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Sulfur-Ligand/Pd-Catalyzed Cross-Coupling Reactions of Aryl Halides with Arylboronic Acids Under Aerobic Conditions

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Abstract An air-and moisture-stable monodentate sulfur-ligand was synthesized. The ligand was found to be effective in Pd-catalyzed cross-coupling reactions of various aryl halides with arylboronic acids under aerobic conditions. This catalytic system is tolerant of a wide range of functional groups. The new complex structure of the sulfur-ligand/Pd^{II} has been determined by single-crystal X-ray diffraction.

Keywords Cross-coupling reaction · Palladium · Sulfur-ligand · Catalysis

1 Introduction

Suzuki cross-coupling reaction represents one of the most widely used processes for the synthesis of biaryls, important building blocks of pharmaceuticals [1], polymers [2] and ligands for catalysis [3]. As a result, considerable efforts have been directed toward the development of efficient Suzuki cross-coupling reactions [4–8]. Phosphine ligands are generally required to stabilize the reactive palladium intermediates, and excellent results have been reported for Pd-catalyzed Suzuki reactions [9–11]. However, many phosphines are sensitive to air and moisture resulting in limitations on their applications [12]. Therefore, the application of alternative ligands in metal-catalyzed synthetic transformations opens up new opportunities in catalysis [13–18]. Sulfur-containing compounds were traditionally categorized as catalyst poisons due to their strong coordinative and adsorptive properties, which rendered them totally ineffective as catalysts [19, 20]. Recently, efforts have been focused on the development of sulfur-ligands/metal catalyzed reactions [21–25], among which thioureas emerged as one of the most efficient ligands owing to their stability to air and moisture, desirable coordinating ability with metal, as well as their greater stability at elevated temperatures relative to phosphine ligands, which may enable their use over a broader range of reaction conditions [26–37]. However, Suzuki coupling reactions catalyzed by simple non-chiral monodentate thiourea has not been attempted so far [7, 8].

Herein we report the synthesis of bulky sulfur-ligand **4** and its application in Pd-catalyzed cross-coupling reactions of various aryl halides with arylboronic acids under aerobic conditions.

2 Experimental

Chemicals and solvents were all purchased from commercial supplies and were used directly. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100.6 MHz with a Varian Mercury 400 spectrometer. Mass spectrometric data were obtained using a Hewlett Packard 5988 GC/MS.

Li and Wu contributed equally to this work.

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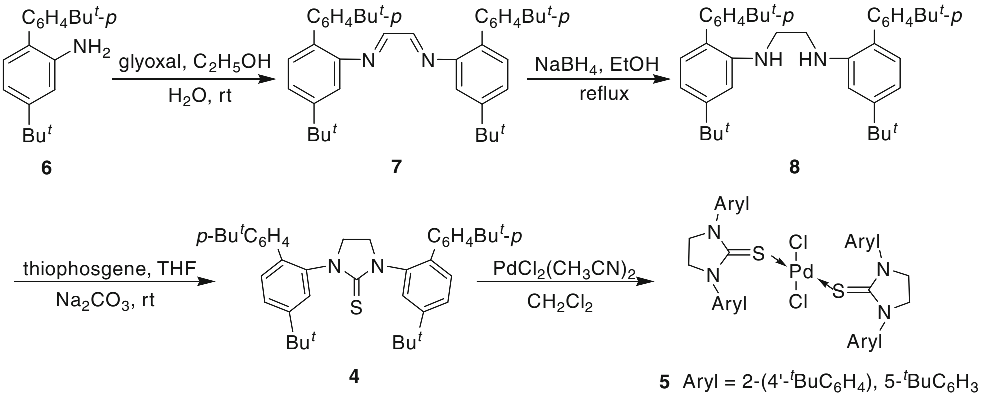


5 Aryl = 2-(4'-^{t}BuC$_6$H$_4$), 5-^{t}BuC$_6$H$_3$

Scheme 1 Synthesis of sulfur ligand **4** and its Pd complex **5**

2.1 Synthesis of 4

The method for preparation of a novel sulfur-containing ligand **4** is shown in Scheme 1. A solution of thiophosgene (1.2 mmol) in dry THF at room temperature was added dropwise to a stirred mixture of *N*,*N′*-disubstituted diamine **8** (588 mg, 1.0 mmol) and Na_2CO_3 (1.5 mmol) in dry THF. After stirred at room temperature for 24 h, water and ethyl acetate were added. The organic layer was washed with dilute HCl and brine, dried and concentrated. The pure sulfur-ligand **4** was obtained through flash chromatography as white solid (371.5 mg, 59% yield). m.p. 258–259 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57–7.52 (m, 6H), 7.44–7.39 (m, 6H), 7.36–7.33 (m, 2H), 3.25 (s, 4H), 1.42 (s, 18H), 1.35 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.2, 151.1, 150.2, 138.1, 136.7, 136.0, 130.3, 128.4, 127.5, 125.1, 49.4, 34.7, 34.5, 31.4, 31.3; IR (CH_2Cl_2) 1468, 1410, 1340, 1244, 1131 cm^{-1}; LRMS (EI, 20 eV): *m/z* 630 (M^+, 100), 631 (49); HRMS (EI) calcd for $C_{27}H_{17}N_2S$ (M^+): 630.4008, found 630.3968.

2.2 Synthesis of Complex 5

0.20 mmol of $PdCl_2(CH_3CN)_2$ and 0.20 mmol of ligand **4** were dissolved in 4 mL of dichloromethane. The solution was stirred at room temperature for 24 h affording a green solid precipitate which was collected by filtration and washed with cold ether. Suitable crystal for X-ray analysis was obtained by slow diffusion of diethyl ether into saturated dichloromethane solution of the complex.

X-ray diffraction data collection was performed on a Bruker Smart APEX CCD diffractometer using graphite monochromated Mo K_α radiation ($\lambda = 0.71073$ Å) at 296 K. The diffraction frames were integrated using the SAINT package. The structure was solved by direct methods using the program SHELXS97. The crystal structure plot is shown in Fig. 1.

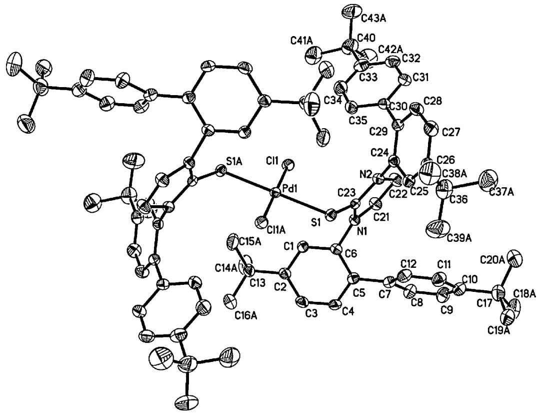


Fig. 1 Structure of complex **5**. Hydrogen atoms have been omitted for clarity

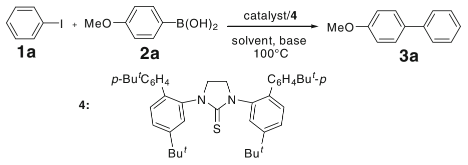
2.3 General Procedure for the Suzuki Coupling Reaction

All reactions were conducted under aerobic conditions. A mixture of aryl halide **1a** (0.2 mmol), arylboronic acid **2a** (0.24 mmol), $Pd(OAc)_2$ (1.5 mol%), sulfur-ligand (3 mol%), K_2CO_3 (3 equivalents), and ^{i}PrOH/H_2O (2 mL) were taken in a sealed tube. Then the mixture was stirred at 100 °C for the desired time (Table 1) until complete consumption of starting material as monitored by TLC. After the reaction mixture was cooled down to room temperature and filtered through a pad of silica gel, the filtrate was concentrated and the residue was purified by column chromatography (hexane or hexane/EtOAc) to afford **3a**.

3 Results and Discussion

As shown in Table 1, the reaction of iodobenzene (**1a**) with 4-methoxy-phenylboronic acid (**2a**) was chosen as a model reaction to test the catalytic activity of palladium/ligand **4** catalyst system. A series of solvent systems including

Table 1 Effects of catalysts, solvents and bases on the Suzuki reaction of iodobenzene (**1a**) and 4-methoxy-phenylboronic acid (**2a**)



Entry	Catalyst	Solvent (v/v)	Base (equiv.)	Isolated yield (%)
1	$Pd(OAc)_2$	${}^iPrOH$	K_2CO_3 (3)	75
2	$Pd(OAc)_2$	${}^iPrOH/H_2O$ (10/1.5)	K_2CO_3 (3)	90
3	$Pd(OAc)_2$	${}^iPrOH/H_2O$ (8.5/1.5)	K_2CO_3 (3)	72
4	$Pd(OAc)_2$	NMP/H_2O (3/1)	K_2CO_3 (3)	68
5	$Pd(OAc)_2$	Dioxane/H_2O (10/1.5)	K_2CO_3 (3)	16
6	$Pd(OAc)_2$	Toluene/H_2O (10/1.5)	K_2CO_3 (3)	77
7	PdI_2	${}^iPrOH/H_2O$ (10/1.5)	K_2CO_3 (3)	87
8	$Pd_2(dba)_3$	${}^iPrOH/H_2O$ (10/1.5)	K_2CO_3 (3)	87
9	$Pd(OAc)_2$	${}^iPrOH/H_2O$ (10/1.5)	K_2CO_3 (2)	66
10	$Pd(OAc)_2$	${}^iPrOH/H_2O$ (10/1.5)	K_3PO_4 (3)	85
11	$Pd(OAc)_2$	${}^iPrOH/H_2O$ (10/1.5)	Cs_2CO_3 (3)	77
12	$Pd(OAc)_2$ (1.0 mol%)	${}^iPrOH/H_2O$ (10/1.5)	K_2CO_3 (3)	86
13	$Pd(OAc)_2$ (0.5 mol%)	${}^iPrOH/H_2O$ (10/1.5)	K_2CO_3 (3)	84

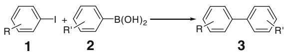
Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), catalyst (1.5 mol%), **4** (3 mol%), base, and solvent (2 mL) at 100 °C under air for 7 h

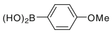
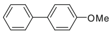
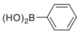
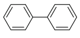
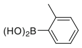
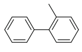
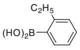
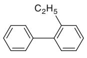
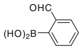
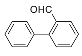
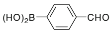
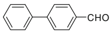
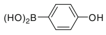
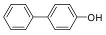
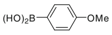
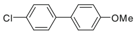
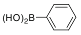
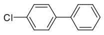
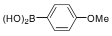
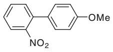
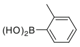
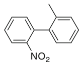
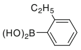
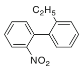
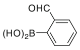
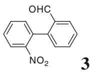
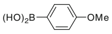
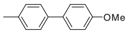
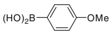
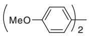
${}^iPrOH$, ${}^iPrOH/H_2O$, NMP/H_2O, dioxane/H_2O, toluene/H_2O were first evaluated (entries 1–6). The mixture of ${}^iPrOH$ and H_2O with a 10/1.5 (v/v) ratio was found to be the optimal solvent system for this reaction, indicating that appropriate amount of water improved the cross-coupling reaction yield (entries 1–3) [5]. It is well-known that Suzuki reaction is catalyzed by Pd(0), and $Pd(OAc)_2$ is readily reduced to the catalytically active Pd(0) state by phosphines and many other reagents [38, 39]. We speculated that ${}^iPrOH$ not only acted as a solvent but also played a role of reductive reagent which reduced Pd(II) to Pd(0) and, thus, facilitated the catalytic reaction [40]. To gain evidence the formation of Pd(0), an ESI–MS study of a ${}^iPrOH$ solution of thiourea **4**/$Pd(OAc)_2$ (2/1 ratio) was performed and a peak at $m/z = 1367.6$ was identified to be $[Pd(0)\cdot(\mathbf{4})_2 + H]^+$ ion. Two other palladium reagents including PdI_2 and $Pd_2(dba)_3$ were then examined, both of which were less effective than $Pd(OAc)_2$ (entry 2 vs. entries 7 and 8). The use of K_2CO_3 as a base led to a higher yield than other commonly used bases such as K_3PO_4 and Cs_2CO_3 (entry 2 vs. entries 10 and 11). Finally, the effects of the amounts of base and $Pd(OAc)_2$ on the reaction were also tested (entries 9, 12 and 13). Lower yields were obtained when the amounts of either base or palladium were reduced.

The catalytic activities of the new palladium catalyst system of Pd^{II} combined with a new ligand **4** for Suzuki–Miyaura coupling reaction of aryl iodides (**1a–e**) with various arylboronic acids (**2a–g**) were then investigated in ${}^iPrOH/H_2O$ at 100 °C and representative results are summarized in Table 2. These results indicated that: (a) Good functional group compatibility was observed. For example, substituents such as chloro, nitro, methyl and methoxy groups on the aryl halide and methoxy, alkyl, hydroxyl and formyl (either ortho- or para-position) groups on arylboronic acids were all tolerated (entries 7–8, 10–15). (b) Notably, this catalytic system was also effective for sterically hindered substrates. Hindered 1-iodo-2-nitrobenzene (**1c**) was successfully coupled with ortho-substituted arylboronic acids (**2c–e**) to give 2, 2'-disubstituted biphenyl in moderate to excellent yields (entries 11–13).

The scope of the Pd^{II}/**4** catalytic system was further extended to the reactions of the less reactive aryl bromides **1f–j** and the challenging aryl chlorides **1k–o** with arylboronic acids **2a** (Table 3). The coupling reactions worked well for aryl bromides of different electronic effects **1f–j**, affording moderate to excellent yields of the corresponding products (entries 1, 2, and 5–7). Remarkably, excellent yield (94%) of the coupling product **3q** could also be achieved at 0.5 mol% catalyst loading (entry 3). Furthermore, in contrast to many phosphine ligands and carbene ligands, good catalytic activity of the recycled sulfur-ligand **4** by column chromatography was observed (entry 4), which gave an opportunity to develop a new kind of

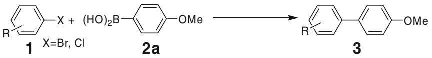
Table 2 Cross-coupling reactions of aryl iodides with arylboronic acids

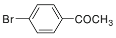
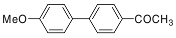
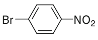
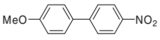
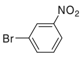
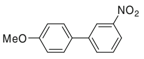
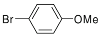
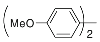
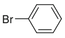
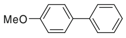
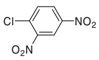
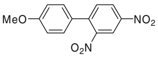
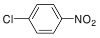
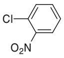
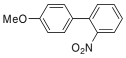
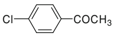
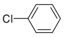


Entry	Aryl halide (R)	Arylboronic acid	Products	T (h)	Isolated yield (%)
1	R=H **1a**	 **2a**	 **3a**	7	90
2	**1a**	 **2b**	 **3b**	7	75
3	**1a**	 **2c**	 **3c**	7	74
4	**1a**	 **2d**	 **3d**	7	90
5	**1a**	 **2e**	 **3e**	3	93
6	**1a**	 **2f**	 **3f**	3	85
7	**1a**	 **2g**	 **3g**	24	70
8	4-Cl **1b**	 **2a**	 **3h**	4	98
9	**1b**	 **2b**	 **3i**	3	93
10	2-NO$_2$ **1c**	 **2a**	 **3j**	6	94
11	**1c**	 **2c**	 **3k**	11	96
12	**1c**	 **2d**	 **3l**	11	92
13	**1c**	 **2e**	 **3m**	8	57
14	4-CH$_3$ **1d**	 **2a**	 **3n**	8	78
15	4-OCH$_3$ **1e**	 **2a**	 **3o**	22	77

Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), catalyst (1.5 mol%, Pd/**4** = 1/2), K$_2$CO$_3$ (3 equivalents), and solvent (^{i}PrOH/H$_2$O = 10/1.5, 2 mL) at 100 °C under air

Table 3 Cross-coupling of aryl bromides/chlorides **1** with 4-methoxy-phenylboronic acid **2a**



Entry	Aryl halide	Product	Isolated yield (%)
1	 **1f**	 **3p**	99
2	 **1g**	 **3q**	99
3	**1g**	**3q**	94[a]
4	**1g**	**3q**	90[b]
5	 **1h**	 **3r**	93
6	 **1i**	 **3o**	89
7	 **1j**	 **3a**	66
8	**1j**	**3a**	73[c]
9	 **1k**	 **3s**	70[c,d]
10	 **1l**	**3q**	65[c,d]
11	 **1m**	 **3j**	55[c,d]
12	 **1n**	**3p**	40[c,d]
13	 **1o**	**3a**	11[c,d]

Reaction conditions: **1** (0.2 mmol), **2a** (0.24 mmol), catalyst (1.5 mol%, Pd/**4** = 1/2), K$_2$CO$_3$ (3 equivalents), and solvent (^{i}PrOH/H$_2$O = 10/1.5, 2 mL) at 100 °C under air for 24 h

[a] Catalyst (0.5 mol%)

[b] Recycled **4** (1 mol%), ^{i}PrOH/H$_2$O = 10/1.5, 1 mL

[c] 20 mol% TBAB was added

[d] **2a** (0.30 mmol), catalyst (3 mol%), 130 °C

immobilized catalyst. For the electronically neutral phenyl bromide **1j**, catalytic amount of TBAB (Tetrabutylammonium bromide) was required to enhance the yield (entry 8). It is believed that three roles of TBAB may play in the reaction: (a) stabilization of the low coordinate Pd(0) species; (b) activation of Pd^0 species with the formation of anionic species; (c) phase transfer catalyst for the inorganic base/solvent/substrate/product phases [18, 41, 42]. It is noteworthy that this catalytic system is effective for electron-deficient aryl chlorides **1k**–**n** in the presence of 20 mol% TBAB, although the catalyst loading and the reaction temperature were increased to facilitate the cross-coupling reactions (entries 9–12). For example, in the presence of 3 mol% of catalyst and 20 mol% TBAB, coupling of **1k**, **1l** with **2a** afforded 70 and 65% yield of **3s** and **3q**, respectively (entries 9 and 10). To our knowledge, these are the best results of thiourea/Pd catalyzed Suzuki coupling for electron-deficient aryl chlorides. The only reported example necessitated high ratio of arylboronic acid to aryl chloride (2/1) to obtain moderate yield (30%) of the desired product **3q** using the bidentate sulfur-ligand [33]. These results demonstrated the potential of such monodentate sulfur-ligands for the use in Pd-catalyzed reactions. Acceptable yields were achieved even for less reactive aryl chloride **1m** and **1n** (entries 11 and 12). However, very low yield (11%) was obtained for electron-neutral chlorobenzene **1o** and homocoupling product of **2a** was observed (entry 13).

4 Conclusion

In summary, an efficient non-chiral monodentate sulfur-ligand **4**/palladium catalytic system for the Suzuki coupling reaction has been investigated. Under aerobic condition, in the presence of this catalytic system, the cross-coupling reactions of various aryl halides with arylboronic acid proceeded smoothly in moderate to excellent yields. The sulfur-ligand can be recovered by column chromatography, and good catalytic activity of the recycled sulfur-ligand was observed. In addition, the cross-coupling reaction by this catalyst is tolerant of a wide range of functional groups. The complex structure of the sulfur-ligand/Pd^{II} has been determined by single-crystal X-ray diffraction. Currently, further efforts to immobilize this new catalyst on mesoporous materials and apply them on C–C bond formation reactions are underway in our laboratory.

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References

1. Capdeville R, Buchdunger E, Zimmermann J, Matter A (2002) Nat Rev Drug Discov 1:493
2. Schlüter AD (2001) J Polym Sci A 39:1533
3. Noyori R (2002) Angew Chem Int Ed 41:2008
4. Miyaura N, Suzuki A (1995) Chem Rev 95:2457
5. Littke AF, Fu GC (2002) Angew Chem Int Ed 41:4176
6. Billingsley K, Buchwald SL (2007) J Am Chem Soc 129:3358
7. Phan NTS, Sluys MVD, Jones CW (2006) Adv Synth Catal 348:609
8. Bellina F, Carpita A, Rossi R (2004) Synthesis 2419
9. Kirchhoff JH, Netherton MR, Hills ID, Fu GC (2002) J Am Chem Soc 124:13662
10. Kataoka N, Shelby Q, Stambuli JP, Hartwig JF (2002) J Org Chem 67:5553
11. Barder TE, Walker SD, Martinelli JR, Buchwald SL (2005) J Am Chem Soc 127:4685
12. Parshall GW, Ittel S (1992) Homogeneous catalysis. Wiley, New York
13. Lappert MF (1988) J Organomet Chem 358:185
14. Gstottmayr CWK, Bohm VPW, Herdtweck E, Grosche M, Herrmann W (2002) Angew Chem Int Ed 41:1363
15. Navarro O, Marion N, Oonishi Y, Kelly R A III, Nolan SP (2006) J Org Chem 71:685
16. Mino T, Shirae Y, Sakamoto M, Fujita T (2005) J Org Chem 70:2191
17. Hahn FE, Jahnke MC, Pape T (2007) Organometallics 26:150
18. Li J-H, Zhang Y-H, Song R-J, Xie Y-X, Deng C-L, Liang Y (2007) Synthesis 2957
19. Hegedus LL, Mccabe RW (1984) Catalyst poisoning. Marcel Dekker, New York
20. Kondo T, Mitsudo T-A (2000) Chem Rev 100:3205
21. Bayon JC, Claver C, Masdeu-Bulto AM (1999) Coord Chem Rev 193–195:73
22. Zim D, Gruber AS, Ebeling G, Dupont J, Monteiro AL (2000) Org Lett 2:2881
23. Evans DA, Michael FE, Tedrow JS, Campos KR (2003) J Am Chem Soc 125:3534
24. Zhang W, Shi M (2004) Tetrahedron Lett 45:8921
25. Kostas ID, Andreadaki F, Kovala-Demertzi D, Prentjas C, Demertzis MA (2005) Tetrahedron Lett 46:1967
26. Safin DA, Babashkina MG, Klein A (2009) Catal Lett 129:363
27. Safin DA, Babashkina MG (2009) Catal Lett 130:679
28. Gabriele B, Salerno G, Costa M, Chiusoli GP (1995) J Organomet Chem 503:21
29. Zhang TY, Allen MJ (1999) Tetrahedron Lett 40:5813
30. Breuzard JAJ, Tommasino ML, Touchard F, Lemaire M, Bonnet MC (2000) J Mol Catal A 156:223
31. Dai M, Liang B, Wang C, You Z, Xiang J, Dong G, Chen J, Yang Z (2004) Adv Synth Catal 346:1669
32. Dai M, Liang B, Wang C, Chen J, Yang Z (2004) Org Lett 6:221
33. Chen W, Li R, Han B, Li B-J, Chen Y-C, Wu Y, Ding L-S, Yang D (2006) Eur J Org Chem 1177
34. Yang M, Yip K-T, Pan J-H, Chen Y-C, Zhu N-Y, Yang D (2006) Synlett 3057
35. Liang B, Liu J, Gao Y-X, Wongkhan K, Shu D-X, Lan Y, Li A, Batsanov AS, Howard JAH, Marder TB, Chen J-H, Yang Z (2007) Organometallics 26:4756
36. Liu J, Liang B, Shu D, Hu Y, Yang Z, Lei A (2008) Tetrahedron 64:9581
37. Wu Z-S, Yang M, Li H-L, Qi Y-X (2008) Synthesis 1415
38. Schlosser M (2002) In: Hegedus LS (ed) Organometallics in synthesis: a manual. Wiley, New York, chap 10
39. Amatore C, Carre E, Jutand A, Mbarki MA (1995) Organometallics 14:1818
40. Hassan J, Penalva V, Lavenot L, Gozzi C, Lemaire M (1998) Tetrahedron 54:13793
41. Lysén M, Köhler K (2005) Synlett 1671
42. Arvela RK, Leadbeater NE (2005) Org Lett 7:2101