THIOUREA COMPOSITIONS AND USES THEREOF

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U.S. Cl. 540/495; 548/312.7

Field of Classification Search 540/495; 548/312.7

References Cited

OTHER PUBLICATIONS
Catalan et al., Gazzetta Chimica Italiana (1988), 118(10), 725-8
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The invention provides N,N-disubstituted monothiourea or bis-thiourea-Pd(0) complexes that are useful as catalysts for palladium-catalyzed Heck reaction of aryl iodides and bromides with olefins, and as catalysts for palladium catalyzed Suzuki reactions of organoboronic compounds and aryl halides.

Ar→X + R

\[
\text{Thioura} \quad \text{Pd(bpy)\textsubscript{2}Cl\textsubscript{2}, base} \quad \text{Ar} \rightarrow \text{Ar}^+ \quad \text{R}
\]

8 Claims, 2 Drawing Sheets
OTHER PUBLICATIONS
Silberg, J. et al., “N-Acyl-N, N-Dipropylidene and N-Acyl-N-Pyridyl-N-
Quinolyl Amine Based Palladium Complexes. . . . . . ,” Journal of
Buchmeiser, M. and Wurst, K., “Access to Well-Defined Heteroge-
eous Catalytic Systems via Ring-Opening Metathesis . . . . .,” J. Am.
Herrmann, W., “N-Heterocyclic Carbene: A New Concept in
vol. 41, Wiley-VCH.
Reetz, M. et al., “A New Catalyst System for the Heck Reaction of
vol. 37, No. 4, Wiley-VCH.
Bedford, R., “Palladacycles Catalysts in C-C and C-Heterostrom
Bond-Forming Reactions,” Chem. Commun. 2003, 1787-1796, Uni-
versity of Exeter.
Dupont, J. et al., “Palladacycles—An Old Organometallic Family
Shaw, B. and Perera, S., “Chelating Diphosphine-Palladium(I)
Dihalides: Outstandingly Good Catalysts for Heck . . . . .,” Chem.
Complexes with Olefin. Origin of the Chelate Effect . . . . .,” Organometal-
Portnoy, M. and Milstein, D., “Chelate Effect on the Structure and
Reactivity of Electron-Rich Palladium . . . . .,” Organometallics, 1993,
Ben-David, Y. et al., “Palladium-Catalyzed Vinylation of Aryl Chlo-
rides. Chelate Effect in Catalysis,” Organometallics, 1992, 1995-
Ehrentraut, A. et al., “A New Efficient Palladium Catalyst for Heck
Reactions of Deactivated Aryl Chlorides,” Synlett, 2000, 1589-1592,
No. 11.
Shaughnessy, K. et al., “A Fluorescence-Based Assay for High-
Throughput Screening of Coupling Reactions. Application to Heck
Litke, A. and Fu, G., “A Versatile Catalyst for Heck Reactions of Aryl
Chlorides and Aryl Bromides under Mild Conditions,” J. Am. Chem.
Litke, A. and Fu, G., “Heck Reactions in the Presence of Pt(t-Bu)3:
Expanded Scope and Milder Reaction Conditions . . . . .,” J. Org.
Whitcombe, N. et al., “Advances in the Heck Chemistry of Aryl
Bromides and Chlorides,” Tetrahedron, 2001, n 7449-7476, vol. 57,
Elsevier Science Ltd.
Donnay, A. and Overman, L., “The Asymmetric Intramolecular Heck
Reaction in Natural Product Total Synthesis,” Chem. Rev., 2003,
2945-2963, vol. 103.
Beletskaya, I. and Cheprakov, A., “The Heck Reaction as a Sharpen-
ing Stone of Palladium Catalysis,” Chem. Rev., 2000, 3009-3066,
vol. 100, American Chemical Society.
Crisp, G., “Variations on a Theme—Recent Developments on the
Mechanism of the Heck Reaction . . . . .,” Chemical Society Reviews,
Cabri, W. and Candiani, J., “Recent Developments and New Perspec-
American Chemical Society.
Heck, R., “Palladium-Catalyzed Reactions of Organic Halides with
Olefins,” Accounts of Chemical Research, 1979, 146-151, American
Chemical Society.
Negishi, E. et al., “Cyclic Carbopalladation. A Versatile Synthetic
Methodology for the Construction of Cyclic Organic Compounds,”
* cited by examiner
Figure 1

1a: R=H
1b: R=2,4,6-mesityl
1c
1d: R=H
1e: R=Me
1f: R=4-MeO-Ph
1g: R=Mesityl
1h: R=2,6-Et₂-Ph
1i: R=2,5-Bu₂-Ph
1j
1k

Figure 2

1l
1m
1n

Figure 3

1o
1p
1q
Figure 4

Cis- PdCl₂(OH)₂

Trans- PdCl₂(OH)₂
THIOUREA COMPOSITIONS AND USES THEREOF

This application claims priority of provisional application U.S. Ser. No. 60/556,570, filed Mar. 26, 2004, the contents of which are being incorporated herein by reference.

FIELD OF THE INVENTION

This invention relates to thiourea ligands and more particularly to thiourea-palladium complexes useful as catalysts for palladium catalyzed arylation of alkenes in a chemical reaction known as the Heck reaction, and as catalysts for palladium catalyzed Suzuki reactions of organoboric compounds and aryl halides.

BACKGROUND OF THE INVENTION

The palladium catalyzed arylation of olefins (the Heck reaction) is one of the most versatile tools for C–C bond formation in organic synthesis. 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 mono-phosphines, diphosphines, cyclopentadienyl phosphines, or phosphites are used as the ligands. 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. Thioureas are air and moisture stable solids and have recently been employed as ligands in Ru—, Rh—, or Pd-catalyzed reactions. Very recently, Z. Yang and coworkers reported the Heck and Suzuki reactions of highly active aminediazonium salts catalyzed by a chiral thiourea-Pd complex.

SUMMARY OF THE INVENTION

The invention provides thiourea-Pd(0) complexes that are air and moisture stable, highly active catalysts for the Heck reactions of aryl halides. More particularly, the invention provides the N,N'-disubstituted monothiourea ligand represented by generic structure I:

alkyl, cycloalkyl, aryl, aralkyl, and —(CH₂)n—Rₓ; Rₓ represents unsubstituted or substituted aryl, cycloalkyl, cycloalkenyl, or polycycle; m is independently for each occurrence an integer in the range of 0 to 8 inclusive; and the ligand, when chiral, is a mixture of enantiomers or a single enantiomer.

The bis-thiourea ligand represented by generic structure II:

wherein n is an integer in the range of 1 to 8 inclusive; Rₓ and Rᵧ are selected, independently for each occurrence, from the groups consisting of alkyl, cycloalkyl, aryl, aralkyl, and —(CH₂)n—Rₓ; Rₓ, Rᵧ, Rzx, Rzx, Rzy, Rzy, Rzy, and Rzy are selected, independently for each occurrence, from the groups consisting of H, alkyl, halogenated alkyl, cycloalkyl, aryl, aralkyl, and —(CH₂)n—Rₓ; Rₓ represents unsubstituted or substituted aryl, cycloalkyl, cycloalkenyl, or polycycle; m is independently for each occurrence an integer in the range of 0 to 8 inclusive; and the ligand, when chiral, is a mixture of enantiomers or a single enantiomer.

The bis-thiourea ligand represented by generic structure III:

wherein n is an integer in the range of 1 to 8 inclusive; Rₓ and Rᵧ are selected, independently for each occurrence, from the groups consisting of alkyl, cycloalkyl, aryl, aralkyl, and —(CH₂)n—Rₓ; Rₓ, Rᵧ, Rzx, Rzx, Rzy, Rzy, Rzy, Rzy, Rzy, Rzy, and Rzy are selected, independently for each occurrence, from the groups consisting of H, alkyl, halogenated alkyl, cycloalkyl, aryl, aralkyl, and —(CH₂)n—Rₓ; Rₓ represents unsubstituted or substituted aryl, cycloalkyl, cycloalkenyl, or polycycle; m is independently for each occurrence an integer in the range of 0 to 8 inclusive; and the ligand, when chiral, is a mixture of enantiomers or a single enantiomer.
and -(CH₂)ₙ-R₂CO; R₂CO represents unsubstituted or substituted aryl, cycloalkyl, cycloalkenyl, or polycycle; m is independently for each occurrence an integer in the range of 0 to 8 inclusive; and the ligand, when chiral, is a mixture of enantiomers or a single enantiomer.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows some representative structures of thiourea ligands I.

FIG. 2 shows some representative structures of thiourea ligands II.

FIG. 3 shows some representative structures of thiourea ligands III.

FIG. 4 shows structures of cis- and trans-PdCl₂(1g)₂ (Hydrogen atoms have been omitted for clarity. Thermal ellipsoids are shown at 30% probability).

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The invention provides acyclic and cyclic thioureas 1a-q (FIGS. 1-3) and complexes thereof with Pd(0) or Pd(II) (FIG. 4), which serve as catalysts for the Heck reaction between iodobenzene and methyl acrylate at 100°C. (Table 1).

TABLE 1

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>Pd (mol %)</th>
<th>time (h)</th>
<th>yield (%)</th>
<th>TON</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1g</td>
<td>0.01</td>
<td>45</td>
<td>&gt;99</td>
<td>10³</td>
</tr>
<tr>
<td>2</td>
<td>1i</td>
<td>0.01</td>
<td>45</td>
<td>&gt;99</td>
<td>10³</td>
</tr>
<tr>
<td>3</td>
<td>1h</td>
<td>0.01</td>
<td>45</td>
<td>&gt;99</td>
<td>10³</td>
</tr>
<tr>
<td>4</td>
<td>1j</td>
<td>0.01</td>
<td>45</td>
<td>&gt;99</td>
<td>10³</td>
</tr>
<tr>
<td>5</td>
<td>1k</td>
<td>0.01</td>
<td>45</td>
<td>&gt;99</td>
<td>10³</td>
</tr>
<tr>
<td>6</td>
<td>1l</td>
<td>0.01</td>
<td>45</td>
<td>&gt;99</td>
<td>10³</td>
</tr>
<tr>
<td>7</td>
<td>1m</td>
<td>0.01</td>
<td>45</td>
<td>&gt;99</td>
<td>10³</td>
</tr>
<tr>
<td>8</td>
<td>1n</td>
<td>0.01</td>
<td>45</td>
<td>&gt;99</td>
<td>10³</td>
</tr>
<tr>
<td>9</td>
<td>1o</td>
<td>0.01</td>
<td>45</td>
<td>&gt;99</td>
<td>10³</td>
</tr>
<tr>
<td>10</td>
<td>1p</td>
<td>0.01</td>
<td>45</td>
<td>&gt;99</td>
<td>10³</td>
</tr>
</tbody>
</table>

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, as was also the case for the cyclic thiourea 1d featuring an NH moiety. Good activity was observed, however, when using the N,N'-disubstituted bulky thioureas 1e-1q of different ring sizes as the ligands (Table 1 entries 1-8); the catalyst loading could be lowered down to 0.0001 mol %. The reaction also could be conducted at high temperature under solvent-free conditions without affecting the catalytic efficacy (entries 12 and 13).

The catalytic efficacy of the thiourea 1g-Pd(0) and 1q-Pd(0) complex in the Heck reaction was studied further with a number of aryl halides and olefins at 100-130°C. Table 2 indicates that high yields were obtained using 0.01 mol % Pd catalyst for olefins such as butyl acrylates (entries 1-2). Olefins that are α- or β-substituted are also suitable substrates and give trisubstituted olefins [12] but higher catalyst loadings and reaction temperatures were required (entries 3-4). In general, higher catalyst loadings and temperatures were required to force the completion of the reactions of the aryl bromides compared to the case of aryl iodides (entries 5-8). 3-Bromopyridine was also efficiently coupled with styrene in 90% yield in the presence of 0.1 mol % of Pd (entry 9). The deactivated bromide could be coupled at higher temperature (entry 10, 160°C).

TABLE 2

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>ArX</th>
<th>Pd (mol %)</th>
<th>time (h)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1g</td>
<td>Phd</td>
<td>0.01</td>
<td>2</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>1q</td>
<td>Phd</td>
<td>0.01</td>
<td>2</td>
<td>99</td>
</tr>
</tbody>
</table>

Heck reaction of aryl iodides and bromides with olefins*
<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>Ar1</th>
<th>Ar2</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>Pd (mol %)</th>
<th>time (h)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>lg</td>
<td>PhI</td>
<td></td>
<td>R1</td>
<td>R2</td>
<td>R3</td>
<td>1</td>
<td>10</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>lg</td>
<td>H2CO</td>
<td></td>
<td>R1</td>
<td>R2</td>
<td>R3</td>
<td>0.5</td>
<td>5</td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td>lg</td>
<td>H2CO</td>
<td></td>
<td>R1</td>
<td>R2</td>
<td>R3</td>
<td>0.1</td>
<td>15</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>lg</td>
<td>H2CO</td>
<td></td>
<td>R1</td>
<td>R2</td>
<td>R3</td>
<td>0.1</td>
<td>15</td>
<td>99</td>
</tr>
<tr>
<td>7</td>
<td>lg</td>
<td>PhBr</td>
<td></td>
<td>R1</td>
<td>R2</td>
<td>R3</td>
<td>0.1</td>
<td>24</td>
<td>74</td>
</tr>
<tr>
<td>8</td>
<td>lg</td>
<td>O2N</td>
<td></td>
<td>R1</td>
<td>R2</td>
<td>R3</td>
<td>0.1</td>
<td>10</td>
<td>99</td>
</tr>
<tr>
<td>9</td>
<td>lg</td>
<td>PhBr</td>
<td></td>
<td>R1</td>
<td>R2</td>
<td>R3</td>
<td>0.1</td>
<td>24</td>
<td>90</td>
</tr>
<tr>
<td>10</td>
<td>lg</td>
<td>H2CO</td>
<td></td>
<td>R1</td>
<td>R2</td>
<td>R3</td>
<td>0.5</td>
<td>24</td>
<td>76</td>
</tr>
</tbody>
</table>
Beller\textsuperscript{(13)} reported that the Heck reactions of aryl chlorides could be greatly improved when using Bu\textsubscript{4}NBr as an ionic liquid solvent\textsuperscript{(14)} In fact, 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. The results were summarized in Table 3. Excellent yields were achieved for deactivated bromides after their reaction for 24 h in the presence of 0.5 mol % of 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 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). Chorobenzene itself, however, was completely inert, even when we used a higher loading of the Pd catalyst (2 mol %) (entry 11).

**TABLE 3**

Heck reactions of deactivated bromides and activated chlorides with olefins

<table>
<thead>
<tr>
<th>entry</th>
<th>ArX</th>
<th>R</th>
<th>Pd (mol %)</th>
<th>time (h)</th>
<th>yield (%)\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H\textsubscript{3}COC\textsubscript{6}H\textsubscript{4}Br</td>
<td>Ph</td>
<td>0.5</td>
<td>24</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>H\textsubscript{3}COC\textsubscript{6}H\textsubscript{4}Br</td>
<td>COO\textsuperscript{\text{t}Bu}</td>
<td>0.5</td>
<td>24</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>H\textsubscript{3}COC\textsubscript{6}H\textsubscript{4}Br</td>
<td>COO\textsuperscript{\text{t}Bu}</td>
<td>0.5</td>
<td>24</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>H\textsubscript{3}COC\textsubscript{6}H\textsubscript{4}Br</td>
<td>Ph</td>
<td>0.2</td>
<td>30</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>H\textsubscript{3}COC\textsubscript{6}H\textsubscript{4}Cl</td>
<td>Ph</td>
<td>1</td>
<td>24</td>
<td>96</td>
</tr>
<tr>
<td>6</td>
<td>H\textsubscript{3}COC\textsubscript{6}H\textsubscript{4}Cl</td>
<td>Ph</td>
<td>0.5</td>
<td>30</td>
<td>67</td>
</tr>
<tr>
<td>7</td>
<td>H\textsubscript{3}COC\textsubscript{6}H\textsubscript{4}Cl</td>
<td>Ph</td>
<td>1</td>
<td>24</td>
<td>99</td>
</tr>
<tr>
<td>8</td>
<td>H\textsubscript{3}COC\textsubscript{6}H\textsubscript{4}Cl</td>
<td>COO\textsuperscript{\text{t}Bu}</td>
<td>2</td>
<td>24</td>
<td>77</td>
</tr>
<tr>
<td>9</td>
<td>H\textsubscript{3}COC\textsubscript{6}H\textsubscript{4}Cl</td>
<td>PhOC</td>
<td>1</td>
<td>24</td>
<td>80</td>
</tr>
<tr>
<td>10</td>
<td>H\textsubscript{3}COC\textsubscript{6}H\textsubscript{4}Cl</td>
<td>COO\textsuperscript{\text{t}Bu}</td>
<td>1</td>
<td>24</td>
<td>90</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Refers to the yield of the product.
### TABLE 3-continued

<table>
<thead>
<tr>
<th>Entry</th>
<th>ArX</th>
<th>R</th>
<th>Pd (mol %)</th>
<th>time (h)</th>
<th>yield (%)</th>
</tr>
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<tbody>
<tr>
<td>11</td>
<td>Cl</td>
<td>Ph</td>
<td>2</td>
<td>24</td>
<td>&lt;5</td>
</tr>
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</table>

The Pd-catalysed Suzuki cross-coupling reaction of aryl halides with aryl boric acids provides a general and efficient synthetic route to biaryl compounds and has found wide application in many areas of organic synthesis.\(^{33}\) The operationally simple and air-stable catalytic system of thiourea-Pd catalyst inspired us to investigate its scope in Suzuki reaction. As revealed in Table 4 using 1q as the ligand, for p-bromoanisole, excellent isolated yield was obtained at a loading of 0.01 mol % Pd at 100°C after 3h under aerobic conditions (Table 3, entry 1).

Encouraged by the result, we began to evaluate the coupling reaction of aryl bromides with aryl boric acids. For activated bromides, almost quantitative yields were achieved within 3h in the presence of 0.1 mol % Pd under the same conditions (entries 2-6). On the other hand, low yield was obtained when deactivated p-bromoanisole was applied at 0.5 mol % Pd at 120°C. (entry 7), and similar results were gained when a bulky monodentate 1i was used (entry 8). However, the yield could be increased adding 20 mol % TBAB (entry 9). For 3,5-difluorophenylboric acid, better result could be obtained when the reaction was conducted in neat TBAB (entry 10). Acceptable yield was achieved for p-nitrochlorobenzene at 1 mol % Pd adding 20 mol % TBAB (entry 11 vs 12). Notably, 1-bromostyrene also displayed high reactivity to phenylboric acid in thiourea-Pd system (entry 13). Moreover, potassium aryl trifluoroborates\(^{10}\) have been found to be more reactive than the corresponding organoboric acid, and high yields were obtained at only 0.1 mol % Pd at 100°C (entries 14 and 15). We also conducted the Suzuki reaction at a further decreased catalyst loading (0.01 mol %), and quantitative yield was obtained for 3-nitro-bromobenzene at 120°C in 3h (entry 16).

### TABLE 4

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar¹X</th>
<th>Ar²B(OH)₂</th>
<th>Pd (mol %)</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OCH₃</td>
<td>PhB(OH)₂</td>
<td>0.01</td>
<td>100</td>
<td>3</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>OHC</td>
<td>PhB(OH)₂</td>
<td>0.1</td>
<td>100</td>
<td>3</td>
<td>92*</td>
</tr>
<tr>
<td>3</td>
<td>MeOOC</td>
<td>PhB(OH)₂</td>
<td>0.1</td>
<td>100</td>
<td>3</td>
<td>90</td>
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<tr>
<td>4</td>
<td>O₂N</td>
<td>PhB(OH)₂</td>
<td>0.1</td>
<td>100</td>
<td>3</td>
<td>99</td>
</tr>
<tr>
<td>5</td>
<td>O₂N</td>
<td>F₃CBOH₂</td>
<td>0.1</td>
<td>100</td>
<td>2</td>
<td>97</td>
</tr>
</tbody>
</table>
### TABLE 4-continued

**Suzuki coupling reaction catalyzed by 1q-Pd(ba)_{3}**

\[
ArX + Ar^2B(OH)_2 \xrightarrow{Pb(ba)_{3}-1q} K_2CO_3, NMP, H_2O \rightarrow Ar \rightarrow Ar^2
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar(^2)X</th>
<th>Ar(^2)B(OH)(_2)</th>
<th>Pt (mol %)</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>O(_2)N-F</td>
<td>Br-F</td>
<td>0.1</td>
<td>100</td>
<td>2</td>
<td>99</td>
</tr>
<tr>
<td>7</td>
<td>H(_3)CO-Br</td>
<td>PhBr(B(OH)(_2))</td>
<td>0.5</td>
<td>120</td>
<td>10</td>
<td>33</td>
</tr>
<tr>
<td>8(^f)</td>
<td>H(_3)CO-Br</td>
<td>PhBr(B(OH)(_2))</td>
<td>0.5</td>
<td>120</td>
<td>10</td>
<td>27</td>
</tr>
<tr>
<td>9(^f)</td>
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<td>H(_3)CO-Br</td>
<td>PhBr(B(OH)(_2))</td>
<td>0.5</td>
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<td>51</td>
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<td>11(^f)</td>
<td>O(_2)N-Cl</td>
<td>PhBr(B(OH)(_2))</td>
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<td>10</td>
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<td>12(^f)</td>
<td>O(_2)N-Cl</td>
<td>PhBr(B(OH)(_2))</td>
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<td>130</td>
<td>24</td>
<td>49</td>
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<td>13</td>
<td>Br-P</td>
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<td>PhBr(B(OH)(_2))</td>
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<td>14</td>
<td>O(_2)N-Br</td>
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<td>PhBF(_3)K</td>
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<td>0.1</td>
<td>100</td>
<td>1.5</td>
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<td>PhBr(B(OH)(_2))</td>
<td>0.01</td>
<td>120</td>
<td>3</td>
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</table>
In conclusion, the palladium complexes of cyclic and acyclic thiourea demonstrated high thermal stability and excellent catalytic activity in Heck and Suzuki coupling reactions under aerobic conditions. Remarkable TONs and TOFs were achieved in the coupling reactions (TONs up to 1,000,000, TOFs up to 200,000, for the reaction of Phl and n-butyl acrylate).

**EXAMPLE 1**

**Synthesis of Cyclic Thioureas 1f-1k**

Two methods were used for the synthesis of cyclic thiourea ligands (Scheme 1)

**Method A:**
To a N,N'-diaryl diamine solution in dry toluene was added 1,1-thiocarbonylmimidazole (1.2 equiv). Then the solution was stirred at 100°C and the reaction was monitored by TLC. After completion, the solution was diluted with ethyl acetate and washed with dilute HCl and brine. The organic layer was concentrated under vacuum. The pure thiourea was obtained through flash chromatography or recrystallization from 95% ethanol.

**Method B:**
To a stirred mixture of N,N'-diaryl diamine and Na₂CO₃ (1.5 equiv) in dry THF was added a solution of thiophosgene (1.2 equiv) in THF dropwise at room temperature. After stirring at room temperature overnight, water and ethyl acetate were added. The organic layer was washed with dilute HCl and brine, dried and concentrated. The pure thiourea was obtained through flash chromatography or recrystallization from 95% ethanol.

**Preparation of 1f:**
Using method A: 75% yield. M.p. 167-168°C; ¹H NMR (300 MHz, CDCl₃) δ 7.42 (d, J=9.0 Hz, 4H), 6.95 (d, J=9.0 Hz, 4H), 4.08 (s, 4H), 3.81 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 182.2, 158.1, 138.8, 127.5, 114.2, 55.4, 49.8; IR (cm⁻¹): 1511, 1443, 1285; LRMS (EI): 314 (M⁺, 100); HRMS (EI): calculated for C₁₂H₁₀N₂O₂S (M⁺) 314.1089, found 314.1088.

**Preparation of 1g:**
Using method B: 85% yield. M.p. 218-218.5°C; ¹H NMR (400 MHz, CDCl₃) δ 6.91 (s, 4H), 3.94 (s, 4H); 2.26 (s, 6H); ²²N NMR (75 MHz, CDCl₃) δ 181.1, 138.2, 136.6, 134.5, 129.5, 47.6, 21.1, 17.8; IR (cm⁻¹): 1488, 1331, 1271; LRMS (FAE): 339 (M⁺+1, 100); HRMS (FAE): calculated for C₁₂H₁₂N₂O₂S (M⁺+1) 339.1894, found 339.1879.

**Preparation of 1h:**
Using method B: 70% yield. M.p. 152-153°C; ¹H NMR (300 MHz, CDCl₃) δ 7.32 (t, J=6.6 Hz, 2H), 7.20 (d, J=7.5 Hz, 4H), 4.02 (s, 4H), 2.80-2.70 (m, 4H), 2.69-2.60 (m, 4H), 1.33 (t, J=7.5 Hz, 12H); ¹³C NMR (75 MHz, CDCl₃) δ 142.5, 136.1, 128.8, 126.5, 49.1, 24.0, 18.8; IR (cm⁻¹): 1484, 1285; LRMS (EI): 366 (M⁺, 39), 337 (100); HRMS (EI): calculated for C₁₂H₁₁N₂S (M⁺) 366.2130, found 366.2120.

**Preparation of 1i:**
Diimine: 92% yield. ¹H NMR (300 MHz, CDCl₃) δ 8.27 (s, 2H), 7.35 (d, J=8.3 Hz, 2H), 7.25 (d, J=8.3 Hz, 2H), 6.86 (s, 2H), 5.43 (s, 1H), 1.34 (s, 18H); ¹³C NMR (75 MHz, CDCl₃) δ 158.6, 150.1, 150.0, 140.4, 126.0, 123.8, 116.0, 35.3, 34.4,
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31.3, 30.5; IR (cm⁻¹): 1609, 1492, 1265; LRMS (EI): 432 (M⁺, 100); HRMS (EI): calculated for C₇₃H₆₀N₂ (M⁺): 432.3504, found 432.3504.

Diamine: 90% yield. H NMR (300 MHz, CDCl₃) δ 7.18 (d, J = 6.1 Hz, 2H), 6.80 (s, 2H), 6.75 (d, J = 6.1 Hz, 2H), 4.18 (brs, 2H, NH), 3.57 (s, 4H), 1.39 (s, 18H), 1.32 (s, 18H); ¹³C NMR (75 MHz, CDCl₃) δ 149.9, 146.2, 131.2, 126.0, 114.6, 110.0, 45.0, 34.4, 33.8, 31.4, 30.2; IR (cm⁻¹): 3688, 3601, 1561, 1265; LRMS (EI): 436 (M⁺, 20), 219 (100); HRMS (EI): calculated for C₇₃H₆₀N₂ (M⁺): 436.3817, found 436.3817.

Thiourea 1b was prepared using method B. A solution of Thiophosphine in dilute THF must be dropped very slowly. It was isolated as a white solid (75% yield) after flash chromatography on silica gel. M.p. 212-214°C; H NMR (400 MHz, CDCl₃) δ 7.45 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 7.02 (s, 2H), 4.06-4.03 (m, 2H), 3.53-3.51 (m, 1H), 1.50 (s, 18H), 1.30 (s, 18H); ¹³C NMR (100 MHz, CDCl₃) δ 183.5, 150.4, 496, 1472, 1422, 1282, 1131; LRMS (EI): 424 (M⁺, 33), 333 (100); HRMS (EI): calculated for C₇₂H₅₉N₂O₂S (M⁺): 424.2151, found 424.2138.

Thiourea 1k was prepared using method B, 85% yield. M.p. 179-180°C; H NMR (400 MHz, CDCl₃) δ 7.27 (t, J = 8.2 Hz, 2H), 7.04-7.00 (m, 6H), 6.88 (d, J = 8.2 Hz, 2H), 6.83-6.80 (m, 6H), 5.72 (d, J = 15.3 Hz, 2H), 4.81 (d, J = 15.3 Hz, 2H), 3.75 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 199.6, 157.2, 147.7, 137.1, 128.7, 127.9, 127.5, 126.7, 121.8, 113.9, 108.8, 56.8, 55.9; IR (cm⁻¹): 3051, 1592, 1579, 1464, 1420, 1245, 1190; LRMS (EI): 466 (M⁺, 100), 379 (86); HRMS (EI): calculated for C₇₂H₅₉N₂O₂S (M⁺): 466.1715, found 466.1718.

EXAMPLE 2

Synthesis of Acyclic Bis-Thiourea Ligands

Scheme 2

Ar = NH₂  glyoxyl  C₆H₁₂OH/CH₃OH  Ar = NH₂

NaBH₄(OAc)  MeCN/reflex  Ar – NH Ar

Thiophosphine  Et₂N/DCM

Diethylamine

Piperidine

N

N

N

Ar

N

Ar

Cl

Cl

Cl

Cl

145.0, 140.8, 128.0, 127.8, 125.3, 53.4, 35.4, 34.3, 32.1, 31.3; IR (cm⁻¹): 1418, 1275; LRMS (FAB): 479 (M⁺+H); FAB HRMS: calculated for C₇₃H₆₀N₂S (M⁺+H): 479.3460, found 479.3460.

Preparation of 1j:

Using method A, 75% yield. M.p. 173-174°C; H NMR (300 MHz, CDCl₃) δ 7.41-7.15 (m, 10H), 3.82-3.77 (m, 4H), 2.32-2.24 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 180.7, 147.4, 129.4, 127.4, 125.8, 51.4, 22.3; IR (cm⁻¹): 1494, 1285; LRMS (EI): 268 (M⁺, 73); EI-HRMS: calculated for C₇₃H₆₀N₂S (M⁺): 268.1034, found 268.1015.

Preparation of 1k:

To a stirred suspension of racemic 2,2‘-diamino-6,6’-dimethoxybiphenyl (60 mg, 0.25 mmol) and Na₂B₄O₇·4H₂O (212 mg, 1 mmol) in dichloromethane (10 mL) was added a solution of benzaldehyde (0.06 ml, 0.58 mmol) in dichloromethane (2 mL) dropwise at room temperature. Then the mixture was stirred overnight. Flash chromatography on silica gel gave N,N-dibenzyl diamine as a white solid (94 mg, 90%). H NMR (300 MHz, CDCl₃) δ 7.26-7.11 (m, 12H), 6.38 (d, J = 8.2 Hz, 2H), 6.32 (d, J = 7.7 Hz, 2H), 4.32 (d, J = 4.1 Hz, 4.17 (brs (2H)), 3.70 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 158.1, 147.3, 139.9, 126.9, 128.4, 126.7, 126.6, 107.2, 104.2, 100.6, 55.7, 47.5; IR (cm⁻¹): 3432, 3086, 3051, 2938, 1586.

A solution of N,N-diaryl diamine (1.0 mmol) and NEt₃ (3 equiv) in THF was dropped to a stirred solution of thiophosphine (3.0 equiv) in dry THF at 0°C. After stirred at room temperature overnight, the organic layer was washed with water, dried and concentrated.

For the synthesis of acyclic bis-thiourea, the dichloride obtained above and excess secondary amine were heated at 100°C in a sealed pressure tube for 24 hours. The solution was diluted with EtOAc and washed with dilute HCl and brine. The organic layer was dried and concentrated. Flash chromatography gave the pure bis-thiourea as a white solid.

1l: White solid, 95% yield; m.p. 225-226°C; H NMR (400 MHz, CDCl₃) δ 7.57-7.34 (m, 2H), 7.21-7.18 (m, 2H), 7.18-7.00 (m, 2H), 4.87-4.79 (m, 2H), 4.15-4.11 (m, 2H), 3.54-3.35 (m, 8H), 1.44-1.19 (m, 48H); ¹³C NMR (100 MHz, CDCl₃) δ 180.0, 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; IR (cm⁻¹): 2958, 2865, 1609, 1454, 1397, 1322, 1244, 1185, 1133, 1026; ESI LRMS: 690(M⁺, 2), 359(100); EI HRMS: calculated for C₇₂H₆₅N₅S₂: 690.4729, found 690.4717.

1m: White solid, 40% yield for two steps; m.p. 222-224°C; H NMR (400 MHz, CDCl₃) δ 6.83 (s, 4H), 4.29 (s, 4H), 3.30-3.27 (m, 8H), 2.25 (s, 6H), 2.18 (s, 12H), 1.39-1.36 (m, 4H), 1.17-1.15 (m, 8H); ¹³C NMR (100 MHz, CDCl₃) δ 188.3, 141.3, 136.1, 134.3, 130.0, 51.9, 50.9, 25.2, 24.2, 20.7,
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Preparation of 1o:

To a stirred mixture of diamine salt (2.0 g, 9.2 mmol) and Na₂CO₃ (0.85 g, 8 mmol) in CH₂CN (15 ml) was added slowly a solution of Bis(bromomethyl) mesitylene (0.72 g, 2.3 mmol) in CH₂CN (10 ml) at 81°C. The resulting mixture was refluxed for 24 h. Then the mixture was diluted with ethyl acetate and washed with brine, dried and concentrated. The resulting oil was dissolved in THF (30 ml) and Na₂CO₃ (1.27 g, 12 mmol) was added. Thiophosgene (0.7 ml, 9 mmol) in THF (10 ml) was dropped very slowly at room temperature. After stirred overnight, 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 1o was obtained through flash chromatography (20% ethyl acetate/petroleum ether) as a white solid (150 mg, 11%).

1o: m.p>230°C, ¹H NMR (400 MHz, CDCl₃) δ 6.97 (s, 11H), 6.95 (s, 4H), 4.97 (s, 4H), 3.66 (t, 3J=8.4 Hz, 4H), 3.41 (t, 3J=8.4 Hz, 4H), 2.43 (s, 3H), 2.40 (s, 6H), 2.29 (s, 6H), 2.22 (s, 12H); ¹³C NMR (100 MHz, CDCl₃) 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; IR (cm⁻¹): 2917, 1609, 1489, 1437, 1480, 1326, 1309, 1273, 1233, 1033; ESI-LRMS: 585 (M+1, 100); ESI-HRMS: calculated for C₃₁H₃₆N₄S₂⁺Na⁺ 607.2905, found 607.2883.

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EXAMPLE 3

Synthesis of Cyclic Bis-Thiourea Ligand 1o

EXAMPLE 4

Synthesis of Cyclic Bis-Thiourea Ligands 1p and 1q
Preparation of 1p and 1q:

Borane-dimethylsulfide (2M in THF) (3.6 ml 7.2 mmol, 2 eq. equiv.) was added to a solution of diiodide (0.9 mmol) in THF (20 ml) at 0°C. Then the solution was refluxed overnight. After cooling to room temperature, methanol was added very slowly to destroy the excess borane. 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.

To a stirred mixture of tetraamine obtained above and Na₂CO₃ (6 equiv.) in dry THF was added a dilute solution of thiophosphene in THF. Then the mixture was stirred at room temperature overnight. The pure cyclic bis-thiourea was obtained as a white solid through flash chromatography and recrystallization from ethanol.

1p: White solid, 45% yield for two steps; m.p.: 230°C; 1H NMR (400 MHz, CDCl₃) δ 8.20 (s, 1H), 7.51-7.44 (m, 3H), 6.97 (s, 4H), 4.29 (t, J = 8.4 Hz, 4H), 3.91 (t, J = 8.4 Hz, 4H), 2.31 (s, 6H), 2.28 (s, 12H); 13C NMR (100 MHz, CDCl₃) δ 180.7, 141.0, 138.3, 136.3, 134.7, 129.4, 128.6, 121.1, 120.2, 40.3, 47.2, 21.0, 17.8, IR (cm⁻¹): 2971, 1604, 1489, 1421, 1306, 1277, 1076; ESI LRMS: 515 (M⁺+1, 100); ESI HRMS: calculated for C₅₆H₅₄N₄O₄S₄·H₂O: 515.2303, found 515.2294.

1q: White solid, 41% yield for two steps; m.p.: 230°C; 1H NMR (400 MHz, CDCl₃) δ 8.24-8.22 (m, 1H), 7.53-7.43 (m, 3H), 7.38 (d, J = 2.0 Hz, 2H), 7.35 (d, J = 2.0 Hz, 2H), 7.11 (s, 2H), 4.29-4.18 (m, 4H), 4.13-4.07 (m, 2H), 4.01-3.93 (m, 2H), 1.48 (s, 18H), 1.34 (s, 18H); 13C NMR (100 MHz, CDCl₃) δ 184.1, 150.5, 145.0, 141.2, 139.6, 128.8, 128.7, 128.2, 127.5, 125.5, 121.8, 121.2, 52.6, 49.4, 35.4, 34.3, 31.9, 31.2; IR (cm⁻¹): 2960, 1604, 1559, 1475, 1414, 1297, 1084; ESI LRMS: 655 (M⁺+1, 37), 639 (100); ESI HRMS: calculated for C₆₀H₅₆N₄O₄S₄·H₂O: 655.3868, found 655.3864.

EXAMPLE 5

General Procedure for Heck Reaction of Aryl Iodides and Olefins

\[
\text{ArI} + \text{R} \xrightarrow{\text{Pd(dba)₂/thiourea, TEA, DMF}} \text{Ar} + \text{R}
\]

Pd(dba)₂ (1.5 mg, 0.0025 mmol) and thiourea (4 equiv.) were stirred in DMF (0.5 mL) for 0.5 h at rt. Iodobenzene (0.28 mL, 2.5 mmol, substrate/catalyst ratio=1000:1) and methyl acrylate (0.27 mL, 3.0 mmol) and TEA (0.42 mL, 3.0 mmol) were then added. The flask was sealed with rubber septa and heated at 100°C. (The same result was obtained when the reaction was conducted with a condenser in open air. After the indicated time, the solution was diluted with ethyl acetate (20 mL) and washed with water and brine. Ethyl acetate was removed under vacuum and nitrobenzene (0.128 mL) was added as an internal standard. The yield of coupling product was determined by 1H NMR (400 MHz or 300 MHz) analysis, by comparing the peak intensities of the c/β-H of the product and the ortho-β-H of nitrobenzene (internal standard).

1H NMR (300 MHz, CDCl₃) δ 7.67-7.63 (m, 2H), 7.54 (d, J = 4.1 Hz, 2H), 7.38 (d, J = 3.3 Hz, 1H), 7.10 (t, J = 6.5 Hz, 1H), 6.44 (d, J = 16.1 Hz, 1H), 3.81 (s, 3H). To determine the reaction yield, the product peak at 6.44 ppm was selected for comparison with that of the ortho-β-H (at 8.20 ppm) of nitrobenzene (internal standard).

1H NMR (400 MHz, CDCl₃) δ 7.73 (d, J = 16.0 Hz, 1H), 7.52-7.57 (m, 2H), 7.40-7.45 (m, 3H), 6.49 (d, J = 16.0 Hz, 1H), 4.26 (t, J = 6.9 Hz, 2H), 1.71-1.78 (m, 2H), 1.54-1.45 (m, 2H), 1.00 (t, J = 7.4 Hz, 3H).

1H NMR (400 MHz, CDCl₃) δ 7.73 (d, J = 16.0 Hz, 1H), 7.53-7.57 (m, 2H), 7.40-7.45 (m, 3H), 6.49 (d, J = 16.0 Hz, 1H), 1.34 (s, 9H).

1H NMR (300 MHz, CDCl₃) δ 7.53 (d, J = 7.2 Hz, 4H), 7.38 (dd, J = 7.1, 1.5 Hz, 4H), 7.28 (d, J = 7.2 Hz, 2H), 7.13 (s, 2H).
EXAMPLE 6

General Procedure for Heck Reaction of Aryl Bromides and Olefins

\[ \text{ArBr} + \text{Pd(dba)$_2$}_3\beta \rightarrow \text{ArCN} \]

Pd(dba)$_2$ (1.5 mg, 0.0025 mmol) and thiourea 1g (3.4 mg, 0.01 mmol) were stirred in NMP (0.5 mL) for 0.5 h at rt. Aryl bromide (2.5 mmol, S/C=1000), olefin (3.8 mmol) and sodium acetate 330 mg (3.8 mmol) were added in turn. Then the flask was sealed with a septum and heated at 150°C. After indicated time, the solution was diluted with ethyl acetate (20 mL) and washed with water and brine. Ethyl acetate was removed under vacuum and nitrobenzene (0.128 mL) was added as internal standard. The yield of coupling product was determined by $^1$H NMR (400 MHz or 300 MHz) analysis, by comparing the peak intensities of the product and the ortho-H of nitrobenzene (internal standard).

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.68 (d, J=16.0 Hz, 1H), 7.51 (d, J=8.9 Hz, 2H), 6.94 (d, J=8.9 Hz, 2H), 6.36 (d, J=16.0 Hz, 1H), 4.25 (t, J=6.8 Hz, 2H), 3.87 (s, 3H), 1.76-1.70 (m, 2H), 1.52-1.46 (m, 2H), 1.02 (t, J=7.5 Hz, 3H).

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.70 (d, J=8.4 Hz, 2H), 7.56 (d, J=15.7 Hz, 1H), 6.62 (d, J=8.4 Hz, 2H), 6.51 (d, J=15.7 Hz, 1H), 6.17 (s, 2H), 4.26 (t, J=6.9 Hz, 2H), 1.781.77 (m, 2H), 1.54-1.45 (m, 2H), 1.00 (t, J=7.4 Hz, 3H).

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.55 (d, J=6.9 Hz, 2H), 7.40-7.19 (m, 4H), 3.82 (s, 3H), 2.13 (s, 3H).

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.53-7.45 (m, 3H), 7.37-7.35 (m, 2H), 6.13 (q, J=1.2 Hz, 1H), 3.75 (s, 3H), 2.58 (d, J=1.3 Hz, 3H).

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.80-7.75 (m, 3H), 7.42 (d, J=6.8 Hz, 2H), 6.34 (d, J=16.1 Hz, 1H), 3.63 (s, 3H), 2.42 (s, 3H).

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.53-7.45 (m, 4H), 7.36-7.32 (m, 4H), 7.28-7.26 (m, 2H), 7.17 (d, J=12.3 Hz, 1H), 7.07 (d, J=12.3 Hz, 1H), 2.55 (s, 3H).

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.53-7.45 (m, 3H), 7.37-7.35 (m, 2H), 6.13 (q, J=1.2 Hz, 1H), 3.75 (s, 3H), 2.58 (d, J=1.3 Hz, 3H).
EXAMPLE 7

General Procedure for Heck Reaction of Deactivated Aryl Bromides and Activated Chlorides with Olefins

Pd(dbazu)₂ (1.5 mg, 0.0025 mmol), thiourea 1g (3.4 mg, 0.01 mmol) and sodium acetate (33 mg, 3.8 mmol) were stirred in molten TBAB (0.5 g) for 10 min at 100°C. Aryl halide (0.25 mmol, S/C=100) and olefin (0.38 mmol) were added in turn. Then the flask was sealed with a septum and heated at 135°C. After indicated time, the solution was diluted with ethyl acetate (20 mL) and washed with water and brine. Ethyl acetate was removed under vacuum and nitrobenzene (0.0128 mL) was added as an internal standard. The yield of coupling product was determined by ¹H NMR (400 MHz or 300 MHz) analysis, by comparing the peak intensities of the α/β-H of the product and the ortho-H of nitrobenzene (internal standard).

¹H NMR (400 MHz, CDCl₃) δ 7.64-7.52 (m, 3H), 7.45-7.40 (m, 3H), 7.33 (d, J=12.1 Hz, 1H), 7.10 (d, J=12.1 Hz, 1H), 6.98 (d, J=8.2 Hz, 2H), 3.88 (s, 3H).

EXAMPLE 8

General Procedure for the Suzuki Reaction of Aryl Halides with Boric Acids

ArBr + boronic acid (0.5 mmol), arylboronic acid (0.6 mmol), K₂CO₃ (1.0 mmol), bis-thiourea-Pd(dbazu)₂ (1.0 g) complex in NMP (2.5x10⁻³ M solution) and NMP/H₂O (0.75 mL/0.25 mL) were added to a flask under aerobic conditions. The flask was sealed with rubber septum and heated at the desired temperature. The reaction mixture was diluted with ethyl acetate, washed with brine, dried over Na₂SO₄ and the solvent was removed and the residue was purified by flash chromatography on silica gel to give the product.

¹H NMR (200 MHz, CDCl₃) δ 7.56-7.50 (m, 4H), 7.44-7.37 (m, 2H), 7.32-7.25 (m, 3H), 3.84 (s, 3H).
$^{1}$HNMR (400 MHz, CDCl$_3$) δ 7.49 (d, J=8.8 Hz, 2H), 7.09-7.03 (m, 2H), 6.98 (d, J=8.8 Hz, 2H), 6.76-6.70 (m, 1H), 3.86 (s, 3H).

$^{1}$HNMR (200 MHz, CDCl$_3$) δ 8.10 (d, J=8.2 Hz, 2H), 7.68-7.60 (m, 4H), 7.49-7.36 (m, 3H), 3.93 (s, 3H).

$^{1}$H NMR (200 MHz, CDCl$_3$) δ 8.45 (m, 1H), 8.21-8.17 (m, 1H), 7.93-7.89 (m, 1H), 7.64-7.56 (m, 3H), 7.50-7.42 (m, 3H).

$^{1}$HNMR (400 MHz, CDCl$_3$) δ 8.50-8.49 (m, 1H), 8.34 (d, J=8.0 Hz, 1H), 8.06 (s, 2H), 7.98-7.95 (m, 2H), 7.73 (t, J=8.0 Hz, 1H).

$^{1}$HNMR (200 MHz, CDCl$_3$) δ 8.41-8.40 (m, 1H), 8.28-8.23 (m, 1H), 7.89-7.84 (m, 1H), 7.68-7.60 (m, 1H), 7.16-7.12 (m, 2H), 6.92-6.83 (m, 1H).

Notes

The following notes correspond to the superscripts contained in the application. Each of the references listed below are incorporated by reference herein.


(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.


We claim:

1. An N,N'-disubstituted thiourea ligand represented by structure I:

   \[
   \begin{array}{c}
   \text{I} \\
   \begin{array}{c}
   \text{R}_{1} \quad \text{R}_{2} \\
   \text{N} \quad \text{N}
   \end{array}
   \end{array}
   \]

   wherein R, and R are independently for each occurrence cyclocarbonyl, aryl, anilaryl, or \(-(\text{CH}_2)_m-\text{R}_{60}\) (m = 1 to 8 inclusive; R, and R are independently for each occurrence cyclocarbonyl, aryl, anilaryl, or \(-(\text{CH}_2)_m-\text{R}_{60}\); R, R, R, and R are independently for each occurrence H, alkyl, haloalkylated alkyl, cyclocarbonyl, aryl, anilaryl, \(-(\text{CH}_2)_m-\text{R}_{60}\) COOR, where R, = alkyl; cyclocarbonyl, aryl, anilaryl, and \(-(\text{CH}_2)_m-\text{R}_{60}\); \text{CONR}_{60}\) (where R, or R, = H; alkyl, cyclocarbonyl, aryl, anilaryl, and \(-(\text{CH}_2)_m-\text{R}_{60}\);

   R, represents unsubstituted or substituted aryl, cyclocarbonyl, cycloalkenyl, or another polycycle;

   m is independently for each occurrence an integer in the range of 0 to 8 inclusive; and

   the N,N'-disubstituted thiourea ligand, when chiral, is a mixture of enantiomers or a single enantiomer.

2. The N,N'-disubstituted thiourea ligand of claim I, wherein:

   R, and R, are independently for each occurrence 2,4,6-trimethylphenyl, 2,5-di-t-butylphenyl, 2,6-diethylphenyl or t-butylyl; R, R, R, and R, are absent; and m = 1 and 2.

3. An N,N'-disubstituted thiourea ligand represented by structure II:

   \[
   \begin{array}{c}
   \text{II} \\
   \begin{array}{c}
   \text{R}_{1} \quad \text{R}_{2} \\
   \text{N} \quad \text{N}
   \end{array}
   \]

   wherein R, and R, are independently for each occurrence alkyl, cyclocarbonyl, aryl, anilaryl, or \(-(\text{CH}_2)_m-\text{R}_{60}\); the A and A' rings of the biphenyl core independently are unsubstituted or substituted with R, and R, respectively, one, two, three, or four times; R, and R, are independently for each occurrence H, alkyl, cyclocarbonyl, aryl, anilaryl, halogen, alkoxyl, \text{SiR}_{60}, or \text{SiR}_{60} (m = 1 to 8 inclusive; R, represents unsubstituted or substituted aryl, cyclocarbonyl, cycloalkenyl, or another polycycle;

   m is independently for each occurrence an integer in the range of 0 to 8 inclusive; and

   the N,N'-disubstituted thiourea ligand, when chiral, is a mixture of enantiomers or a single enantiomer.

4. The N,N'-disubstituted thiourea ligand of claim 3, wherein:

   R, and R, are absent, and R, and R, are independently for each occurrence benzyl, 2,4,6-trimethylbenzyl, cyclocarbonyl or isopropyl.

5. The N,N'-disubstituted thiourea ligand of claim 3, wherein:

   R, and R, are methyl or methoxy, and R, and R, are independently for each occurrence benzyl, 2,4,6-trimethylbenzyl, cyclocarbonyl or isopropyl.
6. An N,N'-disubstituted thiourea ligand represented by structure III:

wherein

R₁ and R₂ are independently for each occurrence alkyl, cycloalkyl, aryl, or -(CH₂)ₘ-Rₜ;

the four aryl rings of the binaphthyl core independently are unsubstituted or substituted with R₃, R₄, R₅, and R₆,

respectively, any number of times up to the limitations imposed by stability and rules of valence:

R₃, R₄, R₅, and R₆ are independently for each occurrence H, alkyl, cycloalkyl, aryl, alkenyl, halogen, alkoxyl,

—SiRₚ, or —(CH₂)ₘ-Rₗ;

Rₘ represents unsubstituted or substituted aryl, cycloalkyl, cycloalkenyl, or another polycycle;

m is independently for each occurrence an integer in the range of 0 to 8 inclusive; and

the N,N'-disubstituted thiourea ligand, when chiral, is a mixture of enantiomers or a single enantiomer.

7. The N,N'-disubstituted thiourea ligand of claim 6, wherein:

R₁, R₄, R₅, and R₆ are absent;

R₁ and R₅ are preferentially selected, independently for each occurrence, from benzyl, 2,4,6-trimethylbenzyl, cyclohexyl and isopropyl.

8. The N,N'-disubstituted thiourea ligand of claim 1, wherein N is an integer between 1 and 8 inclusive; and R₁ and R₅ are independently for each occurrence aryl.