

Hazards associated with laboratory scale hydrogenations

We report hazards associated with laboratory scale hydrogenations and the best practices for handling catalyst and hydrogen with three case studies. Fire, runaway reactions and explosions are commonly associated with hydrogenations due to the involvement of pyrophoric catalysts, hydrogen, flammable solvents and pressure. Laboratory hydrogenation methods as well as procedures to minimize hazards associated with catalyst and hydrogen are presented.

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INTRODUCTION

Catalytic hydrogenations are extremely useful for chemical transformations on small and large industrial scales. Various functional groups (C=O, NO₂, C=C, etc.) are reduced using hydrogen over suitable catalysts such as Pd, Pt, Rh, Ni, and Ru at ambient and/or elevated pressure.^{1–6} The nature of the catalyst, purity of substrates, temperature, pressure, contaminants in the substrate, instability of intermediates, and solvents affect hydrogenation processes. The major safety concern for any hydrogenation reaction is fire and explosion due to the pyrophoric^{7,8a,b} nature of the catalyst, reagent, substrate, intermediate instability, and use of the flammable solvents, hydrogen and pressure (Figure 1). The primary hazard associated with any form of hydrogen is

inadvertently producing a flammable mixture, leading to a fire or detonation when exposed to air, oxygen, or sparks. Thus applying a systematic approach of risk analysis is critical for small as well as large-scale laboratory hydrogenations.

Catalytic hydrogenation of nitro compounds (Figure 2) is an economical route^{2,9–12} for generating pharmaceutical intermediates at laboratory and industrial scales. Such reductions via hydrogenation are a well-defined class of reactions with high hazard potential.¹³ Substrate impurities, the wrong choice of catalyst, contaminated hydrogen (carbon dioxide, carbon monoxide and hydrocarbons) and low concentration of catalyst are major contributing factors for the runaway reactions during hydrogenation of the nitro groups.

The reduction of nitro compounds requires higher temperatures and use of alcoholic/flammable solvents. Evaluation of operating procedures for the apparatus and a thorough inspection of reaction vessels are critical before manipulating any high pressure experiment.

A proper hazard assessment such as a literature search about substrate/intermediate reactivity, catalysts and solvent effects should be conducted for preventing runaway reactions associated to large scale and high pressure hydrogenations. Large scale reaction success also depends on the hands on experience of researchers. Standard operating procedures (SOPs) developed by a subject matter expert for the hydrogenations should be used for training new students and researchers. Proper

handling of catalysts is critical due to high reactivity before and after introducing hydrogen. Existence of any impurity or colored impurity in substrate can inhibit the catalyst activity resulting in partial reduction of the substrate and occasionally in a run-away reaction. Substrates should be completely purified prior to subjecting them to hydrogenations. Hydrogenation reactions are largely exothermic in nature and can eventually increase overall pressure inside the vessel.

LABORATORY HYDROGENATIONS AND HAZARDS

The primary hazard associated with any form of hydrogen is inadvertently producing a flammable mixture, leading to a fire or detonation (Figure 1). Use of hydrogen, pyrophoric catalyst, flammable solvents and generation of in situ unstable intermediates are the main safety concerns during laboratory hydrogenations. Laboratory scale hydrogenations are mostly carried out using a round bottom flask (ambient pressure), balloon method, suitable pressure vessels, shakers^{14,15} (Figure 3), or using a continuous-flow hydrogenation (H-cube). Understanding properties of hydrogen, catalysts, their manipulations and hands-on experience^{16,17} is critical for a successful hydrogenation at both small and large scales. Polar solvents (water) and low flammable solvents are preferred over non-polar and flammable solvents to prevent flash fires during catalyst addition and during spent catalyst isolation. If used properly, water generally

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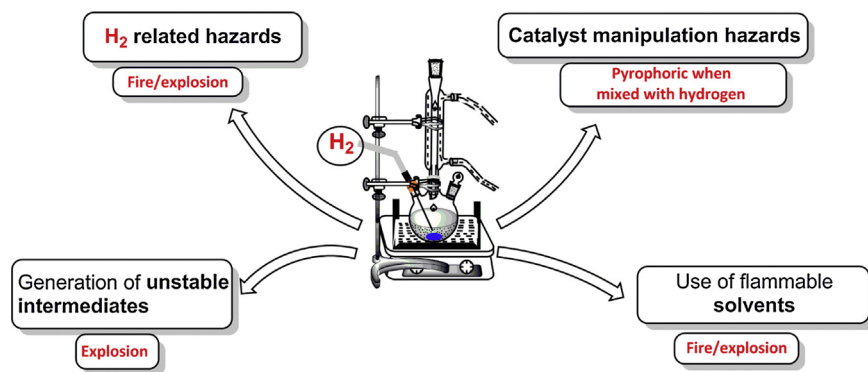


Figure 1. Hydrogenation hazards.

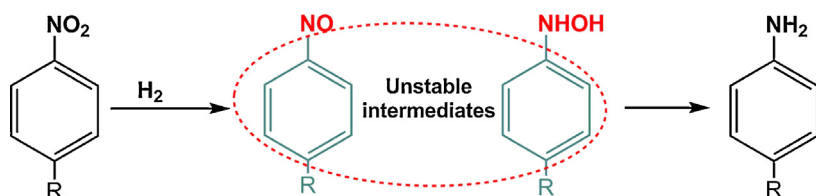


Figure 2. Formation of unstable intermediates during catalytic hydrogenations of nitro compounds.

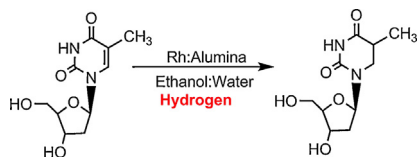


Figure 3. Ambient pressure hydrogenation of thymidine.

keeps the catalyst wet during transfer and filtration. For any hydrogenation reaction, flask and other glassware should be crack free, intact and free of contamination. A properly functional chemical fume hood or designated area for hydrogenation should be used to avoid the accumulation of hydrogen inside the lab. Use of open heating systems, such as oil baths and heating mantles should be circumvented to prevent flash fires. Uses of a water bath, sand bath or heating blocks are safer options.

Ambient Pressure Hydrogenation

Ambient pressure hydrogenations^{18,19} (Figures 3, 4a and 5) are frequently used in laboratories and generally safer to manipulate at smaller and larger scales in a properly functional chemical fume hood using a suitable glass

assembly (condenser, round bottom flask, cannula, septum and rubber tubing). An ambient pressure hydrogenation set-up is shown in Figures 4a and 6.

Although hazards associated with the catalyst, hydrogen and solvents still persist during ambient pressure hydrogenations, explosions associated with pressure are unlikely. In this method a round bottom flask is equipped with a condenser and a bubbler (needle) for hydrogen supply; the same needle is used for nitrogen purging. Hydrogen is directly bubbled from a cylinder (equipped with low flow regulator) by placing a Tygon tube and a cannula into the reaction mixture, comprising a catalyst and a substrate.

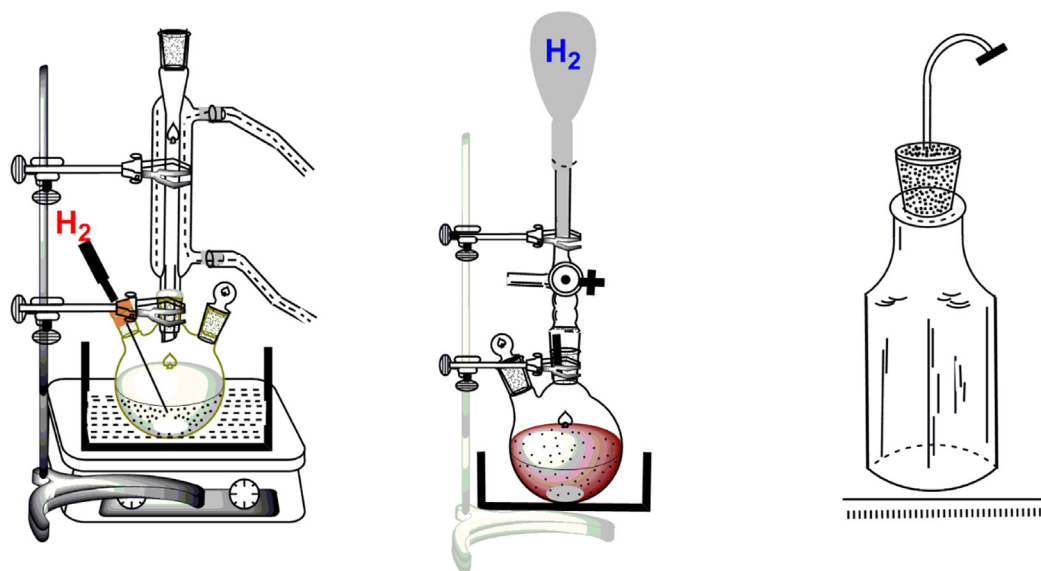
Loss of the solvent from the reaction is prevented using a cold-water condenser (Figure 4a). This is critical for

elevated temperature reactions. Solvent and catalyst loss should be monitored while purging the reaction mixture. Solvents such as methanol and ethanol will escape from the reaction mixture due to hydrogen purging. There is always a possibility of an explosion from the catalyst that was converted into dry powder adsorbed with hydrogen. During transfer, a dry catalyst will disperse into air and around the flask if nitrogen flow is not regulated. Aqueous solvents (water and water: alcohol mixtures) are preferred over organic solvents for hydrogen bubbling due to their high boiling point and low flammability.

A cold condenser is required to avoid a quick evaporation of the solvents from the reaction. A blanket of inert gas can also be supplied, using a funnel, over the beaker containing the solvent and catalyst being transferred to the reaction vessel (Figure 5).

Hazards

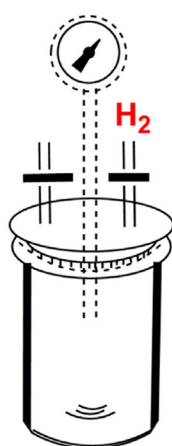
Ambient pressure hydrogenations are the safest among all hydrogenations if conducted using a proper SOP and reaction set-up inside a chemical fume hood. Hazards related to pressure are generally eliminated when hydrogen gas is bubbled through a reaction mixture at ambient pressure. Also, ambient pressure hydrogenations are easy to monitor using TLC, GC and HPLC, and reaction aliquots which are withdrawn easily without dis-assembling the reaction set-up. Although hazards associated with the catalyst and hydrogen are still present, uncontrolled reactions are less likely. Analyzing planned reactions to identify hazards¹⁶ and determining appropriate controls are critical for all hydrogenation reactions in laboratory. The “What if strategy”²⁰ (Table 1) developed by the American Chemical Society’s Committee on Chemical Safety’s can be employed to understand hazards associated with laboratory hydrogenation at various steps. Table 1 highlights some of the safety issues associated with ambient pressure hydrogenations; however various factors such as reaction scale, catalyst nature, substrate and solvent should be taken into consideration during a hazard assessment.



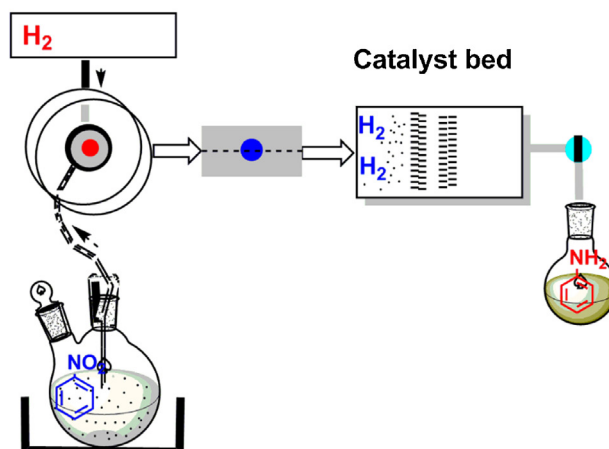
(a) Ambient pressure hydrogenation

(b) Balloon method

(c) Hydrogenation using Parr apparatus



(d) High-pressure vessel



(e) Continuous flow hydrogenation

Figure 4. Various laboratory hydrogenation techniques.

Balloon Method

Balloon hydrogenations are common in the laboratory and are convenient for small-scale hydrogenations. Balloons (Figure 6) used for hydrogenations should be able to provide an oxygen-free atmosphere. Therefore, thick-wall, natural latex rubber balloons are appropriate for filling hydrogen.

Slight positive pressure is maintained inside the balloon, which serves as a reservoir to accommodate pressure changes and to ensure net flow of gas out of the vessel in the event of a small leak in the system. During the process, the hydrogen balloon is attached to a Tygon tube to fit to a three-way adapter attached to a round bottom flask (Figure 6). A three way glass adapter attached to a Schlenk

line is used to supply the inert gas, vacuum²¹ and hydrogen to the flask. The following order is generally preferred for the catalyst addition (Figure 7) to prevent flash fires arising from the catalyst contact with solvent.

Hydrogen filling inside a balloon must be conducted inside a chemical fume hood. The balloon should not be over pressurized during hydrogen filling. Degassing of a reaction mixture

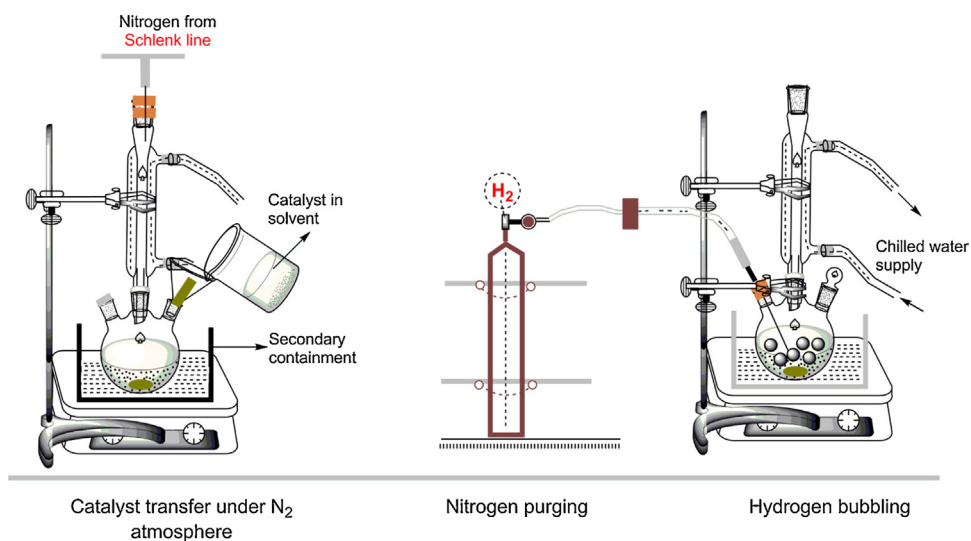


Figure 5. Ambient pressure hydrogenation.

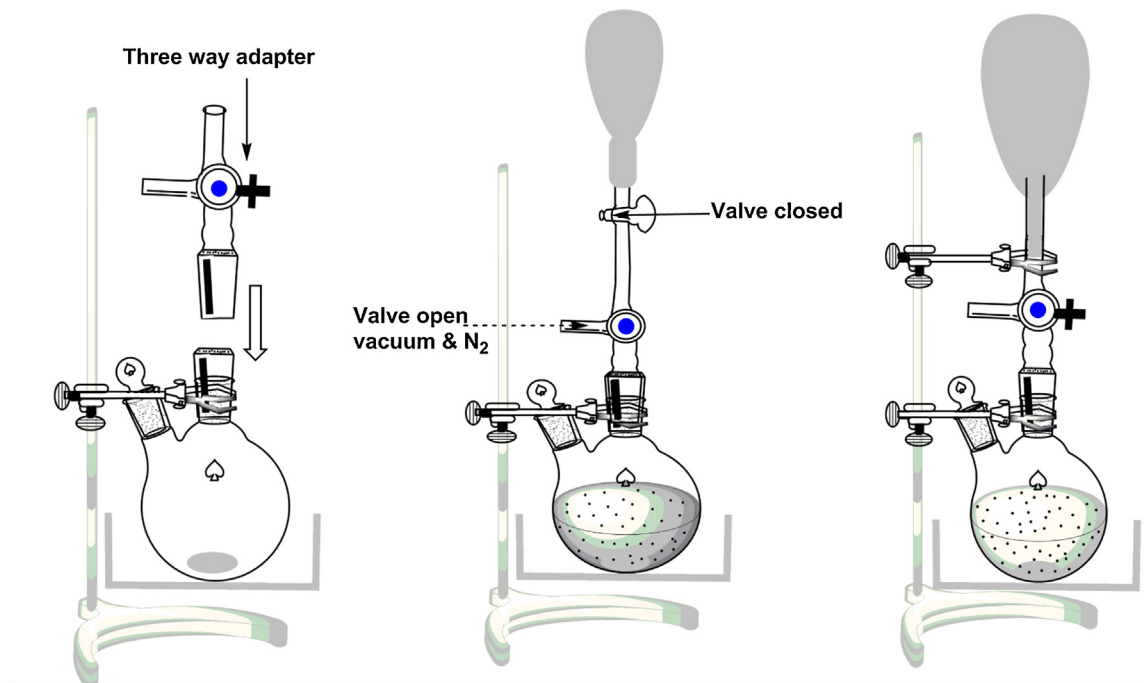


Figure 6. Balloon method hydrogenation techniques (use of a three way adapter, balloon attachment and hydrogen addition to reaction mixture).

is carried out using vacuum or purging with an inert gas (nitrogen or argon) before delivering hydrogen.

Shaker Hydrogenations

Parr reactors (shaker) are used for small scale hydrogenations in laboratory. A variety of shakers are available (250–2,250 mL capacity, heating

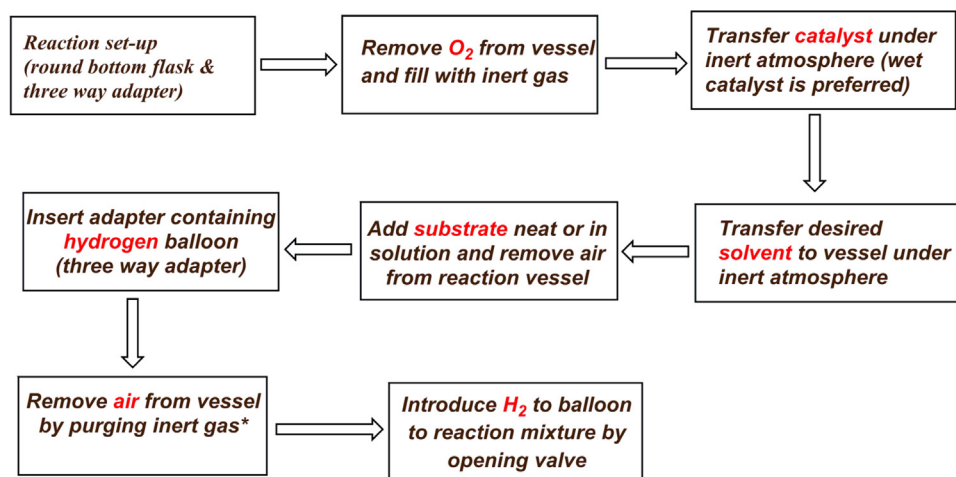
capacity up to 80 °C) from vendors. The instructional manual provided by the vendor must be followed for the instrument and reaction bottle and/or vessel. A dedicated fume hood or other suitable area with a proper barricade is recommended to protect researchers from fire and run-away reactions.

High-Pressure Hydrogenations

A high pressure reaction is generally difficult to manage and also requires hands on experience with the reactor and detailed subject knowledge. Limited alternatives^{22,23} are available for high pressure hydrogenations. High pressure hydrogenations are generally carried out using a suitable pressure

Table 1. Ambient Pressure Hydrogenation Conducted at Reflux Temperature (Use of Flammable Solvent, Pyrophoric Catalyst and Hydrogen Gas).

What if	Answer	Result	Consequences	Recommendations
Cold water supply tubing separated from condenser during reaction	Solvent used for rxn. Will easily escape from the condenser	Catalyst/rexn. mixture becomes dry	Fire, explosions and flooding in the lab and loss of substrate	Make sure water tubing is attached tightly, and water pressure is controlled well
Oxygen is not removed from rxn. mix. before introducing hydrogen	Oxygen hydrogen mix. may form detonable mix.	Explosions and fire	Assembly/product loss	Remove oxygen completely from rxn. mix. before introducing hydrogen
Catalyst dispersed inside the fume hood during transfer	Enough catalyst is not available for the rxn.	Partial transformation of substrate	Fume hood fires, difficulty in product isolation	Proper method should be used to transfer catalyst to the reaction vessel
Hydrogen flow is not controlled well	Catalyst will disperse on the wall of the flask Solvent will easily escape from reaction vessel	Enough catalyst is not available for rxn. Will reduce qty. of solvent from vessel	Difficulty to separate catalyst from flask, incomplete transformation	Hydrogen flow must be controlled using a dual stage regulator



*When vacuum applied, care must be taken to avoid solvent evaporation

Figure 7. Catalyst addition sequence during balloon hydrogenation.

vessel which is normally equipped with an agitator, heating system and a temperature controller. The responsibility for safe usage is that of the researcher not the vendor. A number of pressure vessels are available for high pressure hydrogenations from various vendors. High-pressure vessels are equipped with a pressure release valve to allow the safe venting of reaction contents in

the event of pressure build-up; and to prevent runaway reactions.²⁴

Hazards

Over pressurizing the pressure vessels can cause fatal explosions and fire in the laboratory. Numerous laboratory fires and property damage have been reported across the academic institutions associated to high pressure

hydrogenations. Therefore, a thorough hazard assessment is very critical prior to conducting high pressure hydrogenations (Table 2) along with hands-on experience and subject knowledge.

Maintenance and service of the vessel must be completed according to the vendors guide. High pressure hydrogenations should always be performed inside a chemical hood along with a

Table 2. High Pressure Hydrogenation Conducted at Higher Temperature.

What if	Answer	Result	Consequences	Recommendations
Vessel over-loaded with solvent and reagent	Pressure will increase inside the vessel	Discharge from vessel, uncontrolled rxn.	Fire and explosions	Never fill reactors 2/3 of their ability
Pure substrate is not used for hydrogenation	Hydrogenation will not proceed smoothly	Runaway rxn. pressure rise	Difficulty in product isolation	Use pure substrate for hydrogenations
Reaction temperature is not controlled	High pressure build-up, substrate and product decomposition	Runaway rxn.	Fire and explosion	Temperature of rxn. should be controlled prudently
Reaction mixture is not cooled before catalyst separation	Solvent will evaporate fast	Catalyst will get dry and possibility of solvent ignition	Fire	Reaction mix. should be cooled before catalyst separation (filtration)

blast shield. Chemical fume hood sashes should remain closed at all times except during reaction set-up, addition of the chemical to the reaction vessel as necessary, and during work-up of the reaction mixture. When high pressure hydrogenations are conducted in the laboratory, warning signs should be posted on the chemical fume hood to warn others in laboratory. Routine high pressure hydrogenations in a laboratory should be conducted in a designated facility to contain explosion and fires. Leak detection and an emergency shutoff or excess flow control devices are useful for controlling the leak and preventing pressure build-up.

Continuous-Flow Hydrogenations

Continuous-flow hydrogenations (Figure 8)^{22,23} are safer options for small as

well as large scale laboratory hydrogenations. Continuous-flow hydrogenation systems are superior as compared to batch hydrogenations in terms of hydrogen handling, catalyst manipulation and pressure. During continuous-flow hydrogenations, the catalyst is restricted in a closed cartridge and never comes in contact with air which reduces flash fire and other solvent/catalyst hazards in a laboratory set-up.

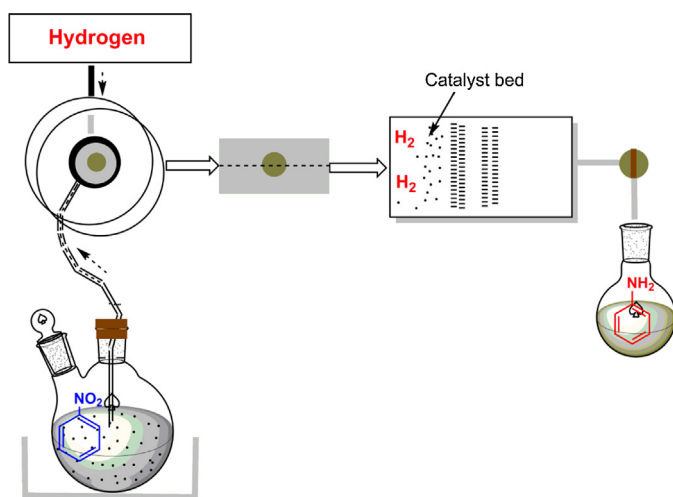
SAFETY

Hydrogen Manipulations

There are many regulations and standards which apply to hydrogen.²⁵⁻²⁷ Hydrogen gas should be stored in well-ventilated areas and away from oxidizers, open flames, sparks and

other sources of heat and ignition.²⁸ Manipulations involving hydrogen are safely conducted when proper guidelines and techniques are applied during hydrogenations. Hydrogen leaks through lines are difficult to detect by humans. Hydrogen is a nontoxic gas classified as a simple asphyxiant. Regulators, joints, flanges, diaphragms, gaskets, and various seals and fittings used for hydrogen manipulations can become a source of leaks due to incorrect alignment and improper maintenance. Any hydrogen delivery system in combination with a reaction set-up should be checked for any leak before pressurizing the line and equipment. Inert gases should be used to check for leaks in the lines as well as pressure vessels. Hydrogen has no threshold limit value (TLV). The primary hazard associated with any form of hydrogen is inadvertently producing a flammable mixture, leading to a fire and detonation. An explosion cannot occur without an oxidizer inside a vessel or cylinder when hydrogen is contained.

Oxygen should be replaced with nitrogen from the mixture of catalyst, solvent and substrate (Figure 9) before introducing hydrogen to the reaction mixture. The hydrogen pressure of the vessel should be monitored prudently to avoid any runaway²⁹ reaction. There should be no ignition sources close to a hydrogenation reaction such as open flames, electrical equipment, or heating equipment (Figure 10). Static electricity can also generate sparks that will ignite hydrogen-air or hydrogen-oxygen

**Figure 8. Continuous-flow hydrogenation set-up.**

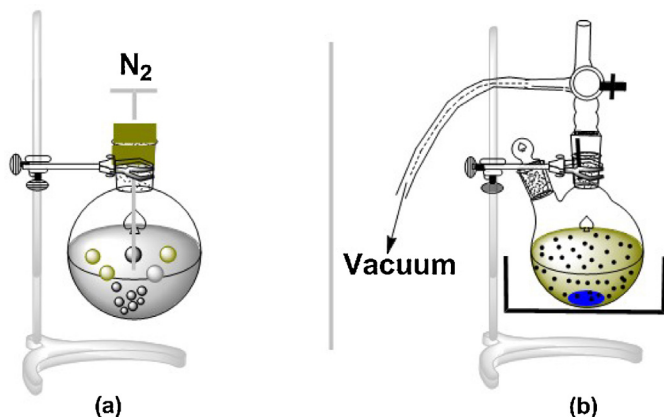


Figure 9. Hydrogen removal from reaction mixture using (a) nitrogen and (b) vacuum.

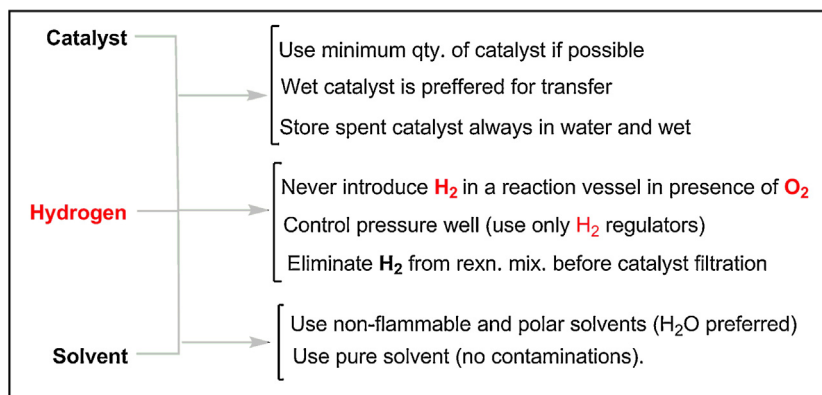


Figure 10. Best practices for catalyst, hydrogen and solvent handling.

mixtures. Many common articles, such as hair or fur when combed or a leather belt operating on a machine can generate a static electricity.

Incident 1

A small fire was started while a researcher was working on a hydrogenation catalyzed by palladium-on-carbon. Upon completion of the hydrogenation, the researcher performed three vacuum/purge cycles with dry nitrogen gas in order to eliminate any remaining hydrogen gas in order to reduce the risk of ignition during filtration. The palladium-on-carbon was filtered through a sintered glass funnel covered with Celite 545. The filter cake was subsequently washed with wet methanol and covered with sand. The contents of the funnel were dumped into a waste container and covered with additional sand. A fire

was ignited when the researcher attempted to transfer a minute amount of residual palladium-on-carbon from the funnel to a designated waste container.

The fire was quickly extinguished with a dry chemical fire extinguisher. No one was injured during the incident and there was no damage to the facility. The researcher performing the reaction was well aware of the precautions required to safely handle palladium-on-carbon.

The safety office recommended making a wet slurry, by adding water to the palladium-on-carbon Celite 545 mixture, prior to transferring the spent palladium-on-carbon to a designated waste container. It must be kept away from any combustible materials.

In another palladium-on-carbon fire, a researcher was performing a hydrogenation reaction using palla-



Figure 11. Catalyst fire inside trash receptacle.

dium on carbon as a catalyst to reduce the nitro group using standard protocol. Upon completion of filtration, the catalyst was separated from diatomaceous earth pad and mistakenly tossed into a normal trash receptacle. That evening the material was placed in the garbage, including the residual catalyst which was contaminated with diatomaceous earth. It ignited the combustible materials in the trash receptacle (Figure 11).

This trash receptacle fire could have been avoided using an appropriate disposal container for the spent catalyst in the lab.

All sources of ignition should be isolated from hydrogen cylinders, reaction set-up. Hydrogen cylinders must be kept away from oxygen, chlorine and other incompatible materials. Never exchange regulators, hoses and other appliances used for hydrogen gas. A regulator or step-down pressure valve should be used to pressurize low-pressure equipment from a high-pressure source. After pressurizing equipment from a high-pressure source, the equipment should either be disconnected or the connecting piping/tubing should be vented to atmospheric pressure. This will prevent the accidental buildup of excessive pressure inside the low-pressure equipment due to leakage from the high-pressure source.

Catalyst Manipulation

Proper selection of a suitable catalyst and solvent and determining their ratio is critical for a catalytic hydrogenation. All catalysts should be considered potentially pyrophoric and must be handled prudently. However, a dry catalyst often requires special attention

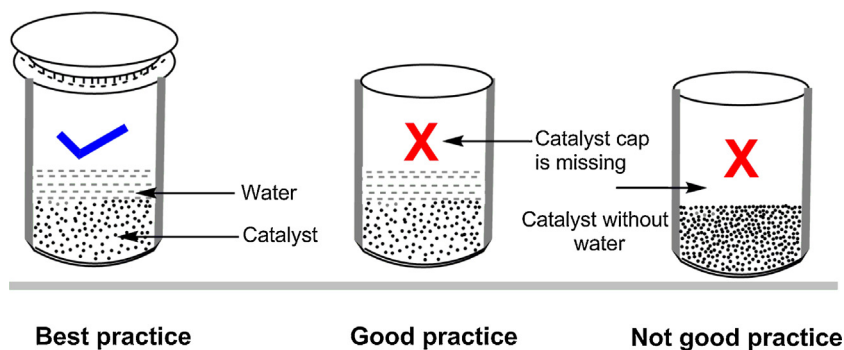


Figure 12. Proper storage of spent catalyst.

because the potential of igniting flammable materials is greater than with a wet catalyst. The risk of spontaneous ignition should be reduced by cooling both the catalyst and the organic materials before performing the mixing process under inert gas atmosphere, such as nitrogen.

Spent catalysts with absorbed hydrogen may ignite if dried in the air, especially in the presence of organic materials. Therefore, used and filtered catalysts should be kept water-wet (Figure 12) and out of contact with combustible solvents and vapors.

Even fresh Pd/C catalyst can catch fire from a small static charge developed from scratching the catalyst bag. Therefore, transfer of the catalyst should be avoided directly from bag into reaction vessel.

Incident 2

A researcher was cleaning out a small gas chromatography vial inside a chemical fume hood using ethyl acetate, when the researcher spilled a few drops of ethyl acetate onto a small cloth pad he had in his hood. Small sparks appeared on the mat which then caught on fire as the ethyl acetate burned. The researcher then noticed that the test tube rack with ethyl acetate-hexanes solvent mixtures had caught on fire. The fire was mostly contained in the back far right corner of the hood and minimal cosmetic damage to the hood occurred. The initial spark likely began from a small amount of activated palladium carbon (Pd/C) on the pad mentioned. The researcher had used Pd/C catalyst to set up a hydrogenation the night before. The drops of solvent must have

disturbed the reagent in the mat, which caused the spark and subsequent fire.

To avoid similar incidents after hydrogenations, prompt cleanup of spent catalyst, solvent and chemical fume hood surfaces should be conducted.

Catalyst Filtration/Isolation

Most catalyst associated fires inside laboratories occur during catalyst separation (filtration), therefore applying prudent steps are critical to avoid fire. Residual hydrogen should be removed completely from the reaction mixture before catalyst filtration separation (filtration) using inert gas (N₂ bubbling; Figure 9a) or by applying a low vacuum (Figure 9b) to the reaction vessel. During catalyst filtration, inert atmosphere can be generated using a plastic funnel

as shown in Figure 13. Catalyst filtration in the laboratory is generally carried out using a bed of Celite (or similar filter aid).

Hydrogenations conducted at an elevated temperature regularly require cooling before work-up to avoid the catalyst drying. Use of high vacuum pump for catalyst filtration will dry the catalyst residue and filtration bed. The residual catalyst that sticks to the flask surface and joints of the vessel should be removed using additional solvent (water or polar solvents preferred) with proper safeguards. When the residual catalyst is difficult to remove from the surface of the reaction vessel, it should be covered with water to keep the catalyst wet.

The vacuum tube from the filtration flask should be detached before drying the catalyst bed. Several mL of water should be added to the cake to keep the catalyst wet. Never leave the catalyst filtration unattended. Applying low vacuum to a reaction vessel will prevent bumping the reaction mixture into vacuum system. The vacuum system contaminated with the catalyst requires proper cleaning and may require an oil change for the pump.

Incident 3

A researcher was performing a Raney nickel catalyst filtration from a reaction

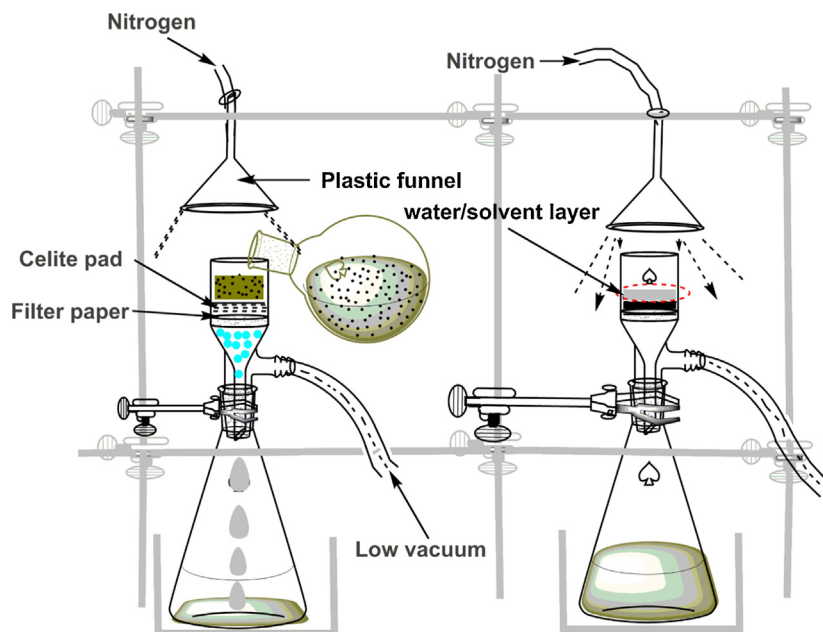


Figure 13. Pd/C catalyst filtration system.

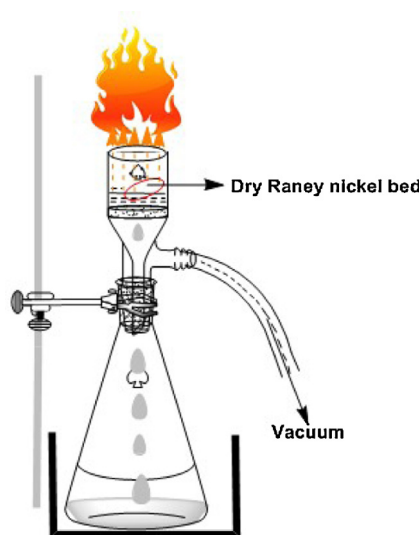


Figure 14. Catalyst fire during filtration.

mixture using a Celite pad. A water aspirator was used for filtration (Figure 14). The researcher left the scene after transferring all reaction mixture to the funnel. After five minutes the catalyst ignited causing a small fire inside the filtration funnel.

This incident could have been avoided if the catalyst was kept wet using water during filtration, and the catalyst filtration was not unattended.

A dedicated waste jar containing water is preferred to collect the spent catalyst recovered from hydrogenations. Removal of the residual catalyst from filter paper and Celite pad is generally difficult due to nature of the catalyst. Therefore, those items should be submerged into water until disposed of safely from the lab. Laboratory scale hydrogenations typically consume a low quantity of the desired catalyst for hydrogenations; therefore the catalyst is not recycled through vendors. When hydrogenation catalysts are used often for the synthesis purpose, two separate small glass containers should be used for storage purpose and one for storing unwanted catalyst and one for paper and Celite. The funnel contaminated with a residual catalyst should be submerged into a water bath before the catalyst becomes dry. Recovery and reuse of the catalyst is recommended when a large quantity of spent catalyst is generated in labs.

Some catalysts are then sold for a high price. Similarly, if there is any catalyst contamination in the Celite pad, the upper layer of the pad should be removed for disposal or storage purpose.

Catalyst should remain wet during entire hydrogenation manipulation. Palladium on carbon recovered from catalytic hydrogenation reactions by filtration requires careful handling,^{17,24} because it is usually saturated with hydrogen and will ignite spontaneously on exposure to air. The filter cake should never be allowed to dry, and the moist material should be added to a large quantity of water and disposed of properly.

BEST PRACTICES FOR LABORATORY HYDROGENATIONS

- Select a vessel/set-up such as a reaction flask, pressure vessel and shakers appropriate for the experiment.
- Review the operating procedures for the apparatus and inspect the vessel before each experiment. Glass vessels with a crack are at risk to break under pressure.
- Remove all oxygen from the vessel/solutions either using nitrogen or vacuum using a Schlenk line.
- Stay well below the rated safe-pressure limit of the vessel due to

exothermic nature of reactions or intermediate unpredictability.

- Monitor the reaction prudently and do not leave hydrogenation reactions unattended.
- All catalysts must be handled prudently because of their high reactivity before and after use.
- Keep a bucket of sand nearby manipulations to quickly smother a smaller fire.
- Use of gas burners, open flames and oxidizers should be avoided near the hydrogenation set-up.

SUMMARY

Laboratory hydrogenations are useful for chemical transformations at gram as well as multi-gram scales. Several high risk operations such as catalyst transfer, use of high pressure hydrogen cylinders, hydrogen purging, vessel pressurization and catalyst manipulations are involved throughout the hydrogenation. Hydrogenations that are conducted at ambient pressure are generally safer compared to high pressure. Hazard identifications and their mitigations are critical for small as well as large scale hydrogenations. Additional care should be taken whenever substrates or intermediates containing nitro groups are reduced using catalytic hydrogenations. Inexperienced researchers should use the lowest scale reduction (hydrogenation) for high hazardous or high pressure reduction and should seek advice from an experienced researcher. First time users of high pressure vessels should practice the manipulations including vessel operation without using catalyst and flammable solvents. The spent catalyst must be kept wet at all times. Dry catalysts are prone to fire. Special precautions should be taken while working with high pressure vessels. Safe pressure limits provided by a vendor should be followed for any high pressure vessel in order to avoid the runaway reactions²⁹ caused by reaction exothermicity or intermediate unpredictability. The proper choice of personal protective equipment (PPE) is imperative. A proper risk assessment should be performed prior to beginning any hydrogenations to identify

the proper PPE for the specific operations.

ACKNOWLEDGEMENTS

I sincerely thank the UW-Chemistry faculty/staff, for providing useful information about hydrogenations to develop this document. I also thank Dr. Paul Umbeck, Dr. Rob McClain and Dr. Neal Langerman for helpful discussion.

Note: The information provided in this manuscript is the author's opinion and does not represent the opinion of organizations where I worked or am working with. "I elucidated my arguments from experience". This manuscript serves only as a guideline and is no way intended to serve as the sole training source for a procedure, method or task. All references or mention of commercial products, trade names, trademarks, manufacture, distributor or otherwise, are meant to be examples and do not represent endorsement of a product or service.

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