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Efficient Synthesis of Ureas by Direct Palladium-Catalyzed Oxidative Carbonylation of Amines

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Received April 1, 2004

A general synthesis of symmetrically disubstituted ureas and trisubstituted ureas by direct Pd-catalyzed oxidative carbonylation of primary amines or of a mixture of a primary and a secondary amine, respectively, with unprecedented catalytic efficiencies for this kind of process, is reported. Reactions are carried out at 90−100 °C in DME as the solvent in the presence of PdI_2 in conjunction with an excess of KI as the catalytic system and under 20 atm of a 4:1 mixture of CO and air. In some cases, working in the presence of an excess of CO_2 (40 atm) in addition to CO and air (60 atm total) had a beneficial effect on substrate reactivity and product yield. Cyclic five-membered and six-membered ureas were easily formed from primary diamines. The methodology has been successfully applied to the synthesis of pharmacologically active ureas, such as those deriving from α-amino esters or urea NPY5RA-972, a potent antagonist of the neuropeptide Y5 receptor.

Introduction

Ureas are a very important class of carbonyl compounds. They find extensive application as agrochemicals, dyes for cellulose fibers, antioxidants in gasoline, resin precursors,[1] and synthetic intermediates,[2] especially for the production of carbamates[3] and isocyanates,[4] whose importance both in industrial and academic fields is well-known. Moreover, many ureic derivatives have displayed a wide spectrum of biological activity.[5] In particular, several substituted ureas have recently been shown to possess a marked inhibiting effect on HIV protease enzyme.[6]

Due to the increasing importance of these compounds, during the last years there has been considerable interest toward the development of new efficient, selective, and environmentally friendly protocols for their preparation, able to supplant the classical syntheses based on phosgene or isocyanates[1,7] (mainly prepared in their turn from phosgene itself).[7d,8] Numerous methods, mainly based on the use of carbonyl derivatives (such as carbonates, carbonyldiimidazole, dicyclohexylcarbodiimide, trihaloacetyl chlorides, and so on) have been reported in the literature.[9] However, the use of such carbonyl derivatives still presents disadvantages from the standpoint of atom economy. In this view, the possibility to produce ureas using a C-1 unit as the carbonyl source, such as CO_2 or CO, is clearly to be preferred.

The carboxylation of amines to ureas (eq 1) usually requires harsh conditions (200 °C and CO_2 pressures higher than 100 atm)[10,11] or the presence of a stoichiometric amount of a dehydrating agent, such as dicyclohexylcarbodiimide, PCl_5, $POCl_3$, and so on.[9a] The reaction has also been reported to occur catalytically, using $RuCl_3$/PBu_3 in the presence of propynyl alcohols as water

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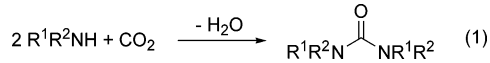
10.1021/jo0494634 CCC: $27.50
Published on Web 06/08/2004

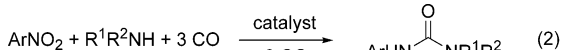
scavengers (at 120−140 °C and 50 atm of CO_2)[12] or Ph_3-SbO/P_4S_{10} in the absence of dehydrating agents (at 80−150 °C and 49 atm of CO_2).[13] Very recently, symmetrically disubstituted ureas have been obtained in modest to excellent yields from primary amines working in ionic liquids in the presence of CsOH at 170 °C and 60 atm of CO_2.[14]



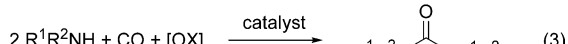
(1)

Carbon monoxide represents a valid alternative to CO_2 as the carbonyl source for the synthesis of substituted ureas. Both the reductive carbonylation of nitro compounds (eq 2) and the direct oxidative carbonylation of amines (eq 3) have been extensively studied.

The reductive carbonylation of nitro compounds is an important method for the synthesis of ureas and can be promoted by several catalysts,[15] mainly based on Pd, Ru, and Rh, and more recently, Se.[16] However, it is usually limited to nitroarenes, since aliphatic nitro compounds tend to lead to different products.[15] On the contrary, oxidative carbonylation of amines can be applied to both aromatic and aliphatic amines. This reaction is particularly interesting when the oxidizing agent is O_2, since in this case it produces water as the coproduct (eq 3, $[OX] = {}^1/_2O_2$, $[OXH_2] = H_2O$]). Many transition metals (including Au,[17] Co,[18] Mn,[19] Ni,[20] Rh,[21] Ru,[21b,22] and especially Pd[23] and, more recently, W[24]) as well as main-group elements (such as sulfur[25] and selenium[26]) have been reported to promote the oxidative carbonylation



(2)



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process. In both cases, there are still disadvantages to be overcome, particularly from the standpoint of catalytic efficiency. Moreover, several procedures are limited to the preparation of symmetrically substituted ureas, while in some instances ureas are obtained in a mixture with different carbonylation products, mainly carbamates and/or oxamides. Importantly, in several cases the oxidative carbonylation process was carried out using mixtures of CO and O_2 that are within the explosion range of CO in O_2.[27]

In this work, we report a full account of our recent accomplishments on the Pd-catalyzed oxidative carbonylation of primary aliphatic or aromatic amines **1** to the corresponding symmetrically disubstituted ureas **2**, with oxygen as the oxidizing agent, and further extension to the synthesis of unsymmetrically trisubstituted ureas. As we have already pointed out in our preliminary communication,[28] the methodology is characterized by unprecedented catalytic efficiencies for this kind of

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reaction, up to 4950 mol of product per mol of catalyst used. This new method has proved useful for the synthesis of very important ureic derivatives, such as cyclic ureas from primary diamines and *N*,*N*-bis(methoxycarbonylalkyl)ureas from primary α-amino esters, still with very high catalytic efficiency. Moreover, the methodology can also be applied for the first time to the direct catalytic preparation of trisubstitued ureas in high selectivity starting from a mixture of a primary and a secondary amine This latter approach has been successfully applied to the synthesis of urea NPY5RA-972, a potent antagonist of the neuropeptide Y5 receptor.[5p]

Results and Discussion

Oxidative Carbonylation of Butylamine. Butylamine **1a** was first used as substrate. The oxidative carbonylation of **1a** was initially carried out at 80 °C under 20 atm of a 4/1 mixture of CO/air[29] in the presence of PdI_2 (0.1 mol %) in conjunction with KI (10 equiv with respect to PdI_2), in 1,4-dioxane as the solvent (0.5 mmol of **1a** per mL of dioxane). After 2 h, GLC analysis of the reaction mixture revealed the formation of 1,3-dibutylurea (DBU) **2a** in 20% GLC yield, together with small amounts (2%) of *N*,*N*′-dibutyloxalamide **5a**, deriving from a double carbonylation process,[23f] at 35% substrate conversion (Table 1, entry 1).[30] Both the substrate conversion rate and product distribution turned out to be considerably dependent on the nature of the solvent (entries 2−6). Thus, while **1a** remained practically unconverted working in a protic solvent such as MeOH (entry 2), higher conversions with respect to dioxane were observed in aprotic dipolar solvents; however, the selectivity of the process in these solvents was in favor of **5a** rather than **2a** (entries 3−5). The use of an aprotic solvent with a polarity similar to that of dioxane (ϵ = 2.21 at 25 °C)[31] but with a higher coordinating ability, such as 1,2-dimethoxyethane (DME) (ϵ = 7.54 at 25 °C, 6.09 at 80 °C),[32] led to a higher selectivity in **2a** (32% at 34% substrate conversion, entry 6). The striking reactivity difference observed in aprotic as compared with aprotic solvents can be related to the effectiveness of the reoxidation of Pd(0) ensuing from the amine carbonylation process (Scheme 1; anionic iodide ligands are omitted for clarity).

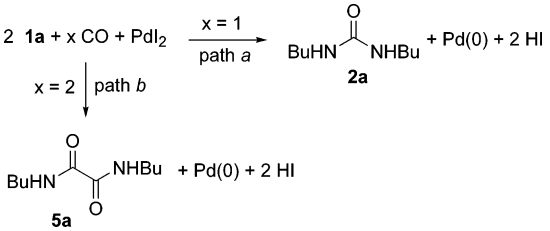
In fact, according to the mechanism we demonstrated several years ago in the case of oxidative dicarbonylation of alkynes,[33] Pd(0) reoxidation under our conditions occurs through oxidation of HI by oxygen, followed by oxidative addition of iodine to Pd(0) (Scheme 2). Clearly, in the presence of a basic substrate such as an amine, an acid−base equilibrium takes place (eq 4), which lowers

TABLE 1. PdI_2-Catalyzed Oxidative Carbonylation Reactions of Butylamine 1a[a]

entry	co-catalyst	solvent	*T* (°C)	*t* (h)	conv of **1**[b] (%)	yield of **2a**[c] (%)	yield of **5a**[c] (%)
1	KI	dioxane	80	2	35	20	2
2	KI	MeOH	80	2	0		
3	KI	DMA	80	2	100	36	54
4	KI	DMSO	80	2	50	4	19
5	KI	NMP	80	2	79	10	24
6	KI	DME	80	2	34	32	2
7	LiI	dioxane	80	2	38	22	3
8	NaI	dioxane	80	2	21	14	3
9	CsI	dioxane	80	2	24	15	1
10	KI[d]	dioxane	80	2	37	30	2
11	KI[e]	dioxane	80	2	36	18	1
12	KCl[f]	dioxane	80	2	0		
13[g]	KI	dioxane	80	2	45	38	3
14	KI	dioxane	100	2	53	34	1
15[h]	KI	dioxane	80	2	55	46	traces
16[i]	KI	dioxane	80	2	0		

[a] Unless otherwise noted, all reactions were carried out using 0.1 mol % of PdI_2 in conjunction with 10 equiv of co-catalyst under 20 atm (at 25 °C) of a 4/1 mixture of CO/air (10 mmol scale based on **1a**, 0.5 mmol of **1a**/mL solvent). [b] Based on starting **1a**, by GLC. [c] GLC yield based on **1a**. [d] The reaction was carried out using 100 equiv of KI with respect to PdI_2. [e] The reaction was carried out using 200 equiv of KI with respect to PdI_2. [f] The reaction was carried out using $PdCl_2$ as catalyst. [g] The reaction was carried out using 1.0 mmol of **1a** per milliliter of dioxane. [h] The reaction was carried out under 60 atm (at 25 °C) of a 4/1/10 mixture of CO/air/CO_2. [i] The reaction was carried out under 44 atm (at 25 °C) of a 1/10 mixture of air/CO_2.

SCHEME 1



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SCHEME 2

$$2\,HI + (1/2)\,O_2 \longrightarrow I_2 + H_2O$$
$$Pd(0) + I_2 \longrightarrow PdI_2$$

the concentration of free HI in solution thus hampering the Pd(0) reoxidation and therefore the overall carbonylation process.

$$\mathbf{1a} + HI \rightleftharpoons Bu\overset{+}{N}H_3 + I^- \quad (4)$$

However, it is well-known that basicity of amines is reduced in aprotic solvents with respect to protic ones.[34] As a consequence, the oxidative carbonylation tends to be inhibited in MeOH but not in aprotic solvents, as we have seen. Interestingly, the *polarity* of the aprotic solvent apparently plays a very important role on the selectivity of the process: the monocarbonylation is strongly favored in low-polar dioxane or DME, while double carbonylation is preferred in the highly polar *N*,*N*-dimethylacetamide (DMA) or *N*-methylpirrolidinone (NMP). The higher nucleophilicity of butylamine in the more polar DMA or NMP with respect to dioxane DME,[35] which favors the formation of the $Pd(CONHBu)_2$ species from which **5a** is generated by reductive elimination,[23f] is responsible for this effect.

The effect of the nature of the metal halide as cocatalyst was then tested (entries 7−11). The best results were obtained using 100 equiv of KI with respect to PdI_2 (entry 10). An iodide excess favored Pd(0) reoxidation, according to Scheme 2 and eq 4; however, in the presence of a large excess of KI, this effect was counterbalanced by the competition between the iodide anions and the substrate for coordination to Pd(II) (entry 11). The reaction did not take place by changing the Pd(II) counterion from iodide to chloride (entry 12), i.e., $PdCl_2$ in conjunction with either 10 or 100 equiv of KCl was unreactive. This is related to the fact that HCl is not oxidized to Cl_2 by oxygen, so Pd(0) reoxidation does not occur. As expected, the reaction was faster working with a higher substrate concentration and at 100 °C rather than 80 °C (entries 13 and 14).

As we have already observed in the oxidative carbonylation of (*Z*)-2-en-4-ynylamines to give pyrrole-2-acetic esters,[36] the use of an excess of CO_2 (40 atm) in addition to CO (16 atm) and air (4 atm) (entry 15)[37] had a beneficial effect on the oxidative carbonylation process (compare entry 15 with entry 1). Under the same conditions of entry 15, but in the absence of CO (entry 16), no reaction occurred: this means that CO_2 acts as a promoter and not as a carbonylation agent. The promoting effect by carbon dioxide is related to its ability to "buffer" the basicity of the amino group with formation of a carbamate species, thus allowing a higher concentration of "free" HI in solution, which favors Pd(0) reoxidation (Scheme 3). Interestingly, the use of CO_2 also led to the curtailment of oxalamide byproduct **5a** (entry 15, to be compared with entry 1). Apparently, CO_2, acting as ligand to Pd(II),[38] tends to further direct the catalytic process toward path *a* rather than path *b* (Scheme 1). In fact, the key intermediate in the obtainment of **5a** derivatives is an $I_2Pd(CONHBu)_2$ complex[23f] whose formation is clearly less favored in the presence of a large excess of CO_2 ligand.

SCHEME 3

$$\mathbf{1a} + CO_2 \rightleftharpoons Bu\overset{+}{N}H_2CO_2^- \rightleftharpoons BuNHCO_2^- + H^+$$

TABLE 2. Synthesis of Ureas 2a−c by PdI_2-Catalyzed Oxidative Carbonylation of Primary Aliphatic Amines 1a−c (RNH_2, R = Alkyl)[a]

entry	1	R	mol **1**/ mol PdI_2	*t* (h)	conv of **1**[b] (%)	2	yield of **2**[c] (%)
17	**1a**	Bu	1000	1	100	**2a**	100
18	**1a**	Bu	5000	15	100	**2a**	99 (96)
19[d]	**1a**	Bu	5000	15	100	**2a**	84[e]
20	**1b**	Bn	5000	4	99	**2b**	(94)
21[d]	**1b**	Bn	5000	4	86	**2b**	78
22	**1c**	*t*-Bu	2000	15	100	**2c**	98 (89)

[a] Unless otherwise noted, all reactions were carried out in DME (1.0 mmol of **1**/mL of DME, 15−20 mmol scale based on **1**) at 100 °C under 60 atm (at 25 °C) of a 4/1/10 mixture of CO/air/CO_2 in the presence of PdI_2 in conjunction with 100 equiv of KI. [b] Based on starting **1**, by GLC. [c] GLC yield (isolated yield) based on **1**. [d] The reaction was carried out under 20 atm (at 25 °C) of a 4/1 mixture of CO/air. [e] The reaction also led to the formation of **5a** (14%).

On the basis of the results obtained above, butylamine **1a** was eventually reacted under the following optimized conditions: PdI_2/KI/**1a** molar ratio = 1:100:1000, solvent: DME, substrate concentration = 1 mmol of **1a** per mL of DME, *T* = 100 °C, P(CO) = 16 atm, P(air) = 4 atm, $P(CO_2)$ = 40 atm: after only 1 h, the yield of **2a** was practically quantitative (Table 2, entry 17). With a substrate to catalyst molar ratio of 5000, substrate conversion was 100% after 15 h with 99% GLC yield of **2a** (96% isolated, entry 18, and eq 5).[39] We also tested the CO_2 effect under these latter conditions: working in the absence of CO_2, substrate conversion was still quantitative, but oxalamide **5a** (14% GLC yield) was also present in the reaction mixture together with **2a** (84% GLC yield, entry 19).[40]

Oxidative Carbonylation of Other Primary Aliphatic Amines and Reaction Mechanism. The oxidative carbonylation reaction, carried out under the optimized conditions found for butylamine **1a**, was successfully extended to other primary aliphatic amines (eq 5, R = alkyl, and Table 2). Benzylamine **1b** was particularly reactive, so the reaction carried out under the same conditions of entry 18 required only 4 h to achieve 99% **1b** conversion, with an isolated yield of **2b** as high as 94% (entry 20). In the absence of CO_2, substrate conver-

(34) Pearson, R. G.; Vogelsong, D. C. *J. Am. Chem. Soc.* **1958**, *80*, 1038−1043.

(35) For general solvent effects on nucleophilicity, see: March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley-Interscience: New York, 1992; pp 357−362.

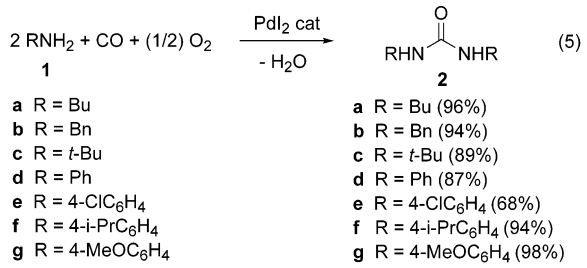
(36) Gabriele, B.; Salerno, G.; Fazio, A.; Campana, F. B. *Chem. Commun.* **2002**, 1408−1409.

(37) The presence of CO_2 in the gaseous mixture further decreases the range of flammability for CO in air: see ref 29.

(38) Palladium complexes with carbon dioxide, stabilized by appropriate ligands, were reported in the literature; see, for example: Yin, X.; Moss, J. R. *Coord. Chem. Rev.* **1999**, *181*, 27−59 and references therein. (b) Sakamoto, M.; Shimizu, I.; Yamamoto, A. *Organometallics* **1994**, *13*, 407−409.

(39) Oxidation of CO to CO_2 may certainly occur to some extent under our conditions. However, we have not carried out a quantitative investigation of the conversion of CO into CO_2 because we were mainly interested in the formation of urea product and in optimizing its yield and selectivity.

(40) We also tested the reaction at lower CO_2 pressures, with less satisfactory results in terms of yield and selectivity towards ureas.

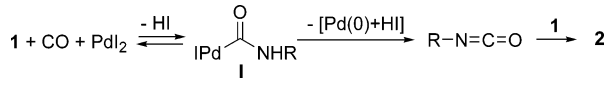


sion and product yield were lower (entry 21). The higher reactivity of **1b** with respect to **1a** can be associated to the coordination of the phenyl group to Pd(II),[41] which increases the coordination ability of **1b**. Excellent results were also obtained starting from a highly hindered amine, such as *tert*-butylamine **1c**, which was, however, less reactive than **1a**,**b**: with a **1c**/PdI_2 molar ratio of 2000, after 15 h the GLC yield of **2c** was 98% (89% isolated, entry 22).

The present methodology could not be applied to secondary amines **3**. For example, no reaction was observed using diethylamine, dibutylamine, or morpholine. The slight difference of basicity and nucleophilicity between primary and secondary amines[42] cannot justify such a striking difference in reactivity. On the other hand, this result cannot even be ascribed to a steric effect, since, as we have seen, the reaction worked well even with *tert*-butylamine. It is therefore clear that the difference in reactivity between the two classes of amines must be due to the possibility only for the primary amines to afford an isocyanate as the reactive intermediate, with carbamoylpalladium complex **I**[43] formed in preequilibrium with starting materials (Scheme 4). This was confirmed by low-conversion experiments, where isocyanates were actually detected (by GLC, TLC, and GLC/MS) in the reaction mixtures deriving from **1**.

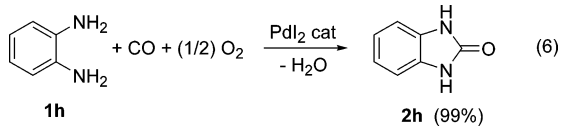
Oxidative Carbonylation of Primary Aromatic Amines and Diamines. Primary aromatic amines were less reactive than aliphatic ones in the PdI_2-catalyzed oxidative carbonylation leading to the corresponding diarylureas (eq 5, R = aryl). This means that nitrogen nucleophilicity plays an important role on reactivity. Thus, under the usual conditions, but in the absence of CO_2 and with a substrate-to-catalyst ratio of 1000, aniline (**1d**) conversion reached 96% after 16 h, with an 87% isolated yield of DPU (Table 3, entry 23). This result can be compared with those reported in entries 17−22 for **1a**−**c**. In any case, a catalytic efficiency of 435 mol of DPU **2d** per mol of palladium has been obtained under these conditions. Slightly less satisfactory results were obtained working with 10 rather than 100 equiv of KI with respect to PdI_2 (entry 24). It is worth noting that, in the oxidative carbonylation of aniline, no promoting effect by CO_2 was observed and, on the contrary, CO_2 tended to inhibit the process (entry 25). This is conceivable, since aniline is much less basic than an aliphatic amine, so the "buffering" effect is now less important; on the other hand, CO_2 may more effectively compete for coordination to Pd(II) with a less reactive substrate.

SCHEME 4

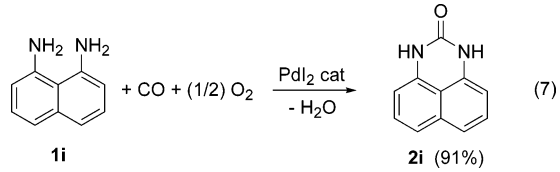


As expected, the presence of an electron-withdrawing or electron-releasing substituent at the *para* position of the ring strongly affected substrate reactivity. Thus, under conditions analogous to those reported in entries 23−25, *p*-cyanoaniline was unreactive even working with 1% of catalyst, while *p*-chloroaniline **1e** reacted to a limited extent (entries 26−27), with CO_2 still inhibiting the reaction (entry 28). On the other hand, *p*-isopropylaniline **1f** was more reactive than aniline, and after 15 h converted into the corresponding urea **2f** in 94% isolated yield starting from an **1f**/PdI_2 ratio of 2000 (entry 29); the CO_2 effect was again negative (entry 30). *p*-Methoxyaniline **1g** turned out to be even more reactive than *tert*-butylamine **1c**, a 98% isolated yield of **2g** being obtained after 15 h starting with a substrate-to-catalyst ratio of 3000 (entry 31); no significant CO_2 effect was observed in this latter case (entry 32).

In the case of 1,2-benzenediamine **1h**, 1,3-dihydrobenzoimidazol-2-one **2h** was selectively obtained in excellent yields (99% isolated) and catalytic efficiencies (up to 4950 mol of **2h** per mol of PdI_2) after only 1−2 h (eq 6 and entries 33−34). This particularly high reactivity is due to the presence of two *ortho* amino groups, which results in a greater nitrogen nucleophilicity and in a more favorable entropy of activation. In agreement with the high substrate basicity, working in the presence of CO_2 had a beneficial effect in this case, as it can be seen by comparing entry 33 with entry 35.



Very good results were also obtained from 1,8-naphthalenediamine **1i**, which after 5 h was converted into 1*H*,3*H*-perimidin-2-one **2i** in 91% isolated yield working with 0.05 mol % of catalyst (eq 7 and entry 36). Also in this case, CO_2 exerted a positive effect on the reaction (compare entry 36 with entry 37).



Oxidative Carbonylation of α-Amino Esters Bearing a Primary Amino Group. *N*,*N*′-Bis[1-(methoxycarbonyl)alkyl]ureas and *N*,*N*′-bis[1-(hydroxycarbonyl)-alkyl]ureas (readily obtainable from the former by hydrolysis under mild conditions through known methods)[44] are particularly important ureic derivatives which

(41) Arene coordination to palladium has been described; for representative examples, see: Davies, J. A. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 9, pp 381−382 and references therein.

(42) Smith, J. W. In *The Chemistry of the Amino Group*; Patai, S., Ed.; Wiley-Interscience: London, 1968; Vol. 4.

(43) Carbamoylpalladium complexes, stabilized by appropriate ligands, were reported in the literature; see, for example: Aresta, M.; Giannoccaro, P.; Tommasi, I.; Dibenedetto, A.; Lanfredi, A. M. M.; Ugozzoli, F. *Organometallics* **2000**, *19*, 3879−3889 and references therein.

TABLE 3. Synthesis of Ureas 2d−i by PdI_2-Catalyzed Oxidative Carbonylation of Primary Aromatic Amines 1d−i (RNH_2, R = Aryl)[a]

entry	1	R	mol 1/mol PdI_2	KI/PdI_2	$P(CO_2)$ (atm)	t (h)	conv of 1[b] (%)	2	yield of 2[c] (%)
23	**1d**	Ph	1000	100		16	96	**2d**	87
24	**1d**	Ph	1000	10		15	89	**2d**	75
25	**1d**	Ph	1000	100	40	15	35	**2d**	11
26	**1e**	4-ClC_6H_4	100	100		15	78	**2e**	68
27	**1e**	4-ClC_6H_4	100	10		15	70	**2e**	40
28	**1e**	4-ClC_6H_4	100	10	40	15	52	**2e**	15
29	**1f**	4-*i*-PrC_6H_4	2000	100		15	95	**2f**	94
30	**1f**	4-*i*-PrC_6H_4	2000	100	40	15	75	**2f**	60
31	**1g**	4-$MeOC_6H_4$	3000	100		15	100	**2g**	98
32	**1g**	4-$MeOC_6H_4$	3000	100	40	15	100	**2g**	90
33	**1h**	2-$H_2NC_6H_4$	5000	100	40	1	93	**2h**	91
34	**1h**	2-$H_2NC_6H_4$	5000	100	40	2	100	**2h**	99
35	**1h**	2-$H_2NC_6H_4$	5000	100		1	72	**2h**	70
36	**1i**	8-aminonaphthyl	2000	100	40	5	97	**2i**	91
37	**1i**	8-aminonaphthyl	2000	100		5	85	**2i**	80

[a] Unless otherwise noted, all reactions were carried out in DME (1.0 mmol of **1**/mL of DME, 10−20 mmol scale based on **1**) at 100 °C under 16 atm of CO, 4 atm of air, and P atm of CO_2 [(20 + P) total pressure at 25 °C], in the presence of PdI_2 in conjunction with 100 equiv of KI. [b] Based on starting **1**, by GLC. [c] Isolated yield based on **1**.

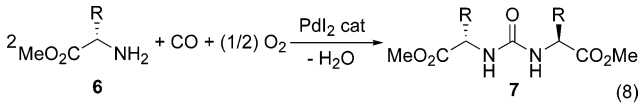
TABLE 4. Synthesis of Ureas 7a−f by PdI_2-Catalyzed Oxidative Carbonylation of α-Amino Esters ($MeO_2CCHRNH_2$) 6a−f[a]

entry	6	R	t (h)	conv of 6[b] (%)	7	yield of 7[c] (%)
38[d]	**6a**	Bn[e]	2	90	**7a**	84
39[d,f]	**6a**	Bn[e]	2	70	**7a**	64
40	**6a**	Bn[e]	2	90	**7a**	83
41	**6a**	Bn[e]	3	100	**7a**	90
42	**6b**	Me[e]	5	100	**7b**	86
43	**6c**	*i*-Bu[e]	5	100	**7c**	89
44	**6d**	*i*-Pr[e]	5	100	**7d**	80
45	**6e**	$(CH_2)_2CO_2Me$[e]	5	100	**7e**	85
46	**6f**	H	5	100	**7f**	75
47[g]	**6f**	H	5	100	**7f**	83

[a] Unless otherwise noted, all reactions were carried out in DME (1.0 mmol of **6**/mL of DME, 10 mmol scale based on **6**) at 100 °C under 20 atm (at 25 °C) of a 4/1 mixture of CO/air, in the presence of PdI_2 (0.1 mol %) in conjunction with 10 equiv of KI. [b] Based on starting **6**, by GLC. [c] Isolated yield based on **6**. [d] The reaction was carried out using 100 equiv of KI with respect to PdI_2. [e] *S* enantiomer. [f] The reaction was carried out under 60 atm (at 25 °C) of a 4/1/10 mixture of CO/air/CO_2. [g] Substrate concentration was 0.5 mmol per mL of DME.

display a very interesting pharmacological activity.[45] Although they can in principle be prepared by oxidative carbonylation of readily available α-amino esters or acids, to our knowledge no such a process has been reported to date.

We have found that our methodology is perfectly applicable to α-amino esters **6**, affording the corresponding ureas **7** in high yield and catalytic efficiency (eq 8 and Table 4). These derivatives were generally less reactive than simple primary aliphatic amines and showed a reactivity similar to that of aromatic amines. This is probably due to the electron-withdrawing effect exerted by the $-CO_2Me$ moiety. Accordingly, CO_2 tended to inhibit rather than promote the process; moreover, in this case the use of a 10-fold or a 100-fold excess of KI with respect to PdI_2 led to comparable results, as exemplified by the results reported in Table 4 (entries 38−41) for L-phenylalanine methyl ester **6a** (R = CH_2Ph). Under the same conditions reported in entry 24 for aniline, substrate conversion reached 100% after 3 h, with an isolated yield of (*S*,*S*)-*N*,*N*′-bis(1-methoxycarbonyl-2-phenylethyl)urea **7a** as high as 90% (entry 41). L-Alanine methyl ester **6b** (R = Me) was slightly less reactive than **6a**, and its conversion was quantitative after 5 h, the corresponding urea **7b** being isolated in 86% yield (entry 42). The higher reactivity of **6a** with respect to **6b** can be ascribed to the presence in **6a** of an additional coordinating group (the phenyl) in addition to the ester group. The methodology was successfully extended to other α-amino esters, such as L-leucine methyl ester **6c** (R = *i*-Bu), L-valine methyl ester **6d** (R = *i*-Pr), and L-glutamic acid dimethyl ester **6e** (R = $(CH_2)_2CO_2$-Me), with isolated yields of the corresponding ureas **7c**−**e** ranging from 80 to 89% (entries 43−45). Interestingly, a lower yield of urea **7f** (75% isolated yield, entry 46) was obtained starting with glycine methyl ester **6f** (R = H) under the same conditions of entries 41−45. In fact, in the absence of an α-substituent, oligo- or polymerization processes leading to unidentified heavy compounds begin to compete with the oxidative carbonylation reaction. As expected, these processes were easily curtailed working under more diluted conditions: with 0.5 rather than 1.0 mmol of **6f** per mL of DME, the isolated yield of **7f** attained 83% (entry 47).



a R = Bn
b R = Me
c R = *i*-Bu
d R = *i*-Pr
e R = $(CH_2)_2CO_2Me$
f R = H

a R = Bn (90%)
b R = Me (86%)
c R = *i*-Bu (89%)
d R = *i*-Pr (80%)
e R = $(CH_2)_2CO_2Me$ (85%)
f R = H (83%)

Oxidative Carbonylation of Primary Amines in the Presence of Secondary Amines. As we have seen, the PdI_2-catalyzed oxidative carbonylation process of primary amines **1** leading to symmetrically substituted

(44) Buntain, I. G.; Suckling, C. J.; Wood, H. C. S. *J. Chem. Soc., Perkin Trans. 1* **1988**, 3175−3182.

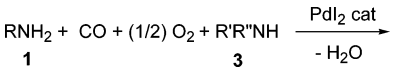
(45) See, for example, ref 5z and: (a) Di Stefano, A.; Mosciatti, B.; Cingolani, G. M.; Giorgioni, G.; Ricciutelli, M.; Cacciatore, I.; Sozio, P.; Claudi, F. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1085−1088. (b) Ohmoto, K.; Yamamoto, T.; Okuma, M.; Horiuchi, T.; Imanishi, H.; Odagaki, Y.; Kawabata, K.; Sekioka, T.; Hirota, Y.; Matsuoka, S.; Nakai, H.; Toda, M. *J. Med. Chem.* **2001**, *44*, 1268−1285.

TABLE 5. Synthesis of Trisubstituted Ureas 4aa−ac by PdI_2-Catalyzed Oxidative Carbonylation Reactions of Butylamine 1a with Secondary Amines (R′R″NH) 3a−c[a]

entry	3	R′R″NH	3/1a/PdI_2	KI/PdI_2	T (°C)	t (h)	conv of 1a[b] (%)	yield of 2a[c] (%)	4	yield of 4[c] (%)
48	**3a**	Bu_2NH	750/500/1	100	100	2	100	20	**4aa**	70
49[d]	**3a**	Bu_2NH	750/500/1	100	100	5	55	28	**4aa**	22
50	**3a**	Bu_2NH	750/500/1	100	90	2	65	8	**4aa**	49
51[e]	**3a**	Bu_2NH	750/500/1	100	90	2	65	10	**4aa**	49
52	**3a**	Bu_2NH	750/500/1	200	90	2	85	11	**4aa**	70
53	**3a**	Bu_2NH	500/500/1	200	90	2	90	29	**4aa**	58
54	**3a**	Bu_2NH	1000/500/1	200	90	2	80	9	**4aa**	65
55	**3a**	Bu_2NH	1500/1000/1	200	90	15	100	17	**4aa**	75
56	**3b**	morpholine	1500/1000/1	200	90	15	100	13	**4ab**	73
57	**3c**	BnNHMe	1500/1000/1	200	90	15	100	14	**4ac**	67
58	**3b**	morpholine	1500/1000/1	200	100	15	100	15	**4ab**	71
59	**3c**	BnNHMe	1500/1000/1	200	100	15	100	20	**4ac**	65
60	**3c**	BnNHMe	1000/1000/1	200	90	15	100	18	**4ac**	62

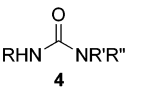
[a] Unless otherwise noted, all reactions were carried out in DME [1.0 (mmol of **1a** + mmol of **3a**)/mL of DME, 10 mmol scale based on **1a**) under 60 atm (at 25 °C) of a 4/1/10 mixture of CO/air/CO_2, in the presence of PdI_2 in conjunction with KI. [b] Based on starting **1a**, by GLC. [c] Isolated yield based on **1a**. [d] The reaction was carried out under 20 atm of a 4/1 mixture of CO/air. [e] The reaction was carried out with 0.5 (mmol of **1a** + mmol of **3a**)/mL of DME.

ureas **2** takes place through the formation of an isocyanate species, which then undergoes nucleophilic attack by **1** to give **2** (Scheme 4). This suggested the possibility to synthesize directly trisubstituted ureas, by "trapping" the isocyanate intermediate with a secondary amine, used in suitable excess with respect to the primary one. We accordingly tried the reaction of butylamine **1a** in the presence of dibutylamine **3a** under conditions analogous to those optimized for **1a** alone (Table 5, entries 48−55). Working with a **3a**/**1a**/PdI_2 molar ratio of 750/500/1 for 2 h, mixed urea **4aa** was indeed obtained as the major reaction product (70% isolated yield), dibutylurea **2a** being also formed in 20% isolated yield (entry 48). Interestingly, working in the absence of CO_2 the reaction was slower and less selective (entry 49). Selectivity toward **4aa** could be further enhanced working at 90 °C (entry 50) and with a KI/PdI_2 molar ratio of 200 (entry 52), while no significant improvement was observed by raising the **3a**/**1a** ratio from 1.5 to 2 (entry 54). With a PdI_2/KI/**1a**/**3a** molar ratio of 1:200:1000:1500 at 90 °C, after 15 h **2aa** and **4aa** were eventually isolated in 17% and 75% yield, respectively (entry 55 and eq 9).



a R=Bu
c R=*t*-Bu
d R=Ph
g R=4-$MeOC_6H_4$

a R'=R"=Bu
b R'-R"=$(CH_2)_2O(CH_2)_2$
c R'=Bn, R"=Me



(9)

aa R=R'=R"=Bu (75%)
ab R=Bu, R'-R"=$(CH_2)_2O(CH_2)_2$ (73%)
ac R=Bu, R'=Bn, R"=Me (67%)
ca R=*t*-Bu, R'-R"=Bu (88%)
da R=Ph, R'-R"=Bu (73%)
db R=Ph, R'-R"=$(CH_2)_2O(CH_2)_2$ (85%)
gb R=4-$MeOC_6H_4$, R'-R"=$(CH_2)_2O(CH_2)_2$ (95%)

The methodology was then extended to mixtures of **1a** with other secondary nucleophilic amines, such as morpholine **3b** or benzylmethylamine **3c** (entries 56−60).[46] Under the same conditions of entry 55, the desired mixed ureas **4ab** and **4ac** were isolated in 73% and 67% yield,

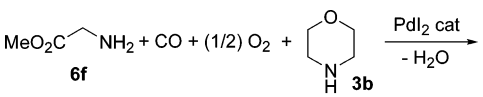
TABLE 6. Synthesis of Mixed Urea 8fb by PdI_2-Catalyzed Oxidative Carbonylation of Glycine Methyl Ester 6f with Morpholine 3b[a]

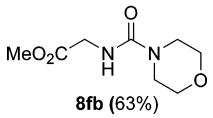
entry	KI/PdI_2	substrate conc[b]	conv of 6f[c] (%)	yield of 7f[d] (%)	yield of 8fb[d] (%)
61	10	1.0	100	8	63
62[e]	10	1.0	80	11	43
63	100	1.0	100	10	60
64	10	0.5	100	14	63

[a] Unless otherwise noted, all reactions were carried out in DME at 100 °C under 20 atm (at 25 °C) of a 4/1 mixture of CO/air in the presence of PdI_2 in conjunction with KI (**3b**/**6f**/PdI_2 molar ratio = 300/200/1, 3−5 mmol scale based on **6f**) for 5 h. [b] (mmol of **6f** + mmol of **3b**)/mL of DME. [c] Based on starting **6f**, by GLC. [d] Isolated yield based on **6f**. [e] The reaction was carried out under 60 atm (at 25 °C) of a 4/1/10 mixture of CO/air/CO_2.

respectively, **2a** being obtained in 13% and 14% yield, respectively (entries 56 and 57). The same reactions carried out at 100 °C were slightly less selective toward ureas **4** (entries 58 and 59).

Good results were also obtained by reacting glycine **6f** with 1.5 equiv of morpholine **3b** (Table 6), even though the **6f**/PdI_2 molar ratio was decreased to 200 in order to compensate for the lower substrate reactivity. Working in the absence of CO_2 with 10 equiv of KI with respect with PdI_2, after 5 h the trisubstituted urea **8fb** and symmetrically disubstituted urea **7f** were isolated in 63% and 8% yield, respectively (entry 61 and eq 10).





(10)

The present methodology for producing mixed ureas worked nicely when primary amines of low nucleophilicy, such as *tert*-butylamine or aromatic amines, were reacted in the presence of secondary nucleophilic amines such

(46) Dibutylurea **2a** was the only product formed when the reaction was carried out with secondary amines of low nucleophilicity, such as diisopropylamine or *N*-methylaniline.

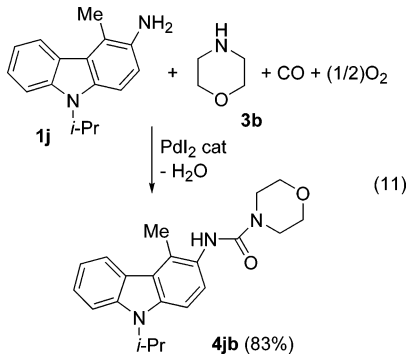
TABLE 7. Synthesis of Trisubstituted Ureas 4 by PdI_2-Catalyzed Oxidative Carbonylation of Primary Amines 1c,d,g,j (RNH_2) in the Presence of Secondary Amines 3a,b (R′R″NH)[a]

entry	1	R	3	R′R″NH	3/1/PdI_2	*t* (h)	conv of 1[b] (%)	4	yield of 4[c] (%)
65	**1c**	*t*-Bu	**3a**	Bu_2NH	300/300/1	15	100	**4ca**	88
66	**1c**	*t*-Bu	**3a**	Bu_2NH	400/400/1	15	95	**4ca**	80
67[d]	**1c**	*t*-Bu	**3a**	Bu_2NH	300/300/1	24	75	**4ca**	68
68	**1d**	Ph	**3a**	Bu_2NH	300/300/1	15	100	**4da**	73
69[d]	**1d**	Ph	**3a**	Bu_2NH	300/300/1	15	95	**4da**	60
70	**1d**	Ph	**3b**	morpholine	200/200/1	24	100	**4db**	85
71	**1g**	4-$MeOC_6H_4$	**3b**	morpholine	300/300/1	15	100	**4gb**	95
72	**1g**	4-$MeOC_6H_4$	**3b**	morpholine	400/400/1	15	98	**4gb**	90
73	**1j**	9IP4M9HC3[e]	**3b**	morpholine	200/200/1	24	100	**4jb**	83

[a] All reactions were carried out in DME [1.0 (mmol of **1** + mmol of **3**)/mL of DME, 10 mmol scale based on **1**) at 100 °C under 20 atm (at 25 °C) of a 4/1 mixture of CO/air in the presence of PdI_2 in conjunction with 10 equiv of KI. [b] Based on starting **1**, by GLC. [c] Isolated yield based on **1**. [d] The reaction was carried out under 60 atm (at 25 °C) of a 4/1/10 mixture of CO/air/CO_2. [e] 9IP4M9HC3 = 9-isopropyl-4-methyl-9*H*-carbazol-3-yl.

as **3a** or **3b** (Table 7 and eq 9). In these cases, in fact, owing to the absence of nucleophilic competition between the primary amine and the secondary one, no symmetrically substituted urea was formed, even starting with a 1/1 molar ratio between the two amines. As expected in view of what observed in the reaction of the primary amines alone (see above), the substrate conversions rate was faster working with a KI/PdI_2 molar ratio of 100 rather than 200; indeed, this ratio could be lowered to 10 without appreciable differences in the reaction outcome. Moreover, as expected, CO_2 tended to inhibit the process. Thus, the reaction of *tert*-butylamine **1c** with dibutylamine **3a** carried out at 100 °C in the absence of CO_2 and with a PdI_2/KI/**1c**/**3a** molar ratio of 1:10:300:300, after 15 h afforded the desired 1,1-dibutyl-3-*tert*-butylurea **4ca** as the sole product in 88% isolated yield (entry 65). With a PdI_2/KI/**1c**/**3a** molar ratio of 1:10:400:400, the yield of **4ca** was still high (80%, entry 66). The negative effect exerted by CO_2 is evident from the results shown in entry 67. Under conditions similar to those of entry 65, aniline **1d** was converted into 1,1-dibutyl-3-phenylurea **4da** in 73% isolated yield (entry 68) (60% yield in the presence of CO_2, entry 69). The reaction between **1d** and morpholine **3b** was quite slower, but a high yield of the corresponding mixed urea **4db** (85% isolated) could be obtained working with a PdI_2/KI/**1d**/**3b** molar ratio of 1:10:200:200 for 24 h (entry 70). As expected, a higher reactivity was observed for *p*-methoxyaniline **1g** with respect to aniline, as it can be seen by comparing entries 71 and 72 with entry 70.

Our methodology was perfectly applicable to the direct synthesis of more complex, biologically active trisubstituted ureas, still with high yields and catalytic efficiencies. By way of example, we have prepared urea NPY5RA-972 **4jb**, which is known to be a potent antagonist of the neuropeptide Y5 receptor,[5p] starting from readily available 9-isopropyl-4-methyl-9*H*-carbazol-3-ylamine **1j** and morpholine **3b** (eq 11). Under conditions similar to those reported in entry 70 for aniline, the desired product was easily obtained in 83% isolated yield (entry 73).



Conclusions

In summary, we have developed a very efficient methodology for performing the Pd-catalyzed oxidative carbonylation of primary amines leading to ureas selectively, under relatively mild reaction conditions and with unprecedented catalytic efficiencies for this kind of reaction. The selective and highly efficient obtainment of ureas turns out to be strongly solvent-dependent, and it is observed in low-polar, aprotic solvents such as dioxane or DME; in polar aprotic solvents (such as DMSO or DMA), the nucleophilicity of amines increases, and this causes the preferential formation of oxalamides (through a double carbonylation process) rather than ureas, while in polar protic solvents (such as MeOH) the catalytic process is completely hindered owing to the inhibition of Pd(0) reoxidation. With particularly basic amines, a peculiar promoting effect by carbon dioxide has been observed; this effect is related to the decreasing of amine basicity (through the formation of a carbamate species), which favors Pd(0) reoxidation.

The methodology has been successfully applied to the synthesis of particularly important ureic derivatives, such as cyclic ureas from diamines, and *N*,*N*-bis-(methoxycarbonylalkyl)ureas from primary α-amino esters. Isocyanates are the intermediates of the process, and working in the presence of a suitable excess of a secondary amine trisubstituted ureas can be obtained selectively; this latter approach has been applied to the preparation of biologically active NPY5RA-972 urea.

Experimental Section

Preparation of Substrates and Analysis of Reaction Mixtures. All substrates **1** and **3**, with the exception of 9-isopropyl-4-methyl-9*H*-carbazol-3-ylamine **1j**, which was prepared according to a literature procedure,[5p] were commercially available and were used without further purifications. α-Amino esters **6** were obtained in situ from the corresponding commercially available hydrochlorides, as described below in the general procedure for their oxidative carbonylation.

All reactions were analyzed by TLC on silica gel 60 F_{254} and by GLC using capillary columns with polymethylsilicone + 5%

phenylsilicone as the stationary phase. Column chromatography was performed on silica gel 60 (70−230 mesh). Evaporation refers to the removal of solvent under reduced pressure.

General Procedure for Oxidative Carbonylation of Primary Amines 1a−i to Symmetrically Disubstituted Ureas 2a−i and Separation of Products (Tables 1−3). A 250 mL stainless steel autoclave was charged in the presence of air with PdI_2, co-catalyst MI, and a solution of **1** (typically, 10−20 mmol) in the reaction solvent (see Tables 1−3 for the **1**/MI/PdI_2 molar ratio, reaction solvent, substrate concentration, temperature, reaction time, and product yield for each substrate). While stirring, the autoclave was pressurized with CO_2 (40 atm, when required; see Tables 1−3), CO (up to 56 atm or, when the reaction was carried out in the absence of CO_2, 16 atm), and air (up to 60 atm or, when the reaction was carried out in the absence of CO_2, 20 atm) and then heated at the required temperature for the required time.[47] After cooling, the autoclave was degassed and solvent evaporated. Usually, some amount of crude product was already present in suspension in the reaction mixture. Crude ureas **2a**−**d**,**h**,**i** were purified by column chromatography (SiO_2): **2a**, pure Et_2O (colorless solid); **2b**, pure $CHCl_3$ (colorless solid); **2c**, pure $CHCl_3$ (whitish solid); **2d**, pure THF (colorless solid); **2h**, hexane−acetone from 3:7 to 2:8 (pale pink solid); **2i**, hexane−acetone from 1:1 to 6:4 (pale pink solid). The reaction crude deriving from **1e** was diluted with MeOH to precipitate the product and filtered, and urea **2e** was washed with acetone; the filtrate was concentrated under reduced pressure, diluted with MeOH, cooled (5 °C), and filtered to afford another crop of the product (pale yellow solid). Urea **2f** was present in the reaction mixture as a whitish precipitate, which was purified by washing with acetone to give the pure product as a colorless solid; the filtrate was evaporated to dryness, and the residue was washed with acetone to afford another crop of the product (colorless solid). Urea **2g** was present in the reaction mixture as a white precipitate, which was purified by washing with acetone to give the pure product as a whitish solid.

General Procedure for Oxidative Carbonylation of Primary Amino Esters 6a−f to Symmetrically Disubstituted Ureas 7a−f and Separation of Products (Table 4). A 250 mL stainless steel autoclave was charged in the presence of air with a solution of the α-amino ester hydrochloride (typically, 10 mmol) and *N*,*N*-diisopropylethylamine (1 equiv) in DME. The mixture was allowed to stir at room temperature for 1 h to generate the free amino ester **6**, and then PdI_2 and KI were added (see Table 4 for the **6**/KI/PdI_2 molar ratio, substrate concentration, reaction time and product yield for each substrate). While stirring, the autoclave was pressurized with CO (16 atm) and air (up to 20 atm) and then heated at 100 °C for the required time. After cooling, the autoclave was degassed, solvent was evaporated, and products were purified by column chromatography (SiO_2): **7a** (colorless solid) hexane−AcOEt from 6:4 to 4:6; **7b** hexane−AcOEt from 1:1 to 2:8 (pale yellow solid; the product could be easily crystallized from dioxane/hexane to give a colorless solid); **7c**, 3:7 hexanes−Et_2O (pale yellow solid; the product could be easily crystallized from Et_2O/hexane to give a colorless solid); **7d**, hexane−acetone from 9:1 to 6:4 (colorless solid); **7e**, hexane−AcOEt from 2:8 to 0:100 (pale yellow solid; the product could be easily crystallized from CH_2Cl_2/hexane to give a colorless solid); **7f**, hexane−acetone from 1:1 to 3:7 (pale yellow solid; the product could be easily crystallized from MeOH to give a colorless solid).

General Procedure for Oxidative Carbonylation of Primary Amines 1 with Secondary Amines 3 to Trisubstituted Ureas 4 and Separation of Products (Tables 5 and 7). A 250 mL stainless steel autoclave was charged in the presence of air with PdI_2, KI, and a solution of **1** (typically, 10 mmol) and **3** in DME (see Tables 5 and 7 for the **3**/**1**/KI/PdI_2 molar ratio, substrate concentration, temperature, reaction time and product yield for each substrate). While stirring, the autoclave was pressurized with CO_2 (40 atm, when required; see Tables 5 and 7), CO (up to 56 atm or, when the reaction was carried out in the absence of CO_2, 16 atm,) and air (up to 60 atm or, when the reaction was carried out in the absence of CO_2, 20 atm), then heated at the required temperature for the required time. After cooling, the autoclave was degassed, solvent was evaporated, and products were separated by column chromatography (SiO_2): **4aa** (pale yellow oil), **2a** (colorless solid): 8:2 hexane−acetone; **4ab** (colorless solid), **2a** (colorless solid): 8:2 hexane−acetone; **4ac** (pale yellow solid), **2a** (colorless solid): 1:1 hexane−AcOEt; **4ca**, 8:2 hexane−AcOEt (colorless solid); **4da**, 8:2 hexane−AcOEt (colorless solid); **4db**, hexane−AcOEt from 2:8 to 0:100 (colorless solid); **4gb**, 3:7 hexane−AcOEt (colorless solid); **4jb**, hexane−AcOEt from 2:8 to 0:100 (colorless solid).

Typical Procedure for Oxidative Carbonylation of Glycine Methyl Ester 6f with Morphiline 3b to Mixed Urea 8fb and Separation of Product (Table 6, entry 64). A 250 mL stainless steel autoclave was charged in the presence of air with a solution of the glycine methyl ester hydrochloride (340.0 mg, 2.71 mmol) and *N*,*N*-diisopropylethylamine (350.0 mg, 2.71 mmol) in DME (5.4 mL). The mixture was allowed to stir at room temperature for 1 h to generate the free amino ester **6f**, and then PdI_2 (4.9 mg, $1.36 \cdot 10^{-2}$ mmol), KI (22.1 mg, 0.13 mmol), and a solution of morpholine **3b** (352.0 mg, 4.04 mmol) in DME (8.0 mL) were added. While stirring, the autoclave was pressurized with CO (16 atm) and air (up to 20 atm) and then heated at 100 °C for 5 h. After cooling, the autoclave was degassed, solvent was evaporated, and products were purified by column chromatography (SiO_2, hexane-acetone from 6:4 to 4:6): **7f** (pale yellow solid), **8fb** (slightly brown solid). The desired mixed urea **8fb** was further purified by crystallization from acetone/hexane to give a colorless solid.

Supporting Information Available: General experimental methods and characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0494634

(47) As we have already pointed out, these conditions are outside the explosion limits for CO−air mixtures (see note 29).