$W(CO)_6$-Catalyzed Oxidative Carbonylation of Primary Amines to N,N′-Disubstituted Ureas in Single or Biphasic Solvent Systems. Optimization and Functional Group Compatibility Studies

Jennifer E. McCusker, A. Denise Main, Kirsten S. Johnson, Cara A. Grasso, and Lisa McElwee-White*

Department of Chemistry, University of Florida, Gainesville, Florida 32611

lmwhite@chem.ufl.edu

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Primary amines undergo carbonylation to N,N′-disubstituted ureas using $W(CO)_6$ as the catalyst, I_2 as the oxidant, and CO as the carbonyl source. Preparation of various N,N′-disubstituted ureas from aliphatic primary amines, RNH_2 (R = *n*-Pr, *n*-Bu, *i*-Pr, *sec*-Bu, or *t*-Bu), was achieved in good to excellent yields. Studies of functional group compatibility using a series of substituted benzylamines demonstrated broad tolerance of functionality during the carbonylation reaction. Preparation of various N,N′-disubstituted ureas from substituted benzylamines, $R-C_6H_4CH_2NH_2$ (R = H, *p*-OCH_3, *p*-CO_2H, *p*-CO_2Et, *p*-CH_2OH, *p*-SCH_3, *p*-vinyl, *p*-Cl, *p*-Br, *m*-I, *p*-NH_2, *p*-NO_2, or *p*-CN), was achieved in good yields. For many substituted benzylamines, yields of ureas were higher when a two-phase CH_2Cl_2/H_2O solvent system was used.

Introduction

Substituted ureas have been of recent interest due to appearance of this functionality in drug candidates such as HIV protease inhibitors,[1,2] FKBP12 inhibitors,[3] CCK−B receptor antagonists[4,5] and endothelin antagonists.[6] In addition, ureas have found widespread use as agricultural chemicals, resin precursors, dyes, and additives to petroleum compounds and polymers.[7] Among the numerous methods for synthesis of N,N′-disubstituted ureas are the reactions of primary amines with isocyanates, phosgene, or phosgene derivatives.[8,9] Yields are usually good to excellent for these reactions, but other aspects can be problematic. Phosgene itself is highly toxic and corrosive while phosgene derivatives can be expensive to use on a large scale. Additional impetus for replacement of phosgene derivatives comes from the standpoint of atom economy[10] by which using CO to install a carbonyl moiety into a urea would be preferable to a method using a typical phosgene derivative such as 1,1-carbonyldiimidazole. The direct metal-catalyzed conversion of amines and CO to ureas provides an alternative to phosgene and its derivatives.

Although catalytic carbonylation has been investigated over many years,[11−13] the topic remains of interest. Oxidative conversion of primary amines into ureas has been reported for transition metal catalysts involving Ni,[14] Co,[15] Mn,[16,17] Ru[18] and, most commonly, Pd.[19−21] Main group elements such as sulfur[22,23] and selenium[24−26] can also serve as catalysts. However, neither the transi-

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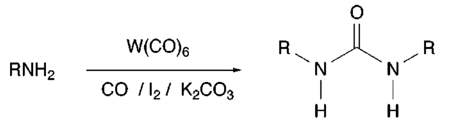
Table 1. Oxidative Carbonylation of *n*-Propylamine with Group 6 Metal Carbonyls

catalyst	yield[a,b] (%)
$W(CO)_6$	67
$Mo(CO)_6$	50
$Cr(CO)_6$	30

[a] Isolated yield of di-*n*-propylurea calculated per equivalent of *n*-propylamine. Values are ± 5%. [b] Reaction conditions: *n*-propylamine (14.2 mmol), $W(CO)_6$ (0.28 mmol), I_2 (7.1 mmol), K_2CO_3 (14.2 mmol), CH_2Cl_2 (40 mL), room temperature., 80 atm CO, 18 h.

tion metal- nor the main group-catalyzed reactions are ideal. The transition metal-catalyzed reactions generally require high temperatures and pressures. In addition, yields for aliphatic amines are generally much lower than those for aromatic cases. Among the main group catalysts, selenium-catalyzed carbonylation reactions can produce high yields of ureas under mild conditions. However, generation of hydrogen selenide as a byproduct and the need for stoichiometric or excess selenium for certain substrates[25,26] are problematic.

We previously reported preliminary studies on the catalytic oxidative carbonylation of primary amines to ureas using either $[(CO)_2W(NPh)I_2]_2$ or $W(CO)_6$ as the precatalyst and I_2 as the oxidant.[27,28] The $W(CO)_6/I_2$ catalyst system also works for the conversion of secondary amines to tetrasubstituted ureas[29] and the preparation of cyclic ureas directly from primary and secondary α,ω-diamines.[30] We now report more extensive optimization studies on oxidative carbonylation of aliphatic primary amines to N,N′-disubstituted ureas using the $W(CO)_6/I_2$ oxidative carbonylation system (eq 1). The product ureas can be obtained in good to excellent yields. Additionally, studies of functional group compatibility using a series of substituted benzylamines demonstrate broad tolerance of substrate functionality during the carbonylation reaction.



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Results and Discussion

Optimization of Reaction Conditions. In the initial report on $W(CO)_6$-catalyzed oxidative carbonylation of aliphatic primary amines to 1,3-disubstituted ureas,[28] we reported conversion of *n*-butylamine to di-*n*-butylurea in 80% yield based on amine. This was a promising but unoptimized result. The system has subsequently been more thoroughly explored. Variables such as catalyst, temperature, solvent, CO pressure and quantity of added base have now been examined and the results are described below.

Table 2. Optimization of the Catalytic Carbonylation of *n*-Propylamine

$W(CO)_6$ (mol %)	K_2CO_3 (equiv)	*T* (°C)	yield[a,b] (%)
1.0	1.0	24	54
2.0	1.0	24	67
2.0	1.0	90	72
2.0	1.5	90	90
2.0	2.0	90	31
2.0	1.0	110	55

[a] Isolated yield of di-*n*-propylurea calculated per equivalent of *n*-propylamine. Values are ± 5%. [b] Reaction conditions: *n*-propylamine (14.2 mmol), I_2 (7.1 mmol), CH_2Cl_2 (40 mL), 80 atm CO, 18 h.

As seen in Table 1, the initial carbonylation of *n*-propylamine in the presence of 2 mol % $W(CO)_6$, 0.5 equiv of I_2, and 1.0 equiv K_2CO_3 in 40 mL CH_2Cl_2 in a glass-lined 300-mL Parr high-pressure vessel pressurized with 80 atm CO and stirred at room temperature for 18 h produced di-*n*-propylurea in a 67% yield with respect to amine. Based on the results with $W(CO)_6$, the congeneric metal carbonyl compounds, $Mo(CO)_6$ and $Cr(CO)_6$, were also examined as catalysts. For comparison purposes, the experiments were all run under identical conditions instead of being individually optimized for each metal.

Using $Mo(CO)_6$ as the catalyst, di-*n*-propylurea was produced in a 50% yield, while with $Cr(CO)_6$ the urea yield decreased further to 30%. Because second row transition metal catalysts are generally more active than their third row analogues, it had been expected that $Mo(CO)_6$ would be an improvement over $W(CO)_6$. However, it is possible that the molybdenum intermediates were not sufficiently robust for the reaction conditions and side reactions became more significant. Following these experiments, further optimization studies involved $W(CO)_6$ as the catalyst.

Once $W(CO)_6$ had been established as the preferred catalyst, other variables were examined. Lowering the amount of $W(CO)_6$ to only 1 mol % resulted in a reduced isolated yield of 54% and observation of unreacted starting material under the conditions specified in Table 2. Subsequent experiments utilized 2 mol % $W(CO)_6$ to obtain complete reaction within a reasonable period of time. Furthermore, increasing the temperature from room temperature to 90 °C improved the yield marginally to 72%. More significant improvement was obtained at 90 °C by increasing the amount of K_2CO_3 to 1.5 equiv with respect to amine, which raised the yield of di-*n*-propylurea to 90%. Further increases in the amount of base caused the yields to decrease, most likely because the additional insoluble K_2CO_3 caused stirring problems in the reactor. Raising the temperature to 110 °C resulted in formation of a brown oil and a decrease in yield to 55%.

The choice of solvent also turned out to be significant, as seen in Table 3. Among the single solvents, chlorinated solvents such as CH_2Cl_2 or $CHCl_3$ gave the best yields of di-*n*-propylurea at room temperature, as well as the cleanest crude products. The remainder of the solvents in Table 3 resulted in decreased urea yields. Surprisingly, changing the solvent to methanol resulted in a change in the carbonylation product. In the presence of methanol, primary amines were carbonylated to the corresponding formamides, instead of the expected ureas or carbamates.

Although CH_2Cl_2 was the best single solvent for the *n*-propylamine case, solubility problems were encountered when CH_2Cl_2 was used as solvent for various substituted benzylamines (vide infra), for which either the amine starting material or the hydroiodide salt was insoluble. Note that the stoichiometry of oxidative car-

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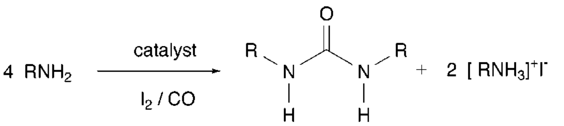
Table 3. Comparison of Solvents in the Oxidative Carbonylation of *n*-Propylamine

solvent	yield[a,b] (%)
CH_2Cl_2/H_2O[c]	73
CH_2Cl_2	62
$CHCl_3$	51
toluene	48
ethyl acetate	43
THF	41
CH_3CN	36
ether	32
water	32
CCl_4	28
hexane	15
acetone	14
benzene	12

[a] Isolated yield of di-*n*-propylurea calculated per equivalent of *n*-propylamine. Values are ± 5%. [b] Reaction conditions: *n*-propylamine (14.2 mmol), $W(CO)_6$ (0.28 mmol), I_2 (7.1 mmol), K_2CO_3 (21.3 mmol), solvent 40 mL, room temperature, 80 atm CO, 24 h. [c] The solvent was CH_2Cl_2 (35 mL) plus H_2O (5 mL). Other conditions are as in footnote a.

bonylation of amines to ureas dictates that two equiv of the amine hydroiodide (RNH_3I) will be produced per equiv of urea (eq 2). In the absence of added base, these



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amine salts are observed in the reaction mixtures. The presence of K_2CO_3 as a sacrificial base increases the product yield by regenerating the free amine from the salt and returning it to the substrate pool. However, insolubility of the amine salts will hinder this deprotonation since the K_2CO_3 and the salt will coexist as immiscible solids. To circumvent the inability of solid K_2CO_3 to deprotonate insoluble amine salts, the two-phase solvent system CH_2Cl_2/H_2O was investigated. Due to the solubility of the hydroiodide salts in basic water, they could be deprotonated and shuttled back into the methylene chloride layer as the free amine. An added advantage was that the base is soluble in the water layer and stirring problems associated with solid K_2CO_3 were eliminated.

For both *n*-propylamine (Table 3) and many of the substituted benzylamines used in the functional group compatibility studies (vide infra), room-temperature yields increased when the solubility problems were resolved with the two-phase CH_2Cl_2/H_2O solvent system. Although there are several examples of two-phase carbonylation reactions in the literature, a biphasic system for the carbonylation of amines is to the best of our knowledge unprecedented. In fact, carbonylation of amines in aqueous medium has only been reported for conversion of amines to formamides with a water-soluble ruthenium carbonyl catalyst.[31]

A study of carbonylation yields as a function of CO pressure was performed as described in Table 4. At 20 atm CO and 90 °C, the yield of di-*n*-propylurea was 63%, while at 80 atm the urea yield was 90%. Increases above 80 atm did not result in further improvements in yield.

Table 4. Variation of CO Pressure in the Oxidative Carbonylation of *n*-Propylamine

pressure (atm)	yield[a,b] (%)
20	63
40	68
60	75
80	90

[a] Isolated yield of di-*n*-propylurea calculated per equivalent of *n*-propylamine. Values are ± 5%. [b] Reaction conditions: *n*-propylamine (14.2 mmol), $W(CO)_6$ (0.28 mmol), I_2 (7.1 mmol), K_2CO_3 (21.3 mmol), CH_2Cl_2 40 mL, 90 °C, 24 h.

Although the carbonylation of *n*-propylamine at room temperature in the two-phase CH_2Cl_2/H_2O solvent system had originally resulted in 73% yield (Table 3), repeating the reaction at 90 °C resulted in a 85% yield which was comparable to the 90% yield achieved in CH_2Cl_2. Therefore, the optimal conditions for the carbonylation of *n*-propylamine were determined to be 2 mol % $W(CO)_6$, stoichiometric amounts of amine and I_2, and 1.5 equiv of K_2CO_3 per equiv amine reacted in CH_2Cl_2 at 90 °C under 80 atm CO pressure. A series of primary amines was reacted under these conditions to give the corresponding N,N′-disubstituted ureas, as seen in Table 5. The ureas were formed in good to high yields, ranging from 90% for N,N′-di-*n*-propylurea to 53% for N,N′-di-*i*-propylurea. In the case of N,N′-di-*n*-propylurea, approximately 5% of the starting material can be recovered at the end of the reaction, so that virtually all of the material can be accounted for. The yields are generally lower if the amine bears secondary or tertiary alkyl substituents. Only a few percent of starting material was recovered for the more highly branched ureas, suggesting that the higher degree of substitution results in undesired side reactions. For comparison, the amines in Table 5 were also run in the CH_2Cl_2/H_2O solvent system. Analogous to the decrease in yield of the *n*-propyl urea in the two-phase system at 90 °C, the other primary amines also suffered a decrease in yield when carbonylated in the mixed solvent system. It is noteworthy that aniline is unreactive under the reaction conditions, considering aromatic amines are generally better substrates than their aliphatic analogues for the formation of ureas under transition metal-catalyzed carbonylation conditions.[31,32] The nucleophilicity of the amine is apparently critical in these reactions. Similar reactivity is observed in the related carbonylation of amines using $[(CO)_2W(NPh)I_2]_2$, in which the first C−N bond is formed by nucleophilic attack of amine on a carbonyl.[28]

Functional Group Compatibility

To explore applications of this reaction in organic synthesis, a study of functional group tolerance was undertaken. Various substituted benzylamines (eq 3) were reacted with CO under similar carbonylation conditions, as seen in Table 6. Substituted benzylamines were

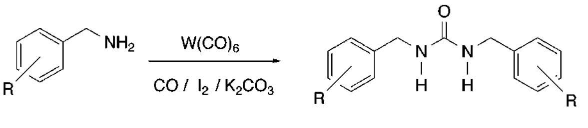

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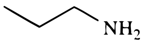
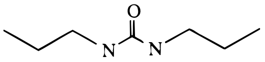
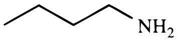
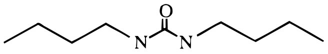
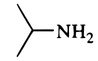
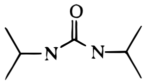
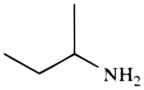
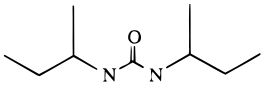
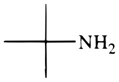
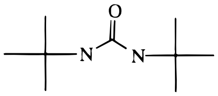
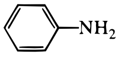
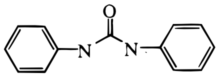
Table 5. Oxidative Carbonylation of Primary Amines to Ureas under Optimized Conditions

Amine	Product	%Yield[a,b] CH_2Cl_2	%Yield[a,c] CH_2Cl_2/H_2O
		90	85
		84	78
		53	27
		55	30
		72	62
		0	0

[a] Isolated yield of urea calculated per equivalent of amine. Values are ± 5%. [b] Reaction conditions: amine (14.2 mmol), $W(CO)_6$ (0.28 mmol), I_2 (7.1 mmol), K_2CO_3 (21.3 mmol), CH_2Cl_2 (40 mL), 90 °C, 80 atm CO, 24 h. [c] The solvent was CH_2Cl_2 (35 mL) plus H_2O (5 mL). Other conditions are as in footnote b.

chosen as model substrates for the compatibility study because the benzene ring provides a rigid backbone which separates the functional group from the reacting amine. The possibility of intramolecular interaction is eliminated in these substrates. This first screen of functional groups addresses interference by simple binding of the catalyst to the functional group or competitive reaction of the functional group by oxidation or carbonylation. More complex substrates, such as conformationally flexible amino alcohols in which carbonylation could lead to different types of products, are the subject of further investigation[33] and will not be discussed here.

Initial studies with the parent benzylamine established that N,N′-dibenzylurea was formed in 63% yield upon reaction under the optimized reaction conditions for *n*-propylamine (Table 6, CH_2Cl_2). As discussed above, the low yields of ureas for many of the substituted benzylamines were attributed to the insolubility of their respective hydroiodide salts in CH_2Cl_2. As shown in Table 6, it was found that yields for many of the substituted ureas were significantly higher when the 7:1 CH_2Cl_2/H_2O solvent system was used (Procedure C, Experimental Section).

The effects of aryl halides were examined first. The *p*-chloro-, *p*-bromo-, and *m*-iodobenzylamines **1b**−**d** produced their respective N,N′-disubstituted ureas **2b**−**d** in surprisingly low 35%, 30%, and 39% yields when the reaction was run in CH_2Cl_2. Although side reactions resulting from oxidative addition of the aryl halide bonds to the W complex were considered,[34,35] the main products of the reactions turned out to be the amine hydroiodides. Upon addition of water to the reaction mixtures, the yields of the ureas increased to 77%, 77%, and 70% respectively.

In experiments with ether and thioether compounds in CH_2Cl_2, the *p*-methoxybenzylamine **1e** was carbonylated to urea **2e** in 47% yield, while *p*-methylthiobenzylamine **1f** was carbonylated to urea **2f** in 24% yield. Under these conditions, the major products were the hydroiodide salts. The solubility problem was again circumvented by addition of H_2O to the solvent system resulting in the ureas forming in 70% and 81% yields, respectively.

The hydroxymethyl compound **1g** produced urea **2g** with yields of 5% in CH_2Cl_2 and 58% in CH_2Cl_2/H_2O. Remarkably, the carbonylation reaction was completely selective for the amine over the alcohol, within the limits of detection. None of the corresponding carbamate or carbonate could be observed in the reaction mixtures. This experiment suggests that the carbonylation of amines could be carried out in the presence of unprotected hydroxyl groups. In contrast, thiol **1h** failed to form the corresponding urea, undoubtedly due to the sensitivity of thiols to oxidation.

The ester-substituted benzylamine **1i** was also successfully carbonylated to the urea **2i** in 36% yield in CH_2Cl_2 with 55% yield obtained in CH_2Cl_2/H_2O. The carboxylic acid analogue **1j** is insoluble in CH_2Cl_2, which hindered efforts to explore the tolerance of the catalyst

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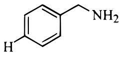
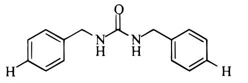
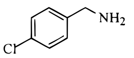
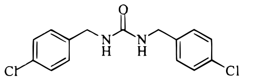
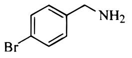
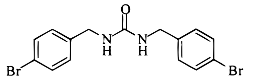
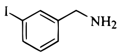
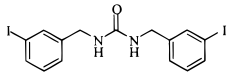
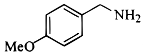
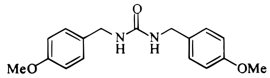
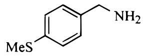
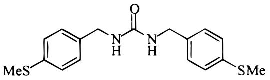
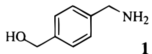
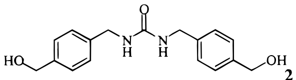
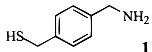
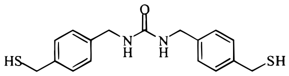
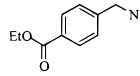
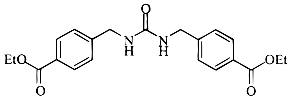
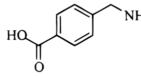
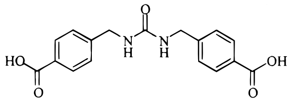
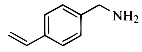
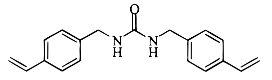
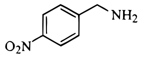
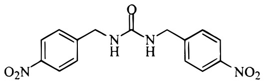
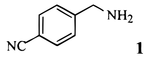
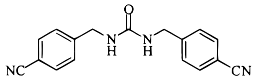
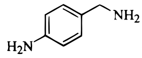
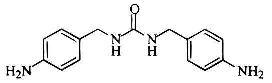
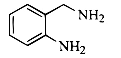
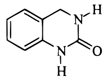
Table 6. Catalytic Carbonylation of Primary Amines to Ureas

Amine	Product	%Yield[a] CH_2Cl_2	%Yield[a,c] CH_2Cl_2/H_2O
 **1a**	 **2a**	63	73
 **1b**	 **2b**	35	77
 **1c**	 **2c**	30	77
 **1d**	 **2d**	39	70
 **1e**	 **2e**	47	70
 **1f**	 **2f**	24	81
 **1g**	 **2g**	5	58
 **1h**	 **2h**	0	0
 **1i**	 **2i**	36	55
 **1j**	 **2j**	0	37
 **1k**	 **2k**	41	69
 **1l**	 **2l**	45	76
 **1m**	 **2m**	37	68
 **1n**	 **2n**	28	14
 **1o**	 **2o**	17	20

[a] Isolated yield of urea calculated per equivalent of amine. Values are ± 5%. [b] Reaction conditions: amine (7.1 mmol), $W(CO)_6$ (0.14 mmol), I_2 (3.5 mmol), K_2CO_3 (10.7 mmol), CH_2Cl_2 (20 mL), 70 °C, 80 atm CO, 24 h. [c] The solvent was CH_2Cl_2 (21 mL) plus H_2O (3 mL). Other conditions are as in footnote b.

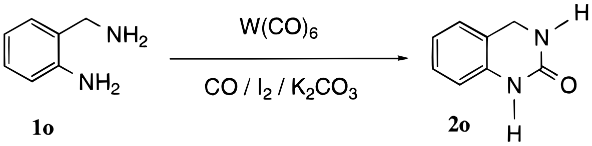
to the presence of carboxylic acids. However, the solubility of **1j** in basic H_2O made it possible to obtain the corresponding urea **2j** in 37% yield from the CH_2Cl_2/H_2O system.

Compatibility of the catalyst system with terminal alkenes was then examined. The olefin **1k** was reacted under the carbonylation conditions to form the urea **2k** in a 41% yield in CH_2Cl_2. Although we anticipated possible problems with reactivity at the double bond, there were no identifiable products in which the double bond had been perturbed. The low yields could, however, be indicative of unidentified side reactions. Unlike the previously described reactions of substituted benzylamines, higher yields were obtained when the reaction using CH_2Cl_2 as the solvent was diluted to 0.03 M in substrate and conducted at room temperature.

In addition, *p*-nitrobenzylamine (**1l**) was successfully carbonylated to urea **2l** in a 45% yield in CH_2Cl_2 with 76% yield obtained in CH_2Cl_2/H_2O. The cyano-substituted benzylamine **1m** was also carbonylated to its respective urea (**2m**) in 37% yield in CH_2Cl_2 and 68% yield in CH_2Cl_2/H_2O. Note that the possibility of the nitrile moiety serving as a ligand for the catalyst did not interfere with the reaction.

Further functional group studies included the reaction of the *p*-aminobenzylamine **1n** under the carbonylation conditions. If both the aliphatic and aromatic amines were to participate in the carbonylation reaction, oligomeric products would be formed. Primary aromatic amines, such as aniline were unreactive under the carbonylation conditions, so formation of the simple urea **2n** was expected to dominate. However the reaction mixture was quite complex and urea **2n** was only isolated in 28% yield. In this case, addition of water to the solvent system decreased the yield to 14%.

The apparent participation of the aromatic amine in the reactions of **1n** result brought up the question of intramolecular carbonylation of the *o*-amino benzylamine **1o** to form 3,4-dihydro-2(*1H*)-quinazolinone (eq 4). Although aromatic amines are apparently not nucleophilic enough to initiate the reaction, they could be sufficiently nucleophilic to complete the cyclization following initial reaction of the aliphatic amine. In fact, under the carbonylation conditions **1n** did form the cyclic urea, albeit in low yields (17% yield in CH_2Cl_2 and 20% yield in CH_2Cl_2/H_2O). The results from **1n** and **1o** suggest that differentiation between aliphatic and aromatic amines is not sufficiently good to obtain selective reactivity in the presence of both.



(4)

Conclusion

In summary, aliphatic primary amines can be catalytically carbonylated to 1,3-disubstituted ureas in good to high yields using the commercially available, inexpensive and air stable $W(CO)_6$ as the catalyst. The preference of this catalyst for aliphatic amines is complementary to the late transition metal catalysts, which are generally more effective for aromatic amines than for aliphatic ones. Not only does this system provide an alternative to phosgene and phosgene derivatives, but it is also compatible with a variety of functional groups, including unprotected alcohols. Further work on these reactions is currently underway.

Experimental Section

General Methods. Diethyl ether and tetrahydrofuran were distilled from sodium/benzophenone. Aniline, benzene, toluene, methylene chloride, chloroform, acetonitrile, and hexane were distilled over calcium hydride. All other chemicals were purchased in reagent grade and used with no further purification unless stated otherwise. Authentic samples of the ureas in Table 5 were prepared from the corresponding amines and isocyanates[7] or were purchased from Aldrich.

Amines **1f**,[36,37] **1g**,[38] **1h**,[39] **1i**,[40] **1k**,[41] and **1m**[37] were synthesized using literature procedures. Compounds **1a**−**e**,**j**,**l**,**n**,**o** were purchased from Aldrich.

General Procedure for the Catalytic Carbonylation of Primary Amines with $W(CO)_6$. To a stirred solution of $W(CO)_6$ (100 mg, 0.28 mmol) in 40 mL of CH_2Cl_2 in the glass liner of a Parr high-pressure vessel was added 50 equiv of *n*-propylamine (1.1 mL, 14 mmol), 75 equiv of K_2CO_3 (2.9 g, 21 mmol) and 25 equiv of iodine (1.8 g, 7.1 mmol). The vessel was then charged with 80 atm of CO, and left to stir under pressure for 18 h at 90 °C. After cooling to room temperature, the pressure was released. The yellow solution was filtered and washed with saturated Na_2SO_3 followed by 1 M HCl and additional saturated Na_2SO_3. The resulting colorless solution was then dried with Mg_2SO_4 and filtered. The solution was concentrated and dried for 1−2 h to yield a white solid (0.92 g, 6.3 mmol, 90% yield). The solid was identified as di-*n*-propylurea by comparison with an authentic sample. If necessary, further purification of ureas obtained by this method could be achieved by rinsing the solid with cold hexane, followed by extraction into 25 mL ether or ethyl acetate and filtration to remove any residual $W(CO)_6$.

General Procedures for the Catalytic Carbonylation of Benzylamines with $W(CO)_6$. Procedure A. To a stirred solution of $W(CO)_6$ (49 mg, 0.14 mmol) in 20 mL of CH_2Cl_2 in the glass liner of a Parr high-pressure vessel was added 50 equiv of *p*-methoxybenzylamine (1.0 mL, 7.1 mmol), 75 equiv of K_2CO_3 (1.47 g, 10.7 mmol) and 25 equiv of iodine (0.89 g, 3.5 mmol). The vessel was then charged with 85 atm of CO, heated to 70 °C and left to stir under pressure for 24 h. The pressure was released and the maroon solution was filtered. The solid collected on the filter paper was heated in CH_2Cl_2, filtered, and both filtrates were combined. The combined CH_2Cl_2 layers were washed with a 1.0 M HCl solution followed by washing with a saturated Na_2SO_3 solution. The resulting pale yellow solution was then dried with Na_2SO_4 and filtered. The solution was concentrated to yield a pale yellow solid, which was then rinsed with 15 mL of ether. The urea was obtained as a white solid (0.50 g, 1.7 mmol, 47% yield). The solid was identified as N,N′-bis(4-methoxybenzyl)urea by comparison with literature values.[42] **Procedure B.** Procedure B is identical to that of procedure A except the reaction was diluted to 0.03 M in substrate and run at room temperature. **Procedure C.** Procedure C is identical to that of procedure A except 21 mL of CH_2Cl_2 and 3 mL of H_2O were employed as solvent. The product urea precipitated out of the reaction mixture, was filtered, washed with Et_2O and collected.

Preparation of *N*,*N*′-Dibenzylurea 2a. Procedure A afforded **2a** in 63% yield. Procedure C afforded **2a** in 73% yield. Urea **2a** was identified by comparison with literature values.[43]

Preparation of *N*,*N*′-Bis(4-chlorobenzyl)urea 2b. Procedure A afforded **2b** in 35% yield. Procedure C afforded **2b** in 77% yield: ^1H NMR (DMSO-d_6) δ 7.37 (d, $J = 7.6$ Hz, 4H), 7.26 (d, $J = 7.8$ Hz, 4H), 6.56 (br s, 2H), 4.20 (d, $J = 5.4$ Hz, 4H); ^{13}C NMR (DMSO-d_6) δ 158.0 (C=O), 140.1, 131.0, 128.8, 128.1, 42.3; IR (Nujol) 1567 cm^{-1}; HRMS (FAB) calcd for $C_{15}H_{15}Cl_2N_2O$ (M + H$^+$) 309.0561, found 309.0561.

Preparation of *N*,*N*′-Bis(4-bromobenzyl)urea 2c. Procedure A afforded **2c** in 30% yield. Procedure C afforded **2c** in 77% yield: ^1H NMR (DMSO-d_6) δ 7.50 (d, $J = 8.1$ Hz, 4H), 7.20 (d, $J = 8.2$ Hz, 4H), 6.53 (br s, 2H), 4.19 (d, $J = 5.9$ Hz, 4H); ^{13}C NMR (DMSO-d_6) δ 158.0 (C=O), 140.5, 131.0, 129.2, 119.5, 42.3; IR (Nujol) 1561 cm^{-1}; HRMS (FAB) calcd for $C_{15}H_{15}Br_2N_2O$ (M + H$^+$) 396.9551, found 396.9560.

Preparation of *N*,*N*′-Bis(3-iodobenzyl)urea 2d. Procedure A afforded **2d** in 39% yield. Procedure C afforded **2d** in 70% yield: ^1H NMR (DMSO-d_6) δ 7.60 (s, 2H), 7.56 (d, $J = 7.7$ Hz, 2H) 7.25 (d, $J = 7.5$ Hz, 2H), 7.10 (t, 2H), 6.49 (t, 2H), 4.19 (d, $J = 5.9$ Hz, 4H); ^{13}C NMR (DMSO-d_6) δ 158.0 (C=O), 143.8, 135.5, 135.2, 130.5, 126.4, 94.8, 42.2; IR (Nujol) 1584 cm^{-1}; HRMS (FAB) calcd for $C_{15}H_{15}I_2N_2O$ (M + H$^+$) 492.9274, found 492.9271.

Preparation of *N*,*N*′-Bis(4-methoxybenzyl)urea 2e. Procedure A afforded **2e** in 47% yield. Procedure C afforded **2e** in 70% yield. Literature reports on **2e**[42] do not contain spectral data: ^1H NMR (DMSO-d_6) δ 7.15 (d, $J = 8.4$ Hz, 4H), 6.85 (d, $J = 8.2$ Hz, 4H), 6.31 (br s, 2H), 4.13 (d, $J = 5.4$ Hz, 4H), 3.71 (s, 6H); ^{13}C NMR (DMSO-d_6) δ 158.04 (C=O), 157.98, 132.8, 128.3, 113.6, 55.0, 42.4; IR (Nujol) 1578 cm^{-1}; HRMS (FAB) calcd for $C_{17}H_{21}N_2O_3$ (M + H$^+$) 301.1552, found 301.1557.

Preparation of *N*,*N*′-Bis(4-methylthiobenzyl)urea 2f. Procedure A afforded **2f** in 24% yield. Procedure C afforded **2f** in 81% yield: ^1H NMR (DMSO-d_6) δ 7.19 (m, 8H), 6.42 (br t, 2H), 4.16 (d, $J = 6.0$ Hz, 4H), 2.44 (s, 6H); ^{13}C NMR (DMSO-d_6) δ 158.0 (C=O), 137.7, 135.9, 127.8, 126.1, 42.5, 15.0; IR (Nujol) 1584 cm^{-1}; HRMS (CI) calcd for $C_{17}H_{21}N_2OS_2$ (M + H$^+$) 333.1095, found 333.1106.

Preparation of *N*,*N*′-Bis(4-hydroxymethylbenzyl)urea 2g. Procedure A afforded **2g** in 5% yield. Procedure C afforded **2g** in 58% yield: ^1H NMR (DMSO-d_6) 7.41 (m, 8H), 6.56 (t, 2H), 5.31 (t, 2H), 4.65 (d, $J = 5.4$ Hz, 4H), 4.39 (d, $J = 6.0$ Hz, 4H); ^{13}C NMR (DMSO-d_6) δ 158.0 (C=O), 140.8, 139.2, 126.8, 126.4, 62.7, 42.8; IR (Nujol) 3331, 1555 cm^{-1}; HRMS (FAB) calcd for $C_{17}H_{21}N_2O_3$ (M + H$^+$) 301.1552, found 301.1533.

Preparation of *N*,*N*′-Bis(ethyl 4-carboxylbenzyl)urea 2i. Procedure A afforded **2i** in 36% yield. Procedure C afforded **2i** in 55% yield: ^1H NMR (DMSO-d_6) δ 7.91 (d, $J = 8.2$ Hz, 4H), 7.38 (d, $J = 8.2$ Hz, 4H), 6.65 (br t, 2H), 4.31 (s, 4H), 4.30 (qt, 4H), 1.32 (t, 6H); ^{13}C NMR (DMSO-d_6) δ 165.7, 158.1 (C=O), 146.7, 129.1, 128.2, 127.0, 60.6, 42.8, 14.2; IR (CH_2Cl_2) 1708, 1678 cm^{-1}; HRMS (FAB) calcd for $C_{21}H_{25}N_2O_5$ (M + H$^+$) 385.1763, found 385.1760.

Preparation of *N*,*N*′-Bis(4-carboxylic acid benzyl)urea 2j. Procedure C was employed except that the product **2j** did not precipitate out until the reaction mixture was acidified with 1 N HCl. Urea **2j** was obtained in 37% yield: ^1H NMR (DMSO-d_6) δ 12.89 (s, 2H), 7.88 (d, $J = 7.6$ Hz, 4H), 7.35 (d, $J = 7.8$ Hz, 4H), 6.62 (t, 2H), 4.29 (d, $J = 5.9$ Hz, 4H); ^{13}C NMR (DMSO-d_6) δ 167.2, 158.1 (NHC=O), 146.2, 129.3, 126.9, 109.4, 42.8; IR (Nujol) 1684, 1561 cm^{-1}; MS (electrospray) for $C_{17}H_{16}N_2O_5$ [M + H$^+$] 329.3, calcd 329.3.

Preparation of *N*,*N*′-Bis(4-ethenylbenzyl)urea 2k. When procedure A was employed, no product was isolated. The viscous material obtained suggested the formation of oligomers. Procedure B afforded a 69% yield of **2k**. When procedure C was employed, **2k** was only isolated in 19% yield: ^1H NMR (DMSO-d_6) δ 7.40 (d, $J = 7.9$ Hz, 4H), 7.21 (d, $J = 7.9$ Hz,

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4H), 6.70 (qt, 2H), 6.45 (br s, 2H), 5.78 (d, $J = 17.7$ Hz, 2H), 5.21 (d, $J = 10.9$ Hz, 2H), 4.21 (d, $J = 5.6$ Hz, 4H); ^{13}C NMR (DMSO-d_6) δ 158.1 (C=O), 140.7, 136.4, 135.5, 127.2, 126.0, 113.7, 42.7; IR (CH_2Cl_2) 1678 cm^{-1}. Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 74.70; H, 6.95; N, 9.03.

Preparation of N,N′-Bis(4-nitrobenzyl)urea 2l. Procedure A afforded **2l** in 45% yield. Procedure C afforded **2l** in 76% yield: ^{1}H NMR (DMSO-d_6) δ 8.20 (d, $J = 8.5$ Hz, 4H), 7.51 (d, $J = 8.5$ Hz, 4H), 6.85 (br t, 2H), 4.34 (d, $J = 6.0$ Hz, 4H); ^{13}C NMR (DMSO-d_6) δ 158.0 (C=O), 149.3, 146.2, 127.8, 123.4, 42.6; IR (Nujol) 1584, 1537 cm^{-1}. Anal. Calcd for $C_{15}H_{14}N_4O_5$: C, 54.54; H, 4.27; N, 16.96. Found: C, 54.07; H, 4.23; N, 16.66.

Preparation of N,N′-Bis(4-cyanobenzyl)urea 2m. Procedure A afforded **2m** in 37% yield. Procedure C afforded **2m** in 68% yield: ^{1}H NMR (DMSO-d_6) δ 7.80 (d, $J = 7.3$ Hz, 4H), 7.44 (d, $J = 7.0$ Hz, 4H), 6.79 (br s, 2H), 4.31 (d, $J = 4.9$ Hz, 4H); ^{13}C NMR (DMSO-d_6) δ 158.0 (C=O), 147.1, 132.2, 127.7, 119.0, 109.2, 42.7; IR (CH_2Cl_2) 2214, 1678 cm^{-1}; HRMS (FAB) calcd for $C_{17}H_{15}N_4O$ (M + H$^+$) 291.1246, found 291.1249.

Preparation of *N,N′*-Bis(4-aminobenzyl)urea 2n. When procedure A was employed, the reaction formed a solid black mass. Procedure B afforded the urea **2n** in 28% yield after recrystallization in EtOH. Procedure C afforded **2n** in 14% yield. The urea **2n** was identified by comparison with literature values.[44]

Preparation of 3,4-Dihydro-2(1*H*)-quinazolinone 2o. Procedure A afforded **2o** in 17% yield. Procedure C afforded **2o** in 20% yield. The urea **2o** was identified by comparison with literature values.[44]

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Supporting Information Available: ^{1}H NMR spectra of ureas **2b**−**d**, **2f**−**g**, and **2i**−**j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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