

**Final Report
NSF CHE-9616601**

**Collaborative Industrial/Academic Research on Alternate Phosgene
Chemistry for Environmentally Benign Chemical Synthesis and Processing**

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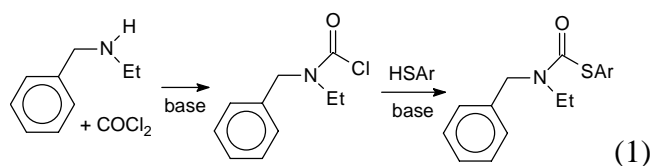
I. Project Summary

This project was aimed at the discovery of new methods for the generation of acyl derivatives through the use of carbon monoxide and transition metal catalysts. The work was aimed specifically at replacing phosgene as an acyl source in the synthesis of thiocarbamates, ureas, and isocyanates as intermediates, and at replacing acid chlorides in amide syntheses. These types of processes are central in the synthesis of hundreds of photographic intermediates used at Kodak, and have been identified as an area where environmentally benign chemistry could have a significant impact. New transition metal based catalysts for the preparation of acyl derivatives that will avoid noxious chemicals and eliminate waste products have been developed. Specifically, new nickel and palladium based systems were developed for the synthesis of thiocarbamates from secondary amines, aryl thiols, and carbon monoxide. The nickel complexes were found to be catalytic with added oxygen, although competitive oxidation of the thiol is problematic. In addition, a new catalytic method for the synthesis of quinolines has been developed using a cobalt catalyst. Students and postdoctoral fellows also gained valuable experience working in industry in process development through a collaboration with Dr. Ronald Valente in Kodak's Chemicals Development Division.

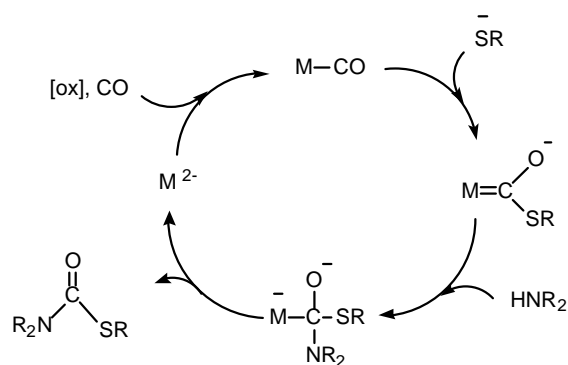
II. Detailed Accomplishments

A. Selective Carbonylation Routes to Thiocarbamates using Palladium.

One particularly toxic chemical which is currently used in the synthesis of thiocarbamates is phosgene (Eq 1). 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. A proposal was made to explore new alternative routes for the synthesis of thiocarbamates using an organometallic complex and CO as described in Scheme I.

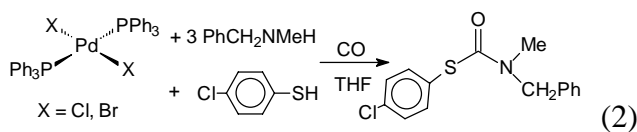


Scheme I: Proposed catalytic cycle.



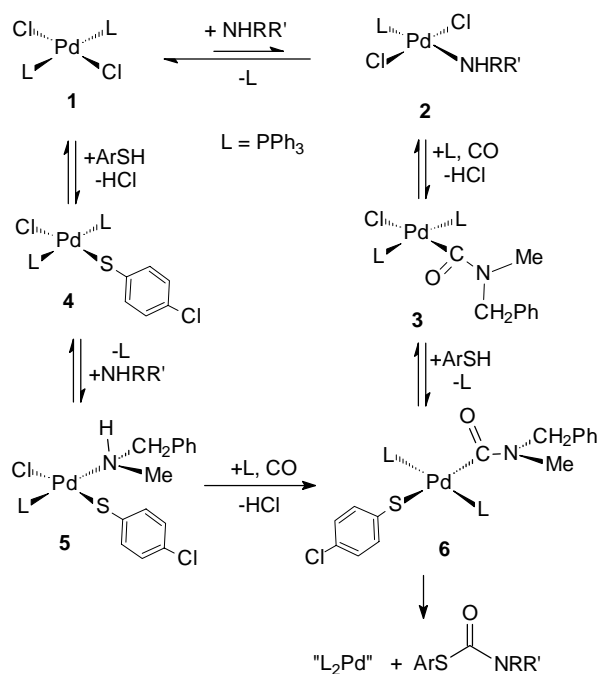
Several metal carbonyl complexes were screened for reactivity. Three classes of compounds were studied: neutral carbonyls, cationic carbonyls, and non-carbonyls under a CO atmosphere. These reactions were performed using a simple secondary amine, N-benzylmethylamine, and an oxidation-resistant aromatic 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 $(\text{PPh}_3)_2\text{PdCl}_2$ (**1**) proved to be successful. A THF solution of **1** was treated with 3 equivalents of amine followed by one equivalent of 4-chlorobenzenethiol. After 24 hours under 1 atm of CO at room temperature, the desired thiocarbamate product was isolated in 47 % yield (Eq 2). The major byproduct of these reactions was the hydrochloride salt of the amine, $[\text{MeH}_2\text{NCH}_2\text{Ph}]\text{Cl}$ which was isolated as a white precipitate from the reaction solution. Similar results were obtained with $(\text{PPh}_3)_2\text{PdBr}_2$. No urea is formed. The chelated compounds, $(\text{dppe})\text{PdCl}_2$ and $(\text{TMEDA})\text{PdCl}_2$ were not active. $(\text{bipy})\text{PdCl}_2$, however, did show formation of thiocarbamate, possibly due to the greater lability of the bipy ligand. $\text{K}_2[\text{PdCl}_4]^{2-}$ was also screened for reactivity, but no thiocarbamate formation was found.



In an attempt to identify the active species in the thiocarbamate forming reaction, several species could be generated in solution, and a mechanism for thiocarbamate formation is shown in Scheme II. Complexes characterized include $(\text{PPh}_3)_2\text{PdCl}_2(\text{MeHNCH}_2\text{Ph})$ (**2**, X-ray), $(\text{PPh}_3)_2\text{PdCl}(\text{C}(\text{O})\text{NMeCH}_2\text{Ph})$ (**3**, NMR), $(\text{PPh}_3)_2\text{PdCl}(\text{SAr})$ (**4**, X-ray) ($\text{Ar} = \text{C}_6\text{H}_4\text{Cl}$), and $(\text{PPh}_3)_2\text{PdCl}(\text{MeHNCH}_2\text{Ph})(\text{SAr})$ (**5**, NMR). In solution, two isomers are observed by ^1H and ^{31}P NMR spectroscopy for **3**, attributed to syn/anti amide rotamers.¹

Scheme II: Proposed Mechanism.



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 **5** occurs concomitantly with the recoordination of a PPh₃ and insertion of CO to give the unobserved intermediate, **6**. In accord with the observation of CO insertion into the Pd-N bond to give **3**, **6** is formulated as containing a Pd carbamoyl moiety. A rearrangement of **6** to a *cis* form (alternatively, **6** 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 (PPh₃)₂Pd(0) which decomposes to Pd metal and PPh₃. No evidence for the formation of (PPh₃)₂Pd(CO)₂ or (PPh₃)Pd(CO)₃ is seen by IR spectroscopy, as these compounds are not stable at 1 atm CO.²

According to the mechanism shown in Scheme I, 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, **5**, is reacting with the CO to give a carbamoyl species such as **6**.

To more closely investigate the details of the reaction using the (PPh₃)₂PdCl₂ 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. The effect of excess N-benzylmethylamine is shown in Figure 1. As can be seen, the reaction does not proceed at reasonable rates with less than three equivalents of this amine. The amine is acting as a base in these reactions to form [MeH₂NCH₂Ph]Cl salts in the process of generating a reactive intermediate. Since the first two equivalents of base are acting only to remove HCl, triethylamine was employed as a sacrificial base. The rate of reaction increases upon the addition of one or two equivalents of triethylamine the rate increases, but the rate no longer increases to an appreciable extent upon the addition of more NEt₃ (Figure 2). This result can be interpreted to mean that the rate increase observed for the addition of three or more equivalents of N-benzylmethylamine is due to its use in the rate-determining step as a ligand, with the first two equivalents acting as a base. The effect of CO pressure was found to be first order, implying that CO is incorporated in or prior to the rate determining step.

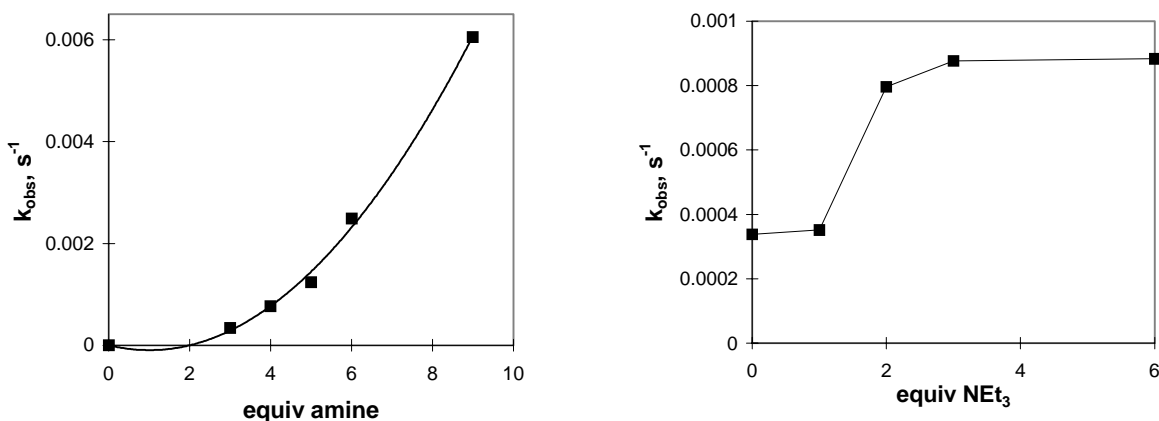


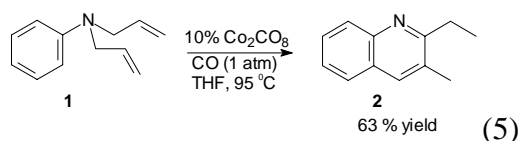
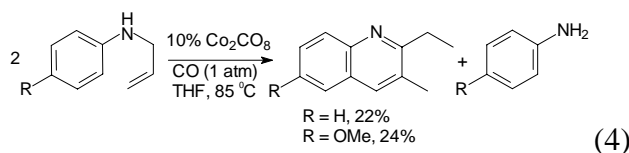
Figure 1 (left). Plot showing the effect of excess N-benzylmethylamine on rate. (PPh₃)₂PdCl₂ = 0.028 M, 4-chlorobenzenethiol = 0.038 M in THF-*d*₈, P_{CO} = 1.5 atm, 22 °C.

Figure 2 (right). Plot showing the effect of added NEt₃ on rate. (PPh₃)₂PdCl₂ = 0.028 M, 4-chlorobenzenethiol = 0.038 M, N-benzylmethylamine = 0.082 M in THF-*d*₈, P_{CO} = 1.5 atm, 22 °C.

C. Cobalt Catalyzed Selective Conversion of Diallylanilines and Arylimines to Quinolines.

Transition metal catalyzed heteroannulation provides a useful and convenient tool for the construction of N-heterocycles.³ Quinolines and their derivatives form an important class of N-heterocycles in that they display attractive applications as pharmaceuticals (eg. antimalarial drugs) as well as being general synthetic building blocks due to their chemical and biological relevance.^{4,5} Many catalytic processes based on palladium,^{6,7,8} rhodium,^{9,10,11} ruthenium^{12,13,14,15} and iron¹⁶ have been developed towards the synthesis of quinoline skeletons. Despite the advances in methodology towards the construction of quinoline derivatives, the development of new catalytic routes towards their synthesis remains an active area of research.¹⁷ We have discovered a novel cobalt catalyzed selective conversion of diallylanilines to quinolines and the cross coupling of arylimines with diallylanilines to generate quinolines.

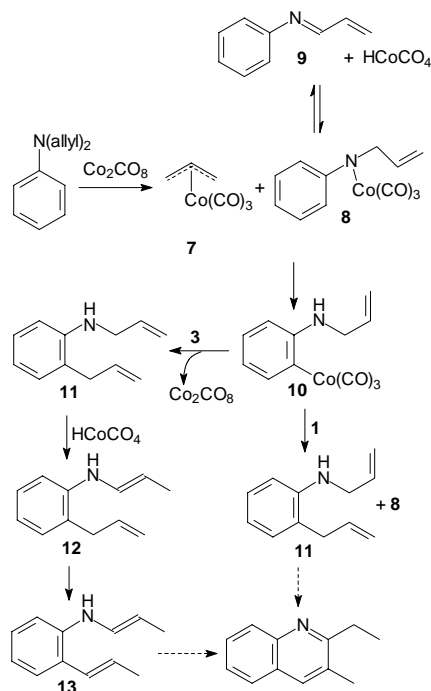
N-allylaniline, when heated in presence of 10 mol % Co_2CO_8 and 1 atm. of CO at 85 °C, leads to the selective formation of 2-ethyl-3-methylquinoline (eq 4). Aniline and propene are also observed in the reaction. The presence of carbon monoxide is necessary to stabilize Co_2CO_8 under the reaction conditions. Use of 4-methoxyallylaniline led to the corresponding 6-substituted quinoline in 24% isolated yield. Although the reaction is selective for quinoline formation, half of the starting material acts as a sacrificial reagent in the reaction. A more atom economical approach is achieved by the use of readily available diallylanilines. Diallylaniline forms the same product with higher yields and the same selectivity under the same conditions (eq 5).¹⁶ The reaction is easily extended to other diallylanilines to generate quinolines in good yields.



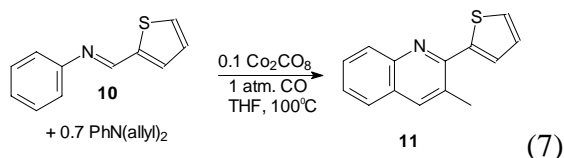
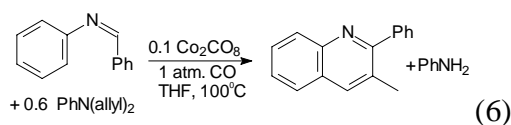
The proposed reaction pathway is shown in Scheme 1. The reaction most likely proceeds by an initial cleavage of the allylic C-N bond by Co_2CO_8 to generate intermediates **7** and **8**. With certain substrates, palladium and ruthenium complexes have been shown in the past to cleave allylic C-N bonds.^{18,19} The detection and isolation of allylcobalttricarbonyl, **7**, from the reaction strongly suggests an initial breaking of the allylic C-N bond. For experiments with diallylaniline, monoallylaniline and allylcobalttricarbonyl are the only intermediates observed in the system by NMR spectroscopy. The formation of monoallylaniline can be explained by reaction of the proposed intermediates **8** or **10** with HCoCO_4 . An orthometallated intermediate as in **10** is proposed which can either react with allylcobalttricarbonyl or the starting diallylaniline to generate an intermediate of type **11**. Intermediate **10** can also react with another molecule of diallylaniline to generate intermediates **11** and **8**. HCoCO_4 has been shown in the literature to effect double bond isomerizations and hence it is reasonable to propose isomerization of **11** to **13** under the reaction conditions.²⁰ **13** is poised for cyclization to generate the quinoline with elimination of hydrogen.

Although a thorough mechanistic understanding is lacking at this stage, imines such as **9** are likely intermediates in the system. To test this hypothesis, the cross coupling of the imine derived from aniline and benzaldehyde with diallylaniline was studied (eq 6). As anticipated, the

Scheme III: Proposed mechanism for the catalytic conversion of diallylaniline to quinoline with Co_2CO_8 .



cross coupled quinoline product was isolated in 59% yield. The imine also underwent competitive reduction to form the secondary amine, accounting for the balance of the reaction. A small amount (<5%) of quinoline derived from diallylaniline is also observed in the reaction. In another experiment, the cross coupling of the imine **14** with diallylaniline was studied and the cross coupled product **15** was isolated in 47% yield (eq 7). Again competitive reduction of the imine to form the secondary amine is observed. Nevertheless, this observation widely expands the scope of this cobalt catalyzed reaction since it facilitates the introduction of various substituents at the 2-position of the quinoline skeleton.



III. Conclusions

The organometallic complex $(\text{PPh}_3)_2\text{PdCl}_2$ 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.

$(\text{PPh}_3)_2\text{NiBr}_2$ and $(\text{PPh}_3)_2\text{NiCl}_2$ are capable of reacting with amines and thiols in the presence of CO to generate thiocarbamate products. Superior yields of thiocarbamate are

obtained with the nickel system compared with the analogous palladium system. A catalytic synthesis is realized by using a mixture of air and CO although the issue of competitive oxidation of the thiol remains to be satisfactorily addressed.

A simple, mild, and efficient synthesis of quinolines from diallylanilines has been discovered. The raw materials are cheap and the catalyst is readily available. The reaction is easily extended to imines where a cross coupling reaction with diallylaniline generates quinoline derivatives. Future studies must be carried out to elucidate the mechanism of these reactions as well as to widen its scope, utility, and yield.

IV. Personnel Involved

Brian Edelbach, Graduate student, *Department of Chemistry, University of Rochester*;
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Stephen A. Godleski, industrial collaborator, *Eastman Kodak Company, Rochester, NY*;
Ronald R. Valente, industrial collaborator, *Eastman Kodak Company, Rochester, NY*

V. Publications Resulting from this Project

1. "Selective Carbonylation Routes to Thiocarbamates. An Alternative to Phosgene," William D. Jones, Kelly A. Reynolds, Caroline K. Sperry, Rene J. Lachicotte, Steven A. Godleski, Ronald Valente, *Organometallics* **2000**, *19*, 1661-1669.
2. "Nickel Mediated Selective Carbonylation Routes to Thiocarbamates," Josemon Jacob, Kelly A. Reynolds, William D. Jones, Stephen A. Godleski, and Ronald R. Valente, *Organometallics* **2001**, *20*, 1028-1031.
3. "Cobalt Catalyzed Selective Conversion of Diallylanilines and Arylimines to Quinolines," Josemon Jacob, William D. Jones, Stephen A. Godleski, and Ronald R. Valente, *J. Am. Chem. Soc.* **2001**, *20*, submitted.
4. "Cobalt Catalyzed Selective Conversion of Diallylanilines and Arylimines to Quinolines," Josemon Jacob and William D. Jones, *Organometallics*, to be submitted when #3 is accepted.

VI. References

- (1) Preliminary X-ray verifies the connectivity of **3**. Cell: $a = 28.328 \text{ \AA}$, $b = 10.619 \text{ \AA}$, $c = 31.432 \text{ \AA}$, $\alpha = \beta = \gamma = 90.00^\circ$.
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