Batch and Flow Green Microwave-Assisted Catalytic Conversion Of Levulinic Acid to Pyrrolidones

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This paper reports a new sustainable protocol for the microwave-assisted catalytic conversion of levulinic acid into *N*-substituted pyrrolidones over tailor-made mono (Pd, Au) or bimetallic (PdAu) catalysts supported on either highly mesoporous silica (HMS) or titania-doped HMS, exploiting the advantages of dielectric heating. MW-assisted reductive aminations of levulinic acid with several amines were first optimized in batch mode under hydrogen pressure (5 bar) in solvent-free conditions. Good-to-excellent yields were recorded at 150 °C in 90 min over the PdTiHMS and PdAuTiHMS, that proved recyclable and almost completely stable after six reaction cycles. Aiming to scale-up this protocol, a MW-assisted flow reactor was used in combination with different green solvents. Cyclopentyl methyl ether (CPME) provided a 99% yield of *N*-(4-methoxyphenyl) pyrrolidin-2-one at 150 °C over PdTiHMS. The described MW-assisted flow synthesis proves to be a safe procedure suitable for further industrial applications, while averting the use of toxic organic solvents.

Introduction

The current drive for transition towards green processes has boosted research, by both academia and industry, into the catalytic conversion of biomass into useful chemicals.[1] In this context, levulinic acid (LA) is generally considered a promising biomass-feedstock-derived platform molecule as it can be converted into several valuable chemicals,[2] including *N*-containing functional compounds and, particularly, 5-methyl-2-pyrrolidones, which are both worthy of note as they are widely used in industry as surfactants, intermediates for pharmaceuticals, dispersants in fuel-additive compositions, solvents and in the manufacturing of agrochemicals etc. (Figure 1).[3]

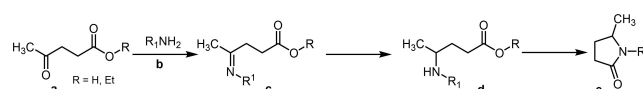Pyrrolidones are mainly synthesized via the reductive amination of LA and its derivatives.[4] Several different heterogeneous catalysts have been tested in recent years,[5] because they are greener and clearly preferred by industry thanks to their easier separation and reuse, integration into existing reactor equipment and waste reduction. The mechanism of
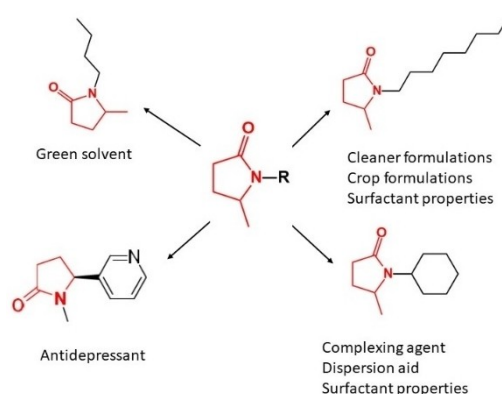
Figure 1. Examples of pyrrolidone derivatives and their industrial applications.

reductive amination in the presence of heterogeneous catalysts has been investigated by Corma et al.,[6] and G. Gao et al..[7] The process involves three steps (Figure 2), starting from the formation of the corresponding imine (**c**) via acid-catalyzed carbonyl-group amination with a primary amine (**b**).

The second step is the metal-catalyzed hydrogenation of the imine to the secondary amine (**d**), followed by acid-catalyzed cyclization with amide-bond formation to form the desired N-substituted-5-methyl-2-pyrrolidones (**e**), with the elimination of either water (levulinic acid) or alcohol (levulinate esters). According to this mechanism, the use of metal nanoparticles on supports with acid properties allows the process to

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Figure 2. Reaction pathway for pyrrolidone synthesis in the presence of heterogeneous catalysis.

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efficiently progress by means of a single catalytic body, with no need for either the addition of soluble acidic co-catalysts, or mechanical mixtures of insoluble acids and supported metals. In this context, Shimizu *et al.* have studied combinations of various metals (Pt, Re, Pd, Rh, Ru, Cu, Ni), support materials (TiO$_2$, Al$_2$O$_3$, ZrO$_2$, SiO$_2$) and co-loaded Lewis-acid metal oxides (V, Cr, Mo, W, Re). Pt and MoOX co-loaded TiO$_2$ showed combined catalytic activity under relatively mild (3 bar H$_2$, 100 °C) and solvent-free conditions.[8] However, long reaction times (20 h) were required. The reductive amination of LA (and its esters) with amines, using metals such as Ni, Pd, Pt, Ru, Rh and Ir supported on either carbon or metal oxides, has also been described in several patents.[9] However, hydrogen pressures of 55–69 bar, reaction temperatures of 150–180 °C and organic solvents, such as dioxane, were required to furnish *N*-alkyl(aryl or cyclohexyl)-5-methyl-2-pyrrolidones.

The common drawbacks to using heterogeneous catalysts in the reductive amination of levulinic acid are the need for high reaction temperatures and H$_2$ pressures, the use of organic solvents, long reaction times and, in some instances, by-product formation. MW irradiation, one of the most effective non-conventional activation methods, is an innovative tool that can overcome these limits. Indeed, substantial decreases in reaction time (hours to minutes) and greater yields make this alternative heating source an attractive green method for chemical syntheses, while it can also offer reaction-parameter tunability, higher selectivity and less chemical waste.[10] In fact, we have recently described a MW-assisted protocol for the reductive amination of aryl aldehydes and ketones in aqueous ammonia over Ni silica eggshell iron-based magnetic nanoparticles.[11]

Other inventive catalysts have been designed to circumvent the limits of catalyst stability and reusability.[12] Luque *et al.* have developed benign-by-design TiO$_2$-based nanocatalysts using orange peel as a sacrificial template and Ru as the supported metal to accomplish the continuous-flow conversion of levulinic acid to 1-ethyl-5-methylpyrrolidin-2-one.[13] Scale-up processes are favored under flow, compared to batch conditions, because of improved heat and mass transfer and the improved control of reaction parameters. Moreover, the use of heterogeneous catalysts in flow mode makes synthesis procedures safer and more environmentally friendly.[14] However, after 50 minutes of reaction in this last case, the catalyst underwent a partial loss of activity and stabilization, leading to a pseudo-stationary state. A graphitic carbon nitride (g-C$_3$N$_4$) functionalized with low platinum loading proved to be more stable (after 3 h reaction) and effective in the continuous flow transformation of levulinic acid to valuable *N*-heterocycles. However, high pressure was applied (50 bars) and acetonitrile was used as the solvent to produce 67.5% 1-ethyl-5-methylpyrrolidin-2-one.[14]

Green solvents, such as γ-valerolactone (GVL)[7,8] and 2-methyltetrahydrofuran (2-MTHF),[15] and solvent-free conditions[16] have sometimes been reported as means to avoid the use of toxic organic solvents.

New and different mono (Pd) and bimetallic (PdAu) catalysts, supported on either highly mesoporous silica (HMS) or titania-doped (10 wt%) HMS (labeled asTi10HMS), have recently been studied in the hydrogenation reaction of LA,

giving total LA conversion and complete selectivity to γ-valerolactone in 1 h of reaction.[17] These catalysts have been tested herein for the efficient MW-assisted conversion of LA into 5-methyl-*N*-substituted pyrrolidones. Batch experiments were performed under solvent-free conditions, while transposition to the flow process entailed the use of cyclopentyl methyl ether (CPME) as a green solvent. A new sustainable MW-assisted protocol for the conversion of a biomass-derived platform chemical into *N*-heterocyclic compounds, both in batch and flow mode, is therefore presented.

Results and Discussion

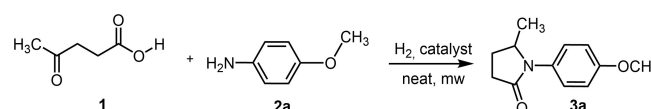### Batch MW-assisted solvent-free reductive amination

As has been demonstrated in the literature, the formation of the imine (**c**) is the rate-determining step, whereas intramolecular cyclisation is so fast that the aminoester intermediate was not detected. The addition of an acidic catalyst may therefore prove to be crucial in enhancing the imine-formation rate. This suggests that bifunctional catalysts can play a key role in the direct conversion of levulinic acid to 5-methylpyrrolidones.[18]

In this context, we synthesized a series of Pd, PdAu and Au nanoparticles that were deposited on mesoporous silica HMS,[19] which was used both pure and doped with 10 wt% Ti. These nanoparticles were characterized (Figures S1–S6) and tested under MW, and their catalytic activity was compared with that of commercial Pd/C.

The reaction parameters were optimized for the reductive amination of levulinic acid (**1**) with 4-methoxyaniline (**2a**) in solvent-free conditions (Figure 3).

The catalytic performance of Pd/C, PdHMS, PdTiHMS and PdAuTiHMS were similar at high metal loadings and hydrogen pressure (Table 1, entries 1, 6, 12), whereas monometallic AuTiHMS exhibited lower activity, only reaching 81% yield, under the same reaction conditions, (Table 1, entry 9). The importance of Pd was even more evident when very low metal loadings were applied at lower hydrogen pressure (5 bar). Indeed, the yield of 1-(4-methoxyphenyl)-5-methylpyrrolidin-2-one dramatically fell when 0.2% AuTiHMS was used as the catalyst, and an increase in reaction time provided no benefit (Table 1, entries 10 and 11).

The activity of PdHMS was also lower under milder reaction conditions (Table 1, entry 4), which suggests that the presence of the titania phase in close contact with the Pd-containing nanoparticles was likely responsible for the improved activity in LA reductive amination. The formation of a Pd$_x$Au$_y$ alloy further promoted the effect of Au and Ti on Pd,[17] resulting in a yield

Figure 3. MW-assisted catalytic reductive amination of LA with 4-methoxyaniline

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Table 1. MW-assisted reductive amination of LA with 4-methoxyaniline[a]

Entry	Catalyst	Metal loading (wt%)	H_2 pressure (bar)	Time (h)	Yield[b] (%)
1	Pd/C	10	20	4	> 99
2	Pd/C	0.2	5	1	90
3	PdHMS	10	20	4	> 99
4	PdHMS	0.2	5	1	75
5	PdHMS	0.2	5	1.5	85
6	PdTiHMS	10	20	4	> 99
7	PdTiHMS	0.2	5	1	82
8	PdTiHMS	0.2	5	1.5	87
9	AuTiHMS	10	20	4	81
10	AuTiHMS	0.2	5	1	6
11	AuTiHMS	0.2	5	1.5	8
12	PdAuTiHMS	10	20	4	> 99
13	PdAuTiHMS	0.2	5	1	92
14	PdAuTiHMS	0.2	5	1.5	88

[a] MW-assisted reaction conditions: LA (0.5 mmol), 4-methoxyaniline (0.5 mmol), neat, 130 °C. [b] Yields as determined by GC-MS.

increase to 92% (Table 1, entry 13) under milder reaction conditions.

The characterization of the PdTiHMS catalyst after the MW-assisted reductive amination reaction under optimized conditions confirmed that the homogeneous distribution of Ti and Pd within the HMS support was also maintained after the reaction (Figure S7a). Furthermore, the metal phase had almost completely avoided agglomeration under reaction conditions, as the average diameter of the nanoparticles was 4.6 ± 1.9 nm (Figure S7b), and the crystalline structure of titania was still maintained (Figure S7c).

Six catalytic cycles were repeated, under the optimized conditions, with the best performing catalysts, PdTiHMS and PdAuTiHMS, in order to evaluate their stability and recyclability (Figure 4).
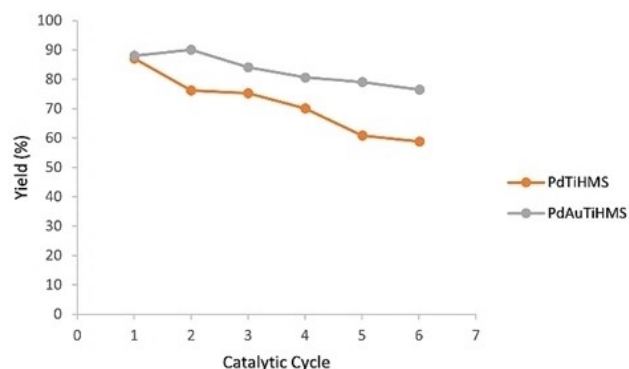
Figure 4. Recycling runs of 1.5 h reaction time with the most active catalysts. Reaction conditions: LA (0.5 mmol), 4-methoxyaniline (0.5 mmol), 130 °C, MW, 5 mg catalyst, H_2 pressure = 5 bar

A slight decrease in activity was observed in both catalysts, although good yields and total selectivity to 1-(4-methoxyphenyl)-5-methylpyrrolidin-2-one were maintained. This decrease can be ascribed to the observed slight Pd-nanoparticle agglomeration.

Indeed, the particle-size distribution appeared much broader after 6 reaction cycles (Figure S8a), resulting in an increased average Pd-nanoparticle diameter of 6.1 ± 3.4 nm, which indicated that some metal agglomeration had occurred.

Nevertheless, the overall morphology of the material was practically unchanged despite the 6 reaction cycles, as the crystalline anatase regions were preserved, which was demonstrated in the HR-TEM characterization (Figure S8b). Moreover, EDS mapping highlighted that Pd and Ti still appeared to be homogeneously distributed on the HMS support despite the observed agglomeration (Figure S8c).

The stability of these catalysts is therefore a promising feature for transposition to flow processes. In addition, the activity of the two catalysts was investigated at 130 °C and 150 °C, under optimized conditions, with the substrate scope being extended to other amines (Table 2). Although PdAuTiHMS was slightly more effective in some cases, the differences in terms of activity between the two catalysts were negligible for almost all substrates. Both electron-rich substituents (entries 1, 3) and electron-poor moieties (entry 6) were tolerated to give high yields with 100% conversions of anilines and LA.

However, the reaction with 2- and 4-aminoacetofenone led to the formation of very low amounts of the desired products **3g** and **3h**, as the acetyl group underwent reduction under the reaction conditions (entries 7 and 8).

The same occurred with other electron-poor anilines with reduction-sensitive groups, such as nitroaniline, and the desired product was not obtained (data not reported). Poor results were also observed in the presence of halogens as the aromatic ring underwent Pd-mediated reductive dehalogenation, which was enhanced by the microwaves and temperature (entries 4 and 5).[20]

Although *p*-anisidine is highly reactive, the reaction was found to be dramatically disfavored when two methoxy groups were present (entry 2), and this is probably because steric hindrance impacts upon imine formation and its subsequent hydrogenation. Indeed, other hindered functional groups also led to lower product yields (entries 10 and 12).
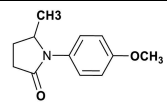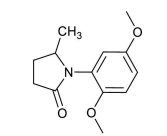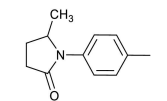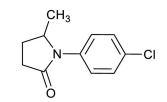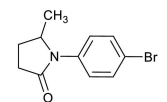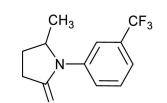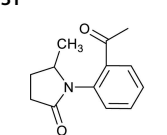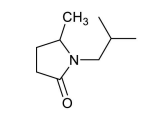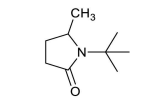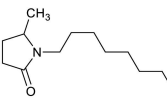
Various aliphatic amines, including branched (entries 9–10) and linear (entry 11) amines, were successfully reacted with LA to form the desired products in good-to-quantitative yields.
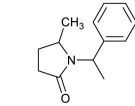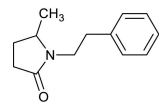
5-methyl-1-octylpyrrolidin-2-one **3k** (entry 11) can be used as industrial solvent, surfactant, complexing agent and additive in functional materials, such as pharmaceuticals, agrochemicals, cleaning compositions and printing ink.[3,9]

Effect of green solvents on MW-assisted reductive amination
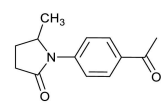
A batch-to-flow transposition should be investigated for further scale-up purposes. However, under these conditions, a solvent becomes necessary, also as a means to overcome the mass-

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Table 2. Substrate scope for MW-assisted reductive amination of LA[a]

Entry	Product	PdTiHMS Yield (%)[b]		PdAuTiHMS Yield (%)[b]	
		130 °C	150 °C	130 °C	150 °C
1	3a	87	86	88	87
2	3b	9	6	8	9
3	3c	94	99	97	99
4	3d	19	31	25	34
5	3e	36	8	27	6
6	3f	97	89	98	89
7	3g	6	5	6	4
8	3h	4	4	6	9
9	3i	70	78	73	80
10	3j	0	17	2	8
11	3k	75	95	81	89

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Table 2. continued

Entry	Product	PdTiHMS Yield (%)[b]		PdAuTiHMS Yield (%)[b]	
		130 °C	150 °C	130 °C	150 °C
12	3l	26	56	32	59
13	3m	65	70	61	75

[a] MW-assisted reaction conditions: LA (0.5 mmol), amine (0.5 mmol), 5 mg catalyst (0.2 % metal loading), 1.5 h, H_2 (5 bar); solvent free; [b] GC yields.

transfer limits that exist when using a heterogeneous catalyst in flow mode. However, the choice of the best solvent can be challenging as it should not only promote substrate conversion, but also not be toxic, inflammable or volatile to make the large-scale process sustainable and safe. The effect of the solvent on substrate conversion has not yet been investigated in detail, although the use of green solvents (e.g. water,[3] GVL,[7,8] MTHF)[21] has been reported. Since the addition of gold did not significantly improve activity, the PdTiHMS catalyst was selected for further experiments.

Several green polar aprotic solvents, GVL, ethyl levulinate (EL) and cyclopentyl methyl ether (CPME), were tested at 130 and 150 °C with different LA concentrations in its reaction with *p*-anisidine. The results were compared with those of traditional polar aprotic solvent; *N,N*-dimethylformamide (DMF) (Table 3).

The worst solvent was DMF (entries 1 and 2), and this was due to the formation of *N*-4-(methoxyphenyl)formamide as the predominant side product. Although the use of DMF as a *N*-formylating agent in combination with other substances, such as hydrochloric acid or oxalyl chloride, has already been described,[22] there are no data on the formylating effect of DMF

alone to the best of our knowledge. Therefore, the presence of formylated *p*-anisidine as a by-product may reveal a potential, innovative MW-assisted application for DMF. The highest yields were achieved using EL and CPME, although GVL also proved to be efficient in promoting the reaction at 150 °C (entry 4).

CPME, however, was the best solvent at higher temperatures, leading to excellent yields at 150 °C and a 0.5 LA concentration (entry 8), meaning that it was chosen for further experiments. CPME is a promising sustainable alternative to volatile organic solvents since it is endowed with valuable properties, such as low peroxide formation rate, stability under basic and acidic conditions and a relatively high boiling point.[23] Furthermore, it is easy to recover and recycle as a solvent; a feature that enables its successful employment as a solvent for the further scale-up of reactions.

Lower reaction times and LA concentrations were tested in batch experiments using CPME as the solvent with a view to optimizing conditions for further MW-assisted flow process experiments (Figure 5).

The results show that, in general, the pyrrolidone yield slightly decreased at lower concentrations. However, this decrease only became significant when the reaction time was reduced to 15 min. It is also worth noting, however, that good

Table 3. Effect of different solvents on substrate conversion[a].

Entry	Solvent	LA concentration (mM)	Yield (%) (3a)[b]	
			130 °C	150 °C
1	DMF	0.25	41	37
2		0.5	32	–
3	GVL	0.25	52	36
4		0.5	51	87
5	EL	0.25	77	75
6		0.5	78	78
7	CPME	0.25	71	69
8		0.5	78	98

[a] MW-assisted reaction conditions: LA (0.5 mmol), *p*-anisidine (0.5 mmol), 5 mg PdTiHMS (0,2 % metal loading, 5.3 mg), 1,5 h, H_2 pressure = 5 bar; [b] GC yields.
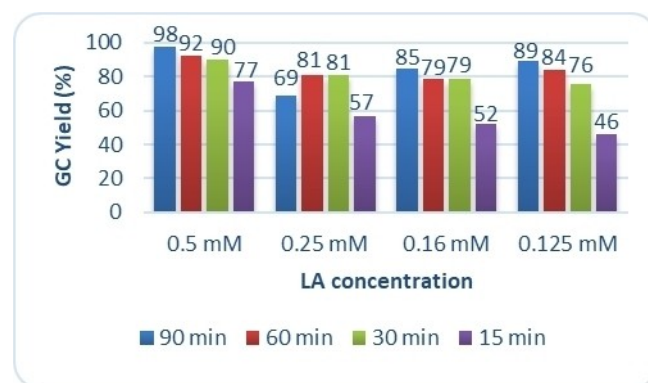

Figure 5. MW-assisted reductive amination of LA with *p*-anisidine using CPME as solvent: optimization of reaction time and LA concentration.

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yields were achieved in shorter reaction times (15 min), but at higher LA concentrations.

Flow MW-assisted reductive amination

The transposition to the flow process was investigated in a multimodal multiphase flow reactor[24] with PdTiHMS as the catalyst and CPME as the solvent under H_2 flow (see Experimental Section). A concentration of 0.25 mM was chosen as the optimized conditions from the batch experiments. A suspension of the heterogeneous catalyst in the LA solution was pumped into the reactor.

In the flow experiments, we decided to test a 45 min reaction time as a good compromise between the tested batch conditions. However, some issues in flow-instrument set-up need to be considered. Indeed, the time spent by the reaction mixture inside the microwave-irradiation chamber is influenced by the time in the dead volume (tubes, feed, etc.).

Therefore, a total reaction time is normally set at twice the time in which the reaction occurs (i.e. 90 min in our case). The reaction was monitored every 15 min. Representative results are reported in Figure 6. Although the product yield was still excellent after a reaction time of 60 min. (97%), it reached its maximum value of 99% at 90 min. Therefore, flow transposition afforded excellent yields in batch experiments, thus paving the way for a sustainable the synthesis of pyrrolidones from LA.

Conclusions

A new, MW-assisted catalytic protocol for the conversion of LA to several N-substituted pyrrolidones has been described. Mono (Pd, Au) and bimetallic (PdAu) catalysts, supported on either HMS or TiHMS, were tested in solvent-free reactions under MW irradiation, showing that the most active catalysts were PdTiHMS and PdAuTiHMS, which gave good-to-excellent yields at 150 °C and in 1.5 h of reaction time. These catalysts were recyclable and almost completely stable after 6 reaction cycles.
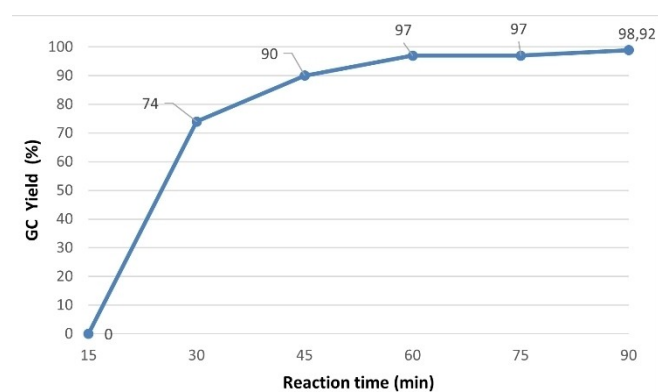
Figure 6. Flow MW-assisted reductive amination of LA with *p*-anisidine using CPME as the solvent. Reaction conditions: flow rate: 30 mL min 1, H_2 flow: 20 mL min^{-1}, H_2 pressure: 5 bar, residence time: 5.5 min, internal temperature: 150 °C.

Indeed, the morphology of the material remained practically unchanged, despite the limited agglomeration of Pd nanoparticles, with Pd and Ti being homogeneously distributed on the HMS support. Moreover, crystalline anatase regions were observed to be in close contact with the Pd nanoparticles. It may be hypothesized that these titania islands are able to stabilize the metal nanoparticles under MW-assisted reaction. A MW-assisted flow reactor was exploited to scale-up the described reductive amination protocol in combination with several green solvents, which were used to enhance the reaction mass transfer of the process previously performed under solvent-free conditions. Although EL gave good product yields, the best results (98%) were achieved using CPME as the solvent. This is a green solvent with low toxicity, a high boiling point and chemical stability under a wide range of conditions.

CPME was therefore used as the solvent for the flow closed-loop MW-assisted reductive aminations of LA with *p*-anisidine, using PdTiHMS as the catalyst, giving 99% pyrrolidone after 90 min. Sustainable processes were therefore optimized both under batch and flow conditions to synthetize N-substituted pyrrolidones. These results pave the way for a greener industrial approach.

Experimental Section

General information

All chemicals and solvents were purchased from commercial suppliers and used without further purification, according to the procedures reported on Safety Data Sheets.

GC-MS analyses were performed on an Agilent Technologies 6850 Network GC System with a 5973 Network Mass Selective Detector and 7683B Automatic Sampler, using a capillary column (HP-5MS; length 30 m; i.d. 0.25 mm; film thickness 0.25 μm) (Agilent Technologies, Santa Clara, CA).

Characterization methods

Diffuse reflectance (DR) UV-Vis-NIR spectra were run at rt on a Varian Cary 5000 spectrophotometer, working in the 50000–4000 cm−1 wavenumber range, with the powders placed in a quartz cell. DR UV-Vis-NIR spectra were collected at room temperature, in air, and the samples were examined without any preliminary activation. Spectra are reported as the Kubelka−Munk function (f(R∞)=(1–R∞)2/2R∞; R∞=reflectance of an "infinitely thick" layer of the sample).

As prepared and used catalysts were characterized by transmission electron microscopy (TEM) and high resolution (HR) TEM measurements. The analyses were carried out on a side entry Jeol JEM 3010 (300 kV) microscope equipped with a LaB6 filament and fitted with X-ray EDS analysis capacity via a Link ISIS 200 detector. The powdered sample was deposited on a Cu grid that was coated with a porous carbon film. Digital micrographs were collected on an Ultrascan 1000 camera and the images were processed using Gatan digital micrograph. The histograms of the sample particle-size distributions were obtained by considering a statistically representative number of particles (at least 150 particles for each sample) in the images, and mean particle diameter (dm) was calculated as $dm = \Sigma d_i n_i / \Sigma n_i$, where n_i is the number of particles of diameter d_i.

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Batch MW-assisted solvent-free reductive amination reactions

Batch MW-assisted reductive aminations were carried out in a multimode reactor, SynthWAVE (Milestone Srl, Italy; MLS GmbH, Germany), with a multiple-gas inlet. This instrument, equipped with a high-pressure stainless-steel reaction chamber, can work up to a maximum temperature of 300 °C and 199 bar. Moreover, integrated reactor sensors continuously monitor internal pressure, temperature and applied power inside the MW cavity during all reaction runs, calibrating the applied MW power in real time to follow a predefined temperature profile.

LA (0.5 mmol), the amine (0.5 mmol) and the catalyst were placed inside a quartz vial equipped with a magnetic stirrer. The required volume of solvent was added for the screening of green solvents. The catalyst/substrate mixture was heated by MW irradiation (600–800 Watt), under H_2 pressure and magnetic stirring (300 rpm), to the required temperature for the selected time.

After cooling, CH_2Cl_2 (1 mL) was added, the crude reaction was filtered, the catalyst was washed 3 times with CH_2Cl_2 (3X2 mL) and then the solvent was evaporated under vacuum. For GC-MS analyses, the crude reaction was dissolved in CH_2Cl_2 (1 mL).

The purification of **3a**, **3c**, **3f**, **3i**, and **3k** was carried out via liquid chromatography on a PuriFlash 5.050-P, interchim, using a Puri-Flash, SepaChrom, Daily plus a standard silica μm column. Petroleum ether (solvent A) and ethyl acetate (solvent B) were used as eluents with the gradient elution method (from 100% A to 100% B). The products were then characterized by 1H-NMR on a Jeol JNM-ECZ600R spectrometer (Jeol, Tokyo, Japan) operating at a frequency of 600 MHz, using $CDCl_3$ as the solvent. Spectra are shown in the supporting information.

Flow MW-assisted reductive amination reactions

MW-assisted flow reactions were carried out using a multiphase flow reactor (FlowSYNTH, Milestone Srl, Bergamo, Italy), which is a multimode system equipped with a vertical PTFETFM flow-through reactor (VR: 20 mL) that can work at up to a maximum of 200 °C temperature and 30 bar pressure, and can operate in open- or closed-loop modes. The equipment was suitably customized for multiphase reactions, as previously reported.[23,24] Instrument setup is reported in Figure 7. The reaction chamber has a volume of 165 mL. The experiments were run in closed-loop mode. LA (8.75 mL) was dissolved into CPME (350 mL), with *p*-anisidine (10.78 g) and PdTiHMS (0.93 g) then being added to the solution. H_2 gas was pumped in from the bottom of the reactor (flow rate: 30 mL/min 1, H_2 flow: 20 mL/min, H_2 pressure: 5 bar, residence time: 5.5 min, internal temperature: 150 °C) and reaction products flowed out of the top into a water-cooled heat exchanger and were recycled into the feed tank (one complete cycle: 11.7 min; calculated as the ratio between volume solution and flow rate).

Aliquots (500 μL) of the solution were extracted from the reaction every 15 min and centrifuged at 26000 rpm for 1 min. The supernatant was diluted with CH_2Cl_2 (900 μL) and analyzed using GC-MS.
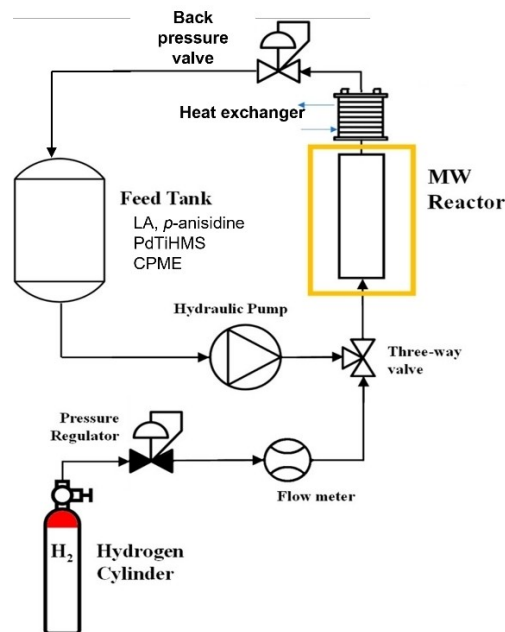
Acknowledgements

Figure 7. Scheme of the MW continuous flow reactor setup for ternary phase catalytic reductive aminations.

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

[1] A. Corma, S. Iborra, A. Vely, *Chem. Rev.* **2007**, *107*, 2411–2502.
[2] E. Calcio Gaudino, G. Cravotto, M. Manzoli, S. Tabasso, *Green Chem.* **2019**, *21*, 1202–1235.
[3] Manzer, L. E. US 6743819B1, 2004.
[4] Z. Xue, D. Yu, X. Zhao, T. Mu, *Green Chem.* **2019**, *21*, 5449–5468.
[5] C. Moreno-Marrodan, F. Liguori, P. Barbaro, *Mol Catal* **2019**, *466*, 60–69.
[6] J. D. Vidal, M. J. Climent, P. Concepción, A. Corma, S. Iborra, M. J. Sabater, *ACS Catal.* **2015**, *5*, 5812–5821.
[7] G. Gao, P. Sun, Y. Li, F. Wang, Z. Zhao, Y. Qin, F. Li, *ACS Catal.* **2017**, *7*, 4927–4935.
[8] A. S. Touchy, S. M. A. H. Siddiki, K. Kon, K. Shimizu, *ACS Catal.* **2014**, *4*, 3045–3050.
[9] L. E. Manzer, US 7129362, 2006.
[10] G. Meera, K. R. Rohit, S. Saranyaa, G. Anilkumar, *RSC Adv.* **2020**, *10*, 36031–36041.
[11] M. Manzoli, E. Calcio Gaudino, G. Cravotto, S. Tabasso, R. B. N. Baig, E. Colacino, R. S. Varma, *ACS Sustainable Chem. Eng.* **2019**, *7*, 5963–5974.
[12] M. V. Bukhtiyarova, G. A. Bukhtiyarova, *Renew. Sust. Energ. Rev.* **2021**, *143*, 110876–110886.
[13] D. Rodríguez-Padrón, A. R. Puente-Santiago, A. M. Balu, A. A. Romero, M. J. Muñoz-Batista, R. Luque, *ACS Sustainable Chem. Eng.* **2018**, *6*, 16637–16644.
[14] N. G. Anderson, *Org. Process Res. Dev.* **2012**, *16*, 852–869.
[15] G. Chieffi, M. Braun, D. Esposito, *ChemSusChem* **2015**, *8*, 3590–3594.

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[16] J. Zhang, B. Xie, L. Wang, X. Yi, C. Wang, G. Wang, Z. Dai, A. Zheng, F. S. Xiao, *ChemCatChem* **2017**, *9*, 2661–2667.

[17] M. L. Testa, L. Corbel-Demailly, V. La Parola, A. M. Venezia, Catherine Pinel, *Catal. Today* **2015**, *257*, 291–296.

[18] P. Barbaro, F. Liguori, C. Moreno-Marrodan, *Green Chem.* **2016**, *18*, 2935–2940.

[19] M. L. Testa, V. La Parola, L. Liotta, A. Venezia, *J. Mol. Catal. A* **2013**, *367*, 69–76.

[20] J. R. Jones, J. S. W. Lockley, S.-Y. Lua, S. P. Thompson, *Tetrahedron Lett.* **2001**, *42*, 331–332.

[21] S. Batuta, M. A. Ali, A. Chatterjee, M. N. Alam, S. Das, D. Mandal, N. A. Begum, *Synth. Commun.* **2016**, *46*, 692–700.

[22] G. de Gonzalo, A. R. Alcantara, P. Dominguez de Maria, *ChemSusChem* **2019**, *12*, 2083–2097.

[23] G. Grillo, M. Manzoli, F. Bucciol, S. Tabasso, T. Tabanelli, F. Cavani, G. Cravotto, *Ind. Eng. Chem. Res.* **2021**, *60*, 16756–16768.

[24] E. Calcio Gaudino, M. Manzoli, D. Carnaroglio, Z. Wu, G. Grillo, L. Rotolo, J. Medlock, W. Bonrath, G. Cravotto, *RSC Adv.* **2018**, *13*, 7029–7039.