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Domino hydrogenation-reductive amination of phenols, a simple process to access substituted cyclohexylamines

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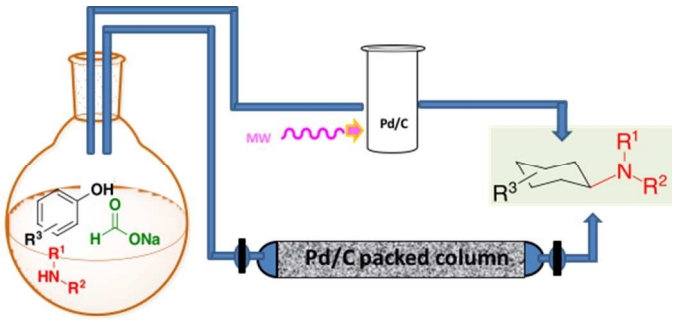
Supporting Information

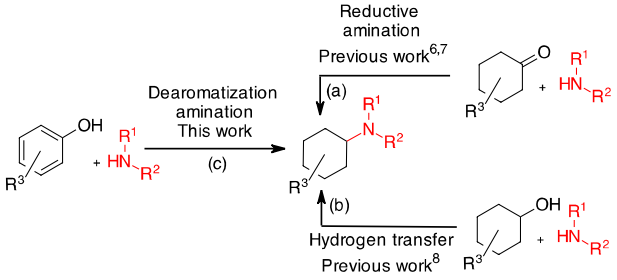


ABSTRACT: Phenols can be efficiently reduced by sodium formate and Pd/C as catalyst in water and in the presence of amines to give the corresponding cyclohexylamines. This reaction works at room temperature for 12 h or at 60 °C under microwave dielectric heating for 20 min. With the exception of aniline, primary, secondary amines, amino alcohols and even amino acids can be used as nucleophiles. The reductive process is based on sustainable hydrogen source and a catalyst that can be efficiently recovered and re-used. The protocol was developed into a continuous-flow production of cyclohexylamines in gram scale achieving very efficient preliminary results (TON 32.7 and TOF 5.45 h^{-1}).

Simplification of organic synthetic processes and development of sustainable protocols are some of the major goals in contemporary synthetic organic chemistry. Amines are very useful compounds as they behave as synthetic tools to prepare pharmaceutically relevant derivatives.[1] In addition many active principle of drugs, agrochemicals and other speciality chemicals feature the amine as functional group.[2] Cyclohexylamines are a relevant part of the amine family including anticonvulsants, kinase inhibitors, anti-diabetics and antiviral compounds.[3]

Reductive amination of carbonyl compounds is one of the most useful methods to prepare substituted amines.[4] Amongst a plethora of synthetic procedures available for reductive amination,[5] one of the milder and most environmentally benign transformation is hydrogenation of the amine-carbonyl compound mixture over an heterogeneous transition metal catalyst.[6] This reaction can be carried out in water or other "green" solvents using gaseous H_2 or other hydrogen sources.[7] A substantial improvement in this transformation is the generation of the carbonyl compound starting from alcohols under conditions compatible with the reductive amination. The red-ox cycle of alcohol oxidation and contemporary reduction of the corresponding imine/iminium salt done by the same catalyst have been largely explored and extensively reviewed.[8] Having a cyclohexylamine as the synthetic target, while reductive amination starts from cyclohexanone (path a in Scheme 1), the hydrogen transfer approach is based on dehydrogenation of cyclohexanol to cyclohexanone and further reduction of the condensation product with the amine (path b in Scheme 1).

Scheme 1. Reductive strategies towards cyclohexylamines.



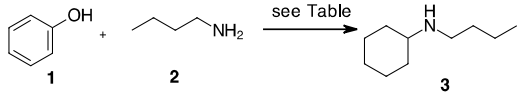
On the other hand, cyclohexanol and cyclohexanone can be obtained in turn by hydrogenation of phenol. This reaction

may occur through a 6 electrons process that directly produces cyclohexanol or a 4 electrons reduction to 1-hydroxycyclohexene that immediately tautomerizes to the corresponding cyclohexanone. Gas phase hydrogenation over a Pd catalyst is one the most effective way to produce cyclohexanone but high temperature and pressure of H_2 are required,[9] while dehydrogenative aromatization of cyclohexanone to arylethers or arylamines is also possible.[10] The use of more complex Pd-based catalysts or reaction media may allow the reaction to occur under milder conditions[11] and recently the use of hydrogen precursors in water has been reported.[12] In addition, under vapour phase conditions (250°-300 °C for 3 h) phenol and ammonia can produce mixtures of aniline, cyclohexylamine, *N*-cyclohexylaniline and *N*,*N*-dicyclohexylamine .[13]

Following our interest in developing sustainable protocols based on heterogeneous catalysis (for heterocycle synthesis and cross coupling reactions)[14,15] we report here the direct transformation of phenols into substituted cyclohexylamines in an efficient domino process carried out under mild and environmentally benign conditions. While this work was in progress, Li and co-workers published a Pd catalysed reductive coupling of phenols with anilines in toluene at 100 °C.[16] We have also proved that the protocol can be used as a trustworthy approach to continuous-flow production. To our experience, the application of flow technology has proven to be an effective tool for the exploitation of heterogeneous catalysis in alternative reaction media, allowing to achieve high environmental efficiency.[17] Although several protocols for the continuous-flow reductive amination of aldehydes, ketones and nitriles have been recently reported,[18] to the best of our knowledge, this is the first example of one-pot hydrogenation of phenol and subsequent amination carried out in batch and/or in continuous flow conditions.

The first exploration of the reaction mode was carried out on phenol and butylamine using Pd/C as catalyst and different hydrogen donor sources. As water is reported to accelerate the hydrogenation of phenol,[11] aqueous HCOONa was firstly explored as reducing agent. We were pleased to obtain acceptable yields of *N*-butyl-cyclohexylamine **3**, although in mixture with some cyclohexanol and unreacted cyclohexanones (Table 1, entry 1). The use of other organic solvents and other organic hydrogen donors gave worse results (Table 1, entry 2), thus we decided to investigate the influence of catalyst and hydrogen source equivalents on the product distribution. Increasing the amount of sodium formate gave better results in terms of conversion and yield of isolated product. Working with 9% mol amount of Pd/C and 20 eq of HCOONa respect to the amount of phenol gave 100% conversion, no cyclohexanol was observed, less than 5% of cyclohexenone was still present in the crude and cyclohexylamine **3** was isolated in 80% yield (Table 1, entry 3). Comparable results were obtained doubling the equivalents of catalyst or sodium formate (Table 1, entries 4 and 5), while a contemporary increase of both components gave no improvements in conversion (data not reported in Table 1). A small increment of the reaction temperature gave a decisive gain of yields. After warming the reaction at 60 °C for 6 h, product **3** was obtained in 96% isolated yield while, when the reaction was submitted to microwave (MW) dielectric heating, the same result, in term of conversion and isolated yield of **3,** was obtained after 20 min (Table 1, entries 6 and 7). The use of MWs permitted also to reduce the amount of Pd/C employed in the reaction up to 5% mol (Table 1, entry 8). This quantity, however, was the lowest possible for a complete conversion, even at higher temperatures, as appears from result reported in Table 1, entries 9 and 10. Also the influence of the nature of Pd/C was studied carrying out the reaction with different types of nanosized Pd/C catalysts. The better and most reproducible results were obtained with the SA and JM1 type catalysts (Table 1, entry 11). Finally, the direct hydrogenation with H_2 gas was also tried under the same reaction conditions employed with HCOONa. A much lower conversion of phenol was observed working at rt after 24 h under 1 atm of H_2 and even under MW dielectric heating at 60° C under 3 atm of H_2 (Table 1, entries 14 and 15).[19] In conclusion of this explorative section, three different protocols are possible for a synthetically useful conversion of phenol into *N*-butylcyclohexylamine: i) 0.09 equiv of Pd at room temperature for 12 h; ii) 0.09 equiv of Pd at 60 °C for 6 h; iii) 0.05 equiv of Pd at 60 °C under MW dielectric heating for 20 min.

Table 1. Reductive amination of phenol. Reaction condition optimisation.



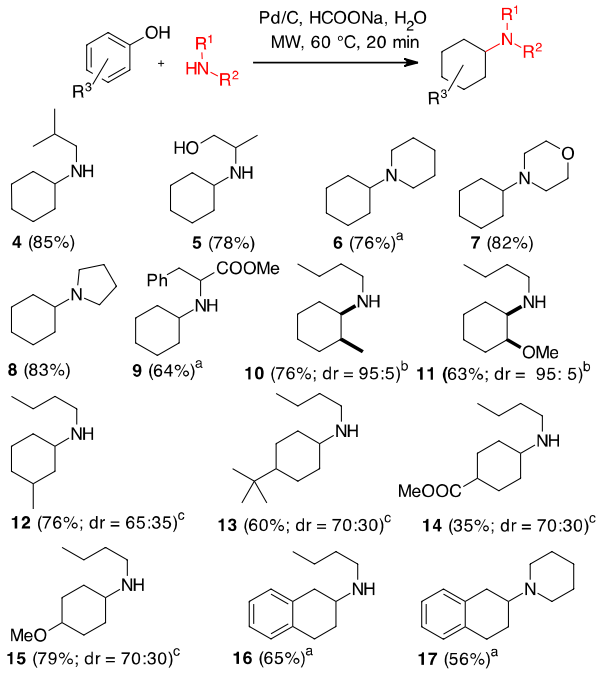
entry	Pd/C equiv	H-donor equiv[a]	conditions	conv.[b] (%)	yield (%)
1	0.09[c]	10	rt, 12 h	63	46[h]
2[d]	0.09[c]	10	rt, 12 h	10	-
3	0.09[c]	20	rt, 12 h	100	80[i]
4	0.18[c]	20	rt, 12 h	100	87[i]
5	0.09[c]	40	rt, 12 h	100	84[i]
6	0.09[c]	20	60 °C, 6 h	100	96[i]
7	0.09[c]	20	60 °C MW, 20 min	100	96[i]
8	0.05[c]	20	60 °C MW, 20 min	100	96[i]
9	0.03[c]	20	60 °C MW, 20 min	86	79[h]
10	0.03[c]	20	100 °C MW, 20 min	82	75[h]
11	0.09[e]	20	rt, 12 h	100	95[i]
12	0.09[f]	20	rt, 12 h	100	80[h]
13	0.09[g]	20	rt, 12 h	85	55[h]
14	0.09[c]	H_2[j]	rt, 24 h	22	-
15	0.09[c]	H_2[k]	60 °C MW, 20 min	20	-

[a] Phenol 1.5 mmol), butylamine (3 mmol) and the catalyst were mixed in 10 mL of H_2O and submitted to the reaction conditions in table. [b] Conversion based on the amount of phenol still present in the crude reaction mixture determined by GC/MS. [c] SA: Pd/C 10% wt loading, matrix activated carbon support (Aldrich); [d] Reaction done in MeOH with cyclohexene as H donor; [e]JM1: Pd 10% wt on activated carbon paste type 487, moisture 55% (Johnson Matthey); [f] JM2: Pd 10% wt on activated carbon paste type 87L, moisture 56% (Johnson Matthey); [g] JM3 Pd 10% wt on activated carbon paste type 434, moisture 53% (Johnson Matthey); [h] GC yield calcd on benzyl alcohol as internal standard (see SI); [i] Isolated yield; [j] 1 atm; [k] 3 atm.

Selecting the third protocol as the most effective procedure, the substrate scope was investigated (Scheme 2, Pd source SA or JM1). Other primary amines different from butylamine were also effective in this transformation (see compounds **4** and **5** in Scheme 2). Secondary amines reacted also

very well giving good yields of the phenol reductive amination products **6-8.** A potential limitation was observed when the lipophilicity of reagents and products increased and a complete solubility in water was no more possible. In these cases, addition of MeOH to the solution (up to 30 % v/v respect to the water) allowed the reaction to proceed successfully. This approach was employed to obtain compounds **6** and **9,** where (*L*)-phenylalanine methyl ester works as the nucleophile. The reaction could be carried out also on substituted phenols giving access to substituted cyclohexylamines (compounds **10-14** in Scheme 2). In general, electrondonating substituents on the aromatic rings were found to promote the reaction, while the presence of electronwithdrawing substituents gave a consistent decrement of the yields as observed, when methyl *p*-hydroxybenzoate was submitted to our reaction conditions. Indeed, amine **14** was formed in low yield and most of the starting material (recoverable) remained unchanged even after longer reaction time. With substituted phenols the stereoselectivity of the reaction was analogue to that observed in the reductive amination of substituted cyclohexanones with H_2, as verified when compounds **10**, **12**, **13** and **14** were prepared starting from the corresponding substituted cyclohexanones.[20]

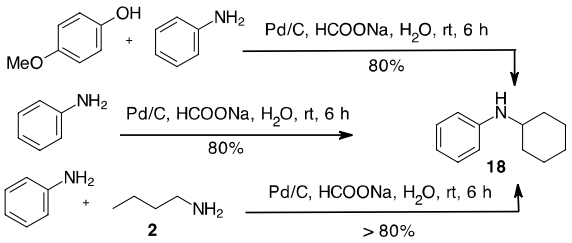
Scheme 2. Substrate scope of reductive amination under MW dielectric heating.



[a] reaction done in MeOH/H_2O 30:70 v/v; [b] *cis/trans* ratio determined by GC/MS analysis; [c] *trans/cis* ratio determined by GC/MS analysis. [d] 78% yield based on the recovered starting material.

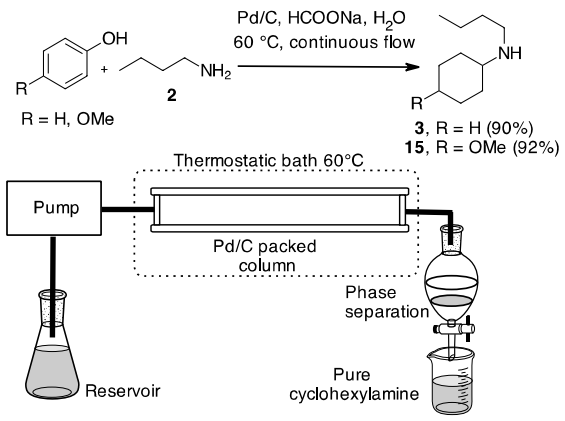
The reaction could be successfully carried out also on β-naphtol that gave the corresponding *N*-substituted -1,2,3,4-tetrahydronaphth-2-ylamines **16** and **17** in acceptable yields. When aniline was used as the nucleophile, the major product of the reaction was *N*-cyclohexylaniline **18** (Scheme 3) independently from the nature of the starting phenol. Under our reaction conditions, aniline was more reactive than phenol, producing the intermediate cyclohexanone that immediately bound the unreacted aniline to give compound **18** that is not further reduced on the aromatic ring. Compound **18** was also formed reacting aniline alone with Pd/C and HCOONa in H_2O or when aniline was used, in the place of phenol, in the presence of the more nucleophilic butylamine **2** (Scheme 3). The possibility of recycling the Pd/C catalyst in batch was investigated on the reaction between phenol and piperidine as a model. The separation of the catalyst was carried out by filtration of the crude reaction mixture and the Pd catalyst was washed with water and used directly in the next run. The recycling experiments showed that at least five consecutive reactions could be run without noticeable decrease in activity. The use of the recycled Pd/C in other catalytic processes was also investigated. Hydrogenation of 1-pentenoic acid (H_2 gas, 1 atm in MeOH/$H_2$0 1:1, rt, 12 h) and alkylation of *p*-nitrotoluene (H_2 gas, 1 atm, MeOH, rt, 24 h) with acetonitrile occurred without differences in terms of yields and purities using both recycled and fresh Pd/C.[15a]

Scheme 3. Reaction with aniline



The Pd catalysed reductive amination of phenols with HCOONa in the presence of amine provides a mild sustainable access to cyclohexylamines. The availability of reductive protocols based on sustainable hydrogen source is timely and highly desirable. At this concern, effective dehydrogenation of formic acid to hydrogen and CO_2 could contribute particularly strongly to the development of a low-carbon economy, where formic acid offers a versatile entry into the chemical supply chain.[21] Formic acid and derivatives are in fact major products of biomass processing, and they have already been identified as a potential H_2 storage material due to the high gravimetric energy density, nontoxicity, and capability of being safely handled in aqueous solutions. Given this contests and the observation that the process has a soft impact on the catalyst efficiency, we decided to focus on the definition of a continuous flow protocol. The Pd/C catalyst (SA in table 1) was packed in two glass columns, while the mixture of phenol **1**, butylamine **2** and sodium formate in water was prepared in a flask, acting as reservoir connected to a HPLC pump. The catalyst columns were placed in a thermostated chamber and heated at 60 °C while the reactant mixture was continuously pumped at a flow rate of 0.4 mL min^{-1}. Initially, the mixture streaming from the catalyst column was collected cyclically into the reservoir for 30 min, to reach a homogenous filling of the solid-containing columns. After reaching a stationary state, the conversion of **1** to **3** reached 98% and the reacted mixture was continuously collected while periodically monitored by GLC. The resulting aqueous mixture was extracted with ethyl acetate and the combined organic layers were subsequently washed with NaOH 5% solution to remove unreacted phenol (Scheme 4).

Scheme 4. Synthesis of 3 under continuous flow conditions



During 6 hours of operation, 1.88 g of **1** were reacted, with a 90% isolated yield of the amine **3**. It should be noted that under continuous flow conditions, only 1.1 mmol of Pd were required to convert 40 mmol of phenol, corresponding to a ratio of 2.7 mol %, which represent a further improvement with respect to our best batch conditions (5 mol % under MW heating). With the flow protocol we were able to achieve TON and TOF values of 32.7 and 5.45 h^{-1} respectively. The flow procedure was extended to the reaction between 4-methoxyphenol and butylamine, to prepare amine **7**, obtaining comparable results in terms of yield (Scheme 4).

In conclusion, we have developed an efficient procedure for the reductive amination of phenols in water under mild sustainable conditions. The reaction proceeds with commercially available Pd/C and the heterogeneous catalyst can be recycled several times. The process proved to be robust enough to be applied to a continuous flow procedure that allowed to obtain substituted cyclohexylamine on a larger scale, with reduced catalyst amount. Extension of the method to biologically relevant substrates is currently underway in our laboratories.

ASSOCIATED CONTENT

Supporting Information

Characterization data and copies of the ^{1}H and ^{13}C NMR spectra for all compounds are available free of charge via the Internet at http://pubs.acs.org.

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REFERENCES

1) (a) Chiral Amine Synthesis: Methods, Developments and Applications. Nugent, T. C. Ed.; Wiley-VCH: Weinheim, 2010. (b) Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Kesseler, M.; Stürmer, R.; Zelinski, T. *Angew. Chem., Int. Ed*. **2004**, *43*, 788. (c) Bradshaw, J. S.; Krakowisk, K. E.; Izatt, R. H. *Tetrahedron* **1992**, 48, 4475-4676.

2) (a) Salvatore, R. N.; Yoon, C. H.; Jung, K. W. *Tetrahedron* **2001**, *57*, 7785. (b) Roughley, S. D.; Jordan, A. M. *J. Med. Chem*. **2011**, *54*, 3451–3479.

3) (a) Malik, S.; Ahuja, P.; Sahu, K.; Khan, S. A. Eur. *J. Med. Chem*. **2014**, *84*, 42–50. (b) Chen, T.; Takrouri, K.; Hee-Hwang, S.; Rana, S.; Yefidoff-Freedman, R.; Halperin, J.; Natarajan, A.; Morisseau, C.; Hammock, B.; Chorev, M.; Aktas, B. H. *J. Med. Chem*. **2013**, *56,* 9457–9470. (c) Du, Y.; Ye, H.; Guo, F.; Wang, L.; Gill, T.; Khan, N.; Cuconati, A.; Guo, J.-T.; Block, T. M.; Chang, J.; Xu, X. *Bioorg. Med. Chem. Lett*. **2013**, *23*, 4258–4262.

4) (a) Baxter, A. E. W.; Reitz, A. B. *Org. React*. **2001**, *59*, 1-714. (b) Lane, C. F. *Synthesis* **1975**, 135-146. (c) Emerson, W. S. *Org. React*. **1948**, *4*, 174-255.

5) Larock, R. C. Comprehensive Organic Transformations, A Guide to Functional Group Preparations, Wiley, 2010.

6) (a) Xu, L.; Wu, X.; Xiao, J. Stereoselective reduction of imino groups, in Science of Synthesis, Stereoselective Synthesis, De Vries, J. G.; Molander, G. A.; Evans, P. A. Eds., Thieme 2011, 2, 251-309. (b) lonso, F. Riente, P.; Yus, M. *Acc. Chem. Res*. **2011**, *44*, 379-391. (c) Tararov, V. I.; Boerner, A. *Synlett* **2005**, 203-211.

7) (a) Nait A. A. *Catal. Today* **2015**, *247*, 177-181. (b) He, R.; Toy, P. H.; Lam, Y. *Adv. Synth. Catal*. **2008**, *350*, 54-60. (c) Pham P. D.; Bertus P.; Legoupy S. *Chem. Commun*. **2009**, 6207-9. (d) Reddy, P. S.; Kanjilal, S.; Sunitha, S.; Prasad, R. B. N. *Tetrahedron Lett*. **2007**, *48*, 8807-8810. (e) Byun, E.; Hong, B.; De Castro, K. A. Lim, M.; Rhee, H. *J. Org. Chem*. **2007,** *72*, 9815-9817. f) V. Berdini, M. C. Cesta, R. Curti, G. D'Anniballe, N. Di Bello, G. Nano, L. Nicolini, A. Topai, M. Allegretti *Tetrahedron* **2002**, 58, 5669-5674. (g) Singh, S.; Sharma, V. K.; Gill, S.; Sahota, R. I. K. *J. Chem. Soc. Perkin Trans 1*. **1985**, *3*, 437-40.

8) (a) Gunanathan, A.; Milstein, D. *Science* **2013**, *341*, 1229712. (b) Bähn, S.; Imm, S.; Neubert, L.; Zhang, M.; Neumann, H.; Beller, M. *ChemCatChem* **2011**, *3*, 1853–1864. (c) Alonso, F.; Riente, P.; Yus, M. *Acc. Chem. Res*. **2011**, *44*, 379–391. (d) Guillena, G.; Ramón, D. J.; Yus, M. *Chem. Rev*. **2010**, *110*, 1611–1641. (e) Guillena, G.; Ramón, D.J.; Yus M. *Angew. Chem. Int. Ed.* **2007**, *46*, 2358–2364. (f) Hamid, M. H. S. A.; Slatford, P. A.; Williams, J. M. J. *Adv. Synth. Catal*. **2007**, *349*, 1555–1575.

9) a) Sikhwivhilu, M.; Coville, N. J.; Naresh, D.; Chary, K. V. R.; Vishwana V. *Appl. Catal. A* **2007**, *324*, 52–61. (b) Claus, P.; Berndt, H.; Mohr, C.; Radnik, J.; Shin, E. J.; Keane, M. A. *J. Catal*. **2000**, *192*, 88 – 97.

10) (a) Izawa, Y.; Pun, D.; Stahl, S. S. *Science* **2011**, *333*, 209–213. (b) Simon, M.-O.; Girard, S. A.; Li, C.-J. *Angew. Chem. Int. Ed. Engl*. **2012**, *51*, 7537–7540. (c) Girard, S. A.; Hu, X.; Knauber, T.; Zhou, F.; Simon, M.-O.; Deng, G.-J.; Li, C.-J. *Org. Lett*. **2012**, *14,* 5606–5609. (d) Hajra, A.; Wei, Y.; Yoshikai, N. *Org. Lett*. **2012**, *14*, 5488–5491

11) (a) Chang, J.; Danuthai, T.; Dewiyanti, S.; Wang, C.; Borgna, A. *ChemCatChem* **2013**, 5, 3041–3049. (b) Yoshida, H.; Narisawa, S.; Fujita, S. I.; Arai, M. *J. Mol. Catal. A Chem*. **2013**, *379*, 80–85. (c) Li, Z.; Liu, J.; Xia, C.; Li, F. *ACS Catal*. **2013**, *3*, 2440–2448.

12) (a) Chen, A.; Li, J.; Chen, J.; Zhao, G.; Ma, L.; Yu Y. *ChemPlusChem* **2103**, *78*, 1370-1378. (b) Cheng, H.; Liu, R.; Wang, Q.; Wu, C.; Yu. Y.; Zhao F. *New J. Chem*., **2012**, *36*, 1085–1090.

13) H. Hamada, M. Yamamoto, Y. Kuwahara, T. Matzsuzuki, K. Wakabayashi *Bull. Chem. Soc. Japn*. **1985**, *58*, 1551-1555.

14) (a) Taddei, M.; Mura, M. G.; Rajamäki, S.; De Luca, L.; Porcheddu, A. *Adv. Synth. Catal*. **2013**, *355,* 3002–3013. (b) Linciano, P.; Pizzetti, M.; Porcheddu, A.; Taddei, M. *Synlett* **2013**, *24*, 2249–2254. (c) Pizzetti, M.; De Luca, E.; Petricci, E.; Porcheddu, A.; Taddei, M. *Adv. Synth. Catal*. **2012**, *354*, 2453–2464.

15) (a) Ballerini, E.; Curini, M.; Gelman, D.; Lanari, D.; Piermatti, O.; Pizzo, F.; Santoro, S.; Vaccaro, L. *ACS Sustain. Chem. Eng*. **2015**, *3*, 1221–1226. (b) Petrucci, C.; Cappelletti, M.; Piermatti, O.; Nocchetti, M.; Pica, M.; Pizzo, F.; Vaccaro, L. *J. Mol.*

Catal. A Chem. **2015**, *401*, 27–34. (c) Petrucci, C.; Strappaveccia, G.; Giacalone, F.; Gruttadauria, M.; Pizzo, F.; Vaccaro, L. *ACS Sustain. Chem. Eng.* **2014**, *2*, 2813–2819.

16) Chen, Z.; Zeng, H.; Gong, H.; Wang, H.; Li, C.-J. *Chem. Sci.* **2015**, *6*, 4174–4178.

17) (a) Vaccaro, L.; Marrocchi, A.; Lanari, D.; Strappaveccia, G. *Green Chem*. **2014**, *16*, 3680−3704. (b) E. Ballerini, P. Crotti, I. Frau, D. Lanari, F. Pizzo, L. Vaccaro *Green Chem*. **2013**, *15*, 2394-2400. (c) Pavia, C.; Ballerini, E.; Bivona, L. A.; Giacalone, F.; Aprile, C. *Adv. Synth. Catal*. **2013**, *355*, 2007−2018.

18) (a) Gilmore, K.; Vukelić, S.; McQuade, D. T.; Koksch, B.; Seeberger P. H. *Org. Process Res. Dev*. **2014**, *18*, 1771−1776. (b) Hizartzidis, L.; Tarleton, M.; Gordon, C. P.; McCluskey A.; *RSC Adv.* **2014**, *4*, 9709-9722. (c) Sharma, S. K.; Lynch, J.; Sobolewska, A. M.; Plucinski, P.; Watson, R. J.; Williams J. M. J. *Catal. Sci. Technol,* **2013**, *3*, 85-88. (d) Liu, J.; Fitzgerald, A. E.; Mani N. S. *Synthesis* **2012**, *44*, 2469-2473. (e) Soloshonok, V. A.; Catt, H. T.; Ono T. *J. Fluor. Chem*. **2010**, *131*, 261–265.

19) This last experiment was carried out using the gas addition kit available with Discover MW ovens.

20) (a) Szabados, E.; Győrffy, N.; Tungler, A.; Balla, J.; Könczöl, L. *React. Kinet. Mech. Catal.* **2013**, *111*, 107–114. (b) McIntosh, A. I.; Watson, D. J.; Burton, J. W.; Lambert, R. M. *J. Am. Chem. Soc.* **2006**, *128*, 7329–7334. (c) Johansson, A M.; Nilsson, J. L.; Karlén, A.; Hacksell, U.; Svensson, K.; Carlsson, A.; Kenne, L.; Sundell, S. *J. Med. Chem*. **1987,** *30*, 1135–1144.

21) (a) Boddien, A.; Gaertner, F.; Mellmann, D.; Sponholz, P.; Junge, H.; Laurenczy, G.; Beller, M., *Chimia* **2011**, *65*, 214-218. (b) Sponholz, P.; Mellmann, D.; Junge, H.; Beller, M., *ChemSusChem* **2013**, *6*, 1172-1176. (c) Wang, W.-H.; Himeda, Y.; Muckerman, J. T.; Fujita, E., *Adv. Inorg. Chem.* **2014**, *66*, 189-222