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Palladium-catalyzed synthesis of symmetrical urea derivatives by oxidative carbonylation of primary amines in carbon dioxide medium

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ABSTRACT

An efficient palladium-catalyzed synthesis of symmetrically disubstituted ureas via oxidative carbonylation of primary amines is described. The reactions are carried out in the presence of a large excess of carbon dioxide as reaction medium or under solvent-free conditions. The adopted catalyst such as potassium tetraiodopalladate, stable and easy to prepare, allows the use of air as a cheap oxidizing agent. The reactions yield urea and water as the only by-product and proceed with high efficiency with aliphatic and aromatic amines as well. While with primary aliphatic amines, no significant improvement on reactivity is observed when carbon dioxide is used as a solvent, in comparison with the conventional ones, a remarkable high efficiency is obtained with aromatic amines, which shows a dramatic increase in the performance of the catalyst, in terms of turnover number (TON), the highest known so far for this kind of process. Reactions take place in two-phase systems consisting of a homogeneous liquid phase formed by the CO_2 expanded amine solution containing the catalyst and a supercritical phase of CO_2, CO, O_2, and N_2.

1. Introduction

The development of new, efficient, selective, and environmentally friendly protocols for the production of ureas has recently attracted great interest in view of their many important applications [1]. The conventional syntheses of ureas have been based on the use of dangerous reagents such as phosgene or isocyanates (mainly prepared in their turn from phosgene itself). In recent years, however, alternative routes have been developed through the use of a variety of carbonyl derivatives, CO_2 or CO [2]. Particularly attractive, also from the standpoint of atom economy [3], is the oxidative carbonylation methodology [4], which employs amines, carbon monoxide, and oxygen as starting materials and produces only water as coproduct.

Same years ago, we developed a new and efficient methodology for performing the Pd-catalyzed oxidative carbonylation of primary amines leading selectively to ureas [Eqs. (1) and (2)], under relatively mild reaction conditions and with unprecedented catalytic efficiencies for this kind of reactions [5].

$$\underset{\mathbf{1}}{2RNH_2} + CO + 1/2O_2 \xrightarrow{\text{Pd cat.}} \underset{\mathbf{2}}{RNHCOHNR} + H_2O \qquad (1)$$

$$RNH_2 + R'_2NH + CO + 1/2O_2 \xrightarrow{\text{Pd cat.}} RNHCONR'_2 + H_2O \qquad (2)$$

Carbonylations of primary aliphatic amines [Eq. (1)] were carried out in 1,2-dimethoxyethane (DME) at 100 °C under 60 bar of a mixture of CO, air, and CO_2 in the presence of a catalytic system consisting of PdI_2 in conjunction with KI [6]. The beneficial effect of CO_2 on carbonylation of primary aliphatic amines was related to the fact that its presence led to the formation of carbamate intermediates, thus buffering the substrate basicity, which would otherwise hinder the palladium reoxidation [5]. In fact, working in the absence of CO_2 less satisfactory results were obtained. Primary aromatic amines were generally less reactive than aliphatic ones, however. The conversion rate and product distribution turned out to be dependent on the nature of the solvent. Thus, while no conversion to urea derivatives was observed in the oxidative carbonylation of *n*-butylamine in a protic solvent such as MeOH, higher conversions were obtained in aprotic polar solvents [5b]. Apparently, the polarity of the aprotic solvent played a very important role on the selectivity of the process: the monocarbonylation was strongly favored in low-polar dioxane ($\varepsilon = 2.21$ at 25 °C) and mainly, for its higher coordination ability, in DME ($\varepsilon = 7.54$ at 25 °C, 6.09 at 80 °C) [7], while double carbonylation was preferred in the high polar *N*,*N*-dimethylacetamide (DMA, $\varepsilon = 37.78$ at 25 °C) or *N*-methylpirrolidone (NMP, $\varepsilon = 32.2$ at 25 °C). The higher

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nucleophilicity of primary amines toward CO in the more polar DMA or NMP [8], favoring the formation of the Pd$(CONHR)_2$ species from which oxamide is generated by reductive elimination [9], was responsible for this effect.

The above mentioned results, showing a considerable improvement in efficiency of the Pd-catalyzed primary amine carbonylation reactions in the presence of aprotic solvents of low polarity such as DME and gaseous CO_2, prompted us to investigate the possibility of carrying out the reactions in the absence of organic solvents using CO_2 as the only reaction medium, with particular attention to the selectivity toward ureas rather than the undesired by-products (oxamides).

In recent years, it has been clearly demonstrated that new solvents, called gas expanded liquids (GXLs), have furnished effective alternative media for performing chemical reactions. A GXL is a mixed solvent composed of a compressible gas (such as CO_2 or ethane) dissolved in an organic solvent [10]. By varying the CO_2 amount, the properties of the liquid media change and in addition, these can be adjusted by tuning the operating pressure. Reaction advantages include higher gas miscibility compared with organic solvents, enhanced mass transport rate, due to the properties of dense CO_2 and increased reaction rates in comparison with the ones in neat organic solvents or in $scCO_2$ [11].

Our investigations is aimed to verify whether the beneficial properties of CO_2 expanded liquids can be fully or in part transferred from organic solvents to liquid reagents thus eliminating the solvent in this particular urea derivative synthesis. The switch from a conventional "wet chemistry" system to a "dry chemistry" system, besides the environmental advantages and the simplification of the work-up procedures, could be particularly attractive for this reaction, since it would provide the opportunity to completely avoid explosion and combustion hazards connected with the use of carbon monoxide/air mixtures [12]. Moreover, the use of CO_2, due to its particular features, could also, in some cases, led to an improvement of the performance of the catalytic system leading to unprecedented efficiencies.

Recently, the synthesis of symmetrical and unsymmetrical ureas has been achieved using amines, diamines, or some of their derivatives in gaseous or supercritical carbon dioxide in the presence of suitable catalytic systems [13]. In particular, it has been reported that dialkylamines react with CO_2 (1 bar) at 60 °C giving tetralkylureas in a single- or two-step procedure in the presence of CCl_4 and PPh_3 or DMAN [1,8-bis(dimethylamino)naphthalene, proton-sponge] in moderate to high yields [14]. Symmetrically disubstituted ureas have also been obtained in modest to excellent yields from primary amines working in ionic liquids in the presence of CsOH at 170 °C and 60 bar of CO_2 [15]. The synthesis of a family of *O*-silylcarbamates from silylamines has been achieved by heating silylamines in $scCO_2$. These *O*-silylcarbamates were shown to be effective precursors for the synthesis of a range of symmetrical and unsymmetrical ureas [16].

In the present work, the reactions of primary aliphatic and aromatic amines with CO and O_2 under high pressure of CO_2 to give symmetrical *N*,*N*′-disubstituted ureas, in the presence of K_2PdI_4 as the catalyst, are described.

2. Experimental

2.1. General

All solvents were dried over activated molecular sieves for 24 h or freshly distilled. All amines were freshly distilled. Purified air, carbon monoxide, carbon dioxide, and all other reagents were purchased from commercial sources and utilized as received.

Reactions under pressure were performed in stainless steel 125 ml Parr autoclaves, equipped with manometer and thermocouple. Carbon dioxide was loaded as a liquid through a dip tube cylinder and the amount was measured by weighing. The temperatures reported in the Results and Discussion section refer to the values measured by the internal thermocouple.

Elemental analyses were carried out with a Carlo Erba Elemental Analyzer Mod. 1106. ^1H, and ^{13}C NMR spectra were taken on a Bruker AC300 (300 MHz) spectrometer. IR spectra were taken on a Nicolet 5700 FT-IR spectrometer. Mass spectra were obtained using a GC system HP6890 Series coupled with a HP 5973 Mass Selective Detector at 70 eV ionization voltage. GC analyses were performed on a HRGC Mega 2 series Fisons Instruments equipped with a polymethylsilicone +5% phenylsilicone as a stationary phase (HP-5) capillary column. Column chromatography was performed on silica gel 60 (Merck, 70–230 mesh).

To monitor the phase behavior of the system consisting of CO_2, CO, O_2, N_2, and amine during the reaction, we used a stainless steel high pressure reactor (Parr Instrument, 200 cm^3 of volume) equipped with two quartz windows placed at the bottom of the reactor. Stirring was provided with a magnetic bar and heating with an electric heater consisting of a fissured mantel in aluminum well. Temperature control was achieved by means of a PID controller connected to a thermocouple located in the reactor. Pressure inside the reactor was measured with a pressure gauge (220 bar end scale).

2.2. Synthesis of potassium tetraiodopalladate (K_2PdI_4)

The catalytic system used was the easily prepared and stable complex K_2PdI_4. 1 mmol of PdI_2 (360 mg), 2 mmol of KI (332 mg), and 15 ml of methanol were introduced in a round-bottom, single-necked flask. The mixture was heated at reflux for one hour. After evaporating the solvent under vacuum, the product was collected as a deep brown powder (Yield: 98%).

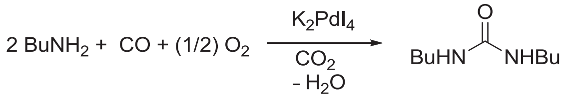
2.3. General procedure for the carbonylation reactions

A 125 ml stainless steel reactor was dried in oven for 12 h, and then cooled under argon to room temperature. The desired amounts of amine and catalyst together with the eventual organic solvent, as reported in the Results and Discussion section, were loaded. Then the reactor was closed and purged three times with purified dry air. The desired amount of liquid CO_2 (99.5% purity) was loaded as a liquid, weighing the reactor prior of and after the charging. Then CO (10 bar) and air (15–17 bar) measured by reading the pressure on the reactor manometer were added at room temperature. The reaction was magnetically stirred and heated in the range of 70–110 °C in a temperature-controlled oil bath for 10–72 h. After the reaction, the reactor was cooled at room temperature (0 °C in the case of the more volatile amines) and carefully depressurized. The solid product was recovered by adding CH_2Cl_2/petroleum ether (1 to 1 mixture, 10 ml, in the case of aliphatic urea derivatives) or acetone (10 ml, in the case of aromatic urea derivatives) to the raw reaction material and by filtering to separate the unconverted amine and the catalyst. The organic solution was analyzed by GC and GC–MS. Unless otherwise specified, yields reported refer to isolated products. Crystallization from suitable solvents gives the pure products. Melting points, elemental analyses, ^1H, ^{13}C NMR, and FT-IR spectra were consistent with the reported literature (see supporting information section).

2.4. Synthesis of 1,3-di-n-butylurea

As an example (entry 2, Table 1), *n*-butylamine (1.46 g, 20 mmol) and K_2PdI_4 (0.014 g, 0.02 mmol) were charged in the reactor. Air was first flushed at low pressure and then CO_2 (43.0 g, 1.0 mol) loaded as a liquid, weighing the reactor prior of

Table 1
K_2PdI_4-catalyzed oxidative carbonylation of *n*-butylamine to *N*,*N*′-di-*n*-butylurea in CO_2 under different conditions.[a]



Entry	mmol of $BuNH_2$	$BuNH_2/K_2PdI_4$ molar ratio	CO_2 loaded (g)	Reaction temperature (°C)	Reactor pressure[b] (bar)	Reaction time (h)	Urea yield (%)[c]	TON[d]
1	20	1000	33	70	111	18	75	375
2	20	1000	43	70	136	18	85	425
3	20	1000	53	70	161	18	87	435
4	20	1000	61	70	180	18	80	400
5	20	1000	74	70	211	18	70	350
6	20	2000	50	80	166	24	91	910
7[e]	20	2000	–	80		24	97	970
8	30	4000	49	90	175	48	93	1860
9	30	10,000	45	100	186	48	42[f]	2100

[a] Reactor capacity = 125 ml. Unless otherwise noted, the P(CO) charged was +10 bar with respect to the pressure reached by the system at room temperature after the loading of CO_2; the P(air) charged was +15 bar with respect to the pressure reached by the system at room temperature after the loading of CO_2 and CO.
[b] Measured at the reaction temperature.
[c] Isolated yield.
[d] TON (turnover number) = mmol of urea obtained per mmol of K_2PdI_4 employed.
[e] The reaction was carried out under solvent-free conditions, under a 4:1 mixture of CO–air (total pressure = 50 bar at room temperature).
[f] Substrate conversion was 45%.

and after the charging. Then CO (10 bar) and air (15 bar) measured by reading the pressure on the reactor manometer were added at room temperature. The reaction was magnetically stirred and heated at 70 °C in an oil bath for 18 h. After the reaction, the reactor was cooled at room temperature and carefully depressurized. Ten milliliter of CH_2Cl_2/petroleum ether (1:1) were added to the raw reaction material, and the insoluble product was recovered as a white solid (1.46 g, 85%) by filtration on a Buchner funnel separating the unconverted amine and the catalyst. The organic solution was analyzed by GC and GC-MS. Recrystallization from diethyl ether/petroleum ether (1:1) gave pure 1,3-di-*n*-butylurea as colorless crystals (m.p. 71–72 °C). All the spectroscopic analyses were consistent with the reported literature (see supporting information section).

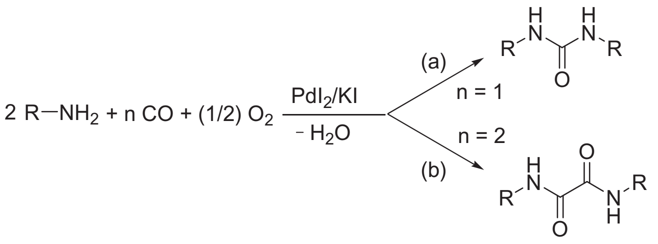
2.5. Procedure for the carbonylation reaction of aniline as a function of the reaction time (Fig. 1)

Aniline (1.862 g, 20 mmol) and K_2PdI_4 (1.4 mg, 0.002 mmol) were charged in a 125 ml stainless steel reactor. Air was first flushed at low pressure and then CO_2 (99.5% purity, 40.0 g, 0.909 mol) loaded as a liquid. Then, air (+15 bar) measured by reading the pressure on the reactor manometer was added at room temperature. The reactor was immersed into an oil bath, magnetically stirred and heated at 95 °C. CO (+10 bar) was added and this was considered the starting reaction time. Total pressure was 170 bar. After established time, the reaction was stopped and the residual liquid was examined by GLC for quantitative determination of aniline and phenylisocianate, whereas diphenyl urea was separated and the yield determined as isolated product.

3. Results and discussion

3.1. Oxidative carbonylation of primary aliphatic amines

As mentioned in the Introduction, the PdI_2/KI-catalyzed oxidative carbonylation of primary amines to the corresponding symmetrical *N*,*N*′-disubstituted ureas has been shown to proceed efficiently better in an aprotic, low polar, and weakly coordinating solvent, such as DME. In this case, monocarbonylation [path (a), Scheme 1] is preferred over dicarbonylation [path (b), Scheme 1], so ureas are selectively formed.



Scheme 1. PdI_2/KI-catalyzed oxidative carbonylation of primary amines leading to ureas (a) or oxamides (b).

Carbon dioxide can behave, under appropriate conditions, like an aprotic solvent of low polarity, so we reasoned that it could be a suitable reaction medium for the selective catalytic synthesis of ureas, also because it is completely miscible with CO and O_2 at temperature higher than 304 °K (31 °C) [17]. We first examined the reaction of *n*-butylamine with CO and air in the presence of a catalytic amount of K_2PdI_4 and determined the yield of the corresponding urea under different pressures of CO_2 (Table 1). To this aim, five experiments were initially carried out loading different amounts of liquid CO_2 in a stainless steel high pressure reactor (125 ml capacity). Thus, the autoclave was charged in the presence of air with K_2PdI_4 (0.02 mmol) and *n*-butylamine (20 mmol). After introduction of the fixed and weighed amount of liquid CO_2, CO (+10 bar with respect to the reached pressure, $\geqslant$25 mmol CO) and air (+15 bar with respect to the reached pressure, $\geqslant$10 mmol O_2) were charged at room temperature. The autoclave was immersed into a thermostated oil bath, and the heating was adjusted to have a temperature of 70 °C, measured with a thermocouple at the bottom of the reactor. The reaction mixture was eventually stirred for 18 h. Under these conditions, *N*,*N*′-di-*n*-butylurea was selectively obtained, with yields ranging from 70% to 87%, depending on the amount of CO_2 loaded (Table 1, entries 1–5). The higher yields were observed in correspondence of about 40–50 g of loaded CO_2 (130–160 bar of total pressure at 70 °C, Table 1, entries 2 and 3). It should be noted, however, that the amount of CO_2 necessary for obtaining the best results may vary depending on the substrate structure and temperatures.

The same substrate was then tested at different molar ratios with the catalyst and at different temperatures (Table 1, entries

$$2BuNH_2 + CO + K_2PdI_4 \longrightarrow BuNHCOHNBu + 2KI + Pd(0) + 2HI \quad (3)$$

$$2HI + (1/2)\,O_2 \longrightarrow I_2 + H_2O \quad (4)$$

$$Pd(0) + I_2 + 2KI \longrightarrow K_2PdI_4 \quad (5)$$

Scheme 2. Catalytic cycle: production of urea and water and regeneration of the catalyst.

6–9). In one case (entry 7), the reaction was carried out under solvent-free conditions, i.e., not adding CO_2, and using a CO/air ratio of 4:1 in order to work outside the CO–air explosion range [18]. As can be seen from Table 1, the results under solvent-free conditions were slightly better than those obtained in presence of CO_2. Yields were still satisfactory for substrate-to-catalyst molar ratios as high as 4000, although it was necessary to raise the reaction temperature and/or to extend the reaction time to achieve complete substrate conversion (Table 1, entry 8). For a substrate-to-catalyst molar ratio of 10,000, the reaction rate decreased significantly, but a remarkable turnover number (TON) of 2100 mol of product per mol of catalyst was achieved (Table 1, entry 9).

The results reported in Table 1 show that the rate of formation of dibutylurea under CO_2 is lower than that observed in DME according to our previous works [5b]. As shown in Scheme 2, the total catalytic process consists of the reactions 3–5, i.e., the substrate carbonylation with reduction of PdI_2 to Pd(0) and concomitant formation of 2 mol of HI (Eq. (3)), the oxidation of the latter by oxygen to give I_2 (Eq. (4)), and the oxidative addition of I_2 to Pd(0) with regeneration of the catalyst (Eq. (5)) [5].

As we have already reported in the case of the reaction carried out in DME, Pd(0) reoxidation can be favored by the presence of an excess of added CO_2, since the basicity of the amine (which would "block" HI, thus hindering Pd(0) reoxidation) is efficiently buffered by CO_2 [5].

In spite of the generally low polarity of primary aliphatic and aromatic amines (n-$BuNH_2$ $\varepsilon = 5.3$ at 21 °C, $PhNH_2$ $\varepsilon = 6.9$ at 20 °C, $\varepsilon = 5.9$ at 70 °C, $PhCH_2NH_2$ $\varepsilon = 4.6$ at 21 °C, $\varepsilon = 4.3$ at 50 °C) [19], K_2PdI_4 was completely dissolved at room temperature in n-$BuNH_2$ and over 40 °C in $PhNH_2$ under high CO_2 pressure of the reaction conditions. In addition, it is known that relatively strong bases, such as primary and secondary aliphatic amines, may readily react with CO_2 to form alkylammonium carbamates (Scheme 3), which in some cases can be rather stable under CO_2 pressure and insoluble in dense CO_2, thus hindering the substrate reactivity toward CO. As a consequence, these unfavorable factors can lower the rate of the carbonylation reaction.

Actually n-$BuNH_2$ ($K_b = 4.37 \times 10^{-4}$ [20]) formed a colorless solid immediately on contact with dense CO_2 [21]. By heating at 70 °C, it melted giving a colorless liquid that absorbed CO_2 expanding of 40–45% its volume compared with the one in the absence of CO_2 under the same conditions. At room temperature, the CO_2 expanded IL (ionic liquid) [$BuNHCO_2^-$ H_3NBu^+] mixture maintained its fluidity under CO_2 pressure [22]. After adding CO, the reaction could start and the mixture turned to pale yellow its color. Precipitation of dibutylurea into the reaction mixture was observed when the conversion of n-$BuNH_2$ reached 25–30% at the temperature of 90 °C.

These factors were even more important with *tert*-butylamine ($K_b = 4.90 \times 10^{-4}$) [20], which showed a lower reactivity with respect to n-butylamine; 1,3-di-*tert*-butylurea being obtained in 33% yield working at 100 °C (Table 2, entry 10). *tert*-Butylamine formed on contact with dense CO_2 immediately a white solid so much stable that even at 100 °C under CO_2 pressure remained unchanged. Under these conditions, CO could only react through a gas solid reaction being the catalyst dispersed into the solid ammonium salt. In order to obtain satisfactory yields, it was necessary to add DME (entries 11 and 12, Table 2) or to carry out the reaction under solvent-free conditions (entry 13, Table 2). This can be related to the high stability and low solubility of the carbamate formed between *tert*-butylamine and carbon dioxide, which lowers the reactivity of the system toward CO. This hypothesis was confirmed by loading *tert*-butylamine and CO_2 in the reactor under the usual reaction conditions; *tert*-butylammonium *tert*-butylcarbamate was isolated as an air-stable white solid (yield 86% working at 100 °C) [23]. Clearly, this salt could not be formed in the absence of CO_2, so the urea yields were higher under solvent-free conditions (entries 13 and 14, Table 2). On the other hand, the addition of an organic solvent (such as DME) along with CO_2, affecting the polarity of the reaction medium, could cause the formation of an homogeneous CO_2 expanded reaction mixture consisting of the substrate, catalyst, DME, and CO_2 [10a]. As a consequence, ammonium carbamate dissolution and decomposition was achieved and the carbonylation reaction, carried out in the presence of CO_2 and DME (entry 12, Table 2), led to practically the same yields obtained under solvent-free conditions (entry 13, Table 2).

$$RNH_2 + CO_2 \rightleftharpoons RN^+H_2CO_2^-$$

$$RNH_2 + RN^+H_2CO_2^- \rightleftharpoons RNH_3^+ \quad RNHCO_2^-$$

Scheme 3. Formation of alkylammonium carbamate derivatives.

These phase behaviors in the reaction course were observed with the autoclave equipped with quartz windows. The corresponding photographs are enclosed in the Supporting Information.

Francis has addressed the effect of basicity of organic compounds on their solubility in CO_2 [21a]. He has concluded that weakly acidic CO_2 has no noticeable affinity for moderately basic aniline ($K_b = 3.98 \times 10^{-10}$) [20], pyridine ($K_b = 2.30 \times 10^{-10}$) [20], and 2-picoline ($K_b = 9.38 \times 10^{-9}$) [20]. However, CO_2 does form salts with stronger bases such as ammonia ($K_b = 10^{-5}$) and aliphatic amines ($K_b = 10^{-4}$). He found p-phenetidine ($K_b = 10^{-9}$) to be the borderline case, permitting observations on metastable liquid–liquid solubilities before solid salt appears.

In the case of benzylamine ($K_b = 9.35 \times 10^{-5}$) [20], on the other hand, the expected *N*,*N*′-dibenzylurea was obtained in high yields both in CO_2 and under solvent-free conditions, as shown in Table 3.

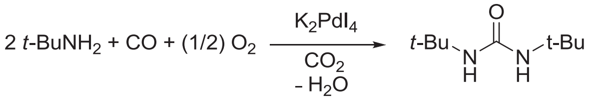
3.2. Oxidative carbonylation of primary aromatic amines

As we previously reported, the yields and catalytic efficiencies of the carbonylation reactions of aromatic amines carried out in DME were lower than those observed with aliphatic amines [5b]. Surprisingly, however, the reaction of aromatic amines, conducted in CO_2 in the absence of any additional organic solvent, proceeded with remarkably high efficiency, particularly in the case of aniline to give *N*,*N*′-diphenylurea (DPU). Table 4 shows the results obtained with aniline in CO_2 under different reaction conditions.

Aniline was found to react efficiently with substrate-to-catalyst molar ratios ranging from 2000 to 100,000. In this latter case, it was sufficient to opportunely raise the reaction temperature and extend the reaction time in order to obtain a DPU yield as high as 87%, with an unprecedented turnover number of 43,500 (Table 4, entry 22). By comparison, the reaction in DME reached a maximum turnover number of 480, as reported in our previous work

Table 2

K$_2$PdI$_4$-catalyzed oxidative carbonylation of *tert*-butylamine to 1,3-di-*tert*-butylurea in CO$_2$ under different conditions.[a]



Entry	mmol of t-BuNH$_2$	t-BuNH$_2$ K$_2$PdI$_4$ molar ratio	CO$_2$ loaded (g)	Reactor pressure[b] (bar)	Reaction temperature (°C)	Reaction time (h)	Urea yield (%)[c]	TON[d]
10	20	2000	45	186	100	24	33	500
11[e]	20	2000	46	205	110	24	62	620
12[f]	20	2000	45	203	110	24	90	900
13[g]	20	2000	–		110	24	91	910
14[g]	40	10,000	–		110	24	67	3350

[a] Reactor capacity = 125 ml. Unless otherwise noted, the P(CO) charged was +10 bar with respect to the pressure reached by the system at room temperature after the loading of CO$_2$; the P(air) charged was +15 bar with respect to the pressure reached by the system at room temperature after the loading of CO$_2$ and CO.

[b] Measured at the reaction temperature.

[c] Isolated yield.

[d] TON (turnover number) = mmol of urea obtained per mmol of K$_2$PdI$_4$ employed.

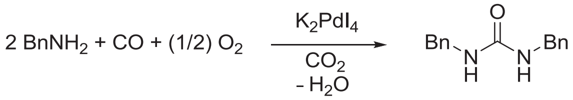
[e] 3 ml of DME was added to the reaction mixture.

[f] 15 ml of DME was added to the reaction mixture.

[g] The reaction was carried out under solvent-free conditions, under a 4:1 mixture of CO–air (total pressure = 50 bar at room temperature).

Table 3

K$_2$PdI$_4$-catalyzed oxidative carbonylation of benzylamine to *N,N′*-dibenzylurea in CO$_2$ under different conditions.[a]



Entry	mmol of BnNH$_2$	BnNH$_2$/K$_2$PdI$_4$ molar ratio	CO$_2$ loaded (g)	Reactor pressure[b] (bar)	Reaction temperature (°C)	Reaction time (h)	Urea yield (%)[c]	TON[d]
15	20	2000	40	142	80	24	99	990
16[e]	30	4000	–		100	36	96	1920
17	20	4000	40	166	100	24	96	1920

[a] Reactor capacity = 125 ml. Unless otherwise noted, the P(CO) charged was +10 bar with respect to the pressure reached by the system at room temperature after the loading of CO$_2$; the P(air) charged was +15 bar with respect to the pressure reached by the system at room temperature after the loading of CO$_2$ and CO.

[b] Measured at the reaction temperature.

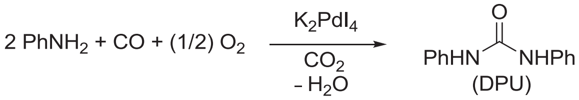
[c] Isolated yield.

[d] TON (turnover number) = mmol of urea obtained per mmol of K$_2$PdI$_4$ employed.

[e] The reaction was carried out under solvent-free conditions, under a 4:1 mixture of CO–air (total pressure = 50 bar at room temperature).

Table 4

K$_2$PdI$_4$-catalyzed oxidative carbonylation of aniline to *N,N′*-diphenylurea (DPU) in CO$_2$ under different conditions.[a]



Entry	mmol of PhNH$_2$	PhNH$_2$/K$_2$PdI$_4$ molar ratio	CO$_2$ loaded (g)	Reactor pressure[b] (bar)	Reaction temperature (°C)	Reaction time (h)	DPU yield (%)[c]	TON[d]
18	30	4000	41	163	90	24	90	1800
19	40[e]	8000	41	169	100	24	95	3800
20	41[e]	20,000	41	175	100	36	92	9200
21	40[e]	60,000	38	172	110	60	96	28,800
22	40[e]	100,000	37	170	110	72	87	43,500
23[f]	20	2000	–		90	24	96	960
24[f]	40	100,000	–		110	72	36[g]	18,000

[a] Reactor capacity = 125 ml. Unless otherwise noted, the P(CO) charged was +10 bar with respect to the pressure reached by the system at room temperature after the loading of CO$_2$; the P(air) charged was +15 bar with respect to the pressure reached by the system at room temperature after the loading of CO$_2$ and CO.

[b] Measured at the reaction temperature.

[c] Isolated yield.

[d] TON (turnover number) = mmol of urea obtained per mmol of K$_2$PdI$_4$ employed.

[e] The P(air) charged was +17 bar with respect to the pressure reached by the system at room temperature after the loading of CO$_2$ and CO.

[f] The reaction was carried out under solvent-free conditions, under a 4:1 mixture of CO–air (total pressure = 50 bar at room temperature).

[g] The substrate conversion was 41%.

[5b]. These results are unprecedented in literature and are about two orders of magnitude higher than the best ones reported with other catalytic systems [5b]. The difference in reactivity between aniline and aliphatic amines may be ascribed mainly to two factors. First, the formation of ammonium carbamates from aromatic amines are prevented or owing to their low basicity (aniline

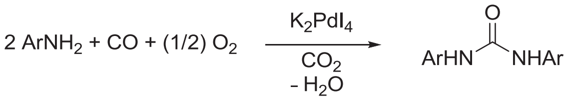
$K_b = 3.98 \times 10^{-10}$) or to their very low stability compared with the ones of aliphatic amines, so their conversion is more favorable, leading to an increase in the carbonylation rate. An inspection through the quartz windows of the mixture of aniline and CO_2 at 25 °C into autoclave showed a 30–35% homogeneous expanded aniline solution and overhanging liquid CO_2. The aniline solution containing the catalyst was homogeneous under CO_2 pressure at 40 °C. Secondly, CO_2 is able to increase the solubility of gases in the mixture of the organic reagent and the catalyst. Recently, it has been shown [24] that a high gas solubility can be achieved by the addition of CO_2 to a gas–liquid system; as a consequence, mass transfer can be substantially enhanced and high reaction rates can be reached in the system, which remains essentially biphasic. In fact, while it is known that aniline is only slightly soluble in $scCO_2$ (3% at 32 °C and 175 bar [21b]), it is acknowledged that gases with critical temperatures below 304 K, including CO and oxygen, are miscible with $scCO_2$ in all proportions [11e]. Thus, the reaction apparently takes place in a biphasic system consisting of a liquid phase formed by the expanded solution of the catalyst in aniline at 90 °C (the catalyst has been found to be completely soluble in aniline at the reaction temperatures under CO_2 pressure) and a supercritical phase formed by carbon dioxide, carbon monoxide, nitrogen, and oxygen. Qualitative visual observations of the biphasic system under the reaction conditions performed carrying out the experiments inside an autoclave equipped with two quartz windows showed that no precipitation of diphenyl urea occurred up to 40–45% of aniline conversion was reached at 90 °C. On the other hand, in the absence of CO_2, diphenyl urea is insoluble in neat aniline at 90 °C. The mutual solubility of the two phases is then efficiently enhanced by the presence of the supercritical medium. This allows overcoming mass transport problems at the interface of the phases, leading to a faster and more efficient reaction. However, in absence of CO_2, the gases reach the liquid phase [11b] more difficultly. When the reaction of aniline was carried out under solvent-free conditions, less satisfactory results were obtained with respect to the experiment conducted in CO_2: under the same conditions of entry 23 (100,000:1 M ratio substrate: catalyst, 110 °C for 72 h, urea yield 87%), the DPU yield lowered to 36% at 41% substrate conversion (entry 24, Table 4), thus confirming the effective role of CO_2 in the reaction course.

Other aromatic amines were then examined, both in the presence and in the absence of CO_2. Tables 5 reports the results obtained for several *para*- and *meta*-substituted anilines.

The results obtained deserve some comments. *p*-Methoxyaniline showed a good reactivity even at 80 °C for 24 h under CO_2 pressure (94% yield, Table 5, entry 27), whereas it showed no reactivity at all under solvent-free conditions (entry 28). This behavior may be connected to the melting point of the considered amine. In fact, *p*-anisidine has a melting point of 57–60 °C, and under the reaction conditions (80 °C) is probably in a very aggregated molten

Table 5

K_2PdI_4-catalyzed oxidative carbonylation of aromatic amines in CO_2 under different conditions.[a]



Entry	$ArNH_2$ (K_b)[b]	$ArNH_2/K_2PdI_4$ molar ratio	CO_2 (g)	T (°C)	Reactor pressure[c] (bar)	Time (h)	Substrate conversion (%)	Urea yield (%)[d]	TON[e]
25	*p*-$CH_3OC_6H_4NH_2$ ($K_b = 2.29{\cdot}10^{-9}$)	20,000	41	100	169	24	75	72	7200
26	*p*-$CH_3OC_6H_4NH_2$	10,000	41	80	148	24	80	77	3850
27	*p*-$CH_3OC_6H_4NH_2$	6000	41	80	146	24	100	94	2820
28[f]	*p*-$CH_3OC_6H_4NH_2$	6000	–	80		24	0	0	0
29	*p*-$CF_3OC_6H_4NH_2$	6000	40	80	150	24	74	70	2100
30	*p*-$CF_3OC_6H_4NH_2$	6000	40	100	165	24	100	94	2820
31[f]	*p*-$CF_3OC_6H_4NH_2$	6000	–	100		24	99	93	2790
32	*p*-$CH_3C_6H_4NH_2$ ($K_b = 1.20{\cdot}10^{-9}$)	6000	41	90	159	20	96	91	2730
33[f]	*p*-$CH_3C_6H_4NH_2$	6000	–	85		24	49	46	1380
34	*p*-$CH_3C_6H_4NH_2$	15,000	42	110	182	70	55	51	3825
35	*m*-$CH_3C_6H_4NH_2$ ($K_b = 5.12 \times 10^{-10}$)	6000	40	80	149	24	100	97	2910
36[f]	*m*-$CH_3C_6H_4NH_2$	6000	–	80		24	79	75	2250
37	*m*-$CF_3C_6H_4NH_2$ ($K_b = 10^{-12}$)[g]	6000	38	80	140	24	88	85	2550
38	*p*-$FC_6H_4NH_2$ ($K_b = 4.47 \times 10^{-10}$)	6000	39	80	142	24	59	56	1680
39[f]	*p*-$FC_6H_4NH_2$	6000	–	80		24	60	57	1710
40	*p*-$ClC_6H_4NH_2$ ($K_b = 9.55 \times 10^{-11}$)	5000	39	80	143	24	45	41	1025
41[f]	*p*-$ClC_6H_4NH_2$	5000	–	80		24	0	0	0
42	*p*-$BrC_6H_4NH_2$ ($K_b = 7.59 \times 10^{-11}$)	5000	38	80	140	24	52	48	1200
43[f]	*p*-$BrC_6H_4NH_2$	5000	–	80		24	0	0	0
44	*p*-$IC_6H_4NH_2$	5000	38	80	141	24	51	32	800
45[f]	*p*-$IC_6H_4NH_2$ ($K_b = 6.55 \times 10^{-11}$)	5000	–	80		24	0	0	0
46	*p*-$NO_2C_6H_4NH_2$ ($K_b = 1.02 \times 10^{-13}$)	2000	38	80	140	48	0	0	0

[a] Reactor capacity = 125 ml. The amount of $ArNH_2$ was 20 mmol in all experiments. Unless otherwise noted, the P(CO) charged was +10 bar with respect to the pressure reached by the system at room temperature after the loading of CO_2; the P(air) charged was +15 bar with respect to the pressure reached by the system at room temperature after the loading of CO_2 and CO.

[b] Ref. [20].

[c] Measured at the reaction temperature.

[d] Isolated yield.

[e] TON (turnover number) = mmol of urea obtained per mmol of K_2PdI_4 employed.

[f] The reaction was carried out under solvent-free conditions, under a 4:1 mixture of CO–air (total pressure = 50 bar at room temperature).

[g] Calculated according to the method reported in reference [25].

phase, which hinders reactivity. In the presence of CO_2, this phenomenon is less important and the reactivity increases. In fact, the presence of compressed CO_2 is known to lower the melting point of organic solids, as long as their temperature is not too far above the critical temperature of CO_2 and this is soluble in the molten organic [10c]. A similar behavior was observed for the reaction of *p*-toluidine, whose melting point is a little higher than room temperature (40–43 °C). Accordingly, under solvent-free conditions, a reduced yield (46%, entry 33) was obtained in comparison with 91% for the reaction carried out in CO_2 (entry 32). The same behavior was observed with *p*-haloanilines [with X = Cl, (m.p. = 69–72 °C), Br, (m.p. = 62–64 °C), or I, (m.p. = 63–65 °C), entries 40–45)]. These compounds have melting points close to or higher than the reaction temperature; thus, no conversion at all was observed in absence of solvent (entries 41, 43, and 45). On the other hand, *p*-fluoroaniline and *p*-trifluoromethoxyaniline are liquid at room temperature: thus, no positive effect of CO_2 was observed and the reactions proceeded smoothly also under solvent-free conditions (see entries 30, 31, 38, and 39). In any case, the reactivity of *p*-haloanilines was found to be lower in comparison with *p*-methoxy and *p*-methylanilines, due to the deactivating effect of the halogen substituent, while their relative reactivity decreased in the order F > Cl ≈ Br > I probably correlated with a different capacity of absorption of CO_2 into the *p*-haloamine. The unusually low selectivity observed with *p*-iodoaniline (urea yield = 32%, entry 44) can be due also to secondary reactions between the palladium intermediates and the C—I bond. Finally, *p*-nitroaniline showed no reactivity at all, due to the strong deactivating effect of the nitro group and/or to the very high melting point (mp 146–149 °C) (entry 46).

The reactivity of some *m*-substituted anilines was also tested in order to better demonstrate the general applicability of this process. The results obtained with *m*-toluidine ($K_b = 5.12 \times 10^{-10}$ [20]) and *m*-trifluoromethylaniline are reported in Table 5, entries 35–37. As expected, for *m*-toluidine (mp < room temperature), the results obtained in the reaction carried out under solvent-free conditions (entry 36) were similar to those observed in $scCO_2$ (entry 35). As already noticed in the case of *p*-substitutes aryl amines, the presence of the halogen atoms slightly decreased the reactivity of the system, due to the deactivating effect on the aromatic ring (entry 37).

3.3. Proposed carbonylation pathway

A series of palladium-catalyzed carbonylation reactions of aniline (20 mmol.) were performed varying reaction times, and the profile of the reaction was obtained (Fig. 1).

The catalyzed reaction exhibits an induction period of ca 2–3 h during which a orange–red color appears. The production of DPU proceeds in two steps. The time-conversion curves in Fig. 1 indicate that the slow step of the Pd-catalyzed formation of PhNCO is followed by the rapid condensation of aniline under reaction conditions. The active catalyst species, which leads to PhNCO formation, likely forms in the first hours after that there is a boost in the urea production. Oxidation of Pd(0) does not appear the limiting step since by varying the O_2 pressure, the reaction rate does not change appreciably.

Formation of ureas **2** can be rationalized as depicted in Scheme 4, involving the formation of a carbamoylpalladium complex **II** in pre-equilibrium with starting materials or with a palladium carbamate intermediate complex **I**. Intermediate **II** then evolves to form isocyanate **III** (by HI elimination from the PhHN–CO–Pd–I moiety), from which ureas are obtained by nucleophilic attack by the amine [5]. In agreement with this hypothesis, isocyanates were detected in the reaction mixture in low conversion experiments.

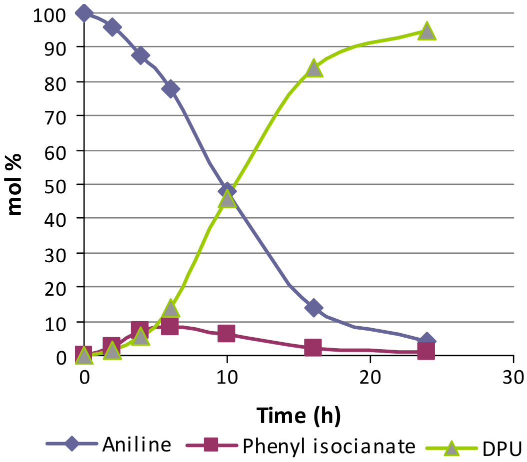


Fig. 1. Composition of the reacting mixture as a function of the reaction time during the synthesis of diphenyl urea from aniline (20 mmol, $PhNH_2/K_2PdI_4$ molar ratio = 10,000), CO_2 (40 g), air 15 bar, CO 10 bar; total pressure 170 bar at 95 °C.

$$RNH_2 + CO_2 + K_2PdI_4 \rightleftharpoons RNHCOOPdI + 2KI + HI$$

$$RNHCOOPdI + CO \rightleftharpoons \underset{\mathbf{I}}{RNHCOOPd(CO)I}$$

$$RNHCOOPd(CO)I \longrightarrow \underset{\mathbf{II}}{RNHCOPdI} + CO_2$$

$$RNHCOPdI \longrightarrow \underset{\mathbf{III}}{RN{=}C{=}O} + HI + Pd(0)$$

$$RN{=}C{=}O + RNH_2 \longrightarrow RNHCONHR$$

$$2HI + 1/2O_2 \longrightarrow I_2 + H_2O$$

$$Pd(0) + 2KI + I_2 \longrightarrow K_2PdI_4$$

Scheme 4. Proposed reaction pathway.

4. Conclusions

A green and efficient catalytic process has been developed for the oxidative carbonylation of primary amines to *N,N'*-disubstituted ureas in the presence of CO_2 as the reaction medium or under solvent-free conditions. The reactions yield no other by-product than water and proceed with high performance with aliphatic as well as aromatic amines. The reactions of aniline and *n*-butylamine take place in a biphasic systems consisting of an homogeneous liquid phase formed by CO_2 expanded aniline solution containing the catalyst and a supercritical phase of CO_2, CO, O_2, and N_2 and in a biphasic system consisting of CO_2 expanded IL of the salt $BuNHCO_2^- \ H_3NBu^+$ containing the catalyst and a supercritical phase of CO_2, CO, O_2, and N_2, respectively. The use of CO_2 as a reaction medium allows several advantages with respect to the reactions carried out in conventional solvents: it allows a greener process since no organic solvent is needed; moreover, the safety of the process is improved since the excess of carbon dioxide prevents any explosion or combustion hazards. While with primary aliphatic amines, no significant improvement on reactivity is observed when carbon dioxide is used as a solvent, a remarkable high efficiency is obtained with aromatic amines, which shows the highest performances known so far for this kind of process. This is a further proof of the fact that the switch to non-conventional reaction media can not only improve the environmental feasibility of a chemical process, but in some cases can also lead to a significant improvement on reactivity.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jcat.2011.06.003.

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