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Selective Carbonylation Routes to Thiocarbamates. An Alternative to Phosgene

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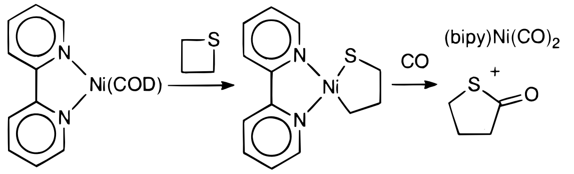
A new route for the synthesis of thiocarbamates using a transition metal complex and CO as a replacement for phosgene has been discovered. The complex $(PPh_3)_2PdCl_2$ reacts with *N*-benzylmethylamine, 4-chlorobenzenethiol, and CO to selectively generate a thiocarbamate. Kinetic studies and the isolation of several intermediates in this reaction allow for the proposal of a mechanistic scheme.

Introduction

The manufacture of acid chlorides as well as carbamoyl chlorides and the corresponding amides, urethanes, and carbamoyl thioesters represent an important class of specialty chemicals produced in large volume by the chemical industry. Many of the products are synthesized via acyl halide intermediates, which in turn are formed by way of acylating reagents such as thionyl chloride, phosphorus oxychloride, or phosgene. Thus, novel and efficient new methods to prepare these intermediates and/or products would have a great impact in reducing process-generated waste as well as in the handling of noxious intermediates.

There are many reports in the literature using carbon monoxide to couple organic and heteroatom-containing fragments. For example, the insertion of CO into σ-bound ligands attached to Ni(II) has been observed by Hillhouse. Reaction of in situ Ni(0) with thietane yields a metallathiacyclopentane that reacts with CO. Insertion occurs to yield a thiobutyrolactone, but no intermediates were seen to distinguish between initial Ni−C or Ni−S insertion (eq 1).[1] Hillhouse has also been successful in inserting oxygen into the analogous metallacyclopentane complex using N_2O, which also inserts CO to give δ-valerolactone.[2] Adams has reviewed reactions of thietanes including CO insertion reactions.[3] Holm has also observed coupling of coordinated alkyl groups with CO and alcohols or amines in a Ni(II) system. Reaction of the dialkyl complex with thiol leads to an alkylthiolate complex, which in turn inserts CO and eliminates thioester (eq 2).[4] Catalytic insertions have also been observed. Alper has reported that either $Co_2(CO)_8$ or $Ru_3(CO)_{12}$ will catalyze the insertion of carbon monoxide into thietanes (eq 3).[5]



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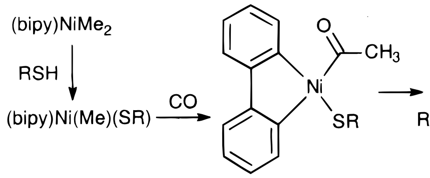

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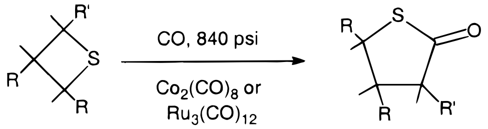

(3)

Of more relevance to the goal of mixed heterosubstituted acyl derivatives, Alper has reported the catalytic synthesis of urethanes in a reductive carbonylation of aromatic nitro compounds. Reaction of the nitroaromatic with CO in methanol solvent in the presence of a montmorillonitebipyridinylpalladium(II) acetate clay (Pd-clay) and $Ru_3(CO)_{12}$ leads to the direct formation of the carbamates (eq 4). The Pd-clay is believed to be responsible for the in situ reduction of the nitroaromatic to the amine, which then undergoes methanolic carbonylation on the ruthenium center. The reaction works for a variety of substituted nitroaromatics, giving urethanes in 70−97% yields.[6] Another recent paper by

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[1] Matsunaga, P. T.; Hillhouse, G. L. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1748.

[2] Matsunaga, P. T.; Mavropoulos, J. C.; Hillhouse, G. L. *Polyhedron* **1995**, *14*, 175.

[3] Adams, R. D.; Falloon, S. B. *Chem. Rev.* **1995**, *95*, 2587.

[4] Tucci, G. C.; Holm, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 6489.

[5] Wang, M. D.; Calet, S.; Alper, H. *J. Org. Chem.* **1989**, *54*, 20.

[6] Valli, V. L, K.; Alper, H. *J. Am. Chem. Soc.* **1993**, *115*, 3778.

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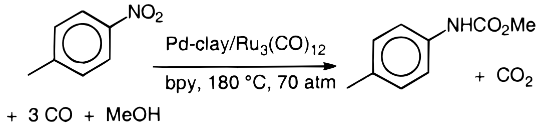
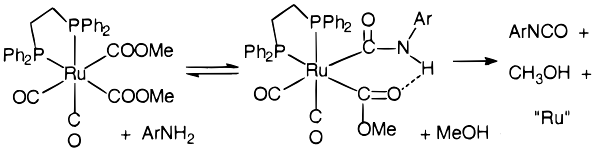
Alper reports the carbonylation of 1,3-thiazolidines to give thiazolidinones. The reaction is catalyzed by [RhCl(COD)]$_2$ and gives yields of 56−88%.[7]



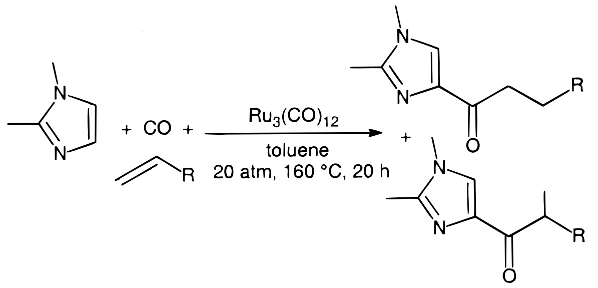
(4)

Gladfelter has also looked at metal-catalyzed carbonylation reactions of amines to aryl carbamates.[8] His work initially examined the catalytic reactions of nitroaromatics and methanol using Ru(dppe)(CO)$_3$ as the carbonylation catalyst. In situ studies were complicated by the high pressures required for the reaction.[9,10] Detailed kinetic studies were performed on the reaction of aromatic amines with Ru(dppe)(CO)$_2$(COOMe)$_2$, a species found to be present under the catalytic conditions. The reactions support the formation of ruthenium amido derivatives by replacement of the methoxy group with the amino group. Elimination of aryl isocyanate then occurs, and the latter reacts rapidly with methanol to give the observed carbamate products (eq 5).[11,12,13]



(5)

Catalytic carbonylation of C−H bonds and olefin insertion has recently been reported by Murai and coworkers.[14] In the report, imidazoles are activated, carbonylated, and reacted with olefins to give ketone products (eq 6). This chemistry might be extended to heteroatom−H bond activation to produce heteroatom substituted acyl derivatives.



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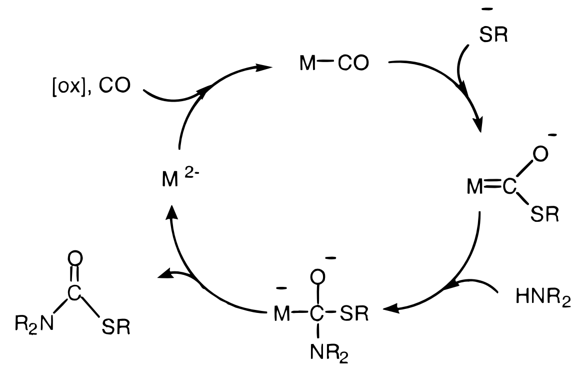
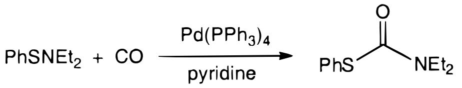
Scheme 1. Proposed Catalytic Cycle



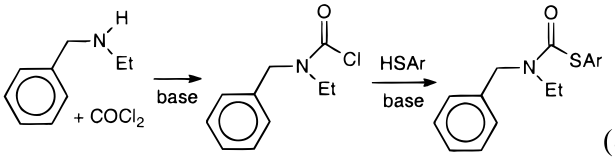
A particularly interesting example of thiocarbamate synthesis has recently appeared.[15] Sulfenamides (RSNR′$_2$) are employed in a palladium-catalyzed insertion into carbon monoxide to give the desired product (eq 7). The mechanism suggested for the reaction involves addition of the sulfenamide S−N bond across a palladium−thioester bond.



(7)

The above examples all indicate that carbonylation of heteroatom-bound ligands can be effected using transition metals. Mechanisms appear to include attack on coordinated CO, attack on coordinated acyl groups, and insertion of CO into metal−heteroatom bonds. While some catalysis has appeared, there is vast room for improvement and discovery in the synthesis of acyl derivatives.

One particularly toxic chemical that is currently used in the synthesis of carbamoyl thioesters is phosgene (eq 8). In light of the restrictions on handling this reagent, we felt that carbon monoxide might be a promising candidate for the replacement of phosgene for the environmentally benign synthesis of acyl products. We describe in this paper an alternate route for the synthesis of carbamoyl thioesters using an organometallic complex and CO.



(8)

Results and Discussion

Carbonylation Reactions. Initial approaches to the synthesis of thiocarbamates focused on Fisher carbene complexes formed from a transition metal carbonyl complex. A potential catalytic cycle is shown in Scheme 1. Attack of a heteroatom nucleophile on coordinated CO generates an acyl derivative that has Fisher carbene character. A second nucleophile then attacks, and the intermediate formed eliminates a difunctionalized acyl product. For a catalytic cycle, the metal would then have to be oxidized by two electrons by an external oxidant. Successful achievement of catalysis would require one nucleophile to be more reactive with the metal carbonyl complex and the second nucleophile to be more reactive with the Fisher carbene complex.

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(7) Khumtaveeporn, K.; Alper, H. *J. Am. Chem. Soc.* **1994**, *116*, 5662.

(8) Gladfelter, W. L.; Gargulak, J. D. In *Benign by Design. Alternative Synthetic Design for Polution Prevention*. Chapter 4. Mechanistic Study of a Catalytic Process for Carbonylation of Nitroaromatic Compounds. American Chemical Society: Washington, DC, 1994.

(9) Kunin, A. J.; Noirot, M. D.; Gladfelter, W. L. *J. Am. Chem. Soc.* **1989**, *111*, 2739.

(10) Gargulak, J. D.; Berry, A. J.; Noirot, M. D.; Gladfelter, W. L. *J. Am. Chem. Soc.* **1992**, *114*, 8933.

(11) Gargulak, J. D.; Gladfelter, W. L. *Inorg. Chem.* **1994**, *33*, 253.

(12) Gargulak, J. D.; Gladfelter, W. L. *Organometallics* **1994**, *13*, 698.

(13) Gargulak, J. D.; Gladfelter, W. L. *J. Am. Chem. Soc.* **1994**, *116*, 3792.

(14) Chatani, N.; Fukuyama, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **1996**, *118*, 493.

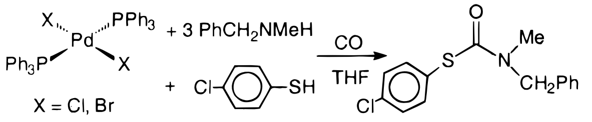
(15) Kuniyasu, H.; Hiraike, H.; Morita, M.; Tanaka, A.; Sugoh, K.; Kurosawa, H. *J. Org. Chem.* **1999**, *64*, 7305.

Table 1. Metal Complexes Screened for Activity

cationic carbonyls	neutral carbonyls	non-carbonyls
$[CpFe(CO)_3]^+[SbF_6]^-$	$Mn(CO)_5Br$	$(PPh_3)_2PtCl_2$
$[(PPh_3)_2PtCl(CO)]^+[BF_4]^-$	$Fe(CO)_5$	$(PPh_3)_2PdX_2$
$[CpRu(CO)_3]^+$	$Ru_3(CO)_{12}$	$(dppe)PdCl_2$
$[Ir(CO)_3(PPh_3)_2]^+$	$Cr(CO)_6$	$(tmeda)PdCl_2$
		$PtCl_4^{2-}$
		$(bipy)PtCl_2$

Several metal carbonyl complexes were screened for reactivity. Three classes of compounds were studied: neutral carbonyls, cationic carbonyls, and non-carbonyls under a CO atmosphere (Table 1). These reactions were performed using a simple secondary amine, *N*-benzylmethylamine, and an oxidation-resistant aromatic thiol, 4-chlorobenzenethiol, as model reagents. Although many of these complexes did react with the amine, further reaction with the thiol was unsuccessful for these carbonyl-containing complexes.

Use of the coordinatively unsaturated non-carbonyl complex $(PPh_3)_2PdCl_2$ (**1**) proved to be successful. A THF solution of **1** was treated with 3 equiv of amine followed by 1 equiv of 4-chlorobenzenethiol. After 24 h under 1 atm of CO at room temperature, the desired thiocarbamate product was isolated in 47% yield (eq 9). The major byproduct of these reactions was the hydrochloride salt of the amine, $[MeH_2NCH_2Ph]Cl$, which was isolated as a white precipitate from the reaction solution. Similar results were obtained with $(PPh_3)_2PdBr_2$. No urea is formed. The chelated compounds $(dppe)PdCl_2$ and $(TMEDA)PdCl_2$ were not active. $(bipy)PdCl_2$, however, did show formation of thiocarbamate, possibly due to the greater lability of the bipy ligand. $K_2[PdCl_4^{2-}]$ was also screened for reactivity, but no thiocarbamate formation was found.



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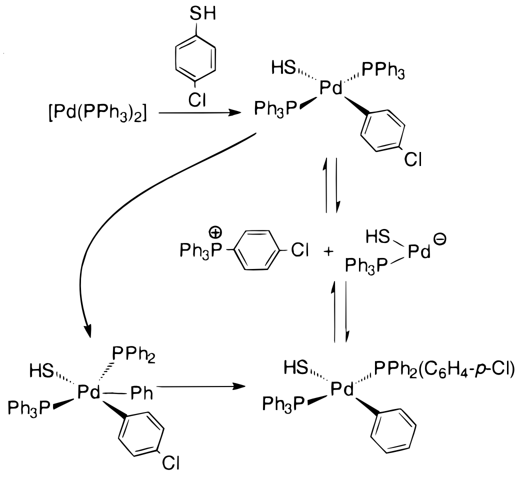
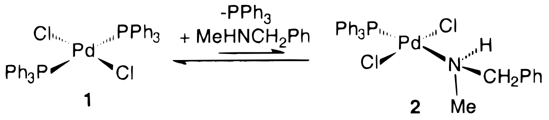
In addition to the desired thiocarbamate product, several other species are detected by GC−MS of the reaction mixture upon the completion of the reactions using the $(PPh_3)_2PdX_2$ complexes (see Supporting Information). The order of addition of thiol and amine does not effect the reaction products obtained. A large quantity of PPh_3 is observed. The dominant sulfur-containing byproduct was identified as $S(C_6H_4Cl)_2$ (approximately 62% of byproducts). Minor quantities of $S{=}PPh_3$ (20%), $S(C_6H_5)_2$ (3%), and $(C_6H_5)S(C_6H_4Cl)$ (15%) were also routinely detected. Similar to this result, the thermolysis of $Ni(SPh)_2(PEt_3)_2$ has been reported to afford PhSPh in quantitative yield.[16] Similar sulfur-containing products have been observed for the thermolysis of $[H{-}SNi(C_6H_4CH_3)(PEt_3)_2]$.[16]

One minor species was identified as being 4-chlorophenyldiphenylphosphine, indicating exchange of aryl groups between the phosphine and the thiol. There is precedence for the formation of substituted phosphines from the reaction of Pd(0) with substituted aromatics.[17] The aryl group exchange can be thought to occur via the oxidative addition of the Ar−SH bond followed by an isomerization to place the aryl ring on the phosphine.[17b] On the basis of the results from these reactions, the reaction pathway shown in Scheme 2 might be operating. The oxidative addition of the thiol involves cleavage of an aryl C−S bond.[18] The *p*-Cl-substituted ring then exchanges with a phenyl group on the phosphine.

Scheme 2. Reaction Pathway for Generation of 4-Chlorophenyldiphenylphosphine

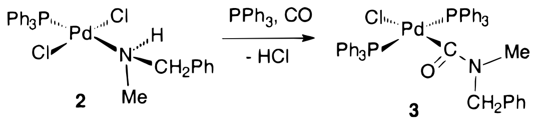


In an attempt to identify the active species in the thiocarbamate-forming reaction (eq 9), *N*-benzylmethylamine was added to $(PPh_3)_2PdCl_2$ suspended in THF-d_8. ^{31}P NMR spectroscopy provides evidence for the formation of the amine adduct, $(PPh_3)PdCl_2(MeHNCH_2Ph)$ (**2**), along with free PPh_3 (eq 10). **2** is stable in the presence of a large excess of *N*-benzylmethylamine, showing no signs of either bis(amine) formation or deprotonation to form the metal amido. The crystallographically determined structure of **2** is shown in Figure 1. The amine hydrogen was located and refined, consistent with the Pd(II) structure with a pyramidal nitrogen. The addition of excess amine and thiol to **2** under CO results in good yields of thiocarbamate.



(10)

When a THF solution of **2** is exposed to an atmosphere of CO in the presence of free PPh_3, approximately 1 equiv (±10%) of CO per Pd is consumed and the CO inserted complex, $(PPh_3)_2PdCl(C(O)NMeCH_2Ph)$ (**3**) is formed (eq 11). In solution, two isomers are observed



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[16] Osakada, K.; Hayashi, H.; Maeda, M.; Yamamoto, T.; Yamamoto, A. *Chem. Lett.* **1986**, *4*, 597.

[17] a) Tunney, S. E.; Stille, J. K. *J. Org. Chem.* **1987**, *52*, 748. (b) Herrmann, W. A.; Broβmer, C.; Öfele, K.; Beller, M.; Fisher, H. *J. Organomet. Chem.* **1995**, *491*, C1.

[18] For examples of oxidative addition of aryl sulfides to Ni see: (a) Wenkert, E.; Shepard, M. E.; McPhail, A. T. *J. Chem. Soc., Chem. Commun.* **1986**, 1390. (b) Osakada, K.; Maeda, M.; Nakamura, Y.; Yamamoto, T.; Yamamoto, A. *J. Chem. Soc., Chem. Commun.* **1986**, 442. For other transition metal mediated C−S bond cleavage reactions, see: (c) Curtis, M. D.; Druker, S. H. *J. Am. Chem. Soc.* **1997**, *119*, 1027. (d) Luh, T.-Y.; Ni, Z.-J. *Synth.* **1990**, 89.

Table 2. Crystal Parameters for 2, 4, and 5

crystal parameter	**2**	**4**	**5**
chemical formula	$C_{26}H_{28}Cl_2NPPd$	$C_{42}H_{34}Cl_2P_2PdS$	$C_{60}H_{46}Cl_4P_2Pt_2S_4$
cryst syst	monoclinic	monoclinic	monoclinic
space group, Z	$P2(1)/n$, 4	$P2(1)/c$, 4	$C2/c$, 8
a, Å	10.84180(10)	18.9364(3)	21.6557(2)
b, Å	15.7204(2)	9.7315(2)	13.6779(2)
c, Å	16.2474(2)	21.5545(2)	24.2998(2)
β, deg	92.1470(10)	106.3830(10)	107.4267(8)
vol, Å^3	2767.22(8)	3810.78(11)	6867.33(8)
temp, °C	−80	−80	−30
abs coeff (mm^{-1})	1.132	0.795	0.465
radiation, λ, Å	Mo, 0.71073	Mo, 0.71073	Mo, 0.71073
range of 2θ	2.0−46.6	2.0−56.6	2.0−43.9
no. of data collected	16 743	14 157	4566
no. of unique data	6480	5290	4446
no. of obsd data	5805	3557	3024
agreement between equiv refs	0.0196	0.0936	0.0322
no. of params varied	312	433	361
range of transmn factors	0.856−0.928	0.831−0.928	0.66−0.999
$R1(F_o)$, $wR2(F_o^2)$, $I > 2\sigma(I)$	0.0229, 0.0552	0.0592, 0.1496	
$R1(F_o)$, $wR2(F_o^2)$, all data	0.0281, 0.0572	0.1078, 0.1690	
$R(F_o)$, $R_w(F_o)$			0.061, 0.092
goodness of fit	1.036	1.038	3.12

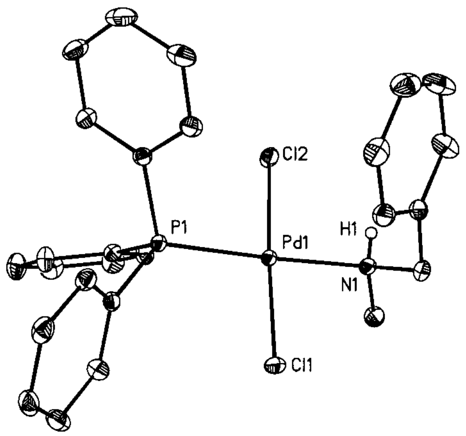


Figure 1. ORTEP drawing of $(PPh_3)PdCl_2(MeHNCH_2Ph)$ (**2**). Ellipsoids are shown at 30% probability. Hydrogen atoms (except on N) have been omitted for clarity. Selected distances (Å) and angles (deg): Pd1−P1, 2.2557(4); Pd1−N1, 2.1217(14); Pd1−Cl1, 2.2851(4); Pd1−Cl2, 2.2968(4), P1−Pd1−N1, 175.07(4); Cl1−P1−Cl2, 176.95(2).

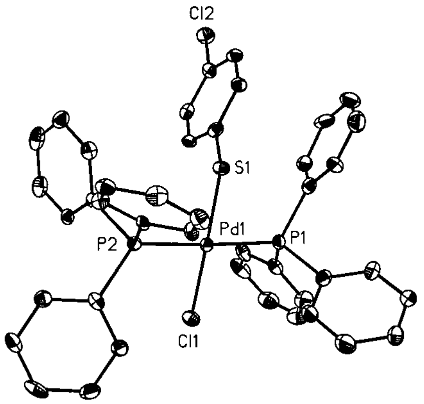
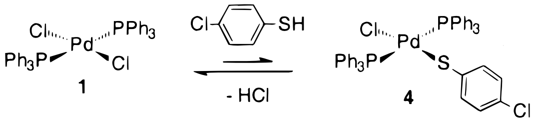


Figure 2. ORTEP drawing of $(PPh_3)_2PdCl(SC_6H_4Cl)$ (**4**). Ellipsoids are shown at 30% probability. Hydrogen atoms have been omitted for clarity. Selected distances (Å) and angles (deg): Pd1−P1, 2.345(2); Pd1−P2, 2.330(2); Pd1−Cl1, 2.331(2); Pd1−S1, 2.300(2), P1−Pd1−P2, 174.09(8); Cl1−P1−S1, 178.87(8).

by ^{1}H and ^{31}P NMR spectroscopy for **3**, attributed to syn/anti amide rotamers.[19] To verify that these isomers were due to the asymmetric amine, the same series of reactions was carried out using the symmetric amine, dibenzylamine. In this case, only a single isomer of the Pd complex analogous to **3** was observed. The formation of Pd carbamoyl complexes under similar conditions has been previously reported.[20]

Addition of 4-chlorobenzenethiol to $(PPh_3)_2PdCl_2$ in THF results in an instantaneous color change to red-orange and the formation of the thiol complex, $(PPh_3)_2PdCl(SAr)$ (**4**) (Ar = C_6H_4Cl) (eq 12). The single-crystal X-ray structure of **4** is shown in Figure 2, showing Pd(II) with a single thiolate ligand. Interestingly, **4** is isostructural with the known complex $(PPh_3)_2PdCl(SC_6H_5)$.[21] In the latter case, however, formation of the benzenethiol complex is difficult with the dimeric form, $[Pd(\mu\text{-}SPh)(Cl)(PPh_3)]_2$, greatly favored in an equilibrium, requiring the use of molten PPh_3 to break the dimer and favor the monomer (eq 13).[22]



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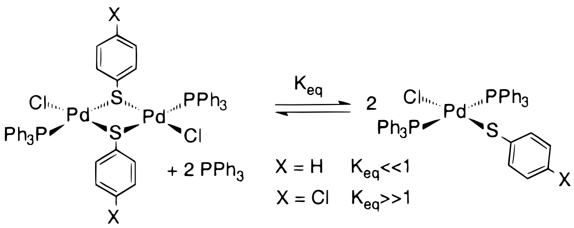

(13)

Similarly, the addition of 4-chlorobenzenethiol to the platinum complex $[(PPh_3)_2PtCl(CO)]^+[BF_4]^-$ in the pres-

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[19] Preliminary X-ray verifies the connectivity of **3**. Cell: $a = 28.328$ Å, $b = 10.619$ Å, $c = 31.432$ Å, $\alpha = \beta = \gamma = 90.00°$.

[20] Green, C. R.; Angelici, R. J. *Inorg. Chem.* **1972**, *11*, 2095.

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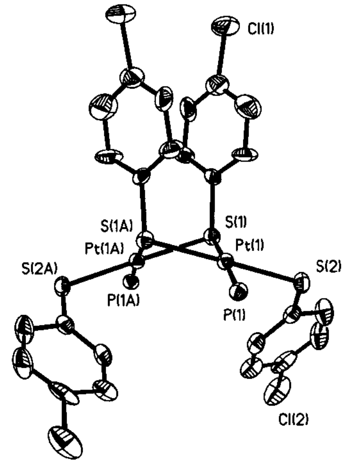
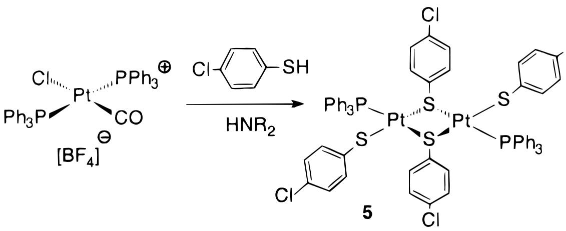


Figure 3. ORTEP drawing of $[(PPh_3)(\mu\text{-}SC_6H_4Cl)(SC_6H_4Cl)Pt]_2$ (**5**) Ellipsoids are shown at 30% probability. Hydrogen atoms and phosphine phenyl groups have been omitted for clarity. Selected distances (Å) and angles (deg): Pt1−P1, 2.269(6); Pt1−S1, 2.373(6); Pt1−S1A, 2.326(6); Pt1−S2, 2.326(6); P1−Pd1−S1, 177.2(2); S1A−P1−S2, 171.9(2).

ence of amine also gives a dimeric thiolate bridged complex, $[(PPh_3)(\mu\text{-}SC_6H_4Cl)(SC_6H_4Cl)Pt]_2$ (**5**) (eq 14).



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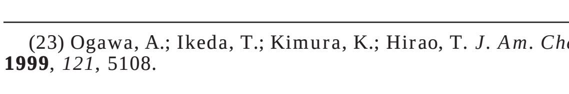
A single-crystal X-ray structure of **5** is shown in Figure 3, showing the replacement of both the chloride and CO ligands by thiolate. We observe no evidence for such dimer formation in the reaction of **1** with 4-chlorobenzenethiol. Likewise, the reported reaction of $(PhCN)_2PdCl_2$ with benzenethiol is proposed to form a *monomeric* $(PhCN)_2Pd(SPh)Cl$ complex with the release of HCl.[23] If the Pd and Pt species react similarly, then these observations suggest the initial substitution of Cl rather than CO in $[(Ph_3P)_2PtCl(CO)]^+$, which then substitutes CO to give **5**.

The ^{31}P signal observed for **4** (s, δ 25.6) is identical to that seen in the solutions containing both the thiol and excess amine. This observation was unexpected in light of the previous observation that the amine adduct, **2**, forms in the presence of excess amine. Upon the addition of an even larger excess of *N*-benzylmethylamine to **4** (15 total equiv), the solution becomes a darker red, free PPh_3 is observed, and a peak at δ 31.5 in the ^{31}P NMR spectrum becomes more prominent. This new species, **6**, is in equilibrium with the thiol complex, with **4** being greatly favored (eq 15). Amines appear to substitute for PPh_3 when they are present in high concentrations.



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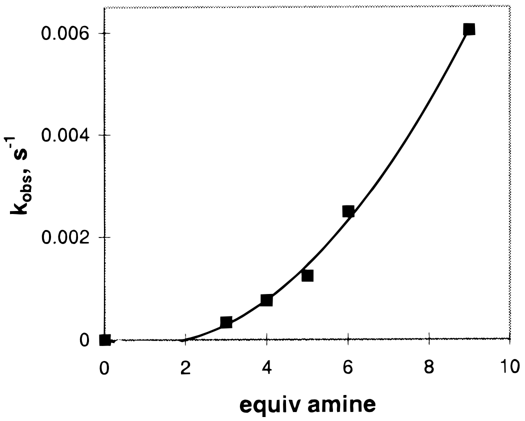
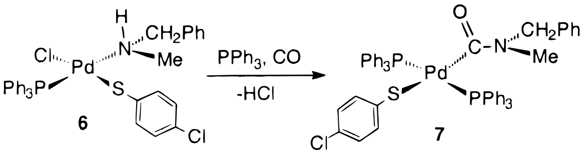


Figure 4. Plot showing the effect of excess *N*-benzylmethylamine on rate. $(PPh_3)_2PdCl_2$ = 0.028 M, 4-chlorobenzenethiol = 0.038 M in THF-d_8, P_{CO} = 1.5 atm, 22 °C.

Addition of CO to a solution of **4** resulted in no reaction. Therefore, the thiol complex itself does not react with CO in the absence of amine. Apparently, deprotonation of the amine adduct and loss of Cl from **6** occurs concomitantly with the recoordination of a PPh_3 and insertion of CO to give the unobserved intermediate, **7** (eq 16). In accord with the observation of CO insertion into the Pd−N bond to give **3**, **7** is formulated as containing a Pd carbamoyl moiety.



(16)

A rearrangement of **7** to a cis form (alternatively, **7** might actually be the cis isomer) is then followed by the reductive elimination of the thiol with the CO inserted amide to yield the thiocarbamate product. The Pd is now $(PPh_3)_2Pd(0)$, which decomposes to Pd metal and PPh_3. No evidence for the formation of $(PPh_3)_2Pd(CO)_2$ or $(PPh_3)Pd(CO)_3$ is seen by IR spectroscopy, as these compounds are not stable at 1 atm CO.[24]

Kinetic Studies. To more closely investigate the details of the reaction using the $(PPh_3)_2PdCl_2$ starting compound, stoichiometric kinetic studies were undertaken. The dominant species observed in solutions containing **1**, amine, and thiol was **4**. The rate of consumption of **4** proved to be first order as monitored by inversed-gated $\{^1H\}^{31}P$ NMR spectroscopy using methyldiphenylphosphine oxide as an internal standard (see Supporting Information). The effect of excess *N*-benzylmethylamine is shown in Figure 4. As can be seen, the reaction does not proceed at reasonable rates with less than 3 equiv of this amine. The amine is acting as a base in these reactions to form $[MeH_2NCH_2Ph]Cl$ salts in the process of generating a reactive intermediate. To check that the rate increase was due in part to the amine's role as a base, additional experiments were performed using the stronger base, NEt_3. The NEt_3 was expected to form $[HNEt_3]Cl$ salts from the deprotonation of the thiol. Upon the addition of 1 or 2 equiv of triethylamine, the rate increases, but the rate no longer

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[23] Ogawa, A.; Ikeda, T.; Kimura, K.; Hirao, T. *J. Am. Chem. Soc.* **1999**, *121*, 5108.

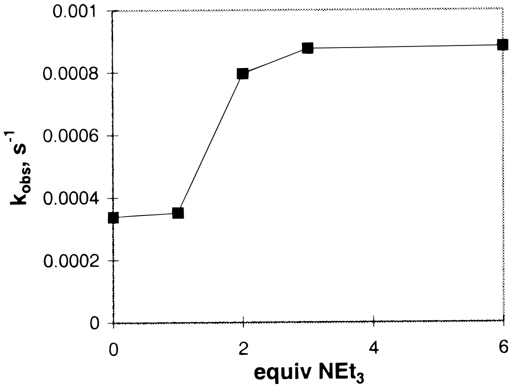


Figure 5. Plot showing the effect of added NEt_3 on rate. $(PPh_3)_2PdCl_2$ = 0.028 M, 4-chlorobenzenethiol = 0.038 M, *N*-benzylmethylamine = 0.082 M in THF-d_8, P_{CO} = 1.5 atm, 22 °C.

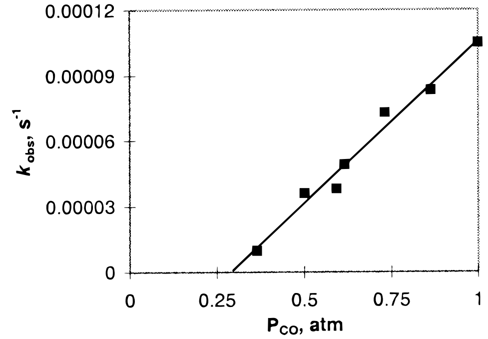


Figure 6. Plot showing the effect of CO concentration. $(PPh_3)_2PdCl_2$ = 0.028 M, 4-chlorobenzenethiol = 0.038 M, *N*-benzylmethylamine = 0.082 M in THF-d_8.

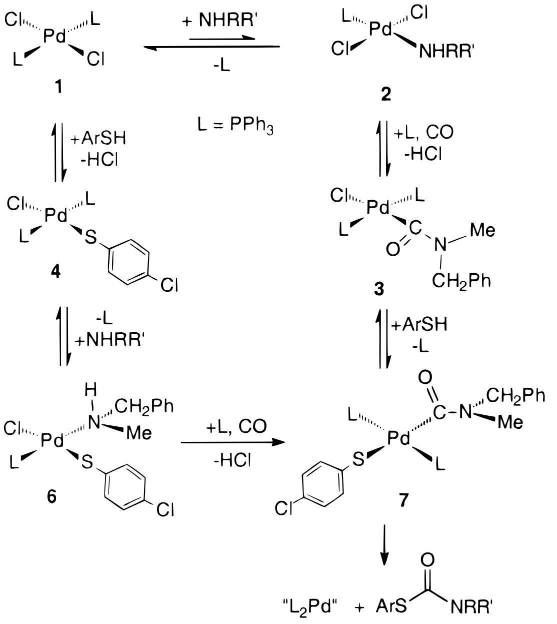
increases to an appreciable extent upon the addition of more NEt_3 (Figure 5). This result can be interpreted to mean that the rate increase observed for the addition of 3 or more equiv of *N*-benzylmethylamine is due to its use in the rate-determining step as a ligand, with the first 2 equiv acting as a base.

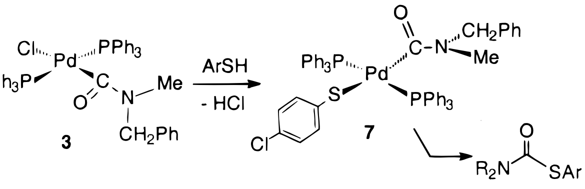
The effect of CO pressure was also examined. The rate increases proportionately with increased CO pressure (Figure 6). This observation implies that CO is incorporated in or prior to the rate determining step. Free PPh_3 was added to the reaction mixture in the expectation that a dramatic rate inhibition might be observed since free PPh_3 is observed in the reaction solution. This proved to be incorrect, and only a slight inhibition was observed with 0.5−2.0 equiv of PPh_3 (see Experimental Section). With 5 equiv of PPh_3, a new species is formed and the reaction does not proceed to form thiocarbamates.

An attempt was made to determine the reaction order in thiol. Rates were not obtained for thiol concentrations above 0.039 M, as a new species is formed and the reaction does not form thiocarbamates. Using a smaller concentration of the thiol, 0.019 M, however, did result in a slightly decreased rate of reaction, indicating that the rate is proportional to the thiol concentration.

During the reaction, significant amounts of the CO-inserted amine complex, **3**, are observed by ^{31}P NMR spectroscopy. **3** is the major species formed as **4** is consumed and then slowly disappears as thiocarbamate is formed. An independent reaction was performed in which the addition of 1 equiv of thiol to a solution of isolated **3** in THF-d_8 yielded significant amounts of the thiocarbamate product (eq 17).[25] The consumption of **3**, as followed by ^{31}P NMR spectroscopy, is relatively fast, however, taking only approximately 15 min. Therefore, although it is possible that **3** is capable of acting as an intermediate species in the reaction, its rate of reaction with thiol must be inhibited in the presence of amine, since we are able to observe the formation and consumption of **3** over a much longer period of time in the presence of both amine and thiol. If **3** is acting as an intermediate, it may be forming the same mixed CO-inserted amide and thiol complex, **7**, as proposed earlier. Again, rearrangement, followed by reductive elimination, would yield the thiocarbamate product and a Pd(0) species.

Scheme 3. Proposed Mechanism





(17)

Combining the information gathered from the above results, the overall mechanistic scheme shown in Scheme 3 can be proposed. According to this mechanism, the thiocarbamate may be formed from either of two routes, through **4** or through **3**. Rates were obtained by following the consumption of the thiol complex, **4**. Due to the lack of reactivity between **4** and CO, it is unlikely that **4** is directly involved in the rate-determining step since there is a definite dependence on CO pressure. Therefore, although the consumption of **4** was monitored, it is more likely that an intermediate complex, **6**, is reacting with the CO to give a carbamoyl species such as **7**.

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(24) Inglis, T.; Kilner, M. *Nature* **1972**, *239*, 13.
(25) See Experimental Section for details.

The slight inhibition of rate with added PPh_3 is likely due to its multiple roles in both the equilibrium between **4** and **6** and the subsequent step to yield **7**. With added phosphine, the equilibrium between **4** and **6** is shifted back toward **4**, decreasing the quantity of **6** available for further reaction. However, added phosphine should assist in the step for the formation of **7** from **6**, increasing the rate of this step. These two competing roles for phosphine would result in little effect on the overall rate of reaction. Unfortunately, a wide range of phosphine concentrations could not be explored as side reactions set in.

The effect of added amine is readily understood, as it will shift the equilibrium between **4** and **6** toward **6**. Two equivalents of amine are consumed by HCl, so that only the third equivalent or greater has an effect on the rate. If the actual rate-determining step is the conversion of **6** to **7**, the dependence of the rate on CO pressure is again easily explained. As **6** is more quickly consumed to form **7** with increased CO, **4** must also be more quickly consumed to maintain the equilibrium.

As we do observe the formation of significant amounts of **3** during these reactions, we invoke it as an intermediate species, capable of reacting with thiol to form **7**, although it is possible that **3** is a "dead-end" intermediate and proceeds to **7** by way of reversion to **2**, **1**, **4**, and then **6**. At this point, we do not know whether the thiocarbamate is generated primarily through formation of **3** or **4**, since the equilibration reactions are faster than the rate of thiocarbamate formation. The recent report of carbonylation of $ArSNEt_2$ was believed to proceed via a similar species, $Pd(PPh_3)_2(SAr)_2$.[24] Finally, from **7**, the reductive elimination of thiocarbamate is accomplished leaving a Pd(0) complex. Oxidation of the Pd(0) complex using an external oxidant could result in a catalytic cycle.

Conclusions

The organometallic complex $(PPh_3)_2PdCl_2$ is capable of reacting with amines and thiols in the presence of CO to generate thiocarbamate products. This observation is significant in that it allows for the replacement of the environmentally toxic reagent phosgene for the synthesis of carbamoyl thioesters. Ureas and/or dithiocarbonates are not formed. Further mechanistic studies using the Ni analogue are in progress.

Experimental Details

General Considerations. Most manipulations were performed under an N_2 atmosphere, either on a high-vacuum line using modified Schlenk techniques or in a Vacuum Atmospheres Corp. glovebox. Tetrahydrofuran (THF), benzene, and toluene were distilled from sodium/benzophenone ketyl solutions. THF-d_8 was purchased from Cambridge Isotope Lab. and distilled under vacuum from sodium/benzophenone ketyl solutions. $(PPh_3)_2PdCl_2$ was purchased from Strem and used as received. Methyldiphenylphosphine oxide was purchased from Alfa-ÆSAR. CO was purchased from Air Products. 4-Chlorobenzenethiol, *N*-benzylmethylamine, and dibenzylamine were purchased from Aldrich Chemical Co. The liquids were freeze−pump−thawed prior to use. $[(PPh_3)_2PtCl(CO)]^+[BF_4]^-$ was synthesized as reported in the literature.[26]

All ^1H, ^{13}C, and ^{31}P NMR spectra were recorded on a Bruker AMX400 spectrometer. All ^1H chemical shifts are reported in ppm (δ) relative to tetramethylsilane and referenced using chemical shifts of residual solvent resonances (THF-d_8, δ 3.58). ^{31}P NMR spectra were referenced to external 30% H_3PO_4 (δ 0.0). GC−MS was conducted on a 5890 Series II Gas Chromatograph fitted with an HP 5970 Series mass selective device. Analyses were obtained from Desert Analytics. A Siemens SMART system with a CCD area detector was used for X-ray structure determination.

General Sample Preparation. Kinetic reactions were carried out using the following general procedure. A sample of $(PPh_3)_2PdCl_2$ (9.6 mg, 0.014 mmol) was placed in a resealable NMR tube along with methyldiphenylphosphine oxide (used as an internal standard). THF-d_8 was vacuum transferred into the NMR tube. In the glovebox, *N*-benzylmethylamine (5.3 μL, 0.041 mmol) was added via microliter syringe. Solid 4-chlorobenzenethiol (2.8 mg, 0.019 mmol) was added as well. The tube was vigorously shaken to give a dark red solution with some white solids. The solution was freeze−pump−thaw degassed, and CO was added to the NMR tube while it was still frozen. Reactions were monitored by NMR spectroscopy.

Preparation and Isolation of Thiocarbamate. $(PPh_3)_2PdCl_2$ (138 mg, 0.196 mmol) and methyldiphenylphosphine oxide were suspended in THF. *N*-Benzylmethylamine (71.3 μL, 0.588 mmol) and 4-chlorobenzenethiol (39.7 mg, 0.274 mmol) were added, resulting in a dark red solution. The solution was freeze−pump−thaw degassed, and CO was added while the solution was frozen. The solution was stirred overnight. Solvents were removed in vacuo. The products were dissolved in minimal THF and filtered through silica gel. The filtrate was coated onto a silica plate, and a solution of 10% ethyl acetate in hexanes was used as eluent to give a clean band of thiocarbamate. The product band was isolated, CH_2Cl_2 was added, and the solution was filtered. Solvents were removed to give a pale yellow oil (yield 27 mg, 47%).

Preparation and Results of Reactions Performed with Excess PPh_3. A sample of $(PPh_3)_2PdCl_2$ (9.6 mg, 0.014 mmol) and PPh_3 (1.8 mg, 0.0069 mmol or 7.2 mg, 0.027 mmol) was placed in a resealable NMR tube along with methyldiphenylphosphine oxide (used as an internal standard). THF-d_8 was vacuum transferred into the NMR tube. In the glovebox, *N*-benzylmethylamine (5.3 μL, 0.041 mmol) was added via microliter syringe. Solid 4-chlorobenzenethiol (2.8 mg, 0.019 mmol) was added as well. The solution was freeze−pump−thaw degassed, and CO was added to the NMR tube while it was still frozen. The rate of disappearance of **4** for 0.5 equiv of PPh_3 was found to be 2.8×10^{-4} s^{-1}; for 2 equiv, 9.7×10^{-5} s^{-1}. These rates are slower than the rate determined for no added PPh_3, 3.4×10^{-4} s^{-1}.

Preparation of $(PPh_3)PdCl_2(MeNHCH_2Ph)$ (2). *N*-Benzylmethylamine (0.550 mL, 4.25 mmol) was added dropwise to a stirred slurry of $(PPh_3)_2PdCl_2$ (249 mg, 0.354 mmol) in THF. The solution became clear yellow-orange after a few minutes. The solution was then filtered. X-ray quality crystals of **2** were obtained from a concentrated methylene chloride solution by vapor diffusion with hexanes. ^1H NMR (THF-d_8): δ 7.62−7.54 (m, 6H, P*Ph*$_3$), 7.42−7.19 (m, 12H, P*Ph*$_3$, NCH$_2$*Ph*), 4.31 (t, 1H, NC*H*$_2$Ph), 4.17 (br, 1H, N*H*), 3.58 (m, 1H, NC*H*$_2$Ph), 2.65 (q, 3H, N*Me*). $^{31}P\{^1H\}$ NMR (THF-d_8): δ 28.39. $^{13}C\{^1H\}$ NMR (C_6D_6): δ 135.3 (P*Ph*$_3$), 135.2 (P*Ph*$_3$), 130.7 (NCH$_2$*Ph*), 130.5 (NCH$_2$*Ph*), 130.3 (NCH$_2$*Ph*), 128.7 (NCH$_2$*Ph*), 128.1 (P*Ph*$_3$), 56.9 (NCH$_2$Ph), 37.9 (N*Me*). Solids suitable for elemental analysis were not obtained due to the sensitivity of the product to solvent loss.

Preparation of $(PPh_3)_2PdCl(C(O)NMeCH_2Ph)$ (3). *N*-Benzylmethylamine (19.9 μL, 0.154 mmol) was added dropwise to a resealable NMR tube containing a slurry of $(PPh_3)_2PdCl_2$ (36.0 mg, 0.0513 mmol) in THF-d_8. The solution was freeze−pump−thaw degassed, and CO was added over the frozen solution. The sample was thawed and then mixed. After 15

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[26] Clark, H. C.; Dixon, K. R.; Jacobs, W. J. *J. Am. Chem. Soc.* **1968**, *90*, 2259.

min, a colorless solution was produced that contained white salts. The salts were then removed by filtration to give a clean solution of **3**. Solids were obtained from a concentrated THF solution vapor diffused with hexanes. Two isomers are observed. ^{1}H NMR (THF-d_8): δ 7.77 (m, H, PPh_3), 7.72 (m, H, PPh_3), 7.39 (m, H, PPh_3), 7.32 (m, H, PPh_3), 7.04 (m, 2H, NCH_2Ph), 6.98 (m, 2H, NCH_2Ph), 6.92 (m, 2H, NCH_2Ph), 6.63 (d, 2H, NCH_2Ph), 6.38 (d, 2H, NCH_2Ph), 4.64(s, 2H, NCH_2Ph), 3.25 (s, 2H, NCH_2Ph), 2.83 (s, 3H, N*Me*), 1.84 (s, 3H, N*Me*). ^{31}P{^{1}H} NMR (THF-d_8): δ 19.87, 19.59. ^{13}C{^{1}H} NMR (THF-d_8): δ 183.7 (m, *C*O), 138.5 (PPh_3), 138.4 (PPh_3), 135.9 (m, PPh_3), 133.5 (t, NCH_2Ph), 133.1 (t, NCH_2Ph), 130.7 (d, NCH_2Ph), 130.0 (m, NCH_2Ph), 129.2 (m, NCH_2Ph), 129.0 (m, NCH_2Ph), 128.7 (m, PPh_3), 52.2 (s, NCH_2Ph), 35.3 (NCH_2Ph), 32.9 (N*Me*), 21.4 (N*Me*). For $C_{45}H_{40}ClNOP_2Pd$, calcd (found): C 66.4 (65.7), H 4.92 (4.90).

Reaction of 3 with 4-Chlorobenzenethiol. $(PPh_3)_2PdCl_2$ (36.0 mg, 0.051 mmol) was placed in a resealable NMR tube. THF-d_8 was vacuum transferred into the tube, and *N*-benzylmethylamine (19.9 μL, 0.154 mmol) was added via syringe. The solution was degassed and CO was added. Within 15 min, the solution became colorless with a white precipitate. The solids were removed by filtration. 4-Chlorobenzenethiol (8.9 mg, 0.062 mmol) was then added to the solution, producing a red color. ^{31}P NMR spectroscopy showed that **3** had been entirely consumed within 15 min. GC−MS analysis of the solution after 6 h showed formation of thiocarbamate.

Preparation of $(PPh_3)_2PdCl(SC_6H_4Cl)$ (4). 4-Chlorobenzenethiol (39.7 mg, 0.274 mmol) dissolved in THF was added dropwise to a stirred slurry of $(PPh_3)_2PdCl_2$ (160.5 mg, 0.2287 mmol). An instantaneous color change to red-orange was observed. The solvent was removed in vacuo after 1 h. The red product was washed with hexanes, then extracted into THF and filtered. Upon slow evaporation of the THF, crystalline material was obtained. ^{1}H NMR (THF-d_8): δ 7.65 (m, H, PPh_3), 7.36 (m, H, PPh_3), 7.29 (m, H, PPh_3), 6.76 (d, 2H, SC_6H_4-Cl), 6.46 (d, 2H, SC_6H_4Cl). ^{31}P{^{1}H} NMR (THF-d_8): δ 25.6. ^{13}C{^{1}H} NMR (CD_2Cl_2): δ 137.5 (PPh_3), 135.1 (PPh_3), 134.1 (SC_6H_4Cl), 130.8 (SC_6H_4Cl), 128.8 (SC_6H_4Cl), 128.2 (PPh_3). For $C_{42}H_{35}Cl_2P_2Pd$: calcd (found): C 62.2 (61.88), H 4.32 (4.04).

Preparation of $[(PPh_3)(\mu\text{-}SC_6H_4Cl)(SC_6H_4Cl)Pt]_2$ (5). Piperidine (0.023 mL, 0.24 mmol) was added dropwise to a THF suspension of $[(PPh_3)_2PtCl(CO)]^+[BF_4]^-$ (42 mg, 0.048 mmol) with vigorous stirring. The resulting bright yellow solution was then stirred at room temperature for 45 min until the color turned to a pale yellow. Solvents were then removed in vacuo to give a pale yellow oil. The oil was then dissolved in benzene and filtered. The benzene was removed in vacuo, and THF was added. 4-Chlorobenzenethiol (7.8 mg, 0.054 mmol) in THF was added to give a bright yellow solution and a precipitate. This solution was stirred for 35 min before solvents were removed in vacuo. ^{1}H NMR ($CDCl_3$): δ 7.54 (m, 12H, PPh_3), 7.39 (m, 6H, PPh_3), 7.19 (m, 12H, PPh_3), 6.67 (m, 8H, SC_6H_4Cl), 6.58 (m, 8H, SC_6H_4Cl).

X-ray Structural Determination of 2, 4, and 5. Crystals of **2** were grown from a solution of CH_2Cl_2/hexanes, and crystals of **4** were grown by slow evaporation from THF. A yellow prism of **2** with approximate dimensions 0.18 × 0.18 × 0.16 mm^3 was mounted under Paratone-8277 on a glass fiber and immediately placed in a cold nitrogen stream at −80 °C on the X-ray diffractometer. A thin purple plate of **4** with approximate dimensions 0.18 × 0.12 × 0.08 mm^3 was mounted in a similar manner, and data were also collected at −80 °C. The X-ray intensity data for both crystals were collected on a standard Siemens SMART CCD area detector system equipped with a normal focus molybdenum-target X-ray tube operated at 2.0 kW (50 kV, 40 mA). For both crystals, a total of 1321 frames of data (1.3 hemispheres) were collected using a narrow frame method with scan widths of 0.3° in ω and exposure times of 30 s/frame using a detector-to-crystal distance of 5.09 cm (maximum 2θ angle of 56.6°). The total data collection time was approximately 12 h. Frames for **2** were integrated to a maximum 2θ angle of 56.6° with the Siemens SAINT program to yield a total of 16 743 reflections, of which 6480 were independent ($R_{\mathrm{int}} = 1.96\%$, $R_{\mathrm{sig}} = 2.51\%$)[27] and 5805 were above $2\sigma(I)$. Frames for **4** were integrated to a maximum 2θ angle of 46.6° with the Siemens SAINT program to yield a total of 14 157 reflections, of which 5290 were independent ($R_{\mathrm{int}} = 9.36\%$, $R_{\mathrm{sig}} = 12.49\%$)[27] and 3557 were above $2\sigma(I)$. Laue symmetry revealed monoclinic crystal systems for both crystals, and the final unit cell parameters (at −80 °C) were determined from the least-squares refinement of three-dimensional centroids of 6801 reflections for **2** and 4570 reflections for **4**.[28] Data were corrected for absorption with the SADABS[29] program.

The space groups were assigned as $P2_1/n$ and $P2_1/c$ for **2** and **4**, respectively. The structures were solved by using direct methods and refined employing full-matrix least-squares on F^2 (Siemens, SHELXTL,[30] version 5.04). For Z values of 4, there is one molecule and a CH_2Cl_2 in the asymmetric unit of **2**, and one molecule in the asymmetric unit of **4**. All of the non-H atoms for both structures were refined anisotropically, and hydrogen atoms were included in idealized positions, except the amine hydrogen (H1) in **2**, which was located and its position and isotropic thermal parameter refined. For **2**, the final refinement revealed a goodness of fit (GOF)[31] of 1.036 and final residuals[32] of R1 = 2.29% ($I > 2\sigma(I)$), wR2 = 5.52% ($I > 2\sigma(I)$). For **4**, the final refinement revealed a goodness of fit (GOF)[31] of 1.038 and final residuals[32] of R1 = 5.92% ($I > 2\sigma(I)$), wR2 = 14.96% ($I > 2\sigma(I)$).

Yellow crystals of **5** were grown from a $CHCl_3$ solution. A fragment of approximate dimensions 0.06 × 0.08 × 0.14 mm^3 was mounted with epoxy on a glass fiber and immediately placed on the X-ray diffractometer in a cold nitrogen stream at −60 °C. The X-ray intensity data were collected on an Enraf-Nonius CAD4 diffractometer with graphite-monochromated Mo Kα radiation. Data were collected to a maximun 2θ angle of 43.9°. A total of 4566 reflections were collected, of which 4446 were independent ($R_{\mathrm{int}} = 0.032$)[33] and 3024 were above $3\sigma(I)$. Laue symmetry revealed a monoclinic crystal system, and the final unit cell parameters (at −60 °C) were determined from the least-squares refinement of reflections. Data were corrected for absorption with the DIFABS[34] program. The space group was assigned as $C2/c$ (No. 15), and the structure was solved by heavy-atom Patterson methods[35] and expanded using Fourier techniques (teXsan).[36] The non-hydrogen atoms were refined anisotropically, and the hydrogen atoms were included in idealized positions. For a Z value of 8, there is half a molecule in the asymmetric unit and one molecule of $CHCl_3$. The structure refined to a goodness of fit (GOF)[37] of 3.12 and final residuals[38] of 6.1% ($I > 3\sigma(I)$, $R_w = 9.2\%$ ($I > 3\sigma(I)$).

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(27) $R_{\mathrm{int}} = \sum|F_o{}^2 - F_o{}^2(\mathrm{mean})|/\sum[F_o{}^2]$; $R_{\mathrm{sigma}} = \sum[\sigma(F_o{}^2)]/[F_o{}^2]$.

(28) It has been noted that the integration program SAINT produces cell constant errors that are unreasonably small, since systematic error is not included. More reasonable errors might be estimated at 10× the listed value.

(29) The SADABS program is based on the method of Blessing; see: Blessing, R. H. *Acta Crystallogr., Sect A* **1995**, *51*, 33.

(30) *SHELXTL: Structure Analysis Program, version 5.04*; Siemens Industrial Automation Inc.: Madison, WI, 1995.

(31) GOF = $[\sum[w(F_o{}^2 - F_c{}^2)^2]/(n - p)]^{1/2}$, where n and p denote the number of data and parameters

(32) R1 = $(\sum||(F_o| - F_c||)/\sum|F_o|$; wR2 = $[\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]]^{1/2}$ where $w = 1/[\sigma^2(F_o{}^2) + (aP)^2 + bP]$ and $P = [(\max;0,F_o{}^2) + 2F_c{}^2]/3$.

(33) $R_{\mathrm{int}} = \sum|F_o{}^2 - F_o{}^2(\mathrm{mean})|/\sum[F_o{}^2]$

(34) *DIFABS*: Walker, N.; Stuart, A. *Acta Crystallogr.* **1983**, *A39*, 158−166. An empirical absorption correction program.

(35) *PATTY*: Beurskens, P. T.; Admiraal, G.; Beurskens, G.; Bosman, W. P.; Garcia-Granda, S.; Gould, R. O.; Smits, J. M. M.; Smykalla, C. The DIRDIF program system, Technical Report to the Crystallography Laboratory; University of Nijmegen: The Netherlands, 1992.

(36) *DIRDIF92*: Beurskens, P. T.; Admiraal, G.; Beurskens, G.; Bosman, W. P.; Garcia-Granda, S.; Gould, R. O.; Smits, J. M. M.; Smykalla, C. The DIRDIF program system, Technical Report to the Crystallography Laboratory; University of Nijmegen: The Netherlands, 1992. *teXsan*, Crystal Structure Analysis Package; Molecular Structure Corporation: 1985 and 1992.

Acknowledgment is made to the National Science Foundation (CHE-9616601) for their support of this work.

Supporting Information available includes kinetic plots for the production of thiocarbamate, a GCMS trace of the reaction mixture, and tables of data collection parameters, atomic coordinates, distances and angles, and anisotropic thermal parameters for **2**, **4**, and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

OM990931N

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(37) GOF $= (\sum[w(F_o - F_c)^2]/(N_o - N_v))^{1/2}$, where N_o = no. of observations and N_v = no. of variables.

(38) $R = (\sum||(F_o| - F_c||)/\sum|F_o|$, $R_w = [\sum[w(F_o - F_c)^2]/\sum[w(F_o^2)]]^{1/2}$ where $w = 1/[\sigma^2(F_o)]$.