



Continuous-Flow Palladium-Catalyzed Synthesis of Cyclohexanones from Phenols using Sodium Formate as a Safe Hydrogen Source

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Continuous-flow Pd-catalyzed synthesis of cyclohexanones from phenols using sodium formate as a safe hydrogen source

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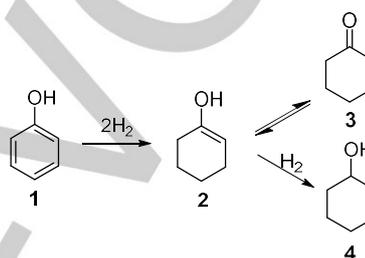
Abstract: We report a procedure for the continuous flow production of cyclohexanone from phenol, based on the use of sodium formate as a biomass derived source of hydrogen and on Pd/C as an easily accessible catalytic system. The reaction works in water at pH = 12.0 and at 90 °C. by setting a packed reactor charged with the catalyst Pd/C (10wt%) at a flow rate of 0.5 mL min⁻¹ we achieved a continuous flow production of cyclohexanone with high yields, selectivity and productivity.

Phenols, mostly in their polymeric forms in lignin, are the second most prevalent naturally occurring structural units of renewable biomass on the planet, and they are regarded possibly valuable materials deriving from biomass treatment. *Indeed removal of the functional groups present in lignin, yields simple aromatic compounds such as phenol, benzene, toluene, and xylene.* Consequently, application of phenols as commodity chemicals or substrates for useful transformation is highly desirable.^[1]

Cyclohexanone is of the main commodities of chemical industry feeding the production of caprolactam and adipic acid, which in turn are transformed into Nylon 6, Nylon 6,6 and polyamide resin.^[2] Large production of cyclohexanone is based either on cyclohexane oxidation under Co catalysis or phenol partial hydrogenation in the presence of different transition metal catalysts. On a different approach, starting from phenol, the industrial process toward cyclohexanone comprises the initial reductive step accessing cyclohexanol which is further dehydrogenated to cyclohexanone in a high temperature gas-phase Pd or Pt catalyzed process. In order to define milder and energy efficient one-step processes, the use of selective homogeneous and heterogeneous catalysts has been investigated in liquid phase resulting in with many successful examples mainly based on single or mixed Pd,^[3] Pt,^[4] Ru,^[5] Rh^[6] and Ni^[7] catalysts on different supports.^[8]

Considering commonly proposed mechanism for the hydrogenation of phenol on supported palladium catalysts, reduction occurs on the phenolate ion adsorbed on the support in proximity of the metal particles that are responsible for the hydrogen activation. The chemical strategy to selectively reduce

phenol is based on controlling the desorption of cyclohexanone from the catalyst surface before further hydrogenation leads to cyclohexanol.^[9]



Scheme 1. Reaction steps in a typical phenol hydrogenation.

The use of formic acid derivatives as hydrogen source in combination with a palladium catalyst, is a promising safer and sustainable alternative to classic methods. Formates are stable, non-toxic and they can be obtained from biomass processing.^[10] Formic acid derivatives have also been proposed as hydrogen storage materials, as they are suitable for safe transportation and handling.^[11] Some examples of phenol reduction using formic acid,^[12] sodium formate^[13,14] or potassium formate^[15] in batch conditions have been recently reported. Although very attractive, some of these protocols feature some limitations, as the requirements for inert atmosphere^[12] or microwave heating.^[14] In addition, complex catalytic systems requiring specific procedures for their preparation, are often necessary to achieve high efficiency and good selectivity towards cyclohexanone production.^[13]

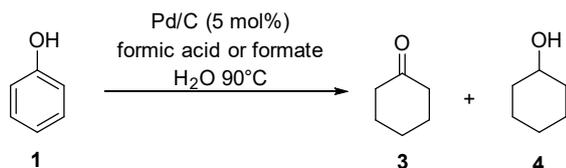
Following our interest in developing sustainable protocols based on the use of safe media, heterogeneous catalysis^[16] and the application of flow technology,^[17] we report herein our approach towards the definition of a continuous-flow protocol using commercially available Pd/C for the catalyzed selective transfer hydrogenation of phenol to cyclohexanone in water, using sodium formate as hydrogen source.

In a preliminary optimization study in batch, we investigated the best reaction conditions suitable for a further transfer to a flow protocol. Based on literature data, Pd/C was selected as the representative commercially available and cheap heterogeneous catalyst to be used in water. The selection of water as medium, beside its environmentally benign and safe nature, allows also an efficient dissolution of H₂.^[18,19] In addition, we also based our approach on the fact that phenol (1) is completely soluble in water at temperatures higher than 66 °C, while cyclohexanone (3) and cyclohexanol (4) are not,^[20] thus facilitating the separation of the products from the aqueous phase at the end of the reaction.

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Scheme 2. Screening of the reaction parameters.

When formic acid was employed as the hydrogen source in water, a complete conversion of phenol was observed at 90 °C after 1 h but, unfortunately, only traces of cyclohexanone (**3**) were obtained while cyclohexanol was the prevailing product (95% of the converted compound). Then, sodium formate was employed and again complete conversion was achieved but still with an unsatisfactory selectivity (48/ 52 ratio of **3/ 4**).

We therefore decided to take under consideration the pH of the reaction mixture by measuring and varying it. The experiments design was based on the preparation of a 0.2 M solution of phenol in water plus 2.5 equivs of sodium formate resulting in a mixture with a pH of 6.90. Then, addition of a 5 M solution of NaOH allowed to adjust the pH to the desired values and then reaction mixture heated at 90 °C for 30 min.

With the increase of pH, selectivity towards cyclohexanone formation was also improved and therefore we decided to study more in details the influence of pH on the process. Results in terms of conversion of phenol and selectivity cyclohexanone (**3**) versus cyclohexanol (**4**) are reported in Figure 1.

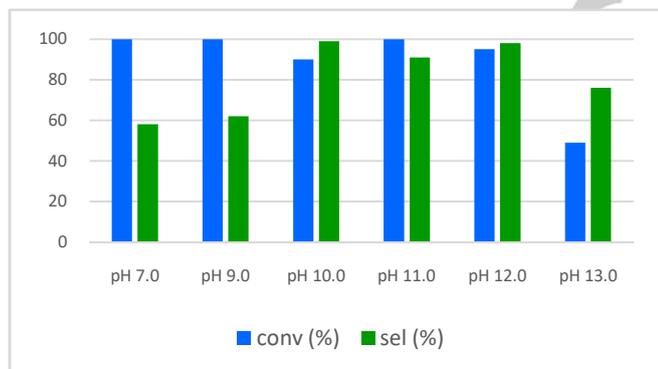


Figure 1. Influence of pH on phenol conversion and selectivity in cyclohexanone formation.

The increase of the pH of the medium proved to be crucial for the selectivity of the hydrogenation of phenol to cyclohexanone and a 95% conversion/98 % selectivity was achieved at pH = 12.0. However, acceptable results were obtained also in the pH range between 10 and 12. At lower pH poorer selectivity was observed while at higher pH conditions conversion was limited. We also performed different experiments with variable reaction times (Figure 2). At pH 12.0, after 1.5 or 2.5 h an evident increase of the cyclohexanol formed was observed (Figure 2). To limit further reduction of cyclohexanone or its enolate ion, we reduced the excess of sodium formate employed in the reaction

(see SI). Using strictly equimolar ratio, 93% of conversion and 97% selectivity were obtained after 2.5 h of reaction at 90 °C (See SI).

The influence of the nature of the base employed was also investigated by heating the reaction at pH 12.0 for 30 min at 90 °C in the presence of different hydroxides (Figure 3). Exclusively NaOH gave good results in terms of conversion and selectivity, underlining a “cation” effect in the process. This observation may also indicate that the reaction could occur with via absorption of the phenolate ion on the support close to H₂ adsorbed on Pd as in this case, an influence of the cation size could be expected.

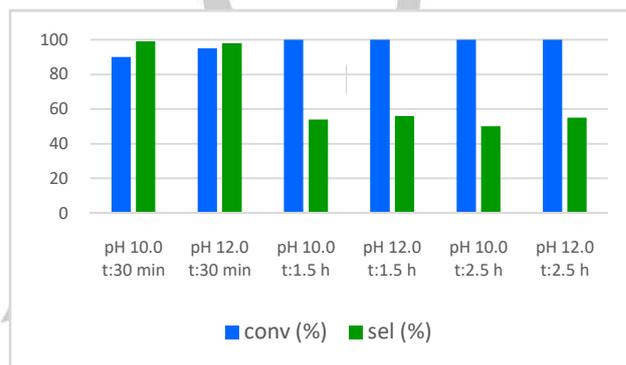


Figure 2. Influence of time and pH on phenol conversion and selectivity in cyclohexanone formation.

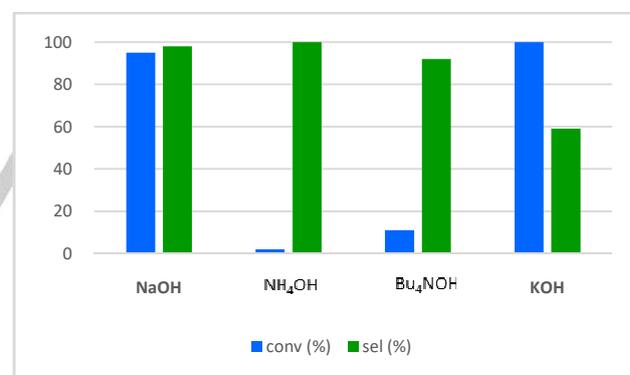


Figure 3. Influence of the base on phenol conversion and selectivity in cyclohexanone formation.

The conclusion of the experiments in batch conditions demonstrated that sodium formate is a suitable source of H₂ in a process where Pd/C decomposes the formate and catalyzes the selective reduction of the phenolate ion generated at pH 12.0. In view of designing the flow reactor for the continuous flow protocol, the reaction was carried out with a larger amount of the Pd catalyst (50 mol%), observing always a high conversion and a good selectivity after only 5 min of reaction time (Figure 4). The continuous flow experiment was set by preparing a packed glass reactor containing Pd/C (1.2 g, 10%wt) dispersed over

glass spheres and charging the catalyst in a glass column located inside to a thermostated bath at 90 °C. The mixture of phenol (**1**) and sodium formate in water was adjusted to pH 12.0 with the addition of aqueous NaOH 5M and placed in a flask acting as a reservoir (Scheme 3). The reservoir was connected to a HPLC pump and the aqueous mixture was pumped through the catalyst reactor (heated at 90°C) at a flow rate of 0.5 mL min⁻¹. As during the reaction gaseous H₂ was formed, a back-pressure regulator (BPR) was placed at the end of the catalysts column, setting the pressure to 5 psi.

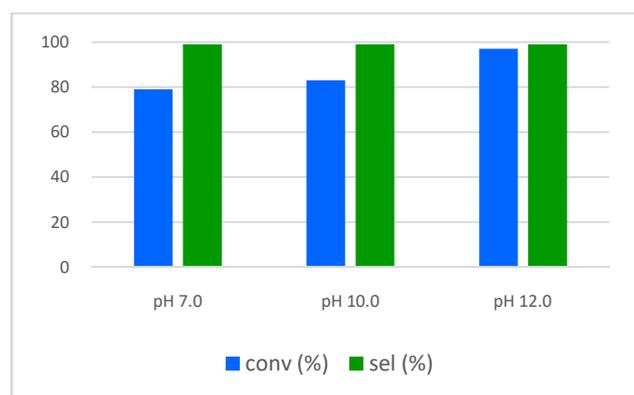
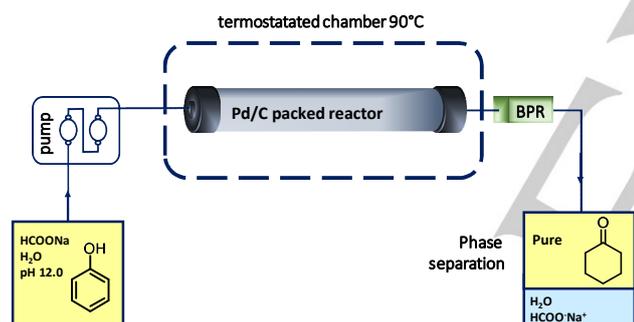


Figure 4. Hydrogenation of phenol over 50 mol% of Pd/C after 5 min reaction time.



Scheme 3. Flow reactor used for the hydrogenation of **1**.

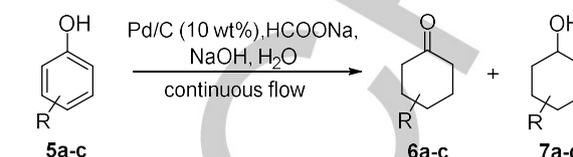
Under these conditions, 90 % conversion of **1** was achieved with 100% selectivity for the formation of desired cyclohexanone (**3**). The product was recovered through extraction with heptane, while most of the unreacted phenol was retained in the aqueous phase, and it was eventually removed from the organic phase by dilute NaOH wash. Isolation of pure product **3** was achieved after evaporation of the organic solvent.

With this setup and using up to 20 mmol of phenol were converted before observing a drop in the conversion from 90 to 65 %. However, after a simple washing of the catalyst column with water (5 times the column volume), the catalyst activity was recovered and the reaction proceeded again with ca. 90% conversion. Probably, this reduction of conversion was due to the deposition of some bicarbonate salts coming from sodium formate oxidation.

During representatively 6 hours of operation, 5 g of phenol were converted in flow allowing 3.9 gr of pure cyclohexanone to be isolated in an overall 80 % yield. It is noteworthy that under continuous flow operation, only 1.1 mol% of Pd were required to

process 50 mmol of phenol, which represents a noticeable improvement with respect of our best batch protocol. With the disclosed flow protocol, a TON value of 70.2 was achieved, corresponding to a TOF value of 11.7 h⁻¹ and further extension of the reaction time would clearly lead to higher productivity.

Table 1. Flow hydrogenation on various substrates.



5a, 6a, 7a R = 2-OH
5b, 6b, 7b R = 2-OMe
5c, 6c, 7c R = 2-Me

Entry	Substrate	Residence time (min)	BPR (psi)	T (°C)	C (%) ^[a]	S (%) ^[a]
1	5a	4	5	65	30	-
2		7	20	65	50	87
3		15	40	65	90	85
4	5b	15	40	90	95	70
5		7	20	90	50	83
6		7	100	90	15	-
7	5c	9	40	65	70	76
8		7	100	90	18	-
9		15	40	90	50	89

[a] (C) Conversion and (S) Selectivity data were measured by GLC analyses

Considering the results obtained with phenol, the flow protocol in Scheme 3 was extended to other substrates relevant in the biomass valorisation research, as they are models of phenol derivatives obtained from lignin depolymerisation (Table 1). With these substrates, we tried to optimize the conversion and the selectivity of the process by varying several parameters, such as the residence time in the catalyst columns, the BPR used to control hydrogen pressure in the reactor and temperature. In the case of guaiacol (**5b**) and 2-cresol (**5c**) the substrate was not completely soluble in water, therefore the mixture was kept under stirring and pumped as an emulsion. From literature, the selectivity in the hydrogenation of catechol (**5a**) and cresols is known to be an issue both when molecular hydrogen^[21] or formic acid^[14] are used. Also in continuous flow, when catechol (**5a**) was selected as substrate, conversion and selectivity obtained with phenol were not achievable since over-hydrogenation to 1,2-cyclohexanediol occurred to a considerable extent. The same issue was observed for guaiacol (**5b**) and 2-cresol (**5c**). Acceptable selectivity was obtained only at a low level of conversion (Table 1, entry 5), while a prolonged residence time led to higher conversion but lower selectivity (Table 1, entry 7). The selection of the pressure limit of the BPR has effect on the outcome of the reaction. In fact, when low pressure (5 psi) or high pressure (100 psi) were employed only minor conversion

were obtained (Table 1, entries 1, 6, 8) while best results were gained at 40 psi.

In conclusion, we have reported the first example of the application of flow technology to the transfer hydrogenation of phenol (**1**) to cyclohexanone (**3**), using sodium formate as safe and bioderived hydrogen source in water. The application of a packed continuous flow reactor allowed the prolonged use of the catalyst (Pd/C), ensuring a good productivity and giving pure cyclohexanone in an efficient protocol. Although a further optimization will be required for substituted phenols these results confirm that transfer hydrogenation process represents an environmentally benign and safe alternative to classical phenol hydrogenation protocols, employing molecular hydrogen, and this report will promote further investigation in this direction to define additional reactor settings and to access the selective reduction of variously substituted phenols.

Experimental Section

Typical procedure for the hydrogenation in batch: Phenol **1** (0.8 mmol, 75 mg), sodium formate (2.5 eq, 120 mg) and water (0.2 M, 4 mL) were placed in a screw capped vial, equipped with a stirring bar. The pH of the mixture was adjusted to 12.0 by adding NaOH (aq 5M). Pd/C (10 wt%, 5 mol%, 42 mg) was added and the reaction mixture was stirred at 90 °C for 30 minutes. After reaction completion, the catalyst was filtered off and the mixture was extracted with heptane, then the combined organic layers were dried over anhydrous Na₂SO₄. The product was recovered after evaporation of the solvent under reduced pressure.

Typical procedure for the flow synthesis of 3: A premixed mixture of phenol **1** and sodium formate (2.5 eq) in H₂O (0.2 M) was prepared in a flask with the function of reservoir and pH was adjusted to 12.0 with the addition of aqueous NaOH (5M). Pd/C (10 wt%, 1.2 g) was dispersed in 0.5-1 mm diameter solid glass beads and charged in two Omnifit glass columns (600 mg each); the equipment was connected, by using the appropriate tubes, to the pump and a 5 psi backpressure regulator was placed on the outlet tube. The catalyst columns were placed into a thermostated box and the reaction mixture was continuously pumped (residence time 7 min) through the catalyst columns at 90 °C. The conversion of **1** was periodically monitored by GLC. The resulting aqueous mixture was extracted with heptane, then the combined organic layers were dried over anhydrous Na₂SO₄. The product **3** was obtained in 80 % yield after evaporation of the solvent under reduced pressure.

Acknowledgements

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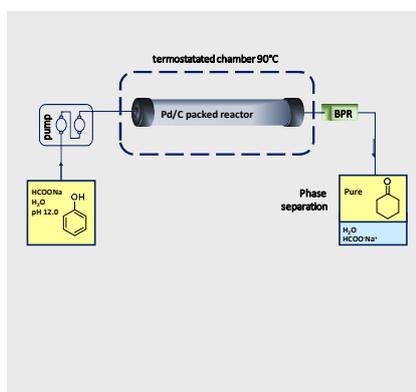
Keywords: phenols • hydrogenation • sodium formate 3 • continuous-flow chemistry

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COMMUNICATION

A continuous flow protocol for the production of cyclohexanone from phenol, has been reported by using sodium formate as a biomass derived source of hydrogen and on Pd/C as an easily accessible catalytic system.



Federica Valentini, Niccolò Santillo, Chiara Petrucci, Daniela Lanari, Elena Petricci, Maurizio Taddei,* Luigi Vaccaro*

Page No. – Page No.

Continuous-flow Pd-catalyzed synthesis of cyclohexanones from phenols using sodium formate as a safe hydrogen source