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2,5-Bis(2-(diphenylphosphino)phenyl)-1,3,4-oxadiazole ligands and their Cu(I) complexes for Sonogashira coupling reaction

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Two diphosphane ligands – 2,5-bis(2-(diphenylphosphino)-5-R)phenyl)-1,3,4-oxadiazole (L1, R = H, L2, R = OMe) and their binuclear complexes, L1Cu and L2Cu, were prepared and characterized. The molecular structures of L1Cu and L2Cu, as perchlorate salts, were established by X-ray crystallography, which showed them to be binuclear complexes with each Cu atom tetrahedrally coordinated by two P atoms and two N atoms. The ligands and their Cu(I) complexes catalyzed Sonogashira coupling reactions of iodobenzene with phenylacetylene in the presence of K_2CO_3 under Pd-free conditions. Coupling reactions catalyzed by L1 or L2 with $Cu(MeCN)_4ClO_4$ *in situ* exhibited better yields than those by the corresponding Cu(I) complexes L1Cu or L2Cu. Detailed studies showed L1 or L2 with $Cu(MeCN)_4ClO_4$ to be suitable catalysts for the coupling reaction of terminal alkynes and aryl halides. The coupling reactions of aryl iodides with electron-withdrawing groups showed better results. Copyright © 2014 John Wiley & Sons, Ltd.

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Keywords: Sonogashira coupling; diphosphane ligands; Cu(I) complexes; Pd-free conditions

Introduction

Transition metal-catalyzed cross-coupling reactions have been widely used in organic synthesis in academic and industrial laboratories.[1–6] Among them, the coupling reaction between terminal alkynes with aryl or vinyl halides (Sonogashira reaction) is commonly utilized for the synthesis of compounds having C (sp^2)—C(sp) bonds, which are frequently employed in areas of natural products, pharmaceuticals, biologically active molecules, liquid crystalline materials, conducting polymers and molecular organic materials.[7–11] Based on the enormous number of applications of coupling in synthetic chemistry, developing new catalysts for the Sonogashira coupling reaction has always been of great interest to chemists.[6,12] Traditionally, the Sonogashira coupling reaction is carried out using phosphane-ligated palladium complexes together with CuI as co-catalyst in the presence of large amounts of amines as base or solvent, which are economically and environmentally malignant.[13–18] Investigating catalysts using a cheaper metal[19–26] instead of the expensive noble metal palladium and developing greener protocols[12,27,28] for the Sonogashira cross-coupling reaction remains a challenge. In recent years, some copper-based catalysts have proved effective for this transformation.[19–22] For example, the combination of CuI and PPh_3 using potassium hydroxide[19]/potassium carbonate[20] as base has been used for the coupling of aryl iodides and terminal alkynes in water. The CuBr/*rac*-BINOL(1-(2-hydroxynaphthalen-1-yl)-naphthalen-2-ol) system can catalyze coupling reactions between terminal alkynes and aryl halides.[29] Moreover, octahedral and rod-like CuI nanocrystals combined with PPh_3 have been used as catalysts for the cross-coupling reaction of 4-iodoanisole and phenylacetylene in the presence of K_2CO_3 as base and PEG400 as solvent.[30] It is noteworthy that suitable ligands are usually required for good coupling efficiency.[6,31] In view of diphosphane ligands and their metal complexes having been widely applied in catalytic chemistry for many years,[32–35] in this paper two diphosphane ligands containing nitrogen donor groups – 2,5-bis(2′-(diphenylphosphino)phenyl)-1,3,4-oxadiazole (**L1**) and 2,5-bis(2-(diphenylphosphino)-5-methoxy)phenyl)-1,3,4-oxadiazole (**L2**) and their binuclear Cu(I) complexes, **L1Cu** and **L2Cu** – as their perchlorate salts, were synthesized and characterized. The catalytic applications of **L1** or **L2**/$Cu(MeCN)_4ClO_4$ as well as **L1Cu** and **L2Cu** were studied for their effectiveness as catalysts in coupling reactions between terminal alkynes and aryl halides.

Experimental

General Procedures

All reactions were carried out under a dry argon atmosphere using standard Schlenk techniques unless stated otherwise. The

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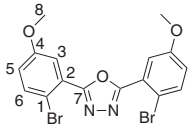
solvents were purified by standard methods. Flash chromatography was performed using 200–300 mesh silica gel with the indicated solvent system according to standard techniques. Analytical thin-layer chromatography was performed on precoated, glass-backed silica gel plates. The melting points were determined with an X-4 binocular microscope melting-point apparatus (Beijing Tech Instruments Co., Beijing, China) without correction. Electrospray (ESI) mass spectra were obtained on a Finnigan LCQ spectrometer. High-resolution mass spectra were obtained on a Varian QFT-ESI mass spectrometer. ^{1}H, $^{13}C\{^{1}H\}$ and $^{31}P\{^{1}H\}$ NMR spectra were recorded on a Bruker AV400/300 spectrometer. Chemical shifts (δ) are reported in ppm relative to the internal standard tetramethylsilane. J values are given in Hz. Additionally, *N*,*N*′-bis(2-bromobenzoyl)hydrazine **3a**, *N*,*N*′-bis(2-bromo-5-methoxybenzoyl)hydrazine **3b** and intermediate **4a** were synthesized according to the literature.[36]

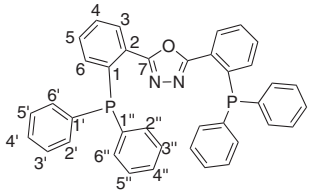
Synthesis of 2,5-bis(2-bromo-5-methoxy-phenyl)-1,3,4-oxadiazole ***4b***



4b

A solution of *N*,*N*′-bis(2-bromo-5-methoxybenzoyl)hydrazine **3b** (4.00 g, 8.73 mmol) in $POCl_3$ (28 ml) was refluxed for 20 h. After cooling to room temperature, the reaction mixture was dripped into ice water slowly with agitation and a white precipitate was formed. After filtration, the crude solid was washed with water and dried under vacuum, and the pure **4b** was obtained by recrystallization with CH_2Cl_2–petroleum ether (1:1, v/v). Yield 1.66 g, 43%; m.p. 107–108 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, 2H, J_{H-H} = 8.8 Hz, C6—*H*), 7.59 (d, 2H, J_{H-H} = 2.6 Hz, C3—*H*), 6.97 (dd, 2H, J_{H-H} = 8.8 Hz, 2.6 Hz, C5—*H*), 3.87 (s, 6H, C8—*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.0 (C7), 158.8 (C4), 135.5 (C2), 125.5 (C6), 119.4 (C5), 116.3 (C3), 111.9 (C1), 55.8 (C8). HRMS (ESI) calcd for $C_{16}H_{12}Br_2N_2O_3Na^+$, [M + Na^+]: 462.9092. Found: 462.9080. Anal. Calcd for $C_{16}H_{12}Br_2N_2O_3$: C, 43.67; H, 2.75; N, 6.37%. Found: C, 43.53; H, 2.54; N, 6.59%.

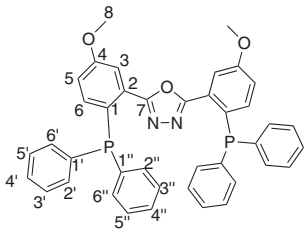
Synthesis of 2,5-bis(2-(diphenylphosphino)phenyl)-1,3,4-oxadiazole ***L1***



L1

Under argon atmosphere, to a mixture of 2,5-bis(2-bromophenyl)-1,3,4-oxadiazole **4a** (1.00 g, 2.63 mmol) in THF (50 ml) was added *n*-butyllithium (2.63 ml, 2.3 M, 6.05 mmol) dropwise at −78 °C. The resulting mixture was stirred at the same temperature for 0.5 h. Chlorodiphenylphosphane (1.04 ml, 5.79 mmol) was then dripped into the mixture. The resulting mixture was stirred at −78 °C for 1 h, and then warmed to room temperature and stirred overnight. The solvent was removed under the protection of argon and the resulting residue was dissolved in CH_2Cl_2 (20 ml). The mixture was washed with water (10 ml) and the organic layer was separated and dried over anhydrous Na_2SO_4. After separation of desiccant, the solvent was evaporated to yield a crude product, which was recrystallized using CH_2Cl_2–petroleum ether (1:2, v/v) to afford a yellow solid of pure **L1**. Yield 0.57 g, 37%; m.p. 83–85 °C. ^{31}P NMR (162 MHz, $CDCl_3$): δ −7.04 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76–7.73 (m, 2H, C3—*H*), 7.36–7.28 (m, 24H, protons of C4, C6 and PPh_2), 7.02–6.99 (m, 2H, C5—*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4 (C7), 138.2 (d, J_{C-P} = 27.2 Hz, C2), 136.9 (d, J_{C-P} = 11.0 Hz, C1), 134.7 (C4), 134.0 (d, J_{C-P} = 20.4 Hz, C2′, C6′, C2″ and C6″), 130.9 (C4′ and C4″), 130.0 (d, J_{C-P} = 4.1 Hz, C3 and C5), 128.8 (C1′ and C1″), 128.6 (d, J_{C-P} = 7.4 Hz, C3′, C5′, C3″ and C5″), 128.2 (d, J_{C-P} = 24.0 Hz, C6). HRMS (ESI) calcd for $C_{38}H_{29}N_2OP_2^+$, [M + H^+]: 591.1755. Found: 591.1752. Anal. Calcd for $C_{38}H_{28}N_2OP_2$: C, 77.28; H, 4.78; N, 4.74%. Found: C, 77.54; H, 4.75; N, 4.79%.

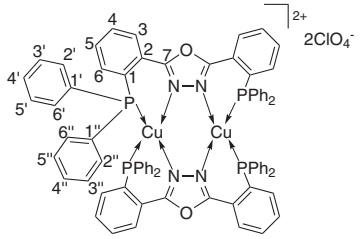
Synthesis of 2,5-bis(2-(diphenylphosphino)5-methoxyphenyl)-1,3,4-oxadiazole ***L2***



L2

L2 was prepared using an analogous procedure as for **L1**. Yield 54%; m.p. 212–214 °C. ^{31}P NMR (162 MHz, $CDCl_3$): δ −9.53 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (m, 2H, C3—*H*), 7.30–7.28 (m, 20H, protons of PPh_2), 6.97–6.89 (m, 4H, protons of C5 and C6), 3.77 (s, 6H, C8—*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5 (C7), 159.9 (C4), 137.6 (d, J_{C-P} = 11.5 Hz, C1), 136.5 (C2), 133.8 (d, J_{C-P} = 20.0 Hz, C2′, C6′, C2″ and C6″), 129.8 (d, J_{C-P} = 26.5 Hz, C6), 128.6 (C3′, C5′, C3″ and C5″), 128.5 (C4′ and C4″), 128.4 (d, J_{C-P} = 11.5 Hz, C1′ and C1″), 117.6 (C3), 114.8 (d, J_{C-P} = 4.9 Hz, C5), 55.5 (C8). HRMS (ESI) calcd for $C_{40}H_{33}N_2O_3P_2^+$, [M + H^+]: 651.1966. Found: 651.1966. Anal. Calcd for $C_{40}H_{32}N_2O_3P_2$: C, 73.84; H, 4.96; N, 4.31%. Found: C, 73.94; H, 4.87; N, 4.31%.

Synthesis of complex ***L1Cu***

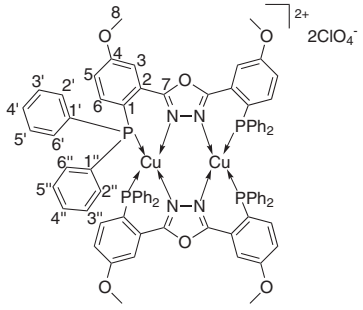


L1Cu

Under argon atmosphere, **L1** (135.7 mg, 0.23 mmol) was dissolved in degassed CH_2Cl_2 (30 ml) and then $Cu(CH_3CN)_4ClO_4$ (76 mg, 0.23 mmol) was added. The resulting mixture was stirred for 1 h and then recrystallized using $CHCl_3$–hexane (1:1, v/v) to obtain a yellow solid. Yield 67.8 mg, 39%; m.p. 220–222 °C. ^{31}P NMR (162 MHz, $CDCl_3$): δ −6.49 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, 4H, J_{H-H} = 7.3 Hz, C3—*H*), 7.75 (t, 4H, J_{H-H} = 7.3 Hz, C4—*H*), 7.52 (t, 4H, J_{H-H} = 7.3 Hz, C5—*H*), 7.20–6.91 (m, 44H, protons of C6 and PPh_2). ^{13}C NMR (100 MHz, CD_3CN): δ 163.6 (C7), 134.9 (C2), 133.0 (C1), 132.5 (C4), 132.2 (d, J_{C-P} = 2.3 Hz, C3 and C5), 131.2 (C4′ and C4″), 130.9 (C1′ and C1″), 130.3 (d, J_{C-}

$_P$ = 15.6 Hz, C2′, C6′, C2″ and C6″), 128.8 (d, J_{C-P} = 5.6 Hz, C3′, C5′, C3″ and C5″), 125.7 (C6). HRMS (MALDI) calcd for $C_{38}H_{28}N_2CuOP_2^+$, [M − 2ClO_4^-]/2: 653.0973. Found: 653.0951.

Synthesis of complex ***L2Cu***



L2Cu

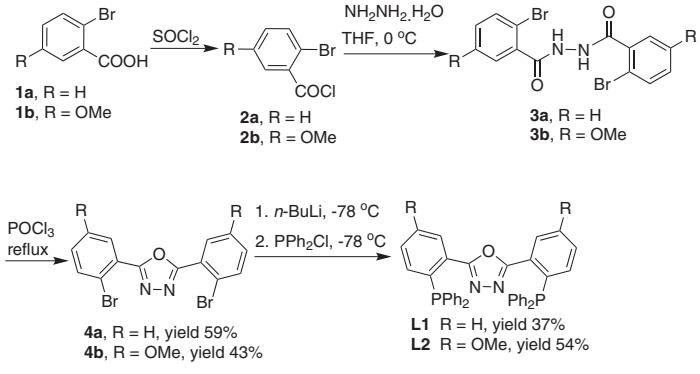
Complex **L2Cu** was prepared using an analogous procedure as for **L1Cu**. Yield 31%; m.p. 220–222 °C. ^{31}P NMR (162 MHz, $CDCl_3$): δ −8.15 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (s, 4H, C3—*H*), 7.24–7.10 (m, 8H, C6—*H* and C5—*H*), 7.00–6.91 (m, 40H, protons of PPh_2), 4.04 (s, 12H, C8—*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.8 (C7), 161.7 (C4), 137.3 (C2), 133.0 (d, J_{C-P} = 8.0 Hz, C1), 130.3 (C4′ and C4″), 129.3 (C6), 128.9 (d, J_{C-P} = 4.8 Hz, C3′, 5′, 3″ and C5″), 127.8 (d, J_{C-P} = 9.0 Hz, C1′ and C1″), 122.3 (d, J_{C-P} = 15.7 Hz, C2′, C6′, C2″ and C6″), 118.9 (C3), 117.1 (d, J_{C-P} = 2.4 Hz, C5), 56.4 (C8). HRMS (ESI) calcd for $C_{40}H_{32}CuN_2O_3P_2^+$, [M 2$ClO_4^-$]/2: 713.1184. Found 713.1181.

General Procedure for Cu(I)-Catalyzed Coupling Reaction of Aryl Halides and Arylacetylenes

Under an argon atmosphere, a Schlenk reaction tube was charged with aryl halide (0.50 mmol), arylacetylene substrate (0.55 mmol), K_2CO_3 (207 mg, 1.50 mmol), catalysts (5 mol% Cu(I) salt with 5 mol % ligand or 2.5 mol% Cu(I) complex) and dioxane (5 ml). After the mixture was stirred at reflux temperature for 16 h, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel to give the product. All NMR data of coupling products are listed online as supporting information.

X-Ray Structure Determinations

Diffusion of diethyl ether into the $CHCl_3$ and DMF solutions, respectively, of complexes **L1Cu** and **L2Cu** produced yellow single crystals. Diffraction intensity data were collected at 293(2) K on a Rigaku Saturn724 CCD diffractometer using Mo-K_α radiation (0.71073 Å). Data reduction and absorption corrections were performed using CrystalClear.[37,38] All the structures were solved using direct methods [39] and refined by full-matrix least-squares on F^2.[40] For the structure of **L1Cu**, the ClO_4^- anion is disordered over two sites of equal weight. In addition, badly disordered unresolved solvent molecules were present. Similar problems were encountered for **L2Cu**. Accordingly, only the basic features of the molecular structures are discussed herein; more details are available online as supporting information. Despite the fact that crystals of **L1Cu** and **L2Cu** have been grown in other mixed-solvent systems, better-quality data sets could not be obtained.



Scheme 1. The synthesis of ligands **L1** and **L2**.

Results and Discussion

Synthesis and Characterization of Diphosphane Ligands, L1, L2 and binuclear complexes L1Cu, L2Cu

As shown in Scheme 1, 2-bromo-5-R-benzoic acid **1** (**1a**, R = H; **1b**, R = OMe) was reacted with $SOCl_2$ to yield corresponding acid chlorides **2a** and **2b** in high yield, which were then treated with hydrazine hydrate to give hydrazide **3a** and **3b**, respectively.[36] Hydrazides **3a** and **3b** were treated with phosphoryl trichloride at refluxing temperature, eliminating an H_2O molecule to produce the oxadiazole intermediates **4a**[36] and **4b**, in moderate yield. Compounds **4a** and **4b** were then treated with chlorodiphenylp hosphane and *n*-butyllithium to obtain the corresponding ligands 2,5-bis(2-(diphenylphosphino)-5-R-phenyl)-1,3,4-oxadiazoles **L1** and **L2** (**L1**, R = H; **L2**, R = OMe), respectively. Ligands **L1** and **L2** were reacted with equimolar amounts of $Cu(MeCN)_4ClO_4$ to yield the corresponding dinuclear Cu(I) complexes **L1Cu** and **L2Cu**, respectively (Scheme 2).

In the ^{31}P NMR spectra of **L1** and **L2**, the signals appeared at −7.04 and −9.53 ppm, respectively, and these were shifted downfield to −6.50 and −8.15 ppm, respectively, for **L1Cu** and **L2Cu**.

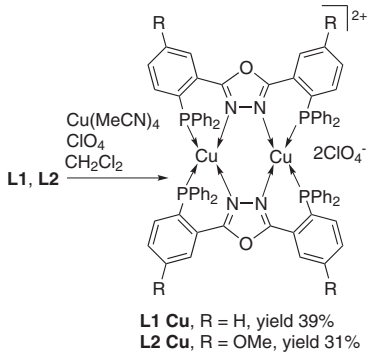
X-Ray Crystallographic Studies of Complexes

As outlined in the Experimental section, the structure analyses of **L1Cu** and **L2Cu** were less than optimal. Accordingly, only rudimentary information concerning the nature of the very similar cations is included herein. As shown in Fig. 1, the molecular structure of binuclear Cu(I) complex **L1Cu** features two bidentate bridging bis(diphenylphosphino) ligands and the N_2P_2 donor defines a distorted tetrahedral coordination geometry.

The molecule is formed about a central and planar six-membered Cu_2N_4 ring. Through the chelation of **L1** via P and N atoms to Cu, four distorted six-membered rings comprising Cu, P, N and three C atoms were formed in each binuclear complex.

Catalytic Activity Study

The coupling reaction between iodobenzene **5a** (102.0 mg, 0.50 mmol) and phenylacetylene **6a** (56.1 mg, 0.55 mmol) with K_2CO_3 (206.9 mg, 1.5 mmol) in dioxane (5 ml) was chosen as the model reaction to identify the catalytic effects of the ligands and their Cu(I) complexes. As shown in Table 1, when using ligand **L1** or **L2** as catalysts the reaction afforded trace product (Table 1, entries 1 and 2). Similarly, a low yield was obtained while the reaction was performed in the



Scheme 2. The synthesis of dinuclear Cu(I) complexes **L1Cu** and **L2Cu**.

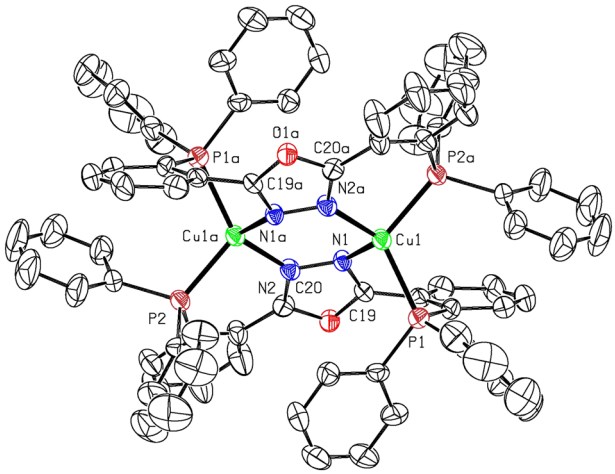
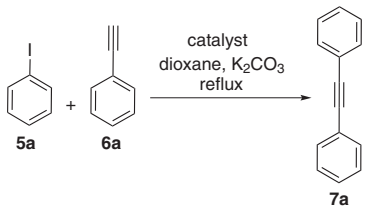


Figure 1. Molecular structure of centrosymmetric **L1Cu**; hydrogen atoms; anions and solvent of crystallization omitted for clarity. Symmetry operation a: 1-x, 2-y, 1-z.

Table 1. Catalysts screening[a]



Entry	Catalyst	Yield (%)[b]
1	**L1** (5 mol%)	Trace
2	**L2** (5 mol%)	Trace
3	$Cu(MeCN)_4ClO_4$ (5 mol%)	13
4	**L1Cu** (2.5 mol%)	65
5	**L2Cu** (2.5 mol%)	73
6	**L1** (5 mol%), $Cu(MeCN)_4ClO_4$ (5 mol%)	92
7	**L2** (5 mol%), $Cu(MeCN)_4ClO_4$ (5 mol%)	99

[a]Reaction conditions: iodobenzene (102.0 mg, 0.50 mmol), pheny lacetylene (56.1 mg, 0.55 mmol), K_2CO_3 (206.9 mg, 1.5 mmol), solvent (5 mL), 16 h.
[b]Yield of isolated product is based on iodobenzene.

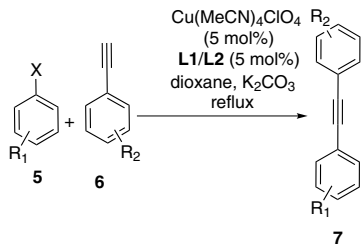
presence of $Cu(MeCN)_4ClO_4$ without any ligands (Table 1, entry 3). When either Cu(I) complex **L1Cu** or **L2Cu** was used as catalyst, the reaction gave the desired product in 65% and 73% yield, respectively (Table 1, entries 4 and 5). When the reaction was catalyzed by **L1** or **L2** with $Cu(MeCN)_4ClO_4$, *in situ*, the coupling product was obtained in higher yields of 92% and 99%, respectively (Table 1, entries 6 and 7). The above results implied that the diphosphane molecules with cuprous salt *in situ* catalyzed the coupling reaction more effectively than the formed Cu(I)–diphosphane complexes. The results may reflect coordination saturation of the Cu(I) atoms in **L1Cu** and **L2Cu**. When the complexes were applied as catalysts for the coupling reaction, there needs be an elimination process first to provide a coordination site for the phenylacetylene to form copper(I) acetylides. However, when using ligands **L1**, **L2** with Cu(I) salts *in situ*, the Cu(I) would directly complex with the large amounts of phenylacetylene to form copper(I) acetylides.[22,31]

Next, the optimal reaction conditions were estimated by investigating the effects of the species of copper salts, solvents, bases, the amount of catalysts and reaction temperature on the model coupling reaction between iodobenzene **5a** and phenylacetylene **6a**. It was found that when applying $Cu(MeCN)_4ClO_4$ as copper salt, K_2CO_3 as base, dioxane as solvent and refluxing temperature as reaction temperature the reaction afforded product in the highest yield of 92% (supporting information, Tables S1–S3). When 3 mol% of catalyst was used, a yield of 67% was obtained for the coupling reaction. An amount of 5 mol% of catalyst was found to be optimal for the reaction and >90% yields could be obtained. When 10 mol% catalyst was used in the reaction the yield did not increase obviously (Table S4).

With the optimized reaction conditions in hand, the coupling reactions of a variety of aryl iodides **5** and three terminal aryl alkynes **6a–c** were carried out with **L1** or **L2** and $Cu(MeCN)_4ClO_4$ as catalysts. In order to avoid possible noble metal contamination,[41] all reactions were performed in carefully cleaned flasks with clean stirring bars. Moreover, the catalysts used in the coupling reaction were treated carefully to confirm the high purity of the Cu(I) salts. For example, $Cu(MeCN)_4ClO_4$ was recrystallized many times and investigated by atomic absorption spectroscopy (AAS) until the indicated Pd content was less than 5 ppb.

As shown in Table 2, the yields of the catalytic coupling reaction with **L2** in the presence of $Cu(MeCN)_4ClO_4$ were higher than those catalyzed by **L1** with $Cu(MeCN)_4ClO_4$. In addition, the aryl iodides carrying election-withdrawing groups consistently gave the desired products in higher yields than the aryl iodides with electron-donating groups. Taking **L1**, for example, for *p*-nitroiodobenzene and *o*-nitroiodobenzene, the coupling yields were both 99% (Table 2, entries 2 and 3). However, the compounds *p*-chloroiodobenzene, *p*-methoxyiodobenzene and *p*-methyliodobenzene were coupled with phenylacetylene **6a** to give **7d–f** only in moderate yields (Table 2, entries 4–6). Notably, *o*-aminoiodobenzene, containing the electron-donating amino group, reacted with **6a** to give the product in 91% yield (Table 2, entry 7), indicating that the *ortho* substituent of the aryl iodides has a great influence on cross-coupling under the reaction conditions employed. For the coupling reactions of aryl iodides **5a–g** and 4-methoxyphenylacetylene **6b** (Table 2, entries 8–13), *p*-nitroiodobenzene, *o*-nitroiodobenzene and *o*-aminoiodobenzene gave good results (Table 2, entries 9, 10 and 13). While iodobenzene, *p*-chloroiodobenzene and *p*-methoxyiodobenzene were reacted with 4-methoxyphenylacetylene, only undesirable yields

Table 2. **L**/$Cu(MeCN)_4ClO_4$-catalyzed Sonogashira coupling[a]



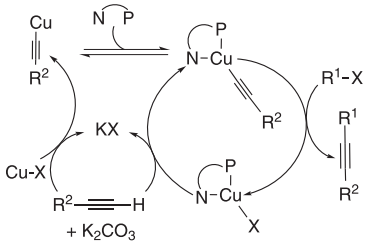
Entry	5	X	R^1	6	R^2	Product	L1 yield (%)[b]	L2 yield (%)[b]
1	**5a**	I	H	**6a**	H	**7a**	92	99
2	**5b**	I	*p*-NO_2	**6a**	H	**7b**	99	99
3	**5c**	I	*o*-NO_2	**6a**	H	**7c**	99	99
4	**5d**	I	*p*-Cl	**6a**	H	**7d**	42	54
5	**5e**	I	*p*-OMe	**6a**	H	**7e**	73	83
6	**5f**	I	*p*-CH_3	**6a**	H	**7f**	78	85
7	**5 g**	I	*o*-NH_2	**6a**	H	**7 g**	91	99
8	**5a**	I	H	**6b**	*p*-OMe	**7e**	72	77
9	**5b**	I	*p*-NO_2	**6b**	*p*-OMe	**7 h**	91	99
10	**5c**	I	*o*-NO_2	**6b**	*p*-OMe	**7i**	95	99
11	**5d**	I	*p*-Cl	**6b**	*p*-OMe	**7j**	54	62
12	**5e**	I	*p*-OMe	**6b**	*p*-OMe	**7 k**	36	48
13	**5 g**	I	*o*-NH_2	**6b**	*p*-OMe	**7 l**	82	89
14	**5a**	I	H	**6c**	*p*-NO_2	**7b**	80	85
15	**5b**	I	*p*-NO_2	**6c**	*p*-NO_2	**7 m**	86	94
16	**5c**	I	*o*-NO_2	**6c**	*p*-NO_2	**7n**	90	99
17	**5d**	I	*p*-Cl	**6c**	*p*-NO_2	**7o**	52	56
18	**5e**	I	*p*-OMe	**6c**	*p*-NO_2	**7 h**	44	52
19	**5f**	I	*p*-CH_3	**6c**	*p*-NO_2	**7p**	52	59
20	**5 g**	I	*o*-NH_2	**6c**	*p*-NO_2	**7q**	87	95
21	**5 h**	Br	H	**6a**	H	**7a**	21	34
22	**5i**	Br	*p*-NO_2	**6a**	H	**7b**	70	78
23	**5j**	Br	*o*-NO_2	**6a**	H	**7c**	64	72
24	**5 k**	Br	*p*-Cl	**6a**	H	**7d**	6	11
25	**5 l**	Cl	*o*-NO_2	**6a**	H	**7c**	Trace	Trace

[a]Reaction conditions: $Cu(MeCN)_4ClO_4$ (8.2 mg, 0.025 mmol, 5 mol%), 5 mol% **L1**/**L2**, aryl halide (0.50 mmol), arylacetylene (0.55 mmol), K_2CO_3 (206.9 mg, 1.5 mmol), dioxane (5 ml), 16 h.
[b]Isolated yield is based on aryl iodide (average of two runs).

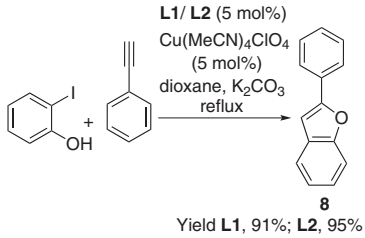
of 72%, 54% and 36%, respectively (entries 8, 11 and 12), were obtained. In coupling reactions between aryl iodides **5a–g** and *p*-nitrophenylacetylene **6c**, those with electron-withdrawing iodides, i.e. **5b–c**, also furnished products in good yields (Table 2, entries 15 and 16). The yields of the coupling for aryl iodides **5d–f** with electron-donating groups were moderate (Table 2, entries 17–19). When aryl bromides or chlorides were coupled with substituted phenylacetylene **6**, lower activity was achieved compared with the reaction with aryl iodides (Table 2, entries 22–25). For example, *p*-nitrobromobenzene and *o*-nitrobromobenzene were treated with phenylacetylene to furnish **7b** and **7c** in yields of 70% and 64%, respectively (Table 2, entries 22 and 23), and bromobenzene or *p*-chlorobromobenzene treated with phen ylacetylene gave the coupling products in very low yields (Table 2, entries 21 and 24). For the aryl chloride, only trace product can be obtained in the catalytic reaction (Table 2, entries 25).

From the above results, it can be concluded that in the presence of $Cu(MeCN)_4ClO_4$ **L2**, with an electron-donating methoxy group, is more useful for catalyzing the coupling reaction between aryl halides and arylacetylenes than **L1**. Based on the reported mechanisms of Sonogashira reaction catalyzed by palladium and copper,[22,28,31,42–44] the possible mechanism of *in situ* Cu(I)-catalyzed Sonogashira coupling reactions under Pd-free conditions is possibly a ligand-accelerated catalytic process, as proposed by Bolm *et al.*[22,31] The Cu(I) salt might first react with excess phenylacetylene in the presence of large amounts of base to form copper(I) acetylides, then react with the oxadiazole-bridged phosphane ligand to generate a highly electron-rich acetylide complex that is able to react with the aryl halide to give the coupling products (Scheme 3).

Intriguingly, when *o*-iodophenol was treated with phenyla cetylene in the **L1**/**L2** and $Cu(MeCN)_4ClO_4$ *in situ* catalytic system,



Scheme 3. Supposed mechanism for the Sonogashira reaction catalyzed by **L1**/**L2** and Cu(I) *in situ*.



Scheme 4. The reaction between *o*-iodophenol and phenylacetylene.

2-phenylbenzofuran **8**, rather than the diphenylacetylene product, was obtained in excellent yield (Scheme 4).

Conclusions

In summary, two ligands – 2,5-bis(2′-(diphenylphosphino)phenyl)-1,3,4-oxadiazole (**L1**) and 2,5-bis(2-(diphenylphosphino)-5-methoxy)phenyl)-1,3,4-oxadiazole (**L2**) – and their Cu(I) complexes (**L1Cu** and **L2Cu**) were synthesized and characterized. The **L1** or **L2**/$Cu(MeCN)_4ClO_4$ and the Cu(I) complexes can catalyze the Sonogashira coupling reaction under Pd-free conditions between aryl halides and terminal aryl alkynes. The reactions were highly dependent on the substituents in the aryl halides, arylacetylenes and ligands. The coupling reaction of electron-deficient aryl iodides and arylacetylenes catalyzed by **L1**/**L2** in the presence of $Cu(MeCN)_4ClO_4$ furnished products in excellent yields, while less reactive aryl bromides gave low yields. Further modification on the ligands and their catalytic activity for Sonogashira cross-coupling reactions will be the subject of future investigations.

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