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Method Article

Experimental protocol for the study of One-pot amination of Cyclohexanone-to-secondary amines over Carbon-supported Pd



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A B S T R A C T

The validation of protocols for carrying out the experimental analysis of amination reactions is of paramount importance to enhance the scientific knowledge and reproducibility of results. Accordingly, in the present paper, a protocol has been proposed for the study of the amination of cyclohexanone-to-secondary amines (Diphenylamine and N-Cyclohexylaniline) over heterogeneous catalysts. The results of activity and selectivity, and the elucidation of a plausible reaction pathway were described in a parent paper. Therefore, the purpose of this document is to inform about the details of the experimental setups, the methods, and the analytical techniques to identify and quantify the reaction products. Finally, some practical and safety considerations are also included.

- One-pot catalytic amination of cyclohexanone with aniline was performed efficiently in liquid phase on Pd/C.
- Stirring, He atmosphere and temperature control were critical to achieve reproducible activity results.
- Ultra-High Performance Liquid Chromatography allows identifying products and reaction intermediates, while nonane performed well as internal standard for GC-FID quantification.

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Materials, analytical methods & experimental design

Secondary amines plays an important role in the synthesis of fine chemicals, dyes, pharmaceuticals, and other products. [1–3]. Current methods for the synthesis of secondary amines, require strict reaction conditions, have a poor carbon economy, and produce toxic residues that represent environmental risks [4,5]. Therefore, new and more sustainable methods based on green chemistry are required to produce secondary amines. In this sense, the sustainable transformation of lignocellulose-based substrates (e.g., aldehydes, ketones, phenols, alkenes and alkynes) into amines have been reported as a promising way to replace oil from its actual applications [6–9]. Among them, the heterogeneously catalyzed reductive amination of ketones has drawn great attention as a method for the synthesis of primary or higher-order amines [10,11]. This paper describes a protocol based on our research on Liquid phase amination of Cyclohexanone-to-Secondary amines over Carbon-supported Pd catalysts. The protocol enhances the information regarding the reaction setup and conditions, catalyst characterization techniques, and products identification and quantification.

Reaction pathway

The amination initiates with the addition of cyclohexanone (**B**) with aniline (**A**) via nucleophilic attack to form the intermediary hemi-aminal N-Anilincyclohexanol (**C'**). The hemi-aminal is then dehydrated to a secondary imine (N-Phenylcyclohexaneimine) (**C**). Thereafter, the imine undergoes disproportionation to form N-cyclohexylaniline (**D**) and (ii) Diphenylamine (**E**), respectively. Hence, the process requires for redox active sites, which will support the dehydrogenation and hydrogenation reactions involved in the disproportionation. A schematic of this reaction pathway is presented below (See [Scheme 1](#)).

*Catalyst**Pre-treatment and characterization of the catalysts*

Commercial 10 wt.% Pd/C (CAS-87104) was acquired from Merck Group (Chile). The catalyst was first dried and sieved to particle sizes <75 μm . This pre-treatment is of great importance to guarantee an efficient stirring in the autoclave reactors, leading to reduce the mass transfer limitations during the experiments (See Section 2.2). The catalysts were thermally treated to 400 °C (heating rate of 1.5 °C/min) for 2 h under a H₂ flow (40 mL/min) in a U-shaped fixed bed reactor (18 mm ID), before use. This reduction process is tremendously important for the reaction, as the Pd zero-valent sites are required for the dehydrogenation and hydrogenation reactions. Experiments with Pd/C without

treatment did not performed well regarding conversion (<15%) and selectivity to secondary amines (<18%).

Morphology and composition

The morphology of catalysts was inspected by Scanning Electron Microscopy (SEM). This analysis was done in a Hitachi SU3500 microscope operated at 20kV acceleration voltage. The SEM was coupled to a Bruker XFlash 610M energy-dispersive X-ray spectroscopy (EDX) accessory for semi-quantitative spectral analysis.

Reducibility

Temperature programmed reduction (TPR) experiments were carried out in a ChemBET-3000 unit from Quantachrome. About 50 mg of catalyst (sieved at 150–380 μm) were loaded in a U-shaped quartz tube (10 mm ID) and heated progressively from 30 °C to 700 °C at a heating rate of 5 °C/min under an airflow of 50 mL/min. The sample was kept under this atmosphere for 1 h to ensure surface oxidation, before cooling to room temperature. The cooling process was performed under a He flow of 50 mL/min. In a second stage, the sample was heated again at 5 °C/min in a flow of 50 mL/min of 5%v/v H₂/Ar mixture up to 700 °C. The sample was kept under this condition for 2 h and then cooled to room temperature. The hydrogen consumption as a function of the reduction temperature was continuously monitored by a cell of thermal conductivity detector (TCD).

Crystal phase analysis and nanoparticle morphology

The X-ray diffraction patterns of the samples were recorded in a Bruker D4 diffractometer provided with CuK α radiation ($\lambda = 0.15418$ nm). The signal was generated at 40 kV and 20 mA. The 2θ was scanned between 3° and 90° at a speed of 0.02°/s. The identification of the crystalline phases was done by a search-match procedure with the software Mercury 3.7, using the Crystallography Open Database (COD) [12]. Besides, the sizes of the metallic particles were estimated through the Scherrer's equation [13].

Synthesis of secondary amines from the liquid-phase catalytic amination of cyclohexanone over Pd/C

The following procedure illustrates the synthesis of secondary amines from cyclohexanone, using Pd/C as catalyst and aniline. Extra details about the system setup and operational advices are provided in Section 2.2.2.

Reagents

- **Toluene** (>99%; Merck Chile, CAS. no. 108-88-3) **!Caution** Highly inflammable and harmful. Avoid contact with skin, eyes or mucous membranes; keep away from sources of ignition.
- **Aniline** (>99%; Merck Chile, CAS. no. 62-53-3) **!Caution** Toxic if ingested, in contact with skin or if inhaled. Avoid contact with skin, eyes or mucous membranes.
- **Cyclohexanone** (>99%; Merck Chile, CAS. no. 108-94-1) **!Caution** Highly inflammable and harmful. Avoid contact with skin, eyes or mucous membranes; keep away from sources of ignition.
- **NaCO₂H** (>99%; Merck Chile, CAS. no. 141-53-7) **!Caution** Toxic if ingested. Wear gloves and protective accessories.
- **Imine (N-cyclohexylideneaniline)** (>95%; AKoS, Ukraine, CAS. no. 1132-38-3) **!Caution** Highly inflammable and harmful. Avoid contact with skin, eyes or mucous membranes.
- **Diphenylamine** (>99%; Merck Chile, CAS. no. 122-39-4) **!Caution** Toxic if ingested, in contact with skin or if inhaled; very toxic to aquatic organisms. Avoid contact with skin, eyes or mucous membranes; prevent its release into the environment.
- **N-Cyclohexylaniline** (>98%; Merck Chile, CAS. no. 1821-36-9) **!Caution** Toxic if ingested. Wear gloves and protective accessories.
- **Nonane** (>99%; Merck Chile, CAS. no. 111-84-2) **!Caution** Highly inflammable and harmful; very toxic to aquatic organisms. Avoid contact with skin, eyes or mucous membranes; prevent its release into the environment; keep away from sources of ignition.
- **Phenol** (>99%; Merck Chile, CAS. no. 108-95-2) **!Caution** Toxic if ingested, in contact with skin or if inhaled. Avoid contact with skin, eyes or mucous membranes.

Table 1

Considerations in the autoclave reaction system.

-
- Pressurization/depressurization of the autoclave must be carried out with sealed autoclave, before opening the reaction vessel.
 - Before carrying out a reaction, the autoclave must be carefully checked to ensure that the device is capable of maintaining pressure without leaks. The heating system, temperature controller and agitation should also be checked and calibrated before each temperature change.
 - Check that the autoclave is operated away from its maximum pressure limit.
 - The autoclave must be properly located in a place that allows protection in case of explosion.
 - Check the sampling port septa prior to experiments to avoid leaks
 - For sampling always use globes, glasses and a mask equipped with organic vapors filters.
-

Reaction procedure & experimental design

A throughput study on the reaction conditions (T , C^0_i) was performed in 4 mL reinforced-glass autoclave reactors, and the kinetic measurements were done under similar conditions in a 20 mL SS316 reactor with a sampling port. The reactors were placed in a Reacti-Therm™ (ThermoFisher, USA) system, equipped with an external temperature probe and magnetic stirring (Fig. 1). More details for using these autoclaves can be found in Table 1 and specific reaction conditions are summarized below.

Procedure for reactions

- (1) The reaction mixture was prepared in an autoclave reactor (4 ml) previously washed and dried. The compounds: ketone (cyclohexanone), aniline and solvent (toluene) were loaded into the autoclave reactor using an automatic micropipette (Gilson Pipetman LP100L, 10–100 μ L) at the specific volumes, to guarantee the concentration of the corresponding experiment (Table 3). **!Caution:** Avoid the contact of reagents with eyes, mucous membranes or skin by using the corresponding protection elements.
- (2) Then the reactor was placed in a precision balance (Biobase BA504B, ± 0.1 mg) to add the solids. Using a SS316 spatula, the NaCOOH (H-donor), and the catalysts were added to the reactor. The catalysts are stable and can be handled in open air without special precautions. However, the laboratory is equipped with temperature and moisture control (18 °C).
- (3) Finally, a Teflon-lined magnetic stirrer was introduced into the reactor.
- (4) The reactor was closed and a leak test with inert He (99.995%, Airliquide, Chile) at 1.5 bar was performed to ensure that the reactor has been hermetically sealed. Leaks can be detected by monitoring the pressure for 10 min in a digital manometer. The He flow into the system was provided by a mass flow controller (Aalborg MFC 17007).
- (5) The reactor was purged three times at 1 bar He (99.995%, Airliquide, Chile), and subsequently, the pressure was fixed to keep 1.5 bar during the reaction. **!Caution:** Mixtures of organics and oxygen can be explosive and highly flammable, thus leaks must be avoided and/or inert atmosphere guaranteed.
- (6) At 1.5 bar of He, the reactor was heated-up to the reaction temperature (the reaction temperature was studied between 80 and 140 °C and the stirring started (900 r.p.m). **Important!:** This mark the initiation of the reaction.
- (7) Reaction time was fixed at 20 h for batch experiments but for kinetic measurements the sampling was carried out for nearly 10 h.
- (8) The sampling was done using a 100 μ L Hamilton syringe and the content was transferred to 2 mL Amber glass vials using a Teflon filter (0.45 μ m).
- (9) Finally, the reactors were cooled to room temperature (<25 °C), and then depressurized using a custom-designed depressurization system. **!Caution:** Ensure that the reactor is at ambient temperature to avoid flash vaporization of organics. In addition, do not depressurize using the reactor caps, to avoid accidents.
- (10) Samples were stored at –40 °C until analysis. **See section:** Product quantification and identification.

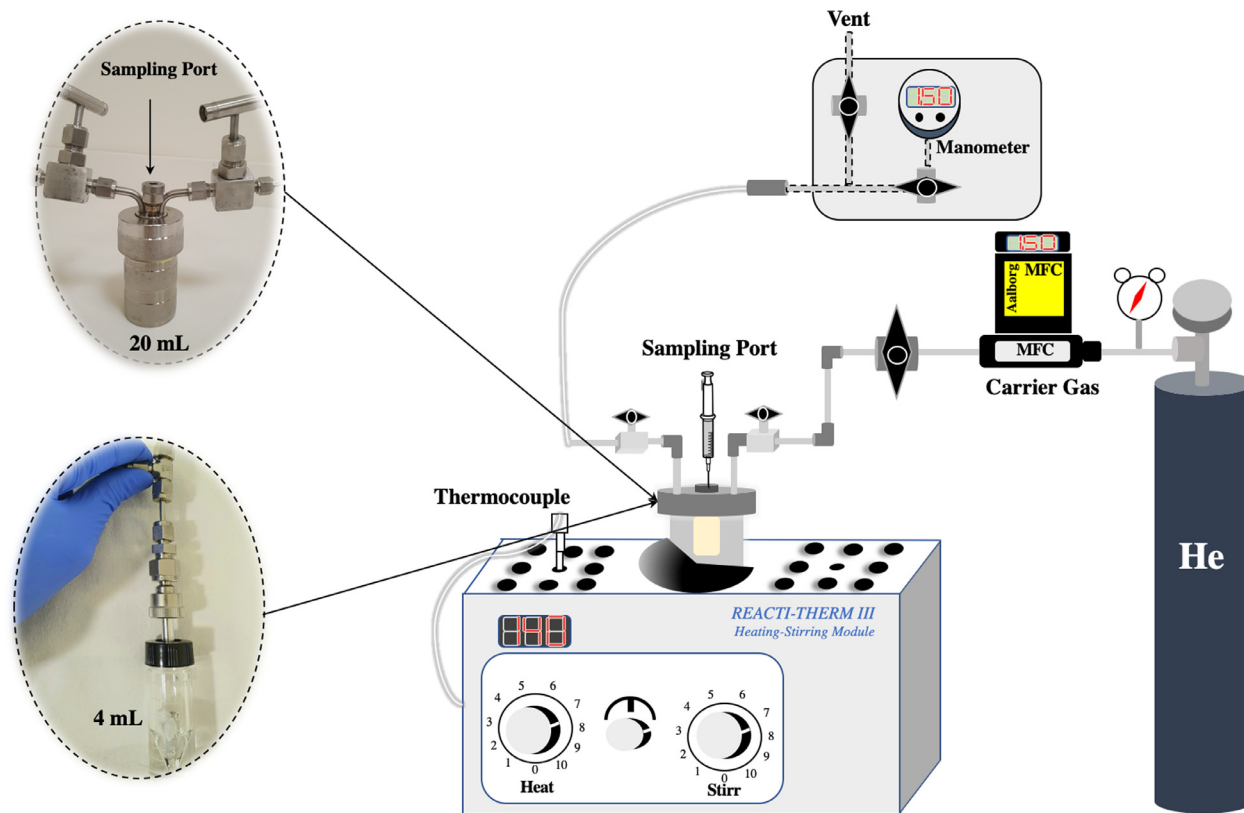


Fig. 1. Reaction system used for reactivity and kinetic measurements.

Table 2

Application of the Weisz–Prater criterion to the reaction system [14].

Parameter	Cyclohexanone	Aniline
D_b	6.94×10^{-5} (cm ² /s)	7.54×10^{-5} (cm ² /s)
D_{eff}	4.80×10^{-6} (cm ² /s)	5.42×10^{-6} (cm ² /s)
R_p	0.0053 (cm)	0.0053 (cm)
$C_{s,i}$	0.19 (mol/L)	0.19 (mol/L)
ri	4.36×10^{-4} (mol/L*min)	4.36×10^{-4} (mol/L*min)
Φ_{WP}	0.00019	0.00017

(11) **Recovering of catalysts:** The catalysts were recovered, washed with toluene and deionized water, filtered and placed into a crucible. Then, the samples were dried at 105 °C in a standard oven during 24 h, and store for recycling experiments.

(12) **The used reactors** were then subject to a strict **Cleaning Procedure** including:

- Washing with toluene for 15 min at 500 rpm using magnetic stirring.
- Washing with deionized water for 15 min at 500 rpm using magnetic stirring.
- The reinforced-glass reactor was washed with HCl (15%) two times.
- Then the stirrer and the reactor were washed again with distilled water and dried overnight in a standard oven at 100 °C.

Note: Original glass reactors were modified to control the gas atmosphere. The modification included a system for injecting the gas into the reaction mixture and to pressurize the system.

Experimental design and mass transfer limitations

Experimental design

A summary of the experimental conditions used for studying the Cyclohexane reductive amination is provided in Table A.1 of the Additional information section.

Prior to the activity test and kinetic measurements, the absence of mass transfer limitations was inspected.

Mass transfer calculations. Internal diffusion

The absence of internal diffusion limitations was assessed by applying the Weisz–Prater criterion (Eq. 1).

$$\Phi_{WP} = \frac{r_{obs} * R_p^2}{C_{s,i} * D_{eff}} \quad (1)$$

Here r_{obs} is the initial reaction rate, R_p is the mean radius of the catalyst particle, D_{eff} is de effective diffusivity of the reactant in the solvent, and C_s is the substrate concentration.

Accordingly, under the following conditions the internal diffusion resistances can be ruled out:

- (1) If the Weisz–Prater modulus (Φ_{WP}) < 1, for first-order reactions.
- (2) If the Φ_{WP} < 6, for zero-order reactions.
- (3) If the modulus Φ_{WP} < 0.3, for second-order reaction.

This criterion was applied to both, Cyclohexanone and Aniline, and according to its value, the internal mass transfer limitations were ruled out from our results (Table 2).

Mass transfer calculations. External diffusion

For inspecting the effect of external diffusion, the Mears criteria (Eq. (2)) was used.

$$Cm = \frac{-r_{obs} * \rho_b * R_p * n}{k_c * C_s} \quad (2)$$

Table 3
Application of the Mears criterion to the reaction system [14].

Parameter	Cyclohexanone	Aniline
Re	16905.8	16905.8
Sc	51.1	47.0
Sh	320.4	311.6
k_c	0.022 (m/s)	0.023 (m/s)
R_p	0.00053 (m)	0.00053 (m)
C_{ab}	0.19 (mol/L)	0.19 (mol/L)
Ri	$4.36 \cdot 10^{-4}$ (mol/L*min)	$4.36 \cdot 10^{-4}$ (mol/L*min)
Cm	0.00275	0.002602

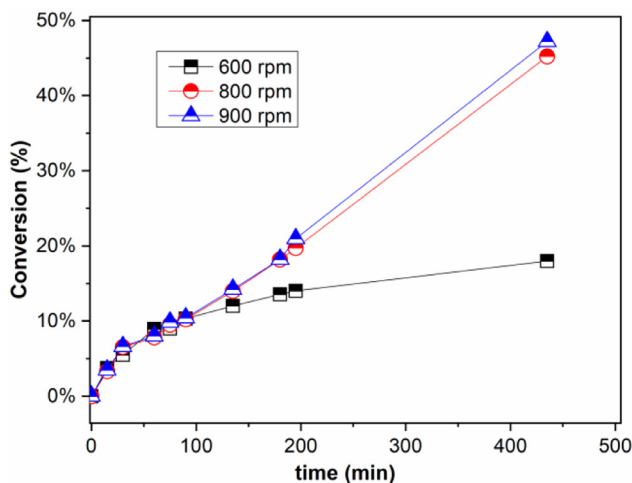


Fig. 2. Conversion vs time dependence for different agitation rates.

In addition, several experiments were performed at different agitation rates (600, 800 and 900 rpm). Results for the *Conversion vs time* profiles at these agitation rates are reported in Fig. 2, where it is demonstrated that above 800 rpm the reaction rate is not affected (Fig. 2). According to Vannice [14] the value obtained for the Mears criteria (Table 3) allows discarding the presence of external mass transfer limitations, thus we assumed that the experiments were performed under kinetically controlled regime for agitation speeds of 900 rpm.

Products identification and quantification

Identification

A higher sensitive LC-MS analytical system was used aiming to explore significant chemical differences among reaction products. It consists of an Ultra-High Performance Liquid Chromatography system (UHPLC, Elute, Bruker) equipped with an Elute DAD, and coupled to a High-Resolution quadrupole-Time-of-Flight Mass Spectrometer (HR-qTOF-MS, Compact, Bruker Daltonik GmbH, Bremen, Germany). Chromatography separation was performed on a Reverse Phase C18 column (100 mm \times 3.0 mm, 1.7 μ m, Kinetex Phenomenex) using a SecurityGuard Ultra Cartridge UHPLC C18 3.0 mm precolumn and maintained at 30 °C. Mobile phase consisted of solvent A (0.1% formic acid in Milli-Q water, v/v) and solvent B (0.1% formic acid in acetonitrile hypergrade, v/v). Elution was performed in gradient mode at a flow rate of 400 μ l min⁻¹, beginning with 2 min equilibration time at 5% B and continuing as follow: 0.0–20.0 min, 5 – 95% B linear; 20.0 – 20.2 min, 95 – 100% B linear;

Table 4

LC-MS data for compound identification.

Rt (min)	Name	Mol. Formula	(+) ESI Theor m/z	(+) ESI Found m/z	m/z error(mDa)	(+) MS/MSm/z [adduct] (int. %)	UV/Vis (nm)
5.7	N-cyclohexylaniline	C ₁₂ H ₁₇ N	176.1434 [M+H] ⁺	176.1442 [M+H] ⁺	-0.8	94.1 [M+H-Cyc] ⁺ (100), 83.1 [M+H-Ani] ⁺ (18), 77.0 [M+H-CyA] ⁺ (89)	202
13.8	N-diphenylamine	C ₁₂ H ₁₁ N	170.0964 [M+H] ⁺	170.0960 [M+H] ⁺	0.4	93.1 [M+H-Phe] ⁺ (100)	282
19.1	N-phenylcyclohexaneimine	C ₁₂ H ₁₅ N	174.1277 [M+H] ⁺	174.1280 [M+H] ⁺	-0.3	n.d.	n.d.

Neutral losses: Cyc, cyclohexenyl; Ani, aniline; CyA, cyclohexylamine; Phe, phenyl.

n.d.: MS/MS not detected due to low abundance of precursor ion.

UV/Vis: absorbance maxima

20.2 – 25.0 min, 100% B. The injection volume was of 2.0 µl. DAD was operated in a wavelength range from 194 nm to 500 nm at 10.0 Hz of data acquisition rate. Mass spectrometer was operated in positive ESI mode, in a data-dependent auto MS/MS acquisition. MS parameters were set as follow: mass range, 50–1000 m/z; scan cycle time, 0.2 s; dry temperature, 200 °C; capillary voltage, 4.5 kV; end plate offset 0.5 kV; desolvation gas flow, 9.0 l min⁻¹ (N₂); nebulizer pressure, 4.0 Bar. From each scan, MS/MS spectra were acquired by subjecting ions (maximum 2) to collision-induced dissociation (CID) if their absolute intensities exceeded 1000 counts in a cycle time of 0.2 s. Active exclusion of precursor ion was used after 1 spectrum, and reconsidered for fragmentation if its intensity was at least equal to that previously measured. Smart exclusion was also used after 25 spectra of a given precursor ion. Variable collision energy in range 20 – 50 eV depending on ion's m/z was used. A solution of sodium formate (10 mM in iso-PrOH/H₂O, 1:1, v/v) was constantly pumped at 1 µl min⁻¹ through a six-port-valve that allowed introduction of 20 µl of it into mass spectrometer just before each analysis. This was used as internal reference to ensure accurate mass measurements by applying the high precision calibration mode (HPC).

After each analysis, acquired data was automatically processed with a Script method in DataAnalysis 4.4 software (Bruker Daltonik GmbH, Germany), which included recalibration. Additional manual processing in DataAnalysis software, allowed for molecular formula determination of individual compound detected, with a tolerance of ±5 mDa. MS/MS fragmentation pattern of each compound, on the other hand, was used to confirm compound identity (Table 4).

Cyclohexanone: Retention time (Rt) (min.): 5.85. MS: 183 (M +, 3.4%); 182 (27.3%); 153 (4.1%); 152 (4.8%); 78 (6.2%); 77 (100%); and 51 (20.7%).

Aniline: Rt (min.): 6.77. MS: 210 (M+, 41.66%); 165 (6.25%); 119 (12.5%); 91 (100%); 65 (29.16%); and 39 (8.33%).

Phenol: Rt (min.): 6.65. MS: 210 (M +, 27.6%); 211 (4.9%); 165 (4.3%); 119 (10.2%); 107 (10.8%); 106 (8.6%); 92 (10.2%); 91 (100%); 65 (20.6%); and 39 (8.4%).

Diphenylamine: Rt (min.): 6.65. MS: 210 (M +, 27.6%); 211 (4.9%); 165 (4.3%); 119 (10.2%); 107 (10.8%); 106 (8.6%); 92 (10.2%); 91 (100%); 65 (20.6%); and 39 (8.4%).

N-Cyclohexylaniline: Rt (min.): 7.38. MS: 238 (M +, 72.1%); 133 (15.6%); 106 (20.4%); 105 (100%); 103 (16%); 79 (28.2%); 77 (32.6%); and 39 (13%).

N-Phenylcyclohexaneimine: Rt (min.): 8.20. MS: 268 (M +, 100%); 134 (13%); 120 (80%); 105 (19%); 91 (10%); 77 (21%); and 42 (23%).

Quantification

The reaction mixtures were analyzed by ex-situ gas chromatography (GC). We have found that nonane is a suitable internal standard for quantitatively analyze the reaction mixtures. Below there is a detailed description of the quantification procedure:

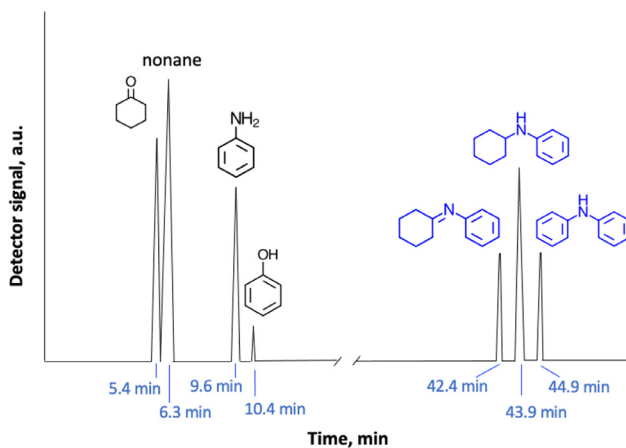
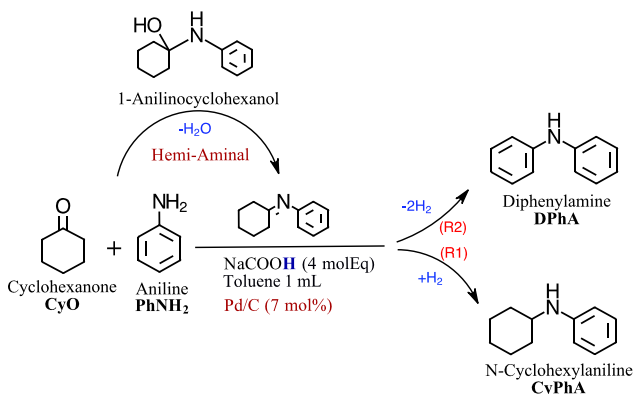


Figure 3. Sample chromatograms for reaction mixture obtained after 20 h. $T = 140\text{ }^{\circ}\text{C}$, $C_{\text{CyO}} = C_{\text{PhA}} = 0.2\text{ mol/L}$, Pd/C (7% mol with respect to CyO).



Scheme 1. Summarized reaction pathway. More detailed discussion is available in the parent manuscript.

- (1) An aliquot ($100\text{ }\mu\text{L}$) of the reaction mixture was transferred to a GC vial containing $500\text{ }\mu\text{L}$ of the solvent (toluene) and $2\text{ }\mu\text{L}$ of nonane. The samples were then analyzed by ex-situ gas chromatography on an SRI chromatograph (Model 8610) equipped with an on-column injection port, a flame ionization detector (FID) and a MTX-5 column ($30\text{ m} \times 0.25\text{ mm} \times 0.1\text{ }\mu\text{m}$). Retention time's assignment was done by injecting solvent-pure products samples prior to samples analysis.
- (2) Standard analysis conditions Injector temperature, $250\text{ }^{\circ}\text{C}$; FI detector temperature, $300\text{ }^{\circ}\text{C}$; and column temperature program, $45\text{ }^{\circ}\text{C}$ (hold 2 min) to $100\text{ }^{\circ}\text{C}$ (hold 3 min) at $2\text{ }^{\circ}\text{C}/\text{min}$ and then ramp at $10\text{ }^{\circ}\text{C}/\text{min}$ until $300\text{ }^{\circ}\text{C}$. As a number of parameters can affect retention times and response factors of products, a calibration of the chromatographic analysis was carried out before the quantitative analysis. All the substituted anilines used here are commercially available.
- (3) Fig. 3 shows an example of a GC Chromatogram, including product identification according to their retention times.
- (4) Results from GC quantification were used to calculate the conversion of reagents and the selectivity to the main product.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.mex.2021.101406](https://doi.org/10.1016/j.mex.2021.101406).

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