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A novel and efficient method for the Pd-catalysed oxidative carbonylation of amines to symmetrically and unsymmetrically substituted ureas

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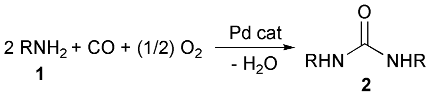
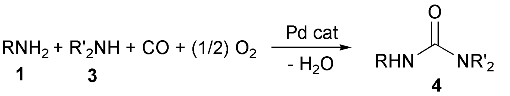
A new method for the Pd-catalysed oxidative carbonylation of amines to symmetrically and unsymmetrically substituted ureas with unprecedented catalytic efficiencies for this kind of reaction has been developed.

The development of new synthetic protocols for the production of ureas has recently attracted great interest in view of their many important applications.[1] The classical syntheses of ureas have been based on the use of dangerous reagents, such as phosgene or isocyanates. In recent years, however, alternative routes have been developed *via* the use of a variety of carbonyl derivatives, CO_2, or CO.[1] Particularly attractive, also from the standpoint of atom economy, is the oxidative carbonylation methodology,[2] which employs amines, carbon monoxide and oxygen as starting materials and produces only H_2O as co-product.[3]

We wish to report here a new method for the Pd-catalysed oxidative carbonylation of amines to symmetrically and unsymmetrically substituted ureas [eqns. (1) and (2), respectively], which is characterized by unprecedented catalytic efficiencies for this kind of reaction.



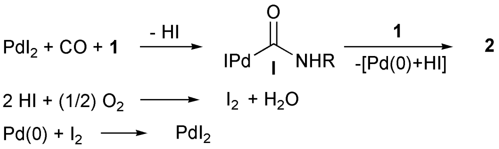
$$2\,\underset{\mathbf{1}}{RNH_2} + CO + (1/2)\,O_2 \xrightarrow[-\,H_2O]{\text{Pd cat}} \underset{\mathbf{2}}{RHN{-}C({=}O){-}NHR} \qquad (1)$$



$$\underset{\mathbf{1}}{RNH_2} + \underset{\mathbf{3}}{R'_2NH} + CO + (1/2)\,O_2 \xrightarrow[-\,H_2O]{\text{Pd cat}} \underset{\mathbf{4}}{RHN{-}C({=}O){-}NR'_2} \qquad (2)$$

Carbonylations of primary aliphatic amines **1** [eqn. (1), R = alkyl] were carried out in 1,2-dimethoxyethane (DME) (1 mmol of **1**/mL of DME) at 100 °C and under a 4 : 1 : 10 mixture of CO : air : CO_2 (60 atm total pressure at 25 °C) in the presence of a very simple catalytic system consisting of PdI_2 in conjunction with KI.[4] Some representative results are shown in Table 1, runs 1–3. As shown in the Table, excellent yields in the corresponding ureas **2** were obtained, with turnover numbers as high as 2400 mol of **2** per mol of Pd used.† Butylamine **1a** (R = *n*-Bu, run 1) was more reactive than sterically demanding *tert*-butylamine **1b** (R = *t*-Bu, run 2), and somewhat less reactive than benzylamine **1c** (R = CH_2Ph, run 3). Working in the absence of CO_2, less satisfactory results were obtained (compare run 4 with run 3).

Primary aromatic amines [eqn. (1), R = Ar] were generally less reactive than primary aliphatic amines. With aniline **1d** (R = Ph), substrate to catalyst ratio was lowered to 1000 (run 5); moreover, carbonylation of aniline gave better results working in the absence of added CO_2. However, a more nucleophilic primary aromatic amine such as 4-methoxyaniline **1e** (R = *p*-$MeOC_6H_4$) turned out to be more reactive than *tert*-butylamine **1b** (compare runs 6 and 2), with no significant CO_2 effect observed in this case.



Scheme 1 Mechanism of formation of ureas **2**.

Formation of **2** can be rationalized as depicted in Scheme 1, involving the formation of carbamoylpalladium species **I** as the key intermediate (anionic iodide ligands are omitted for clarity).

The use of a coordinating aprotic solvent of low polarity, such as DME, was essential for the success of the reaction. In fact, very low yields and catalytic efficiencies were obtained working in polar protic or polar aprotic solvents, such as MeOH or *N*,*N*-dimethylacetamide (DMA), under the above conditions. We interpret this result as follows. As shown in Scheme 1, in the course of the process **1** acts as nitrogen nucleophile, and substrate carbonylation is accompanied by the formation of 2 mol of HI and 1 mol of Pd(0). As we have already reported,[4b] reoxidation of Pd(0) under our conditions occurs through oxidative addition by I_2, generated by oxidation of HI by oxygen. Clearly, in the presence of a basic substrate such as **1**, acid–base equilibrium (3) takes place, which lowers the

$$\mathbf{1} + HI \rightleftharpoons R\overset{+}{N}H_3 + I^- \qquad (3)$$

concentration of both HI [thus hindering Pd(0) reoxidation] and free **1**. As a consequence, the overall carbonylation process tends to be inhibited. This is particularly important in polar solvents, where equilibrium (3) is strongly shifted to the right.[5] However, it is very well known that basicity of amines is significantly reduced in low-polar aprotic solvents with respect to polar solvents.[5] Therefore, in a low-polar solvent the catalytic cycle can run effectively even in the presence of a basic

Table 1 Synthesis of ureas **2** by Pd-catalysed oxidative carbonylation of primary amines **1**[a]

Run	1	R	1/PdI_2	*t*/h	Yield of 2 (%)[b]	Mol of 2/mol of PdI_2
1	**1a**	*n*-Bu	5000	15	96 (99)	2400
2	**1b**	*t*-Bu	2000	15	90 (98)	900
3	**1c**	CH_2Ph	5000	4	94	2350
4[c]	**1c**	CH_2Ph	5000	4	78[d]	1950
5[c]	**1d**	Ph	1000	16	87	435
6[c]	**1e**	*p*-$MeOC_6H_4$	3000	15	98	1470

[a] Unless otherwise noted, all reactions were carried out in DME (1 mmol of **1**/mL of DME, 10–15 mmol scale based on **1**) at 100 °C under 60 atm 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] Isolated yield (GLC yield) based on **1**. Unless otherwise noted, substrate conversion was practically quantitative in all cases. [c] The reaction was carried out under 20 atm of a 4 : 1 mixture of CO : air. [d] Substrate conversion was 86%.

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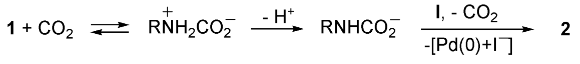
substrate. DME appeared to be the solvent of choice for the present reaction, since it is an aprotic solvent of low polarity (ε = 7.54 at 25 °C, 6.09 at 80 °C),[6] but sufficiently coordinating to allow dissolution of the PdI_2–KI catalytic system.

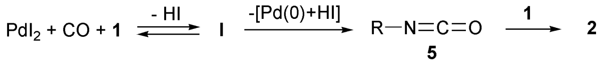
As we have seen, working in the presence of an excess of CO_2 (40 atm) had a beneficial effect on carbonylation of primary aliphatic amines (compare run 4 with run 3), analogous to what we have already observed in the PdI_2–KI-catalysed oxidative cyclization–methoxycarbonylation of (*Z*)-(2-en-4-ynyl)amines to pyrrol-2-acetic esters.[7] This CO_2 effect is related to the fact that substrate basicity is further diminished in the presence of CO_2 through the formation of a carbamate species (Scheme 2). The reaction did not occur in the absence of carbon monoxide, which means that CO_2 indeed acts as a promoter, as shown in Scheme 2, and not as carbonylating agent. The fact that in the case of aniline better results were obtained working in the absence of CO_2 (run 5) is in agreement with the lower nucleophilicity and basicity of aniline as compared with primary aliphatic amines.



$$\mathbf{1} + CO_2 \rightleftharpoons R\overset{+}{N}H_2CO_2^- \xrightarrow{-H^+} RNHCO_2^- \xrightarrow[-[Pd(0)+I^-]]{\mathbf{I},\ -CO_2} \mathbf{2}$$

Scheme 2 Carbon dioxide effect on carbonylation of **1**.

Interestingly, secondary amines **3** were unreactive under the above conditions. This result suggests the formation of isocyanates **5** as the key intermediate of the process, with carbamoylpalladium complex **I** formed in pre-equilibrium with starting materials (Scheme 3). In agreement with this hypothesis, isocyanates were detected in the reaction mixture in low-conversion experiments.



$$PdI_2 + CO + \mathbf{1} \underset{}{\overset{-HI}{\rightleftharpoons}} \mathbf{I} \xrightarrow{-[Pd(0)+HI]} \underset{\mathbf{5}}{R{-}N{=}C{=}O} \xrightarrow{\mathbf{1}} \mathbf{2}$$

Scheme 3 Detailed mechanism of formation of ureas **2**.

Formation of **5** as intermediates also suggested the possibility to synthesise unsymmetrically substituted ureas by carrying out the carbonylation of a primary amine in the presence of a suitable excess of a secondary amine. Indeed, by reacting $BuNH_2$ **1a** (8.3 mmol) and Bu_2NH **3a** (12.5 mmol) in the presence of PdI_2 (3.0 mg, 8.3×10^{-3} mmol) and KI (277 mg, 1.67 mmol) in DME (21 mL) at 90 °C under 60 atm of a 4 : 1 : 10 mixture of CO : air : CO_2 for 15 h, mixed urea **4a** [eqn. (2), R, R′ = Bu] was obtained as the main reaction product (75% isolated yield), symmetrically substituted urea **2a** being formed in only 17% yield. Analogously, the reaction of **1a** and morpholine **3b** [eqn. (2), R = Bu, R′ = $-(CH_2)_2O(CH_2)_2-$] carried out under the same conditions but at 100 °C rather than 90 °C, led to mixed urea **4b** and symmetrically substituted urea **2a** in 71% and 13% isolated yield, respectively.‡

In conclusion, we have developed a new and efficient protocol for the production of symmetrically substituted and unsymmetrically substituted ureas (**2** and **4**, respectively) by direct Pd-catalysed oxidative carbonylation of amines, with unprecedented catalytic efficiencies for this kind of reaction. To our knowledge, the formation of trisubstituted ureas by direct Pd-catalysed oxidative carbonylation of primary and secondary amines is also unprecedented. Ureas are a very important class of carbonyl compounds, which have been shown to possess a marked pharmacological activity.[8]

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Notes and references

† Representative experimental procedure: a 250 mL stainless steel autoclave was charged in the presence of air with PdI_2 (1.1–5.4 mg, 3.0×10^{-3}–1.5×10^{-2} mmol), KI (100 mmol per mmol of PdI_2) and **1** (15 mmol) dissolved in DME (15 mL). The autoclave was pressurized with stirring at rt with CO_2 (40 atm), CO (up to 56 atm) and air (up to 60 atm) and then heated at 100 °C with stirring for the required time. In some cases (Table 1, runs 4–6), the reaction was carried out by pressurizing only with CO (16 atm) and air (up to 20 atm). These conditions (16 atm of CO together with 5 total atm of air, considering that the autoclave was loaded under 1 atm of air) corresponded to 76.2% of CO in air and were outside the explosion limits for CO in air (*ca.* 16–70% at 18–20 °C and atmospheric pressure, 14.8–71.5% at 100 °C and atmospheric pressure. At higher total pressure, the range of flammability decreases: for example, at 20 atm and 20 °C the limits are *ca.* 20 and 60%. See: C. M. Bartish and G. M. Drissel, in *Kirk–Othmer Encyclopedia of Chemical Technology*, 3rd edition, ed. M. Grayson, D. Eckroth, G. J. Bushey, L. Campbell, A. Klingsberg and L. van Nes, Wiley-Interscience, New York, 1978, vol 4, pp. 774–775). After cooling, the autoclave was degassed and solvent removed by rotary evaporation. Generally, some amount of crude product was already present in suspension in the reaction mixture. Crude ureas **2a**–**d** were purified by column chromatography on silica gel using as eluent: Et_2O (**2a**); $CHCl_3$ (**2b**, **2c**); THF (**2d**). Urea **2e** was present in the reaction mixture as a white precipitate, which was purified by washing with acetone to give the pure product as a colorless solid.

‡ Ureas **4a** and **4b** were easily purified by column chromatography on silica gel using hexane–AcOEt from 8 : 2 to 7 : 3 as eluent. All ureas synthesised were fully characterized by IR, ^1H NMR, ^{13}C NMR spectroscopies and MS spectrometry; elemental analyses were satisfactory.

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