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A New Pd-Based Catalytic System for the Reductive Carbonylation of Nitrobenzene to Form N-(4-hydroxyphenyl)-acetamide Selectively in One Pot

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Abstract: N-(4-hydroxyphenyl)acetamide (commonly named paracetamol or acetaminophen) is a target molecules for many industries that produce chemicals for pharmaceutical applications. The industrial processes, however, use multistep procedures with low overall yield and/or severe drawbacks and problems in terms of sustainability. In the present paper, a one-pot synthesis is proposed based on the reductive carbonylation of nitrobenzene catalyzed by Pd(II)-complexes. Usually, such a reaction leads to a mixture of different products, including aniline, 4-aminophenol and 1,3-diphenylurea. However, the selectivity towards the possible products strongly depends by the ligands on the Pd(II)-catalyst, but also by the nature of the solvent. According to this, we have found that when the reaction was carried out in dilute acetic acid as a solvent, the [$PdCl_2$(dppb)] catalyst precursor leads in one pot to N-(4-hydroxyphenyl)acetamide. Under optimized reaction conditions, it was possible to produce N-(4-hydroxyphenyl)acetamide with a 85 mol % of selectivity in ca. 5 h.

Keywords: homogeneous catalysis; palladium catalyst; carbonylation; nitrobenzene; acetaminophen

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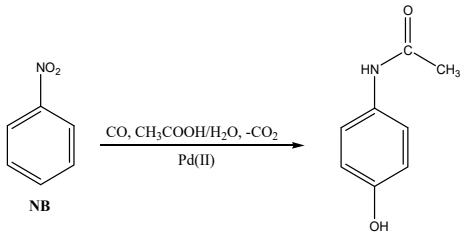
1. Introduction

The synthesis of N-(4-hydroxyphenyl)acetamide (commonly named paracetamol or acetaminophen) has long been attracting the interest of many industries which produce chemicals for pharmaceutical applications, since it is the main ingredient in numerous cold and flu medications [1–5]. Over the last century, among the several routes proposed for acetaminophen production, those that have emerged industrially have used raw materials such as phenol [6–8], 4-nitrophenol [9], or nitrobenzene [10–16]. The corresponding industrial processes, however, have drawbacks and problems in terms of sustainability, mainly due to the use of multistep production procedures with low overall yield and/or severe effluent problems [17–23]. For instance, phenol is first nitrated to 4-nitrophenol, which is reduced to 4-amminophenol, and finally N-acetylated to N-(4-hydroxyphenyl)acetamide [3–6]. Alternatively, phenol can be first acetylated with acetic anhydride to 4-hydroxyacetophenone (e.g., in the Hoechst-Celanese process), which is then converted into the corresponding oxime through reaction with hydroxylamine [7]: in the last step, the acid-catalyzed (H_2SO_4) Beckmann's transposition forms acetaminophen [11,24–29]. This route is very attractive, but suffers from moderate selectivity (aniline is obtained as a by-product) and problems related to the corrosion and the pollution due to the large quantities of sulfate salts generated. To improve the sustainability of such a step, several authors have proposed alternative catalysts for the Beckmann's transposition, to use instead of sulfuric acid [30–39]. On the other hand, new promising routes have been proposed, for instance starting again from phenol but involving at first its direct oxidation to hydroquinone, followed by reaction with acetamide to acetaminophen [40,41].

Similarly, the syntheses of acetaminophen based on nitrobenzene or 4-nitrophenol require, in general, more than two steps, including the selective NO_2-reduction and the acetylation. For instance, the catalytic hydrogenation of 4-nitrophenol leads directly to 4-aminophenol [32,36,42–48], which is then acetylated to N-(4-hydroxyphenyl)acetamide. Alternatively, N-phenyl(hydroxylamine) can be produced from nitrobenzene in a first step, which is then converted in one pot into 4-aminophenol through the catalyzed Bamberger's rearrangement [9–13,32,45–52], followed by the acetylation step. Nowadays, although many solutions have been adopted (or only proposed) to further improve the sustainability of such industrial processes, the realization of a more efficient and eco-friendly process for the production of acetaminophen still represents an interesting target for numerous academic and industrial researchers [53–58].

In the present paper, the authors reported the synthesis of acetaminophen carried out in one pot, starting from nitrobenzene through the Pd-catalyzed reductive carbonylation of the nitro-group in water–acetic acid as a solvent. As pointed out in previous papers, the choice of the catalyst plays a key role in determining the selectivity of such reaction, but no less important is the influence of the solvent. For instance, the Pd-catalyzed reductive carbonylation of nitrobenzene can readily lead to aniline in high yield when methanol was used as a solvent, but the addition of a co-solvent can strongly influence the selectivity [57–71]. According to this, we reported the selective synthesis of 1,3-diphenylurea in one pot by using an appropriate methanol–acetic acid mixture as a solvent [71]. On the other hand, in the same reaction when H_2O–acetic acid was used as a solvent, the selectivity moved again toward the aniline as the main products, even if traces of acetaminophen was also found in the by-products [72]. This suggested to us the chance to obtain acetaminophen in one pot and in high yield. Therefore, the [$PdCl_2$(dppb)] (dppb = 1,4 bis(diphenylphosphine)butane) complex has been selected to carry out the reaction (reaction 1) first, and the influence of some reaction parameters have been studied, with the aim of increasing the selectivity towards acetaminophen.



(1)

2. Materials and Methods

2.1. Reagents

The Pd(II)-diphosphine complexes were prepared as reported in the literature [71,73] and characterized by FTIR and NMR analysis. Carbon monoxide was supplied by SIAD Company, Bergamo, Italy ('research grade', purity > 99.9%); $PdCl_2$, nitrobenzene (NB), acetic acid-glacial (AcOH), 1,2-bis(diphenylphosphino)ethane (dppe), 1,3-bis(diphenylphosphino)-propane (dppp), 1,4-bis(diphenylphosphino)butane (dppb), 1,1′-bis(diphenylphosphino)-ferrocene (dppf), 4-aminophenol, N-(4-hydroxyphenyl)acetamide, aniline, acetanilide, 2-aminophenol, (9,9-Dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphane) (Xantphos), N-(2-hydroxyphenyl)acetamide, 1,3-diphenylurea, N,N′-azobenzene, and N,N′-oxy-azobenzene were Aldrich/Merck products.

2.2. Equipment and Characterization

The catalyst precursors have been weighted on a Sartorious Micro balance (precision 0.001 mg). High-performance liquid chromatography (HPLC) analyses were carried out by a Perkin Elmer 250 equipped with a diode array LC-235 detector and a Lichrosphere 100 (RP-18, 5 μm) column employing water acetonitrile mixtures as eluent; the concentrations of the reagent and products were calculated by calibration with standard solution. GC/MS

analyses were performed on a MS Agilent apparatus 5975C Model, interfaced with an Agilent chromatograph 7890 A Model equipped with a HP1 column (30 m × 0.25 mm × 0.25 µm, oven: 45 °C (3 min) to 250 °C at 15 °C/min). Fourier transform infrared (FTIR) spectra were recorded on a Nicolet Magna 750 instrument in KBr powder. All the NMR spectra were recorded on a Bruker Avance 300 spectrometer.

2.3. Catalytic Reactions

The catalysis has been carried out in a batch reactor of ca. 60 mL provided with a magnetic stirrer. In a typical experiment, 2.48 × 10^{-3} mmol of Pd(II) complex (for instance 1.50 mg of [$PdCl_2$(dppb)]), together with 0.5 mL (0.600 g, 4.87 mmol) of nitrobenzene, were added to 11.5 mL of solvent (H_2O-AcOH). In order to avoid catalyst deactivation due to the presence of air, the reactor was carefully flushed with CO at room temperature with stirring and then pressurized with 0.5 MPa of CO and heated up to 373 K in ca. 10 min without stirring. The pressure was then adjusted to the desired value (typically 5.0 MPa of total pressure) and, while stirring, maintained constant throughout the experiment (3 h) by continuously supplying the carbon monoxide from a reservoir. At the end of each experiment, the reactor was quickly cooled and carefully depressurized.

The reaction products were detected and quantified by the HPLC and GC-MS analysis. All the experiments were repeated at least twice, and the error analysis confirmed the reproducibility of the data within an error of ±1%.

3. Results and Discussion

3.1. Preliminary Experiments

Table 1 shows the results of the preliminary experiments carried out by using some Pd(II) complexes as catalyst precursors in H_2O-acetic acid as a solvent. The reaction conditions adopted in such tests were typically used in a previous paper to produce 1,3-diphenylurea [71]. Among the complexes tested, the [$PdCl_2$(dppb)] led to the best conversion (60 mol %, TON = 1178 mol/mol, entry 3), forming, under reaction conditions adopted, aniline (33%), and acetanilide (25%), together with 4-aminophenol (19%) and acetaminophen (8%), whereas only a trace amount of 1,3-diphenylurea was detected.

Table 1. Catalytic activity of some Pd(II)–diphosphine complexes.

Entry	Catalyst	Conversion	TON	Selectivity (mol %)				
n°		mol * %	mol */mol Pd	4-Aminophenol	Acetaminophen	Aniline	Acetanilide	Other
1	[$PdCl_2$(dppe)]	4	78	15	6	40	30	9
2	[$PdCl_2$(dppp)]	22	432	15	7	36	30	12
3	[$PdCl_2$(dppb)]	60	1178	19	8	33	25	15
4	[$PdCl_2$(dppf)]	55	1080	16	7	32	28	17
5	[$PdCl_2$(Xantphos)]	14	276	15	7	38	25	15
6	[$Pd(AcO)_2$(dppe)]	2	39	13	5	43	30	9
7	[$Pd(AcO)_2$(dppp)]	20	393	14	6	38	30	12
8	[$Pd(AcO)_2$(dppb)]	58	1139	15	6	39	25	15
9	[$Pd(AcO)_2$(dppf)]	57	1119	14	5	36	28	17
10	[$Pd(AcO)_2$(Xantphos)]	15	296	14	6	40	27	13

Run conditions: Pd(II) = 2.48 × 10^{-3} mmol, nitrobenzene = 0.5 mL (0.600 g, 4.87 mmoli), Vtot = 12 mL (H_2O/AcOH = 30/70, mol/mol), T = 373 K, P_{CO} = 5.0 MPa, reaction time = 3 h. * moles of NB converted.

The experiments have been limited to such complexes because they are stable, easily handled at room temperature Pd(II) and effective in several carbonylation reactions, including the reductive carbonylation of nitrobenzene to 1,3-diphenylurea carried out in methanol as a solvent [71,72]. In addition, they are interesting from an industrial point of view, being readily synthesized from commercially available reagents and are very soluble in several solvents (e.g., alcoholic solvents or in H_2O-acetic acid mixture, as in the present case). The results in Table 1 suggest that both catalytic activity and selectivity are strongly influenced by the electronic and steric characteristics of the chelating di-phosphine ligands, according to the studies reported in literature [71,73].

Furthermore, the Table 1 shows also that the nature of ionic ligand have poor influence on the conversion and selectivity under the reaction conditions. This could be ascribed to the nature of the solvent mixture used, in which the amount of acetic acid determinates the solubility of the complexes, whereas H_2O has a key role to form the desired products (see mechanism), but also in determining the dielectric constant of the reaction medium. The latter could favor the solvation and the displacement of ionic ligands from the coordination site of the metal center. In such a way, it is plausible to suppose that such sites become more available for the coordination of the reagents, regardless of the coordinating ability of the ionic ligands.

On the basis of such preliminary results, the [$PdCl_2$(dppb)] complex has been used as catalyst precursor in all the following experiments.

3.2. One-Pot Synthesis of Acetaminophen in H_2O-Acetic Acid as a Solvent

Figure 1 and Table 2 show that the solvent composition strongly influences the conversion and the selectivity to acetaminophen. In fact, the conversion of nitrobenzene increases by increasing the amount of H_2O in the reaction medium, reaching ca. 100 mol % at H_2O 60 mol % (H_2O/acetic acid 60/40 mol/mol). At H_2O higher than 65 mol %, the conversion sharply decreases (it was ca. 22 mol % at H_2O = 80 mol %), probably due to the separation of two liquid phases (nitrobenzene and water) observed at the end of such an experiment.

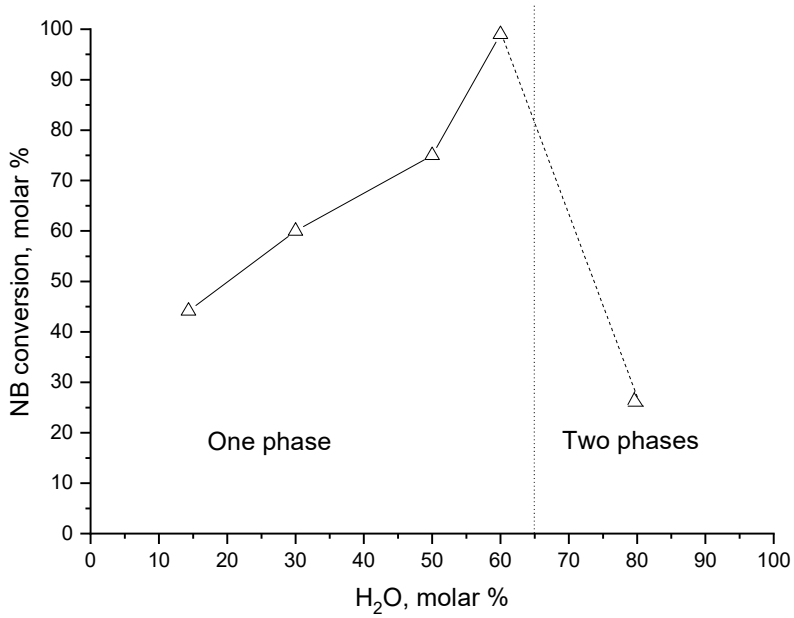


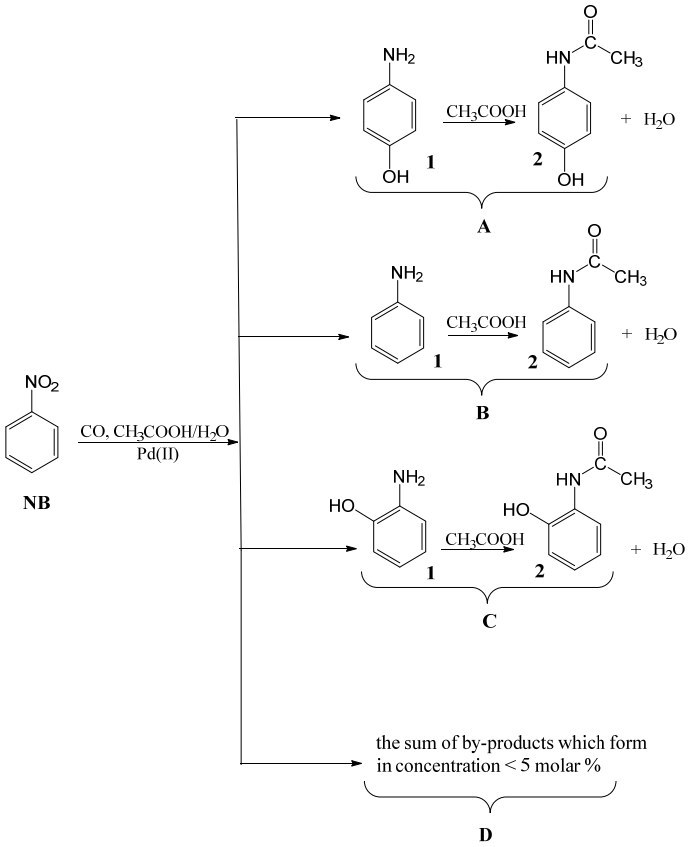
Figure 1. Influence of solvent composition on the conversion. Run conditions: [$PdCl_2$(dppb)] = 1.50 mg (2.48×10^{-3} mmol), nitrobenzene = 0.5 mL (0.600 g, 4.87 mmoli), V_{tot} = 12 mL, T = 373 K, P_{CO} = 5.0 MPa, reaction time = 3 h.

Table 2. Influence of solvent composition on conversion and selectivity.

Entry	H_2O (AcOH) mol %	NB Conversion mol %	TON mol/mol	Selectivity (mol %) A	B	C	D
1	7 (93)	39	765	8	92	n.d.	n.d.
2	14 (86)	44	863	18	80	2	n.d.
3	30 (70)	60	1177	27	58	12	3
4	50 (50)	75	1472	34	42	12	12
5	60 (40)	99	1942	40	30	18	12

Run conditions: [$PdCl_2$(dppb)] = 1.50 mg (2.48×10^{-3} mmol), nitrobenzene = 0.5 mL (0.600 g, 4.87 mmoli), V_{tot} = 12 mL, T = 373 K, P_{CO} = 5.0 MPa, reaction time = 3 h, (n.d. = not detected).

As schematized in Scheme 1, in order to simplify the discussion, we have indicated the molar sum of 4-aminophenol and its acetylated derivative with **A**, the molar sum of aniline and its acetylated derivative with **B**, and the molar sum of 2-aminophenol and its acetylated derivative with **C**. **D** indicates the molar sum of some compounds that, under the experimental conditions adopted, were each formed in concentration < 5 mol % (by-products), such as 1,3-diphenylurea, nitrosobenzene, N,N′-azobenzene, etc.



Scheme 1. Scheme of the possible products formed during the reductive carbonylation of nitrobenzene in H_2O-AcOH as a solvent.

Regarding the selectivity to **A**, it increases with the amount of H_2O in the solvent, reaching 40 mol % when H_2O was ca. 60 mol % (see Table 2, entry 5).

The acid concentration, however, also influences the yield of acetylation. For instance, the percent of acetaminophen in A was 1 mol % when AcOH in H_2O was 40 mol % (Table 3, entry 1; for conversion 99 mol %, see Table 2, entry 5), whereas it was 72 mol % when AcOH in H_2O was 93 mol % (Table 3, entry 5; for conversion 39 mol %, see Table 2, entry 1). The same trend was observed for aniline and acetanilide in B composition (see Table 3).

Table 3. Influence of the solvent on composition of A and B.

Entry n°	H_2O (AcOH) mol %	Sel. to A * mol %	Composition of A (mol %)		Sel. to B * (mol %)	Composition of B (mol %)	
			4-Aminophenol	Acetaminophen		Aniline	Acetaniline
1	7 (93)	8	99	1	92	82	18
2	14 (86)	18	70	30	80	57	43
3	30 (70)	27	60	40	58	47	53
4	50 (50)	34	42	58	42	33	67
5	60 (40)	40	28	72	30	9	91

Run conditions: * see Table 2.

In light of such results, and with the aim to increase the conversion and the selectivity to acetaminophen at the same time, we have carried out the following experiments by using a solvent dilution such as H_2O/acetic acid = 50/50 (mol/mol).

3.3. Influence of Pressure and Temperature on Conversion and Selectivity

The conversion of nitrobenzene linearly increases with the pressure of carbon monoxide in the range 0–6.0 MPa (Table 4), whereas under 5.0 MPa of CO, the conversion reaches its maximum (100%) between 393 K and 403 K (Table 5).

Table 4. Influence of the pressure on the conversion and selectivity.

P	NB Conversion	Selectivity (mol %)			
MPa	mol %	A	B	C	D
2.5	53	65	20	7	8
4.0	75	64	25	6	5
5.0	99	65	19	11	5
6.0	100	67	20	11	2

Run conditions: $[PdCl_2(dppb)]$ = 1.50 mg (2.48×10^{-3} mmol), nitrobenzene = 0.5 mL (0.600 g, 4.87 mmoli), V_{tot} = 12 mL, (H_2O/AcOH = 50/50 mol/mol), T = 393 K, reaction time = 3 h.

Table 5. Influence of the temperature on the conversion and selectivity.

T	NB Conversion	Selectivity			
		A	B	C	D
K	mol %	(mol %)	(mol %)	(mol %)	(mol %)
333	18	17	64	7	12
343	24	19	60	9	12
373	75	34	45	10	11
393	99	65	19	11	5
403	100	85	8	5	2
413	90	81	7	10	2
433	70	80	7	11	2

Run conditions: $[PdCl_2(dppb)]$ = 1.50 mg (2.48×10^{-3} mmol), nitrobenzene = 0.5 mL (0.600 g, 4.87 mmoli), V_{tot} = 12 mL, (H_2O/AcOH = 50/50 mol/mol), P_{CO} = 5.0 MPa, reaction time = 3 h.

The decrease of conversion observed at temperatures higher than 410 K could be ascribed to the progressive thermal decomposition of the Pd(II) complex, which leads to a loss of catalytic activity [71]. Focusing on the reaction at 403 K, it can be observed that nitrobenzene was fully converted with 85 mol % of selectivity towards A, which contains ca. 95 molar % of acetaminophen (see Figure 2). However, under the last conditions but with an increasing reaction time (e.g., 5 h), it was possible to obtain a selectivity of 85 mol % towards A, containing 100% acetaminophen.

3.4. On the Reaction Mechanism

The catalytic reductive carbonylation of nitrobenzene (or nitro-arenes), to form aniline, 1,3-diphenylurea, N-phenylisocyanates, or carbamate (in alcoholic solvents), has been extensively studied by several authors, who generally have proposed a reaction mechanism starting from a Pd (0) species, usually formed in situ from a Pd(II) precursor [69–72]. Such a species can activate the reaction of nitrobenzene with CO to form a complex which eliminates CO_2 to lead to the Pd(II)-nitroso species **1** (see Scheme 2, reaction **a**). As schematized, following the reaction pathway **b′**–**d′**, the species **4′** can form which, in turn, can lead to aniline (reaction **e′**, together with azo-benzene), 1,3-diphenylurea (reaction **e″**) and/or N-phenylisocyanates (reaction **e‴**, together with carbamate in alcoholic solvents) [71].

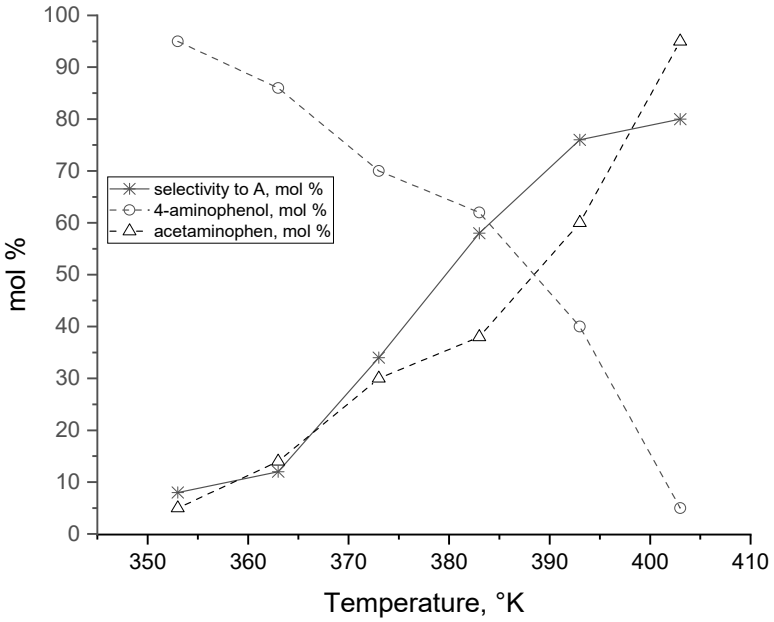
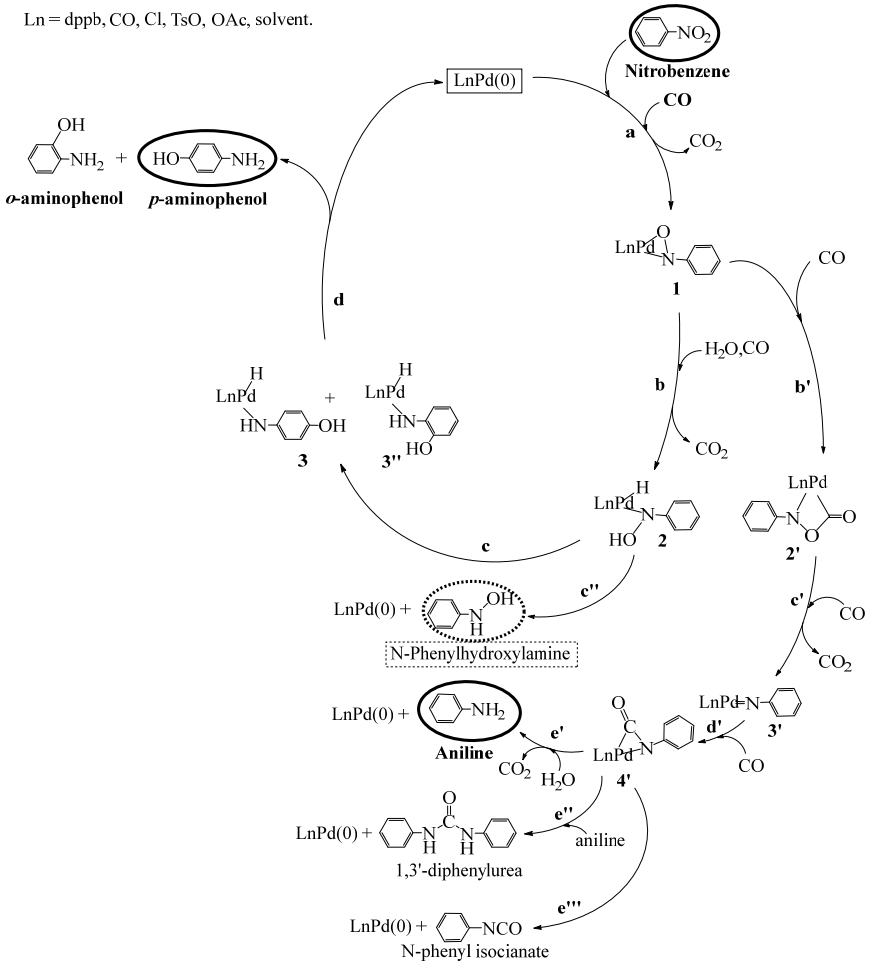


Figure 2. Influence of temperature on the selectivity to A and to its composition in terms of acetaminophen and 4-aminophenol. Run conditions: $[PdCl_2(dppb)]$ = 1.50 mg (2.48×10^{-3} mmol), nitrobenzene = 0.5 mL (0.600 g, 4.87 mmoli), V_{tot} = 12 mL (H_2O/AcOH = 50/50 mol/mol), P_{CO} = 5.0 MPa, reaction time = 3 h.

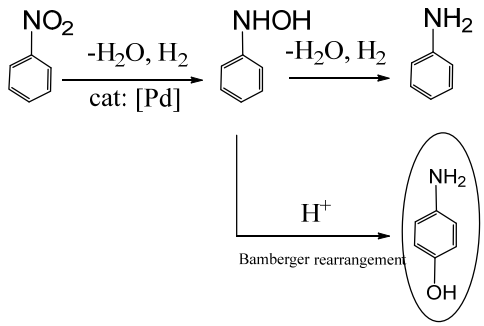


Scheme 2. Proposed reaction mechanism.

However, when the reaction has been carried out in H_2O-acetic acid as a solvent, 4-aminophenol together with aniline and the corresponding acetylated products (not included in the scheme) are mainly formed whereas azo-benzene and 1,3-diphenylurea are detected only in trace amounts (<5 mol %).

Since aniline, azo-benzene and 1,3-diphenylurea were formed even under the experimental conditions of the present work, we can assume the mechanism proposed in the literature is still effective. However, to also include the formation of 4-aminophenol, it is necessary to suppose the presence of parallel reaction pathways. For instance, we can suggest two hypotheses: (i) 4-aminophenol could form from N-phenylhydroxylamine, which in turn forms through reactions **b**–**c″**, and/or (ii) 4-aminophenol could form through reactions **b**–**d**.

Since, in all experiments of the present work, we never detected N-phenylhydroxylamine in the reaction medium, we assumed that it reacted quickly during the reaction. As a matter of fact, it is reported that some metal catalysts (usually Pd/C, Pt/C, or Ru/C, but it could be possible also the Pd(0) species active in the present work) catalyze the fast reaction of N-phenylhydroxylamine with hydrogen to form aniline together with the 4-aminophenol, via the Bamberger's rearrangement (Scheme 3, [50,52,74–78]). By considering that it is plausible also the formation in situ of hydrogen from CO and H_2O, through the Pd(II)-catalyzed water gas shift reaction [79–81], we have carried out some additional experiments to test such a pathway.



Scheme 3. Formation of 4-aminophenol through Bamberger's rearrangement.

At first, N-phenylhydroxylamine was used as feedstock instead of nitrobenzene. It was verified that aniline and 4-aminophenol were not formed under the reaction conditions (H_2O/AcOH = 50/50 mol/mol, 403 K, 3 h). In the second set of experiments, hydrogen (up to 1.0 MPa) was added to the reaction mixture, starting both from nitrobenzene and N-phenylhydroxylamine. Also in these cases, 4-aminophenol was not detected in the reaction medium at the end of the reaction.

Therefore, it has been hypothesized that 4-aminophenol forms through the pathway **c**–**d**, which supposes the formation of Pd-species (**3** and **3″**, Scheme 2) similar to those invoked in literature for the mechanism of the Bamberger's rearrangement [50,52,74–78]. Such point, however, needs further studies, which are in progress.

4. Conclusions

The reductive carbonylation of nitrobenzene, by using the [$PdCl_2$(dppb)] complex as a catalyst precursor, leads to a mixture of acetaminophen and N-phenylacetamide in one pot when carried out in dilute acetic acid as a solvent. Although both products are interesting targets for the pharmaceutical industry, we can produce acetaminophen in one pot, choosing the most suitable reaction conditions (for instance, in H_2O/AcOH = 50/50 mol/mol and at 403 K, 5 h of reaction it has been obtained acetaminophen, with 85% selectivity and 100% conversion of nitrobenzene).

We have pointed out that the selectivity towards **A** (4-aminophenol and acetaminophen) increases by increasing the amount of H_2O but, on the other hand, the high percent of H_2O favors 4-aminophenol rather than acetaminophen. Moreover, by increasing the tempera-

ture and the reaction time, it is possible to favor both the selectivity towards **A** and the acetylation to acetaminophen (100% at 5 h).

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Data Availability Statement: The data presented in this study are available in the main text.

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Conflicts of Interest: The authors declare no conflict of interest.

References

1. Ellis, F. *Paracetamol, a Curriculum Resource*; Osborne, C., Pack, M., Eds.; RSC: London, UK, 2002.
2. Ogemdi, I.K. A Review on the Properties and Uses of Paracetamol. *Int. J. Pharm. Chem.* **2019**, *5*, 31–35. [CrossRef]
3. Eynde, J.J.V. How Efficient Is My (Medicinal) Chemistry? *Pharmaceuticals* **2016**, *9*, 26. [CrossRef] [PubMed]
4. Saragiotto, B.T.; Shaheed, C.A.; Maher, C.G. Paracetamol for pain in adults. *BMJ* **2019**, *367*, l6693. [CrossRef] [PubMed]
5. Friderichs, E.; Christoph, T.; Buschmann, H. Analgesics and Antipyretics. In *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH Verlag GmbH & Co. KGaA: Hoboken, NJ, USA, 2007; pp. 1–97. [CrossRef]
6. Anantharaman, P.N. p-acetamol from phenol via p-nitrophenol. *Bull. Electrochem.* **1985**, *1*, 471.
7. Davenport, K.G.; Hilton, C.B. Process for Producing N-acyl-hydroxy Aromatic Amines. U.S. Patent 4,524,217, 18 June 1985.
8. Fritch, J.R.; Fruchey, S.O.; Horlenko, T.; Aguilar, D.A.; Hilton, C.B.; Snyder, P.S.; Seeliger, W.J. Production of acetaminophen. U.S. Patent 5,155,273, 13 October 1992.
9. Du, Y.; Chen, H.; Chen, R.; Xu, N. Synthesis of p-aminophenol from p-nitrophenol over nano-sized nickel catalysts. *Appl. Catal. A Gen.* **2004**, *277*, 259–264. [CrossRef]
10. Rode, C.V.; Vaidya, M.J.; Chaudhari, R.V. Synthesis of p-Aminophenol by Catalytic Hydrogenation of Nitrobenzene. *Org. Proc. Res. Dev.* **1999**, *3*, 465–470. [CrossRef]
11. Min, K.; Choi, J.; Chung, Y.; Ahn, W.; Ryoo, R.; Lim, P.K. p-Aminophenol synthesis in an organic/aqueous system using Pt supported on mesoporous carbons. *Appl. Catal. A Gen.* **2008**, *337*, 97–104. [CrossRef]
12. Wang, Y.; Wang, S.; Li, F. Process for Synthesizing Paracetamol. CN Patent 1569819(A), 26 January 2005.
13. Takasaki, M.; Motoyama, Y.; Higashi, K.; Yoon, S.-H.; Mochida, I.; Nagashima, H. Chemoselective Hydrogenation of Nitroarenes with Carbon Nanofiber-Supported Platinum and Palladium Nanoparticles. *Org. Lett.* **2008**, *10*, 1601–1604. [CrossRef]
14. Li, M.; Hu, L.; Cao, X.; Hong, H.; Lu, J.; Gu, H. Direct Hydrogenation of Nitroaromatics and One-Pot Amidation with Carboxylic Acids over Platinum Nanowires. *Chem. Eur. J.* **2011**, *17*, 2763–2768. [CrossRef]
15. Xu, K.; Zhang, Y.; Chen, X.; Huang, L.; Zhang, R.; Huang, J. Convenient and Selective Hydrogenation of Nitro Aromatics with a Platinum Nanocatalyst under Ambient Pressure. *Adv. Synth. Catal.* **2011**, *353*, 1260–1264. [CrossRef]
16. Cárdenas-Lizana, F.; Berguerand, C.; Yuranov, I.; Kiwi-Minsker, L. Chemoselective hydrogenation of nitroarenes: Boosting nanoparticle efficiency by confinement within highly porous polymeric framework. *J. Catal.* **2013**, *301*, 103–111. [CrossRef]
17. Anastas, P.T.; Zimmerman, J.B. Peer Reviewed: Design Through the 12 Principles of Green Engineering. *Environ. Sci. Technol.* **2003**, *37*, 94A–101A. [CrossRef] [PubMed]
18. Abraham, M.A.; Nguyen, N. Green engineering: Defining the principles"— Results from the Sandestin conference. *Environ. Prog.* **2003**, *22*, 233–236. [CrossRef]
19. Mitchell, S. *Kirk-Othmer Encyclopedia of Chemical Technology*, 4th ed.; Wiley-Interscience: New York, NY, USA, 1992; Volume 2, pp. 481–580.
20. Juang, T.M.; Hwang, J.C.; Ho, H.O.; Chen, C.Y. Selectivity in the Phase Transfer Catalytic Hydrogenation of Nitrobenzene by Transition VIII Metals. *J. Chin. Chem. Soc.* **1988**, *35*, 135. [CrossRef]
21. Anastas, P.T.; Williamson, T.C. (Eds.) *Green Chemistry: Frontiers in Chemical Synthesis and Processes*; Oxford Univ. Press: Oxford, UK, 1998.
22. Sheldon, R.A. *Industrial Environmental Chemistry*; Sawyer, D.T., Martell,, A.E., Eds.; Plenum: New York, NY, USA, 1992; pp. 99–119.
23. Busacca, C.A.; Fandrick, D.R.; Song, J.J.; Senanayake, C.H. The Growing Impact of Catalysis in the Pharmaceutical Industry. *Adv. Synth. Catal.* **2011**, *353*, 1825–1864. [CrossRef]
24. Fritch, J.R.; Fruchey, O.S.; Horlenko, T. Production of Acetaminophen. U.S. Patent 4,954,652, 4 September 1990.
25. Beckmann, E. Zur Kenntniss der Isonitrosoverbindungen. *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 988–993. [CrossRef]
26. Donaruma, L.G.; Heldt, W.Z. The Beckmann Rearrangement. *Org. React.* **1960**, *11*, 1–156.

27. Gawley, R.E. The Beckmann Reactions: Rearrangement, Elimination-Additions, Fragmentations, and Rearrangement-Cyclizations. *Org. React.* **1988**, *35*, 14–24.
28. Rode, C.V.; Vaidya, M.J.; Jaganathan, R.; Chaudhari, R.V. Hydrogenation of nitrobenzene to p-aminophenol in a four-phase reactor: Reaction kinetics and mass transfer effects. *Chem. Eng. Sci.* **2001**, *56*, 1299–1304. [CrossRef]
29. Nadgeri, J.M.; Biradar, N.S.; Patil, P.B.; Jadkar, S.T.; Garade, A.C.; Rode, C.V. Control of Competing Hydrogenation of Phenylhydroxylamine to Aniline in a Single-Step Hydrogenation of Nitrobenzene to p-Aminophenol. *Ind. Eng. Chem. Res.* **2011**, *50*, 5478–5484. [CrossRef]
30. Quartarone, G.; Rancan, E.; Ronchin, L.; Vavasori, A. Beckmann rearrangement of acetophenone oximes to the corresponding amides organo-catalyzed by trifluoroacetic acid for sustainable NSAIDs synthesis. *Appl. Cat. A Gen.* **2014**, *472*, 167–177. [CrossRef]
31. Chaudhari, R.V.; Divekar, S.S.; Vaidya, M.J.; Rode, C.V. Single Step Process for the Preparation of P-aminophenol. U.S. Patent 6,028,227, 22 February 2000.
32. Komatsu, T.; Hirose, T. Gas phase synthesis of para-aminophenol from nitrobenzene on Pt/zeolite catalysts. *Appl. Catal. A Gen.* **2004**, *276*, 95–102. [CrossRef]
33. Wang, S.; Ma, Y.; Wang, Y.; Xue, W.; Zhao, X. Synthesis of p-aminophenol from the hydrogenation of nitrobenzene over metal–solid acid bifunctional catalyst. *J. Chem. Technol. Biotechnol.* **2008**, *83*, 1466–1471. [CrossRef]
34. Liu, P.; Hu, Y.; Ni, M.; You, K.; Luo, H. Liquid Phase Hydrogenation of Nitrobenzene to Para-Aminophenol over Pt/ZrO2 Catalyst and SO4 2−/ZrO2–Al2O3 Solid Acid. *Catal. Lett.* **2010**, *140*, 65–68. [CrossRef]
35. Wang, S.; Wang, Y.; Gao, Y.; Zhao, X. Preparation of SAPO-5 and Its Catalytic Synthesis of p-Aminophenol. *Chin. J. Catal.* **2010**, *311*, 637–644. [CrossRef]
36. Deshpande, A.; Figueras, F.; Kantam, M.L.; Ratnam, K.J.; Reddy, R.S.; Sekhar, N.S. Environmentally friendly hydrogenation of nitrobenzene to p-aminophenol using heterogeneous catalysts. *J. Catal.* **2010**, *275*, 250–256. [CrossRef]
37. Wang, S.; Jin, Y.; He, B.; Wang, Y.; Zhao, X. Synthesis of bifunctional Pt/MgAPO-5 catalysts and their catalytic performance in the hydrogenation of nitrobenzene to p-aminophenol. *Sci. China Chem.* **2010**, *53*, 1514–1519. [CrossRef]
38. Aricò, F.; Quartarone, G.; Rancan, E.; Ronchin, L.; Tundo, P.; Vavasori, A. One-pot oximation–Beckmann rearrangement of ketones and aldehydes to amides of industrial interest: Acetanilide, caprolactam and acetaminophen. *Cat. Commun.* **2014**, *49*, 47–51. [CrossRef]
39. Rancan, E.; Aricò, F.; Quartarone, G.; Ronchin, L.; Tundo, P.; Vavasori, A. Self-catalyzed direct amidation of ketones: A sustainable procedure for acetaminophen synthesis. *Cat. Commun.* **2014**, *54*, 11–16. [CrossRef]
40. Joncour, R.; Duguet, N.; Métay, E.; Ferreira, A.; Lemaire, M. Amidation of phenol derivatives: A direct synthesis of paracetamol (acetaminophen) from hydroquinone. *Green Chem.* **2014**, *16*, 2997–3002. [CrossRef]
41. Bhattacharya, A.; Purohit, V.C.; Suarez, V.; Tichkule, R.; Parmer, G.; Rinaldi, F. One-step reductive amidation of nitro arenes: Application in the synthesis of Acetaminophen™. *Tetrahedron Lett.* **2006**, *47*, 1861–1864. [CrossRef]
42. Rylander, P.N. *Hydrogenation Methods*; Academic Press: New York, NY, USA, 1985.
43. Gao, Y.; Wang, F.D.; Liao, S.J.; Yu, D.R. Selective hydrogenation of nitrobenzene top-Aminophenol by the polymer-supported palladium-based mono- and bimetallic catalyst. *React. Kinet. Catal. Lett.* **1998**, *64*, 351–357. [CrossRef]
44. Wang, S.F.; He, B.B.; Wang, Y.J.; Zhao, X.Q. MgAPO-5-supported Pt–Pb-based novel catalyst for the hydrogenation of nitrobenzene to p-aminophenol. *Catal. Commun.* **2012**, *24*, 109–113. [CrossRef]
45. Quartarone, G.; Ronchin, L.; Tosetto, A.; Vavasori, A. New insight on the mechanism of the catalytic hydrogenation of nitrobenzene to 4-aminophenol in CH_3CN–H_2O–CF_3COOH as a reusable solvent system. Hydrogenation of nitrobenzene catalyzed by precious metals supported on carbon. *Appl. Cat. A Gen.* **2014**, *475*, 169–178. [CrossRef]
46. Zou, L.Y.; Cui, Y.Y.; Dai, W.L. Highly Efficient Au/TiO2 Catalyst for One-pot Conversion of Nitrobenzene to p-Aminophenol in Water Media. *Chin. J. Chem.* **2014**, *32*, 257–262. [CrossRef]
47. Tanielyan, S.K.; Nair, J.J.; Marin, N.; Alvez, G.; McNair, R.J.; Wang, D.; Augustine, R.L. Hydrogenation of Nitrobenzene to 4-Aminophenol over Supported Platinum Catalysts. *Org. Process Res. Dev.* **2007**, *11*, 681–688. [CrossRef]
48. Serrà, A.; Alcobé, X.; Sort, J.; Nogués, J.; Vallés, E. Highly efficient electrochemical and chemical hydrogenation of 4-nitrophenol using recyclable narrow mesoporous magnetic CoPt nanowires. *J. Mater. Chem. A* **2016**, *4*, 15676–15687. [CrossRef]
49. Joncour, R.; Ferreira, A.; Duguet, N.; Lemaire, M. Preparation of para-Aminophenol from Nitrobenzene through Bamberger Rearrangement Using a Mixture of Heterogeneous and Homogeneous Acid Catalysts. *Org. Process Res. Dev.* **2018**, *22*, 312–320. [CrossRef]
50. Bamberger, E. Ueber das Phenylhydroxylamin. *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 1548–1557. [CrossRef]
51. Chandrashekha, V.R.; Manisha, J.V.; Chaudhari, R.V. Single Step Hydrogenation of Nitrobenzene to P-aminophenol. U.S. Patent 6,403,833 B1, 11 June 2002.
52. De Fonzo, N.; Quartarone, G.; Ronchin, L.; Tortato, C.; Vavasori, A. Kinetics and mechanistic study of the Bamberger rearrangement of N-phenylhydroxylamine to 4-aminophenol in acetonitrile-trifluoroacetic acid: A substrate acid complex as para selectivity driver. *App. Catal. A Gen.* **2016**, *516*, 58–69. [CrossRef]
53. Olariu, T.; Suta, L.M.; Popoiu, C.; Ledeti, I.V.; Simu, G.M.; Balint, G.S. Fulias, Alternative Synthesis of Paracetamol and Aspirin Under Non-conventional Conditions. *Rev. Chim.* **2014**, *65*, 633–635.
54. Mane, S.N.; Gadalkar, S.M.; Rathod, V.K. Intensification of paracetamol (acetaminophen) synthesis from hydroquinone using ultrasound. *Ultrasonics–Sonochemistry* **2018**, *49*, 106–110. [CrossRef]

55. Jung, S.; Kawashima, Y.; Noguchi, T.; Imai, N. Synthesis of Acetaminophen Analogues Containing α-Amino Acids and Fatty Acids for Inhibiting Hepatotoxicity. *Synthesis* **2019**, *51*, 3683–3696. [CrossRef]
56. Ammin, M.; Iqbal, M.S. Solvent Free Synthesis of Acetaminophen. U.S. Patent 9,006,488 B1, 14 April 2015.
57. Corma, A.; Concepción, P.; Serna, P. A Different Reaction Pathway for the Reduction of Aromatic Nitro Compounds on Gold Catalysts. *Angew. Chem. Int. Ed.* **2007**, *46*, 7266–7269. [CrossRef]
58. Zhao, R.; Tan, C.; Xie, Y.; Gao, C.; Liu, H.; Jiang, Y. One step synthesis of azo compounds from nitroaromatics and anilines. *Tetrahedron Lett.* **2011**, *52*, 3805–3809. [CrossRef]
59. Wehman, P.; Dol, G.C.; Moorman, E.R.; Kamer, P.C.J.; van Leeuwen, P.W.N.M.; Fraanje, J.; Goubitz, K. Ligand Effects in the Palladium-Catalyzed Reductive Carbonylation of Nitrobenzene. *Organometallics* **1994**, *13*, 4856–4869. [CrossRef]
60. Wehman, P.; Kaasjager, V.E.; de Lange, W.G.J.; Hartl, F.; Kamer, P.C.J.; van Leeuwen, P.W.N.M.; Fraanje, J.; Goubitz, K. Subtle Balance between Various Phenanthroline Ligands and Anions in the Palladium-Catalyzed Reductive Carbonylation of Nitrobenzene. *Organometallics* **1995**, *14*, 3751–3761. [CrossRef]
61. Bolzacchini, E.; Lucini, R.; Meinardi, S.; Orlandi, M.; Rindone, B. Effect of a proximal substituent on the triruthenium dodecacarbonyl-catalyzed reductive carbonylation of nitroarenes. *J. Mol. Catal. A Chem.* **1996**, *110*, 227–233. [CrossRef]
62. Macho, V.; Kralik, M.; Halmo, F. New catalytic system of N,N′-diphenylurea synthesis from nitrobenzene, carbon monoxide and water or aniline. *J. Mol. Catal. A Chem.* **1996**, *109*, 119–125. [CrossRef]
63. Wehman, P.; Borst, L.; Kamer, P.C.J.; van Leeuwen, P.W.N.M. Influence of an aromatic carboxylic acid as cocatalyst in the palladium-catalysed reductive carbonylation of aromatic nitro compounds. *J. Mol. Catal. A Chem.* **1996**, *112*, 23–36. [CrossRef]
64. Wehman, P.; Kamer, P.C.J.; van Leeuwen, P.W.N.M. Reductive carbonylation of aromatic dinitro compounds with a palladium(phenanthroline)$_2$(triflate)$_2$ catalyst and an aromatic carboxylic acid as cocatalyst. *Chem. Commun.* **1996**, 217–218. [CrossRef]
65. Ya, Y.; Lu, S. Selenium-catalyzed reductive carbonylation of nitrobenzene with amines as coreagents to give unsymmetric phenylureas. *Tetrahedron Lett.* **1999**, *40*, 4845–4846. [CrossRef]
66. Ragaini, F.; Ghitti, A.; Cenini, S. Mechanistic Study of the $Ru_3(CO)_{12}$/Tetraalkylammonium Chloride Catalyzed Carbonylation Reactions of Nitroarenes to Carbamates and Ureas: A Completely Revised Picture. *Organometallics* **1999**, *18*, 4925–4933. [CrossRef]
67. Ragaini, F.; Cenini, S. Mechanistic study of the $Ru_3(CO)_{12}$/chloride catalyzed carbonylation reactions of nitroarenes to carbamates and ureas; the role of the alkylammonium cation. *J. Mol. Catal. A Chem.* **2000**, *161*, 31–38. [CrossRef]
68. Ling, G.; Chen, J.Z.; Lu, S.W. Selenium-catalyzed carbonylation of substituted nitrobenzenes with aminomethylpyrimidines as co-reagents to synthesize N-phenyl-N′-methylpyrimidylurea derivatives. *J. Mol. Catal. A Chem.* **2003**, *202*, 23–29. [CrossRef]
69. Ragaini, F.; Gasperini, M.; Cenini, S.; Arnera, L.; Caselli, A.; Macchi, P.; Casati, N. Mechanistic Study of the Palladium–Phenanthroline Catalyzed Carbonylation of Nitroarenes and Amines: Palladium–Carbonyl Intermediates and Bifunctional Effects. *Chem. Eur. J.* **2009**, *15*, 8064–8077. [CrossRef] [PubMed]
70. Mooibroek, T.J.; Schoon, L.; Bouwman, E.; Drent, E. Carbonylation of Nitrobenzene in Methanol with Palladium Bidentate Phosphane Complexes: An Unexpectedly Complex Network of Catalytic Reactions, Centred around a Pd–imido Intermediate. *Chem. Eur. J.* **2011**, *17*, 13318–13333. [CrossRef]
71. Vavasori, A.; Ronchin, L. Phosgene-free synthesis of 1,3-diphenylurea via catalyzed reductive carbonylation of nitrobenzene. *Pure Appl. Chem.* **2012**, *84*, 473–484. [CrossRef]
72. Vavasori, A.; Capponi, M.; Ronchin, L. One-pot synthesis of paracetamol via the catalytic reductive carbonylation of nitrobenzene in acetic acid-water as a solvent. *Chem. Listy* **2012**, *106*, 1191.
73. van Leeuwen, P.W.N.M.; Kamer, P.C.J.; Reek, J.N.H. The bite angle makes the catalyst. *Pure Appl. Chem.* **1999**, *71*, 1443–1452. [CrossRef]
74. Fishbein, J.C.; McClelland, R.A. Halide ion trapping of nitrenium ions formed in the Bamberger rearrangement of N-arylhydroxylamines. Lifetime of the parent phenylnitrenium ion in water. *Can. J. Chem.* **1996**, *74*, 1321–1328. [CrossRef]
75. Heller, H.E.; Hughes, E.D.; Ingold, C.K. A New View of the Arylhydroxylamine Rearrangement. *Ingold Nat.* **1951**, *168*, 909–910. [CrossRef]
76. Sone, T.; Tokuda, Y.; Sakai, T.; Shinkai, S.; Manabe, O. Kinetics and mechanisms of the Bamberger rearrangement. Part 3. Rearrangement of phenylhydroxylamines to p-aminophenols in aqueous sulphuric acid solutions. *J. Chem. Soc. Perkin Trans.* **1981**, *2*, 298–302. [CrossRef]
77. Sone, T.; Hamamoto, K.; Seiji, Y.; Shinkai, S.; Manabe, O. Kinetics and mechanisms of the Bamberger rearrangement. Part 4. Rearrangement of sterically hindered phenylhydroxylamines to 4-aminophenols in aqueous sulphuric acid solution. *J. Chem. Soc. Perkin Trans.* **1981**, *2*, 1596–1598. [CrossRef]
78. Kohnstam, G.; Petch, W.A.; Williams, D.L.H. Kinetic substituent and isotope effects in the acid-catalysed rearrangement of N-phenylhydroxylamines. Are nitrenium lons involved? *J. Chem. Soc. Perkin Trans.* **1984**, *2*, 423–427. [CrossRef]
79. Vavasori, A.; Dall'Acqua, F.; Cavinato, G.; Toniolo, L. Influence of the operating conditions on the catalytic activity of [$PdCl_2$(dapp)] in the CO–ethene copolymerization in the H_2O–CH_3COOH as a solvent (dapp = 1,3-bis(di(2-methoxyphenyl)phosphino)propane). *J. Mol. Catal. A Chem.* **2010**, *332*, 158–164. [CrossRef]

80. Zudin, V.N.; Ill'inich, G.N.; Likholobov, V.A.; Yermakow, Y.I. New catalyst for the synthesis of dialkyl ketones from olefins, carbon monoxide, and hydrogen. *J. Chem. Soc. Chem. Commun.* **1984**, 545–546. [CrossRef]
81. Zudin, V.N.; Chinakov, V.D.; Nekipelov, V.M.; Rogov, V.A.; Likholobov, V.A.; Yermakow, Y.I. Determination of key intermediates for homogeneous water-gas shift reaction and hydrocarbonylation of ethylene to diethyl ketone catalyzed by the $Pd(OAc)_2$-PPh_3-CF_3COOH/H_2O system. *J. Mol. Catal.* **1989**, *52*, 27–48. [CrossRef]