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The Design and Synthesis of Bis(thiourea) Ligands and Their Application in Pd-Catalyzed Heck and Suzuki Reactions Under Aerobic Conditions

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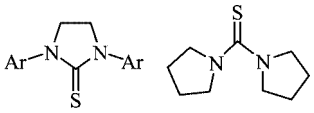
New, bulky *N*,*N*-disubstituted acyclic and cyclic bis(thiourea) ligands have been designed and synthesized. Their palladium(0) complexes are very stable and are active catalysts for Heck and Suzuki coupling reactions of aryl iodides and bromides under aerobic conditions. Good TONs and TOFs were achieved in the coupling reactions [for PhI, TONs up to 1000000 and TOFs up to 200000 (h^{-1}); for activated aryl bromide, TONs up to 89000]. In addition, further studies were conducted to know more about the nature of these catalysts. The active catalyst was found to be the chelate complex containing the bis(thiourea) and Pd in a 1:1 ratio. However, unlike a monothiourea, further coordination can occur to give a coordinatively saturated complex when bis(thiourea) and Pd are combined in a 2:1 ratio; this complex is catalytically inactive in coupling reactions.

Introduction

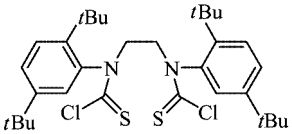
Palladium-catalyzed cross-coupling reactions are very versatile protocols for C–C bond formation in organic synthesis,[1] and bulky, electron-rich organophosphane compounds have been found to behave as highly active ligands, even for inert aryl chlorides.[2] However, their synthetic applications are significantly limited due to the air-sensitivity of these ligands. Over the past few years considerable attention has been focused on the development of air-stable palladium catalysts,[3] amongst which palladacycles[4] and palladium–carbene complexes[5] are outstanding. On the other hand, thioureas are generally air- and moisture-stable solids and their structures can be easily tuned by varying the *N*-substitution. Their potential application as ligands in metal-catalyzed reactions has been reported recently.[6] Yang et al.[7] and our group[8] have also demonstrated that bulky monothiourea–Pd complexes are active catalysts for Heck[9] and Suzuki[10] reactions of aryl halides or arenediazonium salts.

During the synthesis of the bulky monothiourea **7a**, we isolated the bis(thiocarbamoyl chloride) **2a** as a stable by-product. While the Pd complex of acyclic monothioureas such as **7c** show no activity in the Heck reaction,[8] we found that a mixture of [Pd(dba)$_2$] and acyclic **2a** could efficiently catalyze the coupling of PhI with methyl acrylate. Moreover, the complex between **2a** and Pd exhibits excellent thermal stability and no palladium black was formed after heating at 150 °C for 24 h.[11] Considering the possibility that the two sulfur atoms of the bis(thiocarbamoyl chloride) **2a** may coordinate to Pd to form the active complex,[12] we decided to investigate if bulky chelating thiourea ligands could form robust catalysts with transition metals (Figure 1). Here we report the design and synthesis of novel, bulky bis(thiourea) ligands and their application in Pd-catalyzed Heck and Suzuki coupling reactions.



7a: Ar = 2,5-*t*Bu$_2$C$_6$H$_3$
7b: Ar = mesityl

7c



2a

Figure 1. Structures of thiourea ligands.

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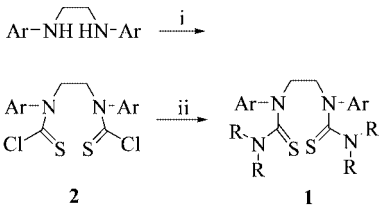
Results and Discussion

Ligand Design and Synthesis

The bis(thiocarbamoyl chloride) **2** could be smoothly obtained from the reaction of *N*,*N*′-diarylethylenediamine[13] with excess thiophosgene. Subsequently, the acyclic bis(thiourea) ligands **1a**–**c** were prepared by heating dichloride **2** with excess secondary amine in a pressure tube (Scheme 1). Unfortunately, this reaction is quite sensitive to the structures of the secondary amines. Attempts to synthesize acyclic bis(thiourea) compounds using more bulky amines such as dibenzylamine failed, probably owing to the steric hindrance and the low reactivity of the dichloride **2**.

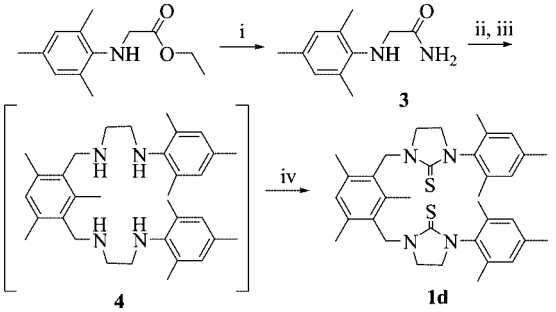


1a: Ar = 2,5-*t*Bu$_2$C$_6$H$_3$, R = R = C$_5$H$_{10}$
1b: Ar = mesityl, R = R = C$_5$H$_{10}$
1c: Ar = mesityl, R = C$_2$H$_5$

Conditions: (i) thiophosgene, Et$_3$N, DCM;
(ii) Excess secondary amine. 38-40% for two steps.

Scheme 1. Synthesis of acyclic bis(thiourea) ligands.

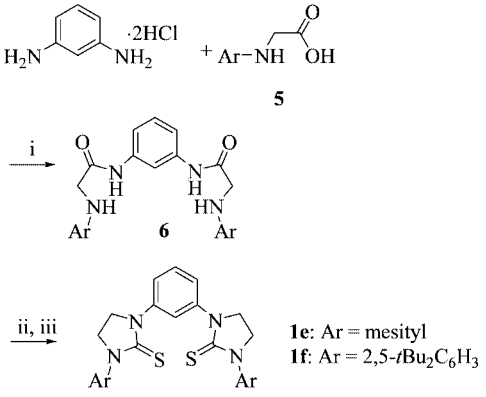
In order to introduce more bulky structures into the bis(thiourea) system, the cyclic bis(thiourea) ligands were designed and synthesized. In the first strategy, *N*-mesitylglycinamide (**3**)[14] was reduced to the diamine, and subsequent reaction with bis(bromomethyl)mesitylene[15] gave the tetraamine **4**. Although attempts to isolate pure **4** were unsuccessful, pure bis(thiourea) **1d** could be obtained after cyclization with thiophosgene in 11% yield for the three steps (Scheme 2).



Conditions: (i) NH$_3$, methanol, 88%; (ii) LAH/THF, then HCl; (iii) Na$_2$CO$_3$, CH$_3$CN, bis(bromomethyl)mesitylene; (iv) thiophosgene, THF, Na$_2$CO$_3$. 11% for three steps.

Scheme 2. Synthesis of cyclic bis(thiourea) ligand **1d**.

Another process was also developed in order to improve the synthesis of bis(thiourea) ligands. The *N*-arylglycine **5**[14] was condensed with *m*-phenylenediamine in the presence of EDCI and HOBt. The resulting bis(amide) **6** was smoothly converted into the tetraamine by borane reduction, and the crude product was subsequently treated with thiophosgene without purification to give the bulky bis(thiourea) systems **1e** and **1f** in good yields (Scheme 3).



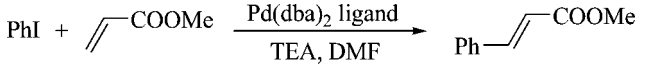
Conditions: (i) EDCI, HOBt, NEt$_3$, DCM. 85-90%;
(ii) BH$_3$–SMe$_2$; (iii) thiophosgene, Na$_2$CO$_3$, THF.
41-45% for two steps.

Scheme 3. Synthesis of cyclic bis(thiourea) ligands **1e** and **1f**.

Heck Reactions under Aerobic Conditions

With the various bis(thiourea) ligands in hand, the catalytic activity of the bis(thiourea)–Pd^0 complexes was screened in the Heck reaction between iodobenzene and methyl acrylate at 100 °C (Table 1). The reactions were conducted in air and all the reagents were used directly as received. Initial studies showed that a 1:1 ratio of bis(thiourea) to Pd is crucial to achieve high catalytic activity; an excess of bis(thiourea) ligand tended to dramatically decrease the conversion rate. The structure of each bis(thiourea) ligand also has a great influence on the catalytic activity of its palladium complex. Good catalytic efficacy was observed for acyclic bis(thiourea)–Pd complexes, and the best activity amongst these compounds was observed for bis(thiourea) **1c**, derived from acyclic diethylamine (Table 1, entries 1–3). Although the **1e**–Pd complex exhibited lower catalytic activity (entry 5), much better results were obtained when more bulky ligands **1d** or **1f** were applied, and, indeed, the **1f**–Pd complex displayed the highest catalytic activity (entry 6). It is notable that all bis(thiourea)–Pd^0 catalysts demonstrate excellent thermal stability, and high catalytic activity was observed at elevated temperature. As indicated in Table 1, high yields were obtained within 0.5 h at 150 °C when 0.01 mol-% catalyst loading was applied for acyclic bis(thiourea) derivatives **1a** or **1c** (entries 7 and 8). At a higher temperature (180 °C), and with **1c** as ligand, the catalyst loading could be lowered even further, and quantitative yields were obtained at 0.001 mol-% or 0.00033 mol-% Pd after 0.5 h or 3.5 h, respectively [entries 9 and 10, TOF (h^{-1}) up to 200000]. Furthermore, solvent-free conditions could be applied in our catalytic system (entries 11 and 12), and a very high TON (up to 1000000) was obtained in the reaction with neat PhI, *n*-butyl acrylate, and NBu$_3$ (entry 12).

Table 1. Screening bis(thiourea) ligands for the palladium-catalyzed Heck reaction.[a]

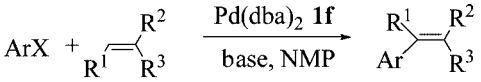


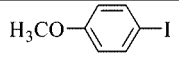
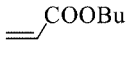
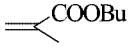
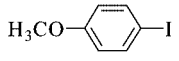
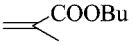
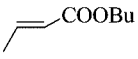
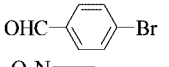
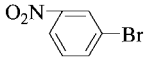
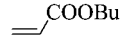
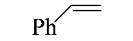
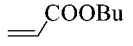
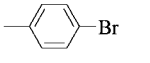
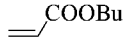
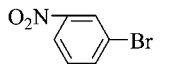
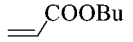
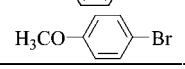
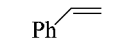
Entry	Ligand	Pd [mol-%]	T [°C]	t [h]	Yield[b] [%]	TON [×10³]
1	**1a**	0.01	100	6	86	8.6
2	**1b**	0.01	100	6.5	64	6.4
3	**1c**	0.01	100	4	95	9.5
4	**1d**	0.01	100	4	99	10
5	**1e**	0.01	100	4	45	4.5
6	**1f**	0.01	100	2	99	10
7	**1a**	0.01	150	0.5	89	8.9
8	**1c**	0.01	150	0.5	92	9.2
9[c][d]	**1c**	0.001	180	0.5	99	100
10[c][e]	**1c**	0.00033	180	3.5	99	300
11[c][f]	**1f**	0.0002	180	5	99	500
12[c][f]	**1c**	0.0001	180	12	99	1000

[a] Reactions were conducted under aerobic conditions. Unless indicated otherwise, the reactions were conducted with 2.5 mmol of PhI, PhI/acrylate/TEA, 1:1.2:1.2, $[Pd(dba)_2]$/bis(thiourea), 1:1. [b] Isolated yield. [c] NBu_3 and *n*-butyl acrylate were used. [d] At 7.5 mmol scale in NMP. [e] At 12.5 mmol scale in NMP. [f] At 25 mmol scale in solven-free conditions.

The reaction scope of the Heck reaction catalyzed by the complex **1f**–Pd^0 was further explored with a number of aryl halides and olefins. The results are summarized in Table 2. For deactivated aryl iodides, complete conversion of the substrate was observed within 3 h using 0.01 mol-% Pd catalyst in the reaction with monosubstituted olefins such as *n*-butyl acrylate (Table 2, entry 1). Under relatively harsh condition (130 °C, 0.5 mol-% Pd), trisubstituted olefins[16] could be prepared starting from 1,1- or 1,2-disubstituted olefins (entries 2–4). Activated *p*-bromobenzaldehyde was a suitable substrate at 0.1 mol-% Pd at 130 °C, and a high isolated yield was obtained (entry 5). Better yields could be achieved for other aryl bromides in the presence of 20 mol-% TBAB (tetrabutylammonium bromide) and 0.1 mol-% catalyst (entries 6–9).[17] Attempts to further decrease the catalyst loading were also successful, and a high TON (89000) could be obtained for the reaction of 3-nitrobromobenzene and *n*-butyl acrylate when the reaction temperature was increased (entry 11). Deactivated *p*-bromoanisole was smoothly coupled with styrene at 0.5 mol-% Pd catalyst at higher temperature (160 °C) (entry 12). Unfortunately, aryl chlorides were inert in this catalytic system, even in the presence of TBAB/base (NaOAc, K_2CO_3, or KO*t*Bu).[8]

Table 2. Heck reaction of aryl iodides and bromides with olefins.[a]



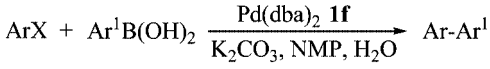
Entry	ArX	R^1 R^2 R^3	Pd (mol-%)	Base	T (°C)	t (h)	Yield[b] (%)
1			0.01	NEt_3	100	3	99
2	PhI		0.5	NBu_3	130	4	85[c]
3			0.5	NBu_3	130	5	68[d]
4	PhI		0.5	NBu_3	130	5	67[e]
5			0.1	NaOAc	130	15	85
6[f]			0.1	NaOAc	130	10	99
7[f]	PhBr		0.1	NaOAc	130	20	93
8[f]	PhBr		0.1	NaOAc	130	20	92
9[f]			0.1	NaOAc	130	12	75
10[f]	PhBr		0.01	NaOAc	150	24	84
11[f]			0.001	NaOAc	150	24	89
12[f]			0.5	NaOAc	160	24	76

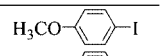
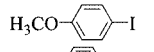
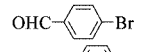
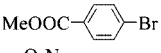
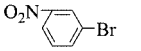
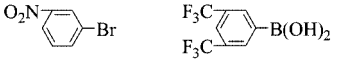
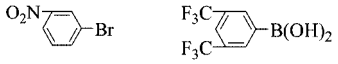
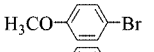
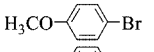
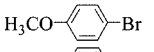
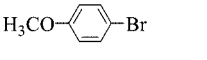
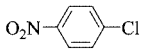
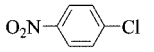
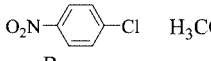
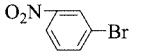
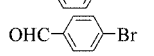
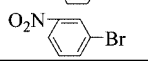
[a] $[Pd(dba)_2]$/bis(thiourea), 1:1; ArX/olefin/base, 1:1.2:1.2. [b] Isolated yield. [c] *E*/*Z* = 4.5:1. [d] *E*/*Z* = 8.2:1. [e] *E* Product. [f] 20 mol-% TBAB was added.

Suzuki Reactions under Aerobic Conditions

The Pd-catalyzed Suzuki cross-coupling reaction of aryl halides with aryl boronic acids is a general and efficient synthetic route to biaryl compounds and has found widespread application in many areas of organic synthesis. The operationally simple and air-stable nature of our thiourea/Pd catalytic system inspired us to investigate its scope in the Suzuki reaction. As revealed in Table 3, an excellent isolated yield was obtained at a loading of 0.01 mol-% Pd at 100 °C after 3 h under aerobic conditions for *p*-iodoanisole (Table 3, entry 1). A quantitative yield could also be achieved at 0.001 mol-% catalyst loading (entry 2). Encouraged by these results, we began to evaluate the coupling reaction of aryl bromides with aryl boronic acids. For activated bromides, almost quantitative yields were achieved within 3 h in the presence of 0.1 mol-% Pd under the same conditions (entries 3–7). On the other hand, only a low yield was obtained when deactivated *p*-bromoanisole was applied at 0.5 mol-% Pd at 120 °C (entry 8). Similar results were gained when bulky, monodentate *N*,*N*′-bis(2′,5′-di-*tert*-butylphenyl)ethylenethiourea (**7a**)[8] was used (entry 9). However, the yield could be increased by adding 20 mol-% TBAB (entry 10). For 3,5-difluorophenylboronic acid, a better result could be obtained by using TBAB as the ionic solvent (entry 11). An acceptable yield was achieved for *p*-nitrochlorobenzene with 1 mol-% Pd and 20 mol-% TBAB (entry 12 vs. entries 13 and 14). However, very low conversions (<5%) were observed when other aryl chlorides were applied. 1-Bromostyrene also displayed high reactivity towards phenylboronic acid in the bis(thiourea)–Pd system (entry 15). Potassium aryl trifluoroborates have been found to be more reactive than the corresponding organoboronic acid,[18] and high yields were obtained at only 0.1 mol-% Pd at 100 °C (entries 16 and 17). We also conducted the Suzuki reaction at further decreased catalyst loading (0.01 mol-%), and a quantitative yield was obtained for 3-nitrobromobenzene at 120 °C in 3 h (entry 18).

Table 3. Suzuki coupling reaction catalyzed by **1f**·Pd(dba)$_2$.[a]

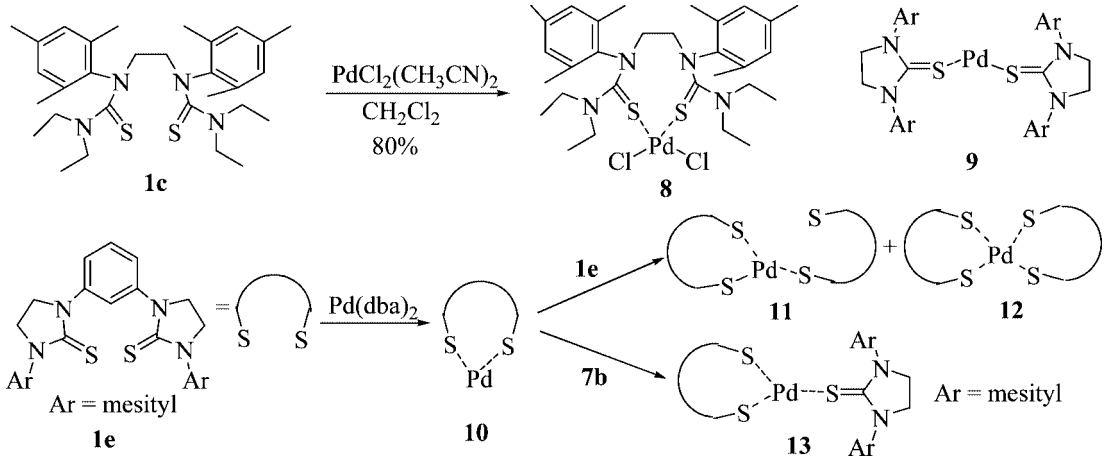


Entry	ArX	$Ar^1B(OH)_2$	Pd (mol-%)	T (°C)	t (h)	Yield[b] (%)
1		$PhB(OH)_2$	0.01	100	3	92
2		$PhB(OH)_2$	0.001	120	5	99
3		$PhB(OH)_2$	0.1	100	3	92
4		$PhB(OH)_2$	0.1	100	3	90
5		$PhB(OH)_2$	0.1	100	3	99
6			0.1	100	2	97
7			0.1	100	2	99
8		$PhB(OH)_2$	0.5	120	10	33
9[c]		$PhB(OH)_2$	0.5	120	10	27
10[d]		$PhB(OH)_2$	0.5	120	12	67
11[e]			0.5	130	12	51
12[f]		$PhB(OH)_2$	1	130	40	10
13[d,f]		$PhB(OH)_2$	1	130	24	49
14[d,f]			1	130	24	30
15		$PhB(OH)_2$	0.1	100	1	80
16		$PhBF_3K$	0.1	100	1	99
17		$PhBF_3K$	0.1	100	1.5	87
18		$PhB(OH)_2$	0.01	120	3	99

[a] [$Pd(dba)_2$]/bis(thiourea), 1:1, ArX/$Ar^1B(OH)_2$/K_2CO_3, 1:1.2:2.0 in 25% H_2O in NMP. [b] Isolated yield. [c] With ligand **7a**. [d] 20 mol-% TBAB was added. [e] The reaction was conducted in neat TBAB. [f] *p*-Nitrochlorobenzene/$PhB(OH)_2$/K_2CO_3, 1:2.0:3.0.

Complexes Study

Since some difference in catalytic behavior was noted for the bis(thiourea) catalysts compared with their monothiourea analogues,[8] more experiments were conducted to investigate the nature of the Pd complexes. As illustrated in Scheme 4, we successfully isolated the chelate complex (**8**) between bis(thiourea) **1c** and $PdCl_2$, which was well characterized by spectroscopic techniques. Moreover, a similar complex was detected for the **1c**/Pd^0 system (see Supporting Information). ESI-MS studies[19] were conducted to know more about the coordinating difference between cyclic monothiourea and bis(thiourea) ligands (Scheme 4). As previously reported, for monothiourea **7b** only the 2:1 complex **9** [Pd^0(**7b**)$_2$ + H, *m*/*z* = 783.2, Figure 2, a] was observed, even in the presence of excess ligand (4 equiv.).[8] Like **1c**, chelate complex **10** (Pd^0·**1e** + H, *m*/*z* = 621.3, Figure 2, b) was detected when cyclic bis(thiourea) **1e** and [Pd(dba)$_2$] were combined in a 1:1 ratio.[20] In contrast, when another equivalent of **1e** was added, the ESI-MS study demonstrated the formation of Pd^0·(**1e**)$_2$ (M + H, *m*/*z* = 1135.0, Figure 2, c), which is completely inactive in the Heck reaction of PhI and methyl acrylate. Nevertheless, we were able to detect the formation of the trigonal palladium complex **13** (Pd^0·**1e**·**7b** + H, *m*/*z* = 959.2, Figure 2, d) when one equivalent of monothiourea **7b** was added to the previously prepared **10** (Scheme 4). Interestingly, this in situ prepared complex solution could efficiently catalyze the Heck reac-



Scheme 4. Preparation of thiourea–Pd complexes.

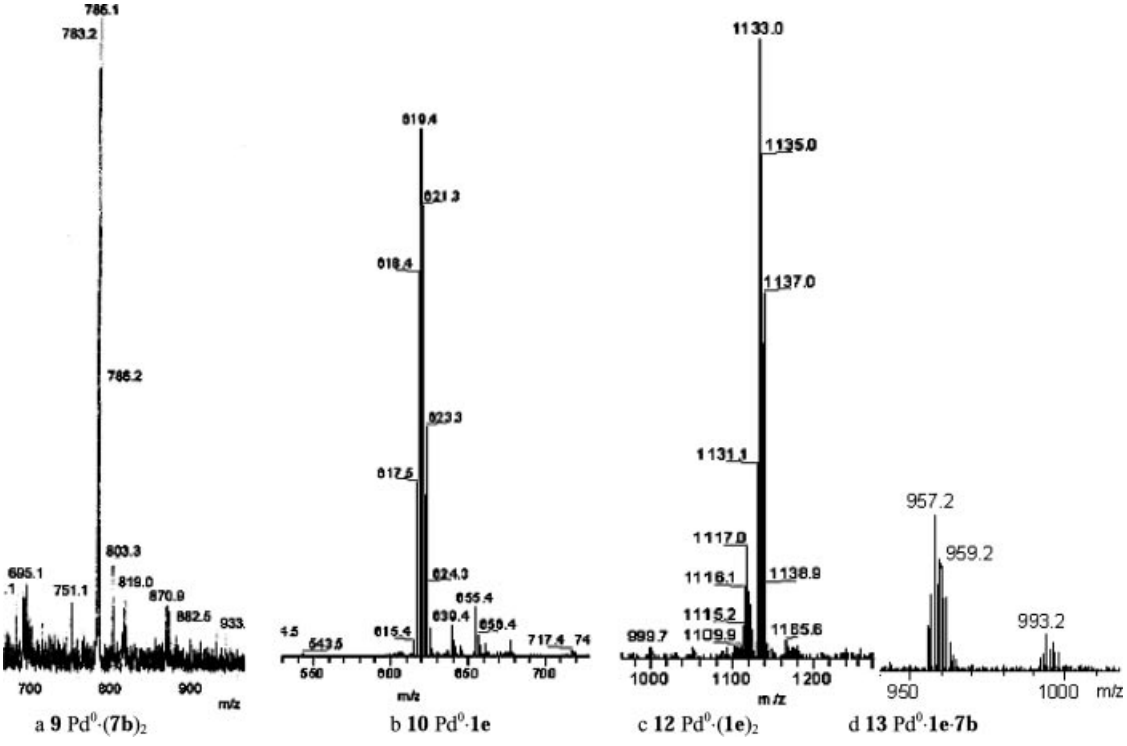


Figure 2. ESI mass spectra of thiourea–Pd^0 complexes.

tion of PhI and methyl acrylate, with even better results than with **10** (0.01 mol-% Pd, 4 h, 83% yield; cf. Table 1, entry 5).[21] Therefore, coordinatively saturated complex **12** might be produced rather than the trigonal complex **11** when bis(thiourea) **1e** and [Pd(dba)$_2$] are combined in a 2:1 ratio, although the exact structure awaits further exploration.[22,23]

Conclusions

We have presented the synthesis of bulky *N*,*N*-disubstituted acyclic and cyclic bis(thiourea) ligands. These compounds act as strong coordinating ligands for palladium and the complexes demonstrate high thermal stability. Good catalytic activity for aryl iodides and bromides in Heck and Suzuki coupling reactions was exhibited under aerobic conditions for the bis(thiourea)–Pd catalysts, and high TONs and TOFs were achieved (for PhI, TONs up to 1000000 and TOFs up to 200000; for activated bromide, TONs up to 89000). Moreover, spectroscopic investigation of the bis(thiourea)–Pd complexes demonstrated that the active catalyst is the chelating species in a 1:1 ratio. In the presence of two equivalents of the bis(thiourea) ligand further coordination gives the coordinatively saturated complex, which is catalytically inactive in these coupling reactions. Work is currently underway to develop recyclable thiourea-Pd catalysts and extend the application of these novel thiourea ligands in palladium- and other transition-metal-catalyzed reactions.

Experimental Section

General Methods: Melting points were determined in open capillaries and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 50 or 100 MHz (Bruker Avance), respectively. The chemical shifts are reported in ppm downfield from $CDCl_3$ (δ = 7.27 ppm) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (δ = 77.0 ppm) for ^{13}C NMR spectroscopy. ESI-mass spectra were measured with a Finnigan LCQ^{DECA} ion trap mass spectrometer. All reagents were used without purification as commercially available.

Preparation of Dichloride 2: A solution of *N*,*N*′-diaryl diamine (1.0 mmol) and NEt_3 (0.42 mL, 3.0 mmol) in THF (10 mL) was added dropwise to a stirred solution of thiophosgene (0.3 mL, 3.0 mmol) in dry THF (10 mL) at 0 °C. After stirring at room temperature overnight, the organic layer was washed with water, dried, and concentrated. Compound **2a** was recrystallized from ethanol to give a stable white solid, whereas **2b** was used directly in the next step.

Dichloride 2a: Yield: 355 mg (60%). M.p. 200–202 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (d, J = 8.5 Hz, 2 H, ArH), 7.29 (dd, J = 8.5, 2.2 Hz, 2 H, ArH), 6.74 (d, J = 2.2 Hz, 2 H, ArH), 5.33–5.28 (m, 2 H, CH*H*), 3.61–3.55 (m, 2 H, CH*H*), 1.30 (s, 18 H, *t*Bu), 1.17 (s, 18 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.6, 150.4, 141.0, 140.7, 130.4, 126.3, 125.5, 53.8, 35.6, 34.1, 31.9, 31.1 ppm. IR (KBr): $\tilde{\nu}$ = 2965, 1734, 1407, 1361, 1240, 1110 cm^{-1}. EI LRMS: *m*/*z* (%) = 592 (12) [M], 310 (100). EI-HRMS: calcd. for $C_{32}H_{46}Cl_2N_2S_2$ 592.2479; found 592.2467.

General Procedure for the Synthesis of Acyclic Bis(thiourea) Ligands: Bis(thiocarbamoyl chloride) **2** (0.5 mmol) and excess secondary amine (5 mmol) were heated at 100 °C in a sealed pressure tube for 24 h. The solution was then diluted with EtOAc (10 mL) and the organic phase was washed with dilute HCl and brine. The organic layer was dried and concentrated. Flash chromatography gave the pure bis(thiourea) derivatives **1a**–**c** as white solids.

Acyclic Bis(thiourea) 1a: Yield: 328 mg (95%). White solid, m.p. 225–226 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.34 (m, 2 H, ArH), 7.21–7.18 (m, 2 H, ArH), 7.18–7.00 (m, 2 H, ArH), 4.87–4.79 (m, 2 H, CH*H*), 4.15–4.11 (m, 2 H, CH*H*), 3.54–3.35 (m, 8 H, NCH_2 of piperidinyl ring), 1.44–1.19 (m, 48 H, piperidinyl ring + *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.0, 149.1, 142.9, 141.3, 129.8, 127.4, 124.1, 54.0, 52.5, 35.6, 34.0, 32.0, 31.1, 25.2, 24.2 ppm. IR (KBr): $\tilde{\nu}$ = 2958, 2865, 1609, 1440, 1397, 1362, 1244, 1185, 1133, 1026 cm^{-1}. EI-HRMS: calcd. for $C_{42}H_{66}N_4S_2$ 690.4729; found 690.4717. $C_{42}H_{66}N_4S_2$ (691.13): calcd. C 72.99, H 9.63, N 8.11; found C 72.90, H 9.52, N 8.13.

Acyclic Bis(thiourea) 1b: Yield: 220 mg (40%) for two steps. White solid, m.p. 222–224 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.83 (s, 4 H, ArH), 4.29 (s, 4 H, CH_2), 3.30–3.27 (m, 8 H, NCH_2 of piperidinyl ring), 2.25 (s, 6 H, $ArCH_3$), 2.18 (s, 12 H, $ArCH_3$), 1.39–1.36 (m, 4 H, piperidinyl ring), 1.17–1.15 (m, 8 H, piperidinyl ring) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.3, 141.3, 136.1, 134.3, 130.0, 51.9, 50.9, 25.2, 24.2, 20.7, 19.1 ppm. IR (KBr): $\tilde{\nu}$ = 2934, 1609, 1473, 1422, 1369, 1131. EI-HRMS: calcd. for $C_{32}H_{46}N_4S_2$ 550.3164; found 550.3158. $C_{32}H_{46}N_4S_2$ (550. 86): calcd. C 69.77, H 8.42, N 10.17; found C 69.52, H 8.44, N 10.09.

Acyclic Bis(thiourea) 1c: Yield: 200 mg (38%) for two steps. White solid, m.p. 197–199 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.82 (s, 4 H, ArH), 4.29 (s, 4 H, CH_2), 3.30 (q, J = 6.8 Hz, 8 H, CH_2), 2.24 (s, 6 H, $ArCH_3$), 2.21 (s, 12 H, $ArCH_3$), 0.73 (t, J = 6.8 Hz, 12 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.2, 141.6, 136.4, 135.0, 51.3, 46.0, 20.8, 19.2, 11.7 ppm. IR (KBr): $\tilde{\nu}$ = 2963, 1651, 1486, 1370, 1348, 1274, 1185, 1152, 1120 cm^{-1}. EI-HRMS: calcd. for $C_{30}H_{46}N_4S_2$ 526.3164; found 526.3168. $C_{30}H_{46}N_4S_2$ (526.84): calcd. C 68.39, H 8.80, N 10.63; found C 68.37, H 8.82, N 10.39.

Synthesis of Cyclic Bis(thiourea) Ligand 1d

Compound 3: Ethyl (mesitylamino)acetate[14] (1.6 g, 7.2 mmol) in methanol (20 mL) was added to a three-necked flask fitted with gas inlet and ammonia was bubbled through it at 0 °C. The flask was then sealed with septa. After standing at room temperature for 48 h the solvent was removed under vacuum. Trituration with petroleum ether gave **3** (1.22 g, 88%) as a white solid. M.p. 107–108 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.02 (s, 1 H, NH), 6.84 (s, 2 H, ArH), 6.02 (s, 2 H, NH_2), 3.62 (s, 2 H, CH_2), 2.27 (s, 6 H, $ArCH_3$), 2.23 (s, 3 H, $ArCH_3$) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.1, 144.2, 129.6, 129.3, 128.2, 50.9, 20.3, 18.5 ppm. IR (KBr): $\tilde{\nu}$ = 3413, 3178, 1682, 1487, 1390, 1321, 1220, 1157, 1091 cm^{-1}. ESI-LRMS: *m*/*z* = 193.1 [M + 1].

Cyclic Bis(thiourea) 1d: $LiAlH_4$ (0.6 g, 16.2 mmol) was suspended in dry THF (50 mL) and the amide **3** (1.0 g, 5.2 mmol) in THF (10 mL) was added dropwise. After heating at reflux overnight, the reaction was quenched with 10% potassium hydroxide solution (0.9 mL). The resulting solid was filtered through a pad of celite and thoroughly washed with THF. HCl gas was introduced to precipitate the corresponding di-HCl salt (1.0 g, 90%). The diamine salt was directly used in the next step. A solution of bis(bromomethyl)mesitylene (0.72 g, 2.3 mmol) in CH_3CN (10 mL) was added slowly, at 80 °C, to a stirred mixture of the diamine salt (2.0 g, 9.2 mmol) and Na_2CO_3 (0.85 g, 8 mmol) in CH_3CN (15 mL). The

resulting mixture was refluxed for 24 h. The mixture was then diluted with ethyl acetate and washed with brine, dried, and concentrated. The resulting oil was dissolved in THF (30 mL) and Na_2CO_3 (1.27 g, 12 mmol) was added. Thiophosgene (0.7 mL, 9 mmol) in THF (10 mL) was added dropwise *very slowly* at room temperature. After stirring overnight the THF was removed and water (20 mL) and ethyl acetate (40 mL) were added. The organic layer was washed with dilute HCl and brine, dried, and concentrated. The pure bis(thiourea) **1d** was obtained by flash chromatography (20% ethyl acetate/petroleum ether) as a white solid (150 mg, 11% for three steps). m.p. > 230 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.97 (s, 1 H, ArH), 6.95 (s, 4 H, ArH), 4.97 (s, 4 H, $ArCH_2$), 3.66 (t, J = 8.4 Hz, 4 H, CH_2), 3.41 (t, J = 8.4 Hz, 4 H, CH_2), 2.43 (s, 3 H, $ArCH_3$), 2.40 (s, 6 H, $ArCH_3$), 2.29 (s, 6 H, $ArCH_3$), 2.22 (s, 12 H, $ArCH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.7, 138.6, 138.1, 137.8, 136.5, 134.7, 130.8, 130.7, 129.4, 46.9, 46.3, 45.5, 21.0, 20.4, 17.7, 16.2 ppm. IR (KBr): $\tilde{\nu}$ = 2917, 1609, 1489, 1437, 1408, 1326, 1309, 1273, 1233, 1033 cm^{-1}. ESI-LRMS: *m*/*z* (%) = 585.2 (100) [M + 1]. ESI-HRMS: calcd. for $C_{35}H_{44}N_4S_2$ + Na 607.2905; found 607.2883. $C_{35}H_{44}N_4S_2$ (584.88): calcd. C 71.88, H 7.58, N 9.58; found C 71.72, H 7.53, N 9.50.

Synthesis of Cyclic Bis(thiourea)s Ligands 1e and 1f

Preparation of Compound 6: 1,3-Phenylenediamine dihydrochloride (0.18 g, 1 mmol), **5**[13] (2.2 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI; 0.46 g, 2.4 mmol) and 1-hydroxybenzotriazole (HOBt; 0.14 g, 1 mmol) were stirred in DCM (20 mL) at 0 °C. After 5 min NEt_3 (5 mmol) was added and the mixture was stirred at room temperature under argon and monitored by TLC. After completion, solvent was removed under vacuum and ethyl acetate (30 mL) was added. The organic layer was washed with saturated $NaHCO_3$ and brine, dried, and concentrated. Pure **6** was obtained by flash chromatography or recrystallization from ethanol.

Diamide 6e: Yield: 390 mg (85%). White solid, m.p. 188–189 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.56 (s, 2 H, NH), 7.92 (s, 1 H, ArH), 7.44–7.41 (m, 2 H, ArH), 7.30–7.25 (m, 1 H, ArH), 6.86 (s, 4 H, ArH), 3.81 (s, 4 H, CH_2), 2.32 (s, 12 H, $ArCH_3$), 2.25 (s, 6 H, $ArCH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.4, 157.3, 141.6, 138.1, 133.0, 129.8, 129.0, 115.5, 110.7, 52.5, 20.5, 18.3 ppm. IR (KBr): $\tilde{\nu}$ = 3314, 2917, 1664, 1608, 1523, 1486, 1425, 1305, 1225 cm^{-1}. ESI-LRMS: *m*/*z* = 459.2 [M + 1].

Diamide 6f: Yield: 538 mg (90%). White solid, m.p. 90–92 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (s, 2 H, NH), 7.71 (s, 1 H, ArH), 7.32–7.23 (m, 5 H, ArH), 6.85 (dd, J = 8.4, 2.0 Hz, 2 H, ArH), 6.61 (d, J = 2.0 Hz, 2 H, ArH), 4.62 (s, 2 H, NH), 3.99 (d, J = 5.2 Hz, 4 H, CH_2), 1.49 (s, 18 H, *t*Bu), 1.24 (s, 18 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.3, 150.5, 144.9, 137.9, 131.8, 129.6, 126.3, 116.3, 116.1, 111.5, 110.5, 50.4, 34.3, 33.8, 31.2, 30.3 ppm. IR (KBr): $\tilde{\nu}$ = 3449, 3349, 2961, 1689, 1610, 1561, 1524, 1416, 1363, 1306, 1258, 1233, 1163, 915 cm^{-1}. ESI-LRMS: *m*/*z* = 599.4 [M + 1].

General Procedure for Preparation of 1e and 1f: Borane–dimethyl sulfide (2 M in THF) (3.6 mL, 7.2 mmol, 8 equiv.) was added to a solution of **6** (0.9 mmol) in THF (20 mL) at 0 °C and the solution was refluxed overnight. After cooling to room temperature, methanol was added very slowly to destroy the excess borane and the solvent was removed. Methanol (10 mL) was added and removed again under reduced pressure. The resulting tetraamine was directly used in the next step. A dilute solution of thiophosgene (0.23 mL, 2.3 mmol) in THF (15 mL) was added *very slowly* to a stirred mixture of the tetraamine obtained above and Na_2CO_3 (0.46 g, 5.4 mmol) in dry THF (20 mL). The mixture was then stirred at room temperature overnight. The pure cyclic bis(thiourea) was obtained as a white solid by flash chromatography and recrystallization from ethanol.

Cyclic Bis(thiourea) 1e: Yield: 208 mg (45%) for two steps. White solid, m.p. > 230 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (s, 1 H, ArH), 7.51–7.44 (m, 3 H, ArH), 6.97 (s, 4 H, ArH), 4.29 (t, J = 8.4 Hz, 4 H, CH_2), 3.91 (t, J = 8.4 Hz, 4 H, CH_2), 2.31 (s, 6 H, CH_3), 2.28 (s, 12 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.7, 141.0, 138.3, 136.3, 134.7, 129.4, 128.6, 121.1, 120.2, 49.3, 47.2, 21.0, 17.8 ppm. IR (KBr): $\tilde{\nu}$ = 2917, 1604, 1489, 1421, 1306, 1277, 1076 cm^{-1}. ESI HRMS: calcd. for $C_{30}H_{34}N_4S_2$ + H 515.2303; found 515.2294. $C_{30}H_{34}N_4S_2$ (514.75): calcd. C 70.00, H 6.66, N 10.88; found C 69.89, H 6.73, N 10.72.

Cyclic Bis(thiourea) 1f: Yield: 242 mg (41%) for two steps. White solid, m.p. > 230 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24–8.22 (m, 1 H, ArH), 7.53–7.43 (m, 3 H, ArH), 7.38 (d, J = 2.0 Hz, 2 H, ArH), 7.35 (d, J = 2.0 Hz, 2 H, ArH), 7.11 (s, 2 H, ArH), 4.29–4.18 (m, 4 H, CH_2), 4.13–4.07 (m, 2 H, CH_2), 4.01–3.93 (m, 2 H, CH_2), 1.48 (s, 18 H, *t*Bu), 1.34 (s, 18 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.1, 150.5, 145.0, 141.2, 139.6, 128.8, 128.7, 128.2, 127.5, 125.5, 121.8, 121.6, 121.2, 52.6, 49.4, 35.4, 34.3, 31.9, 31.2 ppm. IR (KBr): $\tilde{\nu}$ = 2960, 1604, 1559, 1475, 1414, 1297, 1084 cm^{-1}. ESI-LRMS: *m*/*z* (%) = 655.4 (37) [M + 1], 639.5 (100). ESI-HRMS: calcd. for $C_{40}H_{54}N_4S_2$ + H 655.3868; found 655.3864. $C_{40}H_{54}N_4S_2$ (655.01): calcd. C 73.35, H 8.31, N 8.55; found C 73.27, H 8.43, N 8.33.

Synthesis of 1c·$PdCl_2$ Complex 8: Dichloromethane (2 mL) was added to a vial containing **1c** (38.2 mg, 0.073 mmol) and $[PdCl_2(CH_3CN)_2]$ (18.8 mg, 0.073 mmol). After the solids had dissolved an immediate color change to red was observed. The solution was stirred for 0.5 h. All volatile components were then removed in vacuo, and the resulting solid was treated with diethyl ether (5 mL). The resulting powder was washed with toluene and dried under vacuum to give **8** as an orange solid. Yield: 41 mg (80%). m.p. > 220 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.76 (s, 2 H, ArH), 6.52 (s, 2 H, ArH), 5.55 (br. s, 2 H, CH_2), 3.50–3.45 (m, 8 H, CH_2), 2.81 (br. s, 2 H, CH_2), 2.21 (s, 6 H, $ArCH_3$), 2.04 (s, 6 H, $ArCH_3$), 1.63 (s, 6 H, $ArCH_3$), 1.27–1.19 (m, 12 H, CH_3) ppm. ^{13}C NMR (50 MHz, $[D_6]$DMSO+CD_2Cl_2): δ = 184.8, 137.5, 133.1, 130.2, 129.1, 67.2, 52.8, 25.2, 20.2, 18.6, 18.1 ppm. IR (KBr): $\tilde{\nu}$ = 2971, 1636, 1459, 1400, 1076 cm^{-1}. ESI-HRMS: calcd. for $C_{30}H_{46}Cl_2N_4Pd^{II}S_2$ – Cl_2 – H 631.2120; found 631.2115. $C_{30}H_{46}Cl_2N_4PdS_2$ (704.17): calcd. C 51.17, H 6.58, N 7.96; found C 51.08, H 6.69, N 8.24.

Supporting Information Available (for details see the footnote on the first page of this article): Procedure for ESI MS study of the thiourea-Pd complex. ^{1}H NMR spectroscopic data for coupling products; Spectra of bis(thiourea) ligands and complex **8**.

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[1] A. de Meijere, F. Diederich, *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed., volumes 1 and 2, Wiley-VCH, Weinheim, **2004**.

[2] a) A. F. Littke, G. C. Fu, *Angew. Chem. Int. Ed.* **2002**, *41*, 4176–4211; b) G. C. Fu, *J. Org. Chem.* **2004**, *69*, 3245–3249 and references cited therein.

[3] a) M. R. Buchmeiser, K. Wurst, *J. Am. Chem. Soc.* **1999**, *121*, 11101–11107; b) J. Silberg, T. Schareina, R. Kempe, K. Wurst,

M. R. Buchmeiser, *J. Organomet. Chem.* **2001**, *622*, 6–18; c) G. A. Grasa, A. C. Hillier, S. P. Nolan, *Org. Lett.* **2001**, *3*, 1077–1080; d) J. Masllorens, M. Moreno-Mañas, A. Pla-Quintana, A. Roglans, *Org. Lett.* **2003**, *5*, 1559–1561; e) G. Y. Li, *J. Org. Chem.* **2002**, *67*, 3643–3650 and references cited therein. For recent reports on air-stable phosphane ligands, see: f) M. Feuerstein, H. Doucet, M. Santelli, *J. Org. Chem.* **2001**, *66*, 5923–5925; g) N. Kataoka, Q. Shelby, J. P. Stambuli, J. F. Hartwig, *J. Org. Chem.* **2002**, *67*, 5553–5566; h) J. F. Jensen, M. Johannsen, *Org. Lett.* **2003**, *5*, 3025–3028; i) T. J. Colacot, H. A. Shea, *Org. Lett.* **2004**, *6*, 3731–3734.

[4] For recent reviews on palladacycles, see: a) J. Dupont, M. Pfeffer, J. Spencer, *Eur. J. Inorg. Chem.* **2001**, 1917–1927; b) R. B. Bedford, *Chem. Commun.* **2003**, 1787–1796; c) A. Zapf, M. Beller, *Chem. Commun.* **2005**, 431–440; d) J. Dupont, C. S. Consorti, J. Spencer, *Chem. Rev.* **2005**, *105*, 2527–2571.

[5] For recent reviews on N-heterocyclic carbene–palladium catalysts, see: a) W. A. Herrmann, *Angew. Chem. Int. Ed.* **2002**, *41*, 1290–1309; b) B. S. Yong, S. P. Nolan, *Chemtracts: Org. Chem.* **2003**, 205–227; c) V. César, S. Bellemin-Laponnaz, L. H. Gade, *Chem. Soc. Rev.* **2004**, *33*, 619–636.

[6] a) G. De Munno, B. Gabriele, G. Salerno, *Inorg. Chim. Acta* **1995**, *234*, 181–183; b) B. Gabriele, G. Salerno, M. Costa, G. P. Chiusoli, *J. Organomet. Chem.* **1995**, *503*, 21–28; c) F. Touchard, F. Fache, M. Lemaire, *Tetrahedron: Asymmetry* **1997**, *8*, 3319–3326; d) F. Touchard, P. Gamez, F. Fache, M. Lemaire, *Tetrahedron Lett.* **1997**, *38*, 2275–2278; e) F. Touchard, M. Bernard, F. Fache, F. Delbecq, V. Guiral, P. Sautet, M. Lemaire, *J. Organomet. Chem.* **1998**, *567*, 133; f) F. Touchard, M. Bernard, F. Fache, M. Lemaire, *J. Mol. Catal. A: Chem.* **1999**, *140*, 1–11; g) T. Y. Zhang, M. J. Allen, *Tetrahedron Lett.* **1999**, *40*, 5813–5816; h) M. L. Tommasino, M. Casalta, J. A. J. Breuzard, M. Lemaire, *Tetrahedron: Asymmetry* **2000**, *11*, 4835–4841; i) J. A. J. Breuzard, M. L. Tommasino, F. Touchard, M. Lemaire, M. C. Bonnet, *J. Mol. Catal. A: Chem.* **2000**, *156*, 223–232; j) Y. Nan, H. Miao, Z. Yang, *Org. Lett.* **2000**, *2*, 297–299; k) H. Miao, Z. Yang, *Org. Lett.* **2000**, *2*, 1765–1768; l) Y. Hu, Z. Yang, *Org. Lett.* **2001**, *3*, 1387–1390; m) D. Kovala-Demertzi, P. N. Yadav, M. A. Demertzis, J. P. Jasiski, F. J. Andreadaki, I. D. Kostas, *Tetrahedron Lett.* **2004**, *45*, 2923–2926; n) Y. Tang, L. Deng, Y. Zhang, G. Dong, J. Chen, Z. Yang, *Org. Lett.* **2005**, *7*, 593–595 and references cited therein.

[7] a) M. Dai, B. Liang, C. Wang, J. Chen, Z. Yang, *Org. Lett.* **2004**, *6*, 221–224; b) M. Dai, B. Liang, C. Wang, Z. You, J. Xiang, G. Dong, J. Chen, Z. Yang, *Adv. Synth. Catal.* **2004**, *346*, 1669–1673. For furancarbothioamide-based palladacycles, see: c) Z. Xiong, N. Wang, M. Dai, A. Li, J. Chen, Z. Yang, *Org. Lett.* **2004**, *6*, 3337–3340.

[8] D. Yang, Y.-C. Chen, N.-Y. Zhu, *Org. Lett.* **2004**, *6*, 1577–1580.

[9] For recent reviews on the Heck reaction, see: a) I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009–3066; b) N. J. Whitcombe, K. K. Hii, S. E. Gibson, *Tetrahedron* **2001**, *57*, 7449–7476; c) A. B. Dounay, L. E. Overman, *Chem. Rev.* **2003**, *103*, 2945–2964; d) V. Farina, *Adv. Synth. Catal.* **2004**, *346*, 1553–1582.

[10] For recent reviews on the Suzuki coupling, see: a) J. Hassan, M. Sévignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359–1470; b) M. Miura, *Angew. Chem. Int. Ed.* **2004**, *43*, 2201–2203.

[11] Some Pd black deposited when the Pd complex of monothiourea **7a** was heated under the same conditions.

[12] ESI-MS study of the solution of **2a** with $[Pd(dba)_2]$ (1:1) indicated the formation of complex Pd^0·**2a** (*m*/*z* = 720.7 [M + Na]).

[13] a) A. J. Arduengo, R. Krafczyk, R. Schmutzler, H. A. Craig, J. R. Goerlich, W. J. Marshall, M. Unverzagt, *Tetrahedron* **1999**, *55*, 14523–14534; b) S. Lee, J. F. Hartwig, *J. Org. Chem.* **2001**, *66*, 3402–3415.

[14] K. Turnbull, *J. Heterocycl. Chem.* **1985**, *22*, 965–968.

[15] A. W. Van der Made, R. H. Van der Made, *J. Org. Chem.* **1993**, *58*, 1262–1263.

[16] C. Gurtler, S. L. Buchwald, *Chem. Eur. J.* **1999**, *5*, 3107–3112 and references cited therein.

[17] a) T. Jeffery, *Tetrahedron Lett.* **1985**, *26*, 2667–2670; b) M. T. Reetz, E. Westermann, *Angew. Chem. Int. Ed.* **2000**, *39*, 165–168.

[18] a) S. Darses, G. Michaud, J.-P. Genêt, *Eur. J. Org. Chem.* **1999**, 1875–1883; b) G. A. Molander, B. W. Katona, F. Machrouhi, *J. Org. Chem.* **2002**, *67*, 8416–8423; c) S. Darses, J.-P. Genet, *Eur. J. Org. Chem.* **2003**, 4313–4327; d) G. A. Molander, B. Biolatto, *Org. Lett.* **2002**, *4*, 1867–1870; e) T. E. Barder, S. L. Buchwald, *Org. Lett.* **2004**, *6*, 2649–2652.

[19] For recent reports on the use of ESI-MS in Pd-catalyzed mechanism studies, see: a) C. Markert, A. Pfaltz, *Angew. Chem. Int. Ed.* **2004**, *43*, 2498–2500; b) D. M. Tomazela, F. C. Gozzo, G. Ebeling, P. R. Livotto, M. N. Eberlin, J. Dupont, *Inorg. Chim. Acta* **2004**, *357*, 2349–2357; c) A. A. Sabino, A. H. L. Machado, C. R. D. Correia, M. N. Eberlin, *Angew. Chem. Int. Ed.* **2004**, *43*, 2514–2518l; d) C. Chevrin, J. Le Bras, F. Henin, J. Muzart, A. Pla-Quintana, A. Roglans, R. Pleixats, *Organometallics* **2004**, *23*, 4796–4799.

[20] The palladium catalytic precursor in the Heck reaction is generally postulated as a coordinatively unsaturated 14-electron species (PdL_2), see ref.[9b]

[21] The same results were obtained when the Heck reaction of PhI and methyl acrylate was catalyzed by the in situ prepared solution of **10** and 2 mol **7b**, so we believe that the coordinatively saturated complex Pd^0·**1e**·(**7b**)$_2$ could not be formed owing to the steric hindrance.

[22] The same ESI-MS results were obtained with bis(thiourea) ligand **1f**.

[23] Trigonal or coordinatively saturated Pd complexes can be produced from diphosphane ligands and palladium. The latter complexes also display low catalytic activity in the Heck reaction. See: a) M. Portnoy, D. Milstein, *Organometallics* **1999**, *18*, 1655–1664; b) M. Portnoy, Y. Ben-David, I. Rousso, D. Milstein, *Organometallics* **1994**, *13*, 3465–3479.

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