared from

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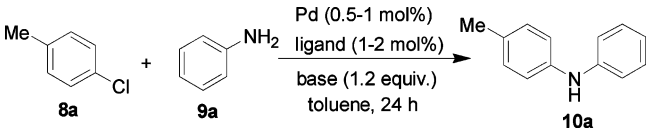
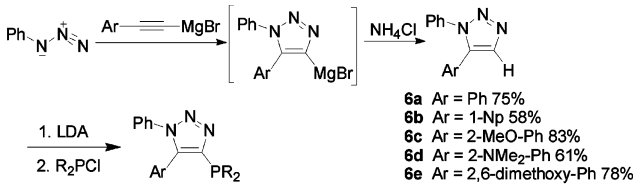
TABLE 1. Screening Ligands and Reaction Conditions for Amination of Aryl Chlorides[a]



entry	Pd (mol %)	ligand (mol %)	base	T (°C)	yield[b] (%)
1	1% $Pd(OAc)_2$	**7c** (2)	KO^{t}Bu	80	87
	1% $Pd(dba)_2$	**7c** (2)	KO^{t}Bu	80	92
2	1% $Pd(dba)_2$	**7c** (2)	KO^{t}Bu	110	94
3	1% $Pd(dba)_2$	**7c** (2)	NaO^{t}Bu	110	94
4	1% $Pd(dba)_2$	**7c** (2)	NaO^{t}Bu	80	88
5	0.5% $Pd(dba)_2$	**7c** (1)	NaO^{t}Bu	110	92
6	0.5% $Pd(dba)_2$	**7c** (1)	NaO^{t}Bu	110	91
7	0.5% $Pd(dba)_2$	**7b** (1)	NaO^{t}Bu	110	90
8	0.5% $Pd(dba)_2$	**7d** (1)	NaO^{t}Bu	110	91
9	0.5% $Pd(dba)_2$	**7e** (1)	NaO^{t}Bu	110	85
10	0.5% $Pd(dba)_2$	**7f** (1)	NaO^{t}Bu	110	95
11	0.5% $Pd(dba)_2$	**7g** (1)	NaO^{t}Bu	110	93
12	0.5% $Pd(dba)_2$	**7h** (1)	NaO^{t}Bu	110	93
13	0.5% $Pd(dba)_2$	**7i** (1)	NaO^{t}Bu	110	90
14	0.5% $Pd(dba)_2$	**7j** (1)	NaO^{t}Bu	110	88

[a] 1 mmol of aryl chloride **8**, 1.2 mmol of arylamine **9**, 1.2 mmol of base, 0.5−1 mol % of Pd, 1−2 mol % of ligand **7**, 3 mL of toluene, 24 h. [b] Isolated yield. Purity was confirmed by ^{1}H NMR.

SCHEME 1. Synthesis of ClickPhos 7a−j



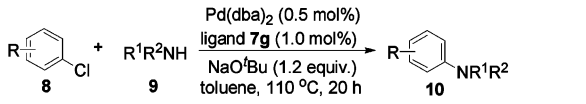
6a Ar = Ph 75%
6b Ar = 1-Np 58%
6c Ar = 2-MeO-Ph 83%
6d Ar = 2-NMe_2-Ph 61%
6e Ar = 2,6-dimethoxy-Ph 78%

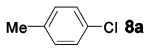
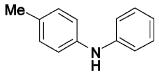
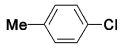
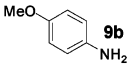
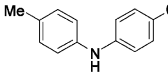
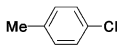
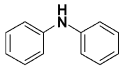
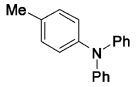
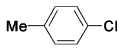
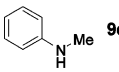
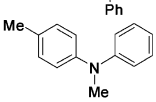
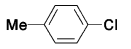
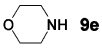
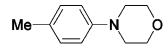
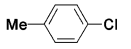
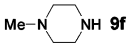
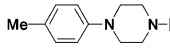
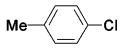
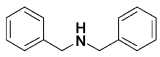
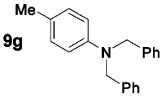
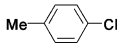
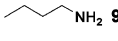
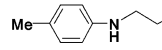
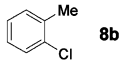
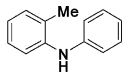
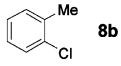
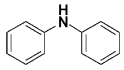
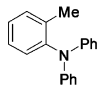
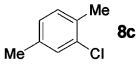
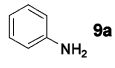
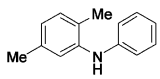
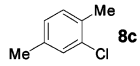
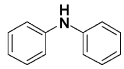
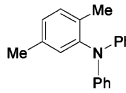
7a Ar = R = Ph 90%
7b Ar = Ph, R = Cy 93%
7c Ar = Ph, R = ^{t}Bu 91%
7d Ar = 1-Np, R = Cy 81%
7e Ar = 1-Np, R = ^{t}Bu 75%
7f Ar = 2-MeO-Ph, R = Cy 64%
7g Ar = 2-MeO-Ph, R = ^{t}Bu 76%
7h Ar = 2-NMe_2-Ph, R = ^{t}Bu 69%
7i Ar = 2,6-dimethoxy-Ph, R = ^{t}Bu 79%
7j Ar = 2,6-dimethoxy-Ph, R = Cy 76%

Corey−Fuchs reaction of commercial available aldehydes.[18b] Treatment of **6a**−**e** with LDA followed by addition of various chlorophosphines furnished ligands **7a**−**j** in good to excellent yields.

To evaluate the effectiveness of ClickPhos in the Pd-catalyzed amination of unactivated aryl chlorides, we first tested the reaction between 4-chlorotoluene (**8a**) and aniline (**9a**) with ligand **7c**, which gave excellent results in the Suzuki−Miyaura reaction (Table 1, entries 1−6). The reactions were performed with 0.5−1 mol % of $Pd(OAc)_2$ or $Pd(dba)_2$. $Pd(dba)_2$ afforded a slightly better yield than $Pd(OAc)_2$ (Table 1, entries 1−3). Different bases have also been tested; both KO^{t}Bu and NaO^{t}Bu gave similar results. When the reaction temperature was increased from 80 to 110 °C, better yields were obtained. In general, ligands bearing di-*tert*-butylphosphino substituents are more efficient than those having dicyclohexylphosphino groups. Catalysts generated from other ligands **7b**, **7d**, **7e**, **7h**, and **7i** provided results comparable to those of **7c**, while **7f** and **7j** gave slightly lower yields (Table 1, entries 7−10 and 12−14). ClickPhos **7g** was found to be the ligand of choice, giving the highest yield of product **10a** (95%, Table 1, entry 11). These results demonstrated that delicate tuning of the electronic and steric properties of the ligands by changing different substituent groups on the triazole ring can enhance the reaction yield.

TABLE 2. Pd/ClickPhos-Catalyzed Amination of Aryl Chloride with Various Amines[a]



entry	aryl chloride	amine	product	yield (%)[b]
1	 **8a**	 **9a**	 **10a**	95
2		 **9b**	 **10b**	93[c]
3		 **9c**	 **10c**	94
4		 **9d**	 **10d**	98
5		 **9e**	 **10e**	97
6		 **9f**	 **10f**	88
7		 **9g**	 **10g**	78
8		 **9h**	 **10h**	89[d]
9	 **8b**	 **9a**	 **10i**	94
10	 **8b**	 **9c**	 **10j**	96
11	 **8c**	 **9a**	 **10k**	95
12	 **8c**	 **9c**	 **10l**	94

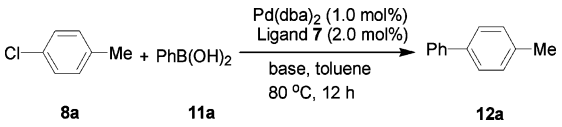
[a] 1 mmol of aryl chloride **8**, 1.2 mmol of arylamine **9**, 1.2 mmol of NaO^{t}Bu, 0.5 mol % of $Pd(dba)_2$, 1 mol % of ligand **7g**, 3 mL of toluene, 20 h, 110 °C. [b] Isolated yield. Purity was confirmed by ^{1}H NMR. [c] KO^{t}Bu was used instead of NaO^{t}Bu. [d] 5 equiv of amine was used.

On the basis of the optimized reaction conditions, the coupling reactions between several aryl chlorides and a variety of primary and secondary amines were carried out to explore the scope of the $Pd(dba)_2$/**7g** catalytic system (Table 2). In most cases, the corresponding anilines were obtained in good to excellent yields (>90%) with a low catalyst loading (0.5 mol % of Pd). For an electron-rich amine **9b**, a better result was obtained when a stronger base, KO^{t}Bu, was used instead of NaO^{t}Bu (Table 2, entry 2). In the case of an aliphatic primary amine (Table 2, entry 8), a large excess of *n*-butylamine (5 equiv) had to be

(17) (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596. (c) Krasinski, A.; Fokin, V. V.; Sharpless, K. B. *Org. Lett.* **2004**, *6*, 1237. (d) Feldman, A. K.; Colasson, B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 3897. (e) Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 210.

(18) (a) Zhu, W.; Ma, D. *Chem. Commun.* **2004**, *7*, 888. (b) Gilbert, A. M.; Miller, R.; Wulff, W. D. *Tetrahedron* **1999**, *55*, 1607.

TABLE 3. Screening of Ligands and Reaction Conditions[a]



8a **11a** **12a**

entry	ligand	base	yield[b] (%)
1	**7a**	K_3PO_4	<5
2	**7b**	K_3PO_4	70
3	**7c**	K_3PO_4	94
4	**7d**	K_3PO_4	88
5	**7e**	K_3PO_4	91
6	**7f**	K_3PO_4	20
7	**7g**	K_3PO_4	91
8	**7h**	K_3PO_4	79
9	**7c**	KF	86
10	**7c**	CsF	57

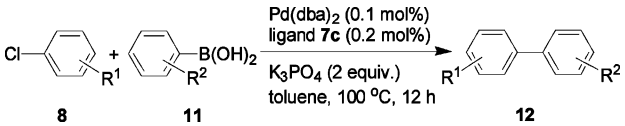
[a] 1 mmol of 4-chlorotoluene **8a**, 1.5 mmol of phenylboronic acid **11a**, 2 mmol of base, 1 mol % of $Pd(dba)_2$, 2 mol % of ligand **7**, 3 mL of toluene, 12 h, 80 °C. [b] Isolated yield. Purity was confirmed by ^1H NMR.

used to suppress the disubstituted products. Ortho substituents on the aryl chlorides can be tolerated as well, leading to the corresponding hindered coupling products in high yields (Table 2, entries 9−12). These results demonstrate the broad substrate scope and high catalytic efficiency of the $Pd(dba)_2$/**7g** system for the amination reactions of aryl chlorides, which are comparable or better than those reported to date with other catalytic systems.[8b,19]

The high activities of the Pd/ClickPhos catalysts in the amination reactions led us to further explore their applications to Suzuki−Miyaura coupling reactions of aryl chlorides. The reaction between 4-chlorotoluene (**8a**) and phenylboronic acid (**11a**) was first tested with ligands **7a**−**h** (Table 3, entries 1−8). The reactions were performed in the presence of the catalysts derived from 1 mol % of $Pd(dba)_2$ and 2 mol % of ligands. While a very low yield (<5%) of the coupling product was observed with diphenylphosphine ligand **7a**, good to excellent yields were achieved with dialkylphosphine ligands **7b** and **7c** (70% and 94%, respectively). These results are consistent with the general trend of the ligand efficiency observed in coupling reactions with other structurally related ligand sets. In general, sterically hindered and electron-rich ligands are more efficient for coupling reactions. Catalysts generated from another two ligands **7e** and **7g**, having di-*tert*-butylphosphino substituents, also provided the coupling product in yields comparable to that of **7c** (Table 3, entries 5 and 7). Ligand **7d** afforded similar results to its analogue **7e**, while **7f**,**h** gave much lower coupling yields (Table 1, entries 4, 6, and 8). Using the best ligand **7c**, various bases, such as K_3PO_4, KF, and CsF, were examined. K_3PO_4 was found to be the base of choice for the Pd/**7c** catalytic system (Table 3, entries 3, 9, and 10).

On the basis of the optimized reaction conditions, the coupling reactions between a range of aryl chlorides and several aryl boronic acids were carried out to explore the general effectiveness of the Pd/**7c** catalytic system (Table 4). Excellent yields were obtained with 0.1 mol % of the catalyst in the reactions between various electron-deficient aryl chlorides and phenylboronic acid (Table 4, entries 5−12). A heteroaromatic chloride **8k** coupled with phenylboronic acid providing product **12l** in nearly quantitative yield (Table 4, entry 13). For more challenging electronically unactivated and deactivated aryl chlorides, the corresponding biaryl products were obtained in good to excellent yields (Table 4, entries 1−4). Ortho substituents on the aryl chlorides can be tolerated as well, leading to the corresponding hindered coupling products in high yields (Table 4, entries 2, 3, and 10−12). Reactions using aryl boronic acid **11b** were also performed, and the yields were as good as those of **11a** (Table 4, entries 12 and 14). Furthermore, when applying very low catalyst loading (0.01 mol % of catalyst), aryl chloride **8d** also coupled with phenylboronic acid (**11a**) efficiently, giving the product **12d** in 93% yield (Table 4, entry 6, 9300 TON).

TABLE 4. Pd-Catalyzed Suzuki-Miyaura Coupling of Aryl Chlorides[a]



8 **11** **12**

entry	aryl chloride	boronic acid	yield[b] (%)
1	R^1 = *p*-Me, **8a**	R^2 = H, **11a**	89 (**12a**)
2	R^1 = *o*-Me, **8b**	R^2 = H, **11a**	92 (**12b**)
3	R^1 = 2,5-di-Me, **8c**	R^2 = H, **11a**	98 (**12c**)
4	R^1 = *p*-OMe, **8d**	R^2 = H, **11a**	86 (**12d**)
5	R^1 = *p*-COMe, **8e**	R^2 = H, **11a**	99 (**12e**)
6	R^1 = *p*-COMe, **8e**	R^2 = H, **11a**	93 (**12f**)
7	R^1 = *p*-NO_2, **8f**	R^2 = H, **11a**	96 (**12g**)
8	R^1 = *p*-CO_2Me, **8g**	R^2 = H, **11a**	94 (**12g**)
9	R^1 = *p*-CF_3, **8h**	R^2 = H, **11a**	91 (**12h**)
10	R^1 = *p*-COMe, **8i**	R^2 = H, **11a**	89 (**12i**)
11	R^1 = *o*-CN, **8j**	R^2 = H, **11a**	90 (**12j**)
12	R^1 = *o*-CN, **8j**	R^2 = *p*-Me, **11b**	92 (**12k**)
13	R^1 = 2-pyridinyl, **8k**	R^2 = H, **11a**	99 (**12l**)
14	R^1 = H, **8l**	R^2 = *p*-Me, **11b**	99 (**12a**)

[a] 1 mmol of aryl chloride **8**, 1.5 mmol of arylboronic acid **11**, 2 mmol of K_3PO_4, 0.1 mol % of $Pd(dba)_2$, 0.20 mol % of ligand **7c**, 3 mL of toluene, 12 h, 100 °C. [b] Isolated yield. Purity was confirmed by ^1H NMR.

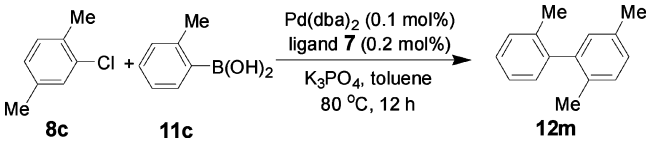
While excellent results have been achieved between the coupling of a wide range of aryl chlorides with several boronic acids, coupling between ortho-substituted aryl chlorides and ortho-substituted boronic acids, forming highly hindered biaryls, are considerably more challenging reactions. The steric hindrance prevents an effective oxidative addition of aryl chlorides to palladium centers. Recently, Buchwald reported a highly active ligand with a 2,6-dimethoxybenzene moiety for this type of reaction,[13b] which prompted us to diversify ClickPhos for Suzuki−Miyaura coupling of more hindered substrates.

Reaction between 2-chloro-*p*-xylene (**8c**) and 2-methylphenylboronic acid (**11c**) was first tested with ligands **7c**−**j** (Table 5). In most cases, moderate to good yields were obtained with the exception that ligand **7d** only gave 17% yield (Table 5, entry 2). A general trend is that ligands bearing a di-*tert*-butylphosphino group (**7c**, **7e**, **7g**, and **7i**) give much higher yields than their dicyclohexylphospino analogues (**7d**, **7f**, **7h**, and **7j**). Ligand **7i**, which has a 2,6-dimethoxybenzene moiety on the triazole ring, provided the best yield of biaryl **12d** (96%, Table 5, entry 7).

Using ligands **7c**, **7i**, and **7j**, several hindered disubstituted aryl chlorides were employed in the Pd-catalyzed Suzuki-Miyaura reaction with boronic acids (Table 6). For 2-chloro-*p*-xylene (**8c**), ligand **7c** gave results comparable to those achieved by **7i** (Table 6, entries 1−4). However, for more hindered substrate 2-chloro-*m*-xylene (**8m**), the coupling with 2-methoxyboronic acid (**11d**) proceeded to give biaryl **12o** in

(19) For most recent examples of Pd-catalyzed amination reactions of aryl chlorides, see: (a) Shen, Q.; Shekhar, S.; Stambuli, J. P.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2005**, *44*, 1371. (b) Stambuli, J. P.; Incavito, C. D.; Buehl, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 1184.

TABLE 5. Screening Ligands and Reaction Conditions[a]



8c 11c 12m

entry	ligand	yield[b] (%)
1	**7c**, Ar = Ph, R = ^{t}Bu	89
2	**7d**, Ar = 1-Np, R = Cy	17
3	**7e**, Ar = 1-Np, R = ^{t}Bu	70
4	**7f**, Ar = 2-MeO-Ph, R = Cy	45
5	**7g**, Ar = 2-MeO-Ph, R = ^{t}Bu	94
6	**7h**, 2-NMe_2-Ph, R = ^{t}Bu	63
7	**7i**, Ar = 2,6-dimethoxy-Ph, R = ^{t}Bu	96
8	**7j**, Ar = 2,6-dimethoxy-Ph, R = Cy	5x

[a] 1 mmol of **8c**, 1.5 mmol of **11c**, 2 mmol of K_3PO_4, 0.1 mol % of $Pd(dba)_2$, 0.2 mol % of ligand **7**, 3 mL of toluene, 12 h, 80 °C. [b] Isolated yield. Purity was confirmed by ^{1}H NMR.

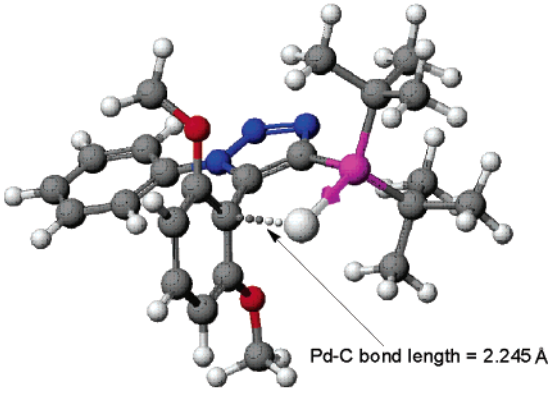
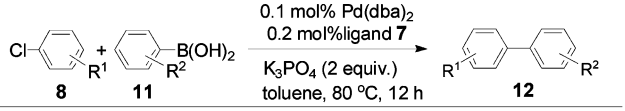


FIGURE 2. MM2 calculations of Pd/**7i** complex based on the CAChe program.

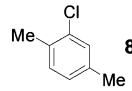
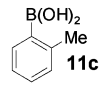
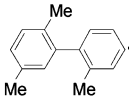
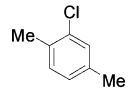
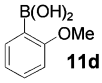
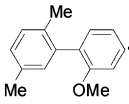
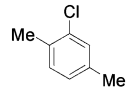
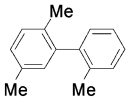
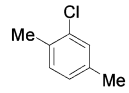
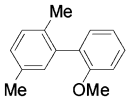
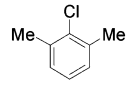
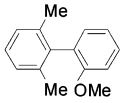
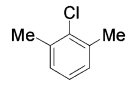
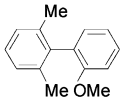
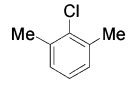
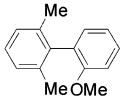
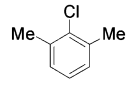
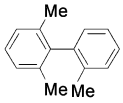
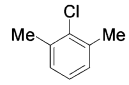
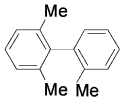
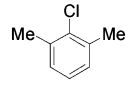
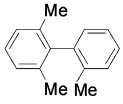
only 12% yield even with 1 mol % of the catalyst derived from **7c**. In constrast, using the catalyst derived from **7i**, the yield was greatly increased to 72% (Table 6, entry 6). Ligand **7j** was also effective for this reaction, affording a moderate yield of 57% (Table 6, entry 7). The electronic property of boronic acids also played an important role in this type of reaction. When a less electron rich boronic acid **11c** was used, higher yields were generally achieved (Table 6, entry 8−10). Ligand **7i** was again found to the most efficient ligand, giving 90% yield of biaryl **12p** (Table 6, entry 9). Compared to ligand **7j**, the higher catalytic efficiency observed with ligand **7i** is likely because the bulky di-*tert*-butyl groups can better facilitate the reductive elimination to form the product.[6c]

To further understand the special activity of ligand **7i**, a CAChe model of Pd/**7i** complex based on the MM2 calculation was obtained. The key feature of the complex structure is the orientation of the arene group on the 5-position of the triazole ring. The distance between the palladium and the sp^2-carbon on the 2,6-dimethoxybenzene moiety (as indicated by the arrow in Figure 2) is around 2.245 Å based on the MM2 calculation, which is appreciably shorter than the sum of the van der Waals radii for Pd and C, 3.33 Å (Pd = 1.63 Å, C = 1.70 Å). This points to the likelihood of a metal−arene interaction, which might stabilize the palladium complex in the catalytic cycle and therefore enhance the catalyst reactivity. Similar observations have previously been reported by Buchwald[13d] and Fink.[20]

TABLE 6. Pd-Catalyzed Suzuki−Miyaura Coupling of Hindered Aryl Chlorides[a]



8 11 12

entry	aryl chloride	boronic acid	ligand	product	yield (%)[b]
1	 **8c**	 **11c**	**7c**	 **12m**	89
2		 **11d**	**7c**	 **12n**	85
3			**7i**		96
4			**7i**		95
5	 **8m**		**7c**[c]	 **12o**	12[d]
6			**7i**[c]		72[d]
7			**7j**[c]		57[d]
8			**7c**[c]	 **12p**	32[d]
9			**7i**[c]		90[d]
10			**7j**[c]		60[d]

[a] 1 mmol of **8**, 1.5 mmol of **11**, 2 mmol of K_3PO_4, 0.1 mol % of $Pd(dba)_2$, 0.2 mol % of ligand **7**, 3 mL of toluene, 12 h, 80 °C. [b] Isolated yield. Purity was confirmed by ^{1}H NMR. [c] 1 mol % of $Pd(dba)_2$ and 2 mol % of ligand were used. [d] The reaction was carried out at 120 °C.

Conclusions

In conclusion, we have developed a new series of monophosphines **7** (ClickPhos) bearing a triazole heterocycle in the backbone. These ligands are readily accessible and could be easily diversified via efficient 1,3-dipolar cycloadditions of various azides and acetylenes. With Pd complex derived from ligand **7g**, up to 98% yield was achieved in the amination reactions of aryl chlorides. Pd/**7c** complex provided highly active catalyst for Suzuki−Miyaura coupling of aryl chlorides with excellent yields and TONs. Among the ClickPhos series, ligand **7i**, which has a 2,6-dimethoxybenzene moiety on the triazole ring, was particularly effective in the Pd-catalyzed Suzuki−

(20) Reid, S. M.; Boyle, R. C.; Mague, J. T.; Fink, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 7816.

Miyaura coupling to form hindered biaryl compounds (up to 96% yield). A CAChe model for the Pd/**7i** complex shows that the likelihood of a Pd−arene interaction might be a rationale for the its high catalytic reactivity.

Experimental Section

General Procedure for the Preparation of ClickPhos 7a−j. 4-Di-*tert*-butylphosphanyl-1,5-diphenyl-1*H*-[1,2,3]triazole (7c). To a solution of 1,5-diphenyl-1*H*-[1,2,3]triazole (**6a**) (0.520 g, 2.35 mmol) in THF (20 mL) was added LDA (2.35 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h followed by addition of P^{t}Bu$_2$Cl (0.446 mL, 2.35 mmol). The resulting mixture was slowly warmed to rt and stirred overnight. TLC showed the reaction was essentially complete after 16 h. The solvent was removed under vacuum. A degassed mixture of brine/H_2O (1:1) was added, and the resulting mixture was extracted with degassed ether (15 mL × 3). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel under nitrogen (hexanes/ether, 80:20) to afford **7c** as a sticky solid (0.78 g, 91%): ^{1}H NMR (CD_2Cl_2, 360 MHz) δ 7.41−7.23 (m, 10H), 1.27 (d, J = 12.1 Hz, 18H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 145.2 (d, J = 39.0 Hz), 142.2 (d, J = 27.9 Hz), 137.2, 131.1 (d, J = 2.5 Hz), 129.4, 129.3, 129.0, 128.6, 128.5, 125.2, 33.1 (d, J = 17.0 Hz), 30.6 (d, J = 14.4 Hz); ^{31}P NMR (CD_2Cl_2, 145 MHz) δ 3.51; HRMS (ESI+) calcd for $C_{22}H_{29}N_3P$ (MH^+) 366.2084, found 366.2099.

4-Diphenylphosphanyl-1,5-diphenyl-1*H*-[1,2,3]triazole (7a). This compound was prepared from triazole compound **6a** and PPh_2Cl following the general procedure as a white solid (90% yield): ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.73−7.69 (m, 4H), 7.44−7.36 (m, 14H), 7.26 (d, J = 7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 143.3 (d, J = 39.5 Hz), 141.1 (d, J = 14.2 Hz), 136.40, 136.38 (d, J = 15.4 Hz), 133.8, 133.5, 130.1 (d, J = 3.5 Hz), 129.2, 129.0, 128.8, 128.6, 128.35, 128.28, 128.2, 126.5, 124.8; ^{31}P NMR ($CDCl_3$, 145 MHz) δ −35.85; HRMS (ESI+) calcd for $C_{26}H_{21}N_3P$ (MH^+) 406.1475, found 406.1473.

4-Dicyclohexylphosphanyl-1,5-diphenyl-1*H*-[1,2,3]triazole (7b). This compound was prepared from triazole compound **6a** and PCy_2Cl following the general procedure as a white solid (93% yield): ^{1}H NMR (CD_2Cl_2, 360 MHz) δ 7.41−7.23 (m, 10H), 2.28−2.21 (m, 2H), 1.87−1.67 (m, 10H), 1.38−1.09 (m, 10H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 144.7 (d, J = 34.8 Hz), 141.2 (d, J = 24.6 Hz), 137.2, 130.9 (d, J = 2.9 Hz), 129.4, 129.3, 129.1, 128.6, 128.0, 125.3, 33.5 (d, J = 8.4 Hz), 30.8 (d, J = 16.3 Hz), 29.8 (d, J = 7.5 Hz), 27.5 (d, J = 18.5 Hz), 27.4 (d, J = 1.6 Hz), 26.8; ^{31}P NMR (CD_2Cl_2, 145 MHz) δ −27.76; HRMS (ESI+) calcd for $C_{26}H_{33}N_3P$ (MH^+) 418.2419, found 418.2412.

4-Dicyclohexylphosphanyl-1-phenyl-5-(1-naphthyl)-1*H*-[1,2,3]-triazole(7d). This compound was prepared from triazole compound **6b** and PCy_2Cl following the general procedure as a white solid (81% yield): ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.93 (dd, J = 8.3, 18.7 Hz, 2H), 7.24−7.53 (m, 10H), 2.36 (t, J = 11.3 Hz, 1H), 2.09 (t, J = 11.2 Hz, 1H), 1.52−1.98 (m, 10H), 0.97−1.48 (m, 10H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 143.5 (d, J = 27.4 Hz), 143.2, 143.0, 137.2, 133.7, 132.4, 130.3, 129.3, 128.9, 128.8, 127.1, 126.7, 125.9, 125.5, 125.3, 124.2, 33.6 (d, J = 9.2 Hz), 30.9 (d, J = 16.3 Hz), 30.0 (d, J = 8.8 Hz), 27.4 (d, J = 10.3 Hz), 27.2 (d, J = 3.7 Hz), 26.8; ^{31}P NMR (145 MHz, CD_2Cl_2) δ −28.31; HRMS (ESI+) calcd for $C_{30}H_{35}N_3P$ (MH^+) 468.2569, found 468.2571.

4-Di-*tert*-butylphosphanyl-1-phenyl-5-(1-naphthyl)-1*H*-[1,2,3]-triazole (7e). This compound was prepared from triazole compound **6b** and P^{t}Bu$_2$Cl following the general procedure as a white solid (75% yield): ^{1}H NMR (CD_2Cl_2, 300 MHz) δ 7.98−7.88 (m, 2H), 7.55−7.21 (m, 10H), 1.34−1.24 (m, 18H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.1 (d, J = 14.9 Hz), 143.7 (d, J = 28.6 Hz), 137.3, 133.7, 132.4, 130.6, 130.3, 129.3, 129.0, 128.8, 127.0, 126.6, 126.1, 125.6, 125.3, 124.2, 32.9 (dd, J = 17.0, 21.7 Hz), 30.8 (dd, J = 10.3, 14.3 Hz); ^{31}P NMR (CD_2Cl_2, 145 MHz) δ 3.63; HRMS (ESI+) calcd for $C_{26}H_{31}N_3P$ (MH^+) 416.2256, found 416.2252.

4-Dicyclohexylphosphanyl-1-phenyl-5-(2-methoxyphenyl)-1*H*-[1,2,3]triazole (7f). This compound was prepared from triazole compound **6c** and PCy_2Cl following the general procedure as a white solid (64% yield): ^{1}H NMR (360 MHz, CD_2Cl_2) δ 7.36−7.42 (m, 6H), 7.30 (dd, J = 1.3, 7.5 Hz, 1H), 7.05−7.09 (m, 1H), 6.89 (d, J = 8.4 Hz, 1H), 3.47 (s, 3H), 2.10−2.33 (m, 2H), 1.61−2.05 (m, 10H), 0.98−1.52 (m, 10H); ^{13}C NMR (90 MHz, CD_2Cl_2) δ 157.2, 141.8 (d, J = 27.4 Hz), 141.5 (d, J = 15.3 Hz), 137.6, 132.4, 131.1, 128.8, 128.4, 123.8, 120.3, 117.1, 111.1, 55.0, 33.0 (d, J = 42.4 Hz), 30.3, 29.4 (d, J = 30.8 Hz), 27.2 (d, J = 19.5 Hz), 27.1, 26.6; ^{31}P NMR (145 MHz, CD_2Cl_2) δ −27.99; HRMS (ESI+) calcd. for $C_{27}H_{35}N_3OP$ (MH^+) 448.2518, found 448.2510.

4-Di-*tert*-butylphosphanyl-1-phenyl-5-(2-methoxyphenyl)-1*H*-[1,2,3]triazole (7g). This compound was prepared from triazole compound **6c** and P^{t}Bu$_2$Cl following the general procedure as a white solid (76% yield): ^{1}H NMR (CD_2Cl_2, 360 MHz) δ 7.47−7.32 (m, 7H), 7.09 (t, J = 7.2 Hz, 1H), 6.90 (d, J = 8.2 Hz, 1H), 3.48 (s, 3H), 1.41 (d, J = 11.8 Hz, 9H), 1.24 (d, J = 11.8 Hz, 9H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 157.3, 142.5 (d, J = 9.3 Hz), 142.2 (d, J = 24.5 Hz), 137.6, 132.6 (d, J = 2.6 Hz), 131.1, 128.8, 128.5, 123.9, 120.3, 117.4, 111.0, 54.9, 32.5 (dd, J = 10.3, 17.0 Hz), 30.2 (dd, J = 14.1, 44.1 Hz); ^{31}P NMR (CD_2Cl_2, 145 MHz) δ 3.47; HRMS (ESI+) calcd for $C_{23}H_{31}N_3OP$ (MH^+) 396.2205, found 396.2202.

4-Di-*tert*-butylphosphanyl-1-phenyl-5-(2-*N*,*N*-dimethylphenyl)-1*H*-[1,2,3]triazole (7h). This compound was prepared from triazole compound **6d** and P^{t}Bu$_2$Cl following the general procedure as a white solid (69% yield). ^{1}H NMR (360 MHz, CD_2Cl_2) δ 7.53 (d, J = 7.6 Hz, 1H), 7.35−7.40 (m, 4H), 7.26−7.29 (m, 2H), 7.05−7.10 (m, 1H), 6.88 (d, J = 8.2 Hz, 1H), 2.16 (s, 6H), 1.38 (d, J = 11.8 Hz, 9H), 1.30 (d, J = 12.1 Hz, 9H); ^{13}C NMR (90 MHz, CD_2Cl_2) δ 151.8, 143.9 (d, J = 38.2 Hz), 141.5 (d, J = 28.6 Hz), 138.2, 133.5 (d, J = 5.0 Hz), 130.4, 128.6, 128.1, 122.8, 120.7, 120.1, 118.8, 41.8, 33.1 (dd, J = 17.1, 22.3 Hz), 30.6 (dd, J = 8.7, 14.4 Hz); ^{31}P NMR (145 MHz, CD_2Cl_2) δ 2.72; HRMS (ESI+) calcd for $C_{24}H_{34}N_4P$ (MH^+) 409.2521, found 409.2537.

4-Di-*tert*-butylphosphanyl-1-phenyl-5-(2,6-dimethoxyphenyl)-1*H*-[1,2,3]triazole (7i). This compound was prepared from triazole compound **6e** and P^{t}Bu$_2$Cl following the general procedure as a white solid (79% yield): ^{1}H NMR (360 MHz, CD_2Cl_2) δ 7.37−7.42 (m, 6H), 6.58 (d, J = 8.4 Hz, 2H), 3.63 (s, 6H), 1.28 (d, J = 12.0 Hz, 18 H); ^{13}C NMR (90 MHz, CD_2Cl_2) δ 158.5, 143.0, 139.5, 137.4, 131.5, 128.7, 128.5, 124.1, 105.7, 103.3, 55.2, 32.3 (d, J = 16.2 Hz), 30.2 (d, J = 14.4 Hz); ^{31}P NMR (145 MHz, CD_2Cl_2) δ 4.73; HRMS (ESI+) calcd for $C_{24}H_{33}N_3O_2P$ (MH^+) 426.2310, found 426.2307.

4-Dicyclohexylphosphanyl-1-phenyl-5-(2,6-dimethoxyphenyl)-1*H*-[1,2,3]triazole (7j). This compound was prepared from triazole compound **6e** and PCy_2Cl following the general procedure as a white solid (76% yield): ^{1}H NMR (360 MHz, CD_2Cl_2) δ 7.38−7.42 (m, 6H), 6.59 (d, J = 8.4 Hz, 2H), 3.65 (s, 6H), 2.16−2.22 (m, 2H), 1.69−1.77 (m, 10H), 1.13−1.39 (m, 10H); ^{13}C NMR (90 MHz, CD_2Cl_2) δ 158.9, 142.6 (d, J = 20.4 Hz), 139.0 (d, J = 40.6 Hz), 137.7, 131.9, 129.1, 128.8, 124.2, 105.9, 103.8, 55.7, 33.2 (d, J = 7.8 Hz), 30.5 (d, J = 16.3 Hz), 29.7 (d, J = 7.9 Hz), 27.5 (d, J = 10.5 Hz), 27.4 (d, J = 6.0 Hz), 26.9; ^{31}P NMR (145 MHz, CD_2Cl_2) δ −27.36; HRMS (ESI+) calcd for $C_{28}H_{37}N_3O_2P$ (MH^+) 478.2623, found 478.2599.

General Procedure for Amination of Aryl Chlorides. To a Schlenk tube, which was flame-dried under vacuum and backfilled with nitrogen, NaO^{t}Bu (1.2 mmol), were subsequently added toluene (3 mL), a stock solution of ligand **7** in toluene (0.01 mmol), a stock solution of Pd(dba)$_2$ (0.005 mmol) in toluene, aryl chloride **8** (1.0 mmol) and amine **9** (1.2 mmol). The flask was sealed, and the reaction mixture was heated at 110 °C with vigorous stirring for 20 h. After the mixture was cooled to rt, 15 mL of EtOAc was added and the mixture was washed with 5 mL of brine. The organic

layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography on basic Al_2O_3.

General Procedure for Suzuki Coupling of Aryl Chlorides. A Schlenk tube was charged with boronic acid **11** (1.5 mmol) and K_3PO_4 (2 mmol). The flask was evacuated and backfilled with nitrogen three times. Toluene (3 mL), a stock solution of ligand **7** in toluene (0.002 mmol), a stock solution of $Pd(dba)_2$ (0.001 mmol) in toluene, and aryl chloride **8** (1.0 mmol) were subsequently added. The flask was sealed, and the reaction mixture was heated at 80 °C with vigorous stirring for 12 h. After the mixture was cooled to rt, 15 mL of EtOAc was added, and the mixture was washed with 5 mL of 1 N NaOH (aq) and 5 mL of brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel.

Acknowledgment. This work was supported by the National Institutes of Health.

Supporting Information Available: General experimental methods, preparation and characterization data for triazole compounds **6a**−**e** and ^1H, ^{13}C NMR spectral data for **10a**−**l** and **12a**−**p**. This material is available free of charge via the Internet at http://pubs.acs.org.

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