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Triazole-Based Monophosphines for Suzuki–Miyaura Coupling and Amination Reactions of Aryl Chlorides

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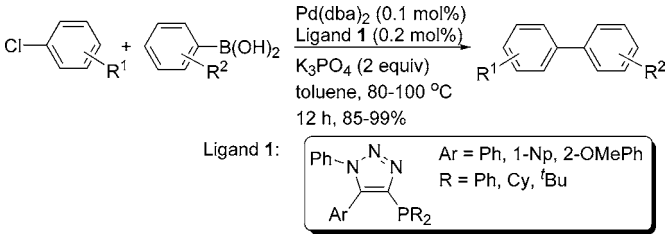
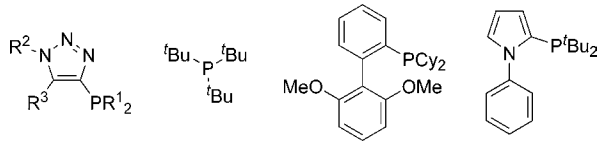
ABSTRACT



A new class of triazole-based monophosphine 1 (ClickPhos) has been prepared via efficient 1,3-dipolar cycloadditions of readily available azides and acetylenes. Palladium complexes derived from these ligands provide highly active catalysts for Suzuki–Miyaura coupling and amination reactions of aryl chlorides.

Transition metal catalyzed cross-coupling reactions have become an extremely versatile tool in organic synthesis for the connection of two fragments via the formation of a carbon−carbon bond or carbon−heteroatom bond.[1] It has been well recognized that ligands employed in these processes have significant impact on the outcome of the reactions.[2] Therefore, designing ligands with appropriate natures and great diversity is crucial for dealing with the challenging substrates in this area. Herein, we wish to report a concise synthesis of a novel class of triazole-based monophosphine **1** (Figure 1), which is a highly efficient ligand for Pd-catalyzed Suzuki−Miyaura coupling (up to 9,300 TON) and amination reactions of unactivated aryl chlorides.

The Pd-catalyzed Suzuki−Miyaura coupling reaction is one of the most attractive methods for the preparation of biaryl compounds because of the advantages of the wide functional group tolerance and the use of stable and nontoxic organoborane reagents.[3] Some of the recent progress in this



1 ClickPhos **2** **3** SPhos **4**

Figure 1. Examples of effective ligands for Suzuki−Miyaura coupling of aryl chlorides.

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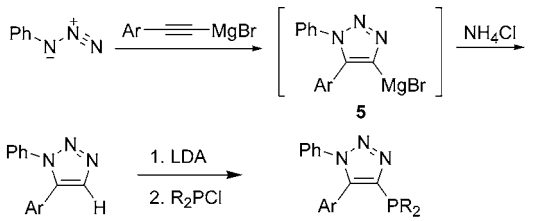
reaction has been focused on the use of aryl chlorides as coupling partners in view of their low cost and readily available diversity.[4] A number of reports have shown that Pd complexes derived from sterically hindered and electron-rich phosphines are effective catalysts for this transformation.[5] Some of the notable examples include the use of bulky trialkylphosphines (i.e., P(^{t}Bu)$_3$, **2**) by Fu,[6] dialkyl biphenylphosphines (i.e., **3**) by Buchwald,[7] and dialkyl heteroaromatic phosphines (i.e., **4**) by Beller.[8] Other strategies such as using sterically hindered *N*-heterocyclic carbenes (NHCs) as ligands[9] and palladacycles as the precatalysts[10] also provide efficient catalytic systems.

Although many ligands have been reported, rapid assembly 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 formation of 1,4- and 1,5-disubstituted triazole compounds via 1,3-dipolar cycloadditions of organoazides and acetylenes.[11] The unique properties such as modularity, wide reaction scope, mild reaction conditions, high yields, and regioselectivity make these reactions excellent examples of click chemistry.[12] We envisioned that triazole-based monophosphines, i.e., **1** (Figure 1), might be a promising and attractive ligand family for coupling reactions because of the facile synthesis of the triazole moiety and the ease of individual tuning of the substituents, i.e., R^1, R^2, and R^3.

On the basis of the efficient formation of 1,5-disubstituted triazoles, a straightforward two-step synthesis of the several ligands **1a**−**e** (ClickPhos) has been developed (Scheme 1).

Scheme 1. Synthesis of ClickPhos **1a**−**e**



6a Ar = Ph 75%
6b Ar = 1-Np 58%
6c Ar = 2-OMePh 83%

1a Ar = R = Ph 90%
1b Ar = Ph, R = Cy 93%
1c Ar = Ph, R = ^{t}Bu 91%
1d Ar = 1-Np, R = ^{t}Bu 75%
1e Ar = 2-OMePh, R = ^{t}Bu 76%

Following the general procedure reported by Sharpless,[11b] 1,5-disubstituted triazoles **6a**−**c** were obtained from phenyl azide and various aryl acetylenes in good yields by quenching the in situ generated 4-halomagnesium triazole intermediates **5** with aqueous NH_4Cl solution. Treatment of **6** with LDA followed by addition of various chlorophosphines furnished ligands **1a**−**e** in good to excellent yields. It is worthy of note that the ligand synthesis could be shortened into a one-pot operation with comparable crude yield of the desired product by directly quenching the intermediate **5** with a chlorophosphine. The isolation of triazole **6** prior to installation of the phosphino substituents is solely because of the ease of purification of the final phosphine ligands. Although only five members of ClickPhos are presented herein, the powerful connectivity of Sharpless click chemistry should allow us to rapidly make a wide variety of ClickPhos derivatives using readily available azides and acetylenes.

To evaluate the effectiveness of ClickPhos in the Pd-catalyzed Suzuki-−iyaura coupling, we first tested the reaction between 4-chlorotoluene (**7a**) and phenylboronic acid (**8a**) with ligands **1a**−**e** (Table 1, entries 1−5). The

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(5) For some recent examples of Suzuki−Miyaura coupling using aryl chlorides, see: (a) Zapf, A.; Ehrentraut, A.; Beller, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4153. (b) Schnyder, A.; Indolese, A. F.; Studer, M.; Blaser, H.-U. *Angew. Chem., Int. Ed.* **2002**, *41*, 3668. (c) Stambuli, J. P.; Kuwano, R.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 4746. (d) Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553. (e) Li, G. Y. *J. Org. Chem.* **2002**, *67*, 3643. (f) Hu, Q.; Lu, Y.; Tang, Z.; Yu, H. *J. Am. Chem. Soc.* **2003**, *125*, 2856. (g) Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 3690. (h) Jensen, J. F.; Johannsen, M. *Org. Lett.* **2003**, *5*, 3025. (i) Roca, F. X.; Richards, C. J. *J. Org. Chem.* **2003**, *68*, 2592. (j) Özdemir, I.; Alici, B.; Gürbüz, N.; Çetinkaya, E.; Çetinkaya, B. *J. Mol. Catal. A* **2004**, 37. (k) Tewari, A.; Hein, M.; Zapf, A. Beller, M. *Synthesis* **2004**, 925. (l) an der Heiden, M.; Plenio, H. *Chem. Eur. J.* **2004**, *10*, 1789. (m) Colacot, T. J.; Shea, H. A. *Org. Lett.* **2004**, *6*, 3731. (n) Arvela, R. K.; Leadbeater, N. E.; Sangi, M. S.; Williams, V. A.; Granados, P.; Singer, R. D. *J. Org. Chem.* **2005**, *70*, 161. (o) Zapf, A.; Beller, M. *Chem. Commun.* **2005**, 431. (p) Lemo, J.; Heuze, K.; Astruc, D. *Org. Lett.* **2005**, *7*, 2253.

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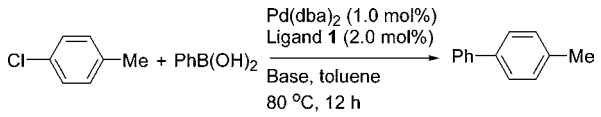
Table 1. Screening of Ligands and Reaction Conditions[a]



7a 8a 9a

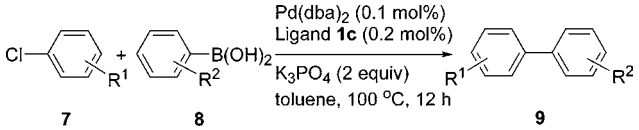
entry	ligand	base	yield (%)[b]
1	**1a**	K_3PO_4	<5
2	**1b**	K_3PO_4	70
3	**1c**	K_3PO_4	94
4	**1d**	K_3PO_4	88
5	**1e**	K_3PO_4	91
6	**1c**	KF	86
7	**1c**	CsF	57

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

reactions were performed in the presence of the catalysts derived from 1 mol % of $Pd(dba)_2$ and 2 mol % of ligands. Although very low yield (<5%) of the coupling product was observed with diphenyl phosphine ligand **1a**, good to excellent yields were achieved with dialkyl phosphine ligands **1b** and **1c** (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 **1d** and **1e**, having a di-*tert*-butylphosphino substituent, also provided the coupling product in yields comparable to that of **1c**. Using the best ligand **1c**, several 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/**1c** catalytic system (Table 1, entries 3, 6, and 7).

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/**1c** catalytic system (Table 2). Excellent yields were obtained with 0.1 mol % of the catalyst in the reactions between various electron-deficient aryl chlorides and phenylboronic acid (Table 2, entries 2−8). A heteroaromatic chloride **7h** coupled with phenyl boronic acid provided product **9h** in nearly quantitative yield (Table 2, entry 9). For more challenging electronically unactivated and deactivated aryl chlorides, the corresponding biaryl products were obtained in good to excellent yields (entries 1 and 10−12). *ortho*-Substituents on the aromatic rings can be tolerated as well, leading to the corresponding hindered coupling products in high yields (Table 2, entries 7, 8, 10, 11, and 14−16). Reactions using other aryl boronic acids **8b**−**d** were also performed, and the yields were as good as those of **8a** (Table 2, entries 13−16). Furthermore, when applying very low catalyst loading (0.01 mol % of catalyst), aryl chloride **7b** also coupled with phenylboronic acid (**8a**) efficiently, giving the product **9b** in 93% yield (Table 2, entry 3, 9,300 TON). Therefore, these results demonstrate the broad substrate scope and high catalytic efficiency of the

Table 2. Pd-Catalyzed Suzuki−Miyaura Coupling of Aryl Chlorides[a]



7 8 9

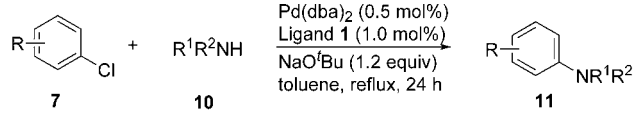
entry	aryl chloride	boronic acid	yield (%)[b]
1	R^1 = *p*-Me **7a**	R^2 = H **8a**	89 (**9a**)
2	R^1 = *p*-COMe **7b**	R^2 = H **8a**	99 (**9b**)
3[c]	R^1 = *p*-COMe **7b**	R^2 = H **8a**	93 (**9b**)
4	R^1 = *p*-NO_2 **7c**	R^2 = H **8a**	96 (**9c**)
5	R^1 = *p*-CO2Me **7d**	R^2 = H **8a**	94 (**9d**)
6	R^1 = *p*-CF3 **7e**	R^2 = H **8a**	91 (**9e**)
7	R^1 = *o*-COMe **7f**	R^2 = H **8a**	89 (**9f**)
8	R^1 = *o*-CN **7 g**	R^2 = H **8a**	90 (**9g**)
9	R^1 = 2-pyridinyl **7h**	R^2 = H **8a**	99 (**9h**)
10	R^1 = *o*-Me **7i**	R^2 = H **8a**	92 (**9i**)
11	R^1 = 2,5-di-Me **7j**	R^2 = H **8a**	98 (**9j**)
12	R^1 = *p*-OMe **7k**	R^2 = H **8a**	86 (**9k**)
13	R^1 = H **7l**	R^2 = *p*-Me **8b**	99 (**9a**)
14	R^1 = *o*-CN **7g**	R^2 = *p*-Me **8b**	92 (**9l**)
15[d]	R^1 = 2,5-di-Me **7j**	R^2 = *o*-Me **8c**	89 (**9m**)
16[d]	R^1 = 2,5-di-Me **7j**	R^2 = *o*-OMe **8d**	85 (**9n**)

[a] 1 mmol of aryl chloride **7**, 1.5 mmol of aryl boronic acid **8**, 2 mmol of K_3PO_4, 0.1 mol % $Pd(dba)_2$, 0.2 mol % ligand **1c**, 3 mL of toluene, 12 h, 100 °C. [b] Isolated yield. Purity was confirmed by ^1H NMR. [c] 0.01 mol % $Pd(dba)_2$ and 0.02 mol % ligand **1c** were used. [d] The reaction was carried out at 80 °C.

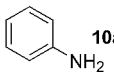
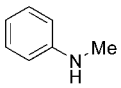
Pd/**1c** system for the Suzuki−Miyaura coupling of aryl chlorides, which are comparable or better than those reported to date with other catalytic systems.

Palladium-catalyzed amination of aryl halides is a powerful method for the synthesis of aniline derivatives. Employing readily available aryl chlorides in this transformation has become a recent focus, and a number of effective catalytic systems have been developed for this purpose.[13] Using Pd catalytic systems based on ligands **1b** and **1c**, we were also

Table 3. Pd-Catalyzed Amination of Aryl Chlorides[a]



7 10 11

entry	aryl chloride	amine	Ligand **1**	yield (%)[b]
1	R = *p*-Me **7a**	 **10a**	**1b**	91 (**11a**)
2	R = *p*-Me **7a**	**10a**	**1c**	92 (**11a**)
3	R = *p*-Me **7a**	 **10b**	**1c**	93 (**11b**)
4	R = *o*-Me **7i**	**10a**	**1c**	92 (**11c**)

[a] 1 mmol of aryl chloride **7**, 1.2 mmol of arylamine **10**, 1.2 mmol of NaO^{t}Bu, 0.5 mol % $Pd(dba)_2$, 1 mol % ligand **1**, 3 mL of toluene, 24 h, reflux. [b] Isolated yield. Purity was confirmed by ^1H NMR.

able to obtain very good yields (91−93%) in the amination reactions of unactivated aryl chlorides **7a** and **7i** with both primary and secondary amines (Table 3). These preliminary results indicate the potential applications of the Pd/ClickPhos catalytic systems to a number of cross-coupling reactions.

In conclusion, we have developed a new type of monophosphine **1** (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. Palladium complexes derived from these ligands provide highly active catalysts for Suzuki−Miyaura coupling and amination reactions of aryl chlorides. Further ligand modifications and their applications to various cross-coupling reactions are currently under investigation in our lab and will be reported in due course.

Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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