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Palladium/iodide catalyzed oxidative carbonylation of aniline to diphenylurea: Effect of ppm amounts of iron salts

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ABSTRACT

The palladium/iodide couple is the most investigated catalytic system for the oxidative carbonylation of amines to give ureas or carbamates. In reinvestigating it, we found that the most prominent role of iodide is to etch the stainless steel of the autoclave employed in most of previous works, releasing in solution small amounts of iron salts. The latter are much better promoters than iodide itself. Iron and iodide have a complex interplay and, depending on relative ratios, can even deactivate each other. The presence of a halide is beneficial, but chloride is better than iodide in this respect. The ideal Fe/Pd ratio is around 10, but even an equimolar amount of iron with respect to palladium (0.02 mol% with respect to aniline, corresponding to 12 ppm Fe with respect to the whole solution) is sufficient to boost the activity of the catalytic system. Such small amount may also come from $Fe(CO)_5$ impurities present in the CO gas when stored in steel tanks. The role of the solvent has also been investigated. It was found that the reason for the better selectivity in some cases is at least in part due to a hydrolysis of the solvent itself, which removes the coproduced water.

1. Introduction

Isocyanates are commodity chemicals mostly employed in polyurethane synthesis. Polyurethanes are widely applied in almost every part of modern life in the form of plastic foams, coatings, adhesives, sealants, elastomers and binders [1,2]. The annual world production of isocyanates is several millions metric tons and it is steadily increasing. The industrial interest for these compounds is evident from the recent investments on new plants by the major producers in both Europe and Asia. The industrial synthesis of isocyanates involves the reaction of an amine with phosgene. From an economical point of view, the phosgene-based route seems to be the most effective strategy and the well-established phosgene technology appears to be difficult to replace. However, phosgene is a very toxic and corrosive material that is listed as a potential chemical weapon by the Chemical Weapon Convention. In 2006, a large plant producing toluene diisocyanate (TDI) was shut in Italy mainly because of the pressure from the local population and authorities against the use of phosgene close to a densely populated area. Thus, it is not surprising that an enormous effort has been made to develop a phosgene-free routes to isocyanates. The two alternatives that have been most heavily investigated both in industrial and academic laboratories are the reductive carbonylation of nitroarenes [3–6] and the oxidative carbonylation of amines [6–9]. The former can afford isocyanates in one step, but the direct synthesis of these products requires forcing conditions and the formed isocyanates tend to oligomerize under these conditions. Thus, research in the last few decades have mostly been focused on reactions performed in the presence of an excess of an alcohol or amine. Under these conditions, the obtained products are carbamates and ureas respectively. Both of them can be thermally cracked in a separate step to give the desired isocyanate and regenerate an equivalent of alcohol or amine [10–16]. Carbamates and ureas are also the products derived from the oxidative carbonylation of amines (Scheme 1).

It should also be recalled that carbamates and urea are not only possible intermediates in the production of isocyanate, but are important chemicals themselves. Carbamates are final products and synthetic intermediates for the pharmaceutical [17,18] and agrochemical industries [19] and ureas have a variety of application [20], from traditional ones such as fertilizers [21] and pesticides [22] to more recent and sophisticated ones such as receptors for anion recognition [23], biosensors [24] and pharmaceutically active agents [25,26]. Thus, the interest in the synthesis of carbamates and ureas goes well beyond their use as intermediates for isocyanate production.

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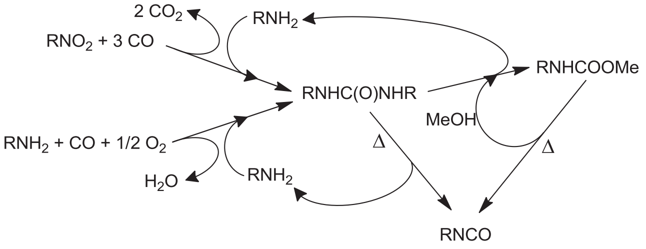


Scheme 1. Reductive carbonylation of nitroarenes and oxidative carbonylation of amines.

The reductive carbonylation approach allows to save one step on the route to carbamates and ureas, but can only be applied to nitroarenes, since nitroalkanes are much more difficult to reduce and usually displace a completely different reactivity with respect to their aromatic counterparts. On the other hand, the oxidative carbonylation route can be applied to both aromatic and aliphatic amines. Our group has worked for many years on the reductive carbonylation of nitroarenes [27–36]. Although this reaction and the oxidative carbonylation reactions of amines may seem at first sight very different, it has been shown that all the most active catalytic systems for the former reaction proceed through a reaction pathway in which the nitroarene is intermediately reduced to the corresponding aromatic amine, which is in turn carbonylated at a later stage [37–43]. During the latter stage, the metal is reduced. The carbonylation step is thus the same in both processes and the main difference between them is that the oxidant is the nitroarene in one case and a separately added oxidant (in most cases dioxygen, possibly in the form of air) in the other. We thus engaged in a study of the oxidative carbonylation of amines, to see if we could improve the current state of the art taking advantage of our previous expertize. Among the different catalytic systems that have been described in the literature for this reaction, the one that has been most investigated and appears to be closer to fulfilling the requirements for an industrial application is that based on the use of a palladium catalyst with an iodide salt or iodine as a promoter [44–73]. The promoting effect of iodide/iodine was first reported by Fukuoka while employing a heterogeneous catalyst [44–47], but the activity of this system was quite low. The activity of heterogeneous systems has been later improved by others [48,51,52,54,63,69,71], but the turnover frequencies (TOF) that can be obtained are nevertheless one or two orders of magnitude lower than those achievable with the use of homogeneous palladium catalysts. We thus decided to focus on homogeneous systems. The products of the reaction can be ureas, oxamides (double carbonylation products) or carbamates. The latter are obtained if an alcohol is employed as solvent. However, at least in the case of aromatic amines and analogously to what it occurs during the reductive carbonylation of nitroarenes, carbamates are only formed at a later stage of the reaction by alcoholysis of the primarily formed urea. Thus, we decided to skip the addition of alcohols in a first investigation to focus on the carbonylation step. Aniline was employed as substrate because aromatic isocyanates are the most important and because oxidative carbonylation of aromatic amines is in general more difficult than that of the more nucleophilic aliphatic amines and finding good conditions for the carbonylation of the former may lead to a system more easily extendable to the latter than the reverse. However, the possibility to extend the obtained results to aliphatic amines was clear to our mind. Thus, as a starting point we selected a system in the literature that would be not only highly active, but that would also give high selectivity for both aromatic and aliphatic amines. Besides some outstanding results obtained in non-conventional solvents such as supercritical CO_2 and ionic liquids [64,68,70], in general highly polar solvents (e.g. DMF) give faster reactions, but when aliphatic amines are employed as substrates, substantial amounts of oxamides are formed as byproducts. Gabriele and coworkers [59] obtained the highest selectivities in ureas by using dimethoxyethane (DME) as solvent and this was our starting point.

2. Results and discussion

2.1. Role of iodide

We first tried to reproduce some of the best results reported in Ref. [59] (Table 1, entries 1 and 2) employing PdI_2 as catalyst and KI as promoter, working in a Teflon-coated autoclave (entry 3). To our surprise, the activity of the catalytic system was quite lower than expected.

Taking into account that Gabriele used a stainless-steel autoclave without Teflon coating, we considered that iodide ion and the hydriodic acid formed during the reaction could partly dissolve the metal of which the autoclave is composed. Thus, we performed a reaction in a non-coated stainless-steel autoclave. In this way, we could indeed reproduce the literature results (entry 4, Table 1).

The role of iodide has been variably interpreted in the previous literature as being due to its adsorption onto heterogeneous palladium nanoparticles [47,48], to the formation of N-iodoaniline [55], to that of carbamoyl iodides (RNHC(O)I) [74], to the generation of anionic low valent palladium complexes such as $[Pd(CO)_3I]^-$, considered to be the catalytically active species [50,57], and especially to the ability of iodine, formed by iodide anion by the action of dioxygen, to reoxidize palladium(0) complexes formed at the end of the catalytic cycle back to palladium(II) [58–60,64,66,75]. Direct oxidation of palladium(0) complexes by oxygen is possible [76], but is generally too slow to avoid precipitation of metallic palladium under carbonylation conditions. Indeed a co-catalyst, that acts as an oxidation catalyst for palladium, must be present and the I_2+KI system is able to play this role by oxidizing even metallic palladium and being quickly reoxidized by dioxygen [75]. However, most of the published oxidative carbonylation works where performed in stainless steel autoclaves and only in a few cases were Hastelloy autoclaves [48,51,52,54] or even less frequently glass reactors [50,57,60] employed and these are not the cases in which the highest activities were obtained.

2.2. Effect of iron-containing promoters

Iron is the most abundant element in stainless steel, so we tested the use of iron salts as promoters for the catalytic reactions [77]. In the literature some examples have been reported of palla-

Table 1
Comparison with previous results and effect of the autoclave internal coating in the PdI_2 catalyzed oxidative carbonylation of aniline.[a]

Entry	KI/Pd mol ratio	t (h)	$PhNH_2$ conv. (%)[b]	Urea sel. (%)[c]
1[d]	10	15	89.0	84.3
2[d]	100	16	96.0	90.6
3[e]	10	16	33.7	60.6
4[f]	10	16	100	94.6

[a] Experimental conditions: the reactions were carried out using 10 mmol of aniline at 100 °C under 16 bar of CO and 4 bar of air, in DME (10 mL). PdI_2 = 0.01 mmol.

[b] Based on starting aniline and on quantitative GC analysis using benzophenone as an internal standard.

[c] Based on reacted aniline and on quantitative HPLC analysis using benzophenone as an internal standard.

[d] Data from Ref. [59].

[e] Performed in a Teflon-lined stainless steel autoclave.

[f] Performed in a stainless-steel autoclave.

dium catalyzed carbonylation reactions of nitroarenes that use iron as co-catalyst, in which aniline appears to be an intermediate [6]. Moreover, recently Krogul and Litwinienko [67] have studied the effect of iron on the $PdPy_2Cl_2/I_2$ catalyzed oxidative carbonylation of amines to carbamates and found an effect of this metal mostly on selectivity. However, the effect of iron in the absence of iodine was not investigated.

Since the reaction at 100 °C is relatively slow (less than 100 turnovers/hour on average) and having as a goal an industrial application, we performed our reactions under harsher conditions, 150 °C, 40 bar of carbon monoxide and 10 bar of air. Note that the ratio between the gases is such that the system is outside the CO/O_2 flammability limits [78]. This is not always the case for the systems reported in the literature. In general, increasing the O_2 relative amount over the lower limit allows getting faster reactions, but the associated risk would not be acceptable at an industrial level. The catalyst loading was also decreased from 0.1 to 0.02 mol%.

We started to test different iron promoters, $FeCl_3$, $FeCl_2$, $FeSO_4\cdot 2H_2O$, $Fe(CO)_5$ and $Fe(OAc)_2$, using PdI_2 as the catalyst.

As a first control experiment, we run our reactions without the catalyst, both with and without potassium iodide, and we checked that no product was formed (entries 1 and 2, Table 2).

Comparing the results of the reactions performed with and without an iron promoter, it clearly emerges that iron has a positive effect on the catalytic cycle, both on the conversion and on the selectivity. The effect of iodide is on the other hand ambiguous. We confirm that it accelerates the reaction when no iron is present (entries 3 and 4, Table 2), but it inhibits it when an iron co-catalyst is present. Iron acetate and iron sulfate give similar results in the catalytic reactions without KI. An addition of the latter has a negative influence mainly on the conversion (entries 8 and 9). This inhibitory effect can be noticed also in the reactions carried out with $FeCl_3$. Comparing the results in entries 15–17, in which the promoter amount is the same, the conversion decreases with an increase in the KI amount. Additionally, the negative influence of KI is more evident in the presence of $FeCl_2$ and $FeCl_3$ (compare entries 13 with 11 and 17 with 15). The best results were obtained using $FeCl_2$ and $FeCl_3$ as co-catalysts without potassium iodide, affording a relatively high conversion and selectivity (entries 11 and 15). Further increasing the iron amount over a Fe/Pd = 50 ratio causes a decrease in selectivity (compare entries 11 and 12).

From the available data on the interplay between iron and iodide, it emerges that the inhibitory role of iodide on the iron promoting ability is stronger when the iodide amount is large with respect to that of iron and the effect is larger if chloride is also present, despite the presence of chloride being beneficial when no iodide is added. Considering that both iodide and chloride are good ligands for iron(II/III) complexes, the best explanation for the trends observed is that when the total halide concentration greatly exceeds that of iron, stable iron complexes (e.g. $[Fe^{II}X_4]^{2-}$ or $[Fe^{III}X_6]^{3-}$) are formed, which are unable to enter the catalytic cycle. Indeed, aniline can coordinate both to palladium and iron and the formation of these complexes may be relevant to the outcome of the catalytic reaction. Conversely, formation of stable halide complexes also decreases the iodide concentration in solution, so that even the promoting effect of iodide is compromised. We will come back to discuss this aspect later in the paper.

Since iodine is toxic and difficult to remove from the reaction products, we tried to completely avoid its presence and tested both $Pd(OAc)_2$ and $PdCl_2$ as catalysts (Table 3).

Palladium acetate alone gave a low conversion and a poor selectivity into diphenylurea (entry 1, Table 3). Conversion was comparable, but selectivity was quite low with respect to the use of PdI_2 under the same conditions (compare entry 1, Table 3, with entry 3 in Table 2). The addition of iron salts not containing halides, $FeSO_4$ and $Fe(OAc)_2$, had a moderate effect on conversion, which may be positive or even negative depending on the relative amounts, and a positive effect on selectivity (entries 2–4). Notably, in the absence of any halide, the addition of $Fe(CO)_5$ inhibited the reaction (entry 5). This is an important observation because $Fe(CO)_5$ is a typical contaminant of carbon monoxide, especially when the latter is stored in steel tanks. We employed aluminum alloy tanks during all this work, which should minimize the $Fe(CO)_5$ content in our CO. The tank material was never declared in the works we cited, but it is obvious that steel tanks were employed at least in the older works, since aluminum alloy tanks have become of common usage only more recently. Thus, it is clear that iron itself is not a promoter and only when a suitable anion is present it efficiently speeds up the reaction.

Table 2
PdI_2 catalyzed reactions using different iron promoters.[a]

Entry	KI/Pd mol ratio	Promoter	Promoter/Pd mol ratio	$PhNH_2$ conv. (%)[b]	Urea sel. (%)[c]
1[d]	–	–		<1	–
2[d]	100	–		<1	–
3	–	–		20.3	88.7
4	100	–		31.5	51.2
5	100	$Fe(CO)_5$	50	40.2	78.1
6	100	$Fe(CO)_5$	100	46.8	45.1
7	100	$FeSO_4\cdot 2H_2O$	30	19.0	79.0
8	–	$FeSO_4\cdot 2H_2O$	50	61.7	80.5
9	100	$FeSO_4\cdot 2H_2O$	50	20.0	92.0
10	–	$Fe(OAc)_2$	50	64.7	85.8
11	–	$FeCl_2$	50	95.8	79.8
12	–	$FeCl_2$	100	95.0	70.3
13	100	$FeCl_2$	50	38.4	74.0
14	100	$FeCl_2$	100	81.6	66.7
15	–	$FeCl_3$	50	100	70.4
16	10	$FeCl_3$	50	91.8	72.5
17	100	$FeCl_3$	50	89.4	68.6
18	100	$FeCl_3$	100	95.7	63.6
19	100	$FeCl_3$	10	30.4	68.9

[a] Experimental conditions: the reactions were carried out in a Teflon-lined stainless-steel autoclave, using 10 mmol of aniline at 150 °C, for 3 h, under 40 bar of CO and 10 bar of air, in DME (10 mL). Catalyst amount 2.0×10^{-3} mmol.

[b] Based on starting aniline and measured by GC analysis using benzophenone as an internal standard.

[c] Based on converted aniline and measured by HPLC analysis using benzophenone as an internal standard.

[d] No palladium was added. The KI/Pd ratio reported is calculated based on a hypothetical 2.0×10^{-3} mmol amount of palladium.

Table 3
$Pd(OAc)_2$ and $PdCl_2$ catalyzed reactions using different iron promoters and in the absence of any iodide source.[a]

Entry	Catalyst	Promoter	Promoter/Pd mol ratio	$PhNH_2$ conv. (%)[b]	Urea sel. (%)[c]
1	$Pd(OAc)_2$	–		22.2	50.0
2	$Pd(OAc)_2$	$FeSO_4{\cdot}2H_2O$	50	30.7	76.7
3	$Pd(OAc)_2$	$Fe(OAc)_2$	50	19.0	75.3
4	$Pd(OAc)_2$	$Fe(OAc)_2$	100	8.3	55.4
5	$Pd(OAc)_2$	$Fe(CO)_5$	50	6.5	55.1
6	$Pd(OAc)_2$	$FeCl_2$	10	95.0	82.3
7	$Pd(OAc)_2$	$FeCl_2$	50	97.0	79.4
8	$Pd(OAc)_2$	$FeCl_2$	100	97.2	74.3
9	$Pd(OAc)_2$	$FeCl_3$	10	95.3	81.2
10	$Pd(OAc)_2$	$FeCl_3$	50	99.6	76.9
11	$Pd(OAc)_2$	$FeCl_3$	100	98.9	72.9
12	$PdCl_2$	$FeCl_3$	50	99.2	76.6
13	$PdCl_2$	$FeSO_4{\cdot}2H_2O$	50	63.5	70.5
14[d]	$Pd(OAc)_2$	$FeCl_2$	10	68.0	86.9
15[e]	$Pd(OAc)_2$	$FeCl_2$	10	41.8	85.0
16		$FeCl_3$	50[f]	3.1	14.3

[a] Experimental conditions: the reactions were carried out in a Teflon-lined stainless-steel autoclave, using 10 mmol of aniline at 150 °C, for 3 h, under 40 bar of CO and 10 bar of air, in DME (10 mL). Catalyst amount 2.0×10^{-3} mmol.

[b] Based on starting aniline and measured by GC analysis using benzophenone as an internal standard.

[c] Based on converted aniline and measured by HPLC analysis using benzophenone as an internal standard.

[d] Reaction time 1 h.

[e] Reaction time 30 min (see text for a discussion of this reaction).

[f] The promoter/Pd ratio is calculated based on the standard 2.0×10^{-3} mmol palladium amount, even if the reaction was run in the absence of any palladium compound.

Much better conversions and selectivities were achieved when palladium acetate was combined with $FeCl_2$ or $FeCl_3$ (Table 3, entries 6–11). A graphical representation of the obtained results (Fig. 1) shows that the effect of $FeCl_2$ and $FeCl_3$ is very similar. Clearly, the initial oxidation state of iron is not important, both precursors will equilibrate to the same complex under the reaction conditions, and the small observed difference is due to the slightly different chloride content of the catalytic mixture.

Noteworthy, just 10 equiv of iron with respect to palladium (0.2 mol% with respect to aniline) is sufficient to boost the activity almost to its highest level. A further increase in the iron amount has only a small positive effect on conversion, but lowers the selectivity of the reaction.

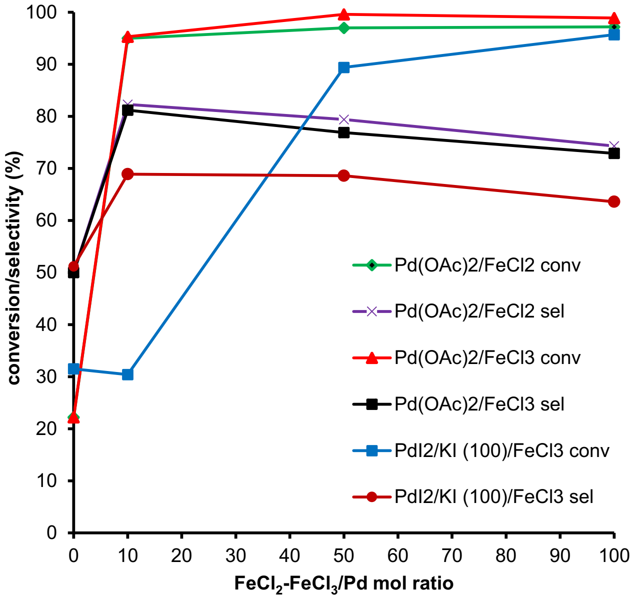


Fig. 1. Effect of $FeCl_2$ and $FeCl_3$ as co-catalysts in the oxidative carbonylation reactions of aniline catalyzed by $Pd(OAc)_2$ and PdI_2+KI (mol ratio KI/Pd = 100). Data from Tables 2 and 3.

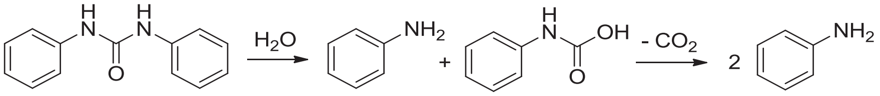
Palladium chloride was also tested as catalyst in the presence of either $FeCl_3$ or $FeSO_4{\cdot}2H_2O$ as promoters. The results were comparable to those obtained employing palladium iodide as catalyst under the same conditions (compare entry 12 in Table 3, with 15 in Table 2 and entry 13 in Table 3 with entry 8 in Table 2). On the other hand, it is worth noting that reactions performed with palladium acetate using $Fe(CO)_5$, $FeSO_4{\cdot}2\ H_2O$, and $Fe(OAc)_2$ as promoters gave worse results with respect to the use of the same promoters with palladium iodide.

As a final test, a reaction was performed in the presence of $FeCl_3$, but in the absence of any palladium compound (entry 16). A very low conversion and trace amounts of diphenylurea were obtained, proving that iron itself has a negligible catalytic activity in this reaction and also that no or negligible palladium contamination of the Teflon coating of the autoclave occurred.

Overall, the trends discussed above indicate that the best results are obtained when palladium and iron are employed together and in the presence of a halide. Iodide is no better than chloride and it does not appear to be relevant whether the halide is initially bound to either palladium or iron or both.

The results obtained when $Fe(CO)_5$ is employed as promoter are worth an additional comment. This compound promotes the reaction when PdI_2 is employed as catalyst, but even inhibits it when $Pd(OAc)_2$ is used. This is a confirmation that the presence of a halide is necessary for iron to act as a promoter and a very small amount of it may already have a measurable effect, even if a larger amount is more effective (see later, paragraph 2.3). The result is important in understanding the data reported in the previous literature. As previously mentioned, some $Fe(CO)_5$ was undoubtedly present in the CO gas of most earlier reports this has likely caused the presence of some iron even when Hastelly or glass reactors were employed. So the role of iodide may have been at least in part linked to its interaction with iron even in those cases in which it did not actively provide the required iron by etching the autoclave.

The possible reason for a negative effect of an excess of halide has been discussed above. The positive effect of a small amount of halide may be explained by the formation of bimetallic Pd-Fe complexes with an halogen bridge (halides are much better bridging ligands than all other anions we tested), but a simpler effect of halides on the redox potentials of the palladium and iron species involved cannot be excluded at this stage.



Scheme 2. Diphenylurea hydrolysis.

Finally, it should be considered that at 150 °C, in 3 h, diphenylurea can be hydrolyzed by the water formed during the reaction (Scheme 2). The so formed aniline may be carbonylated again, but may also originates byproducts. Thus prolonging the reaction time once the reaction is almost complete can only have negative effects. In order to check this possibility, we repeated the reaction corresponding to entry 6 in Table 3, stopping it after one hour or after just 30 min. The results (entry 14 and 15 in Table 3) confirm that a higher selectivity is obtained in a shorter reaction time.

We have independently tested diphenylurea hydrolysis under the reaction conditions in Table 3, starting from the urea and water concentrations that may be present at the end of the reaction if a complete conversion of aniline into diphenylurea and water had occurred, with no side reaction. In the absence of any other compound and in the Teflon-lined autoclave, the hydrolysis was negligible, but the presence of a $FeCl_3$ amount equal to that used in run 12 in Table 3 caused 16% of the urea to hydrolyze. Palladium salts should also be catalysts for this hydrolysis, but we could not add them because they may have caused the back carbonylation of some of the formed aniline.

Notably, already a 41.8% conversion was observed after 30 min, corresponding to a TOF of 4190/h (or 1780/h with respect to the formed urea). However, note that the TOF values measured at a short reaction time are strongly underestimated in our case. Indeed, we placed our autoclaves in a preheated oil bath and considered that moment as the start of the reaction. However, the insertion of the autoclave into the bath caused a temperature drop of the oil temperature, which took 15 min to reach again the set value. The content of the autoclave surely took even longer to equilibrate due to the insulating power of the Teflon coating (2 mm thickness). Thus the reaction was stopped very close to the moment in which the reaction solution reached the set temperature or even earlier than it did [79].

2.3. The effect of different I/Fe and Cl/Fe ratios

Comparing the reactions performed with the Teflon lined stainless-steel autoclave using $Pd(OAc)_2$ (without KI) with those made using PdI_2 (with KI), in the presence of $FeCl_3$ as co-catalyst (Fig. 1), it is clear that the reactions lead to better results when iodide is absent. Moreover, there is a very negative effect on conversion when a low amount of $FeCl_3$ is used, which further confirms the hypotheses made earlier that iodine coordinates to iron. Indeed, the worse result is obtained when a low amount of $FeCl_3$ (Fe/Pd = 10) is added to a solution containing a much larger amount of iodide (I/Pd = 100). Under these conditions, iron is probably completely deactivated and its only role is to withdraw iodide from the solution, so that a mutual deactivation occurs.

To better investigate the effect of the amount of chloride and iodide independently from the amount of iron, we decided to test the effect of different amounts of either tetrabutylammonium chloride or iodide on the activity of a catalytic system, $Pd(OAc)_2$ + $Fe(OAc)_2$ (mol ratio Fe/Pd = 50), that does not initially contain any halide. Results are reported in Table 4 and Fig. 2. Tetrabutylammonium was chosen as a countercation to ensure complete solubility of the salt under the reaction conditions and minimize electrostatic interactions between the cation and the halide, which may alter the reactivity of the latter.

Table 4
$Pd(OAc)_2$ catalyzed reactions using $Fe(OAc)_2$ as promoter in the presence of either $Bu_4N^+Cl^-$ or $Bu_4N^+I^-$.[a]

Entry	Halide	Halide/Pd mol ratio	$PhNH_2$ conv. (%)[b]	Urea sel. (%)[c]
1	–	–	19.0	75.3
2	Cl^-	50	54.3	81.2
3	Cl^-	100	79.9	79.0
4	Cl^-	150	85.2	83.9
5	Cl^-	200	93.5	89.0
6	Cl^-	250	94.7	89.7
7	I^-	50	73.8	85.6
8	I^-	100	60.9	82.0
9	I^-	150	36.7	85.5
10	I^-	200	40.0	83.3
11	I^-	250	27.4	74.5

[a] Experimental conditions: the reactions were carried out in a Teflon-lined stainless-steel autoclave, using 10 mmol of aniline at 150 °C, for 3 h, under 40 bar of CO and 10 bar of air, in DME (10 mL). Catalyst amount 2.0×10^{-3} mmol, mol ratio $Fe(OAc)_2$/Pd = 50.

[b] Based on starting aniline and measured by GC analysis using benzophenone as an internal standard.

[c] Based on converted aniline and measured by HPLC analysis using benzophenone as an internal standard.

Fig. 2 shows a clear trend with respect to chloride amount for the catalytic reactions: both conversion and selectivity increase with increasing tetrabutylammonium chloride content. The effect is more remarkable on the conversion, but tends to flatten at the highest ratios. The effect on selectivity is more limited, but still significant. The ideal amount of $Bu_4N^+Cl^-$ is 250 to 1 compared to the catalyst (at a Fe/Pd ratio of 50), that is a 5:1 ratio with respect to iron (or about 5:1 with respect to the sum Fe + Pd).

The effect of iodide is quite different, though not unexpected, given the previous results. An amount of iodide equimolar to that of iron promotes the reaction even more efficiently than the same amount of chloride, but a further increase leads to an inhibition of the reaction. At a 5:1 I/Fe mol ratio the results both in term of conversion and selectivity are close to those obtained in the absence of iodide, which are in turn close, at least for the conversion, to those obtained with $Pd(OAc)_2$ in the absence of both iron and iodide (Table 3, entry 1).

It may appear surprising that the addition of increasing amounts of chloride increases the conversion whereas that of iodide has an inhibiting effect. However, it should be recalled that the reaction produces water and the latter gives strong hydrogen bonds to chloride, markedly decreasing its nucleophilicity and tendency to coordinate to metals [80,81]. The same occurs with iodide to a much lower extent. Indeed, it is well known that the order of nucleophilicity is F > Cl > Br > I in non-protic solvents, but exactly the reverse in water and alcohols [80,81]. Thus, the amount of halide necessary to give the same number of coordinated halide anions is larger for chloride than for iodide. If we naively suppose than the coordinating ability of iodide is not affected at all by water, then we reach the conclusion that the ideal "coordinated halide"/(Fe+Pd) mol ratio is close to one. This is clearly a simplification, but the actual number cannot be too far from it. Earlier in this paper we have said that the easiest explanation for the inhibiting effect of halides is the possible formation of stable iron complexes of the kind $[Fe^{II}X_4]^{2-}$ or $[Fe^{III}X_6]^{3-}$, where coordination of aniline would be inhibited. However, the results now obtained

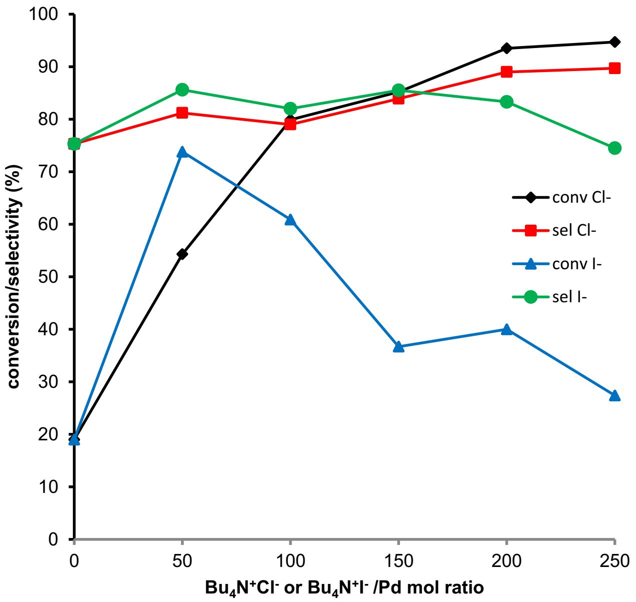


Fig. 2. The effect of $Bu_4N^+Cl^-$ and $Bu_4N^+I^-$ on the oxidative carbonylation of aniline catalyzed by $Pd(OAc)_2$ + $Fe(OAc)_2$ (mol ratio Fe/Pd = 50). Data from Table 4.

show that the amount of iodide sufficient to inhibit the reaction is much lower than that required to generate such complexes. An ideal 1:1 “coordinated halide”/(Fe+Pd) ratio is only consistent with the formation of halogen-bridged Pd-X-Fe or Fe-X-Fe species as catalytically active species [82–85]. Higher halide concentrations would be sufficient to break such complexes even if considerably lower than those required to completely saturate the coordination sphere of the isolated palladium and iron ions.

As previously mentioned, iron compounds have been employed in several cases as promoters for palladium-catalyzed reductive carbonylation reactions of nitroarenes. By analyzing the available information, mostly contained in the patent literature, one of us had noted more than twenty years ago that all active systems also contained chlorides [3]. Since much evidence also suggested that amines were intermediates in the process, it was proposed for the first time that the role of palladium might be that of carbonylating the amine and that of iron to reduce the nitroarene and reoxidize palladium. However, it was also considered that a bimetallic Pd-Fe complex with bridging chlorides might be the real catalytic species [3,39]. At the time, the comparison between the reductive carbonylation of nitroarenes and the oxidative carbonylation of amines was not stressed for the palladium catalysts because it seemed that the oxidative carbonylation reaction did not need a second metal. However, the results just discussed strengthen the similarity between the two reactions and led support to the hypothesis that bimetallic species may be involved in both cases.

2.4. Reactions under milder conditions

The results shown up to now prove that a high conversion can be reached in a short time at 150 °C, but the selectivity of the reaction reaches a maximum around 90%, that would not be enough for an industrial application. In an attempt to increase the selectivity over this limit, we decided to investigate lower reactions temperatures, even if this means to slow down the reaction. Thus, we lowered the temperature to 100 °C and the pressure to a total of 20 bar, and increased the reaction time to 15 h (Table 5).

The effect of small amounts of iron promoter were first investigated (Table 5, entries 1–5). The ideal Fe/Pd ratio is confirmed to be around 10 even under these milder conditions, but it is noteworthy that just a 1:1 ratio Fe/Pd is sufficient to double the conversion with respect to the palladium-only system. This ratio corresponds to just two µmol of iron!

It was also shown that 15 h are not required to reach complete conversion and 6 h are enough (entry 6). A shorter time, 3 h, is however not enough at this temperature, even if the pressure had been increased back to the previously employed values (Entry 7).

Unfortunately, no benefit was observed on selectivity by lowering the reaction temperature. The effect of the catalyst amount was thus investigated by increasing it fivefold at a constant aniline concentration. Both PdI_2 (entries 8–13) and $Pd(OAc)_2$ (entries 14 and 15) were tested at this catalytic ratio, in the presence of either KI or $FeCl_3$ as promoters. The results obtained confirm the generality of the observation made under more forcing conditions: KI is a less effective promoter than $FeCl_3$ for PdI_2 and the catalytic system lacking any iodide is better than those containing it are. However, again no better selectivities were obtained by lowering the catalytic ratio. On the contrary, a direct comparison between entries 6 and 15 evidences that better selectivities are obtained with less

Table 5
Synthesis of diphenylurea under milder conditions.[a]

Entry	Catalyst	Promoter	$PhNH_2$/Pd mol ratio	Promoter/Pd mol ratio	t (h)	$PhNH_2$ conv. (%)[b]	Urea sel. (%)[c]
1	$Pd(OAc)_2$	–	5000	–	15	37.2	86.8
2	$Pd(OAc)_2$	$FeCl_3$	5000	1	15	71.9	83.2
3	$Pd(OAc)_2$	$FeCl_3$	5000	3	15	90.5	85.5
4	$Pd(OAc)_2$	$FeCl_3$	5000	10	15	100	83.4
5	$Pd(OAc)_2$	$FeCl_3$	5000	50	15	100	82.1
6	$Pd(OAc)_2$	$FeCl_3$	5000	50	6	100	80.8
7[d]	$Pd(OAc)_2$	$FeCl_2$	5000	10	3	75.5	87.9
8	PdI_2	KI	1000	10	3	9.0	28.7
9	PdI_2	KI	1000	10	6	19.4	26.2
10	PdI_2	KI	1000	10	16	33.7	60.6
11	PdI_2	$FeCl_3$	1000	10	6	91.5	80.4
12	PdI_2	$FeCl_3$	1000	10	15	96.0	67.7
13	PdI_2	$FeCl_3$	1000	50	15	89.9	66.7
14	$Pd(OAc)_2$	$FeCl_3$	1000	50	15	100	81.9
15	$Pd(OAc)_2$	$FeCl_3$	1000	50	6	100	74.6

[a] Experimental conditions: the reactions were carried out in a Teflon lined stainless-steel autoclave, using 10 mmol of aniline at 100 °C under 16 bar of CO and 4 bar of air, in DME (10 mL).

[b] Based on starting aniline and measured by GC analysis using benzophenone as an internal standard.

[c] Based on converted aniline and measured by HPLC analysis using benzophenone as an internal standard.

[d] Under 40 bar of CO and 10 bar of air.

catalyst, in agreement with the previously reached conclusion that a higher absolute amount of $FeCl_3$ causes a decrease in selectivity.

2.5. Reaction byproducts

Although many studies have been devoted to the oxidative carbonylation of amines with different catalysts, we are not aware of any paper in which the identity of the byproducts (except for oxalamides) has been investigated in detail. The observation of formanilide, derived from the reductive elimination from a PhNHC(O)-Pd-H complex, has occasionally been mentioned [86].

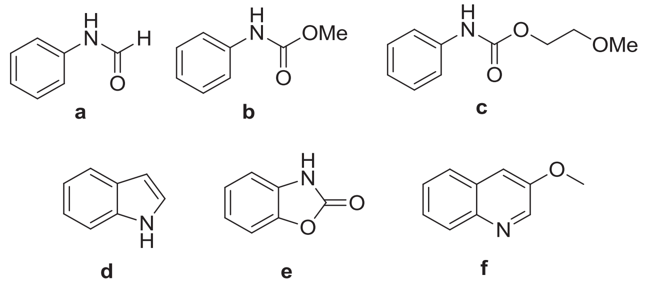
In order to shed light on the lack of full selectivity for the oxidative carbonylation reaction we subjected the reaction mixture of several of the catalytic reactions showing high conversion, but poor selectivity to GC-MS and HPLC-MS analyses.

From the GC-MS analyses (see the Supplementary Material), it immediately emerges that apart from the aniline and phenyl isocyanate peaks (which derive from a thermal cracking of the product diphenylurea, also observable as a weak peak, under the injector conditions) and trace amount of formanilide (**a**), some smaller peaks can be observed. These are clearly identified in the NIRST database as methyl phenylcarbamate (**b**), 2-methoxyethyl phenylcarbamate (**c**) and indole (**d**). Some even smaller peaks could be identified as benzoxazolone (**e**) and 3-methoxyquinoline (**f**) (Scheme 3).

The HPLC chromatogram, on the other hand, was very clean and only the diphenylurea peak could be clearly observed. Specifically, no oligomeric polyanilines could be detected by this technique. The latter would result from the direct oxidation of aniline by dioxygen and would easily escape GC analysis.

The observation of phenyl isocyanate by gas-chromatography should not be taken as a proof of its presence in solution without other supporting evidence. Indeed, diphenylurea can extensively thermally crack in the injector of the instrument. For example, no aniline had remained at the end of the reactions investigated by GC-MS in this work and yet the aniline peak is among the most intense in the GC-MS spectrum (see the chromatogram reported in the Supplementary Material). Gas-chromatographic analysis of aniline and phenyl isocyanate should only been performed by employing a programmed variable temperature injector, so that the temperature can be increased to the final value only after the more volatile (including aniline) compounds of the mixture have left the injector. We routinely used such a procedure in the quantitative analyses of our reaction mixtures and never observed the presence of phenyl isocyanate. Thus, we are confident that the isocyanate observed during the GC-MS analysis is an artefact of the analytical technique.

Although the formation of the products in Scheme 3 was unexpected, it is not difficult to trace back their origin. They are all clearly originating from the hydrolysis of the dimethoxyethane solvent by the water formed during the reaction. The two alcohols so formed originate the two observed carbamates (**b** and **c** in Scheme 3). It should be noted that the reaction between diphenylurea and an alcohol to give a carbamate and an aniline equivalent is well known. It typically occurs to a large extent when oxidative carbonylation reactions of amines or the reductive carbonylation of nitroarenes are performed in an alcohol as solvent. However, it is an equilibrium reaction and only becomes significant in the presence of a large excess of alcohol with respect to the free amine [37]. Thus, the observed carbamates cannot result from the presence of trace amounts of the two alcohols and their formation implies that DME hydrolysis occurs to a significant extent during the reaction.



Scheme 3. Byproducts observed by GC-MS.

Indole (**d**), on the other hand, can derive from a reaction of aniline with ethylene glycol, the doubly hydrolyzed DME. Such reaction is known to occur under oxidizing conditions [87,88].

Two more byproducts could be identified, which were present in trace amounts. Benzoxazolone (**e**) clearly derives from the oxidation of aniline in the *ortho* position to give *o*-aminophenol. The latter easily gives the cyclic carbamate under the reaction conditions [89]. The formation of 3-methoxyquinoline (**f**) is less obvious. The presence of the methoxy group anyway suggests that DME is again involved in its formation.

In order to quantify at least the main byproducts, pure methyl phenylcarbamate, 2-methoxyethyl phenylcarbamate, and indole were used to set a calibration curve at the gas-chromatograph and the reaction was repeated. The selectivities into these three products were respectively 2.4, 1.1 and 1.0%.

The formation of these products raises some concern on the use of DME as the solvent and suggests that one of the reasons for which it seems to be more effective than others may simply be the fact that it acts as internal drying agent, preventing the formed water to hydrolyze the produced urea.

Another solvent that is often employed in oxidative carbonylation reactions is dioxane. Though we did not investigate the use of dioxane in detail, the GC-MS analysis of the solution after a reaction run in this solvent instead of DME evidenced again the formation of carbamates deriving from its hydrolytical ring opening. In this context, it should also be mentioned that the solvent that often gives the best results in most of the cited references, although with low urea/oxalamide selectivity, is dimethylformamide. The declared, and surely at least partly correct, rationale for this is that it has a high dielectric moment, thus stabilizing the likely very polar transition state of the reaction. However, it should not be forgotten that DMF is far from being an inert solvent [90]. Its hydrolysis reaction has been studied in detail [91,92] and DMF has even been used as a drying agent [93]! Clearly, this would not be an acceptable procedure for an industrial production and a different strategy must be pursued to reach complete conversion. This will be the object of future work.

3. Conclusions

In this work we have investigated in more depth the classical Pd/I^- catalytic system for the oxidative carbonylation reaction of amines to ureas, which has been previously the topic of at least 30 papers. Some surprising results have been found that lead to extensively reconsider what is known of this catalytic system:

1) We confirmed that iodide alone promotes the activity of palladium in the oxidative carbonylation reaction of amines, but its promoting ability is much lower than previously estimated.
2) Under most of the previously employed experimental conditions, the main role of iodide is to etch the autoclave walls to provide small amounts of iron in solution.

3) When iron etching from the autoclave walls cannot occur, small, but sufficient, amounts of iron may still come from the $Fe(CO)_5$ present as a contaminant of pressurized CO in all those cases in which iron tanks were used to store it.
4) The ideal absolute iron amount under the presently employed conditions (930 mg aniline) is just 1.1 mg, but even a tenfold lower amount (around 12 ppm with respect to the whole solution weight) is sufficient to double the activity of the palladium catalyst. It is worth to note that contamination of iron catalysts by noble metals is well known to be responsible for the catalytic activity observed in some cases. However, the present work is a rare, if not unique, case in which the contamination of a palladium catalysts by trace amounts of iron has such a large promoting effect.
5) The presence of a halide is anyway required, but chloride can be equally or even more effective than iodide in this respect. The ideal amounts of chloride and iodide differ, likely because chloride coordination to metal ions can be hampered by the formation of strong hydrogen bonds with the water formed during the reaction, whereas iodide is less affected by the presence of water. A molar amount of iodide larger than that of iron causes a deactivation of the system, suggesting that the active catalytic species may be a Pd/Fe dinuclear or higher aggregate hold together by bridging halide ligands.
6) The reason for the good efficiency of DME as a reaction solvent is at least partly due to its ability to act as a dehydrating agent, but the alcohols formed by its hydrolysis can reenter the reaction and give small amounts of the corresponding carbamates and even some indole. Hydrolysis of the solvent is likely involved even in other cases.
7) Though usually not mentioned, iodide is toxic and difficult to remove completely from the reaction products. This is especially a problem if the produced urea is employed as an intermediate in the synthesis of pharmaceuticals. The possibility of substituting it with a very low amount of non-toxic iron chloride should be viewed favorably from an industrial point of view.

The present work has clarified some previously overlooked aspects of the Pd/I^- catalytic system, but at the same time has raised new questions both of industrial and scientific nature: Stainless steel contains other metals apart from iron: do any of them also show any promoting activity? Which is the best way to remove the formed water without resorting to solvent hydrolysis or to the use of any reagent that is stoichiometrically consumed? Which is the exact interplay between palladium, iron and the halide? May a better catalyst be prepared by knowing this? Work is in progress in our laboratories to answer at least some of them.

4. Experimental

4.1. Materials and general procedures

1,2-Dimethoxyethane used in the catalytic reactions was dried by distillation over Na/benzophenone and stored under a dinitrogen atmosphere. Aniline was distilled over KOH under reduced pressure and stored under dinitrogen. It can be weighed under air without problems, but must be stored under an inert atmosphere to avoid oxidation, carbonation and water uptake. $Pd(OAc)_2$ [94], and PdI_2 [95] were prepared by literature methods. $PdCl_2(CH_3CN)_2$ was prepared by refluxing $PdCl_2$ in acetonitrile until the brown solid had completely dissolved and a yellow solution had formed. The solution was filtered while hot to remove any traces of undissolved material and evaporated to dryness. 2-Methoxyethyl phenylcarbamate was prepared as described in the Supplementary Material. All the other reagents and solvents were purchased from Sigma-Aldrich or Alfa-Aesar and used without any further purification.

4.2. Catalytic reactions

All the catalytic reactions were performed in a stainless steel autoclave lined with Teflon (c.a. 140 mL free volume), or, for the control experiments, directly in a stainless-steel autoclave, both equipped with a stirring bar. Since small amounts of catalyst were used, a stock solution of the catalyst (PdI_2 or $PdCl_2$, the latter added as $PdCl_2(CH_3CN)_2$) in aniline was prepared and stored under dinitrogen atmosphere. The solution already contained the correct Pd/aniline ratio, so that the catalyst was weighed together with aniline. When $Pd(OAc)_2$ was used as the catalyst it was freshly dissolved in DME and the appropriate amount of the obtained solution was added by volume. In a typical catalytic reaction, the reagents were transferred to the autoclave following always the same order. First KI, weighted under air, was added. Then the aniline solution, also containing PdI_2 when appropriate, was rapidly weighted under air in a test tube and transferred to the autoclave. To ensure a complete transfer of the reagents to the autoclave, the test tube was washed with the reaction solvent. When $Pd(OAc)_2$ was used as the catalyst, its solution in DME was added by volume and aniline was weighted in a test tube separately. The remaining amount of solvent was then added by volume, using it to wash the test tube used to weigh aniline. Finally, the iron promoter was added. When the amount of the iron promoter was lower than 10 mg, a freshly prepared solution of it in DME was prepared under dinitrogen atmosphere and then it was added by volume to the reaction mixture. Reagent amounts or their molar ratios are reported in the tables or in their footnotes. In all cases, the amine concentration was 1 M. The autoclave was then closed and CO and air were charged in this order at room temperature. The value of pressure after each gas addition was read after complete stabilization of the system (i.e. when it remained constant for at least 5 min). Finally, the autoclave was immersed in an oil bath preheated at the required temperature. This moment was taken as the start of the reaction. At the end of the reaction, the autoclave was quickly cooled in an ice bath and vented. The internal standard, benzophenone, was added to the reaction mixture (1/4 mass ratio with respect to the starting aniline) and 25 mL of THF were also added to completely dissolve both benzophenone and any precipitated diphenylurea. The solution was kept under stirring for half an hour. An aliquot of the obtained solution was then diluted with CH_2Cl_2 in order to perform the GC and HPLC analyses.

4.3. Quantitative analysis methods for catalytic reactions

For catalytic reactions, quantitative analyses were performed on a DANI 86.10 HT gas chromatograph equipped with a SUPELCO Analytical SLB™-5 ms column (Fused Silica Capillary Column 30 m × 0.32 mm × 0.5 μm film thickness), on a Shimadzu GC-2010 equipped with a Supelco SLB™-5 ms capillary column (GC-FAST technique), or on a HP 1050 series modular HPLC system equipped with a MERCK LiChroCART® 125-4 HPLC-Cartridge Purospher® RP-18e (5 μm). HPLC grade solvents – CHROMASOLV® were used for HPLC analyses, which were degassed by sonication in an ultrasonic bath for half an hour before use. Quantitative analyses were carried out using the internal standard method. Benzophenone was used as the internal standard. The wavelength of the UV detector was set at 265 nm because this frequency is close to the maximum absorption of both diphenylurea and benzophenone, thus maximizing the accuracy of the analysis. Unfortunately, aniline absorbs weakly at this wavelength and its analysis is less reliable. This is the reason for which it was routinely quantified by GC.

A standard GC analysis involves the preparation of a sample solution in CH_2Cl_2. An aliquot of the reaction solution, treated as mentioned above, was diluted in CH_2Cl_2 in order to obtain a final standard concentration of 0.05 mg/mL for the analysis made with DANI 86.10 HT and 0.1 mg/mL for the analysis made with Shimadzu GC-2010. Then 1 μL was injected into the GC. This analysis method was used to determine the residual amount of aniline after the catalytic reaction because it showed a higher reproducibility with respect to HPLC analysis. A complete list of the instrumental parameters employed is present in the Supplementary Material.

A standard HPLC analysis involves the preparation of a sample solution in CH_3OH/H_2O 55:45. An aliquot of the previously prepared reaction solution was diluted with CH_3OH/H_2O 55:45 in order to obtain a final standard concentration of 0.01 mg/mL of benzophenone. Then 100 μL of this sample solution were injected into the HPLC (injection loop 20 μL). This analysis method was used to determine the amount of diphenylurea.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcat.2018.11.010.

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[79] Higher TOF values have been reported in a few cases among the cited literature. While it is difficult to compare rate values obtained by using different pressure equipment and we claim no record activity for our system, we want to emphasize that the highest TOF values have been obtained by running reactions for a short time (15-20 min). Moreover, it appears that the reaction time was measured from the onset of the reaction temperature, which may take up to one hour to be reached. Clearly, the reaction starts before and the heating time contributes to the proceeding of the reaction in a non-negligible way. On the contrary, we placed our autoclaves in a preheated oil bath and considered that moment as the start of the reaction.
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