H-Cube Mini Plus™

Lab Manual

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Hydrogenation

Hydrogen is the simplest atom, and yet the most versatile. Hydrogen is the most abundant element in the universe, and its wide-range of applications mirrors its universal abundance. At the heart of organic, inorganic, biochemical, and quantum chemistry, hydrogen is an indispensible asset to the chemist, and a thorough comprehension of its importance can lead to profound results.

Hydrogenation is the addition of hydrogen across a functional group. This very important reaction type is used in several industries, like pharma, flavour and fragrance, agrochemical or petrochemical industries. Moreover, it is estimated that between five and ten percent of all reactions performed worldwide are hydrogenations. The hydrogenation includes a high number of reaction types, like double or triple bond reduction, nitro group reduction or deprotection reactions, just to mention a few. Hydrogenation can be accomplished in a number of ways, and appropriate methodology depends upon the functional groups present and the stereochemical nature of the desired product.

Catalysts

Of the many procedures available to the practicing chemist for hydrogenation, metal catalysis is predominant owing to its versatility, reactivity, and controllability. These metal catalysts come in two flavors: homogeneous catalysts are readily soluble, whereas heterogeneous catalysts are not. Though each type has its advantages, the latter is particularly useful because it simplifies purification efforts. Heterogeneous catalysts exist in a different phase than the reactants, so they can often be removed by simple filtration.

More often than not, catalysts are impregnated upon a solid support. These solid supports come in various forms including carbon, silica, alumina or polymer just to mention the most common types. The main distinction between various supports is their pore size and the porosity of the powder. These factors, in combination with the available surface area and particle size, determine the catalytic activity. Supporting the catalyst stabilizes the metallic particles and increases the number of available catalytic atoms. With carbon supports, metals are more easily recovered, refined, and recycled. Supported catalysts can be applied to both batch and flow chemistry, with the former being suspended in the reaction medium as fine particles and the latter being fixed as granulated beds of catalyst over which the bulk chemicals flow. The industry tends to favor palladium (~30 percent) catalysts, which are used to reduce nitro groups to amines and to saturate carbon-carbon and carbon-heteroatom bonds. As non-supported catalyst, there is to mention the pure metal-type catalysts (eg. palladium black), the alloy-type catalysts (eg. Raney nickel) and the metal-oxide type catalysts (eg. platinum oxide).

The supported palladium is the most widely adopted catalyst, with applications ranging from saturation of olefins to reduction of carboxylic acids to alcohols and encompassing just about everything in between. A number of

poisoned versions exist as well, which reduce the palladium's reductive capacity. For example, the Rosenmund reaction reduces acid halides to aldehydes using palladium poisoned with barium sulfate, which prevents palladium from further reducing the aldehyde. Lindlar's catalyst is a form of palladium poisoned with lead that reduces triple bonds to double bonds without further reduction to the single bond. Platinum is similarly versatile, though not to the same extent. It can do many of the same reactions, but is not as affective at oxime reduction or hydrogenolysis reactions. Ruthenium and rhodium are more specialized catalysts. Rhodium—and ruthenium to a lesser extent—is a particularly powerful catalyst that efficiently reduces aromatic and heteroaromatic rings, and it reduces imines to amines more effectively than competitors. Raney nickel, which is composed of a nickel-aluminum alloy, is excellent for debenzylation reactions, desulfurizations, and carbonyl reductions.

The Usual Protocol

Hydrogenations, though vital in virtually every facet of chemistry, are notoriously dangerous. The most popular hydrogenation techniques involve a Parr reactor, autoclave, or balloon set-up. All three are batch processes (as opposed to a flow process), meaning that the reactants are mixed and the reaction proceeds in a given vessel. The reaction comes to completion, and the product(s) is transferred. Both autoclaves and Parr reactors involve high pressures in combination with high temperatures. The balloon technique is conducted at atmospheric pressure, and the hydrogen is delivered through a balloon fastened to the top of the setup. The typical approach involves flushing the entire setup with inert atmosphere several times, adding in the catalyst, flushing with inert atmosphere again, attaching the balloon filled with hydrogen gas, and stirring the reaction vigorously. This experiment can be dangerous for several reasons: hydrogen gas is flammable and most catalysts are pyrophoric. While these hydrogenation techniques are especially dangerous during operation, they can also cause trouble after disposal. Catalytic residue can dry out sitting in the waste container and eventually
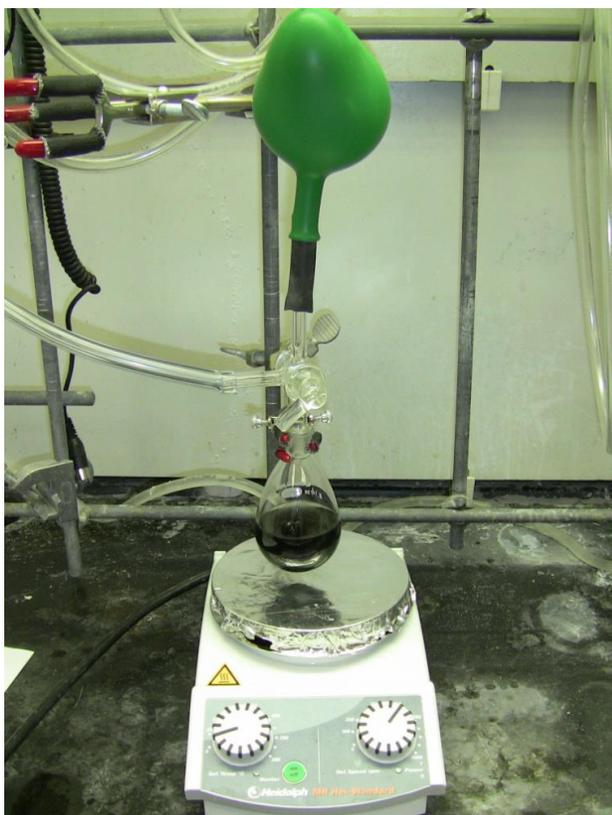

Figure 1. Hydrogenation using a balloon setup

ignite. While the procedure can be conducted safely, even a small mistake can escalate into a dangerous situation, so care must be taken with hydrogenations.

The H-Cube Mini Plus™

The H-Cube Mini Plus™ is an improvement over the standard paradigms for a number of reasons. It uses flow chemistry to bestow higher yields and real time monitoring of the reaction coordinates. It also minimizes the amount of substrate reacting at any given time, which effectively increases the available catalyst without decreasing product collected. The heterogenous packed catalyst cartridge eliminates the need to purify the product from the catalyst, and it reduces the hazards often associated with pyrophoric metal catalysts. The electrolytic cell conveniently produces hydrogen gas while simultaneously eliminating the necessity for storage cylinders or balloons. Furthermore, the machine is simple to use.

Flow Chemistry

The H-Cube Mini Plus™ utilizes a continuous flow approach, which contrasts with batch processing in that it allows reactants to combine and react dynamically. Flow chemistry is a quickly expanding field that allows control over a number of variables during a reaction. Pressure, temperature, and flow rate can be manipulated as necessary during a reaction. A High pressure liquid chromatography (HPLC) pump continuously flows a reactant solution through a stationary phase (or in some instances, another flowing solution) where the reaction takes place, and the products flow out over time, allowing real time manipulation of parameters to maximize yield. Consequently, the experimenter can monitor the rate of product turnover using TLC throughout the experiment, offering analytical advantages over the batch predecessor.

Electrolysis

Electrolysis applies electricity to water in order to generate hydrogen gas. As indicated by Equation 1, the reaction also generates diatomic oxygen as a side product.

$$2H_2O \rightarrow O_2 + 2H_2 \hspace{4cm} \text{(Eq. 1)}$$

The entire process is carried out within an electrolytic cell, which is composed of three essential components: a cathode attracts cations, an anode accumulates anions, and the electrolyte carries ions between the two. Water enters the electrolytic cell at the anode, where an electric current dissociates each molecule of water, producing a proton and a hydroxide anion. The protons traverse the proton exchange membrane and reach the cathode, where they are reduced to hydrogen gas. Simultaneously, the anode side produces oxygen and water from the accumulated hydroxide anions. In this scheme, electrons are pumped into the

cathode to reduce the protons and pumped out of the anode to oxidize the hydroxide anions.

Structure

The H-Cube or H-Cube Pro can be perplexing machines to the untrained eye, but they are actually quite intuitive. The H-Cube Mini Plus™ is an even cleanersystem from outside. Electrolysis occurs within the machine; it is fueled by thewater reservoir on the left side (10) which is magnetically attached. Solutionentering the machine follows the path highlighted in Figure 1: it traverses the (1)sample inlet line, (2) HPLC pump, (3) inlet pressure sensor, (4) gas/liquid mixer,(6) heated CatCart® unit, (7) back pressure regulator, and finally makes it to the(8) magnetically detachable product collector. The residual water from the hydrogen gas is removed by an internal drying system. As long as the machine is working properly, you will not have to adjust most of these components. Also, depending upon the reaction, you will need to unscrew the cartridge holder cap (5) to insert the appropriate catalyst. When doing so, be consistent with the direction that the arrow (illustrated on the CatCart® itself) points, since flow through the CatCart® causes channeling.
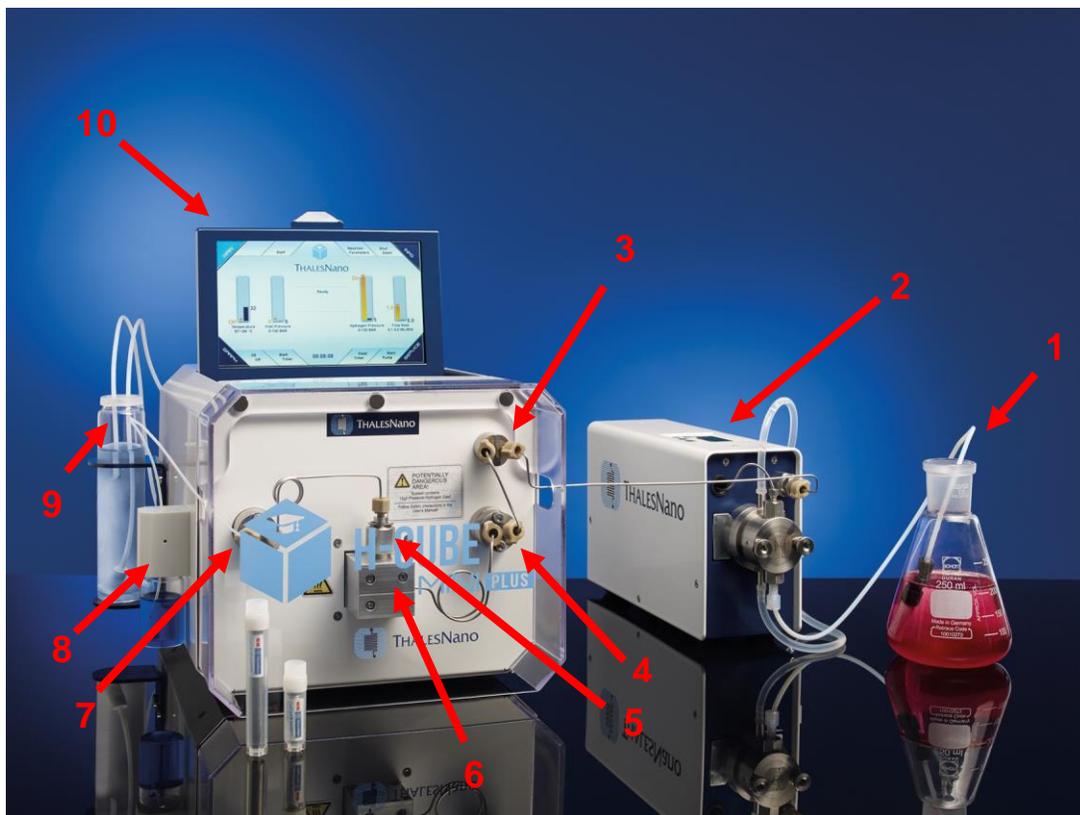

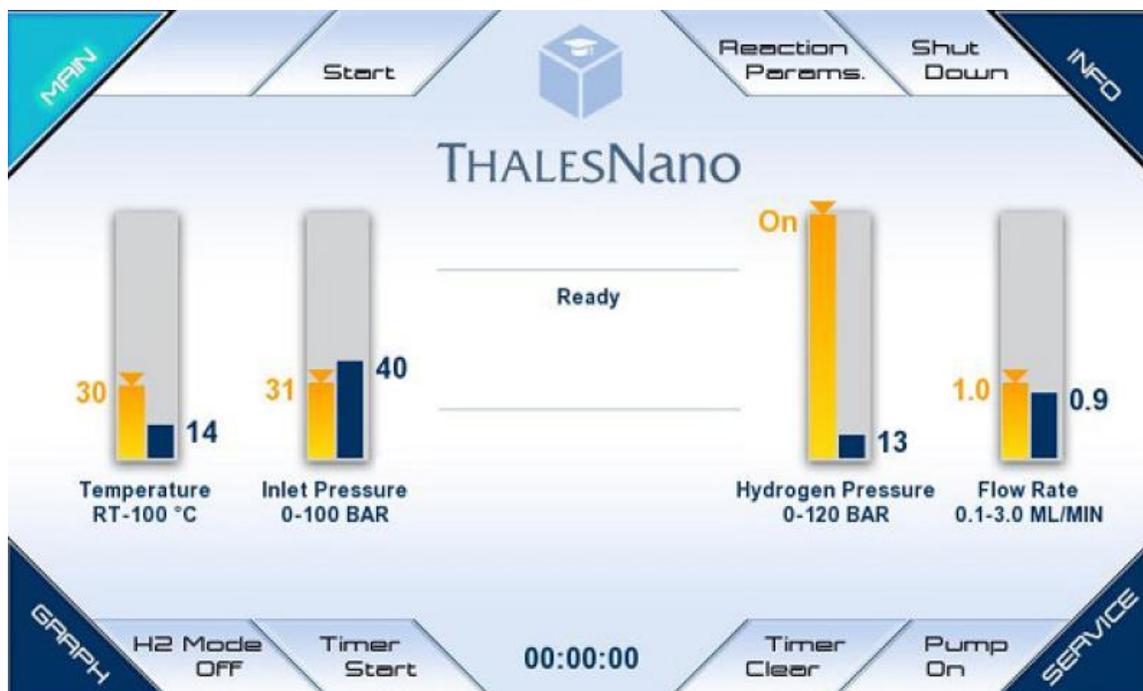**Figure 2. Front view of H-Cube Mini Plus™**

Figure 3. Main screen of H-Cube Mini Plus™

The (10) touch-screen panel atop the machine contains the four parameters adjusted preceding operation. The flow rate determines the residency time of the reactants, meaning that slower flow rates result in more time spent in contact with the catalyst. The temperature affects the kinetics and solubility of the solution, with higher temperatures amounting to higher solubility. Pressure determines the amount of gas solubilized in the solvent. Henry's law approximates the amount of gas present under certain constraints, according to Equation 2.

$$p = k_h c \qquad\qquad\qquad \text{(Eq. 2)}$$

The equation relates partial pressure, p, to the concentration, c, scaled by Henry's constant, k_h, which is in units of pressure over concentration. This parameter changes depending on the particular solute, solvent, and temperature. More complex versions of Henry's law are temperature dependent, but they are beyond the scope of this application. The final parameter is the amount of hydrogen produced. It has three selections: controlled hydrogen gas mode produces a steady stream of hydrogen at constant pressure; full hydrogen gas mode maximizes hydrogen production for reactions at atmospheric pressure requiring numerous equivalents of hydrogen (such as nitro reductions); and no hydrogen gas mode grants a flow reaction vessel without hydrogen gas.

Safety

One of the main advantages of the H-Cube Mini Plus™ over other hydrogenation techniques lies in its safety. However, a few issues must be addressed before using the machine. Hydrogen gas, which is expelled from the hydrogen exhaust tube connected to the gas separator unit, is flammable. Accordingly, there should be no open flames during this lab. Though the catalysts are contained within the CatCart®, metal catalysts are pyrophoric, meaning that they can spontaneously ignite at room temperature—especially Raney Nickel—so they should be handled with care.

Reactions

Hydrogenations that take place over a metal catalyst occur via a syn addition, meaning that the hydrogen add to the same side of the functional group. When working with alkynes and alkenes, this factor comes into play, generating cis products selectively over their trans counterparts. With other functional groups like nitro and carbonyl moieties, this mechanism bears less stereochemical significance.

Figure 2. Syn addition of hydrogen across a double bond

Double bond saturation is used to transform double bonds into single bonds. It is perhaps the simplest reduction to perform and can be performed using virtually any catalyst. Paul Sabatier (a Nobel laureate, thanks to his efforts in conjunction with Victor Grignard) discovered the process of hydrogenation in 1897 using nickel. Though Sabatier only reduced gases, the process was soon adapted by Wilhelm Normann in 1901 to include liquids. The process was almost immediately patented and gave rise to margarine and its various hydrogenated vegetable oil derivatives. Hydrogenating gases plays a crucial role in the production of methanol, which is produced from carbon monoxide and two equivalents of hydrogen gas.

While animals generate fatty acids that are predominantly aliphatic—meaning that they lack double bonds—plants generate unsaturated fats. These fats are unsaturated by cis double bonds that kink the fat, confining its flexibility and affecting its melting point. As opposed to these cis bonds, double bonds in the trans conformation are less kinked, though equally restricted. Trans fats are rarely found in nature, but rather are a result of human processing. Hydrogenating unsaturated plant fatty acids provides saturated fats with higher melting points, which are appealing for their consistency and reluctance to souring (due to free radicals attacking double bonds). This is why margarine—referred to as partially hydrogenated vegetable oil—is a solid at room temperature while vegetable oil

itself is a liquid. One side effect of the hydrogenation process is the conversion of some cis bonds to their trans counterparts, which are more likely to cause cardiovascular issues.

The goal of this particular reduction is to saturate a double bond without affecting the aromaticity of the ring nor the ketone. Because these latter two reductions require harsh conditions, this process can be achieved using palladium on carbon with mild conditions.
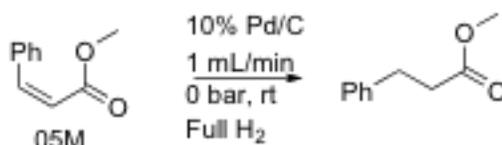

Figure 3. Double bond saturation

Protocol

1) Insert 10% Pd/C CatCart® (THS 01131).

2) Set parameters accordingly:

    Flow rate = 1.0 mL/min

    Hydrogen gas production = ON

    Pressure = 0 bar

    Temperature = 25°C

3) Run isopropanol and hydrogen through the machine for five minutes to cleanse the reaction vessel of impurities and load the catalyst with hydrogen.

4) Dissolve 81 milligrams of methyl cinnamate (0.5 mmols) in 10 milliliters of isopropanol.

5) Remove the Teflon inlet line from the solvent reservoir, and insert it into the reactant solution. Complete this step as quickly as possible to prevent air bubbles from entering the line.

6) Attach a clean, empty collection vial to the hydrogenated product collector.

7) As the reactant solution approaches dryness, refill the graduated cylinder with 2-3 milliliters of isopropanol to maximize yield. Complete this rinse three times.

8) Before the reactant solution reaches dryness, switch the Teflon inlet line back to the solvent reservoir, and run solvent through the machine for five minutes.

9) Hit the stop button, and wait for hydrogen gas and pressure to be released from the machine.

10) Hit the shutdown button, and turn off the machine.

11) Remove isopropanol from the product using a rotary evaporator.

Reducing a sterically hindered substrate can demonstrate the mechanism by which metal catalyzed hydrogenation occurs. Note how the bicyclic structure must sit upon the catalyst with the second ring facing away. In effect, the hydrogen are added to the less hindered side of the ring, and the methyl substituent is propelled forward. To affect this sterically bulky transformation, activated palladium, which exhibits enhanced catalytic activity, is used.
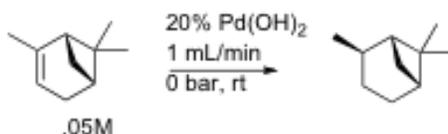

Figure 4. Sterically hindered reduction

Protocol

1) Insert 20% Pd(OH)2 CatCart® (THS 01135).

2) Set parameters accordingly:

Flow rate = 1.0 mL/min

Hydrogen gas production = ON

Pressure = 0 bar

Temperature = 25°C

2) Run isopropanol and hydrogen through the machine for five minutes to cleanse the reaction vessel of impurities and load the catalyst with hydrogen.

3) Dissolve 79 microliters of alpha-pinene (0.5 mmols) in 10 milliliters of isopropanol.

4) Remove the Teflon inlet line from the solvent reservoir, and insert it into the reactant solution. Complete this step as quickly as possible to prevent air bubbles from entering the line.

5) Attach a clean, empty collection vial to the hydrogenated product collector.

6) As the reactant solution approaches dryness, refill the graduated cylinder with 2-3 milliliters of isopropanol to maximize yield. Complete this rinse three times.

7) Before the reactant solution reaches dryness, switch the Teflon inlet line back to the solvent reservoir, and run solvent through the machine for five minutes.

8) Hit the stop button, and wait for hydrogen gas and pressure to be released from the machine.

9) Hit the shutdown button, and turn off the machine.

10) Remove isopropanol from the product using a rotary evaporator.

Lindlar's catalyst is used to reduce alkynes to alkenes. It consists of palladium impregnated upon calcium carbonate that has been treated with lead. Typically, palladium would reduce a triple bond down to a single bond, but the lead

inhibits palladium's catalytic potency. The addition of quinoline further reduces palladium's activity. Lindlar's catalyst is used in the industry to produce styrene from phenylacetylene, and vitamin A.

In this application, Lindlar's catalyst is used to reduce methyl phenylpropiolate to methyl cinnamate. This substrate can then be further reduced using the procedure outlined above in the double bond saturation section. Without the quinoline, the reaction will produce a combination of the reduced product, methyl cinnamate, and the over-reduced product, methyl 3-phenylpropanoate.
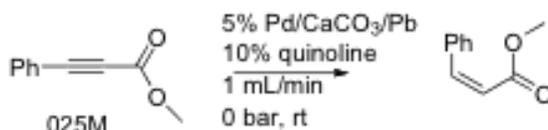

Figure 5. Alkyne to alkene reduction

Protocol

1) Insert Lindlar's catalyst CatCart®, 5% Pd/CaCO3/Pb (THS 02114).

2) Set parameters accordingly:

    Flow rate = 1.0 mL/min

    Hydrogen gas production = ON

    Pressure = 0 bar

    Temperature = 25°C

2) Run isopropanol and hydrogen through the machine for five minutes to cleanse the reaction vessel of impurities and load the catalyst with hydrogen.

3) Dissolve 37 microliters of methyl phenylpropiolate (0.25 mmols) in 10 milliliters of isopropanol.

4) Dissolve 3 microliters of quinoline (0.025 mmols) in the same 10 milliliters of isopropanol.

5) Remove the Teflon inlet line from the solvent reservoir, and insert it into the reactant solution. Complete this step as quickly as possible to prevent air bubbles from entering the line.

6) Attach a clean, empty collection vial to the hydrogenated product collector.

7) As the reactant solution approaches dryness, refill the graduated cylinder with 2-3 milliliters of isopropanol to maximize yield. Complete this rinse three times.

8) Before the reactant solution reaches dryness, switch the Teflon inlet line back to the solvent reservoir, and run solvent through the machine for five minutes.

9) Hit the stop button, and wait for hydrogen gas and pressure to be released from the machine.

10) Hit the shutdown button, and turn off the machine.

11) Remove isopropanol from the product using a rotary evaporator.

Nitro reductions were among the first reductions conducted owing to their relative ease. They are usually reduced using palladium or platinum in a straightforward fashion. The protocol sometimes calls for the addition of acetic acid (or other weak acids) to prevent the subsequent amine from poisoning the catalyst. Nitro reductions are useful in the more general process of adding amines to aromatic rings, which progresses from nitration of the ring to reduction of the nitro group. The first step is the addition of nitric acid and sulphuric acid to the aromatic ring; the subsequent nitronium ion, NO_2^+, contains a positively charged nitrogen that acts as an electrophile that is attacked by the nucleophilic ring to generate nitrobenzene. Passing nitrobenzene over palladium reduces the functional group to the corresponding amine, generating aniline. In the industry, nitrobenzene is usually passed over nickel catalysts rather than palladium, which accounts for the vast majority of the metric tones of aniline produced each year.

In this experiment, we use a substituted form of nitrobenzene because it is less toxic. In either case, use care when handling this substrate. Because nitro groups are easily reduced, the reaction conditions are mild. This allows reduction of the nitro group without affecting most other functional groups, save nonconjugated double bonds.
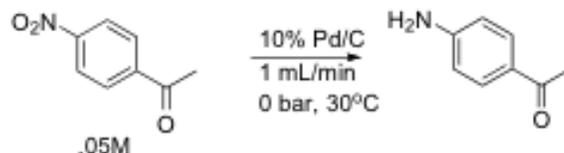

Figure 6. Nitro reduction

Protocol

1) Insert 10% Pd/C CatCart® (THS 01131).

2) Set parameters accordingly:

Flow rate = 1.0 mL/min

Hydrogen gas production = ON

Pressure = 0 bar

Temperature = 30°C

2) Run dichloromethane and hydrogen through the machine for five minutes to cleanse the reaction vessel of impurities and load the catalyst with hydrogen.

3) Dissolve 51 microliters of 1-(3-nitrophenyl)-1-propanone (0.5 mmols) in 10 milliliters of dichloromethane.

4) Remove the Teflon inlet line from the solvent reservoir, and insert it into the reactant solution. Complete this step as quickly as possible to prevent air bubbles from entering the line.

5) Attach a clean, empty collection vial to the hydrogenated product collector.

6) As the reactant solution approaches dryness, refill the graduated cylinder with 2-3 milliliters of dichloromethane to maximize yield. Complete this rinse three times.

7) Before the reactant solution reaches dryness, switch the Teflon inlet line back to the solvent reservoir, and run solvent through the machine for five minutes.

8) Hit the stop button, and wait for hydrogen gas and pressure to be released from the machine.

9) Hit the shutdown button, and turn off the machine.

10) Remove dichloromethane from the product using a rotary evaporator.

      Aromatic ring reduction is one of the most difficult reductions to affect, attesting to the stability of aromatic molecules like benzene. Though many catalysts are incapable of completely reducing aromatic rings even under harsh conditions, Raney nickel can do so. Industrially, benzene is reduced to cyclohexane before other synthetic procedures can proceed. Aromatic components must be eliminated from gasoline to ensure an appropriate firing rate, and they must be removed from the environment since benzene is toxic. The former process is an area of active research with numerous protocols attempting hydrogenation of varying fractions and at different pressures. The latter is being remedied using bacteria that mimic the catalytic ability of these metals, acting as sorts of bioreactors that process aromatics, multiplying to accommodate the aromatic load, and then dying as the toxin is cleared. These are just a few of the avenues being explored to employ hydrogenation in remedying hazardous situations.

      Because naphthalene is incredibly stable, harsh conditions are necessary to affect reduction. The addition of acetic acid further enhances the rate of reduction. The lack of other functional groups allows repeated cycling of the substrate to ensure maximum turnover. By placing the capillary tube that releases the product into the reactant solution reservoir, the substrate can be hydrogenated repeatedly until completion. Though this procedure does not call for such recycling of the substrate, substituted derivatives might necessitate milder conditions be used in combination with multiple runs through the machine.
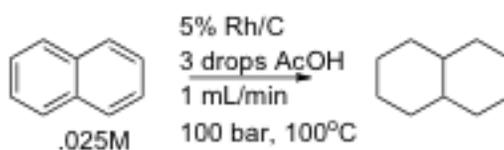

5% Rh/C
3 drops AcOH
1 mL/min
100 bar, 100°C
.025M

Figure 7. Aromatic ring reduction

Protocol

1) Insert 5% Rh/C CatCart® (THS 01134).

2) Set parameters accordingly:

Flow rate = 1.0 mL/min

Hydrogen gas production = ON

Pressure = 100 bar

Temperature = 100°C

2) Run ethyl acetate and hydrogen through the machine for five minutes to cleanse the reaction vessel of impurities and load the catalyst with hydrogen.

3) Dissolve 32 milligrams of naphthalene (0.25 mmols) in 10 milliliters of ethyl acetate.

4) Add 3 drops of acetic acid to the same 10 milliliters of ethyl acetate.

5) Remove the Teflon inlet line from the solvent reservoir, and insert it into the reactant solution. Complete this step as quickly as possible to prevent air bubbles from entering the line.

6) Attach a clean, empty collection vial to the hydrogenated product collector.

7) As the reactant solution approaches dryness, refill the graduated cylinder with 2-3 milliliters of ethyl acetate to maximize yield. Complete this rinse three times.

8) Before the reactant solution reaches dryness, switch the Teflon inlet line back to the solvent reservoir, and run solvent through the machine for five minutes.

9) Hit the stop button, and wait for hydrogen gas and pressure to be released from the machine.

10) Hit the shutdown button, and turn off the machine.

11) Remove ethyl acetate from the product using a rotary evaporator.

       Carbonyl reduction involves the addition of hydrogen to either a ketone—which generates a secondary alcohol—or an aldehyde—which generates a primary alcohol. While palladium can in some instances do an adequate job of reducing carbonyls, ruthenium or platinum are typically favored because of their selectivity of carbonyls over olefins.

       Carbonyls are not particularly easy to reduce, so they can be tricky to reduce in the presence of other functional groups. Benzaldehyde is a simple case that shows the relative difficulty of reducing aldehydes, but it should be noted that bulkier aldehydes and ketones in general will be more difficult to reduce.
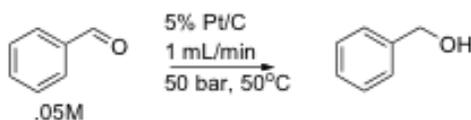

Figure 8. Carbonyl reduction

Protocol

1) Insert 5% Pt/C CatCart® (THS 08132).

2) Set parameters accordingly:

Flow rate = 1.0 mL/min

Hydrogen gas production = ON

Pressure = 50 bar

Temperature = 50°C

2) Run isopropanol and hydrogen through the machine for five minutes to cleanse the reaction vessel of impurities and load the catalyst with hydrogen.

3) Dissolve 51 microliters of benzaldehyde (0.5 mmols) in 10 milliliters of isopropanol.

4) Remove the Teflon inlet line from the solvent reservoir, and insert it into the reactant solution. Complete this step as quickly as possible to prevent air bubbles from entering the line.

5) Attach a clean, empty collection vial to the hydrogenated product collector.

6) As the reactant solution approaches dryness, refill the graduated cylinder with 2-3 milliliters of isopropanol to maximize yield. Complete this rinse three times.

7) Before the reactant solution reaches dryness, switch the Teflon inlet line back to the solvent reservoir, and run solvent through the machine for five minutes.

8) Hit the stop button, and wait for hydrogen gas and pressure to be released from the machine.

9) Hit the shutdown button, and turn off the machine.

10) Remove isopropanol from the product using a rotary evaporator.

Hydrogenolysis, in general, refers to the process by which a catalyst in combination with hydrogen cleaves a molecule. **N-debenzylation,** in particular, converts a tertiary amine to a secondary amine by replacing the benzyl substituent with a hydrogen atom. This process essentially deprotects the amine, allowing intermittent modification and re-protection of the moiety, as deemed necessary by the reaction scheme. Protection of amines is important when dealing with amino acid and protein syntheses, where free amino and carboxyl groups must be repeatedly protected and deprotected to achieve the appropriate peptide sequence.

Protection is an unavoidable aspect of synthetic chemistry. Benzylic protecting groups alone are found in over a thousand drug syntheses. When working with amines, as well as alcohols and acids, protection hides the particular moiety and prevents it from interfering with reactions occurring elsewhere on the molecule. A number of protecting groups exist to cover a broad spectrum of

situations and circumstances. Once the protection is accomplished, the protecting group is cleaved using catalytic hydrogenation under mild conditions.

When carrying out debenzylation reactions, solvent can play an important—and perhaps often overlooked—role. Simple alcohols like methanol and ethanol can lead to reductive alkylation of the amine group under certain conditions. Essentially, the methanol is oxidized to formaldehyde, which is subsequently attacked by the amine to produce the N-methylated product. Depending on the catalyst, hydrogenolysis can have stereochemical implications. Though this particular substrate will not be affected, palladium and platinum can invert configuration while nickel will preserve it. This phenomenon has been implicated as a result of metal affinity for oxygen when carbonyls are attacked and the associated anion when amines (via the quaternary ammonium species) are attacked.

Due to the presence of a ketone moiety in this substrate, it is difficult to achieve complete debenzylation without at least partially reducing the ketone. Accordingly, the resulting product will have over-reduced product as well. It is important to note that amines can poison the catalyst, killing after only a few reactions. By including acetic acid, this process is mitigated; however, the presence of acid in the reaction mixture means that this process cannot be coupled to reprotection steps like tBOC (N-tert-butoxycarbonyl, derived from di-tert-butyl dicarbonate) protection. If such a transformation is desired, the product must first be filtered and then reprotected. Conversely, the reaction could proceed in one step if the experimenter is willing to resupply the catalyst often.
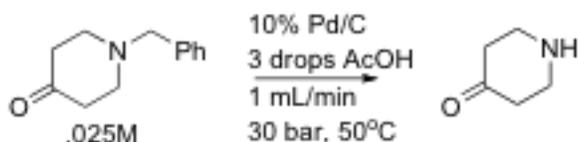

Figure 9. Hydrogenolysis of N-benzyl protecting group

Protocol

1) Insert 10% Pd/C CatCart® (THS 01131).

2) Set parameters accordingly:

Flow rate = 1.0 mL/min

Hydrogen gas production = ON

Pressure = 30 bar

Temperature = 50°C

2) Run 50% tetrahydrofuran in water solution and hydrogen through the machine for five minutes to cleanse the reaction vessel of impurities and load the catalyst with hydrogen.

3) Dissolve 47 microliters of 1-benzyl-4-piperidinone (0.25 mmols) in 10 milliliters of tetrahydrofuran:water : 5mL:5mL.

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4) Add 3 drops of acetic acid to the same 10 milliliters of solution.

5) Remove the Teflon inlet line from the solvent reservoir, and insert it into the reactant solution. Complete this step as quickly as possible to prevent air bubbles from entering the line.

6) Attach a clean, empty collection vial to the hydrogenated product collector.
7) As the reactant solution approaches dryness, refill the graduated cylinder with 2-3 milliliters of 50% tetrahydrofuran in water to maximize yield. Complete this rinse three times.

8) Before the reactant solution reaches dryness, switch the Teflon inlet line back to the solvent reservoir, and run solvent through the machine for five minutes.

9) Hit the stop button, and wait for hydrogen gas and pressure to be released from the machine.

10) Hit the shutdown button, and turn off the machine.

11) Remove solvent from the product using a rotary evaporator.

12) Add about 5 milliliters of dichloromethane to the white precipitate. While stirring, add sodium hydroxide to the product solution dropwise until the precipitate dissolves. Extract the organic layer and remove the dichloromethane from the product using a rotary evaporator.