Catalytic Oxidative Carbonylation of Primary and Secondary Diamines to Cyclic Ureas. Optimization and Substituent Studies

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$W(CO)_6$-catalyzed oxidative carbonylation of 1,3-propanediamine to the corresponding urea has been examined under a variety of conditions. Following optimization, the Thorpe−Ingold effect on ring closure was studied using 2,2-dialkyl-1,3-propanediamines. For the 2,2-dimethyl- and 2,2-dibutyl-1,3-propanediamines, the yields were increased significantly as compared to that of the unsubstituted case. The eight-membered cyclic urea 5-butyl-5-ethyl-1,3-diazepan-2-one (**5f**) was formed in 38% yield, while only trace amounts of the cyclic urea were produced from the parent 1,5-pentanediamine. In a study of secondary diamines, yields from the carbonylation of *N*,*N*′-dialkyl-2,2-dimethyl-1,3-propanediamines were lower than those obtained from the primary diamines. The main byproducts from secondary diamines were tetrahydropyrimidine derivatives formed from a competitive reaction of the substrate with the oxidant and base.

Introduction

Cyclic ureas have recently attracted attention due to their presence in biologically active molecules, such as the HIV protease inhibitors DMP 323 and DMP 450.[1] Furthermore, cyclic ureas have found use as chiral auxiliaries for asymmetric synthesis.[2−4] Among the reported methods for synthesis of cyclic ureas,[5] the earliest involved the nucleophilic attack of primary diamines on phosgene.[6−9] The primary diamines can be silylated before treatment with phosgene if polymerization is problematic.[10] More recently, phosgene itself has been replaced by derivatives such as 1,1-carbonyldiimidazole (CDI).[11−14] Other carbonyl sources that have been used in the preparation of cyclic ureas include dialkyl carbonates,[15,16] dialkyl dithiocarbonates,[17] carbonyl sulfide,[18] carbonyl selenide,[19] carbon dioxide,[20] and urea.[2−4]

The conversion of ethylenediamine to 2-imidazolidinone has served as a test case for many of these reagents. Despite the generally facile closure of five-membered rings, phosgene itself affords the cyclic urea from ethylenediamine in only 13% yield.[6] In comparison, *S*,*S*-dimethyl dithiocarbonate[17] or hexachloroacetone[21] can be used to convert ethylenediamine to the imidazolidinone in 80−90% yield. Carbonate derivatives such as disuccinimido carbonate (DSC)[15] and benzyl succinimido carbonate[22] also generate the product urea in 80−90% yield. Urea itself can be transaminated in the presence of water to produce the imidazolidinone from ethylenediamine in about 75% yield.[23]

Despite multiple synthetic routes to prepare cyclic ureas directly from primary diamines, there is still room for further development of methodology. The direct conversion of secondary diamines to *N*,*N*′-disubstituted cyclic ureas is plagued by the difficulty of preparing tetrasubstituted ureas.[24] As a result, *N*,*N*′-disubstituted

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cyclic ureas are generally prepared either by reaction of phosgene[6,25,26] or urea[27] with the secondary diamine or by *N*-alkylation of the unsubstituted ring structures.[28−31] Also, there are problems with the use of phosgene and its derivatives.[32] Phosgene is highly toxic and corrosive, and phosgene derivatives can be expensive to use on a large scale. The direct metal-catalyzed conversion of diamines and CO to cyclic ureas could provide an attractive alternative to the use of phosgene and its derivatives.

Although catalytic carbonylation has been investigated for some time,[33−35] the topic remains of interest. Other groups have reported catalytic conversion of primary amines and CO to acyclic ureas using complexes of several transition metals including Ni,[36] Pd,[37−39] Ru,[40] Mn,[41,42] and Co.[43] Main-group elements such as sulfur[44,45] and selenium[46−49] have also been reported to catalyze this reaction.

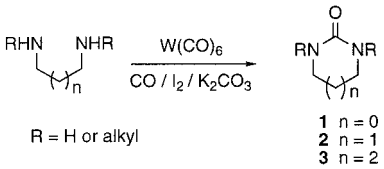
Reports of catalytic carbonylation of diamines to cyclic ureas are rarer. The selenium-catalyzed reaction can produce high yields, but certain substrates such as 2-(2-aminoethyl)aniline afford the cyclic urea only in the presence of stoichiometric or excess selenium.[46−48] Transition-metal-catalyzed carbonylation of diamines has generally yielded cyclic ureas only as minor products. Carbonylation of the diamines $H_2N(CH_2)_nNH_2$ (n = 2−4, 6) catalyzed by $Mn_2(CO)_{10}$ produces no cyclic products when n = 2, 4, or 6 and only 6% of the six-membered urea when n = 3.[42] Carbonylation of ethylenediamine catalyzed by $Ni(CO)_4$ affords 2-imidazolidinone as a minor product in 10% yield.[50] In addition to the catalytic processes using CO as the carbonyl source, there is a related conversion of both primary and secondary diamines to cyclic ureas with CO_2 using Ph_3SbO/P_4S_{10} as catalyst.[51]

Disadvantages exist for both the main-group- and transition-metal-catalyzed amine carbonylation reactions that have been previously reported. For the main-group catalysts, selenium-catalyzed carbonylation generates hydrogen selenide as a byproduct and certain substrates require stoichiometric or excess selenium.[46−48] Aromatic amines are also problematic in the selenium-catalyzed reactions,[19] although a switch from elemental selenium to K_2SeO_3 has been reported to produce high yields of 1,3-diarylureas.[52] The transition-metal-catalyzed reactions usually require stringent reaction conditions such as high temperatures and pressures. Moreover, yields from aliphatic amines tend to be lower than those from aromatic substrates when transition-metal catalysts are used.

In an effort to improve upon the transition-metal-catalyzed amine carbonylation methods, we have explored the use of tungsten catalysts.[53−57] We previously reported preliminary studies on the catalyzed oxidative carbonylation of α,ω-diamines to cyclic ureas using $W(CO)_6$ as catalyst and I_2 as the oxidant.[55] Those preliminary results established that both primary and secondary diamines are substrates for the reaction. We have now expanded the range of substrates and carried out optimization studies. The results of these further investigations are reported here.

Results and Discussion

Optimization of Reaction Conditions. In the initial paper on $W(CO)_6$-catalyzed oxidative carbonylation of primary and secondary α,ω-diamines to cyclic ureas (eq 1),[55] we reported conversion of 1,3-propanediamine to the corresponding urea in 52% yield. Ring closure of this substrate under varying conditions has subsequently been examined.



As seen in Table 1, yields of the cyclic urea were

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Table 1. Effect of Solvent and Temperature Variation on the Catalytic Carbonylation of 1,3-Propanediamine

solvent	*T* (°C)	yield[a,b] (%)	solvent	*T* (°C)	yield[a,b] (%)
CH_2Cl_2	0[d]	23	THF	25	28
CH_2Cl_2	25	52	THF	50	22
CH_2Cl_2	50	33	CH_2Cl_2/H_2O[c]	25	33
CH_2Cl_2	90	24	CH_2Cl_2/H_2O[c]	50	23
$CHCl_3$	0[d]	21	Et_2O	25	24
$CHCl_3$	25	43	Et_2O/H_2O	25	13
$CHCl_3$	50	29	$PhCF_3$	25	16
EtOAc	25	32	$PhCF_3/H_2O$	25	12
EtOAc	50	21			

[a] Isolated yield of tetrahydro-2-pyrimidinone calculated per equivalent of diamine. [b] Reaction conditions: 1,3-propanediamine (4.27 mmol), $W(CO)_6$ (0.0425 mmol), I_2 (3.84 mmol), K_2CO_3 (8.9 mmol), solvent (90 mL), 80 atm of CO, 24 h. [c] CH_2Cl_2, 80 mL; H_2O, 10 mL. [d] The reaction time was increased to 72 h.

lowered upon raising the temperature. Instead, reaction mixtures from higher temperature reactions contained larger amounts of intractable material that we have attributed to oligomers. Lowering the temperature to 0 °C and increasing the reaction time to 72 h also resulted in decreased yields.

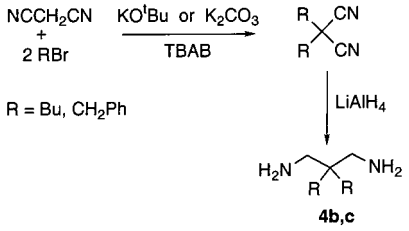
Different solvents were also explored at room temperature and 50 °C. As seen in Table 1, of the solvents examined, yields were highest in CH_2Cl_2, with $CHCl_3$ producing comparable but somewhat lower yields. Although the addition of water to produce a biphasic CH_2Cl_2/H_2O solvent system resulted in dramatically increased yields of ureas from substituted benzylamines,[57] similar improvements are not observed using 1,3-propanediamine.

One problem with 1,3-propanediamine as a substrate arises from the solubility of the product in water. Our inability to use the standard aqueous Na_2SO_3 wash and extraction to remove residual I_2 and inorganic salts from the reaction mixtures led us to examine different workup procedures. A "dry wash" method, in which $Na_2S_2O_4$ slurry was stirred vigorously with the reaction mixture for 30 min, was more successful. Although sublimation of the product was required to obtain analytically pure material, this method made the workup procedure more straightforward.

Oxidative carbonylation of 1,2-ethylenediamine under the optimized conditions produced 2-imidazolidinone (**1**) in 40% yield. The seven-membered cyclic urea 1,3-diazepan-2-one (**3**) was prepared in 38% yield under the same conditions. Individual optimizations for different substrates were not carried out.

Effect of Substitution in the Linker of Primary Diamines. Previous studies on oxidative carbonylation of diamines have established that preparation of the parent five-, six-, and seven-membered cyclic ureas can be achieved in moderate yields.[55] However, these are intrinsically difficult substrates in two regards. First, their solubility in water leads to difficulties with the workup (vide supra). In addition, ring closure of the unsubstituted diamines cannot take advantage of the Thorpe−Ingold effect[58] to facilitate ring closure. To explore the influence of substitution in the linker, a study

Scheme 1



of the carbonylation of several substituted diamines was undertaken.

The 2,2-dialkyl-1,3-propanediamines **4a**−**c** were chosen as the first set of substrates because in the initial study, the carbonylation of 1,3-propanediamine gave the highest yield of cyclic urea. In addition, diamine **4a** is commercially available. The other requisite diamines (**4b,c**) were synthesized by the double alkylation of malononitrile to afford the corresponding disubstituted dinitrile compound followed by reduction with lithium aluminum hydride to yield the diamine[59] (Scheme 1). Acceptable yields (60−70%) were obtained for each step where R = benzyl and butyl.

The 2,2-dialkyl-1,3-propanediamine substrates **4a**−**c** were subjected to the oxidative carbonylation conditions as described in Table 2. For the methyl and butyl cases, the yields were significantly higher than for the unsubstituted case. 2,2-Dimethyl-1,3-propanediamine (**4a**) produced its respective *N*,*N*′-disubstituted urea **5a** in 80% yield, while the butyl derivative **4b** afforded the cyclic urea in 70% yield. Yields from the benzyl substrate **4c** were somewhat lower.

Further studies on diamines **4d,e** probed the effects of methyl substitution on the formation of five-membered rings. In contrast to the results from substrates **4a,b**, the yields of cyclic ureas **5d,e** were comparable to those of the unsubstituted cases. This can be attributed to competing effects of the methyl groups. On one hand, the Thorpe−Ingold effect would be expected to facilitate ring closure by bringing the amino groups closer on average. However, the methyl groups also introduce steric hindrance around the amino groups, a factor that has been found to lower the yields in oxidative carbonylation of alkylamines to dialkylureas.[57]

A more promising result was obtained in the oxidative carbonylation of pentanediamine **4f**. Although the parent 1,5-pentanediamine produced the eight-membered cyclic urea in only trace amounts,[55] the disubstituted eight-membered ring urea **5f** was formed in 38% yield under similar reaction conditions. Apparently, the alkyl substituents promote ring closure. It is thus possible that other substituent patterns and/or conformational constraints could render this method more general for the formation of eight-membered cyclic ureas.

Effect of Substitution in the Linker of Secondary Diamines. On the basis of the promising results obtained for carbonylation of substituted primary diamines, we carried out a similar study on the carbonylation of secondary diamines to *N*,*N*′-disubstituted cyclic ureas. The substrates for this investigation were derived from 2,2-dimethylpropane-1,3-diamine because **4a** could be converted to **5a** in 80% yield. The secondary diamine substrates **4g** and **4h** were synthesized by CsOH-

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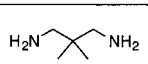
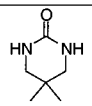
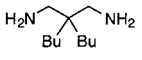
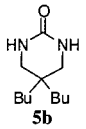
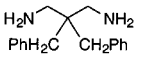
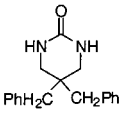
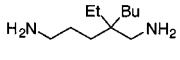
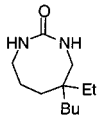
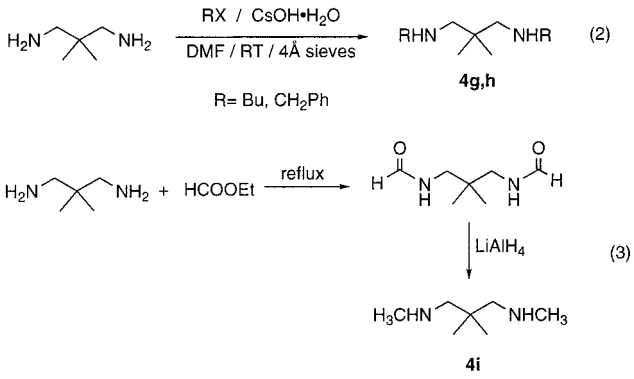
Table 2. Oxidative Carbonylation of Substituted Primary Diamines

Amine	Product	% Yield[a,b]
 **4a**	 **5a**	80
 **4b**	 **5b**	70
 **4c**	 **5c**	48[c]
 **4d**	 **5d**	50[c]
 **4e**	 **5e**	33[c]
 **4f**	 **5f**	38

[a] Isolated yield of urea calculated per equivalent of amine. [b] Reaction conditions: amine (7.07 mmol), $W(CO)_6$ (0.28 mmol), I_2 (7.1 mmol), K_2CO_3 (14.4 mmol), CH_2Cl_2 (40 mL), 90 °C, 80 atm of CO, 24 h. [c] Reaction conditions as in footnote *b* except 25 °C.

promoted *N*-alkylation,[60] which produced the requisite substituted secondary diamines in moderate to good yields (eq 2). Due to difficulties in preparing **4i** by direct alkylation, an alternative preparation via reduction of the diformamide[61] was utilized for that particular substrate (eq 3).

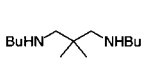
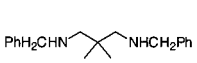
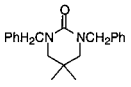
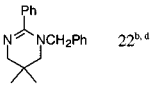
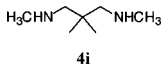
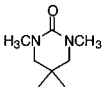
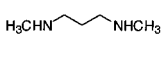
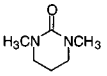


(2)

(3)

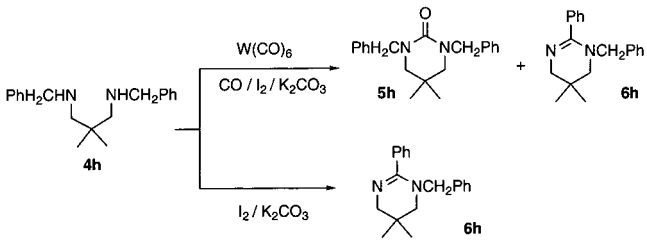
In contrast to the behavior of *gem*-dialkyl-substituted primary diamines **4a**−**c**, in which the improved solubility properties and Thorpe−Ingold effect combined to raise the urea yields with respect to that of the parent propanediamine, *gem*-dialkyl substitution was detrimental in the carbonylation of secondary diamines. As shown in Table 3, yields from the carbonylation of substituted secondary diamines are lower than those previously obtained from *N*,*N*′-dimethylpropane-1,3-diamine (**4j**).[55] Diamines **4g** and **4h** produced the corresponding ureas **5g** and **5h** in low yields, and concomitant formation of tetrahydropyrimidine derivatives occurred in both cases. In an attempt to make urea formation faster than the accumulation of byproducts, the reaction was carried out at 90 °C. Unfortunately, there was no improvement in the yield of the urea. Subsequent control experiments established that the tetrahydropyrimidine formation did not require the presence of the catalyst or CO (Scheme 2). In the experiment without CO, the benzyl-substituted diamine afforded an 80% yield of the tetrahydropyrimidine **6h** under the same conditions. Furthermore, in the absence of both CO and the catalyst, **6h** was still formed in 33% yield.

Table 3. Oxidative Carbonylation of Substituted Secondary Diamines

Amine	Product	% Yield[a]	Product	% Yield[a]
 **4g**	 **5g**	10[b,d]	 **6g**[e]	17[b,d]
 **4h**	 **5h**	19[b,d]	 **6h**[e]	22[b,d]
4h	**5h**	28[c,d]	**6h**	51[c,d]
 **4i**	 **5i**	37[b,d]	 **6i**	0[b,d]
 **4j**	 **5j**	52[f]		

[a] Isolated yield of urea calculated per equivalent of amine. [b] Reaction conditions: amine (7.07 mmol), $W(CO)_6$ (0.28 mmol), I_2 (7.1 mmol), K_2CO_3 (14.4 mmol), CH_2Cl_2 (40 mL), room temperature, 80 atm of CO, 24 h. [c] Reaction conditions as in footnote *b* except the solvent was CH_2Cl_2 (35 mL) plus H_2O (5 mL). [d] This work. [e] Isolated as the hydroiodide salt. [f] Reference 55.

Scheme 2



The formation of tetrahydropyrimidines **6g** and **6h** from the secondary diamines **4g** and **4h** was unexpected since we had previously carbonylated several secondary diamines to the corresponding cyclic ureas[55] (e.g., the

(60) Salvatore, R. N.; Nagle, A. S.; Schmidt, S. E.; Jung, K. W. *Org. Lett.* **1999**, *1*, 1893−1896.
(61) Betschart, C.; Schmidt, B.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 1999−2021.

conversion of the parent *N*,*N*′-dimethylpropanediamine **4j** to urea **5j)**. Although the yield of **5j** was moderate, no major byproduct was detected in the reaction mixtures. The difference in the behavior of **4g,h** vs **4j** led us to prepare **4i** to determine whether the tetrahydropyrimidine formation was due to conformational effects from the *gem*-dimethyl group in the backbone of **4g,h** or the presence of the larger *N*-alkyl groups. As expected from the reactivity of **4j**, *N*,*N*′-dimethyldiamine **4i** produced urea **5i** in 37% yield. Attempts to detect tetrahydropyrimidine **6i** among the reaction products by ^{1}H NMR spectroscopy and GC−MS were unsuccessful. The mechanism for the formation of tetrahydropyrimidines is not clear yet. However, for the diaminopropane substrates, the critical feature for competitive tetrahydropyrimidine formation appears to be the presence of an alkyl substituent larger than a methyl group. In light of these results, it is also interesting to note that the five-membered cyclic urea can be obtained from *N*,*N*′-diethylethylenediamine in 46% yield and *N*,*N*′-dibenzylethylenediamine can also be converted to the corresponding urea.[55] Clearly, the sizes of the ring, backbone substituents, and *N*-alkyl substituent are involved in a complex interplay which determines the ratio of urea to alternative heterocyclic products.

Another possible cause of the modest yields of ureas may involve the difficulties encountered in deprotonating the byproduct amine salts of secondary substrates.[56] Amine salts are produced during the oxidative carbonylation, and in previous experiments with secondary amines, the amine salts have been detected in significant quantities in the reaction mixtures despite attempts to scavenge the protons with base.

Conclusion

In conclusion, optimization studies on the carbonylation of propane-1,3-diamine have been carried out. Yields of cyclic ureas are significantly higher for the 2,2-dialkyl-1,3-propanediamines as a result of the Thorpe−Ingold effect and improved solubility in organic solvents during workup. 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 derivatives were formed in significant amounts when the substrates bore *N*-alkyl substituents larger than methyl. Comparison of these results with previously reported carbonylations of secondary diamines to form five-membered cyclic ureas suggests that the effects of ring size and *N*-substituent size on the carbonylation reaction are complex. On the basis of these results, primary diamines with substituted linkers are promising substrates for this reaction, making utilization of catalytic carbonylation in more complex systems a possibility.

Experimental Section

General Information. Diethyl ether and tetrahydrofuran were distilled from sodium/benzophenone. Methylene chloride and chloroform were distilled over calcium hydride. *N*,*N*-Dimethylformamide and ethyl acetate were dried with 4 Å molecular sieves. All other chemicals were purchased in reagent grade and used with no further purification unless stated otherwise. Diamines were purchased unless specified below. $W(CO)_6$ was purified by chromatography on alumina using hexane as eluent.

General Procedure for the Catalytic Carbonylation of Unsubstituted Primary Diamines with $W(CO)_6$. The following procedure is typical for the parent primary diamines. To a stirred solution of $W(CO)_6$ (15 mg, 0.042 mmol) in 90 mL of CH_2Cl_2 in the glass liner of a 300 mL Parr high-pressure vessel were added 1,3-diaminopropane (0.35 mL, 4.27 mmol), K_2CO_3 (1.2 g, 8.9 mmol), and I_2 (0.97 g, 3.8 mmol). The vessel was then charged with 80 atm of CO, and the solution was stirred under pressure at room temperature for 24 h. The pressure was released, and the maroon solution was filtered away from a red solid. The CH_2Cl_2 was removed by evaporation and the residue washed with methanol, while the initial red solid was rinsed with methanol. The methanol layer was treated with 3 g of $Na_2S_2O_4$ that had been slurried with 2 mL of deionized water. The solution was then stirred vigorously for 30 min. The $Na_2S_2O_4$ was removed by filtration, and the solution was concentrated to obtain a pale yellow powder. The yellow powder was then sublimed to obtain a white solid (0.23 g, 52% yield). The solid was identified as tetrahydro-2-pyrimidinone (**2**) by comparison with an authentic sample.

2-Imidazolidinone (1). The general procedure afforded the product in 40% yield. The product was identified as 2-imidazolidinone by comparison with an authentic sample.

1,3-Diazepan-2-one (3). The general procedure afforded the product in 38% yield. The product was identified as 1,3-diazepan-2-one by comparison of its spectroscopic data with literature values.[62,63]

General Procedure for the Synthesis of 2,2-Dialkylmalononitriles. The following procedure is typical. To a two-necked flask provided with a reflux condenser were added malononitrile (1.65 g, 25 mmol), *n*-butyl bromide (7.5 g, 55 mmol), and tetrabutylammonium bromide (0.52 g, 1.6 mmol). After the reaction mixture had been stirred for 30 min at room temperature, potassium *tert*-butoxide (6.17 g, 55 mmol) was added little by little at 0 °C, and the stirring was continued for 18 h. The reaction mixture was washed with CH_2Cl_2, and the organic fractions were combined and concentrated in vacuo. The crude product mixture was further purified by flash chromatography on silica gel (CH_2Cl_2/hexanes, 1:1) to afford pure 2,2-dibutylmalononitrile in 67% yield. The product was identified by comparison with literature data.[64]

2,2-Dibenzylmalononitrile. From 2.64 g of malononitrile and 15.05 g of benzyl bromide, the general procedure afforded the product in 58% yield. The product was identified by comparison with literature data.[64]

General Procedure for the Synthesis of 2,2-Dialkylpropane-1,3-diamines. The following procedure is typical. To a suspension of lithium aluminum hydride (0.9 g, 24 mmol) in 50 mL of dry diethyl ether at 0 °C was added a solution of 2,2-dibutylmalononitrile (1.7 g, 9.5 mmol) in 30 mL of diethyl ether. After the addition was complete, the mixture was heated under reflux for 1 h and then stirred at room temperature for another 24 h. Water (5 mL) was then added to hydrolyze the remaining $LiAlH_4$. The granular solid was isolated by vacuum filtration and washed with diethyl ether. The ether layer was dried with $MgSO_4$ and filtered. Removal of the solvent afforded pure 2,2-dibutylpropane-1,3-diamine (**4b**) as a colorless oil in 70% yield. ^{1}H NMR ($CDCl_3$): δ 3.54 (br, 4H), 2.74 (s, 4H), 1.30 (m, 8H), 1.13 (t, J = 3.6 Hz, 4H), 0.88 (t, J = 7.2 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 45.9, 40.2, 32.1, 25.0, 23.6, 14.1. HRMS (FAB): m/z calcd for $C_{11}H_{26}N_2$ ($M + H^+$) 187.2174, found 187.2173.

2,2-Dibenzylpropane-1,3-diamine (4c). The general procedure afforded the product as a colorless oil in 65% yield. ^{1}H NMR ($CDCl_3$): δ 7.15 (m, 10H), 2.60 (s, 4H), 2.47 (s, 4H), 0.99 (br s, 4H). ^{13}C NMR ($CDCl_3$): δ 138.5, 130.3, 129.0, 128.0, 45.1, 40.4, 38.2. HRMS (FAB): m/z calcd for $C_{17}H_{22}N_2$ ($M + H^+$) 255.1861, found 255.1863.

(62) Irsch, G.; Rademacher, P. *J. Mol. Struct.* **1990**, *222*, 265−273.
(63) Lien, E. J.; Guadauska, G.; Chou, J. T. *Spectrosc. Lett.* **1972**, *5*, 293−305.
(64) Diez-Barra, E.; De la Hoz, A.; Moreno, A.; Sánchez-Verdú, P. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2589−2592.

General Procedure for the Catalytic Carbonylation of Substituted Primary Diamines with $W(CO)_6$. Procedure A. The following procedure is typical. To a stirred solution of $W(CO)_6$ (100 mg, 0.284 mmol) in a 40 mL solution of CH_2Cl_2 in the glass liner of a 300 mL Parr high-pressure vessel were added 2,2-dimethyl-1,3-propanediamine (0.85 mL, 7.1 mmol), K_2CO_3 (1.95 g, 14.1 mmol), and iodine (1.8 g, 7.1 mmol). The vessel was then charged with 80 atm of CO, and the solution was stirred under pressure at room temperature for 24 h. The pressure was released, and the maroon solution was filtered away from a yellow solid. The CH_2Cl_2 layer was treated with 3 g of $Na_2S_2O_4$ that had been slurried with 2 mL of deionized water, and then the solution was stirred vigorously for 30 min. The NaS_2O_4 was removed by filtration, and the solution was concentrated in vacuo. The resulting pale yellow oil was recrystallized from CH_2Cl_2/ether to afford a white solid (0.78 g, 50% yield).

Procedure B. Procedure B is identical to procedure A except that the CH_2Cl_2 layer was washed with a 1.0 M HCl solution followed by a saturated $Na_2S_2O_4$ solution. The resulting pale yellow solution was then dried with $MgSO_4$ and filtered. The solution was concentrated in vacuo. The resulting pale yellow oil was recrystallized from CH_2Cl_2/ether to afford a white solid.

5,5-Dimethyltetrahydro-2(1*H*)-pyrimidinone (5a). Procedure A at room temperature afforded the product in 50% yield. Procedure A at 90 °C afforded the product in 80% yield. The solid was identified as 5,5-dimethyltetrahydro-2(1*H*)-pyrimidinone by comparison with literature data.[17]

5,5-Dibutyltetrahydro-2(1*H*)-pyrimidinone (5b). From 0.35 g of 2,2-dibutylpropane-1,3-diamine, procedure B afforded the product as a yellow solid in 63% yield. IR (CH_2Cl_2): ν_{CO} 1678 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.15 (br, 2H), 2.95 (s, 4H) 1.28 (m, 12H), 0.87 (t, J = 7 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 157.0 (C═O), 48.9, 32.7, 32.6, 25.2, 23.2, 14.0. HRMS (FAB): m/z calcd for $C_{12}H_{24}N_2O$ ($M + H^+$) 213.1966 found 213.1970.

5,5-Dibenzyltetrahydro-2(1*H*)-pyrimidinone (5c). Procedure B afforded the product as a yellow solid in 48% yield. IR (CH_2Cl_2): ν_{CO} 1671 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.33 (m, 10H), 4.12 (br s, 2H), 3.08 (s, 4H), 2.38 (s, 4H). ^{13}C NMR ($CDCl_3$): δ 164.5 (C═O), 136.4, 130.6, 128.1, 126.6, 46.5, 40.3, 34.7. HRMS (FAB): m/z calcd for $C_{18}H_{20}N_2O$ ($M + H^+$) 281.1654, found 281.1658.

4,4-Dimethyltetrahydro-2*H*-imidazol-2-one (5d). Procedure A at room temperature afforded the product in 50% yield. Procedure A at 90 °C afforded the product in 30% yield. The product was identified by comparison with literature data.[17]

4-Methyltetrahydro-2*H*-imidazol-2-one (5e). Procedure A at room temperature afforded the product in 20% yield. Procedure A at 90 °C afforded the product in 30% yield. The product was identified by comparison with literature data.[65]

5-Butyl-5-ethyl-1,3-diazepan-2-one (5f). Procedure B afforded the product as a white solid in 38% yield. Mp: 55−57 °C. IR (CH_2Cl_2): ν_{CO} 1651 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.59 (br, 1H), 5.32 (br, 1H), 3.31 (s, 2H), 3.00 (m, 2H), 1.66 (m, 2H), 1.42 (m, 2H), 1.11 (m, 8H), 0.83 (t, J = 6.9 Hz, 3H), 0.70 (t, 3H, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$): δ 160.7 (C═O), 48.7, 41.4, 40.4, 33.8, 28.9, 27.0, 25.9, 24.9, 23.4, 14.1, 7.3. HRMS (FAB): m/z calcd for $C_{12}H_{24}N_2O$ ($M + H^+$) 213.1966, found 213.1971.

General Procedure for the Synthesis of *N,N′*-Dialkyl-2,2-dimethylpropane-1,3-diamines. The following procedure is typical. To activated powdered 4 Å molecular sieves (2 g) in anhydrous *N,N*-dimethylformamide (15 mL) was added cesium hydroxide monohydrate (5.6 g, 34 mmol). After the white suspension was vigorously stirred for 10 min, 2,2-dimethylpropane-1,3-diamine (2.02 mL, 16 mmol) was added. Following an additional 30 min of stirring, 1-bromobutane (4.0 mL, 37 mmol) was added to the white suspension. The reaction was stirred for 20 h, filtered to remove the molecular sieves and undissolved inorganic salts, and rinsed with EtOAc. After the filtrate was concentrated in vacuo, the residue was taken up in 1 N NaOH and extracted with EtOAc. The solvent was removed, and the crude product was chromatographed on neutral alumina using EtOAc/MeOH as eluent to afford clean *N,N′*-dibutyl-2,2-dimethyl-1,3-propanediamine (**4g**) as a colorless oil in 67% yield. ^1H NMR ($CDCl_3$): δ 2.52 (t, J = 6.6 Hz, 4H) 2.38 (s, 4H), 1.41 (m, 4H), 1.30 (m, 4H), 0.87 (s, 6H), 0.83 (t, J = 7.5 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 60.7, 50.6, 34.6, 32.1, 24.8, 20.4, 14.0. Anal. Calcd for $C_{13}H_{30}N_2$: C, 72.94; N, 13.32; H, 14.46. Found: C, 72.08; N, 13.06; H, 14.10.

***N,N′*-Dibenzyl-2,2-dimethylpropane-1,3-diamine (4h).** The general procedure afforded the product as a colorless oil in 43% yield from 1.63 g of 2,2-dimethyl-1,3-propanediamine. ^1H NMR ($CDCl_3$): δ 7.21 (m, 10H), 3.68 (s, 4H), 2.37 (s, 4H), 0.84 (s, 6H). ^{13}C NMR ($CDCl_3$): 140.7, 128.2, 127.9, 126.6, 59.0, 54.5, 34.7, 24.8. HRMS (FAB): m/z calcd for $C_{19}H_{26}N_2$ ($M + H^+$) 283.2174, found 283.2178.

***N,N′*-Diformyl-2,2-dimethylpropane-1,3-diamine.** The diamine was synthesized according to a literature procedure and identified by comparison with published data.[65]

***N,N′*-Dimethyl-2,2-dimethylpropane-1,3-diamine (4i).** To a mixture of 250 mL of Et_2O and 10 g of $LiAlH_4$ (95%) at 0 °C was added 9.88 g (62.5 mmol) *N,N′*-diformyl-2,2-dimethylpropane-1,3-diamine in small portions. After the addition was finished, the reaction mixture was stirred at room temperature for 20 h. The mixture was then hydrolyzed with Et_2O and H_2O, and the white solid was removed by filtration through Celite. After the filtrate was dried over $MgSO_4$, removal of the solvent afforded **4i** as 6.1 g (75% yield) of a colorless oil. The product was identified by comparison with literature data.[61]

General Procedure for the Catalytic Carbonylation of Secondary Diamines. The following procedure is typical. To a stirred solution of $W(CO)_6$ (50 mg, 0.14 mmol) in 40 mL of CH_2Cl_2 in the glass liner of a 300 mL Parr high-pressure vessel were added *N,N′*-dibutyl-2,2-dimethylpropane-1,3-diamine (0.85 mL, 3.6 mmol), K_2CO_3 (0.98 g, 7.1 mmol), and iodine (0.90 g, 3.6 mmol). The vessel was then charged with 80 atm of CO, and the solution was stirred under pressure at room temperature for 24 h. After the pressure was released, a yellow solid was removed from the maroon solution by filtration. The CH_2Cl_2 layer was washed first with a 1.0 M HCl solution and then with saturated $Na_2S_2O_4$ solution. The resulting pale yellow solution was then dried with $MgSO_4$ and filtered. The solution was concentrated in vacuo. The crude mixture was chromatographed on neutral alumina (EtOAc/MeOH) to afford pure 1,3-dibutyl-5,5-dimethyltetrahydro-2(1*H*)-pyrimidinone (**5g**) as a yellow oil in 10% yield. To isolate 1-butyl-2-propyl-5,5-dimethyl-1,4,5,6-tetrahydropyrimidine (**6g**), the crude mixture was washed with EtOAc and MeOH instead of chromatography to afford the hydroiodide salt **6g**·HI as a white solid in 17% yield. The following are the data for **5g**. IR (CH_2Cl_2): ν_{CO} 1622 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.23 (t, J = 7.5 Hz, 4H), 2.87 (s, 4H), 1.42 (m, 4H), 1.27 (m, 4H), 0.98 (s, 4H), 0.89 (t, J = 7.2 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 155.1 (C═O), 57.3, 47.0, 29.9, 28.3, 24.4, 20.0, 13.8. HRMS (FAB): m/z calcd for $C_{14}H_{28}N_2O$ ($M + H^+$) 241.2273, found 241.2241. The following are the data for **6g**·HI. Mp: 106−107 °C. ^1H NMR ($CDCl_3$): δ 9.91 (br s, 1H), 3.38 (t, J = 7.5 Hz, 2H), 3.19 (s, 2H), 3.11 (s, 2H), 2.79 (t, J = 7.8 Hz, 2H), 1.82 (m, 2H), 1.62 (m, 2H), 1.38 (m, 2H), 1.1 (t, J = 7.5 Hz, 3H), 1.07 (s, 6H), 0.99 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 163.0 (C═N), 57.5, 51.8, 49.6, 32.5, 30.3, 26.6, 24.2, 21.3, 19.9, 13.9, 13.8. HRMS (FAB): m/z calcd for $C_{13}H_{27}IN_2$ ($M - I$)$^+$ 211.2174, found 211.2172. Anal. Calcd for $C_{13}H_{27}IN_2$: C, 46.16; H, 8.05; N, 8.28. Found: C, 46.15; H, 8.18; N, 8.13.

1,3-Dibenzyl-5,5-dimethyltetrahydro-2(1*H*)-pyrimidinone (5h) and 1-Benzyl-2-phenyl-5,5-dimethyl-1,4,5,6-tetrahydropyrimidine (6h). The general procedure afforded **5h** as a yellow oil in 19% yield and the hydroiodide salt of **6h** as a white solid in 22% yield from 0.27 g of *N,N′*-dibenzyl-2,2-dimethylpropane-1,3-diamine. The following are the data for **5h**. IR (CH_2Cl_2): ν_{CO} 1627 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.24 (m, 10H), 4.52 (s, 4H), 2.77 (s, 4H), 0.82 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 155.7 (C═O), 138.4, 128.3, 128.1, 127.0, 56.7, 51.6, 28.5, 24.4. HRMS (FAB): m/z calcd for $C_{20}H_{24}N_2O$ ($M + H^+$) 309.1971, found 309.1970. The following are the data for **6h**·

(65) Cortes, S.; Kohn, H. *J. Org. Chem.* **1983**, *48*, 2246−2254.

HI. Mp: 198−201 °C. ^{1}H NMR ($CDCl_3$): δ 10.0 (br s, 1H), 7.14−7.80 (m, 10H), 4.58 (s, 2H), 3.39 (s, 2H), 3.30 (s, 2H), 1.05 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 161.7 (C═N), 133.6, 132.7, 129.7, 129.5, 129.0, 128.7, 127.9, 56.5, 56.4, 50.4, 27.0, 24.5. HRMS (FAB): *m*/*z* calcd for $C_{19}H_{23}IN_2$ $(M - I)^+$ 279.1861, found 279.1853. Anal. Calcd for $C_{19}H_{23}IN_2$: C, 56.17; H, 5.71; N, 6.89. Found: C, 56.72; H, 6.10; N, 6.60.

1,3,5,5-Tetramethyltetrahydro-2(1*H*)-pyrimidinone (5i). The crude product from the general procedure was chromatographed on silica using hexane/EtOAc as eluent to afford pure **5i** as a colorless oil in 37% yield from 0.20 g of *N*,*N*′-dimethyl-2,2-dimethylpropane-1,3-diamine. IR (Nujol): ν_{CO} 1644 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.86 (s, 10H), 0.97 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 156.2 (C═O), 60.0, 36.1, 29.1, 24.8. HRMS (FAB): *m*/*z* calcd for $C_8H_{16}N_2O$ (M^+) 156.1262, found 156.1248.

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Supporting Information Available: ^{1}H NMR spectra of compounds **4b,c**,**h** and **5b,c**,**f**−**i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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