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in recyclable water at room temperature**

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## ARTICLE

# Environmentally responsible, safe, and chemoselective catalytic hydrogenation of olefins: ppm level Pd catalysis in recyclable water at room temperature

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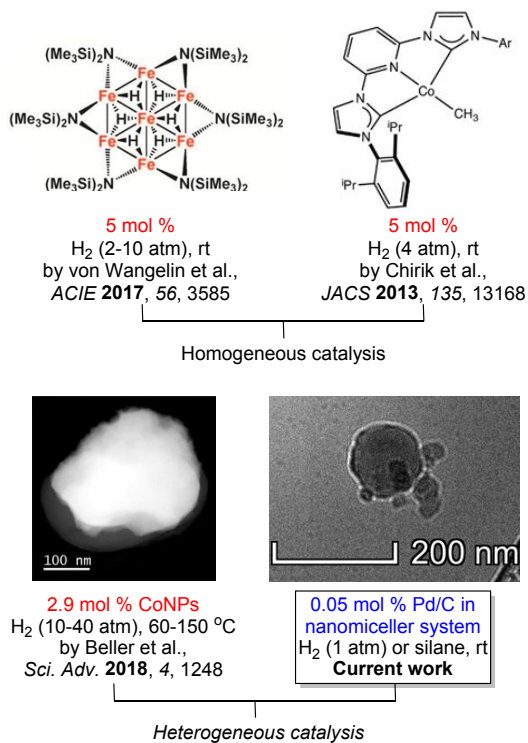
Textbook catalytic hydrogenations are typically presented as reactions done in organic solvents and oftentimes under varying pressures of hydrogen using specialized equipment. Catalysts new and old are all used under similar conditions that no longer reflect the times. By definition, such reactions are both environmentally irresponsible and dangerous, especially at industrial scales. We now report on a general method for chemoselective and safe hydrogenation of olefins in water using ppm loadings of palladium from commercially available, inexpensive, and recyclable Pd/C, together with hydrogen gas utilized at 1 atmosphere. A variety of alkenes is amenable to reduction, including terminal, highly substituted internal, and variously conjugated arrays. In most cases, only 500 ppm of heterogeneous Pd/C is sufficient, enabled by micellar catalysis used in recyclable water at room temperature. Comparisons with several newly introduced catalysts featuring base metals illustrates the superiority of chemistry in water.

## 1. Introduction

Catalytic hydrogenation of olefins is among the most powerful of reactions used by many chemical industries, being applied to the preparation of pharmaceuticals,<sup>1</sup> commodity chemicals, agrochemicals, and many other valued products.<sup>2</sup> In most cases, hydrogenations are catalyzed by transition metals such as Pd, Rh, Pt, and Ru<sup>3</sup> due to their high activity, availability, and ease of handling. Unfortunately, these catalysts are typically required in relatively large amounts, especially under homogeneous conditions<sup>4,5</sup> where direct catalyst recycling can be especially challenging.<sup>6</sup> By contrast, olefin hydrogenation based on heterogeneous catalysis allows for facile catalyst recycling, which can be a more attractive option.<sup>7</sup> However, the catalyst itself oftentimes contains a transition metal that is unequivocally endangered.<sup>8</sup> Moreover, such catalysis requires use of organic solvents in pressurized containers, and at catalyst loadings that can lead to products containing excessive amounts of residual metal beyond FDA limits.<sup>9</sup>

In response to these concerns, many processes showcasing homo- or heterogeneous *base* metal-catalyzed hydrogenation<sup>10,11</sup> of olefins have been reported of late. For example, a complex iron catalyst under hydrogen pressure has been used successfully by von Wangelin *et al.*<sup>12</sup> The Chirik group<sup>13,14</sup> has described an earth-abundant Co catalyst to achieve

hydrogenation, also relying on hydrogen pressure (Figure 1).<sup>15</sup>



**Figure 1.** Representative previously used catalysts vs. Pd/C in micellar media (water) applied to the hydrogenation of olefins.

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Very recently, Beller *et al.* identified a bio-mass-derived chitosan-supported Co-catalyst requiring both high temperatures and very high hydrogen pressures.<sup>16</sup> Hence, in moving away from highly active precious metal-based hydrogenations, harsh reaction conditions may be needed which raises safety concerns, especially as olefin-containing substrate complexity increases. Independent of metal, loadings, and conditions, all current processes are utilized in organic solvents, further depleting the world's petroleum reserves, which is undeniably unsustainable (Fig. 1).

Alternatively, commercially available 2-10 mol % Pd/C<sup>17</sup> in methanol is widely used for hydrogenation of olefins. However, such a general reagent oftentimes lacks chemoselectivity towards olefins in the presence of other reducible functional groups.<sup>18</sup> Typically, a catalyst poison may be required to achieve the desired selectivity.<sup>19</sup>

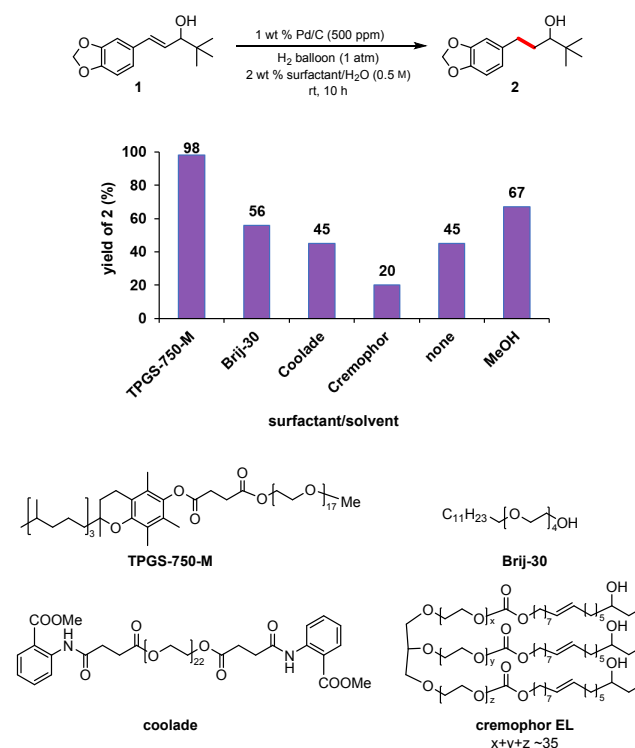
Our research programs focus on developing technologies<sup>20</sup> that include recognition of the need, on occasion, to address time-honored, fundamental processes such as olefin hydrogenation that today, lack an environmentally responsible yet general protocol. In an effort to minimize usage of precious metals, and in particular, palladium, while offering especially valuable options for realizing chemoselectivity, we have endeavored to convert traditional catalytic hydrogenation into a reaction that relies not only on ppm levels of an otherwise inexpensive and readily available catalyst, Pd/C, but also a reaction that can be run in recyclable water at ambient temperatures using micellar catalysis conditions.<sup>21</sup> The "nano-to-nano" effect,<sup>22</sup> only operable in water, was anticipated to deliver the nanomicelle-housed substrate olefin directly to the heterogeneous nanoparticles as catalyst, thereby avoiding the typical need for heating of heterogeneous reactions.<sup>16</sup> Moreover, the far greater solubility of hydrogen in hydrocarbon media relative to water, leading to very high concentrations within micellar cores, works further to the advantage of chemistry in water and was anticipated to add to the mildness of conditions needed.<sup>23</sup> In this report we describe an unprecedented, environmentally attractive process, documenting that a wide variety of alkenes can now be hydrogenated *safely* using hydrogen gas in the absence of special equipment, and in water at room temperature using only 500 ppm of Pd derived from inexpensive and commercially available Pd/C.

## 2. Results and Discussion

Screening of the reaction medium was performed using substrate olefin **1** (Fig. 2), with TPGS-750-M<sup>24</sup> being the most effective. Neither the recently introduced surfactant Coolade,<sup>25</sup> nor cremophore EL (kolliphore EL)<sup>26</sup> was as effective, while the reaction performed "on water" was very sluggish, as was use of a traditional organic solvent (MeOH) under these very mild conditions; only a balloon of hydrogen is needed for these reductions.<sup>18</sup>

Further evaluation of this ppm Pd/C-catalyzed heterogeneous hydrogenation was conducted on several styrene derivatives under an atmosphere of hydrogen (Table 1;

Conditions A). Conversion to the corresponding product of reduction occurred quickly (ca. 1-2 h, products **3-6**) at room temperature. In general, alkenes conjugated either directly to an aromatic or heteroaromatic ring (products **7** and **8**) gave excellent yields of the desired products. Both nitrile (entries **9** and **10**) and ester groups (products **12-15**, **17** and **18**) were stable under these conditions. Phenylcyclohexene (product **16**) and ethyl acrylate (product **14**), which led to poor yields using high pressures of H<sub>2</sub> as previously described,<sup>12</sup> reacted smoothly in water under atmospheric hydrogen gas. Amide, carbamate, and lactam functionalities were all tolerated (products **19-22**). A conjugated phosphine oxide could also be reduced efficiently without compromising the P=O bond (product **24**). Allylic and vinyl sulfones behaved similarly (entries **25** and **26**, respectively), while various alkenylboron derivatives were hydrogenated without noticeable deborylation (products **27-30**). Further extension to the synthesis of intermediates en route to pharmaceutical targets (e.g., Pfizer's SSRI sertraline; **32**, and the anti-inflammatory agent nabumetone; **33**)<sup>27</sup> is suggestive of broad utility of this process.

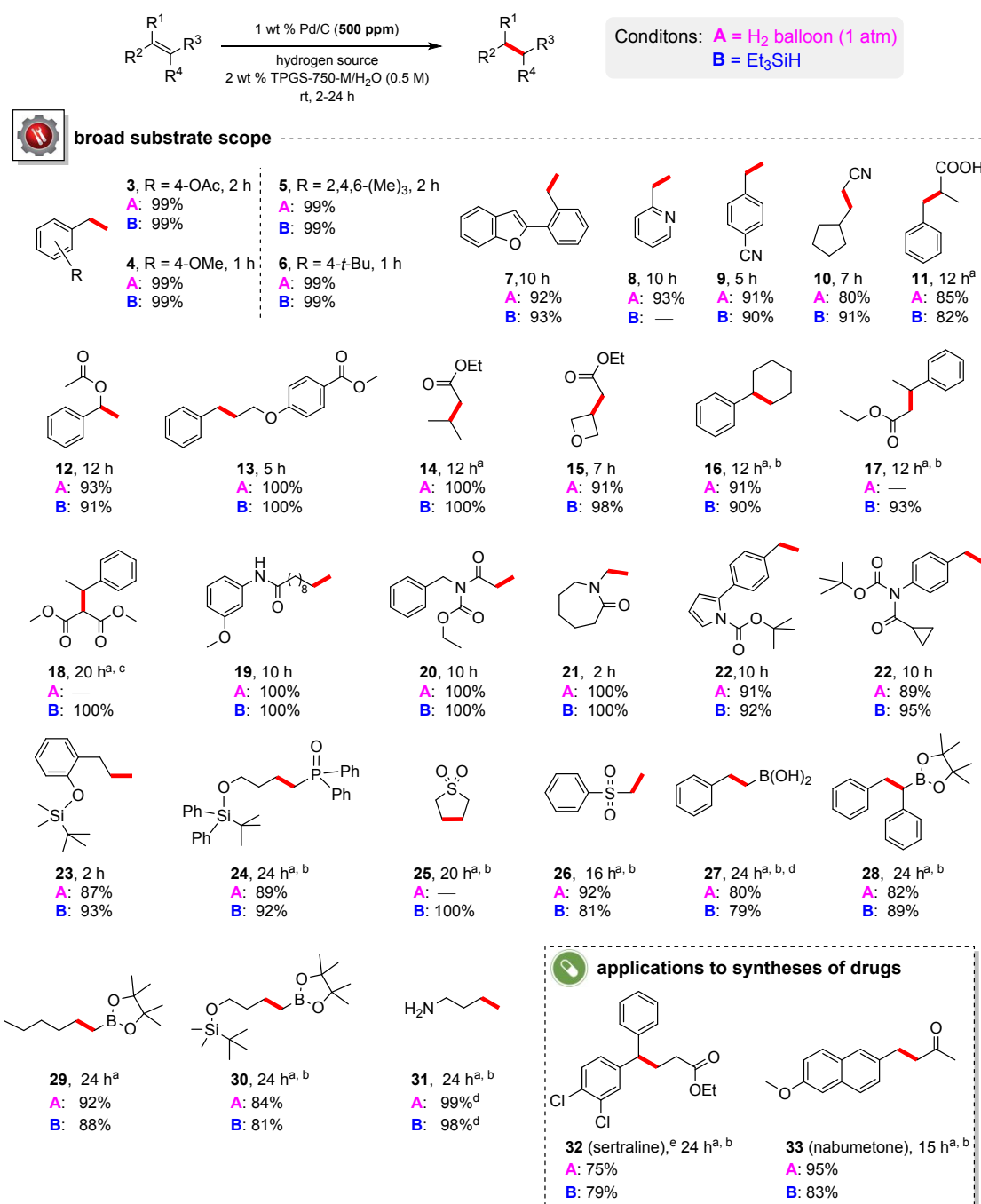


**Figure 2.** Screening of reaction conditions for hydrogenation using alkene **1**.

This protocol has also been applied to several olefin-containing natural products (Table 2). Noteworthy is the case of  $\alpha$ -damascone, where the enone was reduced to product **34** chemoselectively, leaving the isolated alkene intact. Other examples include reductions of carvone (product **35**), linalool oxide (product **36**), and rose oxide (product **37**), among others or as their allylated derivatives (products **38-41** and **46**), all undergoing reduction efficiently at room temperature under atmospheric hydrogen, and using only 500 ppm of the Pd catalyst. Bridged bicyclic systems containing olefins were

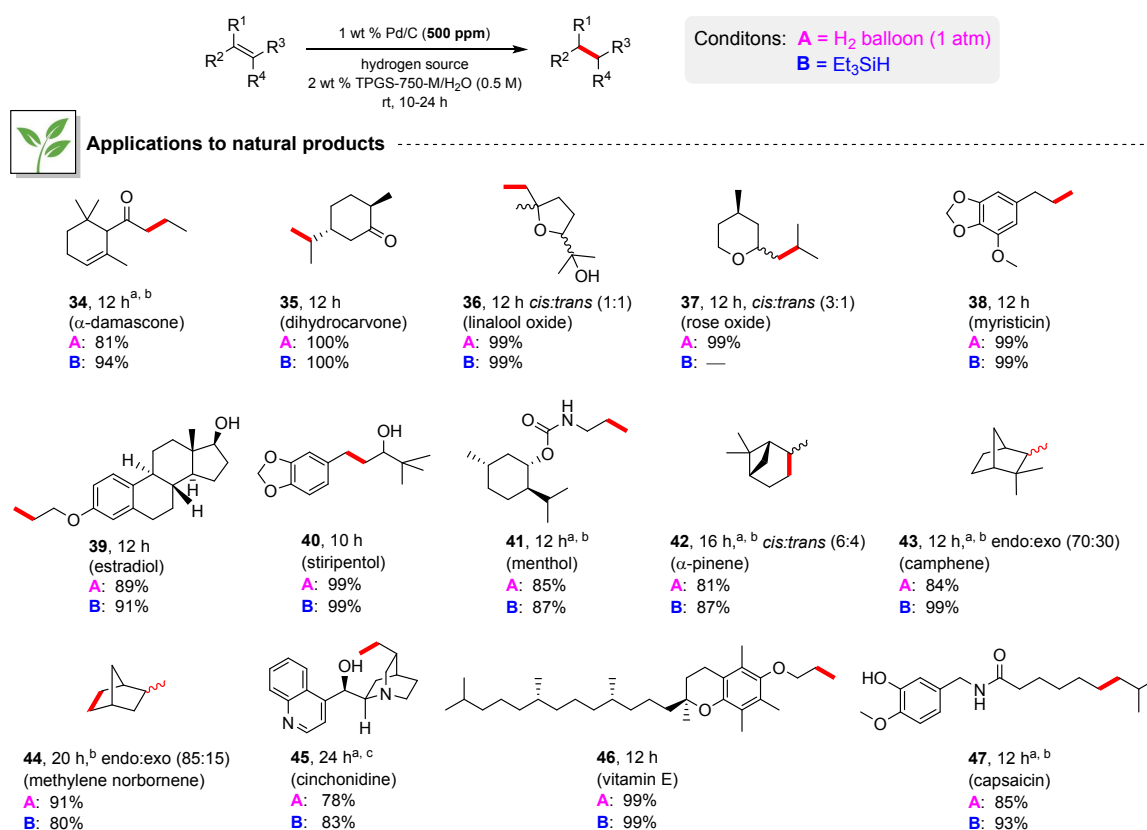
also hydrogenated under identical conditions (products **42-44**). Hence, as illustrated, several types of olefin-containing natural products can be efficiently hydrogenated without impacting other functionality in these molecules, attesting to the very mild conditions involved.

**Table 1.** Functional group tolerance for hydrogenation of olefins.



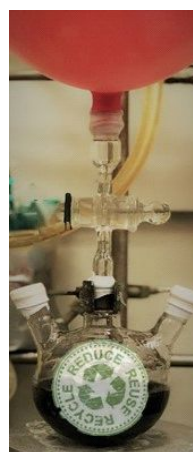
Reaction conditions: 0.25 mmol substrate, 500 ppm of 1 wt % Pd/C stirred at rt in TPGS-750-M/H<sub>2</sub>O [0.5 M] under Conditions A or B; Conditions A = H<sub>2</sub> balloon (1 atm); Conditions B = 1.2-1.5 equiv Et<sub>3</sub>SiH. <sup>a</sup>Reaction temperature was 45 °C. <sup>b</sup>Pd/C loading was 1000 ppm. <sup>c</sup>Pd/C loading was 2000 ppm. <sup>d</sup>NMR yield. <sup>e</sup>Intermediate en route to sertraline.

In some cases, e.g., camphene (Table 2, product **43**), hydrogenation was especially challenging due to the volatility of the starting alkene. Hence, an alternative to hydrogen gas was developed based on readily available and inexpensive triethylsilane and H<sub>2</sub>O in the presence of Pd/C, likewise leading to the desired products in high yields. Several additional examples using this source of hydrogen can also be found in Tables 1 and 2 (Conditions B).

**Table 2.** Hydrogenation of olefins found in various natural products.

Reaction conditions: 0.25 mmol of substrate, 500 ppm of 1 wt % Pd/C was stirred at rt in TPGS-750-M/H<sub>2</sub>O (0.5 M) under Conditions A or B; Conditions A = H<sub>2</sub> balloon (1 atm); Conditions B = 1.2-1.5 equiv Et<sub>3</sub>SiH per double bond. <sup>a</sup>Reaction temperature was 45 °C. <sup>b</sup>Pd/C loading was 1000 ppm. <sup>c</sup>Pd/C loading was 2000 ppm.

A particularly meaningful study further highlighting the “greenness” of this process (in addition to the ppm levels of Pd involved) comes in the form of its potential for recycling of *both* the catalyst and aqueous reaction medium (Scheme 1), properties which are uncharacteristic of alternative processes. Here, four successive 1-pot reactions, each at the multi-gram scale, were performed on different substrates involving an initial investment of only 500 ppm Pd/C, using a balloon as the source of hydrogen. An additional 100 ppm Pd/C was added to the final recycling so as to account for the loss of catalyst during handling. Nonetheless, this brought the total use of palladium to 600 ppm, or 150 ppm Pd/reduction. Since each of these products could be obtained by simple distillation from the reaction mixture, no organic solvent was needed at any point (e.g., for extraction, leading to an overall E Factor,<sup>28</sup> as a measure of waste created, of zero. Even taking into account the water associated with use of aqueous TPGS-750-M (a total of 98 mL were used), the E Factor *over four reactions* is still only 4.2 (i.e., weight of waste water/weight of product = 98 g/23.2 g). Recycling experiments on the same substrate leading to product **6** were also performed for five runs. The first three led to isolated yields of 90-93%, while the fourth gave an isolated yield of 85%. The last recycling afforded a 75% yield, suggesting that additional catalyst or extended reaction times might be needed (see SI).

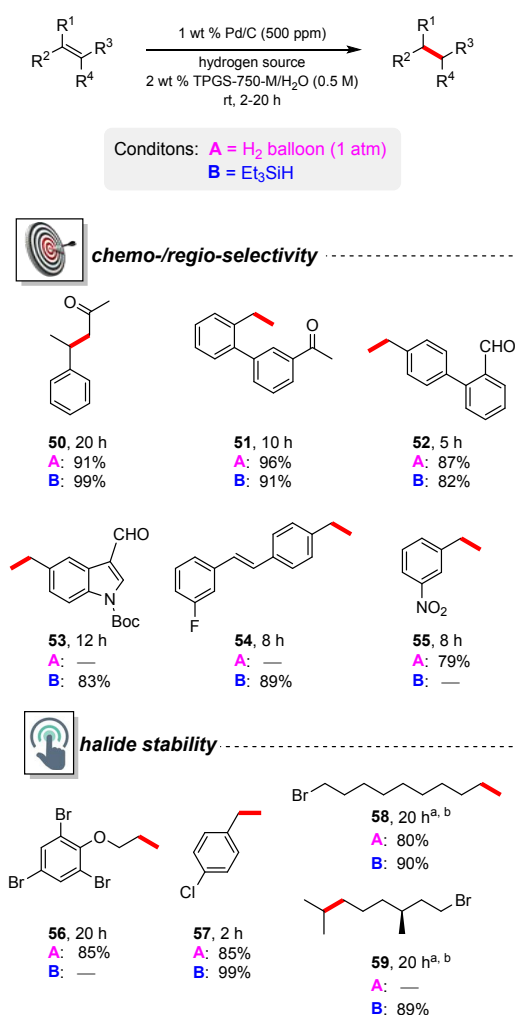


recycle	product, time	g (yield) of product
initial reaction	 <b>21</b> , 4 h	6.4 (91%)
1 <sup>st</sup>	 <b>48</b> , 5 h	4.7 (92%)
2 <sup>nd</sup>	 <b>49</b> , 12 h	6.3 (89%)
3 <sup>rd</sup>	 <b>14</b> , 20 h	5.8 (90%)
<b>E Factor (organic solvents) = 0</b>		
E Factor (based on water) = 4.2		

**Scheme 1.** E Factor, recycling of solvent and catalyst. Reaction conditions: 50 mmol of substrate, 500 ppm of 1 wt % Pd/C was stirred at rt in TPGS-750-M/H<sub>2</sub>O [0.5 M] under Conditions A (hydrogen balloon) until the second recycle. Then, 100 ppm Pd/C and 1.5 equiv Et<sub>3</sub>SiH were added for the 3<sup>rd</sup> recycle.

Metal-catalyzed hydrogenations, especially those that rely on relatively harsh conditions required to achieve full conversions to the desired product, oftentimes present selectivity issues. We have examined model substrates bearing additional easily reducible functionality, such as adducts containing a ketone, aldehyde, or nitro group (Table 3). Presumably due to the mildness of these conditions, excellent selectivities were observed. For example, in the case where a substrate contains a conjugated ketone, the corresponding products (**50** and **51**) were obtained in high yields. Compounds with an aldehyde present, however, afforded somewhat lower yields of products (**52** and **53**) reflecting competitive carbonyl reduction. Regioselective reduction of a terminal alkene in the presence of an internal olefin could also be achieved (product **54**). Selective reduction of the alkene in *m*-nitrostyrene to 3-ethylnitrobenzene **55** is also noteworthy.<sup>29</sup> Additional applications to more challenging substrates, including aryl (poly)halides (products **56** and **57**) as well as alkyl bromides gave the expected results (**58** and **59**).

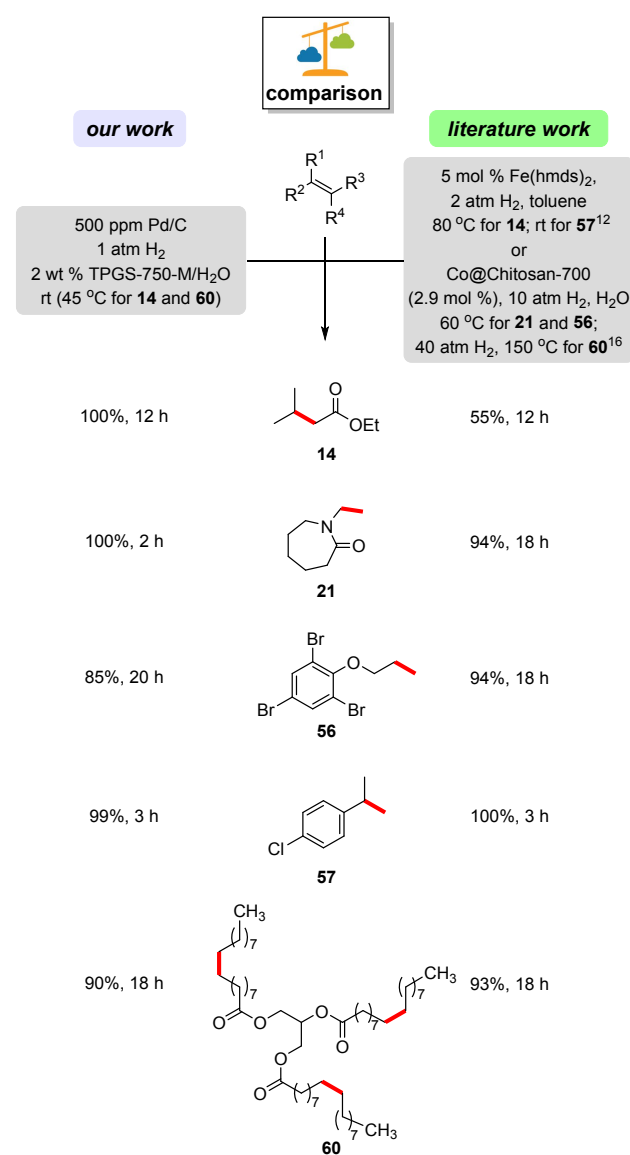
**Table 3.** Chemo- or regio-selective hydrogenation and halide stability studies



Conditions: 0.25 mmol substrate, 500 ppm of 1 wt % Pd/C stirred at rt in TPGS-750-M/H<sub>2</sub>O [0.5 M] under Conditions A or Conditions B; Conditions A = H<sub>2</sub> balloon (1 atm); Conditions B = 1.2–1.5 equiv Et<sub>3</sub>SiH

per double bond. <sup>a</sup> Reaction temperature was 45 °C. <sup>b</sup> Pd/C loading was 1000 ppm.

Comparison studies illustrate additional merits of this new, green technology in water relative to other very recent, albeit traditional processes that feature base metal catalysts (Scheme 2). Under similar conditions, the desired saturated ester **14** was prepared quantitatively using 500 ppm of Pd/C under a balloon of hydrogen at room temperature. On the other hand, only a 55% yield was obtained, as reported, upon treatment with an iron catalyst under pressure after heating at 80 °C. Hydrogenation of olefins using a heterogeneous cobalt catalyst<sup>16</sup> offers reaction conditions that call for specialized equipment to accommodate ten atmospheres of hydrogen pressure, along with a temperature of 60 °C.



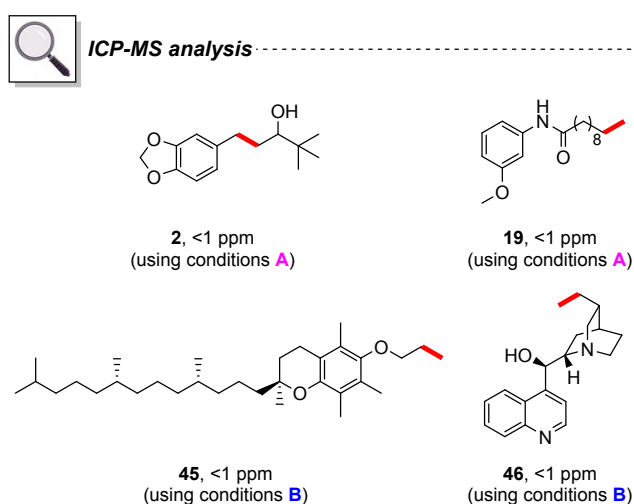
**Scheme 2.** Comparison of ppm Pd/C vs. literature processes.

Alternatively, both targets **21** and **56** could be prepared using the same low loadings of heterogeneous Pd/C (500 ppm) at rt, in water. Notably, in the case of the *N*-olefinic lactam, the reaction time was dramatically reduced from eighteen to two hours to give **21**. Hydrogenation of  $\alpha$ -methyl *p*-chlorostyrene proceeded smoothly



under nano-to-nano conditions without dehalogenation to give the desired product **57** in 99% yield. By contrast, to achieve similar results, 100 times higher loading of an iron catalyst was used in organic solvent in a system designed to handle hydrogen under high pressure.<sup>12</sup> Lastly, a triglyceride underwent triple hydrogenation to arrive at stearin **60** (90% isolated yield), also run on a gram scale using 1000 ppm Pd/C, or only 333 ppm Pd (0.0333 mol %) per alkene. The same cobalt catalyst (2.9% loading) required 150 °C at 40 bar of hydrogen pressure to obtain 93% conversion.<sup>16</sup>

Heterogeneous catalysis oftentimes offers the advantage of low levels of catalyst leaching into a reaction mixture, leading to limited product contamination by residual metal(s). Given the low loadings of Pd involved in these hydrogenations, and as expected from prior studies,<sup>20,21,22</sup> ICP-MS analyses of products **2**, **19**, **45**, and **46** (Scheme 3) led, in all cases, to residual levels below 1 ppm Pd;<sup>30</sup> the FDA limit for residual Pd per dose is  $\leq 10$  ppm.<sup>9</sup>



**Scheme 3.** ICP-MS analysis of residual Pd in products **2**, **19**, **45**, and **46**. Conditions A = H<sub>2</sub> balloon (1 atm); Conditions B = 1.2–1.5 equiv Et<sub>3</sub>SiH.

### 3. Conclusions

In conclusion, the time-honored, fundamental process of alkene hydrogenation has been newly defined as a modern protocol that (1) avoids waste-generating organic solvents, using recyclable water; (2) eliminates the investment of energy in the form of heating past ambient temperatures; and (3) is respectful of our limited access to, and therefore, endangered status of, palladium, which can now be used and recycled at the ppm level. Moreover, no special equipment designed to handle pressures of hydrogen gas are required, as is typical of most existing procedures, thereby offering an important element associated with green chemistry: safety. In cases where H<sub>2</sub> is not sufficient, an alternative source in the form of a commercially available and inexpensive silane (Et<sub>3</sub>SiH) suffices. Overall, this *unprecedented technology in water* allows for hydrogenations to be run on many types of olefins without recourse to alternative catalysts, whether derived from base or precious metals, that must

first be made and then used under more vigorous and far less environmentally responsible conditions. Switching to olefin hydrogenations in water, following Nature's lead, is long overdue.

### Conflicts of interest

There are no conflicts to declare.

### Acknowledgements

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  30. An ICP-MS experiment was performed at UC-CEIN, a facility at the University of California, Los Angeles, USA.

## ToC graphic

