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Sterically Bulky Thioureas as Air- and Moisture-Stable Ligands for Pd-Catalyzed Heck Reactions of Aryl Halides

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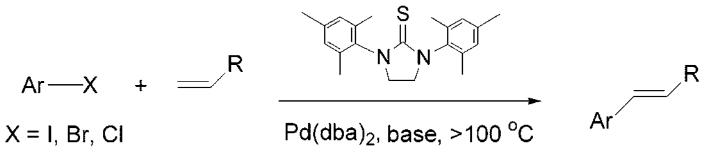
ABSTRACT



We demonstrate that sterically bulky N,N′-disubstituted cyclic thiourea–Pd(0) complexes are air- and moisture-stable and highly active catalysts for palladium-catalyzed Heck reaction of aryl iodides and bromides with olefins (TONs up to 500 000 for the reaction of PhI and methyl acrylate). Even activated aryl chlorides can undergo complete conversion in Bu_4NBr in the presence of 1 mol % Pd catalyst.

The palladium-catalyzed arylation of olefins (the Heck reaction) is one of the most versatile tools for C−C bond formation in organic synthesis.[1] Phosphine ligands are generally used to stabilize the reactive palladium intermediates, and excellent results have been reported for Pd-catalyzed Heck reactions when sterically bulky monophosphines,[2] diphosphines,[3] cyclometalated phosphines, or phosphites are used as the ligands.[4,5] The air-sensitivity of phosphine ligands, however, places significant limits on their synthetic applications. Therefore, the development of phosphine-free palladium catalysts is a topic of enormous interest.[6−8] Thioureas are air- and moisture-stable solids and have recently been employed as ligands in Ru-, Rh-, and Pd-catalyzed reactions.[9,10] Very recently, Z. Yang and coworkers reported Heck and Suzuki reactions of highly active

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[1] (a) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146. (b) De Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed.* **1994**, *33*, 2379. (c) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2. (d) Negishi, E.; Coperet, C.; Ma, S.; Liou, S.; Liu, F. *Chem. Rev.* **1996**, *96*, 365. (e) Crisp, G. T. *Chem. Soc. Rev.* **1998**, *27*, 427. (f) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (g) Whitcombe, N. J.; Kuok Hii, K.; Gibson, S. E. *Tetrahedron* **2001**, *57*, 7449. (h) Dounay, A. B.; Overman, L. E. *Chem Rev.* **2003**, *103*, 2945.

[2] (a) Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10. (b) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989. (c) Shaughnessy, K. H.; Kim, P.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 2123. (d) Stambuli, J. P.; Stauffer, S. R.; Shaughnessy, K. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 2677. (e) Ehrentraut, A.; Zapf, A.; Beller, M. *Synlett* **2000**, 1589.

[3] (a) Ben-David, Y.; Portnoy, M.; Gozin, M.; Milstein, D. *Organometallics* **1992**, *11*, 1995. (b) Portnoy, M.; Milstein, D. *Organometallics* **1993**, *12*, 1655. (c) Portnoy, M.; Ben-David, Y.; Milstein, D. *Organometallics* **1993**, *12*, 4734. (d) Portnoy, M.; Ben-Dvid, Y.; Rousso, I.; Milstein, D. *Organometallics* **1994**, *13*, 3465. (e) Shaw, B. L.; Perera, S. D. *Chem. Commun.* **1998**, 1863.

[4] For recent reviews on palladacycles for Heck reactions, see: (a) Dupont, J.; Pfeffer, M.; Spencer, J. *Eur. J. Inorg. Chem.* **2001**, 1917. (b) Benford, R. B. *Chem. Commun.* **2003**, 1787.

[5] For the use of tetraphenylphosphonium salts in Heck reactions, see: Reetz, M. T.; Lohmer, G.; Schwickardi, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 481.

[6] For phosphorus-free palladacycles as catalysts, see ref 4.

[7] For recent reviews on N-heterocyclic carbene−palladium catalysts, see: (a) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290. (b) Yong, B. S.; Nolan, S. P. *Chemtracts: Org. Chem.* **2003**, 205.

[8] For recent reports on Heck reactions using catalysts that are air- and moisture-stable, see: (a) Buchmeiser, M. R.; Wurst, K. *J. Am. Chem. Soc.* **1999**, *121*, 11101. (b) Silberg, J.; Schareina, T.; Kempe, R.; Wurst, K.; Buchmeiser, M. R. *J. Organomet. Chem.* **2001**, *622*, 6. (c) Masllorens, J.; Moreno-Manas, M.; Pla-Quintana, A.; Roglans, A. *Org. Lett.* **2003**, *5*, 1559.

[9] (a) Touchard, F.; Fache, F.; Lemaire, M. *Tetrahedron: Asymmetry* **1997**, *8*, 3319. (b) Touchard, F.; Gamez, P.; Fache, F.; Lemaire, M. *Tetrahedron Lett.* **1997**, *38*, 2275. (c) Touchard, F.; Bernard, M.; Fache, F.; Delbecq, F.; Guiral, V.; Sautet, P.; Lemaire, M. *J. Organomet. Chem.* **1998**, *567*, 133. (d) Tommasino, M. L.; Casalta, M.; Breuzard, J. A. J.; Lemaire, M. *Tetrahedron: Asymmetry* **2000**, *11*, 4835. (e) Breuzard, J. A. J.; Tommasino, M. L.; Touchard, F.; Lemaire, M.; Bonnet, M. C. *J. Mol. Catal. A: Chem.* **2000**, *156*, 223. (f) Touchard, F.; Bernard, M.; Fache, F.; Lemaire, M. *J. Mol. Catal. A: Chem.* **1999**, *140*, 1.

10.1021/ol049697+ CCC: $27.50

arenediazonium salts catalyzed by a chiral thiourea−Pd complex.[11] Here, we report that sterically bulky thiourea−Pd(0) complexes are air- and moisture-stable, highly active catalysts for Heck reactions of aryl halides.

We have synthesized the acyclic and cyclic thioureas **1a**−**j** (Figure 1)[12] and tested the catalytic activity of their complexes with Pd(0) in the Heck reaction between iodobenzene and methyl acrylate at 100 °C (Table 1). We stress that the reactions were conducted in air and that all the reagents were used directly as received. The structure of each thiourea ligand has a great influence on the catalytic efficacy of its palladium complex. Acyclic thioureas **1a**−**c** were almost completely inactive (entries 1−3), as was also the case for the cyclic thiourea **1d** featuring an NH moiety (entry 4). Good activity was observed, however, when using N,N′-disubstituted bulky cyclic thioureas **1e**, **1f**, **1j**, and **1k** of different ring sizes as the ligands; indeed, quantitative yields were achieved within 1 h when 0.1 mol % Pd was applied (entries 5−8). The catalyst loading could be decreased even further, to 0.001 and 0.002 mol %, when using ligands **1g** and **1k**, respectively (entries 15−17). In general, the palladium complexes formed with relatively bulky thiourea ligands (**1g**−**i**) exhibit the highest catalytic activities (cf. entries 11−13 vs entries 9 and 10). Attempts to decrease the catalyst loading even further, to 0.00033 mol % Pd, resulted in the incomplete conversion of iodobenzene, but a good yield could still be obtained after prolonged heating (entry 18; TON $= 2.6 \times 10^5$). We performed a reaction using our lowest catalyst loading (10^{-4} mol % Pd) at a higher temperature (130 °C) using bulky **1i** as the ligand and obtained a moderate yield (50%) of product (entry 19; TON $= 5.0 \times 10^5$). It is noteworthy that the thiourea−Pd(0) catalysts demonstrated excellent stability, and almost no palladium black was formed throughout the reaction. *Moreover, the DMF stock solution of Pd(0) complex of* ***1g*** *retained its activity even after standing in air at room temperature for two months* (cf. entry 11 vs entry 20).

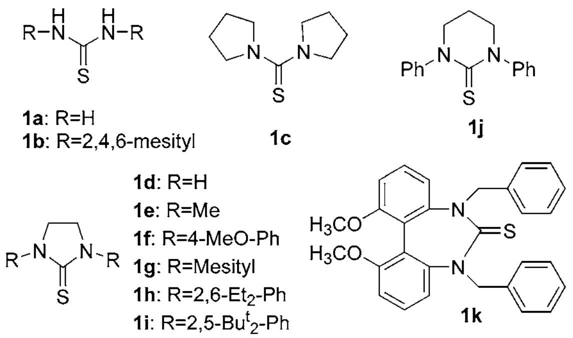
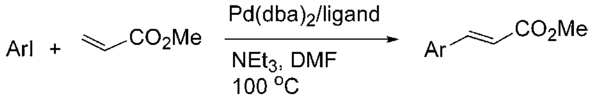


Figure 1. Structures of thiourea ligands.

Table 1. Screening of Thiourea Ligands for the Pd-Catalyzed Heck Reaction of Iodobenzene with Methyl Acrylate[a]



entry	ligand	Pd (mol %)	time (h)	yield[b]	TON
1	**1a**	2	4	0	0
2	**1b**	2	4	3	1.5
3	**1c**	2	4	8	4
4	**1d**	1	4	1	1
5	**1e**	0.1	1	>99	10^3
6	**1f**	0.1	1	>99	10^3
7	**1j**	0.1	1	>99	10^3
8	**1k**	0.1	1	>99	10^3
9	**1e**	0.01	4	>99	10^4
10	**1f**	0.01	4	>99	10^4
11	**1g**	0.01	2	>99	10^4
12	**1h**	0.01	2	>99	10^4
13	**1i**	0.01	1.5	>99	10^4
14	**1f**	0.002	12	18	9×10^3
15	**1k**	0.002	12	>99	5×10^4
16	**1k**	0.001	20	51	5.1×10^4
17	**1g**	0.001	10	>99	10^5
18[c]	**1g**	0.00033	30	88	2.6×10^5
19[d]	**1i**	0.0001	48	50	5×10^5
20[e]	**1g**	0.01	2	>99	10^4

[a] Reactions were conducted under aerobic conditions. Unless indicated otherwise, reactions were conducted using 2.5 mmol of PhI, with PhI/acrylate/NEt$_3$ = 1:1.2:1.2, and Pd(dba)$_2$/thiourea = 1:4. [b] Yield was determined by ^{1}H NMR spectroscopy using nitrobenzene as the internal standard. [c] On a 7.5 mmol scale at 120 °C. [d] On a 25 mmol scale at 130 °C. [e] Using a stock solution of the catalyst in DMF that had been standing in air for 2 months.

The catalytic efficacy of the thiourea **1g**−Pd(0) complex in the Heck reaction was studied further with a number of aryl iodides and olefins. Table 2 indicates that high yields were obtained within 4 h using 0.01 mol % Pd catalyst for olefins such as butyl acrylates and styrene (entries 1−3), but not for methyl vinyl ketone due to a lower reactivity (entry 4). Excellent yields were obtained for Heck reactions between butyl acrylate and para-substituted aryl iodides (entries 5−7). Olefins that are α- or β-subsituted are also suitable substrates and give trisubstituted olefins,[2b,13] but higher catalyst loadings and reaction temperatures were required (entries 8−10).

Aryl bromides and chlorides are cheaper and more readily available substrates than the corresponding iodides, but they are more reluctant to undergo the catalytic Heck reactions.[1g,14] Therefore, we tested the catalytic efficacy of our thiourea **1g**−palladium(0) complex using aryl bromides as the substrates, and the results are summarized in Table 3. In

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(10) (a) De Munno, G.; Gabriele, B.; Salerno, G. *Inorg. Chim. Acta* **1995**, *234*, 181. (b) Gabriele, B.; Salerno, G.; Costa, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1995**, *503*, 21. (c) Zhang, T. Y.; Allen, M. J. *Tetrahedron Lett.* **1999**, *40*, 5813. (d) Nan, Y.; Miao, H.; Yang, Z. *Org. Lett.* **2000**, *2*, 297. (e) Miao, H.; Yang, Z. *Org. Lett.* **2000**, 2, 1765. (f) Hu, Y.; Yang, Z. *Org. Lett.* **2001**, *3*, 1387.

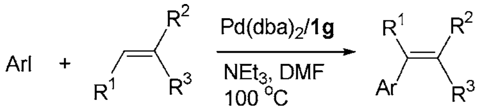
(11) Dai, M.; Liang, B.; Wang, C.; Chen, J.; Yang, Z. *Org. Lett.* **2004**, *6*, 221.

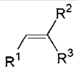
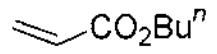
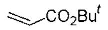
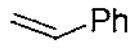
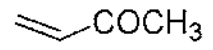
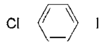
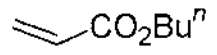
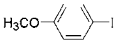
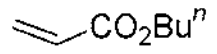
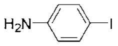
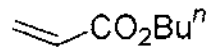
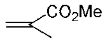
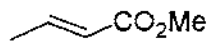
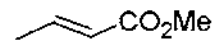
(12) For the synthesis of the thiourea ligands, see Supporting Information.

(13) Gurtler, C.; Buchwald, S. L. *Chem. Eur. J.* **1999**, *5*, 3107 and references therein.

(14) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.

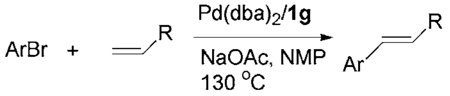
Table 2. Heck Reaction of Aryl Iodides with Olefins[a]



entry	ArI		Pd (mol%)	time (h)	yield (%)[b]
1	PhI		0.01	2	>99
2	PhI		0.01	2	>99
3	PhI		0.01	3	91
4	PhI		0.01	3	54
5			0.01	1.5	>99
6			0.01	3	>99
7			0.01	4	80
8	PhI		1	4	61[c]
9	PhI		1	10	34[c]
10[d]	PhI		1	10	88[c]

[a] Pd(dba)$_2$/**1g** = 1:4; PhI/olefin/NEt_3 = 1:1.2:1.2. [b] Yield was determined by ^1H NMR spectroscopy using nitrobenzene as the internal standard. [c] (*E*)-Configuration products. [d] Reaction was conducted at 120 °C.

Table 3. Heck Reaction of Aryl Bromides with Olefins[a]



entry	ArBr	R	Pd (mol%)	time (h)	yield (%)[b]
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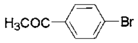
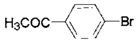
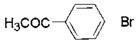
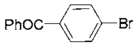
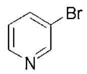
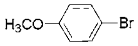
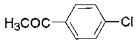
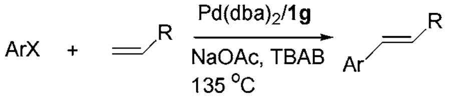
2		COOMe	0.1	15	92
3		Ph	0.1	15	99
4		Ph	0.02	24	94
5		Ph	0.02	24	98
6	PhBr	COOMe	0.5	12	99
7	PhBr	Ph	0.1	24	74
8		Ph	0.1	24	90
9		COOMe	1	24	<5
10		COOMe	1	24	<1

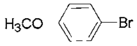
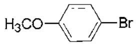
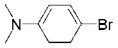
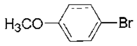
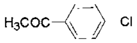
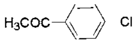
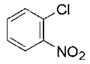
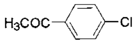
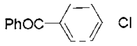
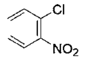
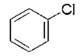
[a] Pd(dba)$_2$/**1g** = 1:4; ArX/olefin/NaOAc = 1:1.5:1.5. [b] Yield was determined by ^1H NMR spectroscopy using nitrobenzene as the internal standard.

general, higher catalyst loadings and temperatures[15] were required to force the completion of the reactions of the aryl bromides compared to the case of aryl iodides. For activated bromides, complete conversions of the substrates were observed after 15 h in the presence of 0.1 mol % Pd using NMP as the solvent and NaOAc as the base (entries 1−3). Moreover, the catalyst loading could be decreased further, to 0.02 mol % Pd, without significantly decreasing the yields (entries 4 and 5). Bromobenzene was a suitable substrate at a loading of 0.5 mol % Pd but not at 0.1 mol % (entries 6 and 7). 3-Bromopyridine was also efficiently coupled with styrene in 90% yield in the presence of 0.1 mol % Pd (entry 8). On the other hand, we observed very poor conversions when a deactivated bromide or an activated chloride was applied as the substrate (entries 9 and 10).

Recently, Beller[16] reported that the Heck reactions of aryl chlorides can be greatly improved when using Bu_4NBr as an ionic liquid solvent.[17] In fact, we have found that this system is also suitable for the thiourea **1g**−Pd(0)-catalyzed Heck reactions of deactivated bromides and activated chlorides when the reaction temperature is elevated slightly. As reported in Table 4, excellent yields were achieved for deactivated bromides after their reaction for 24 h in the presence of 0.5 mol % Pd (entries 1−3), but incomplete conversion occurred when using 0.2 mol % Pd catalyst (entry 4). Under the same conditions, activated aryl chlorides were coupled successfully with styrene within 24 h when using 1

Table 4. Heck Reactions of Deactivated Bromides and Activated Chlorides with Olefins[a]



entry	ArX	R	Pd (mol%)	time (h)	yield (%)[b]
1		Ph	0.5	24	99
2		COO^{n}Bu	0.5	24	99
3		COO^{n}Bu	0.5	24	97
4		Ph	0.2	30	80
5		Ph	1	24	96
6		Ph	0.5	30	67
7		Ph	1	24	99
8		COO^{n}Bu	2	24	77
9		COO^{n}Bu	1	24	80
10		COO^{n}Bu	1	24	90
11		Ph	2	24	<5

[a] Pd(dba)$_2$/**1g** = 1:4; PhI/olefin/NaOAc = 1:1.2:1.2. [b] Yield was determined by ^1H NMR spectroscopy using nitrobenzene as the internal standard.

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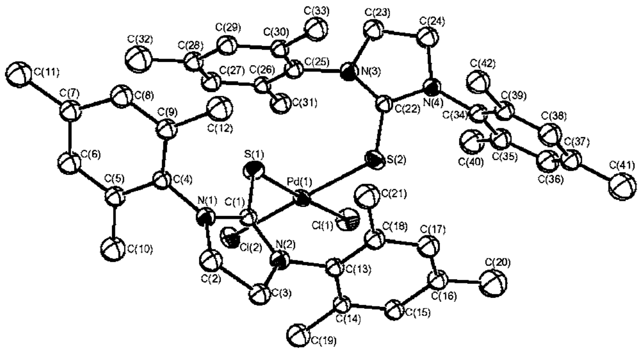
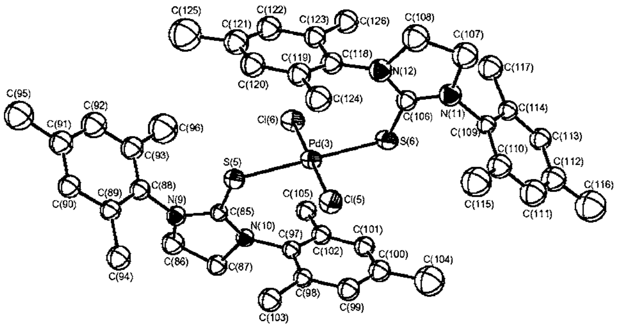
(15) Almost no reaction occurred at 100 °C using ArBr as substrates.
(16) Selvakumar, K.; Zapf, A.; Beller, M. *Org. Lett.* **2002**, *4*, 3031.
(17) For recent reviews on the use of ionic liquids as solvents, see: (a) Olivier-Bourbigou, H.; Magna, L. *J. Mol. Catal. A: Chem.* **2002**, *182–183*, 419. (b) Dupont, J.; de Souza, R. F.; Suarez, P. A. Z. *Chem. Rev.* **2002**, *102*, 3667. (c) Davis, J. H., Jr.; Fox, P. A. *Chem. Commun.* **2003**, 1209.



(a) *cis*-PdCl$_2$·(**1g**)$_2$



(b) *trans*-PdCl$_2$·(**1g**)$_2$

Figure 2. Structures of *cis*- and *trans*-PdCl$_2$·(**1g**)$_2$. Hydrogen atoms have been omitted for clarity. Thermal ellipsoids are shown at 30% probability.

mol % of the Pd catalyst (entries 5−7). *n*-Butyl acrylate displayed reactivity that was slightly lower than that of styrene, but good yields were also obtained (entries 8−10). Chlorobenzene itself, however, was completely inert, even when we used a higher loading of the Pd catalyst (2 mol %) (entry 11).

Having established that thiourea−Pd(0) complexes prepared in situ are active catalysts for Heck reactions of aryl halides with olefins, we investigated the nature of the thiourea−Pd(0) complexes to gain further insight with regard to the possible reaction mechanism. It is known that four molecules of unsubstituted thiourea **1a** can coordinate simultaneously to Pd(II) centers.[10a,b] An X-ray structure of the thiourea **1g**−PdCl$_2$ complex shows, however, that only two of these thiourea molecules and two chloride ions are coordinated with the Pd(II) center, which has a square-planar geometry in which the two sulfur atoms are positioned in either cis or trans form with respect to one another (Figure 2). While attempts to isolate the thiourea **1g**−Pd(0) complex failed, the ESI-MS study of the DMF solution of thiourea **1g** and Pd(dba)$_2$ (4:1) revealed one peak at $m/z = 783.2$, which corresponds to the [Pd(0)·(**1g**)$_2$ + H]$^+$ ion, in addition to the peak of free ligand **1g**. Therefore, we believe it is likely that the sterically bulky thiourea ligands form a 2:1 complex with palladium that is the catalytically active species, although the detailed mechanism awaits further investigation.[18]

In summary, we have demonstrated that sterically bulky N,N′-disubstituted cyclic thiourea−palladium complexes are highly active catalysts for Heck reactions of aryl halides with olefins (TONs up to 500 000 for the reaction of PhI and methyl acrylate). These novel thiourea ligands are air- and moisture-stable, and the reactions can be readily conducted in open air. Work is in progress in our laboratory to extend the applications of thiourea ligands in asymmetric catalysis as well as in other palladium-catalyzed transformations.

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Supporting Information Available: Synthetic schemes and characterization data of compounds **1b**, **1c**, and **1f**−**k**; ^{1}H NMR data of coupling products; general procedures for the Heck reactions of aryl halides with olefins catalyzed by Pd−thiourea complexes; and X-ray structural analysis of PdCl$_2$·(**1g**)$_2$, containing tables of atomic coordinates, thermal parameters, bond lengths, and angles. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) When the Heck reactions of aryl halides were performed using a 1:2 ratio of Pd(dba)$_2$ and thiourea **1g**, both the yield and reaction rate were quite similar to those obtained when using a 1:4 ratio. Generally, however, almost no palladium black was formed when using Pd−thiourea in a 1:4 ratio, whereas trace amounts of Pd black could be observed when using the 1:2 ratio, especially after heating for an extended period of time.