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Transition Metal-Catalyzed Oxidative Carbonylation of Amines to Ureas

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The synthesis of ureas from amines has traditionally been accomplished with stoichiometric reactions of phosgene or its derivatives, which are associated with environmental and waste disposal issues. Because of the prevalence of urea moieties in molecules of interest for several applications, alternative catalytic routes for the oxidative conversion of amines to ureas using CO as the carbonyl source have been developed. This microreview discusses recent developments in transition metal-catalyzed oxidative carbonylation of amines to ureas as an alternative to phosgene and its derivatives.

Introduction

The development of new synthetic protocols for the preparation of ureas has recently attracted interest because of the presence of this functional group in pharmaceutical candidates,[1–5] agrochemicals, resin precursors, dyes and additives to petrochemicals and polymers.[6] The classical syntheses of ureas from amines have been based on the use of toxic and/or corrosive reagents, such as phosgene or isocyanates.[7,8] In recent years, however, alternative routes have been developed that utilize phosgene derivatives, CO_2, or CO itself as the source of the carbonyl moiety.[9] Particularly attractive from the standpoint of atom economy[10] is oxidative carbonylation,[11,12] which employs amines, carbon monoxide and an oxidant as starting materials and

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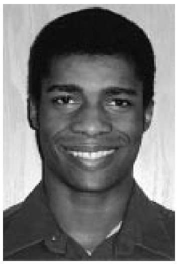

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produces only the reduced form of the oxidant and protons as byproducts.

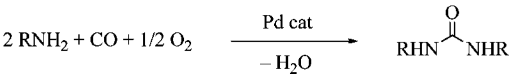
In an effort to develop new methodologies for preparing moieties with carbonyl–nitrogen bonds, metal-catalyzed carbonylation of amines has been extensively studied. Mono- and dicarbonylations of amines catalyzed by Mn,[13,14] Fe,[15] Co,[16,17] Ni,[18,19] Ru,[20–23] Rh,[23,24] Pd,[25–34] W,[35–40] Pt,[41] Ir,[41] or Au[42,43] have been reported, and many different types of products, including ureas,[14,16,18,23,44] urethanes,[45] oxamides,[46] formamides,[47–51] and oxazolidinones,[52] have been obtained. These carbonylations have generally been carried out at high temperatures under moderate-to-high pressures of CO and efforts to find catalysts that are effective under mild conditions continue. This microreview highlights some selected recent advances in the transition metal catalyzed oxidative carbonylation of amines to ureas.

1. Palladium-Catalyzed Oxidative Carbonylation of Amines

Carbonylation of amines using Pd catalysts has been extensively studied since Tsuji reported the first Pd-catalyzed carbonylation of amines in 1966.[34] Methods for oxidative carbonylation using $PdCl_2$ as catalyst with copper oxidants or O_2 as the terminal oxidant and CuX or CuX_2 as a mediator have been developed for preparation of ureas,[53–55] carbamates,[25,56] and oxamides.[25,44,57,58] Since a recent review of Pd-catalyzed reactions is available,[12] this Microreview will highlight a few selected examples.

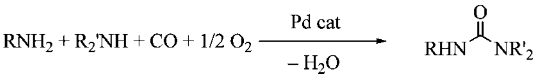
1.1. Homogeneous Carbonylation of Amines to Ureas

Fukuoka[59] and Chaudhari[60] reported the oxidative carbonylation of alkylamines using Pd/C as catalyst and iodide salts as promoters in the presence of O_2, which afforded the corresponding ureas and/or carbamates in good yields. Related results have been reported by Gabriele[61] for the oxidative carbonylation of amines using PdI_2 and O_2, which led to formation of ureas, carbamates, and their cyclic derivatives in good yields. New conditions for the PdI_2-catalyzed oxidative carbonylation of amines to ureas [Equations (1) and (2)], afforded ureas in high yields with turnover numbers as high as 4950.[28,62] Carbonylations of primary aliphatic amines [Equation (1), R = alkyl] were carried out at 100 °C under a mixture of CO, air, and CO_2 in the presence of a simple catalytic system consisting of PdI_2 in conjunction with a KI promoter. In the absence of CO_2, less satisfactory results were obtained.[62] The choice of solvent was critical to product selectivity. Monocarbonylation to the urea was favored in dioxane or 1,2-dimethoxyethane (DME), while double carbonylation to the oxamide predominated in the more polar solvents *N*,*N*-dimethylacetamide (DMA) or *N*-methylpyrrolidinone (NMP). The selectivity was attributed to higher nucleophilicity of the amine substrates in DMA or NMP, which favors the formation of $Pd(CONHBu)_2$ species that generate the oxamide by reductive elimination. Primary aromatic amines [Equation (1), R = Ar] were generally less reactive than primary aliphatic amines under these conditions but addition of an electron-donating methoxy group increased the nucleophilicity of the aromatic amine enough to improve the activity.



$$2\,RNH_2 + CO + 1/2\,O_2 \xrightarrow[-\,H_2O]{\text{Pd cat}} RHNC(O)NHR$$

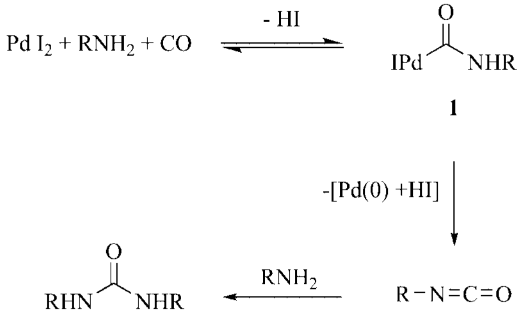
(1)



$$RNH_2 + R_2'NH + CO + 1/2\,O_2 \xrightarrow[-\,H_2O]{\text{Pd cat}} RHNC(O)NR'_2$$

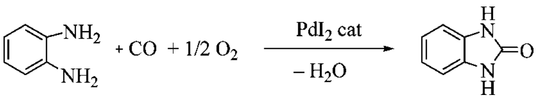
(2)

The mechanism for the carbonylation of primary amines was examined in more detail after it was determined that the secondary amines diethylamine, dibutylamine, and morpholine were unreactive under the same conditions. The difference in reactivity was attributed to the formation of isocyanate intermediates from the primary amine, with carbamoylpalladium complex **1** formed in preequilibrium with starting materials (Scheme 1). In agreement with this hypothesis, isocyanates were detected (by GLC, TLC, and GLC/MS) in the reaction mixtures in low-conversion experiments. Under these conditions, Pd^0 is reoxidized to Pd^{II} by oxidative addition of I_2, which is regenerated through oxidation of HI by oxygen.



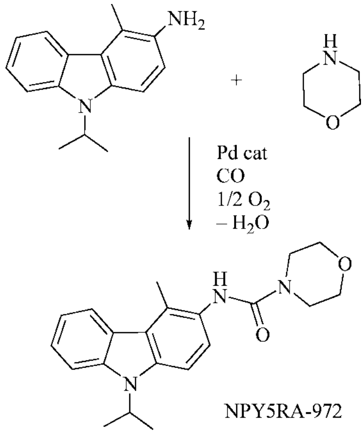
Scheme 1.

This catalytic system proved to be effective for the synthesis of cyclic ureas from the corresponding diamines, with 1,3-dihydrobenzoimidazol-2-one obtained in 99% isolated yield [Equation (3)]. This particularly high reactivity was attributed to increased nitrogen nucleophilicity and a less negative entropy of activation due to the proximity of the *ortho* amino groups.[28]



(3)

Direct catalytic preparation of trisubstituted ureas in high selectivity [Equation (2)] was possible under these conditions if the primary amine was carbonylated in the presence of an excess of a secondary amine.[28] This methodology has proven to be effective for the synthesis of several types of urea derivatives, such as cyclic ureas from primary diamines and *N*,*N*-bis(methoxycarbonylalkyl)ureas from primary α-amino esters. A showcase synthesis of the neuropeptide Y5 receptor antagonist NPY5RA-972 was also reported [Equation (4)].[28]

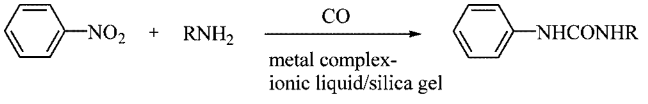


(4)

1.2 Palladium Catalysis in Ionic Liquids

Recently, many catalytic reactions have been reported to proceed in ionic liquids with excellent results.[63] This approach has been adapted by Deng for Pd-catalyzed carbonylation of amines to ureas.[64] A solubility study of the catalyst Pd(phen)Cl$_2$ established that the ionic liquids BMImBF$_4$ (BMIm = 1-butyl-3-methylimidazolium), BMImPF$_6$, BMImFeCl$_4$, and BMImCl were candidate media for the carbonylation reaction and that catalyst solubility could be adjusted through the tuning of either the cation or anion of the ionic liquids. Carbonylation of aniline to the carbamate in the presence of O$_2$ and methanol was used to demonstrate catalytic activity and recyclability of the catalyst/ionic liquid mixture.

Subsequent work by the Deng group developed a new method using silica gel-immobilized ionic liquids, in which a Pd complex acts as a heterogenized catalyst for the carbonylation of amines and nitrobenzene to ureas. Heterogenization of the metal catalyst by preparation of a silica gel confined ionic liquid was followed by the carbonylation of amines and nitrobenzene to the corresponding ureas (Scheme 2).[65] No additional oxidant is necessary since the nitrobenzene serves as both substrate and oxidant. In terms of green chemistry, the advantages of this method are the low quantities of ionic liquids used and the avoidance of potentially explosive CO/O$_2$ mixtures. The authors suggested that the enhanced catalytic activity of this system may be derived from the high concentration of ionic liquid containing the metal complex confined within the cavities of the silica gel matrix.[65]



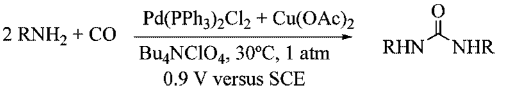
R = phenyl, butyl, hexyl, cyclohexyl, *p*-methylphenyl
p-methoxyphenyl, *o*-nitrophenyl

Scheme 2.

Experiments with the ionic liquids DMImBF$_4$ (1-decyl-3-methylimidazolium tetrafluoroborate) and EMImBF$_4$ (1-ethyl-3-methylimidazolium tetrafluoroborate) and the catalysts HRu(PPh$_3$)$_2$Cl$_2$, Rh(PPh$_3$)$_3$Cl, Pd(PPh$_3$)$_2$Cl$_2$ and Co(PPh$_3$)$_3$Cl$_2$ afforded good to excellent yields of *N*,*N'*-diphenylurea (DPU) from nitrobenzene and aniline. The Rh-DMImBF$_4$/silica gel catalyst produced 93% conversion of starting materials with a selectivity of 92% for the urea. Conversion of aliphatic amines and nitrobenzene to the unsymmetrically substituted ureas could also be achieved with this particular catalyst.

1.3 Electrocatalytic Carbonylation

Another method for the synthesis of alkylureas is the electrocatalytic carbonylation of aliphatic amines, as reported by Deng.[66] Electrocatalytic carbonylation of a series of aliphatic amines to dialkylureas and isocyanates using Pd^{II} complexes with a Cu^{II} cocatalyst could be achieved under mild reaction conditions, with particularly good results for primary amines [Equation (5)]. The additional steric hindrance in secondary amines apparently prevents the reaction, as diisopropylamine was unreactive under the same conditions. In addition, no conversion of primary diamines to cyclic ureas was observed although one long chain diamine did afford a low yield of the corresponding isocyanate.



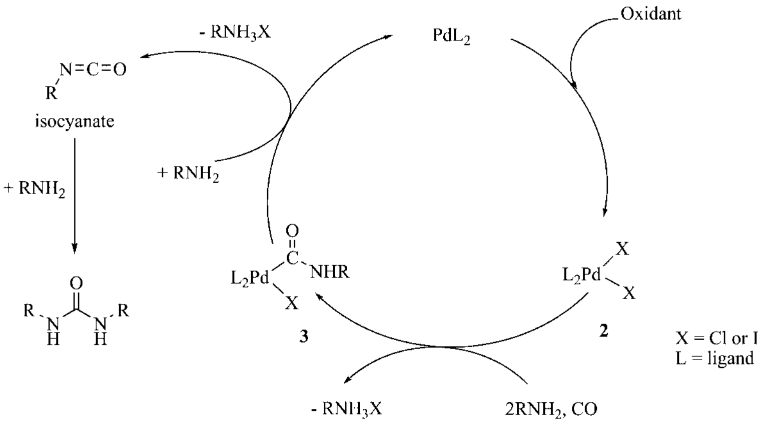
$$2\,RNH_2 + CO \xrightarrow[\substack{Bu_4NClO_4,\ 30^\circ C,\ 1\ atm\\ 0.9\ V\ versus\ SCE}]{Pd(PPh_3)_2Cl_2\ +\ Cu(OAc)_2} RHN\overset{O}{\overset{\|}{C}}NHR$$

(5)

Although products were obtained with a single complex as catalyst [Cu(OAc)$_2$, PdCl$_2$ or Pd(OAc)$_2$], catalytic activity and selectivity for the urea were improved when both a Pd complex and Cu(OAc)$_2$ were present in the reaction mixtures. Quantitative conversion and 98% selectivity for the urea were achieved in the case of *n*-butylamine when Pd(PPh$_3$)$_2$Cl$_2$ and Cu(OAc)$_2$ were used together as catalysts.[66] The authors suggested a synergistic effect between Pd^{II} and Cu^{II}, as opposed to simple mediation of electron transfer, which had been invoked in a related case of electrocatalysis.[67]

1.4 Mechanistic Studies

Recent progress has also been made in understanding the mechanism of the carbonylation of amine nucleophiles. Shimizu and Yamamoto have reported a mechanistic study fo-



Scheme 3.

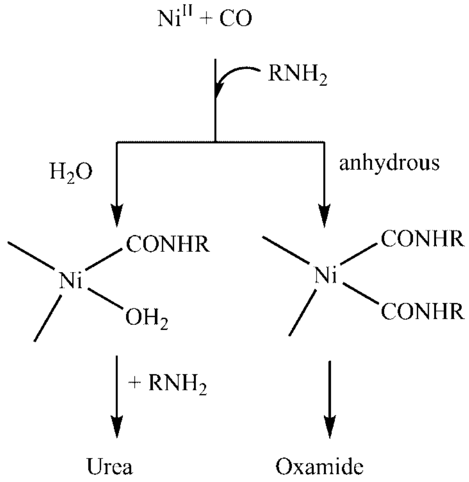
cusing on the role of the reoxidation of Pd^0 species formed in the principal catalytic cycle to electrophilic Pd^{II} species during the selective carbonylation of amines to oxamides and ureas.[46] Their work revealed the importance of the oxidant in selectivity as 1,4-dichloro-2-butene (DCB) afforded oxamides from primary and secondary amines while the use of I_2 as the oxidizing agent resulted in formation of ureas. Further insight was obtained through independent generation of carbamoylpalladium complexes as models for species in the catalytic cycle.

Two possible mechanisms for the conversion of primary amines to ureas by palladium-catalyzed carbonylation were discussed in conjunction with this study. In the first, the critical step is reductive elimination of carbamoyl and amido ligands to generate the urea, as previously proposed by Alper.[44] The crucial step in the second possible route involves formation of an intermediate alkyl isocyanate from *N*-monoalkylcarbamoylpalladium species **3** (Scheme 3). The urea product is then derived from nucleophilic attack of a primary or secondary amine on the isocyanate to release a symmetrically or unsymmetrically substituted urea. This second possibility is based on an earlier proposal by Gabriele for a related system.[62] Support for the isocyanate pathway came from the inability of secondary amines to form tetrasubstituted ureas. Kinetic studies on the reaction of the *N*-monoalkylcarbamoyl complex in the presence of triethylamine provided further evidence for generation of isocyanates by the deprotonation pathway.[46]

2. Other Late Transition Metal Catalysts

2.1 Nickel-Catalyzed Oxidative Carbonylation

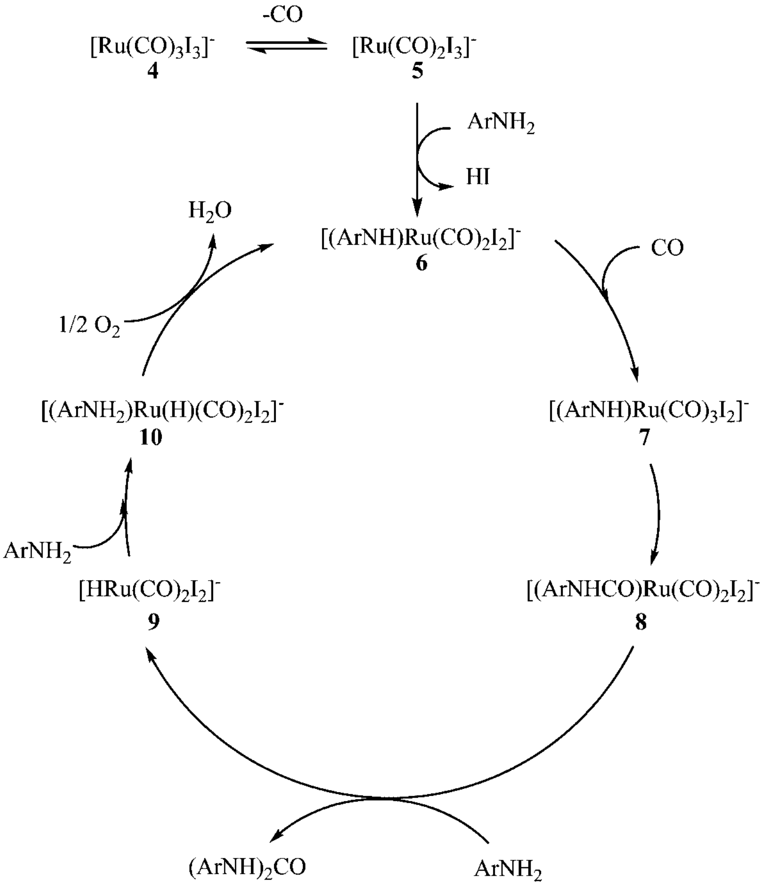
The extensive development of palladium-catalyzed oxidative carbonylation reactions along with the ability of Ni complexes to undergo carbonylation and produce stable carbamoyl derivatives suggested investigation of nickel complexes as catalysts for the oxidative carbonylation of amines.[18] Giannoccaro obtained *N*,*N′*-dialkylureas, rather than the previously reported oxamides,[19] by reacting aliphatic primary amines with the nickel amine complexes $NiX_2(RNH_2)_4$ (X = Cl, Br; R = alkyl). However, yields were low, and at temperatures higher than 50 °C, side reactions became significant. On the other hand, at lower temperatures the reductive step, in which amine carbonylation occurs, failed. The product selectivity depended on the amount of water present, with anhydrous conditions favoring the oxamide, while the presence of water promoted urea formation (Scheme 4). The authors suggested that water could coordinate to the nickel center, allowing the formation of only one carbamoyl group. Under aqueous conditions, this intermediate would then undergo nucleophilic attack by the amine to form the urea. In the absence of water, the oxamide would arise from reductive elimination of two carbamoyl groups.[18]



Scheme 4.

2.2 Ruthenium-Catalyzed Oxidative Carbonylation

Gupte utilized ruthenium catalysts for the selective formation of *N*,*N′*-diphenylurea (DPU) from the oxidative carbonylation of aniline.[23] High selectivity (99%) for the formation of DPU was obtained with $[Ru(CO)_3I_3]NBu_4$ as the catalyst and NiI as the promoter. The key step in the proposed mechanism involves the formation of the carbamoyl



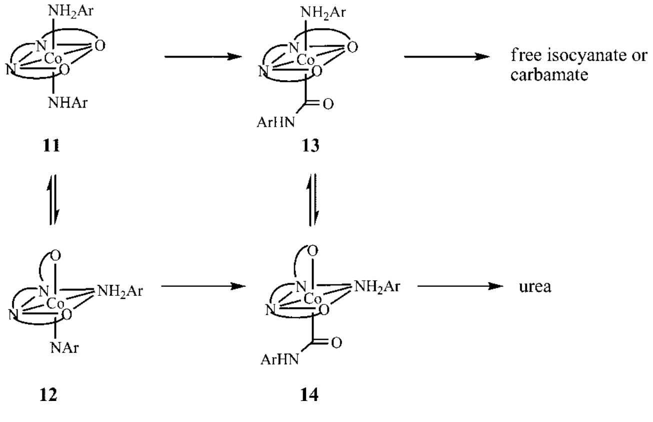
Scheme 5.

species **8** (Scheme 5). Loss of CO from the catalyst precursor $[Ru(CO)_3I_3]^-$ (**4**) generates the intermediate **5**, which reacts with aniline to form **6** and HI. Addition and insertion of CO affords the carbamoyl complex **8**, which reacts with aniline to yield the urea and the hydrido carbonyl species **9**. Addition of aniline to form **10** is followed by oxidation with O_2 to regenerate the active species **6** (Scheme 5).[23] Related chemistry with alkylamines has been reported by Chaudhari.[60,68]

2.3 Cobalt- and Rhodium-Catalyzed Oxidative Carbonylation

Rindone reported the synthesis of acyclic and cyclic ureas from aromatic primary amines, using *N*,*N*′-bis(salicylidene)ethylenediaminocobalt(II) [Co(salen)] as the catalyst.[16] Optimal reaction conditions varied with the substrate. For example, the urea yields from 4-methylaniline were higher at high pressure of O_2, while 4-fluoroaniline reacted better at lower O_2 pressure. Substituent effects were also examined. Electron-withdrawing groups in the *para* position lowered the conversion of the starting amine while *ortho*-aminophenol was more reactive than the other amines. The substituent effects were elaborated in a subsequent paper.[69]

The proposed mechanism involved equilibrium between planar and non-planar salen ligands (**11** and **12**) on a cobalt(III) amido complex, either of which could undergo carbon monoxide insertion to give an equilibrium mixture of carbamoyl complexes **13** and **14**. Compound **13**, having the planar salen ligand and a *trans* relationship between the carbamoyl and amine ligands, could lead to free isocyanate or carbamate, while complex **14**, having a nonplanar salen and a cis relationship between the carbamoyl and amine ligands, would lead to the urea (Scheme 6).[16]



Scheme 6.

Claver prepared modified Co(salen) complexes (Figure 1) and utilized them as catalysts for oxidative carbonylation of aniline.[70] Results revealed that the *tert*-butyl-substituted catalyst **16** produced 100% selectivity for diphenylurea in the presence of butanol, while the other complexes afforded mixtures of the urea and the corresponding butyl carbamate. The phenanthroline derivative **19** also showed high selectivity (94%) for the urea.

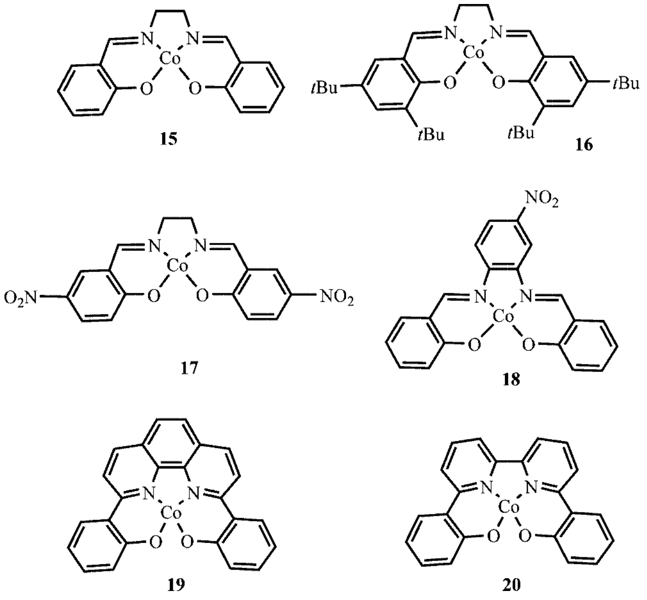
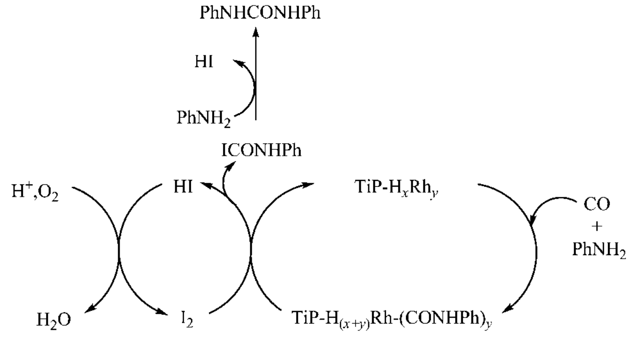


Figure 1. Co(salen) (**15**) and modified Co(salen) complexes **16**–**20**.

Efforts in the rhodium-catalyzed carbonylation of amines to ureas have been sparse in recent years. An early study by Chaudhari investigated various factors that affect activity and selectivity of rhodium-catalyzed oxidative carbonylation.[71] Although the primary objective was the synthesis of carbamates, some conditions were found to favor the formation of ureas. In studies focused on the oxidative carbonylation of aniline, a Rh/C-NaI system was determined to be best for the catalytic process. Using this catalyst, polar solvents like acetonitrile or DMF favored formation of diphenylurea, while most other solvents favored the carbamate. Modifying pressure, temperature, and concentration also affected selectivity and activity.[71]

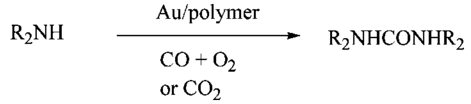
Giannoccaro reported preparation of Rh^{3+} and Rh^{3+}–diamine complexes intercalated into γ-titanium phosphate (TiP), and measured their activity towards oxidative carbonylation of aniline.[72] Intercalation provided a way to heterogenize an otherwise homogeneous catalyst. Typical conditions involved acetonitrile or methanol as the solvent, a CO/O_2 mixture at atmospheric or higher pressure, temperatures between 70–120 °C, and the presence of $PhNH_3^+I^-$ as a promoter. The highest catalyst activities were obtained with increased pressure of the CO/O_2 mixture, higher temperature, and a molar ratio of co-catalyst to $Rh^{3+}(PhNH_3^+I^-/Rh^{3+})$ between 5 and 6. It was found that the materials containing simple Rh^{3+} salts worked better than those prepared from Rh^{3+}–diamine complexes. The key intermediate in the postulated reaction mechanism (Scheme 7) is the Rh^{3+}–carbamoyl complex **21** which reacts with molecular iodine to form the iodoformate intermediate, ICONHPh. The latter reacts with aniline to afford diphenylurea.[72]



Scheme 7.

2.4 Gold-Catalyzed Oxidative Carbonylation

Deng has investigated gold compounds as catalysts for the carbonylation of amines.[43,73–76] Although simple Au^I salts afforded carbamates from aniline, the reactions of aliphatic amines also yielded the urea in some cases.[73] Polymer-immobilized gold catalysts, prepared from commercially available ion exchange resins and $HAuCl_4$, were found to catalyze the carbonylation of arylamines to their methyl carbamates in the presence of methanol.[43] In the absence of methanol, the diarylureas became the major products. In contrast to previously reported gold catalysts, the polymer-immobilized variety showed enhanced catalytic efficiency, could easily be separated from the product, and could be used in the absence of organic solvents. Subsequent work demonstrated that use of this system with aliphatic amines and CO_2 could afford symmetrical dialkylureas, with high yields and turnover frequencies (Scheme 8).[76] The mechanism is unclear, but it was postulated that the high activity can be attributed to some synergistic relationship between gold nanoparticles and the polymer support.



$$R_2NH \xrightarrow[\substack{CO + O_2 \\ \text{or } CO_2}]{\text{Au/polymer}} R_2NHCONHR_2$$

Scheme 8.

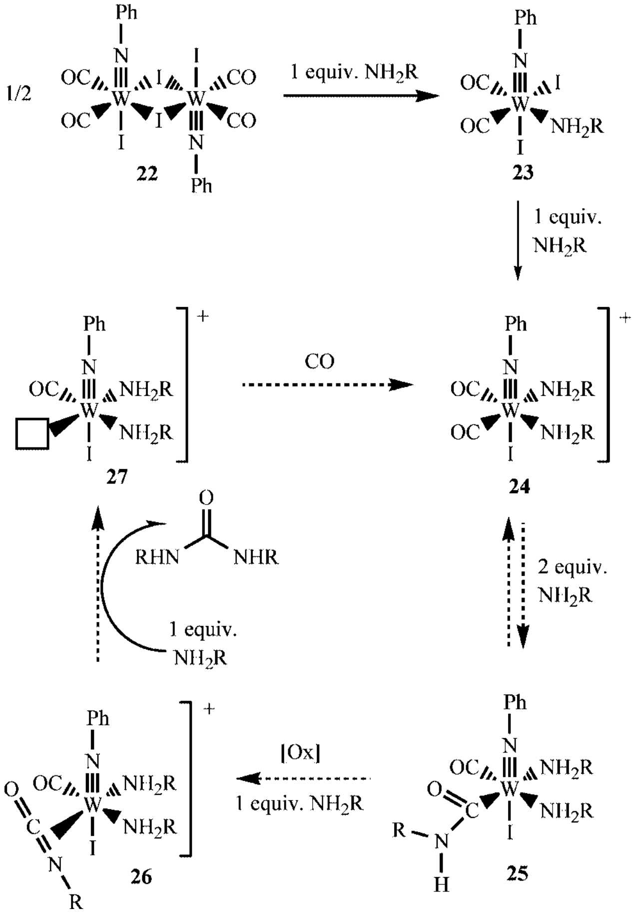
3. Tungsten-Catalyzed Oxidative Carbonylation of Amines

3.1 Carbonylation of Primary Amines

Despite extensive investigation of transition-metal-catalyzed carbonylation reactions, examples involving Group 6 metals still remain rare. During the last decade, we have been exploring conversion of amine substrates to the corresponding ureas using carbonyl tungsten complexes as the catalysts and I_2 as the oxidant.

The initial report described catalytic oxidative carbonylation of primary amines using the iodo-bridged tungsten dimer $[(CO)_2W(NPh)I_2]_2$ (**22**) as the precatalyst.[35] During those studies, it was shown that primary aromatic and aliphatic amines could be carbonylated to 1,3-disubstituted ureas, while secondary amines afforded formamides in modest yields.

Mechanistic studies on this process established that primary amines reacted stoichiometrically with the dimer **22** to yield the amine complexes $(CO)_2I_2W(NPh)(NH_2R)$ (**23**) (Scheme 9), which undergo reaction with excess amine to afford the corresponding ureas.[37] Nucleophilic attack of the amine on a carbonyl ligand of **24**, followed by proton abstraction using a second equivalent of the amine would afford the carbamoyl complex **25**. IR spectra of the reaction mixtures were consistent with the presence of the carbamoyl complexes. The intermediacy of the carbamoyl complex **25** is precedented by Angelici's work on the carbonylation of methylamine by $[(\eta^5\text{-}C_5H_5)W(CO)_4]PF_6$,[77] for which the first step is conversion of $[(\eta^5\text{-}C_5H_5)W(CO)_4]^+$ to the carbamoyl complex $(\eta^5\text{-}C_5H_5)W(CO)_3(CONHCH_3)$ upon reaction with 2 equiv. of methylamine.



Scheme 9.

Assignment of the next step as oxidation was supported by IR spectra that showed the disappearance of the carbamoyl stretches after the reaction mixtures were exposed to air. It is expected that following oxidation of the complex, the carbamoyl proton would be more acidic and deprotonation of **25** with the excess amine would produce the isocyanate complex **26**. Nucleophilic attack of an amine on either coordinated or free isocyanate would afford the 1,3-disubstituted urea, producing coordinatively unsaturated complex **27**, which could undergo addition of CO to regenerate the cationic intermediate **24** and close the catalytic cycle.

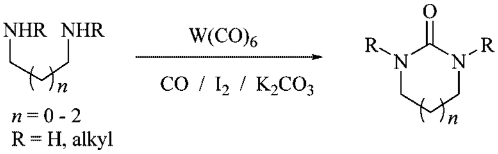
The previous results implied that other tungsten carbonyl iodide complexes might also serve as catalysts. The simplest choice as precatalyst was the readily available, inexpensive, and air stable $W(CO)_6$. Preliminary studies were carried out using $W(CO)_6$ as catalyst for the catalytic carbonylation of *n*-butylamine. Reaction of $W(CO)_6$, 100 equiv. of *n*-butylamine, 50 equiv. of I_2, and 100 equiv. of K_2CO_3 in a 125-mL Parr high-pressure vessel pressurized with 100 atm CO produced di-*n*-butylurea in an amount corresponding to 39 turnovers per equivalent of $W(CO)_6$, or 80% yield with respect to amine.[37]

Subsequent optimization studies using *n*-propylamine established that *N*,*N*′-disubstituted ureas could be obtained in good to excellent yields using the $W(CO)_6/I_2$ oxidative carbonylation system.[38] Once $W(CO)_6$ (2 mol-%) was established as the preferred catalyst, other variables were examined. Optimal conditions were 90 °C, 80 atm CO, 1.5 equiv. of K_2CO_3, and a chlorinated solvent such as CH_2Cl_2 or $CHCl_3$. Selected primary amines were converted into the corresponding *N*,*N*′-disubstituted ureas using these conditions. The results of these experiments showed that the yields decreased when the substrate contained secondary or tertiary alkyl substituents. In the case of aniline, it was not possible to find conditions under which diphenylurea could be obtained, presumably due to lower nucleophilicity of the arylamine.

3.2 Carbonylation of Primary and Secondary Diamines to Cyclic Ureas

Many methods for conversion of diamines to the corresponding cyclic ureas have been reported.[7,8] Most of them are stoichiometric reactions based on nucleophilic attack of amines on phosgene and related derivatives. Catalytic oxidative carbonylation of diamine substrates provides an alternative route to cyclic ureas in which CO is used as the carbonyl source. However, the synthesis of cyclic ureas via metal-catalyzed carbonylation has received limited attention. Early reports of transition-metal-catalyzed carbonylation of diamines mentioned cyclic ureas only as minor side products. In the case of $Mn_2(CO)_{10}$-catalyzed carbonylation of the diamines $H_2N(CH_2)_nNH_2$ ($n = 2$–4 and 6), no cyclic products were observed when $n = 2$, 4, or 6 and only 6% of the six-membered urea when $n = 3$.[78] We thus explored the catalytic carbonylation of diamines to cyclic ureas using $W(CO)_6$ as the catalyst, I_2 as the oxidant, and CO as the carbonyl source.[36] Both primary and secondary α,ω-diamines were substrates for the reaction, with secondary diamines being converted directly to the corresponding *N*,*N*′-disubstituted cyclic ureas.

Synthesis of the five-, six-, and seven-membered cyclic ureas from the primary diamines could be achieved in moderate to good yields [Equation (6)],[36] with the highest isolated yield for the six-membered cyclic urea. Only trace amounts of the eight-membered ring compound could be detected in the reaction mixtures, which was not surprising as there are no reports in the literature of preparation of this compound from 1,5-pentanediamine. In addition, (+)-(1*R*,2*R*)-1,2-diphenyl-1,2-ethanediamine was carbonylated to the 2-imidazolidinone in 46% yield with no epimerization. Reaction of the secondary diamines $RNHCH_2CH_2NHR$ [Equation (6)]; [R = Me, Et, *i*Pr, Bn] under similar conditions resulted in conversion of the diamines to the corresponding *N*,*N*′-disubstituted cyclic ureas. For both primary and secondary substrates, it was necessary to employ high dilution conditions to minimize formation of oligomers, a problem also encountered during the reactions of phosgene and its derivatives with diamines.[79]

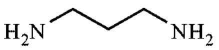
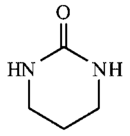
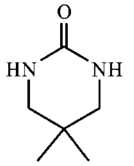
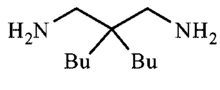
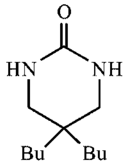
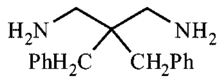
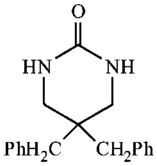
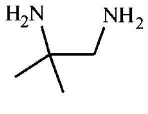
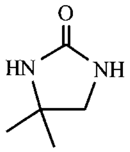
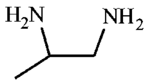
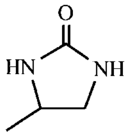
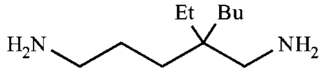
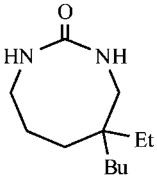


(6)

Steric effects on the ring-closure reaction were probed by carbonylating *N*,*N*′-dimethyl, diethyl, diisopropyl, and dibenzyl diamines under the standard conditions.[36] As expected, 1,3-diethyl-2-imidazolidinone and 1,3-dimethyl-2-imidazolidinone were produced in nearly identical yields. Changing the substituents to benzyl groups lowered the yield only modestly but the presence of bulky isopropyl groups dramatically reduced the yield of the imidazolidinone to only 10%. Yields in the sterically hindered cases could not be improved by raising the reaction temperature. Although primary amines reacted much more readily than secondary amines, *N*-methylpropanediamine reacted under the oxidative carbonylation conditions to produce the corresponding monosubstituted *N*-methyl cyclic urea in preference to acyclic urea formation through the more reactive primary amines.[36]

A more extensive study on the carbonylation of α,ω-diamines to cyclic ureas involved further optimization of the conditions using propane-1,3-diamine as the test substrate, $W(CO)_6$ as catalyst and I_2 as the oxidant.[80] Effects of solvent and temperature variation on the yields of the cyclic urea from propane-1,3-diamine were examined. Additional experiments probed the effect of alkyl substituents in the linker of primary diamines (Table 1). In the cases of simple *n*-alkyl substituents, the yields of cyclic ureas are significantly higher for the 2,2-dialkyl-1,3-propanediamines than for the parent propane-1,3-diamine as a result of the Thorpe–Ingold effect[81] and improved solubility in organic solvents during workup.

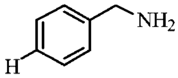
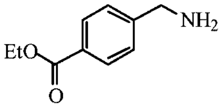
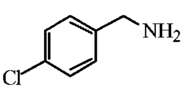
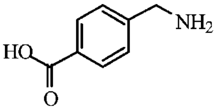
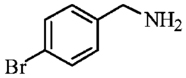
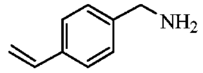
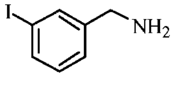
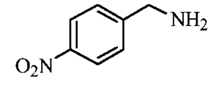
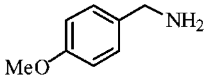
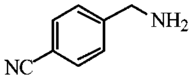
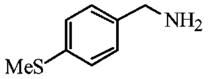
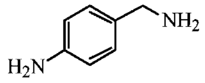
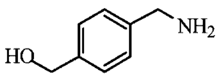
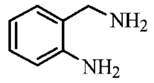
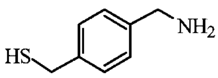
Table 1. Tungsten-catalyzed oxidative carbonylation of substituted primary diamines.

Amine	Product	% Yield
		52
		80
		70
		48
		50
		33
		38

The carbonylation of *N*,*N*′-dialkyl-2,2-dimethylpropane-1,3-diamines afforded tetrasubstituted ureas; however, the products were obtained in modest yields, and tetrahydropyrimidine byproducts were formed in significant amounts when the substrates bore *N*-alkyl substituents larger than methyl. Comparison of these results with the carbonylations of secondary diamines to form five-membered cyclic ureas suggested that the effects of ring size and *N*-substituent size on the carbonylation reaction are complex.

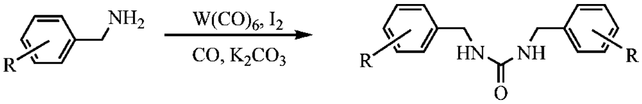
Success with conversion of diamines to cyclic ureas suggested the use of $W(CO)_6$-catalyzed oxidative carbonylation in the synthesis of complex targets. However, before considering applications in synthesis, it was necessary to evaluate the functional group compatibility of the catalyst, often a critical issue in the use of early metal systems. Studies of

Table 2. Tungsten-catalyzed oxidative carbonylation of substituted benzylamines to ureas.

Amine	% Yield[a]	% Yield[b]	Amine	% Yield[a]	% Yield[b]
	63	73		36	55
	35	77		0	37
	30	77		41	69
	39	70		45	76
	47	70		37	68
	24	81		28	14
	5	58		17	20
	0	0			

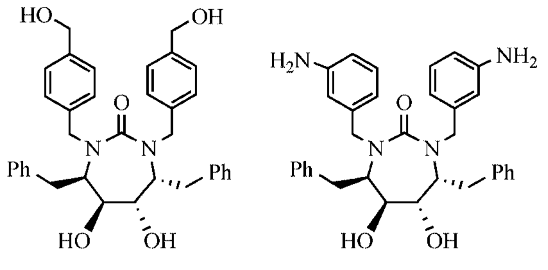
[a] Reaction conditions: amine (7.1 mmol), $W(CO)_6$ (0.14 mmol), I_2 (3.5 mmol), K_2CO_3 (10.7 mmol), solvent: CH_2Cl_2 (20 mL), 70 °C, 80 atm CO, 24 h. [b] Solvent: $CH_2Cl_2 + H_2O$ (21 + 3 mL, respectively). Other conditions are as in footnote a.

functional group compatibility using a series of substituted benzylamines [Equation (7), Table 2] demonstrated that the oxidative carbonylation of amines using the $W(CO)_6/I_2$ system is tolerant of a wide variety of functionality, including halides, esters, alkenes, and nitriles. A distinguishing feature is the tolerance of unprotected alcohols, which would be problematic with phosgene derivatives.[38] A critical result of this study is the observation that the addition of water to generate a biphasic solvent system produced dramatic increases in the yields of functionalized ureas. In order for the reaction to work efficiently, it is necessary to solubilize the catalyst, the starting amine, the hydroiodide salt of the starting material which is formed when protons are scavenged, and the base (K_2CO_3). The biphasic solvent system provides phase transfer conditions in which the amine salt can be deprotonated by aqueous carbonate and then returned to the organic phase for carbonylation.



(7)

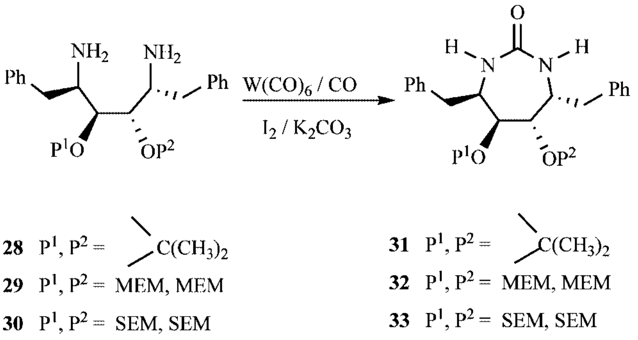
After broad functional group tolerance during $W(CO)_6/I_2$-catalyzed oxidative carbonylation of amines to ureas had been established,[38] use of this methodology to install the urea moiety into the core structure of the HIV protease inhibitors DMP 323 and DMP 450 (Figure 2)[82,83] was investigated.[84] Direct comparison of the catalytic carbonylation reaction with stoichiometric reaction of the same substrates with phosgene derivatives was possible due to the extensive literature on the synthesis of these targets.



DMP 323 DMP 450

Figure 2. Structures of the HIV protease inhibitors DMP 323 and DMP 450.

It has been reported in the literature that the urea moiety of DMP 323 and DMP 450 was installed by reaction of phosgene or a phosgene equivalent with an *O*-protected diamine diol. In the initial small-scale preparations, a primary diamine was treated with the phosgene derivative 1,1′-carbonyldiimidazole (CDI)[83,85–87] followed by *N*-alkylation as appropriate. The practical preparation of DMP 450 involves reaction of a secondary diamine with phosgene to form the cyclic urea. Since use of phosgene or CDI requires protection of the diol, extensive protecting group studies have been carried out.[85,88] Three of the previously described *O*-protected diamine diols, acetonide **28**,[88] MEM ether **29**,[83,89] and SEM ether **30**[83] were tested in the catalytic carbonylation reaction as representative examples containing cyclic and acyclic protecting groups, respectively [see Equation (8)].[84]



(8)

Carbonylation of the diamine substrates **28**–**30** [Equation (8)] to the cyclic ureas **31**–**33** provided a means for comparison of the $W(CO)_6$-catalyzed process to the stoichiometric reactions of the phosgene derivative CDI. Yields of the ureas from the catalytic reaction depended on the protecting group on the diol, as was also observed for ring closure with stoichiometric CDI (Table 3). These results demonstrate that the catalytic oxidative carbonylation reaction can be used to convert diamines to cyclic ureas in examples relevant to the preparation of complex targets.

Table 3. Tungsten-catalyzed oxidative carbonylation of diamines **28**–**30** to ureas **31**–**33**.

Diamine	Reagent	Solvent	Urea % yield	Ref.
28	CDI	CH_3CN	15	[85]
28	CDI	TCE	67	[85]
28	$W(CO)_6/CO$	CH_2Cl_2/H_2O	38	[84]
28	$W(CO)_6/CO$	CH_2Cl_2	23	[84]
29	CDI	CH_2Cl_2	62, 76	[83,86,89]
29	$W(CO)_6/CO$	CH_2Cl_2/H_2O	49	[84]
30	CDI	CH_2Cl_2	52, 93	[83,86]
30	$W(CO)_6/CO$	CH_2Cl_2/H_2O	75	[84]

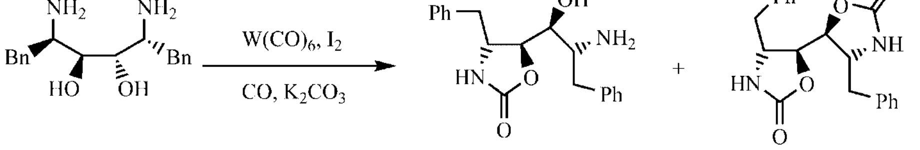
Efforts to avoid the protecting-group chemistry in reported syntheses of DMP 323 and DMP 450 by carbonylating the diamine diol **34** were frustrated by the reaction of the diol hydroxy groups to generate oxazolidinones **35** and **36** [Equation (9)].[40] Oxazolidinone formation had also been reported as the result of reaction of **34** with CDI and phosgene.[90] The earlier functional group compatibility study had suggested that the catalyst was tolerant of -OH groups [Equation (7), Table 2] but the test substrate in that study was [4-(aminomethyl)phenyl]methanol, in which the -OH group is *para* with respect to the amine so as to eliminate the possibility of formation of a cyclic carbamate. For that substrate, the corresponding urea was produced without competing carbamate or carbonate formation.[38] For the diamine diol **34**, oxazolidinone formation had been preferred under the reaction conditions tested.

More recently, the catalytic carbonylation of a series of amino alcohols of varying tether lengths and substitution patterns was carried out to probe the selectivity of the $W(CO)_6/I_2$ carbonylation system for reactivity of alcohols vs. amines. The phosgene derivatives dimethyl dithiocarbamate (DMDTC) and 1,1′-carbonyldiimidazole (CDI) were used as representative stoichiometric reagents for comparison purposes.[40]

A series of 1,2-, 1,3-, 1,4- and 1,5-amino alcohol substrates was subjected to $W(CO)_6$-catalyzed oxidative carbonylation for evaluation of the selectivity of the $W(CO)_6/I_2$ system toward formation of the ureas or carbamates, either cyclic or acyclic (Table 4). As a comparison of the stoichiometric reactions of phosgene derivatives to the catalytic $W(CO)_6/I_2$ methodology, the results of reaction of CDI and DMDTC with the amino alcohol substrates also appear in Table 4.

The results indicated that the $W(CO)_6/I_2$ methodology can indeed be applied to carbonylation of amino alcohols to the ureas without protection of the hydroxy group. The $W(CO)_6$-catalyzed oxidative carbonylation was consistently selective for the urea over the cyclic carbamate for all tether lengths and substitution patterns studied. Acyclic carbamates were not detected in the reaction mixtures. In contrast, reactions of the phosgene derivatives CDI and DMDTC with 1,3- and 1,2-amino alcohol substrates exhibited variable selectivities between ureas and cyclic carbamates. It is important to note that the reaction conditions for these studies were not the same as for the initial work on diamine diol **34**. Optimized conditions for carbonylation of amino alcohols to the ureas involved use of pyridine as the base, removing the necessity for the biphasic solvent system used in the original functional group compatibility study.[38]

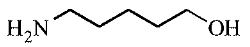
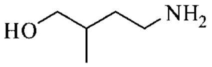
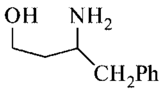
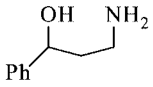
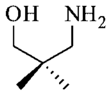
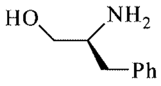
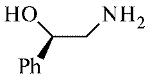
Other targets that were prepared to investigate the scope of the $W(CO)_6/I_2$ system were biotin and related heterocyclic ureas.[91] Biotin (**37b**), also known as Vitamin H, is produced on large scale as a feed additive for poultry and



34 **35** **36**

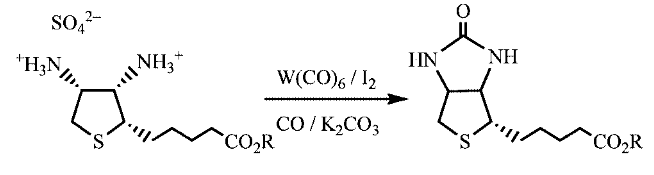
(9)

Table 4. Carbonylation of amino alcohols to ureas and carbamates.

Substrate	Reagent	Urea (%)	Cyclic carbamate (%)
	$W(CO)_6$ /CO	64	2
	CDI	80	trace
	DMDTC	45	0
	$W(CO)_6$ /CO	93	0
	CDI	70	trace
	DMDTC	93	0
	$W(CO)_6$ /CO	95	trace
	CDI	36	60
	DMDTC	30	8
	$W(CO)_6$ /CO	72	14
	CDI	49	30
	DMDTC	34	47
	$W(CO)_6$ /CO	60	5
	CDI	55	28
	DMDTC	32	29
	$W(CO)_6$ /CO	78	10
	CDI	18	22
	DMDTC	72	trace
	$W(CO)_6$ /CO	79	14
	CDI	30	52
	DMDTC	73	trace

swine. It has also been the target of more than 40 total and formal syntheses.[92] One recurring theme in these syntheses has been installation of the urea moiety by reaction of phosgene with a diaminotetrahydrothiophene derivative.

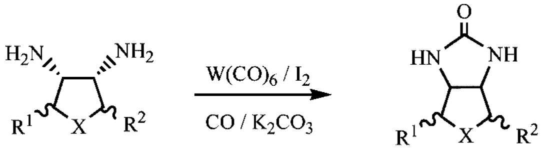
Although biotin itself could not be produced directly from the carboxylic acid **37a** [Equation (10)], biotin methyl ester (**38b**) was obtained in 84% yield upon $W(CO)_6$-catalyzed oxidative carbonylation of diamine **38a**. The related heterocycles **39b–42b** were also prepared by the carbonylation procedure and the yields compared to those ob-



37a R = H
38a R = Me

37b R = H (0%)
38b R = Me (84%)

(10)



39a-42a

39b-42b

		X	R^1	R^2
39a	**39b**	O	H	H
40a	**40b**	O	H	$(CH_2)_4CH_3$
41a	**41b**	N-BOC	CH_3	CH_3
42a	**42b**	CH_2CH_2	H	H

(11)

Table 5. Yields of bicyclic ureas from diamines **39a–42a**.

Amine	Urea	$W(CO)_6/I_2$ % yield	CDI % yield
39a	**39b**	Trace	20
40a	**40b**	47	67
41a	**41b**	46	37
42a	**42b**	57	56

tained by reaction of the same substrates with CDI [Equation (11), Table 5]. Yields of the ureas were moderate to good and depended on the solubility of the diamine and urea in dichloromethane.

4. Conclusions

Transition-metal-catalyzed carbonylation of amines offers new and efficient methodology for the selective synthesis of ureas under relatively mild reaction conditions. Use of CO as the carbonyl source in the presence of a catalyst and an oxidant provides an alternative to the traditional methods for conversion of amines to ureas, which involve stoichiometric use of phosgene and its derivatives. From the perspective of green chemistry, the replacement of phosgene and the minimization of the waste streams associated with phosgene derivatives would be beneficial.

Recent developments in metal-catalyzed oxidative carbonylation of amines include new techniques such as the use of ionic liquids, microwave irradiation and electrocatalytic carbonylation. In addition to extensive work with palladium complexes, carbonylation reactions that utilize other late transition metals, such as Ni, Ru, Rh, Co, Au, have also been demonstrated to afford ureas. Indications that tungsten-catalyzed oxidative carbonylation of functionalized amines could be of use in the synthesis of complex targets have also been reported. Given the prevalence of urea functionality in compounds with a wide range of applications, further work in this area is no doubt forthcoming.

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