

INVESTIGATIONS OF HETEROBIMETALLIC CATALYSIS OF VARIOUS ORGANIC
REACTIONS AND METAL-FREE CARBONYLATION OF AMINES TO UREAS USING
THE HYPERVALENT IODINE SPECIES SODIUM PERIODATE

By

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For Abigail, without her everything would be a little darker.

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The homogeneous heterobimetallic catalysts $\text{CpRu}(\text{PPh}_3)\text{Cl}(\mu\text{-dppm})\text{AuCl}$, $\text{CpRu}(\text{PPh}_3)\text{I}(\mu\text{-dppm})\text{AuI}$, $\text{CpRu}(\text{PPh}_3)(\mu\text{-Cl})(\mu\text{-dppm})\text{PdCl}_2$, $\text{CpRu}(\text{PPh}_3)(\mu\text{-I})(\mu\text{-dppm})\text{PdI}_2$, and $\text{CpRu}(\text{PPh}_3)_2\text{SnCl}_3$, were used in the cyclization of enyne starting materials. The reaction required high temperatures (90 °C) were used. At this temperature the catalyst also showed signs of decomposition. A new method was also developed that used Ru/Au catalysts $\text{CpRu}(\text{PPh}_3)\text{Cl}(\mu\text{-dppm})\text{AuCl}$ and $\text{CpRu}(\text{PPh}_3)\text{I}(\mu\text{-dppm})\text{AuI}$ to dimerize 2-ethynylaniline in formation of quinoline derivative 2-(4-methylquinolin-2-yl)aniline. The quinoline was obtained in a moderate 41% yield when solvent free conditions were utilized.

Metal-free oxidative carbonylation of amines to ureas was investigated as an alternative to phosgene, phosgene derivatives and heavy metal-catalyzed oxidative carbonylation. The current industrial practice involves phosgene which is highly toxic and corrosive. While not toxic, phosgene derivatives generate organic byproducts which in turn increase the waste stream. Metal-free oxidative carbonylation of amines also eliminates the need for expensive, possibly toxic metal catalysts.

Conditions for this reaction involve addition of NaIO_4 as oxidant, NaI as a promoter, dimethylaminopyridine (DMAP) as base and an amine in a vessel charged with CO . After

optimization of this reaction for choice of base, amount of oxidant, promoter, solvents, CO pressure and temperature, ureas from simple primary amines and aromatic amines have been isolated in excellent yields (72-96%).

CHAPTER 1

HOMOGENEOUS BIMETALLIC CATALYSIS: AN OVERVIEW

Introduction

Interest in the production of bimetallic species for the catalysis of chemical reactions has increased sharply in recent times.¹⁻⁴ Although the majority of these reactions have been catalyzed with heterogeneous bimetallic species, their homogeneous counterparts offer three distinct advantages. The first is heightened activity of the catalyst since the reaction can take place throughout the solution, as opposed to heterogeneous catalysis where the reaction must take place on the surface of the catalyst. Secondly, homogeneous catalysis is known to be more selective when multiple products could be formed. A third advantage is ease of chemical manipulation of the homogeneous catalyst, which is not as readily carried out with heterogeneous aggregated nanoparticles.

A variety of organic and inorganic studies have shown the potential of homogeneous bimetallic catalysis. Polymerization,^{1,5-7} methanol oxidation,⁸⁻¹¹ hydrogenation,¹² hydroformylation,¹³⁻¹⁵ ring-closing metathesis,¹⁶ and ring-opening metathesis¹⁶ processes have all been catalyzed via bimetallic catalysis. In addition to advantages over heterogeneous catalysis, the bimetallic nature of these catalysts has also shown benefits over their monometallic derivatives. The presence of two metals in close proximity can allow a unique activation of starting materials, leading to an increase in rate, percent yield, or selectivity. On some occasions, different products are formed. This chapter discusses some recent results that display the improvement of homogeneous bimetallic catalysts over the homogenous monometallic analogues.

Some mono and bimetallic catalysts are depicted in Figure 1-3. Small variations in the catalyst construction can affect large differences in the activities of the catalyst. For instance, **4** is locked into a geometry that obliges close proximity of the two zirconium centers, as observed

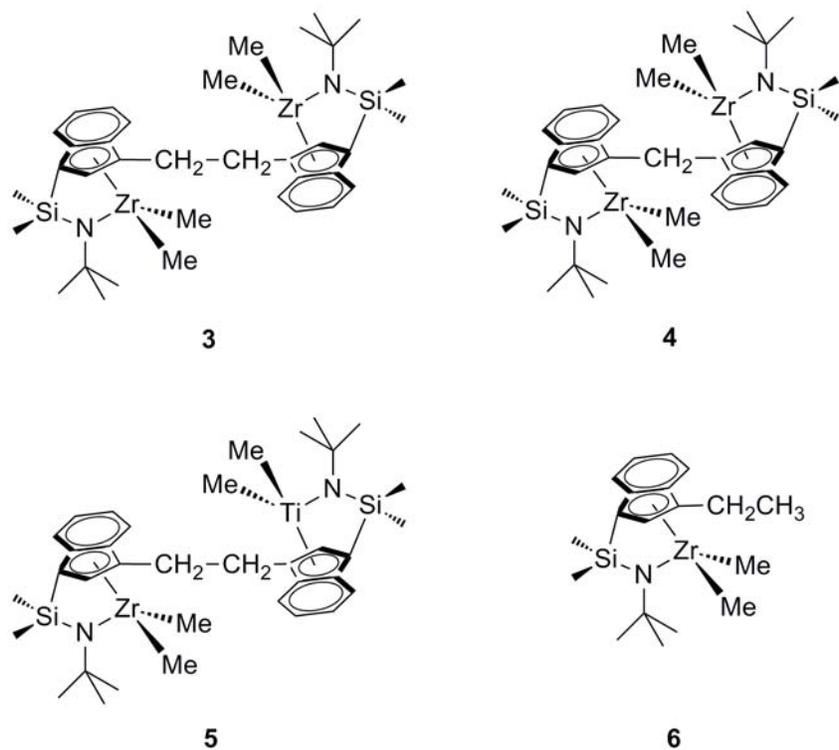


Figure 1-3. Mono- and bimetallic constrained geometry catalysts

in its crystal structure.⁵ This is in contrast to **3**, which has almost no barrier to rotation around the ethylene bridging unit. It is postulated that the close proximity of the two metal centers might afford added activation for polymerization of ethylene.

Although the focus of this chapter is to present the advantages of homogeneous bimetallic catalysts versus monometallics, this chemistry is also greatly affected by the cocatalysts used. Therefore some discussion on cocatalyst characteristics must be undertaken. Use of a group IV metal in conjunction with cocatalysts like that shown in Figure 1-2 create an electrophilic species that reacts to form a polymer product. This is usually carried out by one of three routes: protonolysis, alkylidene abstraction, or oxidative heterolysis (Figure 1-4).¹ Cocatalysts

from Figure 1-2 can be divided into two categories: mononuclear and binuclear. Binuclear cocatalysts are superior to the mononuclear variety for creating highly branched ethylene derivatives.

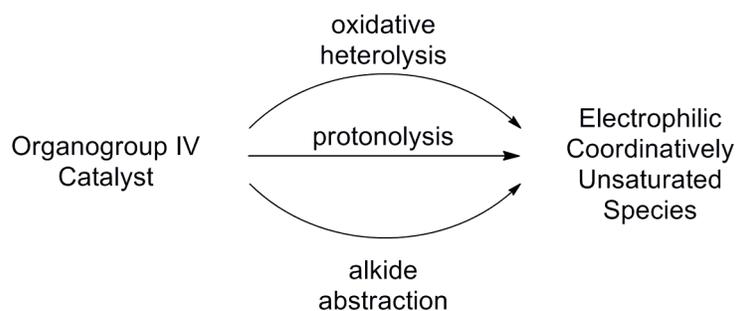


Figure 1-4. Pathways to formation of active olefin polymerization catalysts

Highly branched polyethylene can be produced by the use of single-site constrained geometry catalysts to generate re-enchainment between growing polymer chains.^{17,18} In this process, two separate metal centers on two different monometallic catalysts can incorporate new chain growth into each other, leading to increased branching. However, monomer concentrations in typical polymerizations are dilute, resulting in an insufficient proximity of the two metal centers for this intermolecular reaction to take place. A homo- or heterobimetallic catalyst could lead to increased re-enchainment reactions due to the proximity of the two metal centers.

The effect of bimetallic catalysts in this field is realized in comparison of polymerization of ethylene with the catalyst / cocatalyst systems **4** + **2** versus **6** + **1**.⁶ The bimetallic version of this transformation yields greater than ten times the number of ethylene branches than the monometallic derivative. The method of this ethylene insertion is thought to utilize both metals through a chain transfer followed by a reinsertion of the ethylene moiety (Figure 1-5). Further results also show advantage to this chemistry through use of bimetallic catalysts.⁶ As discussed earlier, catalyst **4** is predicted to perform better than catalyst **3** since the removal of one

methylene unit constrains the catalyst to place the two zirconium centers proximal to one another. The ethylene-bridged catalyst leads to a seventy-fold decrease in molecular weight of the polyethylene formed.

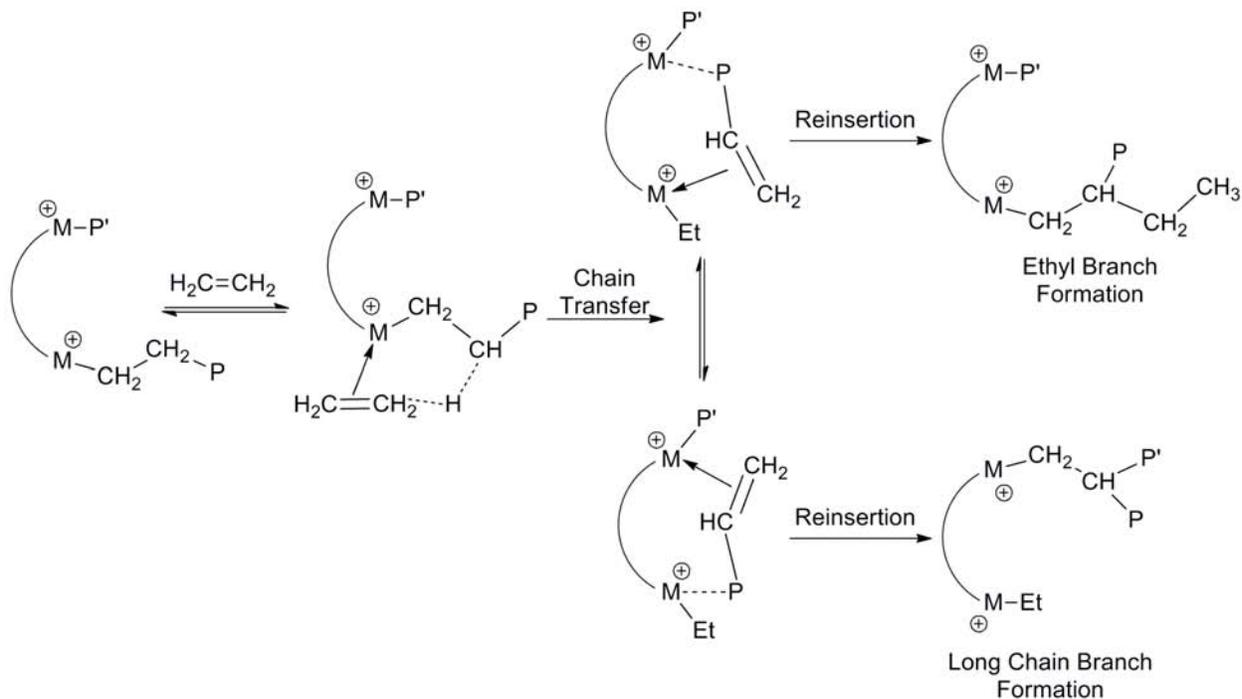


Figure 1-5. Mechanism for ethyl branch formation and long chain branch formation in polymerization of ethylene

To this point only homobimetallic catalysis has been discussed. Investigations into the heterobimetallic complements have also been examined. Group IV zirconium and titanium metals lend different advantages to olefin polymerization. Therefore, use of both of these metals might lead to increased selectivity. Use of the binuclear cocatalyst (**1**) proved to be far superior to the mononuclear **2**.⁷ This is purported to be due to the formation of electrostatic complexes shown in Figure 1-6. For cooperation between the two different metal centers, electrostatic complex B is desired; however, the control of which complex is formed is difficult. Therefore, heterobimetallic complex **5** was synthesized and used to catalyze ethylene polymerization.⁶ This

catalyst did produce the desired product with branches that were greater than six carbons in length in addition to being active.

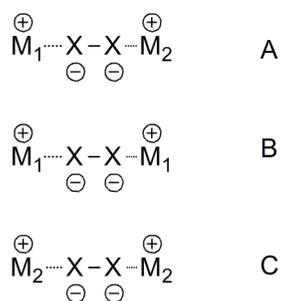


Figure 1-6. Random formation of electrostatic complexes

The utility of these catalysts is not limited to ethylene polymerization. Although these results will not be discussed in length here, it is interesting to note that other olefin polymerizations benefit from the use of bimetallic metal catalysts. Both styrene polymerization¹⁹ and ethylene/ α -olefin copolymerization^{5,20,21} have shown increased branching, molecular weight, and/or selectivity when binuclear metal complexes were used with binuclear cocatalysts.

Other C-C Bond Forming Reactions

Heck Coupling

Coupling reactions have proven vital to synthetic chemistry by providing a cost-effective, reliable method toward making a large variety of compounds. Transition metal catalyzed coupling reactions have been known since 1869, when Glaser homocoupled a terminal alkyne with a copper (I) catalyst.²² However, not until palladium (II) catalysts were found to carry out the transformations exceptionally well in the 1970's did cross-coupling reactions become widely used. Homo- and heterobimetallic catalysts have been found valuable for such reactions, as will be discussed below.

The Heck reaction was studied by James with a Pd homobimetallic complex, **7**, and a heterobimetallic Pt/Pd complex, **8** (Figure 1-7).² This study was prompted by the discovery that the mixed catalyst system RhCl(PPh)₃ and Pd(OAc)₂ performed an intramolecular Heck cyclization with increased selectivity and activity when compared to the monometallic palladium reagent.²³ Styrene was reacted with phenyl iodide in the presence of K₂CO₃ to produce cis- or trans-stilbene in a DMF/H₂O solvent mixture.

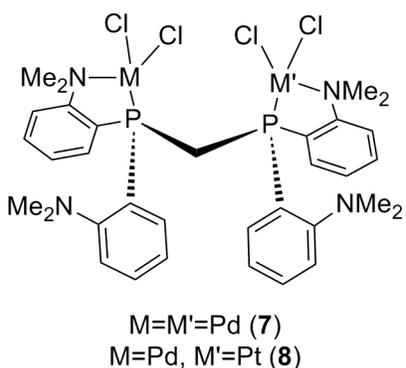


Figure 1-7. Bimetallics used in Heck coupling

Palladium and platinum monometallic catalysts were tested along with compounds **7** and **8**. With the exception of the platinum monometallic species, which displayed no activity, all were shown to be competent catalysts for the Heck reaction. By comparison of the turnover frequencies (TOF) of the active catalysts, it was concluded that summation of the platinum (0 /s) and palladium ($161 \times 10^3/s$) monometallic portion of the complex was less than either the homobimetallic, **7**, ($510 \times 10^3/s$) or heterobimetallic, catalyst **8**, ($266 \times 10^3/s$). Therefore, the bimetallics were deemed the more active catalysts.

Alkenylation of Indoles

An area of interest is the synthesis of indoles that mimic those in natural products, where the 3-position is substituted with an alkyl group (Figure 1-8). Although these compounds are



Figure 1-8. Important 3-substituted indoles

common targets, current syntheses has failed to produce a generally successful method to locate a vinyl group on the 3-position, especially when the 2-position is substituted.²⁴ Recently, this deficiency was addressed by the development of a system where 3-vinylindoles could be selectively synthesized via a palladium (II) catalyst.²⁵ Djakovitch and Rouge noted that the reactions that used copper (I) salts were particularly effective for this reaction, so a bimetallic Pd/Cu dimer, **9**, (Figure 1-9) was synthesized and tested.⁴

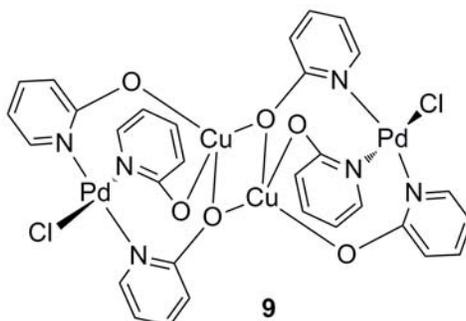


Figure 1-9. Bimetallic dimer used for C3-alkenylation of free indoles

Reaction of the free indole with an alkenylester substrate, 10 mol% catalyst, and DMF/DMSO as solvent (Figure 1-10) gave the corresponding coupled product. Initial results showed that at reaction times longer than 20 hours, the bimetallic dimer **9** gave better results than the monometallic species. Typical results were seen at 50 h, when monometallic

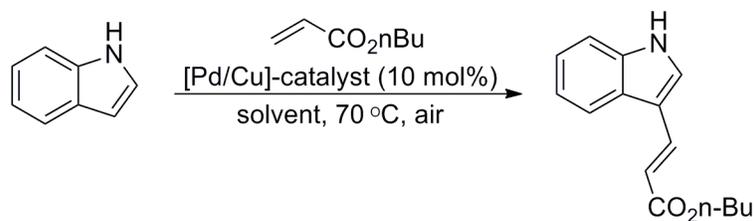


Figure 1-10. Formation of 3-alkenylated indoles

[Pd(OAc)₂/Cu(OAc)₂] and [PdCl₂/CuCl₂] salts gave approximately 50% and 30% conversion to the coupled product, respectively. This is in contrast to **9** that yielded about 90% conversion.

Optimization of the reaction conditions showed that DMF as all or part of the solvent mixture led to decreased product yield by deactivation of the catalyst. DMSO/AcOH was found to be the best solvent for these catalyst systems and was applied toward alkenylation of a 2-substituted indole (Table 1-1). Under the optimized conditions at low time, 1 h, **9** showed

Table 1-1. Comparison of bimetallic and monometallic 3-vinylation of 2-substituted indoles

Entry	2-Substitution	Catalyst	Conversion (1 h) (%)
1	H	[Pd(OAc) ₂ /Cu(OAc) ₂]	55
2	H	[PdCl(hp) ₃ Cu] ₂ 9	55
3	Me	[Pd(OAc) ₂ /Cu(OAc) ₂]	61
4	Me	[PdCl(hp) ₃ Cu] ₂ 9	85
5	Ph	[Pd(OAc) ₂ /Cu(OAc) ₂]	32
6	Ph	[PdCl(hp) ₃ Cu] ₂ 9	52

Increased production of the 2,3-disubstituted indole product when compared to the monometallic mixture (Entries 3-6). Conversely, under the same conditions no advantage was found with the bimetallic dimer when the unsubstituted indole was used as starting material (Entries 1-2).

Although these effects are not dramatic, definite advantages can be seen through use of the heterobimetallic catalysts versus the monometallic equivalents.

Carbonylation Reactions

A series of papers have been published by Hidai, et al. reporting the synergistic effect of two monometallic complexes toward homologation of methanol,²⁶ carbonylation of aryl iodides²⁷ and hydroformylation of alkenes.¹³⁻¹⁵ A recent publication by this group has proposed that these complexes are forming heterobimetallic complexes in-situ that once formed, carry out an array of carbonylation reactions.³ $\text{PdCl}_2(\text{PPh}_3)_2$ and $\text{Co}_2(\text{CO})_8$ are added as catalysts and it is suggested that compound **10** is formed (Figure 1-11). Although this catalyst was not isolated, the Pt

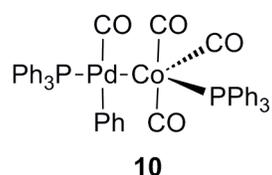


Figure 1-11. Proposed Pt/Co heterobimetallic intermediate

analogue was synthesized from $\text{Pt}(\text{R})(\text{OTf})(\text{PPh}_3)_2$ and $\text{K}[\text{Co}(\text{CO})_4]$. Interestingly, the platinum center has exchanged the triphenylphosphine group for one carbon monoxide ligand from the cobalt. Furthermore, as this compound is decomposed via heating, the cobalt portion was isolated and shown to be similar to that obtained with the palladium analogue (Figure 1-12).

While not definitive, these results are a strong indication that a homogeneous heterobimetallic catalyst is being formed.

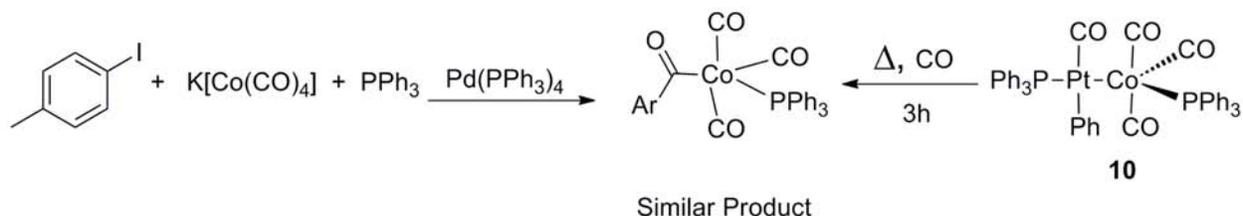


Figure 1-12. Support that the Pd/Co system has an intermediate similar to **10**

Although palladium catalyzes the formylation of aryl halides when CO and hydrogen are present, $\text{PdCl}_2(\text{PPh}_3)_2$ converts *p*-TolI to carbonyl products in very poor yields when reacted with

CO and HSiEt₃.²⁸ This is surprising since hydrosilanes are often known to react very similarly to elemental hydrogen. When palladium and cobalt cocatalysts were used together, three different carbonyl derivatives were formed (Figure 1-13).³ Table 1-2 demonstrates how effective the bimetallic was compared to either of the model compounds. The major compound formed was the hydrosilation product **11**, but the dimerized hydrosilation product **12** predominated upon addition of NEt₃.

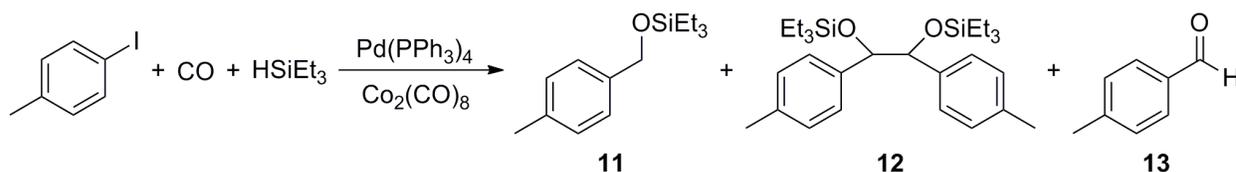


Figure 1-13. Compounds produced through Pd/Co heterobimetallic carbonylation

Table 1-2. Percent GLC conversion of aryl iodides with CO and HSiEt₃ to the corresponding carbonyl derivatives of Figure 1-13

Complex	3 mmol NEt ₃	11	12	13
PdCl ₂ (PPh ₃) ₂	No	0	0	3
PdCl ₂ (PPh ₃) ₂	Yes	0	0	2
Co ₂ (CO) ₈	No	0	0	0
Co ₂ (CO) ₈	Yes	0	0	0
PdCl ₂ (PPh ₃) ₂ - Co ₂ (CO) ₈	No	76	0	0
PdCl ₂ (PPh ₃) ₂ - Co ₂ (CO) ₈	Yes	6	57	2

A similar catalytic system was also used to carbonylate symmetrical and unsymmetrical internal alkynes (Figure 1-14).³ Optimized results were obtained for this reaction when the Pd catalyst contained the P(Cy)₃ ligand instead of the triphenylphosphine previously used.

Excellent results were obtained: GLC yields of 95% of the aldehyde from 4-octyne, 88% from 3-hexyne, 90% from 5-decyne and 95% from dodecyne. Unsymmetrical alkynes showed good selectivity to carbonylate the less sterically encumbered end of the alkyne. This system gave

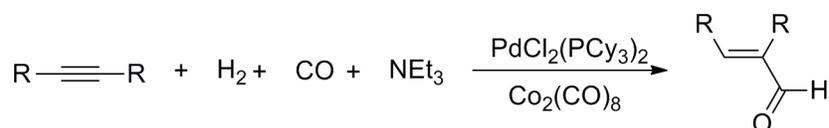


Figure 1-14. Generic reaction of an alkyne with CO to form vinylaldehydes

excellent chemoselectivity for the reaction of alkynes over alkenes. For instance, when 5-decyne was reacted with this catalyst system in the presence of cyclooctene, only the alkyne reacted.

The alkene was recovered in 100% yield.

Methanol Oxidation

Electrooxidation of methanol in direct methanol fuel cells has shown much promise as a power source. This type of cell is proficient at generating small amounts of energy over long periods of time. Methanol fuel cells are therefore ideal for small devices such as cell phones and laptops; such devices have been prototyped. The electrooxidation of methanol has been catalyzed by a variety of monometallic complexes.²⁹⁻³¹ However, studies have shown that some bimetallic systems produce even better results.⁸⁻¹¹

Specifically, catalysis at the surface of a Pt/Ru anode was shown to work by a mechanism where the platinum metal first sequesters methanol, then dehydrogenates it. The ruthenium metal helps further oxidize the methanol by oxygen transfer from water.³² Figure 1-15

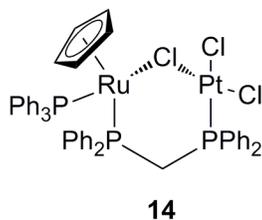


Figure 1-15. Heterobimetallic catalyst for oxidation of methanol

depicts a heterobimetallic ruthenium/platinum catalyst, **14**, which was synthesized to take advantage of this synergistic effect but in a homogenous catalyst.³³

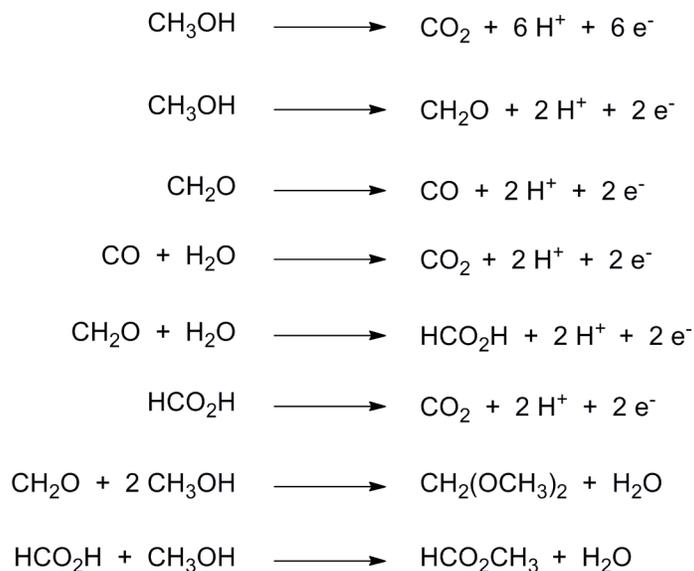


Figure 1-16. Various pathways for oxidation of methanol to the complete oxidation product, CO_2 , or the partial oxidation products, $\text{CH}_2(\text{OCH}_3)_2$ (dimethoxymethane) and HCO_2CH_3 (methyl formate)

Methanol oxidation to the fully oxidized CO_2 gas is a 6-electron process (Figure 1-16), however incomplete oxidation of methanol often takes place. Bulk electrolysis of methanol with catalyst **14** showed incomplete oxidation to two main products: the major product dimethoxymethane (DMM) and the minor product methyl formate (MF). The ratio of DMM to MF was 2.35 when the experiment was conducted at a charge of 50 C. When at the same charge but with a small addition of water, the ratio of DMM to MF was only 1.34. This finding is consistent with the hypothesis that ruthenium is acting as an oxo transfer reagent between water and the palladium center.

Upon comparison of **14** to the monometallic model compounds $\text{Cl}_2\text{Pt}(\eta^2\text{-dppm})$ and $\text{RuCpCl}(\eta^2\text{-dppm})$, it was found that current efficiencies obtained for the oxidation of methanol with a mixture of the two monometallic compounds (42%) were lower than that of the bimetallic complex (49%). Lastly, bulk electrolysis was faster when the bimetallic was used as compared to the monometallic: 1.7 h versus 2.8 h for passage of 50 C of charge.

Another investigation examined a variation on this group of compounds while expanding the bimetallic skeleton to a ruthenium-gold series (Figure 1-17).³⁴ The results from the bulk electrolysis of methanol can be compared by the ratio of DMM versus MF formation. As

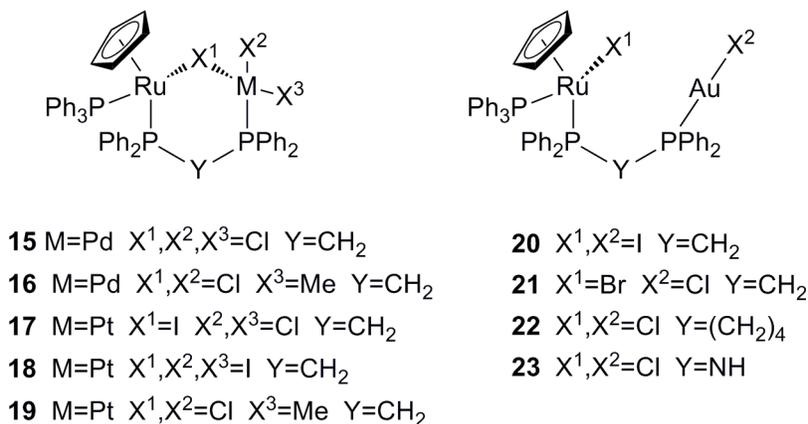


Figure 1-17. Ru/Pt, Ru/Pd, and Ru/Au homogeneous bimetallic catalysts for methanol oxidation charge increases, it was found the amount of the more oxidized product, MF, also increases.

This is presumably because water is being formed through condensation reactions via the pathways shown in Figure 1-16. The Au compounds **20-23** yielded similar results. While all product ratios introduced have been in dry methanol, the net result of addition of small amounts of small amounts of H₂O was an increased production of MF over DMM. However, the current efficiencies did not undergo much change.

A third type of bimetallic species used in the literature consists of ruthenium/tin catalysts where the two metals are bonded to one another (Figure 1-18). Complexes **24-26** were first used to oxidize methanol for production of acetic acid as an alternative to the Monsanto process utilized in industry.³⁵⁻³⁷ This alternative has various advantages, not the least of which is the use of only methanol. The Monsanto process, which employs methanol and CO₂, also uses rhodium, leading to expensive catalysts and increased production costs. The heterobimetallic catalyst **26**³⁷ showed double the activity over the monometallic (η^5 -C₅H₅)L₂RuX derivatives.

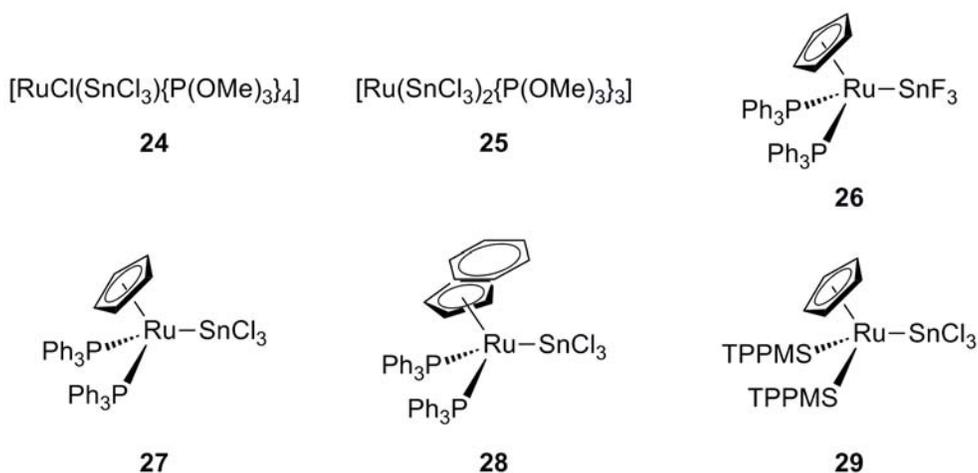


Figure 1-18. Ruthenium/tin catalysts for oxidation of methanol

Ruthenium/tin catalysts can also be used in the electrooxidation of methanol. Catalysts **27-29** gave high current efficiencies and specificity for production of DMM.³⁸ Manufacture of DMM is desirable since it is used in the perfumes, resins, and adhesives industries.³⁹ The monometallic analogues, $CpRu(PPh_3)_2Cl$ and $CpRu(TPPMS)_2Cl$, where TPPMS is a triphenylphosphine monosulfonate ligand, were found to give lower current efficiencies when compared with catalysts **27-29**. Major improvement in DMM selectivity was observed upon use of the TPPMS ligand where even the monometallic derivative $CpRu(TPPMS)_2Cl$ showed total selectivity for DMM, and a drastic increase was observed in the turnover number (from 3.00 to 13.4). $Cp(Ru(TPPMS)_2(SnCl_3))$, **29**, gave the best results: complete production of DMM, 33.4 turn over number, and current efficiencies of around 90%, approximately 30% higher than the monometallic derivative.

Conclusions

Homogeneous monometallic, homobimetallic, and heterobimetallic species are frequently employed as catalysts in a wide range of reactions and applications. The use of heterobimetallic catalysts have resulted in increased re-enchainment reactions and selectivity within olefin polymerization, higher TOF with C-C coupling reactions, improved product conversion within

indole alkenylations and aryl iodide carbonylations, and enhanced current efficiencies and bulk electrolysis for methanol oxidation. As such, these homogeneous heterobimetallic catalysts are useful reagents for potential use in organometallic reactions.

CHAPTER 2 HETEROBIMETALLIC CATALYSIS OF CARBON-CARBON BOND FORMING REACTIONS

Introduction

Heterobimetallic catalysts have been used in organometallic synthesis to carry out a wide variety of transformations. Examples have been shown that depict increased yield, reactivity, and/or selectivity of the reaction when a bimetallic catalyst was used as opposed to the monometallic derivatives (*vide supra*). With this in mind a series of heterobimetallic compounds was synthesized in an attempt to catalyze organic reactions. This chapter will discuss the synthesis of these catalysts and results from the reactions undertaken.

Synthesis of the Heterobimetallic Catalysts

Heterobimetallic catalysts **30-34** were used for the reactions presented in this discussion (Figure 2-1). The first of these, **30** and **31**, are cyclized through a halide bridge between Ru and Pt centers. Complexes **32** and **33** contain Ru for the first metal but Au for the second. Due to the preferred linear bonding by of Au (I), this complex is unable to overcome the geometric constraints to cyclize. Finally, a Ru/Sn heterobimetallic, **34**, was also examined.

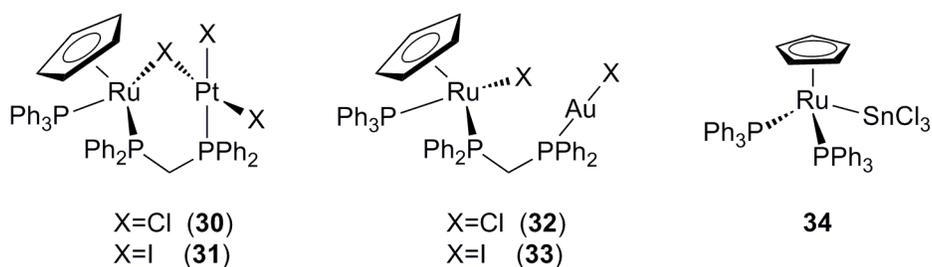


Figure 2-1. Heterobimetallic catalysts used for the exploration of organic reactions

Compounds **30** and **31** were provided by Ying Yang but Ru/Au complexes **32** and **33** and Ru/Sn complex **34** were synthesized. Shown is the synthetic route to complex **33** (Figure 2-2). Compounds **30-34** are moderately moisture sensitive in solution, and care must be taken to keep the system air and water free. The first step was carried out in refluxing, dry ethanol and 62%

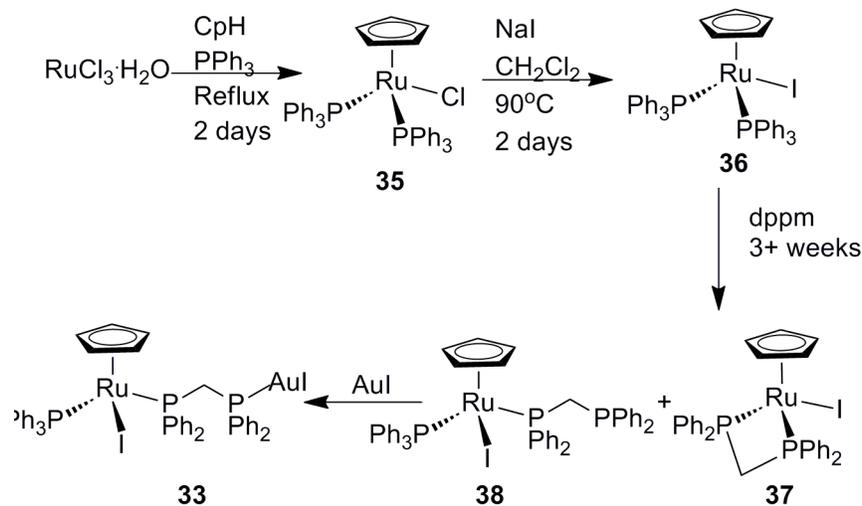


Figure 2-2. Synthesis of CpRu(PPh₃)Cl(dppm)AuI

yield of **35** was obtained. Further reaction of intermediate **35** with sodium iodide for 2 days in a pressure vessel at 90 °C yielded product **36** in 97% yield. If the reaction did not go to completion, the product was purified by column chromatography with air and water free solvents.

The time-limiting step was reaction of compound **36** with dppm for 3-5 weeks at room temperature. Separation of **37** and **38** is exceedingly difficult. Therefore, the reaction cannot be heated to reflux or dppm displaces the triphenylphosphine leading to a mixture of the κ^2 -dppm product **37** and intended product **38**. It was found that if the reaction is gently heated to 40-50 °C, **37** is not formed and the reaction takes place in less than a third of the time. Finally, compound **33** is obtained in greater than 90% yield when compound **38** is reacted with AuI for 30 minutes. The overall reaction yielded roughly 40% of **33** based on RuCl₃·H₂O but with a long window of reaction time. Chloride complex **32** was obtained in a similar manner except reaction of **35** with NaI was not required, and AuCl was used in place of AuI in the final step.

For synthesis of the Ru/Sn complex **34**, $\text{RuCl}_3 \cdot \text{H}_2\text{O}$ was added to PPh_3 in a molar ratio of 1 to 4, respectively. After refluxing in dry ethanol overnight, the solvent was removed under reduced pressure and unpurified $\text{RuCl}_2(\text{PPh}_3)_3$ was reacted with one equiv SnCl_2 , based on $\text{RuCl}_3 \cdot \text{H}_2\text{O}$, in refluxing dichloromethane. After filtering through diatomaceous earth the bright-orange product **34** was isolated in 68% yield.

Enyne Cyclization

Background

Cyclization of enyne **39** is an atom economical reaction that forms complex structures in good yields. This process can be an inter- or intramolecular reaction where the former forms a mixture of dienes and the latter (Figure 2-3) forms cyclic products. Early uses of this reaction were uncatalyzed and were somewhat hindered by the need for high temperatures and poor functional group compatibility.⁴⁰ In the 1980's, catalyzed versions of this reaction began to

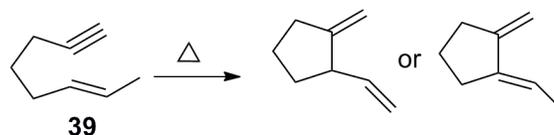


Figure 2-3. The enyne cyclization reaction

overcome those problems as evidenced in a 1985 example where 85% yield of an intramolecular cyclized product was realized in only 1.5 hours at 60 °C (Figure 2-4).⁴¹

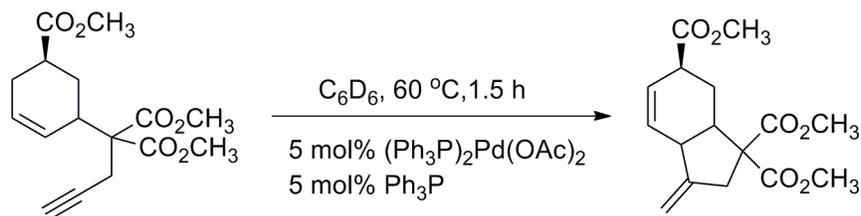


Figure 2-4. Example of a metal-catalyzed enyne cyclization

Figure 2-5 depicts the mechanism for a Pd catalyzed intramolecular enyne cyclization. Because two open coordination sites are required to generate intermediate **40**, complexes **30-34** seem unlikely to catalyze such a reaction. Although generation of two empty coordination sites on one metal of the bimetallic would most likely lead to dissociation of the catalyst, a possibility exists wherein one site opens on each of the metals. This unique complexation could lead to new modes of reactivity.

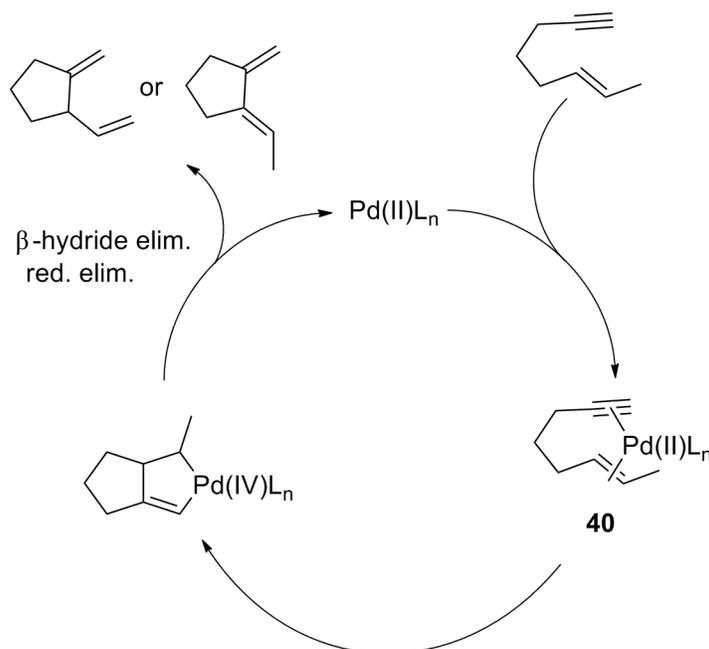


Figure 2-5. Mechanism proposed for enyne cyclization

Results and Discussion

Synthesis of the organic substrate **43** is depicted in Figure 2-6. Allylation of malonate derivatives **41** with **42** yields **43** in greater than 85% yield. Experiments were then conducted with enyne **43** to assess the reactivity of the bimetallic catalysts. First the iodide bridged Ru/Pt catalyst **31** was used, and no reaction was seen. The equivalent Ru/Pd catalyst, **44**, was examined but again yielded no product. Ru/Pt complex **30** and Ru/Au complexes **32** and **33**

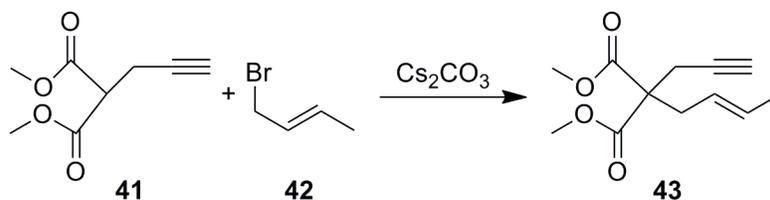


Figure 2-6. Synthesis of starting materials for the enyne reaction

were then studied and no cyclized product was observed. Each of these reactions was conducted in acetone, dimethylformamide, and dichloromethane. However, changing the solvent did not affect the results.

For comparison with known catalysts for the enyne reaction, two experiments were performed. The first of these used the known literature catalyst **45** and the second used the model compound **46** (Figure 2-7).⁴² The literature preparation worked in 68% yield whereas the

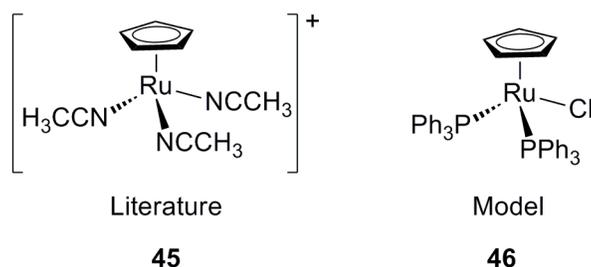


Figure 2-7. Readily available catalysts used to test reactivity of the enyne reaction

model compound was completely unsuccessful. Reactions up to this point were all conducted at 25 °C, but when the temperature was increased to 75 °C, the model compound did result in product. This temperature is presumably high enough to dissociate the triphenylphosphine ligands and open coordination sites similar to what has been postulated for acetonitrile complex **45**.

This result suggests that use of the bimetallic catalyst **30** or **31** in the enyne reaction will not be successful. If the temperature is high enough for dissociation of triphenylphosphine, then dissociation of the halide or dppm bridge might be competitive. Table 2-1 shows the results of

Table 2-1. Effect of increasing temperature on enyne **43** formation versus bimetallic catalysts **30-33** decomposition

Temperature	Time	³¹ P NMR	¹ H NMR	Appearance
40°C	2 h	No Decomposition	No Product	Orange
65°C	2 h	No Decomposition	No Product	Orange
75°C	2 h	No Decomposition	No Product	Orange
90°C	4 h	Decomposition	Product Formed	Black

four subsequent reactions at increasing temperatures. No appreciable reaction took place until a temperature of 90 °C was reached. At 40 °C, 65 °C and 75 °C the solution remained orange, no appreciable product was formed, and the bimetallic stayed intact as indicated by the ³¹P NMR spectra. When the solution reached 90 °C, however, the solution turned black and product was formed, but decomposition of the catalyst was also observed. When high temperatures were used, both cyclic catalysts **30-31** and Ru/Au catalysts **32-33** were able to cyclize the enyne but catalyst decomposition also occurred.

One final attempt was made to carry out the enyne reaction with a more robust bimetallic catalyst. Synthesis of the Ru/Sn compound **34** was straightforward and bright orange crystals were obtained in 68% yield. The bimetallic complex **34** was stable to the enyne reaction conditions, but no reaction took place at temperatures up to 120 °C. No conditions were found where both the bimetallic catalyst remained intact and the desired product was observed.

Heterobimetallic Cascade Reactions

Background

Another possible mode of reactivity for the bimetallics is cascade reactions. If, for example, Ru is known to catalyze reaction A, and Au is known to catalyze reaction B then it is possible that a system can be set up to conduct both reactions in a successive manner (Figure 2-8). The bimetallic complex could have the possible advantage over mononuclear species in

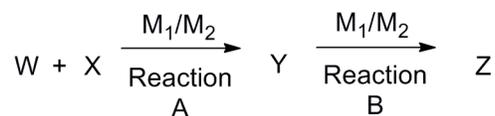


Figure 2-8. Simple representation of two sequential reactions with one catalyst that the proximity effect⁴³ could play a part. That is, the proximity of the second metal could bring about the second transformation before any unwanted intermolecular reactions take place. Once again it was possible that with so many components, unexpected but interesting products might arise. With this in mind, efforts to probe the reactivity of these bimetallic complexes for such systems were initiated.

Results and Discussion

To find suitable reactions for the attempt at cascade reactions, reactions of ruthenium, palladium, and gold complexes were considered. While gold complexes are now becoming accepted catalysts, less is known about their reactivity compared to ruthenium and palladium systems. Many of the reactions considered included transformations involving alkynes, which are known to have a high affinity to gold. Thus, reaction design centered around the gold-alkyne interaction.

Figure 2-9 shows two reactions of interest. The first literature reaction involves preparation of **47** by the coupling of an alkyne with a conjugated diene,⁴⁴ and the second is a gold catalyzed cyclization to form the indole **48**.⁴⁵ The cascade reaction is expected to generate indole **51**.

Dienes used for the combination reaction were isoprene and 1,3-cyclohexadiene. When all components were combined in methylene chloride at 70 °C, however, neither **50** nor **51** was detected, but an unexpected product was formed. As depicted in Figure 2-9, the normal action of

gold (III) catalyst, NaAuCl₄, on a substrate like 2-ethynylaniline should give rise to an indole derivative, but this derivative was not detected. MS, IR, and NMR data were all consistent with dimerization of the 2-ethynylaniline to form quinoline derivative **52** (Figure 2-10). Further, the IR showed a hydrogen bonding stretch in between the amine hydrogens and the quinoline nitrogen. This material, while the major product, was isolated in only about 20% yield. This unexpected product shows that the bimetallic might give unique activation as compared to similar monometallic complexes.

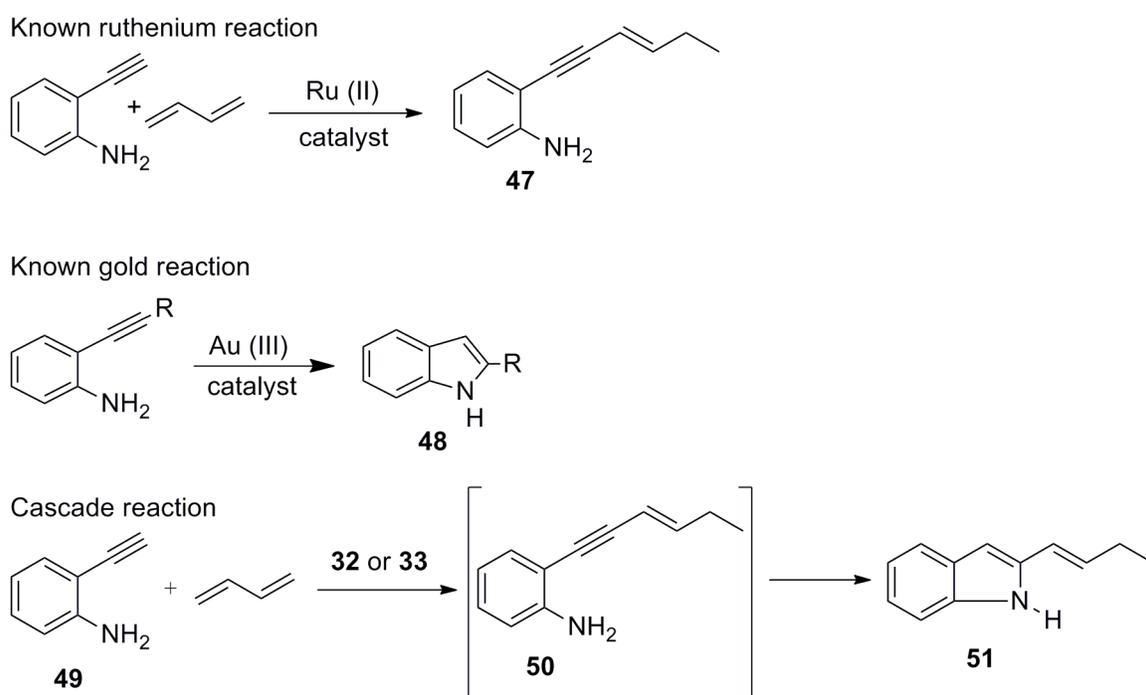


Figure 2-9. Cascade reaction designed using known Au and Ru reactions

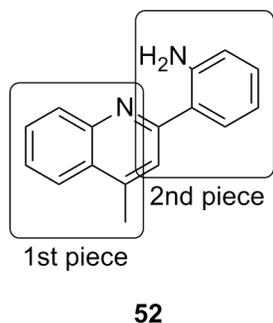


Figure 2-10. Unexpected quinoline derivative

Quinoline Synthesis

Background

Quinoline derivatives are used in a wide variety of applications including optics, pharmaceuticals, and dyes (Figure 2-11).⁴⁶⁻⁴⁸ With the original endeavor with the bimetallic catalysts **32** and **33** producing so little product, attempts were made to optimize these conditions for production of the quinoline derivative **52**. Optimization of these conditions could well lead to insight into reactivity pathways of the heterobimetallic.

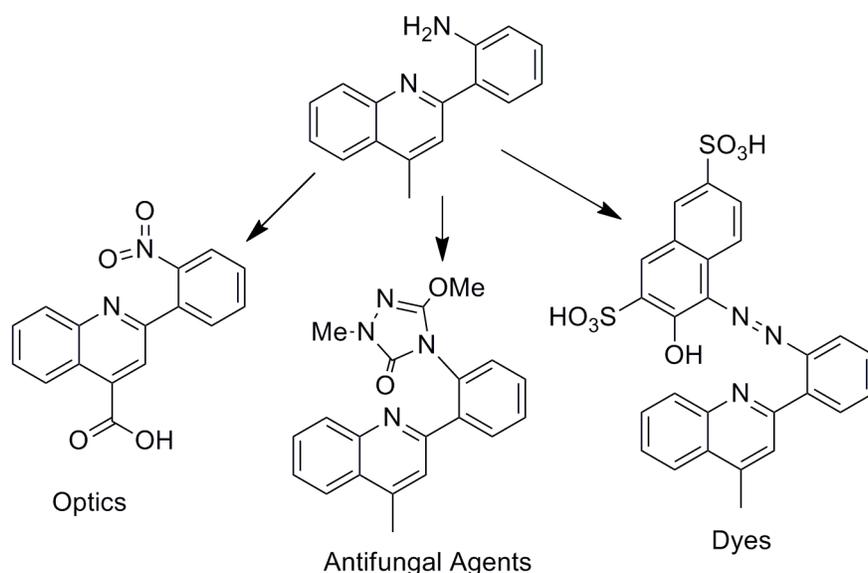


Figure 2-11. Applications of quinoline derivatives

Results and Discussion

Complexes **32** and **33**⁴⁹ were investigated as possible catalysts for a series of reactions specifically intended to take advantage of the reactivity of gold with alkynes while simultaneously promoting reactivity at the proximate ruthenium center. As stated above these heterobimetallic catalysts formed the quinoline species **52** when reacted in the presence of 2-ethynylaniline **49** (Figure 2-12). This transformation has previously been reported for reaction of 2-ethynylaniline with InBr_3 as the catalyst.^{50,51} InBr_3 , however, is known to act as a simple Lewis

acid, whereas gold is believed to proceed through a gold-carbene intermediate.⁵² Although gold-carbene complexes as reactive intermediates have been proposed,^{53,54} recent results indicate that some gold (I) catalyzed reactions are proceeding through Lewis acidic dipolar complexes.^{55,56} The latter results would support the similarities between the InBr_3 and **32** or **33** catalyzed reactions.

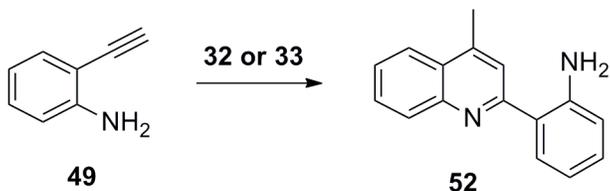


Figure 2-12. Formation of quinoline from 2-ethynylaniline

Model compounds **35** and **53** (Figure 2-13) were first studied to eliminate the possibility that the reaction proceeds at one metal center with no contribution from the other. Results show that in methylene chloride at 90 °C, neither **35** nor **53** produced quinoline (Table 1, Entries 1 and

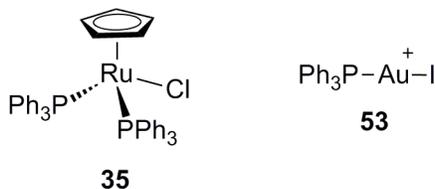


Figure 2-13. Model compounds used to test dimerization of 2-ethynylaniline

2), nor was **52** produced when both **35** and **53** were present (Entry 3). When catalyst **32** was reacted with ethynylaniline, a low yield of **52** was observed (Entry 4) but was slightly improved in the absence of solvent (Entry 5). Employment of catalyst **33** resulted in 34% yield (Entry 6), but lengthening the reaction time further did not increase the quinoline production. The same reaction with **33** was conducted neat (Entry 7) with a slight increase in reaction yield observed. Better yields of **52** with iodide catalyst **33** as opposed to the chlorine homologue **32** probably arises from increased stability of catalyst **33**.

Table 2-2. Yields of quinoline derivative **52** using catalysts **32** and **33**

Entry	Catalyst	Solvent	% Yield ^{a,b}
1	Ru 35	CH ₂ Cl ₂	0%
2	Au 53	CH ₂ Cl ₂	0%
3	Ru 35 and Au 53	CH ₂ Cl ₂	0%
4	Ru/Au-Cl 32	CH ₂ Cl ₂	7%
5	Ru/Au-Cl 32	None	18%
6	Ru/Au-I 33	CH ₂ Cl ₂	34%
7	Ru/Au-I 33	None	41%

^a 5 mmol 2-ethynyl aniline, 0.05 mmol catalyst, 5 mL solvent at 90 °C for 24 h under N₂ atmosphere.

^b Yields based on NMR results.

Optimization efforts included reactions at three different temperatures: 25 °C, 45 °C, and 90 °C. Formation of quinoline **52** required the highest temperature. Control experiments where the bimetallic catalyst **33** was placed in an NMR tube in CDCl₃ and heated for three hours at 125 °C did not produce decomposition products within the limits of detection by ³¹P NMR. Upon addition of one equivalent of substrate, however, decomposition of the starting material was observed with no formation of quinoline derivative **52**.

Various solvents were also used in efforts to optimize production of quinoline **52**. Nonpolar (hexane and toluene), polar (tetrahydrofuran, ether and ethanol), oxidizing (nitromethane) and coordinating solvents (dimethylformamide and acetonitrile) were examined with catalyst **33** as well as the model compounds **35** and **53**. These monometallic complexes, whether together or separate, did not produce quinoline **52** in any appreciable yield. In any solvent heterobimetallic complex **33** afforded some production of the quinoline as observed by trace amounts in NMR spectra. These yields were, however, lower than that of the reaction in methylene chloride and the neat reaction reported above.

An attempt to perform a similar reaction with 2-ethynylphenol was carried out. Aromatization of a 2-ethynylphenol derivative to its corresponding benzofuran has been

previously reported via AuCl_3 catalysis.⁵⁷ The starting material 2-ethynylphenol (**55**) can be synthesized in two steps (Figure 2-14). Addition of TMS-acetylene to *o*-iodophenol in a Sonagashira reaction generated intermediate **54** which was followed by deprotection of the alkyne to form **55** in 69%. The compound was used immediately after preparation, due to its lability. Reaction of **55** with heterobimetallic catalyst **33** produced a mixture of compounds as observed by GC/MS, in which the only identifiable product was the indole analogue, benzofuran (Figure 2-15). None of the desired dimerized product was generated. This was not totally unexpected since the dimerized product cannot be fully aromatized as can the nitrogen analogue **52**.

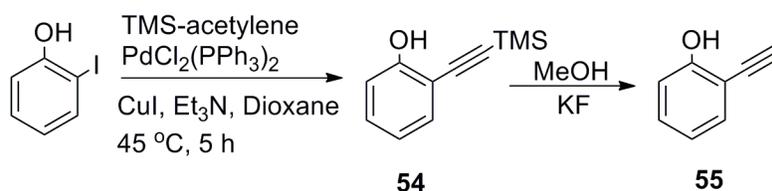


Figure 2-14. Synthesis of 2-ethynylphenol

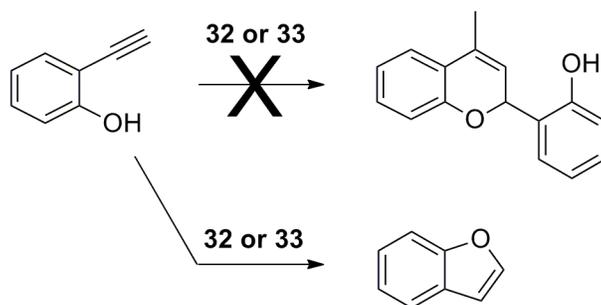


Figure 2-15. Formation of benzofuran from 2-ethynylphenol

Conclusions

We have observed dimerization of 2-ethynylaniline in the presence of heterobimetallic complexes **32** and **33** to form quinoline derivative **52**. This reaction demonstrates a case where the reactivity of the heterobimetallic complex affords a different product than the monomeric model compounds. Solvent-free reactions afforded higher yields than those obtained in the

presence of solvent. It is also of particular interest that the bimetallic catalyst used still reacted differently than when both the model compounds were used in conjunction. The fact that the bimetallic catalyst is indeed inducing a different transformation than that of monometallic compounds, opens new venues of exploration for other catalyzed organic reactions.

CHAPTER 3 OXIDATIVE CARBONYLATION OF AMINES TO UREAS

Introduction

Apart from being common functional groups in medicinal compounds,⁵⁸⁻⁶⁴ ureas are frequently found in agricultural products and dyes.⁶⁵⁻⁶⁷ Drawbacks to current urea syntheses include toxic reagents, problematic waste streams, high pressure reactors, high temperatures and poor reactivity of secondary amines and/or aniline derivatives.

The common ways to synthesize these ureas have historically been reactions with phosgene or phosgene derivatives, such as 1,1'-carbonyldiimidazole (Figure 3-1).^{68,69} Such

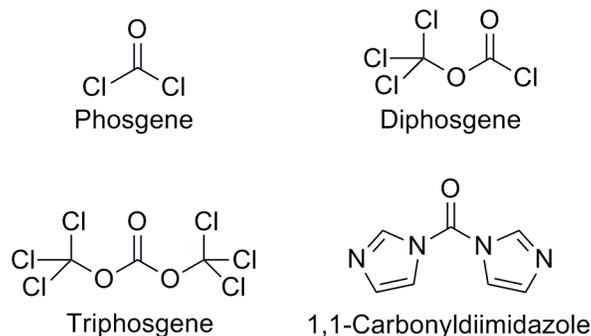


Figure 3-1. Structure of phosgene and some phosgene derivatives

reactions tend to produce excellent yields to symmetrical or unsymmetrical ureas. Phosgene, however, is extraordinarily toxic with a lethal concentration in fifty percent of a rat population (LC_{50}) of only 5 ppm. In comparison, carbon monoxide gas has an LC_{50} of 3760 ppm: a greater than 750-fold decrease in toxicity.

While phosgene derivatives do not exhibit high toxicity levels, a large amount of waste is generated in these reactions.⁷⁰ Since transformation of amines to ureas with phosgene derivatives is performed via nucleophilic acyl substitution, the carbonyl moiety is the only portion of the starting material retained in the product. The reactions have very low atom economy⁷¹ which leads to increased pollutants and production costs.

Metal-Catalyzed Oxidative Carbonylation of Amines to Ureas

The disadvantages exhibited by phosgene and phosgene derivatives have led to the development of a wide variety of methods to avoid these issues. One such reaction that has emerged in urea synthesis is metal-catalyzed carbonylation of amines with carbon monoxide (Figure 3-2).^{72,73} This method has shown marked improvement over the shortcomings of the phosgene mediated synthesis. It offers safer conditions than phosgene syntheses and due to the high degree of atom economy is more environmentally friendly than phosgene. In a palladium

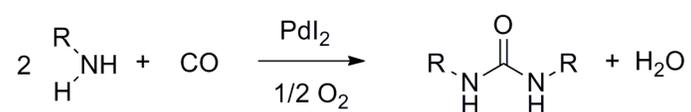


Figure 3-2. Palladium catalyzed example of oxidative carbonylation

catalyzed carbonylation, all non-hydrogen atoms in the starting material are also present in the product (Figure 3-2).

In addition to palladium catalysts, a wide variety of other metal complexes can be used in oxidative carbonylations. For example, Ni, Ru, Co, Rh, Au, Cu and W complexes have also been investigated as catalysts.⁷⁴⁻⁸² Although different metal catalysts offer different advantages and disadvantages, they often seem to share mechanistic steps: specifically, a key carbamoyl intermediate (Figure 3-3) is often proposed. Such species have been observed by IR in the tungsten-catalyzed system.^{83,84}

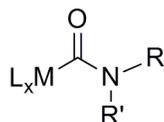


Figure 3-3. Carbamoyl intermediate in metal catalyzed oxidative carbonylation of amines

A typical mechanism that involves carbamoyl formation is shown in Figure 3-4.⁷² The first mechanistic step is formation of **56** by oxidative addition of the X_2 oxidant to the Pd center where X is usually I or Cl. Secondly, reaction of a primary or secondary amine and carbon monoxide effects substitution of the amine for halide and subsequent CO insertion, resulting in the observed carbamoyl intermediate **57**. To regenerate the catalyst, this intermediate is deprotonated with one equivalent of the amine leading to expulsion of isocyanate **58**. A second equivalent of the amine then nucleophilically attacks **58** to form the urea.

Secondary amines, in some cases, do not react to form tetrasubstituted ureas.⁷² This result supports the idea that a secondary amine starting material cannot form the proposed

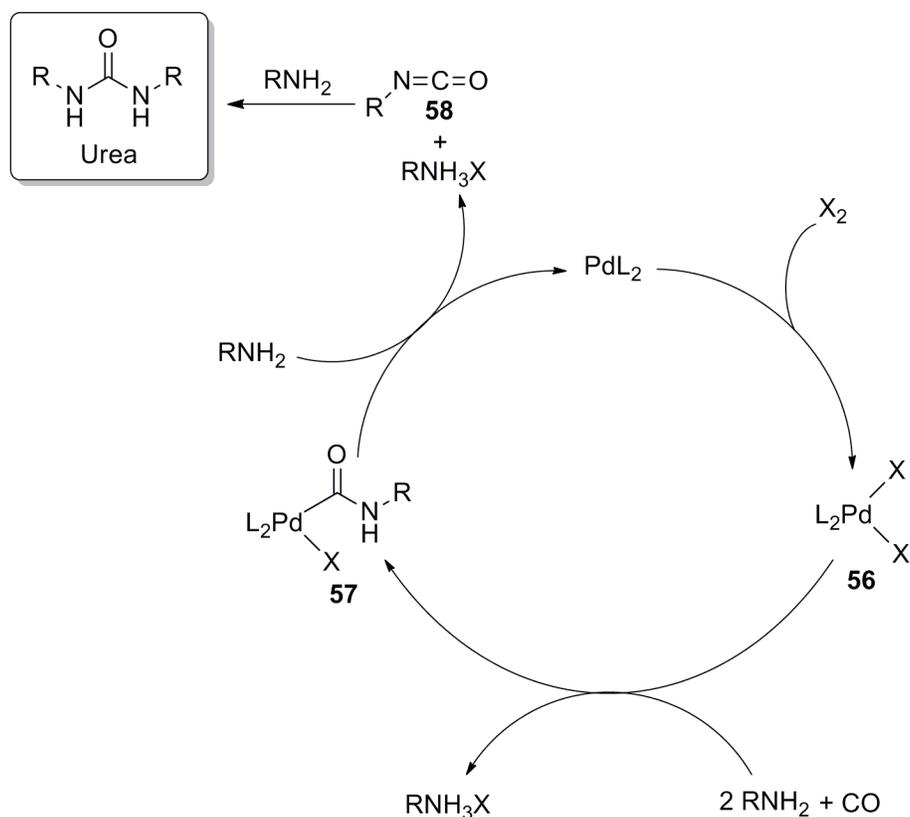


Figure 3-4. Proposed mechanism for palladium catalyzed oxidative carbonylation of amines to ureas

isocyanate intermediate, **58**, since there would be no acidic hydrogen on the carbamoyl nitrogen of **57**. Trisubstituted ureas were, however, obtainable when the less reactive secondary amine was used in excess as compared with the primary amine (Figure 3-5). This conversion would be possible if the primary amine were first converted to the carbamoyl intermediate followed by abstraction of the acidic hydrogen to form the isocyanate derivative. Attack by a secondary amine would then result in the trisubstituted urea. Isocyanates have been observed in reaction mixtures by GC and GC/MS.⁸⁵

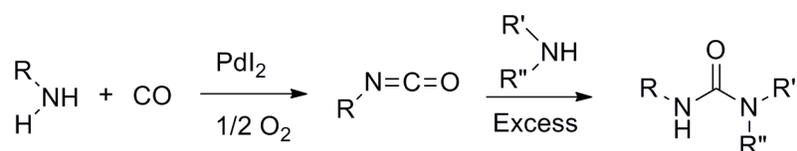


Figure 3-5. Unsymmetrical urea formation via palladium catalyzed oxidative carbonylation

With some metal catalysts, unique side products are observed. When the nickel (II) catalyst $\text{NiCl}_2(\text{RNH}_2)_4$, carbon monoxide, and a primary amine are combined under anhydrous conditions, oxamide product **60** is formed (Figure 3-6).⁷⁸ This product is not observed, however, when the reaction is carried out in aqueous media. The urea is formed when water is present, because the coordination of an aquo ligand can block formation of the bis-carbamoyl complex **59**.

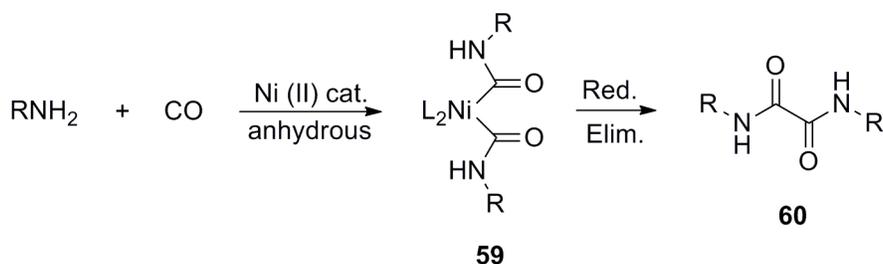


Figure 3-6. Anhydrous formation of an oxamide product with a nickel catalyst

Transition Metal-Free Catalyzed Carbonylation

While metal-catalyzed reactions provide an alternative to phosgene systems, many transition metal catalysts are expensive, air sensitive and in some cases toxic. It would be ideal if a process could be devised that would allow for the avoidance of the toxicity of phosgene, the waste stream problems and poor atom economy of phosgene derivatives, but would also eliminate the high pressure, high temperature, and presence of heavy metals, conditions which are commonly used in metal catalysis. To our knowledge, only two examples of such systems are known. One such method employs selenium and a second sulfur to promote this transformation.

Selenium Promoted Carbonylation to Urea Derivatives

Selenium was first shown to produce ureas in good yields from simple amine starting materials as reported by Sonoda et al. in 1971.⁸⁶ This group first investigated the selenium-promoted reaction under very harsh conditions, where a reactive form of selenium (**61**) was generated in high yields at 650 °C from elemental selenium and carbon monoxide (Figure 3-7).⁸⁷ Selenium carbonyl **61** has an unusually weak $4p\pi-2p\pi$ bond making it particularly susceptible to nucleophilic attack.

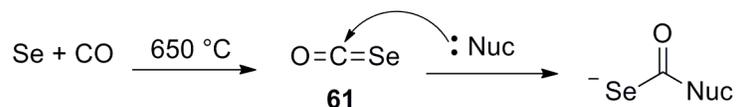


Figure 3-7. Unusually reactive selenium carbonyl

These conditions were improved when it was observed that selenium carbonyl **61** could be trapped in the form of the carbamoyl derivative, **63**, rather than being synthesized separately (Figure 3-8).⁸⁸ At only 25 °C when tetrahydrofuran (THF) was used as a solvent, it was purported that salts **62** were formed. The hypothesis was confirmed by attack of the selenium anion on a primary alkylhalide, butylbromide, to generate **63** in quantitative yields.

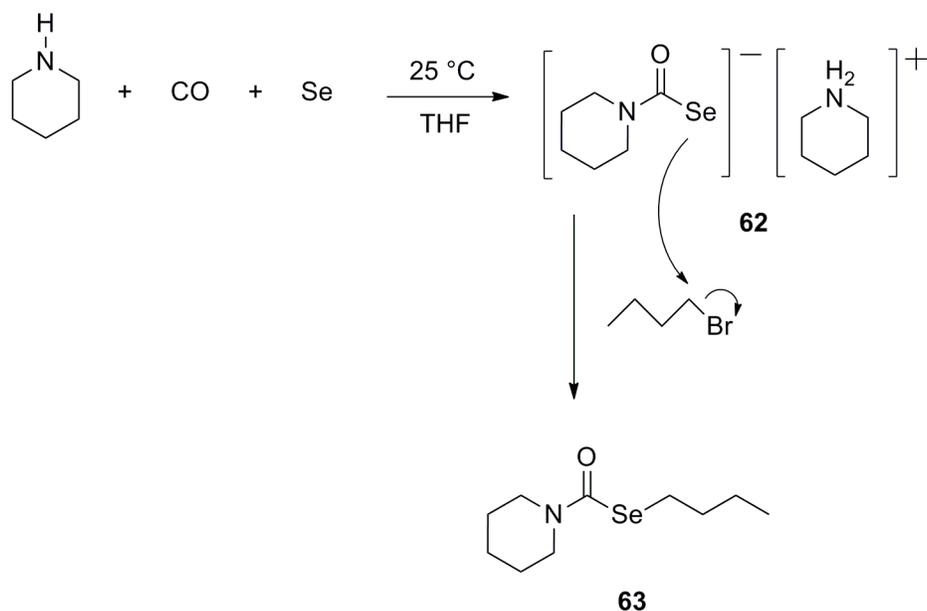


Figure 3-8. Selenium carbamoyl formation under mild conditions

Sonoda et al. also found that when O_2 was present, selenium promoted carbonylation of amines to ureas could be made catalytic.⁸⁶ The presence of oxygen can be used to regenerate elemental selenium through reaction with H_2Se . This is advantageous in two ways. First, the improved reaction is more environmentally friendly since less selenium is used. Secondly, H_2Se gas is toxic, and if removal of the toxin is complete, a possible hazard of the reaction can be removed. The catalytic cycle is shown in Figure 3-9.

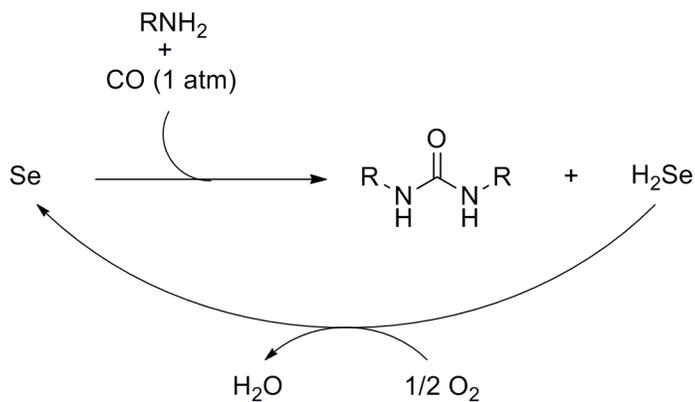
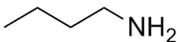
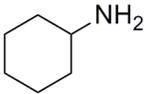
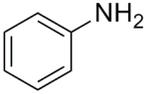
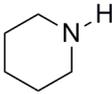
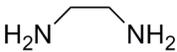
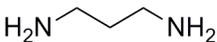


Figure 3-9. Regeneration of selenium catalyst

Urea formation via the carbamoyl selenide proved to be facile under mild conditions (Table 3-1).^{86,89-92} Entries 1-5 show the ease at which this reaction takes place at only 15 °C and 1 atm CO, giving yields from 90-99%. Even secondary amines (Entry 5) and aniline (Entry 4) reacted in excellent yields. While cyclic ureas were more problematic, increased temperature of 40-60 °C and pressure of 50 atm gave excellent results (Entries 6 and 7).

Table 3-1. Selenium catalyzed urea formation of primary amines

Entry	Amine	Yield (%)
1	NH ₃	98
2		99
3		96
4		90
5		95
6		98
7		96

Since the intermediate in these reactions is a stable salt, it is possible to form unsymmetrical ureas by attack on the carbamoyl selenide with a second amine. As early as 1971 unsymmetrical ureas were formed by attack of piperidine on the butyl derivative of the carbamoyl salt **64** (Figure 3-10).⁸⁶ The unsymmetrical urea **65** was produced in 98% yield. When the piperidyl derivative of **64** was formed then reacted with n-butylamine, the same unsymmetrical urea **65** was formed quantitatively.

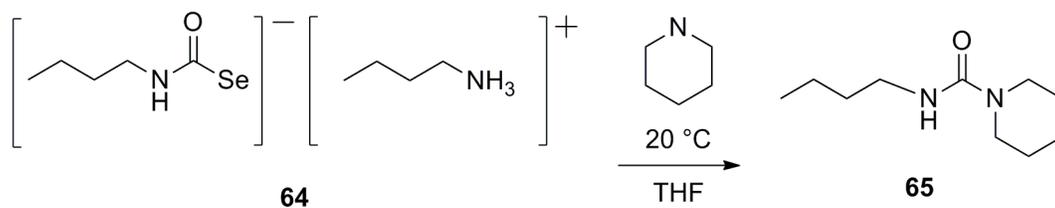


Figure 3-10. Formation of unsymmetrical ureas

It has been found that anilines react poorly compared to other primary amines when subjected to selenium promoted carbamate formation.⁹³ In a subsequent paper, however, conditions were improved so that ureas could be formed in high yields from primary aromatic amines.⁹⁴ At 100 °C and 30 atm CO in THF solvent urea products were obtained. A few examples are presented in Table 3-2. Near quantitative yields were observed when N-methylpyrrolidine (NMP) was used as a base. Conditions for the reactions with excess selenium (column 3) and that with catalytic selenium (column 4) were identical except that 2 kg/cm² oxygen was added to the catalytic reaction.

Table 3-2. Selenium catalyzed formation of ureas from aniline derivatives

Entry	Amine	Yield of urea with 3 equiv Selenium	Yield of Urea with 5 mol% selenium
1		99	99
2		98	97
3		97	95

Secondary amines can also be used to give ureas under conditions similar to those used with aromatic amines (*vide supra*). Most ureas from geometrically constrained secondary amines were generated in excellent yields (Table 3-3).⁸⁷ Only 1 mol% selenium was necessary to catalyze this reaction at 120 °C in 4 hours under 30 atm CO in THF, after which 4 atm of O₂ was added to complete urea formation. Sterically hindered amines do not react as well since 2-methyl piperidine yielded only 6% urea product.

Table 3-3. Selenium catalyzed formation of ureas from secondary amines

Entry	Amine	Yield of urea(%)
1		100
2		99
3		96
4		99

Although early methods for making selenium carbonyl **61** involved high temperature⁸⁷ (650 °C), a method has been found to make this molecule. The addition of an equivalent of sulfuric acid at -78 °C to the diethyl amide salt **66**, gives selenium carbonyl (**61**) in 98 % yield (Figure 3-11). Since **66** can be made quantitatively, this procedure can produce selenium carbonyl in extremely high yields from inexpensive materials under mild conditions.

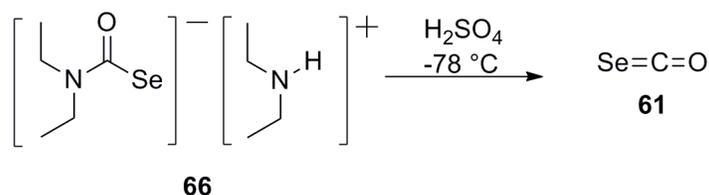


Figure 3-11. Formation of selenium carbonyl in under mild acidic conditions

Sulfur Promoted Carbonylation to Urea Derivatives

Selenium catalyzed carbonylation of amines to ureas afforded excellent results for primary, secondary and aromatic amines. Unsymmetrical ureas were also produced under mild reaction conditions. This reaction, however, forms H₂Se which is toxic and corrosive. Elemental selenium is also toxic; even if the H₂Se can be oxidized by O₂ back to elemental selenium, the reaction still suffers from a toxicity problem.

Because it is in the same group as selenium, sulfur exhibits similar reactivity. The carbonylation of amines to ureas in the presence of sulfur was first discussed in 1961 when a group from Monsanto published a series of three papers on the topic.⁹⁵⁻⁹⁷ The first of these papers introduced this process and specified the reaction conditions.⁹⁵ At 120 °C, one equivalent of sulfur, and 2 equivalents of ammonia were reacted under carbon monoxide gas to form urea and hydrogen sulfide in methanol solvent (Figure 3-12).

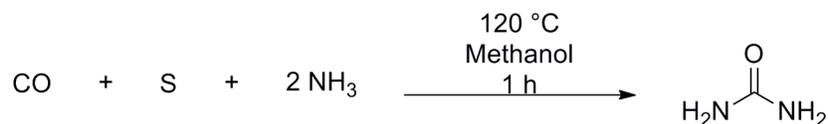


Figure 3-12. Original sulfur catalyzed urea formation from ammonia

Observations during experimentation led to mechanistic insight. First, it was noted that carbonyl sulfide was detected by infrared spectroscopy (IR) when the temperature was 150 °C. Secondly, at low temperature (25 °C to 30 °C) ammonium salt **67** was isolated and characterized. A final insight into the mechanism is that the isocyanate intermediate **68** was also detected with IR. Based on these observations, a mechanism was proposed (Figure 3-13). Although subsequent papers have examined the mechanism in more detail, *vide infra*, these observations go a long way toward illumination of the reaction pathway.

The second paper in the series optimized conditions and further explored the scope of this reaction.⁹⁶ It was found that 2 hours and 130 °C were optimal for time and temperature of this reaction. In fact, in reactions where the temperature was kept below 70 °C, the reaction was found to rapidly approach 0% yield. Some amine substrates were converted to ureas in high

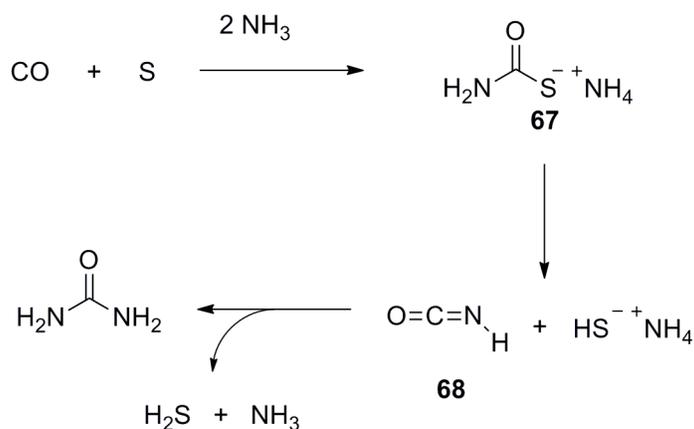


Figure 3-13. Earliest proposed mechanism for urea formation with sulfur catalyst

yield in less than two hours. For example, isobutylamine yielded approximately 90% urea at 130 °C in only 20 minutes.

The optimal ratio of amine to sulfur to CO gas was determined to be 2 : 1 : 1.2. The reaction was hindered when less than one equivalent of sulfur was used, but addition of excess sulfur did not increase the efficiency of the reaction. Finally, CO pressure did not seem to affect the outcome of the reaction significantly when at the optimal temperature, 120 °C, though at lower temperatures, higher CO pressure led to higher yield.

To test the scope of this reaction, various aliphatic amines were reacted under the optimized conditions (2 equiv. amine : 1 equiv. sulfur in methanol solvent under 70 psig. CO gas at 120 °C for 2 h, Table 3-4). Simple aliphatic amines give good to excellent yields. As the steric hindrance increases however, the reaction becomes poorer (Entries 3-5).

Table 3-4. Sulfur-catalyzed formation of ureas from primary aliphatic amines

Entry	Amine	Yield %
1	n-butyl	80
2	<i>iso</i> -butyl	79
3	<i>sec</i> -butyl	71
4	<i>tert</i> -butyl	54
5	<i>tert</i> -octyl	29

The final paper in this series was devoted to the conversion of anilines to their corresponding ureas.⁹⁷ Low yields were obtained via the sulfur catalyzed formation of aromatic ureas; the reaction yield can be optimized to 50% when triethylamine (TEA) was used as a base. Franz used complex statistical analysis to optimize the reaction for temperature, time, CO pressure, amount of base and ratio of amine to sulfur. The optimized conditions were 130 °C, 3.5 h, 500 psig. CO pressure, 4.4 g of TEA, and a ratio of 50 g : 34.4 g of aniline to sulfur. Additionally, the reaction worked best under solvent free conditions.

Of the twenty-two anilines tested, only five ureas were made in greater than 45% yield. Among these were 1,3-bis(4-methoxyphenyl) urea (63%), 1,3-bis(4-chlorophenyl) urea (65%), 1,3-di-*p*-tolyl urea (79%), 1,3-diphenyl urea (86%), and 1,3-bis(4-hydroxyphenyl) urea (92%). The last of these ureas was made without the addition of TEA as base.

As an extension of the Monsanto findings, Mizuno has further developed this research in a series of publications.⁹⁸⁻¹⁰³ Solvent effects were found to be an important factor.¹⁰⁰ When cyclohexylamine is employed as reactant with one atmosphere of CO and O₂ gas at 20 °C, the more polar solvents DMF and DMSO gave 88% and 82% yields of the corresponding urea, respectively. THF as solvent gave only 8% under the same conditions. The reaction proceeds first through formation of salt **69**, followed by oxidation with O₂ to produce the urea (Figure 3-14). From research carried out at Monsanto, it is known that H₂S is formed in this reaction.⁹⁵

Elemental oxygen then is used to oxidize this toxic gas back to elemental sulfur. Like selenium, the reaction can then be made catalytic in sulfur when 1 atm of O₂ is used.

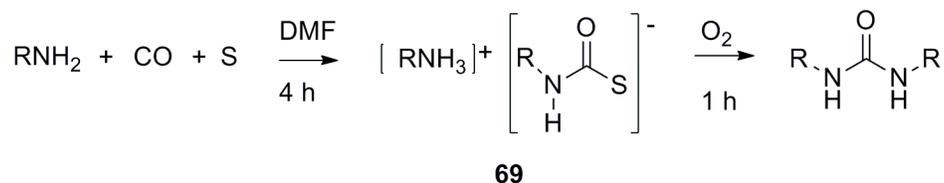
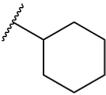
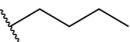
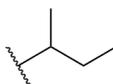
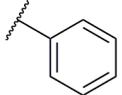
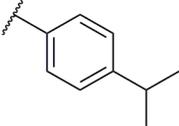


Figure 3-14. Sulfur promoted formation of disubstituted ureas from primary amines

While yields ranging from 49%-98% were obtained (Table 3-5) there were still disadvantages. Primary, unhindered, aliphatic allyl substituents worked well to support urea formation (Entry 1-3). When steric crowding was added (Entry 4) or aniline derivatives were tested (Entries 5 and 6) yields became much lower. The less electron-rich aniline derivatives yielded no product unless 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was used as base. The withdrawing capabilities of aromatic substituents affected formation of the urea. When the electron withdrawing substituent -NO₂ was used, no urea was formed even when DBU was added as base. On the other hand, the electron donating methoxy substituent gave 83% yield. Secondary amines notably did not react at all, which could indicate an isocyanate intermediate.

NaNO₂ can also be employed as an oxidant in place of O₂.¹⁰⁴ One advantage to this system is that a CO/O₂ system can be explosive when reacted at high temperatures and high pressures. Additionally, the oxygen system was affording good yields with 40 mol% S when compared to the amine starting material. However, the NaNO₂ system was able to achieve better conversion for most substrates at only 5 mol % S. Conditions for this reaction were harsher than those reported by Mizuno. Optimized conditions consisted of a 1 : 0.5 : 0.05 ratio of amine : NaNO₂ : sulfur in methanol for 10 h at 120 °C under 40 atm of CO pressure. Although H₂S gas was

Table 3-5. Yields of various ureas from carbonylation of primary amines with sulfur

Entry	1	2	3	4	5	6
Amine						
Urea yield (%)	88	92	98	59	51	49

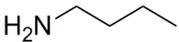
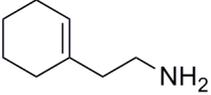
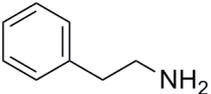
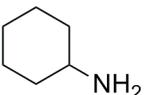
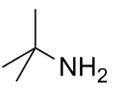
formed as a byproduct, it was quantitatively oxidized by NaNO_2 to elemental sulfur.

Unfortunately, formamide was also produced as a byproduct in the reaction. However, high selectivity could be obtained for many substrates.

Table 3-6 shows a selection of some of the results for this system where % conversion and selectivity were determined by gas chromatography (GC). Simple alkyl, unhindered amines gave the urea in excellent yields and selectivities (Entries 1-4). Alkenes (Entry 3) remain untouched under the reaction conditions. Cyclohexylamine was not able to produce the urea in good yields (Entry 5) suggesting that more sterically encumbered amines may not generate ureas well under these reaction conditions. Contrary to this observation, however, *t*-butyl amine gave 97% conversion and 99% selectivity. Secondary amines and aniline derivatives did not work in this system.

β -Amino alcohols can also undergo this process selectively to form 2-oxazolidones.^{104,105} Mechanistic studies led the authors to propose a general intermediate that first goes through the same thiocarbamate (**70**) that would lead to urea production (Figure 3-15). This intermediate could then be oxidized by O_2 to induce disulfide bond formation to form intermediate **71**. Intramolecular ring closing could then form the final oxazolidone product, **72**.

Table 3-6. Sulfur-catalyzed urea formation with secondary oxidant NaNO₂

Entry	Amine	% Conversion	% Selectivity for Urea
1		100	> 99
2		98	>99
3		92	>99
4		98	91
5		35	21
6		97	99

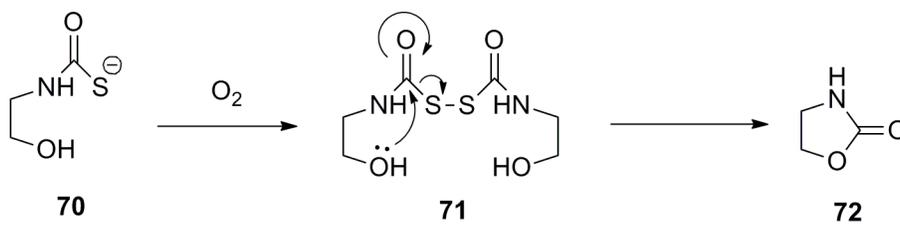


Figure 3-15. Mechanistic proposal for sulfur catalyzed oxazolidinone production

In 2007, Mizuno reported sulfur catalyzed urea formation of primary amines under solvent free conditions.⁹⁹ In order to find new environmentally friendly avenues toward sulfur-catalyzed urea production, 1*H*-quinazoline-2,4-diones were synthesized under conditions where either no solvent was used¹⁰⁶ or supercritical CO₂ acted as the solvent.¹⁰⁷ Solvent free conditions were then developed for a similar reaction to form urea derivatives. A successful system was found when the reaction was optimized for *n*-octylamine.⁹⁹

The original conditions used were 1.25 equiv octylamine, 1 equiv sulfur, 1 atm carbon monoxide gas, 1 atm oxygen gas for 4 h at 20 °C. Under these conditions 1,3-dioctyl urea (**73**) was formed in only 30% yield. By increasing the amount of the amine to 2 equiv and the temperature to 80 °C, the urea production could be increased to 99% isolated yield (Figure 3-16). Primary aliphatic amines, benzylamines, and 3-methoxy-propylamine underwent facile transformation to ureas under solvent free conditions in 76-99% yield. Aniline derivatives could not be converted to the ureas in significant amounts: the maximum yield achieved was 30% with the electron donating para-methoxy aniline. Again, DBU had to be employed or no urea formed. Secondary amines did not produce any ureas under these solvent-free conditions.

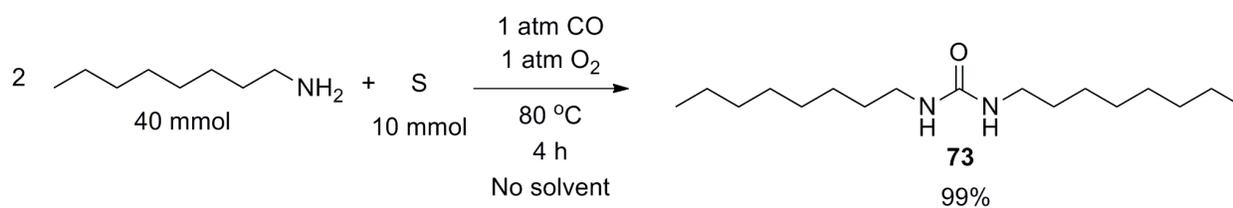


Figure 3-16. Formation of 1,3-dioctyl urea with solvent free sulfur-catalyzed carbonylation

Most papers discussed up to this point have shown how primary and/or secondary amines can react with CO gas to form symmetrical ureas. A 2009 paper discussed attempts to make unsymmetrical ureas by reaction of a secondary amine and an aniline derivative.⁹⁸ Of particular interest was the formation of N-butyl-N-methyl-N`-3,4-dichlorobenzene urea (**74**) otherwise known as neburon, a powerful herbicide. By using a 2 : 1 ratio of the secondary amine to aniline derivative, excellent yields of a variety of unsymmetrical ureas could be generated.

Dimethylformamide (DMF) proved to be the optimal solvent and only 1 atm of CO gas was required. Figure 3-17 shows some of the unsymmetrical ureas that were synthesized. The reaction conditions included heating at 20 °C for 16 h and then heating for an additional 4 h under O₂ gas.

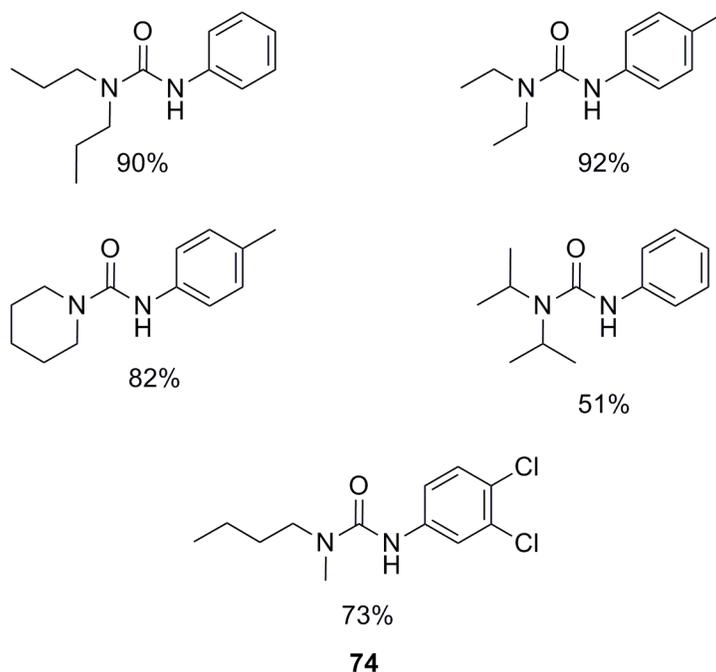


Figure 3-17. Unsymmetrical ureas produced through sulfur-catalyzed carbonylation of a secondary amine and aniline derivative

The mechanism for generation of these unsymmetrical ureas was postulated to involve the formation of the disulfide bond shown in compound **76** (Figure 3-18). Aniline is not a strong nucleophile and does not react with the CO/S reagents to form intermediate **75**. However, the secondary amine is a stronger nucleophile, enabling **76** to form. Attack by aniline on intermediate **76** would then give the unsymmetrical urea **77**. For steric reasons, the disulfide complex is not attacked by a second equivalent of dipropylamine.

In work by Macho, nitrobenzene is reductively carbonylated in the presence of aniline and sodium metavanadate (**78**) to form N,N'-diphenyl urea on route to methyl-N-phenyl-carbamate (Figure 3-19).¹⁰⁸ Building on this finding, Wang carried out a similar transformation without the vanadium oxidant to afford the urea in excellent yields.¹⁰⁹ Since this reaction is thought to proceed through an ionic intermediate and polar solvents, DMF, and

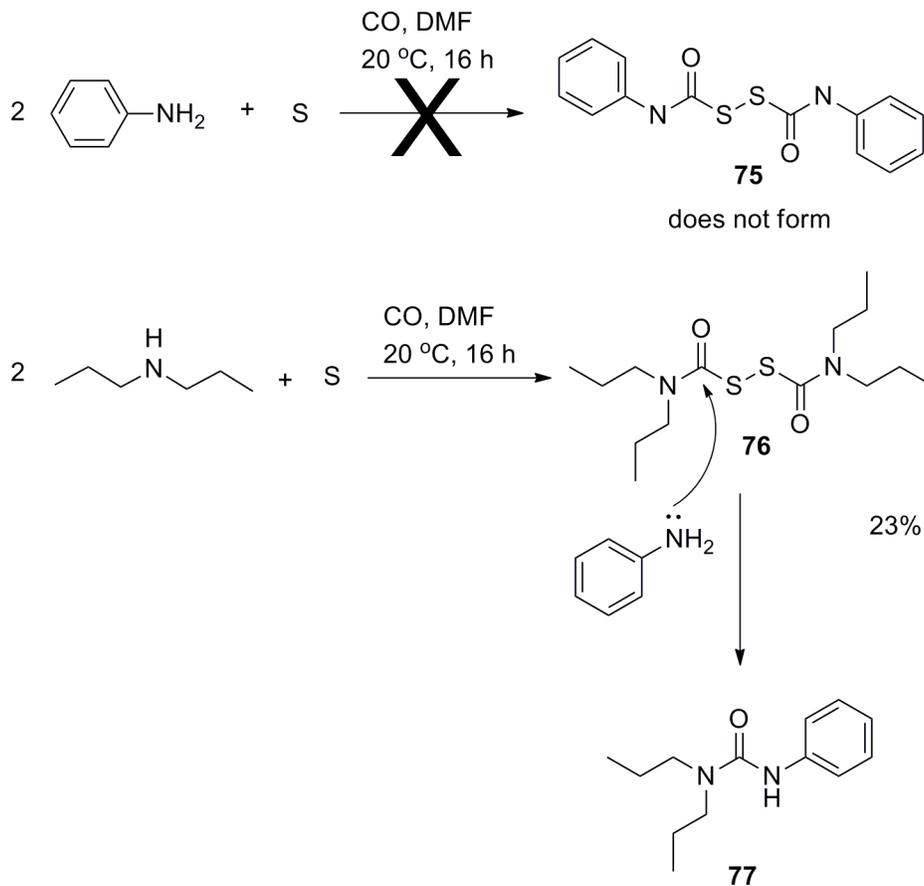


Figure 3-18. Proposed mechanism for unsymmetrical urea formation

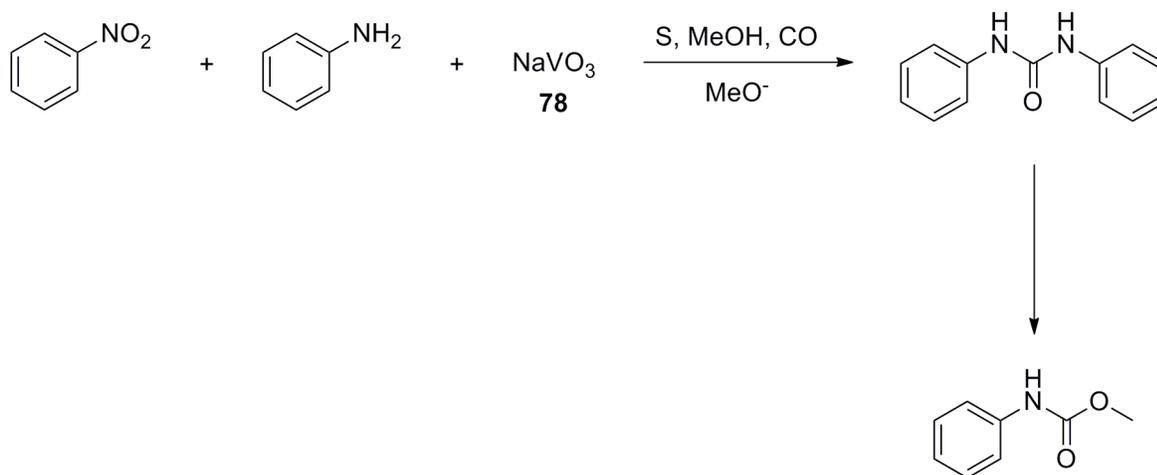


Figure 3-19. Oxidative carbonylation of nitrobenzene with aniline to form methyl-N-phenyl carbamate

dimethylsulfoxide (DMSO), promote urea formation in the sulfur catalyzed carbonylation of amines to ureas,^{110,111} ionic liquids were used as solvents for the sulfur catalyzed carbonylation of aniline/nitroaromatic systems to ureas.

Various solvents were used, but it was found that the ionic liquid, 1-butyl-3-methylimidazolium (BMI) salt (**79**) was superior to the typical polar solvents, tetrahydrofuran (THF), DMSO, or DMF (Figure 3-20). The reaction could almost be run to completion (96%) when a 1.0 : 1.0 nitrobenzene : aniline mixture was reacted with approximately 33 mol% sulfur catalyst under 30 atm CO at 150 °C in BMIImBF₄ for 8 h. Cl⁻, PF₆⁻, and BF₄⁻ were used as counterions and a significant difference was detected. When chloride ion was used in formation of N,N'-diphenyl urea, only 57% urea was obtained, but when BF₄⁻ and PF₆⁻ were used, 75 and 96% yields were formed, respectively. The base was also found to be vital and was optimized at 1 equivalent of triethylamine (96% yield of urea). When no base was added only 10% urea was isolated. When three times less catalyst was used, the yield dropped from 96% to 41%.

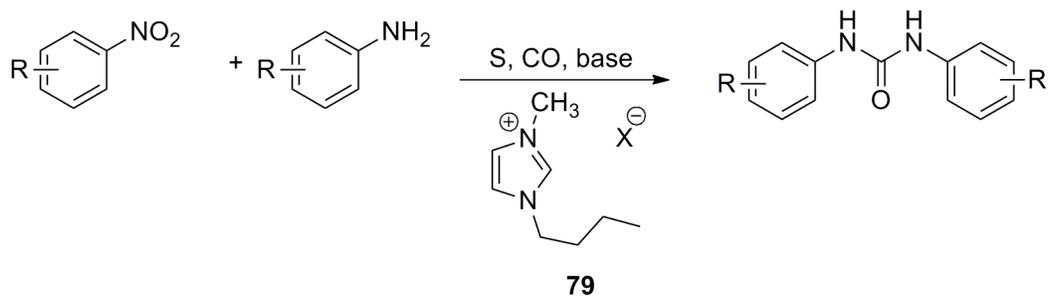


Figure 3-20. Ionic liquid mediated urea formation from nitroaromatic and aniline derivatives

Yields in the range of 74-96% were obtained for a number of substrates where substitutions of electron withdrawing groups (EWG) and electron donating groups (EDG) were employed. Unsymmetrical ureas could be generated since two different starting materials were used to make these ureas. As an example, Figure 3-21 shows the reaction of piperidine and nitrobenzene to form a urea product (**81**) in 70 % yield.

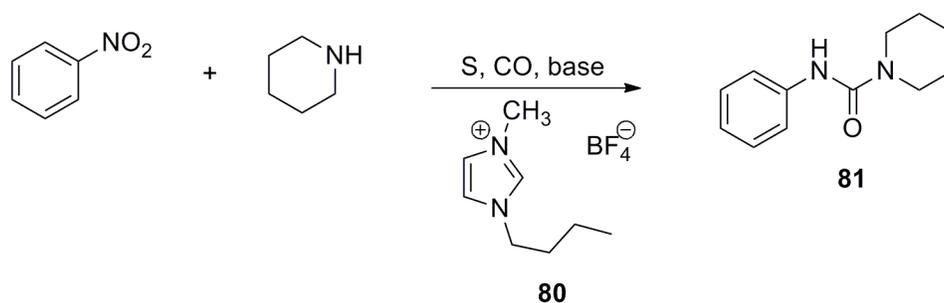


Figure 3-21. Unsymmetrical urea formation in ionic liquid media

Mizuno has proposed a reaction mechanism for the transformation of primary amines to ureas that proceeds through ionic intermediate **82** much like the selenium catalyzed reaction in Figure 3-22.¹⁰⁰ The nucleophilic, anionic sulfur of this salt attacks the electrophilic carbon monoxide, forming salt **83**, which undergoes rearrangement to give the thiocarbamate derivative **84**. Proposed loss of the penultimate sulfur to leave a stabilized anion followed by deprotonations of the ammonium counterion and then of the thiocarbamate N-H bond allows formation of an isocyanate derivative, **85**, and expulsion of H₂S. The toxic H₂S byproduct can be reoxidized with elemental oxygen to reform sulfur and water. Finally, attack with a second equivalent of amine gives the urea product **86**.

The sulfur and selenium catalyzed carbonylations of amines to ureas are methods to generate ureas under mild, transition metal-free conditions. Preliminary research has been conducted and uncovered another such reaction. Herein will be reported these investigations into a hypervalent iodine promoted system.

CHAPTER 4
METAL-FREE CARBONYLATION OF AMINES TO UREAS WITH THE HYPERVALENT
IODINE SPECIES SODIUM PERIODATE

Hypervalent Iodine as an Alternative to Metal Complexes

Iodine reagents are known to accomplish a number of transformations, but less recognized is their similarity to metal catalysts. Though utilizing different mechanistic pathways, iodine species frequently form the same products as heavy metal catalysts. Precious metal catalysts tend to be toxic, air-sensitive, and expensive: undesirable traits for research laboratories. Iodine reagents suffer from none of these problems and can provide useful, environmentally friendly alternatives to metal catalysis.

Hypervalent Iodine as an Alternative to Metal Catalyzed Syn Hydroxylation

Organic reactions often involve metal-catalyzed transformations, such as metal mediated oxidation of alkenes to diols. The mechanism for the formation of diol, **87**, through the reaction of OsO₄ with an alkene (Figure 4-1a) is thoroughly understood. Not as well known is the use of PhI(OH)OTos to produce the bis-tosylated derivative of the diol (**88**) in a similar manner (Figure 4-1b).^{112,113}

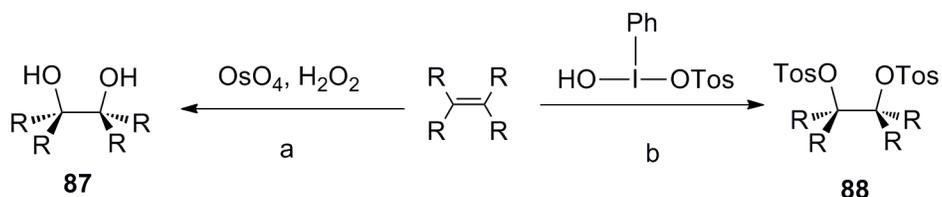


Figure 4-1. Hypervalent iodine alternative to osmium tetroxide for dioxxygenation of alkenes

Hypervalent Iodine as an Alternative to Metal Catalyzed Oxidation of Primary Alcohols to Aldehydes

In a second example, Dess-Martin periodinane (DMP) and 2-iodoxybenzoic acid (IBX) give the same products as the chromium-containing pyridinium chlorochromate (PCC) when used as oxidizing agents. These iodine species oxidize primary alcohols to their corresponding

aldehydes (Figure 4-2b). The chromium counterpart PCC (Figure 4-2a), is much more hazardous than the Dess-Martin analogue.

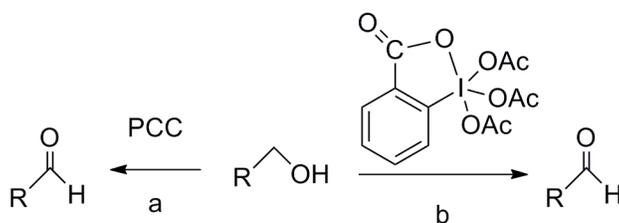


Figure 4-2. Dess-Martin periodinane as hypervalent iodine alternative to metal oxidants

Hypervalent Iodine as an Alternative to Metal Catalyzed Sonogashira Coupling

Hypervalent iodine reagents can also replace metal catalysts for coupling reactions, as observed in the Sonogashira reaction. A palladium-catalyzed reaction between a copper-substituted alkyne and an aryl or alkenyl halide yields the aryl or alkene coupled product **90**, respectively (Figure 4-3a). The hypervalent iodine species, RCCIPh⁺OTs (**89**) provides the same result (Figure 4-3b).¹¹⁴

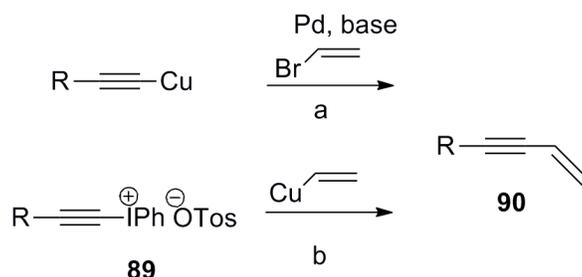


Figure 4-3. Hypervalent iodine alternative to the metal-catalyzed Sonogashira reaction

Hypervalent Iodine as an Alternative to Metal Catalyzed Hydroamination

Hydroamination is an important industrial process that manufactures tons of amine products annually. This field has been reviewed frequently.¹¹⁵⁻¹¹⁷ From these reviews, it is seen that hydroamination is often achieved with a metal catalyst, typically an early transition metal complex. Hydroamination ultimately adds a N-H bond across an alkene leading to the production of a Markovnikov (**91**) or anti-Markovnikov (**92**) product (Figure 4-4a). The

hypervalent iodine reagent phenyliodine(III) bis-trifluoroacetate (PIFA) can promote the hydroamination of alkyne-amide **93** to cyclized product **94** in a similar manner (Figure 4-4b).¹¹⁸

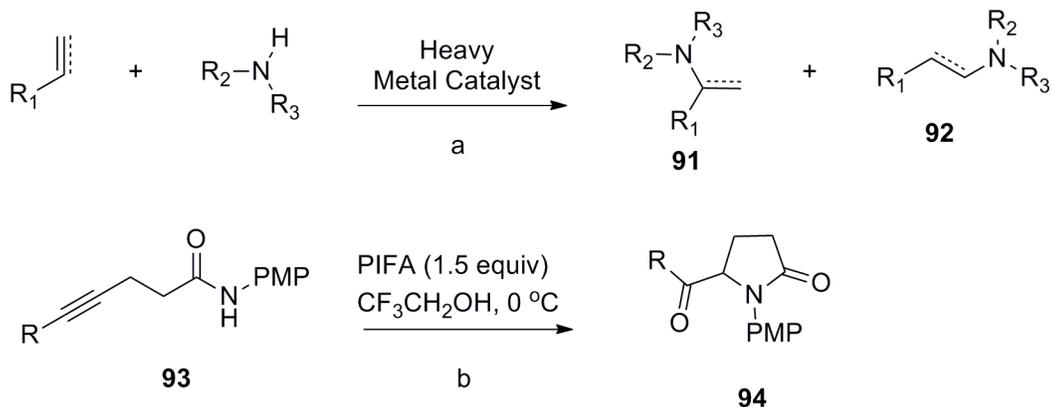


Figure 4-4. Hypervalent iodine alternative to metal-catalyzed hydroamination of alkenes and alkynes

Another example has been noted where a urea derivative (**95**) has also cyclized under similar conditions (Figure 4-5).¹¹⁹ In this reaction **95** reacts with iodosylbenzene in the presence

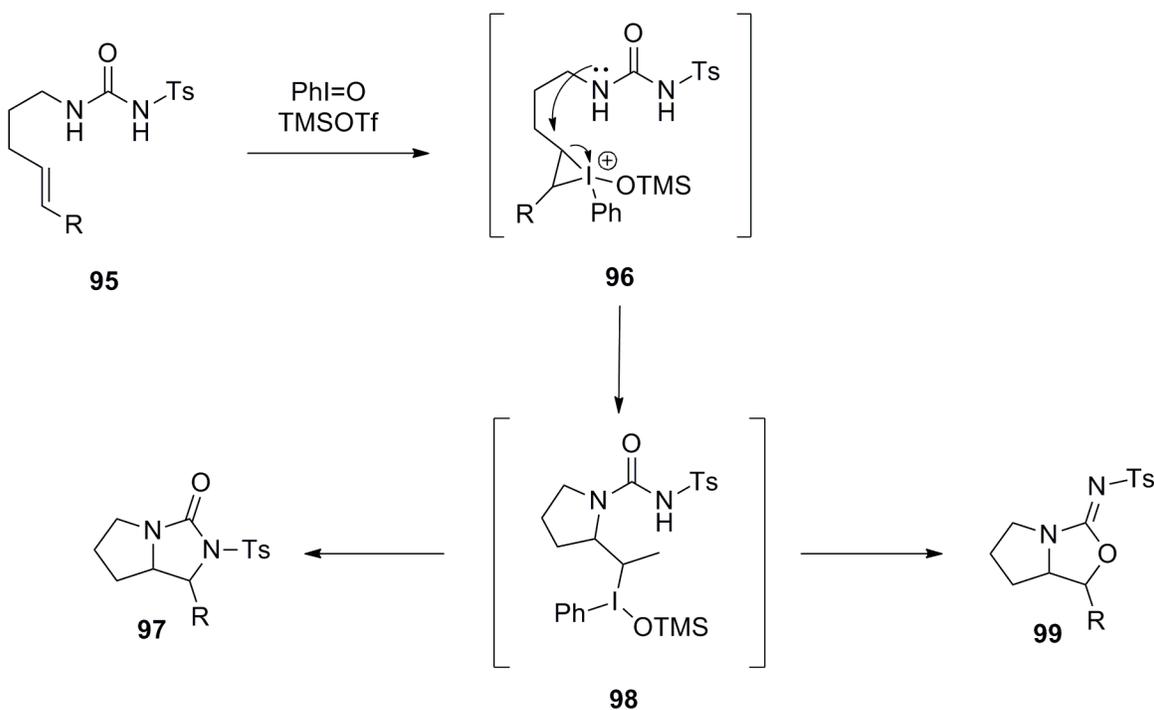


Figure 4-5. Hypervalent iodine promoted hydroamination with a urea moiety

of TMSOTf to form the iodonium salt **96**. Opening of the iodine-containing three-membered ring completes the formal hydroamination step to yield intermediate **98**. Bicyclic urea **97** was the expected product, but isourea **99** was the predominant product unless the weak acids BzOH or AcOH were used in place of TMSOTf.

Hypervalent Iodine as an Alternative to Metal Catalyzed Ring Expansion

Seven membered rings are found in important biologically active compounds including the anti-cancer compound theaflavin and the anti-HIV drugs, TAK-779 and DMP 450 (Figure 4-6). Seven or eight membered rings, however, can often be difficult to synthesize. One possible route is heavy-metal-catalyzed ring expansion from six to seven membered rings. Thallium (III),¹²⁰ Pd (II),¹²¹ and Hg (II)¹²² have been used to carry out such transformations (Figure 4-7a). Alternatively, the hypervalent iodine reagent hydroxy-tosyl iodobenzene (HTIB or Koser's reagent) can be used to carry out a similar reaction (Figure 4-7b).¹¹⁷

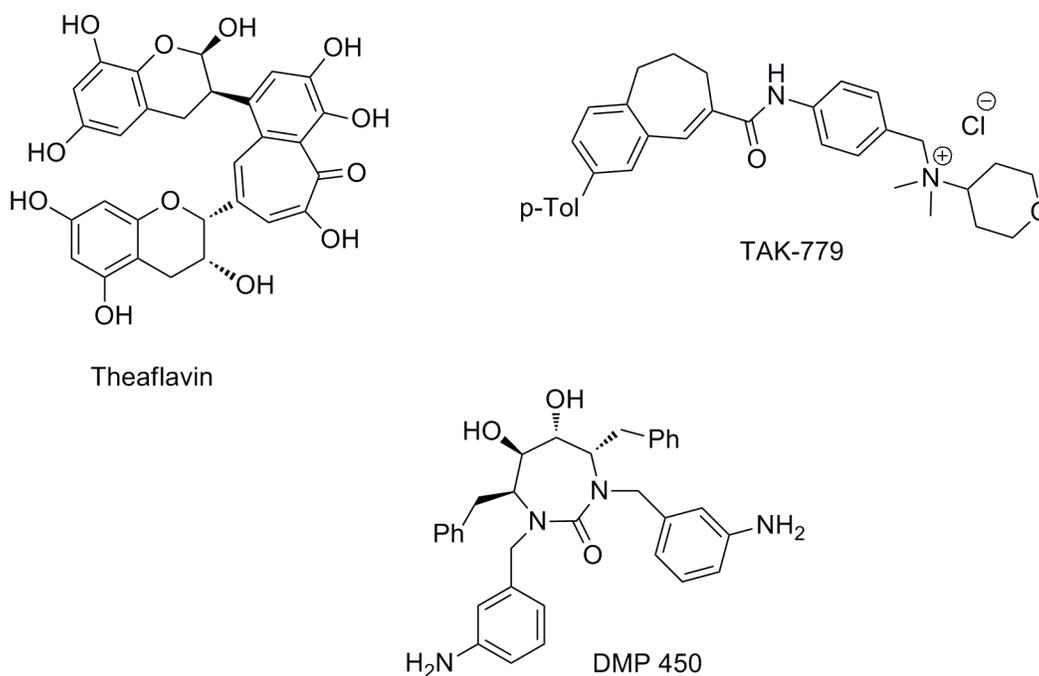


Figure 4-6. Biologically active compounds containing seven membered rings

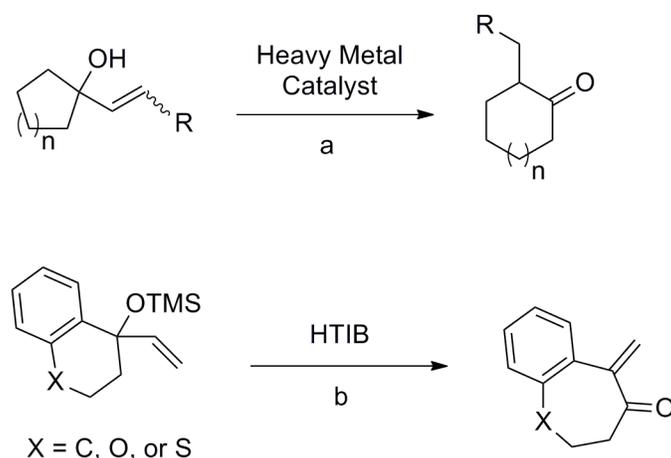


Figure 4-7. Hypervalent iodine alternative to metal-catalyzed ring expansions

Hypervalent Iodine as an Alternative to Metal Catalyzed Suzuki Coupling

Suzuki coupling is a palladium-catalyzed reaction of an aryl halide and an arylboronic acid to form aryl-aryl products (Figure 4-8). As early as 1953 was known that this transformation can also take place through hypervalent iodine catalysis with diaryliodonium salts.¹²³ In this and subsequent articles, a variety of aryl-aryl couplings have been catalyzed by hypervalent iodine reagents some of which are shown in Table 4-1. All reactions, except Entry 6, are proposed to go through radical intermediates generated by the PIFA intermediate. Radical intermediates are proposed to be generated through single electron transfer (SET) and have been observed using Electron Spin Resonance (ESR).¹²⁴

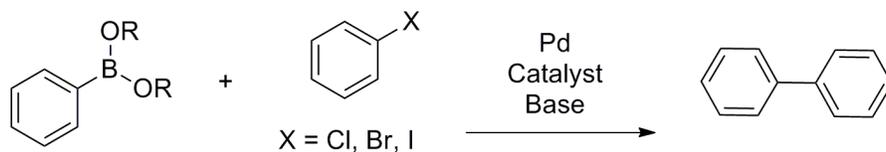
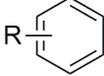
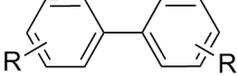
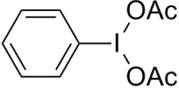
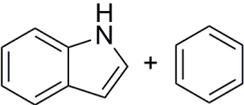
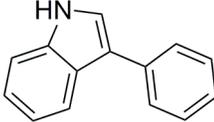
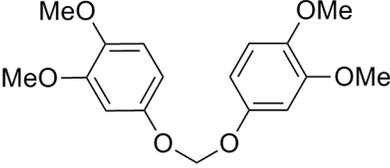
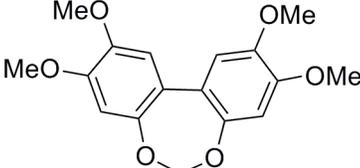
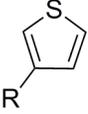
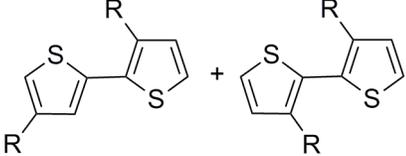
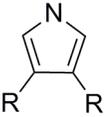
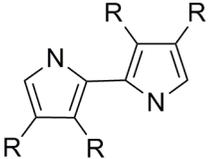
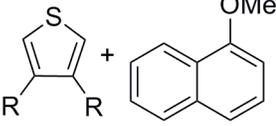
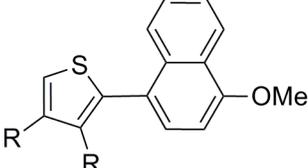


Figure 4-8. Metal catalyzed Suzuki coupling reaction

Application to Urea Synthesis

In a similar hypervalent iodine mediated transformation, ureas can be formed from amines as an alternative to metal catalyzed reactions. This report will discuss advances in hypervalent

Table 4-1. Hypervalent iodine alternative to metal-catalyzed Suzuki coupling

Entry	Iodine Reagent	Arene	Product	Ref
1	RPhI ₂ -or- PIFA			125 124
2				126
3	PIFA			127
4	PIFA			128
5	PIFA			129
6	PhI(OH)OTs			130

iodine chemistry that allow aliphatic and aromatic amines to be transformed into their urea derivatives in excellent yields. Mild, oxidative carbonylation using hypervalent iodine derivatives provides yet another way to prepare important urea moieties.

Results

Initial Findings

In conjunction with previous work on $W(CO)_6$ -catalyzed carbonylation of ureas as methodology for synthesis of complex targets,¹³¹⁻¹³⁴ carbonylation of amines was investigated using various combinations of oxidants, promoters and bases.⁸³ Among the oxidants studied were $NaIO_4$, 30% H_2O_2 , $I_2/FeCl_3$, I_2 , 4-methylmorpholine N-oxide and O_2 . Extensive control experiments established that the $W(CO)_6$ catalyst was necessary to obtain high yields of the urea products, with one exception.¹³⁵ When the oxidant was $NaIO_4$ and iodide ion was present as a promoter, 4-methoxybenzylamine was converted to the corresponding urea (**63**) in excellent yield, whether or not the $W(CO)_6$ catalyst was added to the reaction mixture (Figure 4-9).

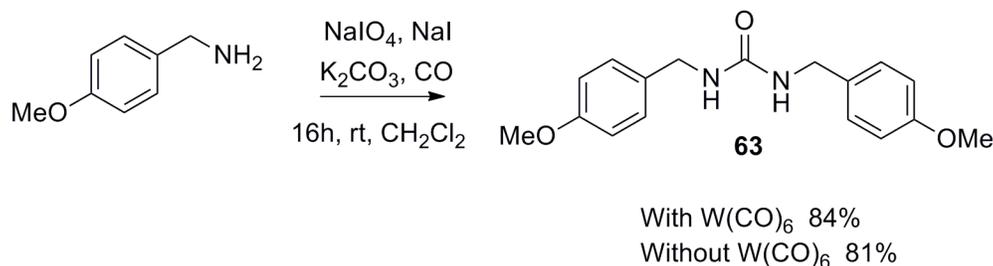


Figure 4-9. Carbonylation of *p*-methoxybenzylamine with and without the $W(CO)_6$ catalyst
The $W(CO)_6$ -catalyzed version of this reaction afforded the urea in only 3% higher yield than the experiments in which no metal carbonyl had been added (84% vs. 81%). Negligible yields of the urea were formed when every other oxidant was reacted in the absence of the metal catalyst. These results led us to carry out experiments designed to learn how this system was operating. Optimization studies were also conducted on the $NaIO_4$ -oxidized carbonylation reaction with the goal of developing conditions that did not require the addition of a metal catalyst.

Control Experiments

Control experiments were performed with 4-methoxybenzylamine as substrate, H₂O/CH₂Cl₂ as solvent and K₂CO₃ as base. Initial experiments addressed the need for the presence of both the NaIO₄ oxidant and the NaI promoter. When NaI was used in the absence of oxidant, no urea was produced under CO pressures of 45 atm. Analogously, an experiment with only NaIO₄ as oxidant but no iodide promoter yielded similar results, confirming that both components must be present in the reaction mixture.

Iron and ruthenium carbonyl are known to carry out carbonylation of amines to ureas.^{136,137} These complexes are present in trace amounts in carbon monoxide cylinders. Control experiments were then designed to investigate the possibility that iron or ruthenium carbonyl present in trace amounts in the carbon monoxide¹³⁸ could be catalyzing this reaction. When authentic Fe(CO)₅ or Ru₃(CO)₁₂ (4.0 x 10⁻⁵ mol, 2 mol%) was added to a reaction of 4-methoxybenzylamine under the standard conditions, the yield of urea was similar to that obtained in the absence of the metal carbonyl complex (68% and 62%, respectively). In efforts to minimize the possibility of contamination of the CO by Fe or Ru carbonyl, the reaction was repeated with CO from an aluminum cylinder.¹³⁸ Fe(CO)₅ is known to be a contaminant in CO from steel cylinders, however the use of aluminum tanks minimizes the content of Fe(CO)₅ in the CO. Under conditions similar to those when the steel cylinder was used (81% yield of urea) but with CO from the aluminum cylinder, 80% yield of bis(4-methoxy)benzylurea was obtained. Together, these control experiments lead us to believe that catalysis by adventitious metal carbonyls is unlikely.

In an additional reaction, I₂ was used as cooxidant/iodide source in place of the NaI. This reaction did yield complete conversion of the starting material but afforded a 1:1.7 ratio of urea to formamide (Figure 4-10). When the solvent is CH₂Cl₂ without the addition of water as a

cosolvent, only trace amounts of the urea can be detected in the ^1H NMR spectra. Failure of the reaction under these conditions is probably due to insolubility of the NaIO_4 and NaI salts in the organic solvent. These experiments have established that NaIO_4 , base and a source of iodide are required to carry out metal-free urea synthesis under these conditions.

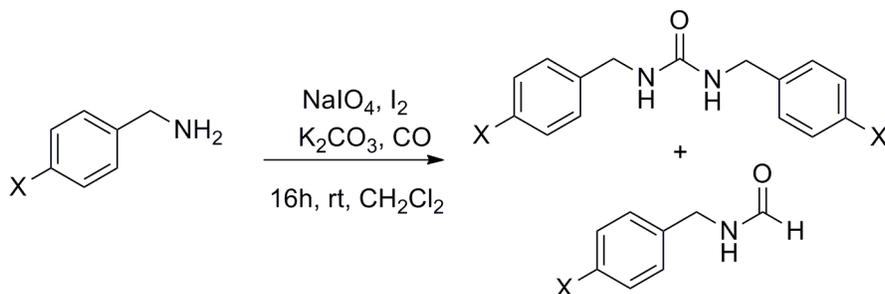


Figure 4-10. Urea and formamide products when I_2 was used as promoter

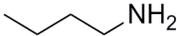
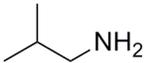
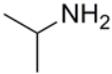
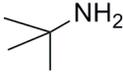
Scope of the Reaction

With the conditions from the initial findings, reactions were conducted to determine the scope of this transformation. Simple amines could be converted to the urea in a 15 mL H_2O / 15 mL CH_2Cl_2 biphasic solvent system with 0.8 equiv NaIO_4 / 0.5 equiv NaI oxidant mixture. These results are found in Table 4-2. Yields indicate that with these conditions, simple amines can be converted to the corresponding ureas in excellent yields (Entries 1 and 2). When steric bulk increases on the amine, however, reaction yields suffer (Entries 3 and 4).

Although sodium metaperiodate is a strong oxidant, functional group tolerance of this reaction is moderate. To examine this, a variety of functionalized benzylamines were reacted under the metal-free conditions to yield urea products. Results for this series can be seen in Table 4-3.

Results show moderate functional group tolerance for this reaction, but the presence of

Table 4-2. Hypervalent iodine mediated carbonylation of simple amines to ureas

Entry	Amine	% Yield ^{a,b}
1		86
2		84
3		38
4		33

^aIsolated yield per equivalent of amine.

^bConditions: 2.0 mmol amine, 1.0 mmol NaI, 3.0 mmol K₂CO₃, 15 mL H₂O/15 mL CH₂Cl₂, room temperature, 45 atm CO, 16 h.

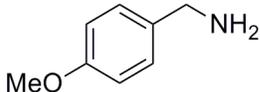
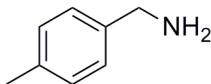
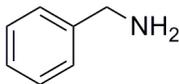
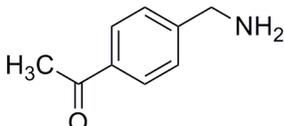
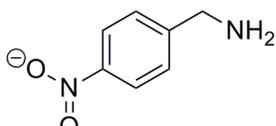
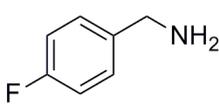
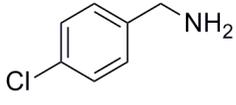
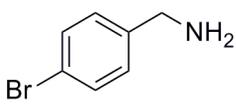
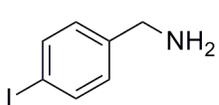
electron withdrawing groups in the para position of the benzylamine result in decreased yields (Entries 4-9). Placement of halogens in the para position indicate the trend in electron withdrawing power versus reactivity. Fluorine, the most electron withdrawing halogen, is the least reactive of the halogen derivatives. Reactivity increases to the least electron withdrawing iodine derivative. This observation coupled with electron withdrawing ester and nitro substituents yielding only 10 and 1% of the urea, respectively, supports the finding that electron withdrawing groups hinder urea production. The only detectable products were urea derivatives indicating that this reaction is tolerant of ester, nitro, halogen, aromatic, and ether functional groups.

Optimization

Optimization studies were conducted with 4-methoxybenzylamine as substrate beginning with the conditions optimized for the initial finding of this reaction. These conditions consisted of 1 equiv. starting amine, 1.5 equiv K₂CO₃ base, 0.8 equiv NaIO₄ oxidant and 0.5 equiv NaI promoter under 90 atm CO pressure in a 15 mL H₂O / 15 mL CH₂Cl₂ biphasic system for 16

h at 90 °C. Conditions were then optimized for CO pressure, equivalents of base, identity of base, equivalents of oxidant, equivalents of promoter, solvent, reaction time, and reaction temperature.

Table 4-3. Hypervalent iodine mediated carbonylation of benzylamines

Entry	Amine	% Yield ^{a,b}
1		82
2		61
3		46
4		10
5		1
6		0
7		7
8		21
9		27

^aIsolated yield per equivalent of amine.

^bConditions: 2.0 mmol amine, 1.0 mmol NaI, 3.0 mmol K₂CO₃, 15 mL H₂O/15 mL CH₂Cl₂, room temperature, 45 atm CO, 16 h.

CO pressure

Optimization of this system was carried out at a much lower pressure, 45 atm, than that originally used, 90 atm, and it was found that the yield was greatly increased (Table 4-4). By decreasing the pressure by half (90 atm to 45 atm) we were able to increase the yield by 24% (Entries 3 and 5). This proved to be the optimal pressure giving 81% yield of urea. An

Table 4-4. Optimization of CO pressure

Entry	CO Pressure (atm)	Yield (%)
1	1	2
2	20	27
3	45	81
4	60	68
5	90	57

interesting result was observed when 1 atm of pressure was used. Only trace amounts of bis-4-methoxybenzylurea were isolated and the major product, 40%, was the unsaturated nitrile **100**

(Figure 4-11). A similar transformation has been observed by Nicolaou when using the

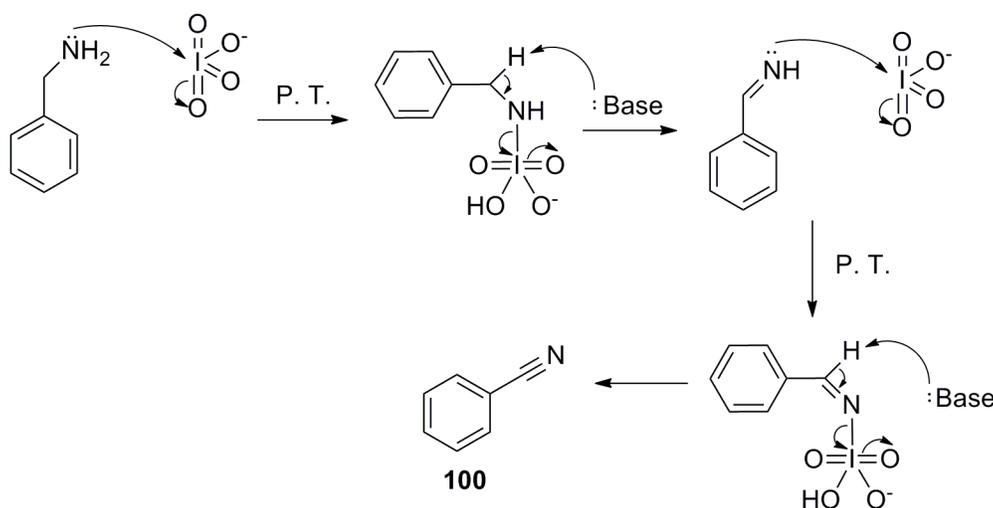


Figure 4-11. Proposed mechanism for nitrile formation with sodium periodate

hypervalent iodine reagent, Dess-Martin periodinane (DMP).¹³⁹ As each condition was optimized, the next series of reactions employed the new optimized conditions. For example, each experiment discussed heretofore will use 45 atm CO pressure.

Identity of base

Many reactions are dependent on the strength and solubility of the base used. Therefore, several and water soluble bases with a range of pK_b 's were tested for this reaction. NaHCO_3 , K_2CO_3 , pyridine, dimethylaminopyridine (DMAP), and 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) were used. DMAP proved to be the best of the bases for this reaction as shown in Table 4-5. DMAP is a strong base and an increase in reaction efficiency is expected, but surprisingly the more basic DBU gave a lower yield (Entries 5 and 6).

Table 4-5. Optimization of identity of base

Entry	Base	Yield (%)
1	NaHCO_3	49
2	K_2CO_3	55
3	Pyridine	27
4	DMAP	76
5	DBU	10

Equivalents of base

The initial conditions for this reaction used 1.5 equivalents of DMAP. Variation of the equivalents of the base indicated that lower or higher quantity led to decreased reactivity (Table 4-6).

Table 4-6. Optimization of equivalents of base

Entry	DMAP (equiv)	Yield (%)
1	1.0	65
2	1.5	76
3	2.0	62
4	3.0	55

Equivalents of oxidant

Optimization of this reaction for the identity of the oxidant led to the discovery that hypervalent iodine reagents can catalyze the formation of ureas from their corresponding amine starting materials (vide supra).¹³⁵ The quantity of oxidant was next optimized. Analogous to reactions catalyzed by $W(CO)_6$, it was determined that 0.8 equivalents of $NaIO_4$ oxidant are also the optimized conditions for the metal-free carbonylations (Table 4-7).

Table 4-7. Optimization of equivalents of oxidant

Entry	Oxidant (equiv)	Yield (%)
1	0.5	40
2	0.8	76
3	1.0	71
4	1.5	74

Equivalents of promoter

The identity of promoter was not optimized, but it should be noted that earlier observations indicate that I_2 also promotes this reaction. However, the formamide derivative was afforded as a key side product in this reaction when I_2 was utilized as a promoter. The result of this optimization indicate that the equiv of promoter are the same for the $W(CO)_6$ -catalyzed reaction and the metal-free conditions (Table 4-8, Entry 2).

Table 4-8. Optimization of equivalents of promoter

Entry	Equivalents of promoter	Yield (%)
1	0.25	48
2	0.5	76
3	0.8	62
4	1.0	53

Solvent

Initial experiments utilized a biphasic 15 mL H_2O /15 mL CH_2Cl_2 solvent mixture. Several different organic solvents were then tested in a 50/50 mixture by volume with 15 mL H_2O .

Results are displayed in Table 4-9 and show that halogen-containing solvents are best for this reaction. This is probably due to solubility of the reagents in these solvents. Reactions in nonpolar solvents did not afford any bis-4-methoxybenzyl urea product. Surprisingly, dimethylformamide only yielded 1 % urea product even though it is a common solvent for many hypervalent iodine reactions.

Table 4-9. Optimization of solvent choice

Entry	Solvent	Yield (%)
1	Dichloromethane	76
2	THF	2
3	1,2-Dichloroethane	62
4	Hexane	0
5	Dimethylformamide	1

Reaction time

Previous $W(CO)_6$ catalyzed carbonylations were reacted for 16 h periods. However, 8 h afforded the maximum yield (Table 4-10, Entry 4) for the metal-free analogue. Unfortunately the reaction could not be sampled at different time intervals during the carbonylation reaction because the experiment is conducted at high pressures and there is no access point into the autoclave. Release of the pressure would interrupt the reaction. Seven different reactions were carried out (Table 4-10). At higher reaction times, the yield begins to fall off. This is probably due to decomposition of product.

Table 4-10. Optimization of reaction time

Entry	Time (h)	Yield (%)
1	1	30
2	4	62
3	8	81
4	12	70
5	16	76
6	24	71
7	48	60

Reaction temperature

A final condition that was optimized was reaction temperature. Yields for reactions at 0 °C, 25 °C, and 40 °C were 10%, 81% and 46 %, respectively. The reaction did not generate high yields at 0 °C, most likely due to the freezing of the water solvent. However, the reaction also freezes at 10 °C due to the high pressures employed. The optimized condition has been shown to be room temperature.

Simple Alkyl Amines

Several primary amines have been subjected to the NaIO₄/NaI carbonylation conditions (Table 4-11). Unhindered alkylamines form the urea readily under these conditions (Entries 1 and 2). Sterically hindered *t*-butylamine gives low yields (Entry 4), but moderately hindered isopropyl amine still gives excellent results (Entry 3).

Aromatic Amines

Various 4-substituted benzylamines were subjected to the optimized reaction conditions (Figure 4-12). Again, excellent yields were obtained when optimized conditions were used

Table 4-11. Carbonylation of amines with NaIO₄/NaI

Entry	RNH ₂ R =	% Yield ^{a,b} (NaIO ₄ /NaI)
1	<i>n</i> -Bu	94
2	<i>i</i> -Bu	96
3	<i>i</i> -Pr	91
4	<i>t</i> -Bu	20

^aIsolated yield per equivalent of amine.

^bConditions: 2.0 mmol amine, 1.0 mmol NaI, 1.6 mmol NaIO₄, 3.0 mmol DMAP, 15 mL H₂O/15 mL CH₂Cl₂, room temperature, 45 atm CO, 8 h.

(Table 4-12). Little substituent effect was observed except that more electronegative halide derivatives give slightly lower yields (Entries 6-9). Interestingly, when a weaker base, K_2CO_3 , was used proton acidities do become relevant (Table 4-3).

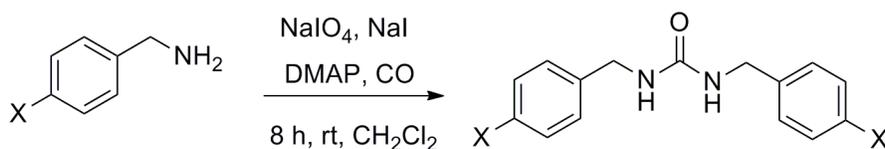


Figure 4-12. Reaction of 4-substituted benzylamines to ureas

Table 4-12. Carbonylation of 4-substituted benzylamines

Entry	X	% Yield ^{a,b}
1	-OMe	81
2	-CH ₃	78
3	-H	88
4	-COOMe	85 ^d
5	-NO ₂	79 ^d
6	-I	87 ^d
7	-Br	78
8	-Cl	72
9	-F	72

^aIsolated yield per equivalent of amine.

^bConditions: 2.0 mmol amine, 1.0 mmol NaI, 1.6 mmol NaIO₄, 3.0 mmol DMAP, 15 mL H₂O/15 mL CH₂Cl₂, room temperature, 45 atm CO, 8 h.

^dOne extra equiv of base was added since the amine was added as the HCl salt.

In an effort to extend these results, aniline was also subjected to metal-free carbonylation conditions, but oxidation occurred in preference to carbonylation, yielding benzoquinone (**101**) as the major product (Figure 4-13). This result is consistent with similar observations by Srivastava et al.¹⁴⁰ during studies on oxidation of aromatic amines using periodate.

Secondary Amines to Tetrasubstituted Ureas

One difficulty for many metal-catalyzed and non-metal-catalyzed conversions of amines to ureas is conversion of secondary amines to tetrasubstituted ureas. Many of these reactions are

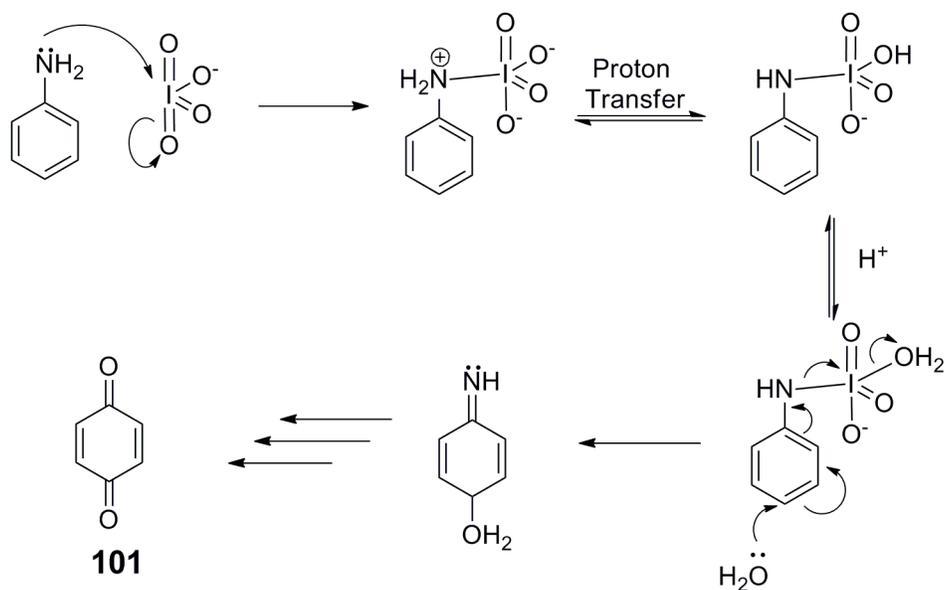


Figure 4-13. Formation of benzoquinone from aniline and sodium periodate¹⁴⁰

postulated to involve isocyanate intermediates that cannot be formed when secondary amines are used.⁷² Experiments were then designed to test the scope of this hypervalent iodine promoted system on reactions with secondary amines. Unfortunately, negligible to poor yields resulted when the optimized conditions were applied to secondary amines (Table 4-13). Of these amines, piperidine yielded the best results at 10.7% yield of urea under the conditions optimized for primary amines (1.5 equiv DMAP, 0.8 equiv NaIO₄, 0.5 equiv NaI 45 atm CO pressure for 8 h at room temperature).

Table 4-13. Hypervalent iodine-mediated carbonylation of secondary amines to ureas

Entry	Amine	Yield of urea (%)
1	N,N-diethylamine	0
2	N,N-dibutylamine	0
3	N,N-dibenzylamine	9
4	N-benzyl,N-methylamine	9
5	piperidine	11
6	N,N-diisopropylamine	0
7	pyrrolidine	0

As an optimization study for secondary amines, time, temperature, and CO pressure were increased one at a time while holding the others constant for carbonylation with piperidine.

Table 4-14 shows the results of these tests. Changing the temperature from room temperature to 45 °C yielded a 5% higher yield (Entry 1), whereas increasing the CO pressure from 45 to 80 atm gave over a two fold increase (Entry 2). Despite these changes, yields were still low.

Table 4-14. Optimization of reaction conditions for hypervalent iodine mediated carbonylation of secondary amines to tetrasubstituted ureas

Entry	Condition Changed	% Isolated Yield
1	45 °C	16
2	80 atm CO	24
3	24 h	7

Reoxidation of Catalytic Iodide Species

It has been shown that in some systems hypervalent iodine can be used in catalytic amounts when a secondary oxidant is added. The hypervalent iodine source will be reduced in most reactions (Figure 4-14). Therefore, a secondary oxidant can be used to reoxidize the iodine species to establish a catalytic cycle. Successful, secondary oxidants used in this manner include

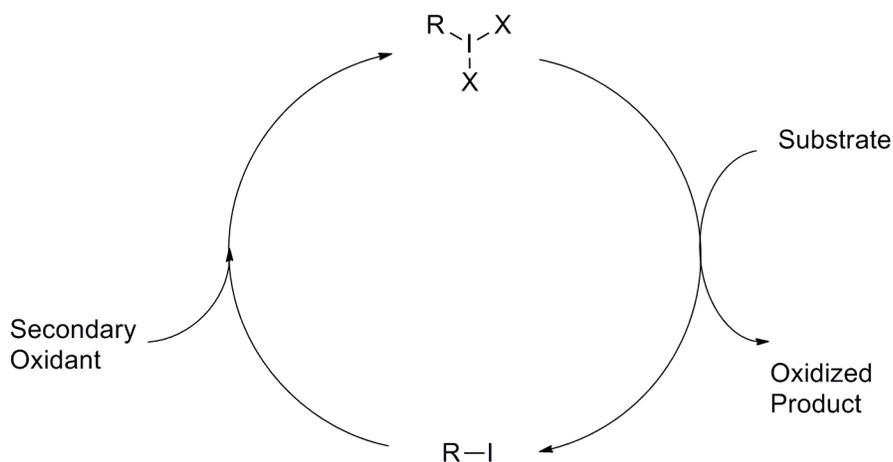


Figure 4-14. Catalytic cycle for reoxidation of hypervalent iodine species

m-chloroperoxybenzoic acid (*m*-CPBA),¹⁴¹ oxygen,¹⁴² and oxone.^{143,144}

Biphasic systems also favor a catalytic system since this typically allows separation of the oxidant from the substrate: i. e., this will ensure that the secondary oxidant does not react with the starting material. Since *m*-CPBA has been successful as a secondary oxidant in the literature, it was chosen to stoichiometrically reoxidize sodium metaperiodate in the carbonylation of amines to ureas. Optimized conditions were used (*vide supra*) but with 10 mol% of NaIO₄ and 1.5 equiv *m*-CPBA (Table 4-15). Without optimization of the reaction conditions this system is unacceptable for establishment of a catalytic cycle. A maximum yield of 17% was afforded when NaIO₄ and NaI were used in 10 mol% each and no further experiments were carried out.

Table 4-15. Attempts at iodine catalysis with secondary oxidant for carbonylation of *p*-methoxybenzylamine

Entry	Iodine source ^a	Yield of urea (%)
1	None	0
2	NaI	5
3	NaIO ₃	9
4	NaIO ₄	12
5	NaIO ₄ /NaI ^b	17

^a10 mol% iodine source.

^b10 mol% of both iodine and NaI components.

Summary

In conclusion, conversion of amines to ureas using mild and atom economical conditions has been realized in the absence of a transition metal catalyst. These transformations take place at room temperature under CO pressures as low as 20 atm. The strength and amount of base, the equivalents of oxidant and promoter, the solvent choice, reaction time, and reaction temperature all directly influence the formation of urea. High yields of urea have been obtained for unhindered primary alkyl amines and benzylamines. The reaction is sensitive to steric hindrance in the alkyl substituent, as evidenced by lower yields from *t*-butylamine. The mechanism of this

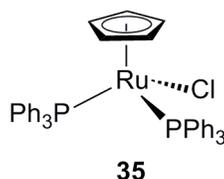
reaction is still under study but preliminary results suggest that a hypervalent iodine species could be responsible for the reactivity. Further research on this reaction is underway.

CHAPTER 5 EXPERIMENTAL

Instrumental Parameters

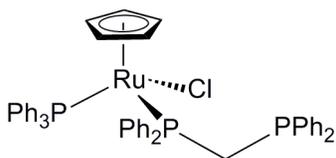
^1H and ^{13}C NMR spectra were obtained on Varian Gemini 300 and VXR 300 and Mercury 300 spectrometers. Infrared spectra were measured on a Perkin-Elmer Spectra One FTIR. Mass spectrometry was performed by the University of Florida analytical service. All chemicals were purchased from Sigma-Aldrich Chemical company except for metal containing reagents (Strem) in reagent grade and used with no further purification unless stated otherwise. High pressure reactions were conducted within the hood in a 300 mL glass liner placed in a Parr autoclave behind a blast shield. Carbon monoxide gas was purchased from Air Gas and Praxair, Inc.

Synthesis of Bimetallic Catalysts



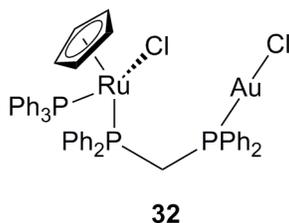
CpRu(PPh₃)₂Cl (**35**)

RuCl₃•H₂O (2.00 g, 19.3 mmol) was added to a 500 mL Schlenk flask filled with 400 mL dry ethanol. CpH (4 equiv, 5.01 g, 77.2 mmol) and 4 equiv (20.2 g, 77.2 mmol) PPh₃ were added and the solution was allowed to reflux for two days. The solvent was evaporated and subsequent recrystallizations (hexane/dichloromethane) were conducted until the solution was no longer orange. Product **35** was obtained in 62% yield and was identified by comparison to literature values.¹⁴⁵ ^{31}P NMR (CDCl₃) δ 39.51 (s).



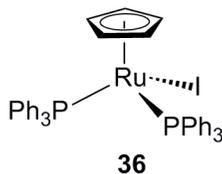
CpRu(PPh₃)(κ¹-dppm)Cl

CpRu(PPh₃)₂Cl (**35**) (2.00 g, 2.75 mmol) was further reacted with 1.1 equiv dppm (1.16 g, 3.03 mmol) in THF at room temperature for 4.5 weeks. An orange powder was recrystallized from hexane/dichloromethane until pure product was obtained. The product was afforded in 43% yield and was identified by comparison to literature values.⁴⁹ ³¹P NMR (CDCl₃) δ 40.39 (d), 38.10 (dd), -28.10 (d).



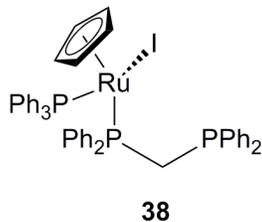
CpRu(PPh₃)Cl(μ-dppm)AuCl (32**)**

CpRu(PPh₃)(κ¹-dppm)Cl (0.500 g, 0.585 mmol) was reacted with 1 equiv AuI (0.189, 0.585 mmol) in 50 mL CH₂Cl₂ at room temperature to yield 90% **32**. The product was identified by comparison to literature values.⁴⁹ ³¹P NMR (CDCl₃) δ 44.34 (d), 36.90 (dd), -21.32 (d).



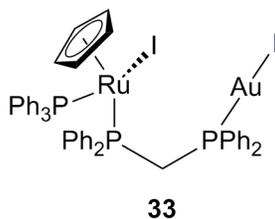
CpRu(PPh₃)₂I (36**)**

A pressure vessel was charged with **35** (2.00 g, 2.75 mmol) and 10 equiv NaI (4.12 g, 27.5 mmol) and left to react for 2 days in 250 mL CH₂Cl₂ at 90 °C. The reddish-orange powder **36** was recrystallized from hexane/dichloromethane in 97% yield and was identified by comparison to literature values.¹⁴⁵ ³¹P NMR (CDCl₃) δ 37.59 (s).



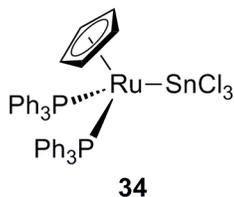
CpRu(PPh₃)(κ¹-dppm)I (38)

Intermediate **36** (2.00 g, 2.45 mmol) was further reacted with 1.1 equiv dppm (1.04 g, 2.70 mmol) in THF at room temperature for 4.5 weeks. An orange powder was recrystallized from hexane/dichloromethane until pure **38** was obtained in 68% yield. The solid was identified by comparison to literature data. ¹⁴⁶ ³¹P NMR (CDCl₃) δ 42.57 (d) 33.41 (dd), -26.88 (d).



CpRu(PPh₃)I(μ-dppm)AuI (33)

Complex **38** (0.500 g, 0.532 mmol) was reacted with 1 equiv AuI (0.172 g, 0.532 mmol) in 50 mL CH₂Cl₂ at room temperature to yield 91% **33**. The solid was identified by comparison to literature data. ¹⁴⁶ ³¹P NMR (CDCl₃) δ 41.6 (d), 31.4 (dd) 27.9 (d).

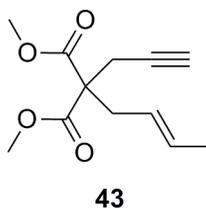


CpRu(PPh₃)₂SnCl₃ (34)

RuCl₃·H₂O (1.00 g, 4.28 mmol) was added to a 500 mL round bottom flask, charged with PPh₃ (4.00 g, 15.3 mol), and allowed to sit under vacuum for 20 min. The powder was then dissolved in 250 mL of dry ethanol and refluxed overnight. The solution turned from black to

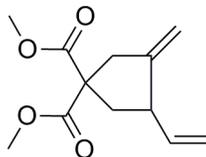
brownish-orange and upon cooling to 0 °C for 10 min., orange crystals of RuCl₂(PPh₃)₃ formed. HCp (4ml) was added to the RuCl₂(PPh₃)₃ crystals in 250 ml dry ethanol and the solution was again refluxed overnight. The resulting suspension was filtered and washed with a small volume of first ethanol, then hexanes, and were finally dissolved in 100 mL dichloromethane. SnCl₂ (0.812 g, 4.28 mmol) was then added and the solution was refluxed overnight. The resulting mixture was filtered through diatomaceous earth, and the solution was evaporated under reduced pressure to yield an orange yellow product in 68% yield. The solid was identified by comparison to literature data.¹⁴⁷ ³¹P NMR (CDCl₃) δ 45.4 ¹H NMR (CDCl₃) δ 7.35-7.10 (m, 30H), 4.56 (s, 5H).

Synthesis of Enyne Starting Materials



(E)-Dimethyl 2-(but-2-enyl)-2-(prop-2-ynyl)malonate (43)

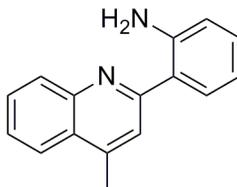
Alkyne **41** ((MeO₂C)₂CHCH₂C≡CH) (0.200 g, 1.17 mmol) was added to a 50.0 mL round bottom flask containing a stirred solution of cesium carbonate (0.570 mg, 1.75 mmol) and crotyl bromide **42** (0.120 mL, 1.17 mmol) in 3.00 mL acetone. The resulting solution was stirred at reflux for 12 h. After reflux the solution was diluted with 5.00 mL diethyl ether, filtered, and the solid was washed with two 5 mL portions of diethyl ether. Flash chromatography (6 : 1 petroleum ether : diethyl ether) yielded 75 % of the pure white crystals. The solid was identified by comparison to literature values.¹⁴⁸ ¹H NMR (CDCl₃) δ 5.61 (m, 1H), 5.21 (m, 1H), 3.73 (s, 6H), 2.78 (m, 4H), 2.01 (t, 1H), 1.67 (d, 3H).



Dimethyl 3-methylene-4-vinylcyclopentane-1,1-dicarboxylate

Malonate **43** (0.0560 g, 0.250 mmol) was reacted with $\text{CpRu}(\text{N}\equiv\text{CCH}_3)_3$ (0.011 g, 0.0250 mmol) at 70 °C for 3 h in 1.20 mL methylene chloride. Solvent was removed under reduced pressure and the resulting solid was extracted into hexane yielding **43** in 52% NMR yield. After removal of hexane solvent the product was identified by comparison to literature values.¹⁴⁹ ^1H NMR (CDCl_3) δ 5.62 (m, 1H) 4.90-5.15 (m, 3H), 4.82 (m, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 3.08-3.21 (m, 2H), 2.95 (d 1H), 2.57 (dd, 1H), 2.01 (m, 1 H).

General Procedure for Conversion of 2-Ethynylaniline to 2-(4-Methylquinolin-2-yl)Aniline (**52**)



52

The catalyst (**32** or **33**, 1 mol%) was placed in a 50.0 mL Schlenk and allowed to sit under vacuum for 20 minutes. CH_2Cl_2 solvent (5.00 mL) was then added followed by 5.00 mmol of 2-ethynylaniline and the solution was allowed to stir for 1 day at 70-90 °C. A reflux condenser was used for solvents with boiling points under 70 °C. The reaction mixture was extracted with hexane and the solvent was removed by evaporation. Yields were obtained by GC or NMR unless the pure quinoline was isolated after 10 % ethylacetate/hexane column chromatography.

General Procedure for Carbonylation of Amines to Ureas

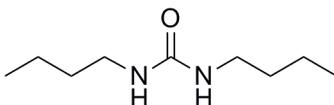
Procedure A

To a 300 mL glass liner in a 300 mL Parr high pressure vessel were added 4-methoxybenzylamine (0.260 mL, 2.00 mmol), K_2CO_3 (0.414 g, 3.00 mmol), NaI (0.150 g, 1.00 mmol), $NaIO_4$ (0.342 g, 1.60 mmol) and 15.0 mL of CH_2Cl_2 /15.0 mL of H_2O . The vessel was then charged with 45 atm of CO and left to stir at room temperature for 16 h. The pressure was released and the aqueous layer was separated from the CH_2Cl_2 solution, and extracted twice with a 3 : 1 mixture of $CHCl_3$ /EtOH. The combined organic layers were removed under reduced pressure. The solid was redissolved in CH_2Cl_2 and washed with 20 mL of 1 M HCl. Removal of the organic solvent afforded an off-white solid which was recrystallized from CH_2Cl_2 to provide 1,3-bis(4-methoxybenzyl)urea in 81% yield. The solid was identified by comparison with literature data.¹⁵⁰

Procedure B

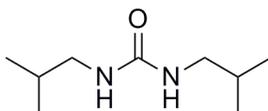
Identical to procedure A except 4-dimethylaminopyridine (0.367 g, 3.00 mmol) was used as base and the reaction time was 8 h.

Carbonylation Products



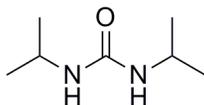
1,3-Dibutylurea

The product was obtained in 86% yield by procedure A and in 94% yield by procedure B. The solid was identified by comparison with literature data.¹⁵¹ 1H NMR ($CDCl_3$) δ 5.24 (br s, 2H) 3.15 (t, 4H), 1.45 (m, 4H), 1.35 (m, 4H), 0.90 (t, 6H).



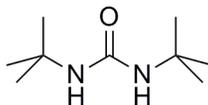
1,3-Diisobutylurea

The product was obtained in 84% yield by procedure A and in 96% yield by procedure B. The solid was identified by comparison with literature data.¹⁵¹ ¹H NMR (CDCl₃) δ 5.67 (br s, 2H) 2.97 (d, 4H), 1.73 (m, 2H), 0.87 (d, 12H).



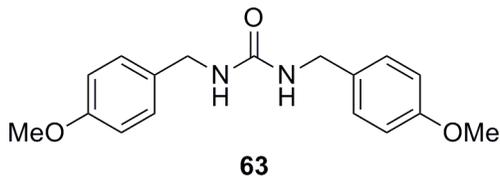
1,3-Diisopropylurea

The product was obtained in 38% yield by procedure A and in 91% yield by procedure B. The solid was identified by comparison with literature data.¹⁵² ¹H NMR (CDCl₃) δ 4.15 (m, 2H) 1.32 (d, 12H).



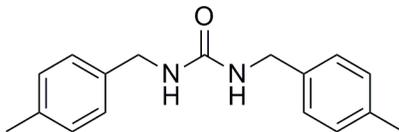
1,3-Di-tert-butylurea

The product was obtained in 33% yield by procedure A and in 20% yield by procedure B. The solid was identified by comparison with literature data.¹⁰⁰ ¹H NMR (CDCl₃) δ 5.70 (br s, 2H), 1.46 (s, 18H).



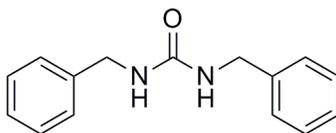
1,3-Bis(4-methoxybenzyl)urea (63)

Procedure A and B both afforded the product in 81% yield. The solid was identified by comparison with literature data.¹⁵⁰ ¹H NMR (DMSO) δ 7.89 (d, 4H), 7.37 (d, 4H), 6.65 (t, 2H), 4.30 (d, 4H), 3.73 (s, 6H) ¹³C NMR (DMSO) δ 166.77, 158.68, 147.39, 128.56, 127.71, 52.69, 43.45.



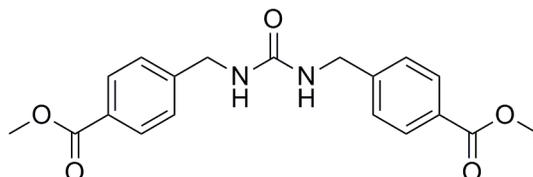
1,3-Bis(4-methylbenzyl)urea

The product was obtained in 61% yield by procedure A and in 78% yield by procedure B. The solid was identified by comparison with literature data. 151 ^1H NMR (CDCl_3) δ 7.12 (q, 8H) 4.50 (br t, 2H), 4.32 (d, 4H), 2.33 (s, 6H).



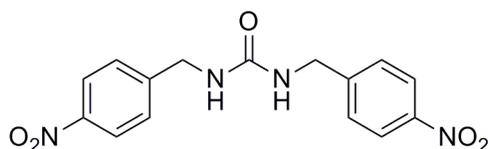
1,3-Dibenzylurea

The product was obtained in 46% yield by procedure A and in 34% yield by procedure B. The solid was identified by comparison with literature data. 151 ^1H NMR (CDCl_3) δ 7.27 (m, 10H) 4.64 (br t, 2H), 4.35 (d, 4H).



Dimethyl 4,4'-(carbonylbis(azanediyl)bis(methylene))dibenzoate

The product was obtained in 10% yield by procedure A and in 85% yield by procedure B. ^1H NMR ($\text{DMSO}-d_6$) δ 7.86 (d, 4H), 7.33 (d, 4H), 6.60 (br t, 2H), 4.26 (d, 4H), 3.79 (s, 6H); ^{13}C NMR ($\text{DMSO}-d_6$) δ 166.77, 158.68, 147.39, 129.80, 128.56, 127.71, 52.69, 43.45; IR (solid) 3313, 1718, 1611, 1568 cm^{-1} . Anal. Calcd. for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_5$: C, 64.04; H, 5.66; N, 7.86. Found: C, 64.27; H, 5.56; N, 7.85.

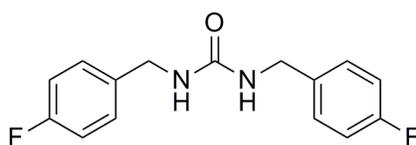


1,3-Bis(4-nitrobenzyl)urea

The product was obtained in 1% yield by procedure A and in 79% yield by procedure B.

The solid was identified by comparison with literature data.¹³⁴ ^1H NMR (DMSO) δ 8.39 (d, 4H)

7.50 (d, 4H), 6.82 (t, 2H), 4.35 (d, 4H).



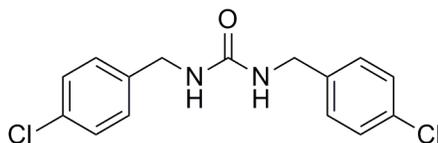
1,3-Bis(4-fluorobenzyl)urea

The product was obtained in 0% yield by procedure A and in 72% yield by procedure B.

^1H NMR (DMSO) δ 7.28 (t, 4H), 7.20 (t, 4H), 6.44 (br t, 2H), 4.18 (d, 4H); ^{13}C NMR (DMSO-

d_6) δ 158.00, 137.15, 126.86, 115.04, 114.76, 42.26; IR (solid) 3321, 1611 cm^{-1} . Anal. Calcd.

for $\text{C}_{15}\text{H}_{14}\text{F}_2\text{N}_2\text{O}$: C, 65.21; H, 5.11; N, 10.14. Found: C, 65.09; H, 5.12; N, 10.03.

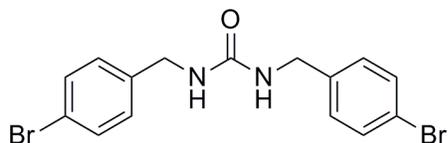


1,3-Bis(4-chlorobenzyl)urea

The product was obtained in 7% yield by procedure A and in 72% yield by procedure B.

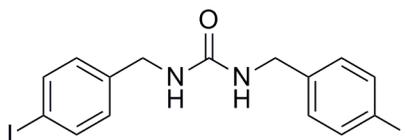
The solid was identified by comparison with literature data.¹³⁴ ^1H NMR (CDCl_3) δ 7.32 (m, 8H),

4.21 (d, 4H).



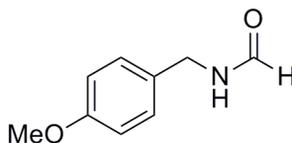
1,3-Bis(4-bromobenzyl)urea

The product was obtained in 21% yield by procedure A and in 78% yield by procedure B. The solid was identified by comparison with literature data.¹³⁴ $^1\text{H NMR}$ (CDCl_3) δ 7.79 (t, 4H), 7.12 (t, 4H), 4.24 (d, 4H), 4.18 (d, 4H).



1,3-Bis(4-iodobenzyl)urea

The product was obtained in 27% yield by procedure A and in 87% yield by procedure B. $^1\text{H NMR}$ ($\text{CD}_3\text{CO}_2\text{D}$) δ 7.74 (d, 4H), 6.95 (d, 4H), 4.48 (s, 4H); IR (solid) 3317, 1609. Anal. Calcd. for $\text{C}_{15}\text{H}_{14}\text{I}_2\text{N}_2\text{O}$: C, 36.61; H, 2.87; N, 5.69. Found: C, 36.31; H, 2.73; N, 5.48.



N-(4-methoxybenzyl)formamide

Procedure A was altered in that I_2 replaced NaI. This procedure afforded the formamide in 68% NMR yield. The product was identified by comparison with literature data.¹⁵³

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BIOGRAPHICAL SKETCH

Phillip Shelton was born in Morgantown, KY in a town of around two thousand people. Many subjects interested Phillip, but he began to develop a love for science, and especially chemistry in a class taught by Mr. Herman Owens. Upon graduation he went to Western Kentucky University while retaining a strong connection with family and friends in Morgantown. At Western he found his future wife, Abigail whom he married in 2007. Phillip graduated with the ACS accredited bachelors of science in 1997 and with his masters from the same institution in 2001. Dr. Donald Slocum was his advisor at Western and he introduced Phillip to research on the directed ortho-metallation reaction. Dr. Lisa McElwee-White continued Phillip's training when he entered graduate school at the University of Florida in 2004. Here he developed a reaction to carbonylate amines through a hypervalent iodine reagent. Phillip is expecting to receive his Ph.D. in May of 2010 after which he has accepted an assistant professor position at the University of Tennessee at Martin. The rest has yet to be written.