# Green Chemistry

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# ROYAL SOCIETY OF CHEMISTRY

## Journal Name

### ARTICLE

Received 00th January 20xx, Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

New insights into the catalytic reduction of aliphatic nitro compounds with hypophosphites under an ultrasonic irradiation

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This work describes an efficient process for the reduction of nitro compounds to the corresponding amines with a catalytic amount of Pd/C (0.6%mol), a mixture of sodium hypophosphite and hypophosphorous acid as a reducing agent in  $H_2O/2$ -MeTHF at 60°C. The reaction was optimized under silent conditions. The conditions for the *in-situ* production of  $H_2$  using the mixture NaH\_2PO\_2/H\_3PO\_2 were studied. The influence of ultrasonic activation was investigated both in terms of efficiency and kinetics. The reaction was shown to be efficient in water, at 70°C with a quantitative conversion and a maximal yield in only 15 min. thanks to the ultrasonic activation. Finally, ultrasound was proved to act as a physical agent of phase transfer.

#### Introduction

The amine function is fundamental by its presence in natural products, fine chemicals, dyes and drugs such as, benzodiazepines, β-carbolines or phenethylamine derivatives. Its classical preparation relies on the reduction of a wide variety of nitro precursors via several synthetic methods, leading to the corresponding amines. Among them, heterogeneous or homogeneous hydrogenation catalyzed by metals<sup>1</sup> such as Pd/C, Pt/C, Raney-Ni, PtO<sub>2</sub>, RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub> is still the most important method used in petrochemical and pharmaceutical industries. However, these protocols are often associated with a lack of chemoselectivity in the presence of other reducible functions. In addition, the reaction is very exothermic, and special equipment, pressurized hydrogen and flammable solvents are required, involving particular precautions in terms of safety.<sup>2</sup> Transfer hydrogenation processes do not require pressurized hydrogen but present some drawbacks as well. The Bechamp reduction process is the oldest commercial process for the preparation of amines.<sup>3</sup> It is performed<sup>4</sup> under acidic conditions, which are incompatible with certain functional groups, in the presence of a large excess of metal, generating water-soluble metal salts as waste. Sodium borohydride (NaBH<sub>4</sub>) or lithium aluminium hydride (LiAlH<sub>4</sub>), as a hydrogen source, in combination with transition metals<sup>5</sup> leads to some boron or aluminium and lithium salts but is very efficient for the conversion of nitro to amines. Other hydrogen donors such as formic acid and its derivatives,<sup>6</sup> or hydrosilanes and hydrosiloxanes<sup>7</sup> have been used. Unfortunately, most of them have a limited scope and can only reduce aromatic nitro compounds into their corresponding amines.<sup>7b</sup> Thus, in the context of Green Chemistry, the development of an efficient, eco-friendly, economical and safe general method for the nitro-to-amine conversion is still a major issue.

Although it has hitherto been less used, sodium hypophosphite seems particularly interesting since its registration in 2010 by REACH as a non-hazardous substance for human beings and for the environment.<sup>8</sup> Indeed, hypophosphorous acid and its salts are wellknown, mild, economical, and powerful reducing agents that are widely used for the electroless deposition of metal.<sup>9</sup> They have demonstrated their ability to reduce a large number of functional groups,<sup>10</sup> with a good chemoselectivity depending on the nature of the associated metallic catalyst.<sup>11</sup> These reductive systems have been shown to be effective for the hydrogenolysis of certain functional groups through *in-situ*  $H_2$  production.<sup>12</sup> Thus, they have been used to reduce alkynes to alkenes,<sup>13</sup> alkenes to alkanes,<sup>14,15</sup> azides to amines,<sup>15</sup> epoxides to alcohols,<sup>15</sup> nitriles to aldehydes,<sup>16</sup> ketones and aldehydes to alcohols,<sup>17</sup> carboxylic acids to aldehydes,<sup>18</sup> aryl or alkyl halides to arenes or alkanes,<sup>15,19</sup> diazonium salts to arenes,<sup>20</sup> nitroolefins to ketones,<sup>21</sup> oximes to carbonyls,<sup>17</sup> aryl ethers to arenes.<sup>22</sup> They have also shown abilities to deprotect benzyl ethers,<sup>14,23</sup> benzyl carbonates<sup>14</sup> and *N*-benzyl derivatives<sup>24</sup> and to achieve reductive desulfurization.<sup>25</sup>

In 1910, Mailhe and Murat proposed the first procedure for the reduction of nitro compounds to amines with hypophosphites.<sup>26</sup> Later, a few examples were published.<sup>27,28</sup> However, in many cases, the reactions were specific to peculiar substrates and no general

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<sup>†</sup> Electronic Supplementary Information (ESI) available. See DOI: 10.1039/x0xx00000x

DOI: 10.1039/C7GC01622K

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process was described. Moreover, some examples were confined to nitroarenes that are easier to reduce.  $^{\rm 28}$ 

Thus, we aimed to establish a general method to reduce both aliphatic and nitroarenes compounds respectively to amine and aniline derivatives with sodium hypophosphite under acceptable risk conditions, with respect to the safety of man and environment protection. Indeed, contrary to the procedures of reduction of nitro aromatic derivatives into anilines reported by Parfenov and Smirnov in 1992<sup>29</sup> and by Meshram in 2000,<sup>30</sup> and requiring an overstoechiometric amount of metallic catalyst, a methodology using catalytic quantity would be of great interest.

Power ultrasound assisted reactions proceed through the formation, the growth and the quasi-adiabatic collapse of transient cavitation bubbles. The consequences of this phenomenon are extreme conditions of transient high temperature (up to 5000K) and high pressure (up to 1000 atm) within the collapsing bubbles, the formation of radicals (e.g. in water hydrogen and hydroxyle ones) and shock wave generation, which lead to radical reactions but also generate some interesting physical effects.<sup>31</sup> Thus, the enhancement of catalyst activity under low frequency ultrasonic irradiation (e.g. f = 20 kHz) is assumed to be due to an improvement of mass transfer between the liquid and the catalyst surface, the reduction of particle size, an increase in specific surface and also to an acceleration of suspended particle motion induced by shock waves and microstreaming.<sup>32</sup>

In a previous paper<sup>33</sup> a process was proposed for the reduction of aliphatic and aromatic nitro groups to amines/anilines in a mixture H<sub>2</sub>O / 2-MeTHF under ultrasonic activation, using the hypophosphite reductive system catalyzed by Pd/C. Sonication was shown to have a significant importance, however, its role was not elucidated.

The present study aims to elucidate the peculiar role of ultrasonic irradiation and to give important information on the reducing system in order to control and to judiciously exploit their combination. Then, we report the screening of the influencing parameters of the reduction of  $\beta$ -nitroethylbenzene, chosen as a model substrate, with NaH<sub>2</sub>PO<sub>2</sub>/H<sub>3</sub>PO<sub>2</sub> and Pd/C as catalyst. After optimization, the best conditions were applied under ultrasonic activation, in order to determine the predominant effects of sonication on our benchmark reaction, which scope was then extended to the reduction of other nitroalkanes.

#### **Results and discussion**

2-Nitroethylbenzene, our model substrate, and was synthesized in two steps. Based on a protocol published in the literature<sup>33</sup>, nitrostyrene was first prepared by Henry reaction between benzaldehyde and nitromethane with an excellent yield of 80%.<sup>34</sup> A subsequent chemoselective reduction of the olefin was performed in the presence of sodium borohydride providing isolated  $\beta$ -nitroethylbenzene that was isolated in 52% yield (Scheme 1).

The reduction of  $\beta$ -nitroethylbenzene to phenylethylamine in the presence of sodium hypophosphite and/or hypophosphorous acid was then carried out as the model reaction (Scheme 1).



 $\label{eq:scheme1} \begin{array}{l} \mbox{Scheme 1} \mbox{Synthesis of the $\beta$-nitroethylbenzene, as a model, and subsequent} \\ \mbox{reduction} \end{array}$ 

The influence of the solvent nature was evaluated by the comparison of two solvent systems: water or a combination of two non-miscible solvents,  $H_2O$  / 2-MeTHF, in order to prevent the solubility problems of the nitro compound while facilitating the isolation and purification processes (Table 1). Indeed, 2-methyltetrahydrofuran is a non hydrosoluble solvent derived from renewable sources, sugar cane.

The model reaction was then carried out with NaH<sub>2</sub>PO<sub>2</sub>/ H<sub>3</sub>PO<sub>2</sub> in two different proportions: 2 eq /1 eq and 3 eq /1 eq respectively, in the presence of 0.6 mol% of Pd/C (5%, 50% water) at 60°C for 16 h. In both cases, the addition of the organic solvent had a slight positive effect. Indeed, when the substrate was stirred in H<sub>2</sub>O at 60°C, a complete conversion was observed but the yield (70-72%) (Table 1, entries 1-3) was lower than in H<sub>2</sub>O/2-MeTHF (1/1, v/v) (78-80%) (Table1, entries 2-4).

In water, with two different amounts and ratio of reducing reductive system NaH<sub>2</sub>PO<sub>2</sub>/H<sub>3</sub>PO<sub>2</sub> (2 eq /1 eq and 3 eq /1 eq), no significant improvement on the isolated yield was observed, respectively 70 and 72% (Table 1, entries 1 and 2). A second run of experiment was carried out with additional organic solvent 2-methyltetrahydrofuran to enhance the solubility of the  $\beta$ -nitroethylbenzene. The comparison showed that the addition of the organic solvent had a slight positive effect with a significant increase of the yield to 78-80% (Table1, entries 3 and 4).

After a brief study on the ratio of  $NaH_2PO_2$  /  $H_3PO_2$  in different solvents (Table1), the optimal conditions were conscientiously evaluated (Table 2).

Table 1 Influence of solvent as a function of $NaH_2PO_2/H_3PO_2$ ratio.				
Entry	NaH <sub>2</sub> PO <sub>2</sub> (eq)	H₃PO₂ (eq)	Solvent	Yield <sup>ª</sup> (%)
1	2	1	H <sub>2</sub> O	70
2	3	1	H <sub>2</sub> O	72
3	2	1	H₂O/2-MeTHF (2/1 (v/v))	78
4	3	1	H <sub>2</sub> O/2-MeTHF (2/1 (v/v))	80

The reaction mixture was stirred at  $60^{\circ}$ C with 0.6 mol% Pd/C (5%, 50% water) for 16h.<sup>a</sup> The yields were determined by GC/MS with benzylamine as internal standard after derivatization with BSTFA.

Entry	$NaH_2PO_2$ (eq)	H₃PO₂ (eq)	n-P (eq)	$\mathbf{pH}_{cal}$	Yield <sup>a</sup> (%)
1	0	1	1	1.15	27
2	1	0	1	7.83	27
3	0	2	2	1.00	71
4	1	1	2	1.98	80
5	2	0	2	7.98	73
6	2	1	3	2.28	78
7	3	1	4	2.46	80
8	4	1	5	2.58	90
9	5	0	5	8.18	84
10	0	5	5	0.80	82

The reaction mixture was performed at 60°C for 16h with 0.6 mol% Pd/C (5%, 50% water), H<sub>2</sub>O / 2-MeTHF (2/1, v/v) <sup>a</sup>The yields were determined by GC/MS with benzylamine as internal standard after derivatization with BSTFA.

The reduction mechanism by hypophosphite possibly involves two reactions, i.e., hypophosphite ions are catalytically oxidized and water is reduced. A part of the released hydrogen is adsorbed onto the catalytic surface, which reduces the nitro-compound.

With only one equivalent of hypophosphorous acid (Table 2, entry 1) or one equivalent of sodium hypophosphite (Table 2, entry 2), the reduction started but the conversion was not complete and the yields were low, estimated at around 27% by GC/MS analysis, detecting the starting nitro substrate as the major compound. The conversion was complete by the use of 2 equivalents of hypophosphites (acid or salt) but the yield was maximal with the reducing system sodium hypophosphite / hypophosphorous acid (4eq/1eq) (Table 2, entry 8).

On Eh-pH diagram of phosphorous<sup>35</sup>, the position of predominance domain of hypophosphorous acid and hypophosphites, indicates that these compounds are strong reducing agents. thermodynamically instable in the presence of aqueous solutions whatever their pH. Theoretically, they should decompose water with hydrogen gas production, whereas they are transformed in phosphorous acid,  $H_3PO_3$ , or phosphites,  $H_2PO_3^{-1}$  and  $H_2PO_3^{-2}$ , depending on pH. In fact, this reductive action on water is infinitely slow. In aqueous solution, hypophosphorous acid and hypophosphites are almost stable in the absence of oxidant and their reductive character is usually little marked. However, in the presence of catalysts such as Pd, their reductive character fully reveals itself ((Eq. 1) and (Eq. 1)

$$\begin{split} H_2PO_2^- + H_2O &\xrightarrow{Pd/C} H_2PO_3^- + H_2 \ (\text{Eq. 1}) \\ H_2PO_2 + H_2O &\xrightarrow{Pd/C} H_2PO_3 + H_2 \ (\text{Eq. 2}) \\ H_2PO_2^-/H_2PO_3^- & E_0 = -0,504 - 0,0591pH \ (\text{Eq. 3}) \\ H_3PO_2/H_3PO_3 & E_0 = -0,499 - 0,0591pH \ (\text{Eq. 4}) \end{split}$$

From the equations of the Eh-pH diagram ( (Eq. 3 and (Eq. 4)) and its calculation, the pH has a low influence both on the  $E_0$  of the two couples and on the yields in amines. Only the latter seems however

closely correlated with the number of phosphorous, n-P, present in the reaction mixture (Table **2**). For a same total number of P (Table2, entries 3, 4, 5 and 8, 9, 10), the best yield was obtained when both NaH<sub>2</sub>PO<sub>2</sub> and H<sub>3</sub>PO<sub>2</sub> are present in the reaction mixture. On one hand, introduction of the hypophosphite salts in the biphasic system may help the transfer of the organics from one phase to the other via salting in effect<sup>36</sup>. On the other hand, protonation of the amine leads to an increase of the E<sub>0</sub> of the corresponding oxido-reductive couple<sup>37</sup>, making the nitro function more easily reducible.

In the present situation, it is nevertheless difficult to give a rational explanation for these results, and further experiments will be needed to explain them.

Then, the minimal load of the metallic catalyst necessary to preserve a quantitative conversion and a maximal yield was evaluated from the defined conditions (16h. 60°C) (Table 3). Only the palladium catalyst was investigated: as previously reported no conversion occurred with Ir/C 1%, Pt/C 5%, Rh/C 5% and Ru/C 5%.<sup>26</sup> As expected, the presence of the metallic catalyst was essential because no reaction was observed without palladium: the substrate was fully recovered at the end of the reaction (Table 3, entry 1). When the load of the catalyst was ranged from 0.6 mol% to 2.5 mol%, the conversion was complete and yields were good to excellent (Table 3, entries 2-13). Moreover, the influence of the load of the catalyst was determined with different amounts of reducing agents. This study showed that after 16 h of reaction at 60°C the increase in the amount of catalyst did not improve the conversion and the yield in a substantial way (Table 3. entries 2 to 4. entries 5 to 7, entries 8 to 10 and entries 11 to 13). These results are in accordance with those already obtained in Table 2, with a fixed load of the catalyst.

The conversions and the yields were also evaluated at different temperatures between 5°C and 60°C. The reaction was performed with  $NaH_2PO_2/H_3PO_2$  (4 eq / 1 eq), 0.6 mol% Pd/C (5%, 50% water) for 16h. The results showed that the conversion was complete after 16 h at 20°C, 30°C or 60°C leading to similar yields (Table 3, entries 2 to 3). However, at 5°C, the conversion was incomplete and the yield only reached 33% after 16 h (Table 3, entry 4).

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Table 3 Influence of the amount of catalyst.

Entry	Pd/C <sup>a</sup>	NaH <sub>2</sub> PO <sub>2</sub> (eq)	Yield <sup>b</sup> (%)
1	0	3	0
2	0.6	1	80
3	1.25	1	82
4	2.5	1	78
5	0.6	2	78
6	1.25	2	85
7	2.5	2	86
8	0.6	3	80
9	1.25	3	85
10	2.5	3	88
11	0.6	4	90
12	1.25	4	90
13	2.5	4	92

The reaction mixture was stirred at 60°C for 16h. <sup>a</sup> Pd/C (5%, 50% H<sub>2</sub>O) (mol%), H<sub>2</sub>O / 2-MeTHF (2/1, v/v) <sup>b</sup>The yields were determined by GC/MS with benzylamine as internal standard after derivatization with BSTFA.

No significant difference in terms of yield was observed when the reaction was run at temperatures above 20°C for 16 h. A kinetics monitoring of the reaction was then achieved as a function of the temperature (Fig. 1). Although the temperature was not a pivotal parameter for 16 hours of reaction, this parameter should be studied when the reaction time was shortened. Indeed, when the reaction was carried out at 60°C, the total conversion and a maximal yield of 90% were reached after 1.5 h in comparison to the 36% observed at 30°C and 33% at 20°C during the same time. At 30°C, the reaction was completed in 5h. Moreover, the effect of the 2-methyltetrahydrofuran was more significant when the reaction was performed at 60°C for only 1.5 h. Indeed, when the reaction was carried out in water, the conversion was incomplete and the yield only reached 35%. These differences could be due to a better solubility of the nitro substrate in the additional organic solvent 2-MeTHF, enhancing the kinetics of the reduction.

Table 4 Influence of the temperature on the reduction.			
Entry	Temp (°C)	Yield <sup>ª</sup> (%)	
1	5	33	
2	20	88	
3	30	89	
4	60	90	

The reaction mixture was performed for 16h with NaH<sub>2</sub>PO<sub>2</sub> (H<sub>3</sub>PO<sub>2</sub> (H eq), 0.6 mol% Pd/C (5%, 50% water), H<sub>2</sub>O / 2-MeTHF (2/1, v/v) <sup>a</sup> The yields were determined by GC/MS with benzylamine as internal standard after derivatization with BSTFA.



**Fig. 1** Kinetics monitoring of the reaction at 20°C ( $\blacksquare$ ), 30°C ( $\blacktriangle$ ) and 60°C ( $\bullet$ ). The reaction mixture was performed with NaH<sub>2</sub>PO<sub>2</sub> (4 eq), H<sub>3</sub>PO<sub>2</sub> (1 eq), 0.6 mol% Pd/C (5%, 50% water) in H<sub>2</sub>O/2-MeTHF (2/1).



Fig. 2 Influence of the ultrasounds on the reduction. The reaction was performed under ultrasonic activation for 15 min in  $H_2O$  ( $\blacktriangle$ ) or in  $H_2O/2$ -MeTHF (2/1) ( $\bullet$ ). The yields were determined by GC/MS with benzylamine as internal standard after derivatization with BSTFA.

In an attempt to increase the rate of the reaction while increasing the yields in amines, the reduction was performed under ultrasonic activation. In order to differentiate the effects of sonication from those of temperature, the reactions were thermostatically controlled. The results obtained were then compared with those under silent conditions. The reaction was carried out for 15 minutes in the two solvent systems (H<sub>2</sub>O and H<sub>2</sub>O / 2-MeTHF (2/1, v/v) (Fig. 2).

The study showed that the biphasic solvent system is once again more efficient than water. Indeed, in a temperature range from 35°C to 65°C, the yield was higher in the mixture  $H_2O/2$ -MeTHF (2/1, v/v) rather than in water. The differences between the two solvent systems started being significant from 35°C (Fig. 2). Ultrasonic irradiation speeded up the reduction reaction in both solvent systems. In the mixture  $H_2O/2$ -MeTHF (2/1) a complete conversion with a maximal yield of 92% was obtained in only 15 min under sonication whereas 1.5 h were required at 60°C under silent conditions. Furthermore, when the reaction was not thermostated, the temperature reached 73°C and the yield achieved 92% in 15 min, confirming that the reaction is temperature dependent.

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In H<sub>2</sub>O, the effects of the ultrasounds are more significant. Under silent conditions, the yield achieved 35% only after 1.5 h at 60°C but under ultrasonic activation it reached around 60% at 60°C in only 15 min. Moreover, in H<sub>2</sub>O, complete conversion and maximal yield of 90% are obtained after 15 min of irradiation when the reaction temperature was increased to 70°C. This result showed that it is possible to get the desired amine without an organic solvent with a quantitative conversion and a maximal yield in only 15 min thanks to the ultrasonic activation.

The effects of ultrasounds can be chemical, physical or both. Thus, to understand how sonication influences the reduction, the reaction mixture was stirred with a vibroacoustic mixer, also called vibromixer, which gives rise to hydrodynamic cavitation leading only to physical effects.



**Fig. 3** Comparison between ultrasonic activation and the vibromixer Ultra Turrax in water. The reaction was performed under ultrasonic activation ( $\bullet$ ) or with the vibromixer UltraTurrax ( $\bullet$ ) for 15 min with NaH<sub>2</sub>PO<sub>2</sub> / H<sub>3</sub>PO<sub>2</sub> (4 eq /1 eq), 0.6 mol% Pd/C (5%, 50% water) in H<sub>2</sub>O.The yields were determined by GC/MS with benzylamine as internal standard after derivatization with BSTFA.



Fig. 4 Comparison between ultrasonic activation and the vibromixer Ultra Turrax in water / 2-MeTHF. The reaction was performed under ultrasonic activation ( $\bullet$ ) or with the vibromixer UltraTurrax ( $\blacksquare$ ) for 15 min with NaH<sub>2</sub>PO<sub>2</sub> / H<sub>3</sub>PO<sub>2</sub> (4 eq /1 eq), 0.6 mol% Pd/C (5%, 50% water) in H<sub>2</sub>O/2-MeTHF (2/1). The yields were determined by GC/MS with benzylamine as internal standard after derivatization with BSTFA.

The reaction was carried out for 15 min. In the two solvent systems (H<sub>2</sub>O and H<sub>2</sub>O / 2-MeTHF (2/1, v/v) the results were compared to those obtained under ultrasonic activation. The yields in amines observed under ultrasonic activation and under vibromixing are similar in water (Fig. 3) and in the biphasic solvent system H<sub>2</sub>O / 2-MeTHF (2/1) (Fig. 4).

DOI: 10.1039/C7GC01622K ARTICLE

Finally, these two last graphs clearly showed that sonication and vibromixing led to the fairly same yields. Thus the predominant effects of the ultrasonic activation on the reduction reaction are of physical nature: the reaction mechanism is not affected by cavitation, and its chemical intermediates are not coming from cavitation. Indeed, in this case of two-phase liquid / liquid system, sonication causes a phenomenon of intense micro-emulsion. Microdroplets with high interfacial surface area<sup>38</sup> are propelled from one phase to the other, providing significant contact between the reactants present in each of the non-miscible phases. By acting as physical agent of phase transfer, ultrasound allows a highly efficient mass transfer thereby facilitating the reaction, without a chemical phase transfer catalyst. Moreover, it improves the hydrogen production by improving degassing<sup>39</sup> of the medium. Finally, it probably decreases the size of the metallic catalyst particles, increasing and activating then the specific surface<sup>40</sup>. This reaction can be classified as type II reaction, termed "false sonochemistry"<sup>41</sup>. The methodology scope was extended to other aliphatic nitro compounds to prove the versatility of the reduction method; results were compared to those obtained with 2-Nitroethylbenzene, our model substrate (Table 5). The (1-methyl-2-nitroethyl)benzene was reduced with NaH<sub>2</sub>PO<sub>2</sub>/ H<sub>3</sub>PO<sub>2</sub> (4 eq / 1 eq), 0.6 mol% Pd/C (5%, 50% water) in H<sub>2</sub>O / 2-MeTHF (2/1) at 60°C for 1.5 h under magnetic stirring (Table 5, Entry 3) and for 15 min under ultrasonic activation (Table 5, Entry 4). The results were similar, with a complete conversion and a yield of 84%. The reduction was then tested on the 3-(2-nitroethyl)-1H-indole (Table 5, Entries 5-9), that is less reactive, and the crude product was analysed by <sup>1</sup>H NMR. Under silent conditions, the desired amine was synthesized with a yield of 98%. However, the reduction was a little more difficult under ultrasonic activation. Indeed, with the same load of the catalyst, the yield in amine only reached 61% in 10 min (Table 5, Entry 6), 78% in 20 min (Table 5, Entry 7) and 84% in 30 min (Table 5, Entry 8). Thus, under these conditions, the conversion was total, but although the amine was the main product, it was obtained with another compound that was not identified. Finally, the reaction required 30 min and a higher load of the catalyst (1.25 mol% Pd/C) to afford the expected compound in an almost quantitative 98% yield (Table 5, Entry 9). The 3-(1-methyl-2-nitroethyl)-1H-indole was then reduced but under the previous conditions (silent or ultrasonic), a mixture of the desired product with another minor side product was observed (Table 5, Entries 10-13). It was necessary to increase the amount of catalyst up to 1.25 mol% and to run the reaction for 30 min under ultrasonic activation; under these conditions, the conversion was complete and the yield achieved 90% (Table 5, Entries 14).

Finally, the reduction was tested on the  $\beta$ -nitrostyrene (Table 5, Entry 15). However, we did not obtain the corresponding unsaturated amine nor the saturated one but a mixture of the (*E*)-and (*Z*)-2-phenylacetaldehyde oxime. The yields were respectively 38% and 44% for the *E* and *Z* stereoisomers, after treatment for <sup>1</sup>H NMR analysis. These results are consistent with the previous research work published by Kabalka *et al.* in 1986,<sup>42</sup> describing the reduction of  $\alpha$ , $\beta$ -unsaturated nitroalkenes to oximes in the presence of palladium on charcoal with sodium hypophosphite.

DOI: 10.1039/C7GC01622K Journal Name

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Table 5 Extension of the methodology scope to other aliphatic nitro compounds.

Entry	Substrate	Product	Reaction conditions	Yield (%)
1	NO <sub>2</sub>	NH <sub>2</sub>	1h30, silent*	90%ª
2			15 min, ))))**	90%ª
3	NO <sub>2</sub>	NH <sub>2</sub>	1h30, silent	84% <sup>ª</sup>
4			15 min, ))))	84% <sup>ª</sup>
5		NH <sub>2</sub>	1h30, silent	98% <sup>ª</sup>
6			10 min, ))))	61% ª
7	NO <sub>2</sub>		20 min, ))))	78% <sup>ª</sup>
8			30 min, ))))	84% <sup>a</sup>
9			30 min, ))))	98% <sup>b</sup>
10	NO <sub>2</sub>	NH <sub>2</sub>	1h30, silent	80% ª
11			15 min, ))))	78%ª
12			20 min, ))))	80% <sup>a</sup>
13			30 min, ))))	85% <sup>a</sup>
14			30 min, ))))	90% <sup>b</sup>
15	NO <sub>2</sub>	NOH	30 min, ))))	38% ( <i>E</i> ) <sup>b</sup>
				44% (Z) <sup>b</sup>
* without the use of ultrasound: silent, ** under ultrasound irradiation: ))))				

The reaction mixture was performed at 60°C with NaH<sub>2</sub>PO<sub>2</sub>/H<sub>3</sub>PO<sub>2</sub> (4 eq / 1 eq) in

 $H_2O/2$ -MeTHF (2/1). The yields were determined by GC/MS (Entries 1-4) or by NMR (Entries 5-15) with benzylamine as internal standard. The conversion is 100%. <sup>a</sup> 0.6%mol Pd/C. <sup>b</sup>1.25%mol Pd/C

However, the authors did not specify the ratio of the E and Zstereoisomers and the global yield was lower and only reached 56%. In addition, in our work, the reduction was performed in a biphasic mixture of  $H_2O$  / 2-MeTHF (2/1, v/v) with a catalytic amount of Pd/C for only 15 min under ultrasonic activation whereas

the reaction described by Kabalka and al.42 was carried out in THF for 2 hours with 30% (w/w of nitroalkene) of Pd/C. Indeed, the authors underlined that the reactions were incomplete with catalytic amounts of Pd/C even after 24 hours.

#### **Experimental section**

The commercially available reagents and solvents were used without further purification. N,O-Bis(trimethylsilyl)trifluoroacetamide (BSTEA) with 1% trimethylchlorosilane used for the derivatization procedure was purchased from Aldrich. Because of its low boiling point (78°C), reactions with 2-methyltetrahydrofuran were performed in a closed tube. The reactions under ultrasonic activation were carried out with a sonotrode at 20 kHz frequency, P<sub>acoustic</sub>= 3.94 W. The reactions with the vibromixer were performed with an Ultra-turrax T25 Janke & Kunkel IKA apparatus at 24'000 tr.min<sup>-1</sup>. The reactions were monitored by thin-layer chromatography (TLC) on a plate of silica gel 60 F254. Developed plates were visualized using ultraviolet light and/or by dipping the plates into a solution of ninhydrin in ethanol followed by heating with a heat gun. <sup>1</sup>H NMR spectra were recorded on a BRUKER, Avance III HD at 400 MHz. Chemical shifts were assigned relatively to the reference solvent in ppm. Electrospray ionization (ESI) mass spectrometry (MS) experiments were performed on a Thermo Finnigan LCQ Advantage mass spectrometer. Purifications were carried out by flash chromatography on silica gel (230–400 mesh; 40–63 µm).

#### General reduction procedure

In a closed tube, 1-(2-nitroethyl)benzene (151 mg, 1 mmol) was solubilized in solvent (water or 2-methyltetrahydrofurane) (1 mL) and Pd/C (5% wt, 50% in water) (27 mg, 0.6 mol %) was added. After the addition of a mixture of sodium hypophosphite monohydrate (4 mmol) and hypophosphorous acid (50% in water) (1 mmol) solubilized in water (2 mL), the reaction mixture was stirred for 16 hours at 60°C. After cooling down to room temperature, the reaction mixture was diluted with ethyl acetate (20 mL), basified with a 2.5 M sodium hydroxide solution (10 mL) and filtered on celite<sup>®</sup>. The aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (10 mL), and dried over magnesium sulfate.

For an analysis by GC/MS, the dried organic phase was filtered on a volumetric flask. The volume was adjusted to the graduation mark with ethyl acetate to prepare the standard solution.

For an analysis by <sup>1</sup>H NMR, the dried organic phase was filtered and concentrated under reduced pressure to get the crude product.

Before each experiment, the tube was washed twice with hydrochloric acid.

#### General analysis procedure by GC/MS Trimethylsilyl derivatization

The yields of some reduction reactions were determined by GC/MS after derivatization of the product. As the silvlation is one of the widely used derivatization procedure, BSTFA was chosen to replace hydrogen of the amine function by the trimethylsilyl group $^{43}$ .

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Derivatized benzylamine was chosen as an internal standard to eliminate instrumental and sample preparation errors. Several solutions containing increasing concentrations of derivatized analyte and fixed concentration of derivatized benzylamine were prepared to establish a calibration curve. First, stock solutions of benzylamine (the internal standard) and phenethylamine (the analyte) in ethyl acetate were prepared. Then, the standard solutions were prepared by mixing an identical volume of the stock benzylamine solution with crescent volumes of the stock phenethylamine solution and the volume is completed to 200µL with a BSTFA-1% TMCS solution. The standard solutions were derivatized by stirring for 2h at 50°C. After cooling to room temperature, each standard solution was analyzed by GC-MS. The ratio of the areas of the analyte and the standard were plotted against the concentration ratio of the two compounds in the mixture. Then, each crude product was mixed with the internal standard and derivatized in the conditions previously described. The analysis by GC/MS allowed determining the yield of the reduction via the calibration curve.

#### GC–MS conditions

GC-MS analysis was performed using an Agilent apparatus equipped with an Optima 5-MS capillary column. The oven temperature was held at 60°C for 3 min following injection and increased to 250°C at a rate of 15°C/min. The temperature of the injection port and ion source was set at 250°C. Helium was used as the carrier gas. The mass spectrometer was operated under electron ionization (EI) mode at an ionization energy of 70 eV. The mass spectrometer was operated with a mass scan range of 30 to 400 m/z.

#### Conclusions

In this work, we have optimized the parameters to get a green, mild and efficient reduction method of nitro derivatives into the corresponding amines. Using  $\beta$ -nitroethylbenzene as a model substrate, we have finalized the optimal parameters of the reaction to get a maximal yield under the greenest conditions. Thus, with the  $NaH_2PO_2/H_3PO_2$  combination (4 eq / 1 eq) as reducing agent, 0.6 mol % Pd/C (5%, 50% H<sub>2</sub>O), in H<sub>2</sub>O / 2-MeTHF (2/1) at 60°C for 1,5 h under silent conditions and for 15 min under vibromixing or ultrasonic activation a yield of 90% of amine was obtained with 100% of conversion; the reaction is possible in water, at 70°C with a quantitative conversion and a maximal yield in only 15 min thanks to the ultrasonic activation. Moreover, the reaction of reduction was shown to be not pH-dependant; its efficiency is suspected to depend both on nitro-compound solubility and on its corresponding amine protonation. Ultrasound was shown to improve the kinetics performance of the reaction with a significant decrease of the reaction time, in comparison with silent conditions. In addition, similar results obtained under vibromixing and under ultrasonic irradiation led us to the conclusion that for this reaction, the predominant effects of the ultrasounds are physical. Finally, these conditions were extended to other nitro derivatives. Even if it was necessary to increase the reaction time and the amount of catalyst

with some nitro indole derivatives, the conditions described in this work are nevertheless very competitive, especially for aliphatic nitro compounds that are usually difficult to reduce. For all these reasons, this protocol could be of great interest for further industrial applications.

#### Acknowledgements

The authors gratefully thank Jean-Charles Francony for good technical assistance and advices.

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