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Synthesis of a Novel C_2-Symmetric Thiourea and Its Application in the Pd-Catalyzed Cross-Coupling Reactions with Arenediazonium Salts under Aerobic Conditions

Mingji Dai,[†] Bo Liang,[†] Cuihua Wang,[†] Jiahua Chen,*[,†] and Zhen Yang*[,†,‡]

Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry, Peking University, Beijing, 100871 China, and VivoQuest, Inc., 711 Executive Blvd., Valley Cottage, New York 10989

zyang@chem.pku.edu.cn.

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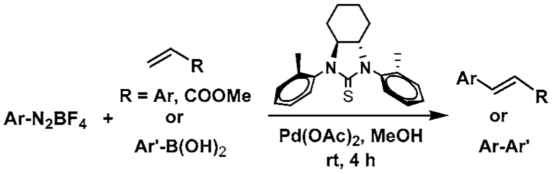
ABSTRACT



A novel thiourea-based C_2-symmetric ligand was synthesized, and its application in the palladium-catalyzed Heck and Suzuki coupling reactions of arenediazonium salts was evaluated. The reactions, which were performed at room temperature, without added base, and under aerobic conditions, produced product in 4 h with good yield. The corresponding arenediazonium salts were easily generated in one step from anilines.

The palladium-catalyzed cross-coupling reaction is a reliable method for C−C bond formation.[1] In this context, aryl or vinyl halides or triflates have found broad utility as electrophilic coupling partners.[2]

Recently, considerable attention has been focused on the metal-catalyzed coupling reactions that incorporate arenediazonium tetrafluoroborate salts as aryl electrophilic components in order to take advantage of several of their important features.[3] First, arenediazonium salts can be easily synthesized from the corresponding aniline with high yield.[3m,q,u,w,4] Second, the arenediazonium salts are more reactive than the corresponding aryl halides in the palladium-catalyzed Heck and Suzuki reactions.[3q,3w] Third, palladium-catalyzed reactions can usually be carried out at lower temperature (between 20 and 50 °C)[3n−w] than the typical Heck and Suzuki reactions (over 100 °C), and they can also be carried out without added extra base or salt (such as silver chloride or thallium ethoxide),[5] which extend the reaction scope to substrates with sensitive functional groups. Fourth, although certain aryl halides and triflates are difficult to synthesize, the corresponding arenediazonium salts can be generated easily from the corresponding arylamines, and this is a significant consideration for combinatorial synthesis. Thus, development of an arenediazonium salt that can be used in the metal-catalyzed coupling reaction could poten-

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[†] Peking University.

[‡] VivoQuest, Inc.

(1) (a) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998. (b) Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; John Wiley and Sons: Chichester, 1995; p 19. (c) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*; Springer: Berlin, 1999; Vols. 1−3. (d) *Catalytic Asymmetric Synthesis*, 2nd ed; Ojima, I., Ed.; Wiley-VCH: New York, 2000.

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tially both simplify the synthesis of certain types of advanced intermediates and reduce the steps involved in the synthesis of pharmaceuticals and agrochemicals.[6]

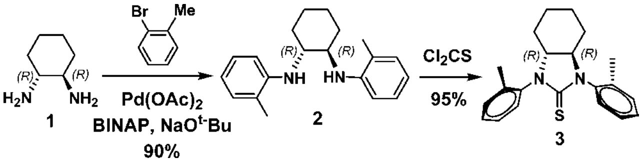
Previously described transition-metal-catalyzed reactions of diazonium salts with high affinity ligands (such as phosphines) are deficient because of their low catalytic activity, modest yields, and loss of diazonium salts as a result of decomposition.[3n,p,s] To avoid this problem, a ligand-free catalytic process has frequently been used.[3j,n,o,r−v] In 1997, the Sengupta group reported that a ligand-free palladium-catalyzed coupling reaction using diazonium salts with aryl boronic acids produced good yields when 10 mol % of $Pd(OAc)_2$ was included in the reaction.[3t] Later Andrus' group reported a similar coupling with 2 mol % of $Pd(OAc)_2$; however, the yield dropped to 21%.[3p]

To improve this reaction, new ligand-based metal-catalyzed reactions needed to be developed. Very recently, two groups reported that the imidazolium carbene based palladium complex[3q,w] effectively catalyzed the Heck and Suzuki reactions with arenediazonium tetrafluoroborate. In this report, we describe our successful efforts to synthesize a novel type of C_2-symmetric thiourea that is air-, moisture-, and heat-stable and can be successfully used in the Suzuki and Heck reactions at room temperature with $Pd(OAc)_2$ (1 mol %) under aerobic conditions and without added base.

Historically, the strong coordinative and adsorptive properties of sulfur-containing compounds have rendered them totally ineffective as catalysts, causing them to be categorized as catalyst poisons.[7] Recently, efforts have been made to synthesize sulfur-containing ligands, and several notable successes have been reported.[8] Complexes of thiourea with transition metals were first reported in 1894,[9] followed by their crystal study.[10]

Recently, we have observed an increase in the use of thiourea derivatives as ligands and catalysts in organic synthesis, but most often their use has been restricted to the polymer-supported palladium or rhodium catalysts.[11]

Scheme 1. Synthesis of C_2-Symmetric Thiourea **3**



The pioneering work of Chiusoli demonstrated that thiourea was a useful ligand in Pd-catalyzed carbonylations.[12] On the basis of these results, we began to study the function of thiourea in the Pd-catalyzed carbonylation.[13] Encouraged by our initial studies, we decided to attempt to synthesize a palladium complex based on a C_2-symmetric thiourea ligand, which would be able to catalyze the arenediazonium-based cross-coupling reaction. If these studies were successful, we reasoned that we might have a ligand that could be used for asymmetric synthesis of biaryl compounds.[14]

To this end, ligand **3** (see Scheme 1) was designed, and synthesized from the diamine **1**. Synthetically, commercially available (1*R*,2*R*)-(−)-1,2-diaminocyclohexane **1** (Aldrich) was coupled with *o*-methyl bromobenzene to give **2**,[15] which was then condensed with thiophosgene to generate **3**.[16] Its structure was confirmed by the X-ray analysis.

In early attempts to test the effect of ligand **3** in the Pd-catalyzed coupling reaction of the diazonium salt **4**[17a] (Table

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(3) For Heck reaction with arenediazonium salt, see: (a) Kikukawa, K.; Nagira, K.; Terao, N.; Wada, F.; Matsuda, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2609. (b) Akiyama, F.; Miyazaki, H.; Kaneda, K.; Teranishi, S.; Fujiwara, Y.; Abe, M.; Taniguchi, H. *J. Org. Chem.* **1980**, *45*, 2359. (c) Kikukawa, K.; Nagira, K.; Wada, F.; Matsuda, T. *Tetrahedron* **1981**, *37*, 31.(d) Kikukawa, K.; Maemura, K.; Kiseki, Y.; Wada, F.; Matsudo, T. Giam, C. S. *J. Org. Chem*. **1981**, *46*, 4885. (e) Ikenaga, K.; Kikukawa, K.; Matsuda, T. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1959. (f) Ikenaga, K.; Matsumoto, S.; Kikukawa, K.; Matsuda, T. *Chem. Lett.* **1988**, 873. (g) Wang, Y.; Pang, Y.; Zhang, Z.; Hu, H. *Synthesis* **1991**, 967. (h) Sengupta, S.; Bhattacharyya, S. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1943. (i) Beller, M.; Fischer, H.; Kühlein, K. *Tetrahedron Lett*. **1994**, *35*, 8773. (j) Beller, M.; Kühlein, K. *Synlett* **1995**, 441. (k) Sengupta, S.; Sadhukhan, S. K.; Bhattacharyya, S. *Tetrahedron* **1997**, *53*, 2213. (l) Sengupta, S.; Sadhukhan, S. K.; Bhattacharyya, S. Guha, J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 407. (m) Colas, C.; Goelder, M. *Eur. J. Org. Chem*. **1999**, 1357. (n) Brunner, H.; Le Cousturier de Courcy, N.; Genêt, J.-P. *Tetrahedron Lett*. **1999**, *40*, 4815. (o) Severino, E. A.; Correia, C. R. D. *Org. Lett*. **2000**, *2*, 3039. (p) Andrus, M. B.; Song, C.; Zhang, J. *Org. Lett*. **2002**, *4*, 2079. (q) Selvakumar, K.; Zapf, A.; Spannenberg, A.; Beller, M. *Chem. Eur. J*. **2002**, *8*, 3901. For Suzuki reaction with arenediazonium salt, see: (r) Darses, S.; Jeffery, T.; Genêt, J.-P.; Brayer, J.-L,; Demoute, J.-P. *Tetrahedron Lett*. **1996**, *37*, 3857. (s) Darses, S.; Genêt, J.-P.; Brayer, J.-L,; Demoute, J.-P. *Tetrahedron Lett*. **1997**, *38*, 4393. (t) Sengupta, S.; Bhattacharyya, S. *J. Org. Chem*. **1997**, *62*, 3405. (u) Darses, S.; Michaud, G.; Genêt. J.-P. *Eur. J. Org. Chem*. **1999**, 1875. (v) Willis, D. M.; Strongin, R. M. *Tetrahedron Lett*. **2000**, *41*, 6271. (w) Andrus, M. B., Song, C. *Org. Lett*. **2001**, *3*, 3761.

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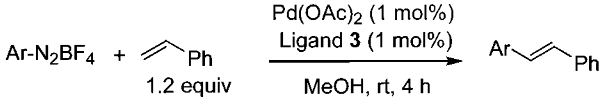
Table 1. Pd-Catalyzed Coupling of Arenediazonium Salts with Styrene under Aerobic Conditions



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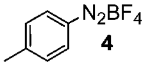
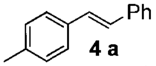
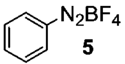
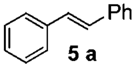
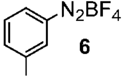
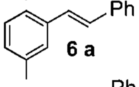
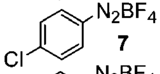
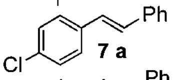
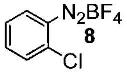
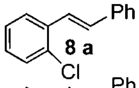
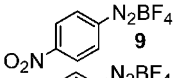
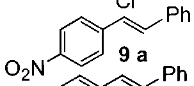
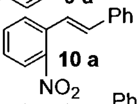
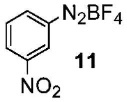
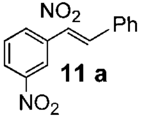
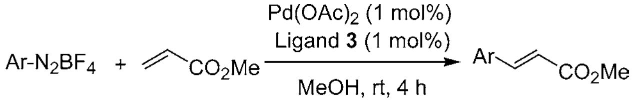
1	 **4**	 **4 a**	69%
2	 **5**	 **5 a**	50%
3	 **6**	 **6 a**	26%
4	 **7**	 **7 a**	89%
5	 **8**	 **8 a**	86%
6	 **9**	 **9 a**	98%
7	 **10**	 **10 a**	70%
8	 **11**	 **11 a**	73%

Table 2. Pd-Catalyzed Coupling of Arenediazonium Salts with Methyl Acrylate under Aerobic Conditions



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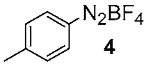
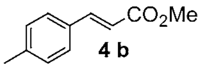
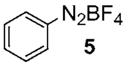
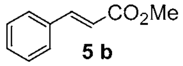
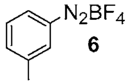
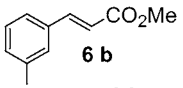
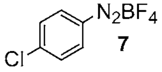
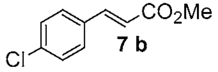
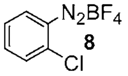
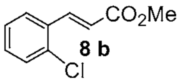
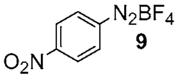
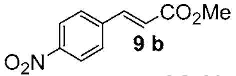
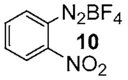
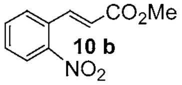
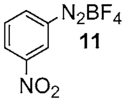
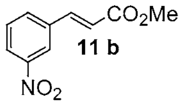
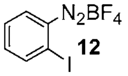
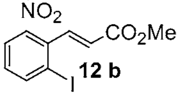
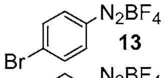
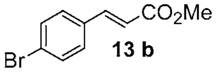
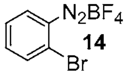
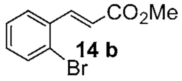
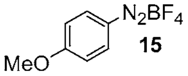
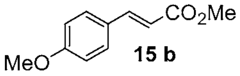
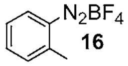
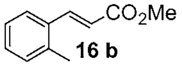
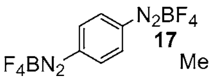
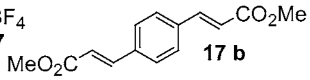
1	 **4**	 **4 b**	82%
2	 **5**	 **5 b**	77%
3	 **6**	 **6 b**	87%
4	 **7**	 **7 b**	93%
5	 **8**	 **8 b**	94%
6	 **9**	 **9 b**	99%
7	 **10**	 **10 b**	89%
8	 **11**	 **11 b**	62%
9	 **12**	 **12 b**	66%
10	 **13**	 **13 b**	85%
11	 **14**	 **14 b**	84% (E/Z = 6:1)
12	 **15**	 **15 b**	86%
13	 **16**	 **16 b**	75%
14	 **17**	 **17 b**	47%

1) with styrene, six solvents (MeOH, 1,4-dioxane, THF, CH_2Cl_2, CH_3CN, toluene) were screened, and methanol turned out to be the best solvent, producing 69% yield of coupling product **4a** (see Table 1, entry 1).[17b]

We next investigated the scope of this coupling reaction, and seven additional diazonium salts **5**−**11** (see entries 2−8 in Table 1) were tested. Interestingly, the diazonium salts **9**−**11** with NO_2 groups gave better results than the diazonium salts **4**−**6**. This observation was significant since low yields of coupling products were obtained by both Kikukawa[3c] and

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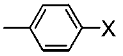
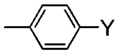
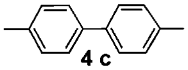
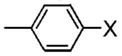
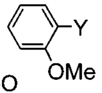
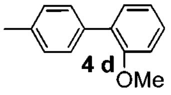
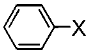
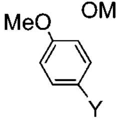
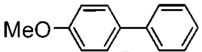
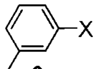
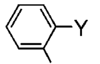
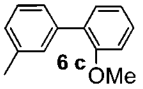
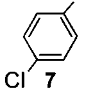
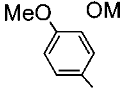
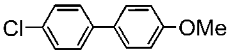
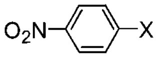
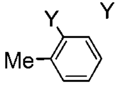
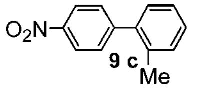
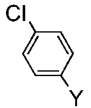
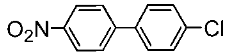
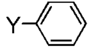
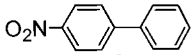
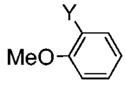
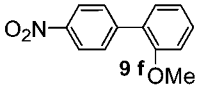
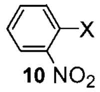
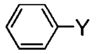
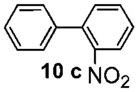
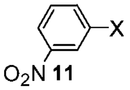
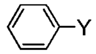
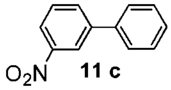
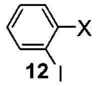
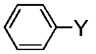
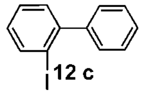
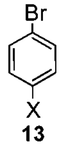
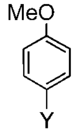
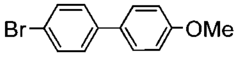
(16) López, O.; Maya, I.; Ulgar, V.; Robina, I.; Fuentes, J.; Fernández-Bolaños, J. G. *Tetrahedron Lett.* **2002**, *43*, 4313.

(17) (a) General procedure for the synthesis of the arenediazonium tetrafluoroborate salts employed Doyle's method;[4] see Supporting Information for detail. (b) General procedure for the Pd-catalyzed coupling reactions: Pd(OAc)$_2$ (0.005 mmol), ligand **3** (0.005 mmol), olefin or arylboronic acid (0.6 mmol), and arenediazonium tetrafluoroborate salt (0.5 mmol) were mixed in methanol (5.0 mL), and the reaction mixture was stirred at room temperature for 4 h under aerobic conditions. The reaction was worked up by removing the solvent under vacuum, and the residue was purified by chromatography on silica gel.

Table 3. Pd-Catalyzed Coupling of Aryldiazonium Salts with Aryl Boronic Acids under Aerobic Conditions

$$\underset{1.0\text{ equiv}}{{}^{1}\text{Ar-N}_2\text{BF}_4} \; + \; \underset{1.2\text{ equiv}}{{}^{2}\text{Ar-B(OH)}_2} \xrightarrow[\text{MeOH, rt, 4 h}]{\text{Pd(OAc)}_2\text{ (1 mol\%)}\;\;\text{Ligand } \mathbf{3}\text{ (1 mol\%)}} {}^{1}\text{Ar-Ar}^{2}$$

entry	diazonium salt	boronic acid	product	yield
1	 **4**		 **4 c**	77%
2	 **4**		 **4 d**	75%
3	 **5**		 **5 c**	79%
4	 **6**		 **6 c**	66%
5	 **7**		 **7 c**	67%
6	 **9**		 **9 c**	86%
7	**9**		 **9 d**	84%
8	**9**		 **9 e**	92%
9	**9**		 **9 f**	87%
10	 **10**		 **10 c**	74%
11	 **11**		 **11 c**	54%
12	 **12**		 **12 c**	76%
13	 **13**		 **13 c**	65%

$X = N_3BF_4$; $Y = B(OH)_2$

Sengupta[3h] and colleagues when they utilized the nitro-based diazonium salts in their ligand-free palladium-catalyzed coupling reactions.

Encouraged by these results, we began to evaluate the coupling reaction of arenediazonium salts with methyl acrylate,[3p] and the results are shown in Table 2. Notably, most of the reactions gave good results, and the halogen-based salts **7** and **8** and **12**−**14** underwent chemoselective couplings to generate the organohalides **7**b and **8b** and **12b**−**14b**. The remaining halides can undergo further chemical modification to generate structurally more complex molecules. Once again, the nitro-based diazonium salts **9**−**11** (see Table 2) produced good to excellent yields of coupling products **9b**−**11b**.

To extend the applicability of ligand **3** for use in the coupling reaction, additional studies in the Suzuki-type coupling was conducted. Nine arenediazonium salts were reacted with five arylboronic acids under the identical conditions listed in Table 1. The results, listed in Table 3, indicate that moderate to good yields of coupling products were obtained. It is also important to point out that good chemoselectivity was achieved in these coupling reactions using halogen-based diazonium salts, which suggests their potential utility in additional synthetic chemistry applications.

In summary, these results represent the first report of the synthesis of a novel C_2-symmetric thiourea **3** and its application in the palladium-catalyzed Heck and Suzuki coupling reactions with arenediazonium salts under aerobic conditions without added base. The results demonstrate the utility of ligand **3** in the palladium-catalyzed Heck and Suzuki coupling reactions that incorporate arenediazonium salt as an eletrophilic coupling partner. Further evaluation of chiral ligand **3** in the palladium-catalyzed asymmetric synthesis of biaryl molecules is currently underway.

Acknowledgment. We thank Dr. Maryann Donovan for her assistance in editing this manuscript and Mr. Guangbin Dong and Mr. Liang Zhao for their efforts in obtaining the X-ray structure of ligand **3**. Financial support from the NSFC (grants 20142004 and 20242002), and the sponsored research program of VivoQuest, Inc. is gratefully acknowledged.

Supporting Information Available: Experimental procedure and ^{1}H NMR and ^{13}C NMR spectra for the known product compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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