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Phase-Separation Aided Heterogeneous Catalysis
For Selective Hydrogenation of Nitriles to
Primary Amine and Its Derivatives

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2017

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Chapter 1

Introduction

1.1 Green Chemistry

*Definition of Green Chemistry: the utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture, and applications of chemical products.*¹

Green Chemistry plays a vital role by advancing/developing technology/methodology in key research areas, such as catalysis, design of safer chemicals and environmentally benign solvents, and development of renewable feedstocks. Advances in green chemistry can solve global issues such as climate change, energy production, and availability of a safe and adequate water supply, food production, and release of toxic substances in the environment. This global issues lead chemists into developing a new methodology for clean and safer chemical process. The design of environmentally benign products and processes may be guided by the 12 Principles of Green Chemistry.^{1, 2}

1. It is better to prevent waste than to treat or clean up waste after it is formed.
2. Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
3. Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. Chemical products should be designed to preserve efficacy of function while reducing toxicity.
5. The use of auxiliary substances (e.g. solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.
6. Energy requirements should be recognized for their environmental and economic impacts and should be conducted at ambient temperature and pressure.
7. A raw material of feedstock should be renewable rather than depleting wherever technically and economically practicable.
8. Unnecessary derivatization (blocking group, protection/deprotection, and temporary modification of physical/chemical process) should be avoided whenever possible.
9. Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
10. Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products.
11. Analytical methodologies need to be developed further to allow for real-time in-process monitoring and control prior to the formation of hazardous substances.
12. Substances and form of substance used in a chemical process should be chosen so as to minimize the potential for chemical accidents, including releases, explosions, and fires.

Tang *et al.* have produced a simpler statement of the principles of green chemistry that is understandable to wide range of audience.²

Principles of green chemistry = productively.

- P- Prevent wastes
- r- Renewable materials
- o- Omit derivatization steps
- d- Degradable chemical products
- u- Use safe synthetic methods
- c- Catalytic reagents
- t- Temperature, pressure ambient
- i- In-process monitoring
- v- Very few auxiliary substances
- e- E-factor, maximize feed in product
- l- Low toxicity of chemical products
- y- Yes, it is safe

Hazard is not simply defined as toxicity but it includes acute and chronic toxicity, carcinogenicity, flammability, direct ecological impact and atmospheric damage. The goal of Green Chemistry is to reduce the hazards associated with the products and processes and also maintain the quality of life. Risk can be summarized in simple term as the product of hazard of particular substance and the exposure to that substance. $Risk = Hazard \times Exposure$. Green Chemistry seeks to reduce the risk through reducing the hazard and controlling exposure. Generally, risk reduction approaches focus on reducing exposure to hazardous substances.

1.2 Green reaction media for organic synthesis

Green chemistry marked a paradigm shift from traditional concepts of product innovation and chemical yield to economic value, eliminating waste and avoiding the use of toxic and/or hazardous substances. Environmental acceptability of any chemical processes depends mainly on E factor. *E factor can be defined as the mass ratio of waste to desired product.* It is the actual amount of waste produced in the process taking into account chemical yield, reagents, solvents losses, all process aids and, in principle, even fuel (although this is often difficult to quantify), except for water. In the case of aqueous waste only the inorganic salts and organic compounds contained in the water are counted to avoid exceptionally high E factors. A higher E factor means more waste and, consequently, greater negative environmental impact.

These enormous quantities of waste consist primarily of inorganic salts, such as sodium chloride, sodium sulfate, and ammonium sulfate that are formed in the reaction or in subsequent neutralization steps. The E factor is dramatically larger on going downstream from bulk to fine chemicals and pharmaceuticals, partly because the production of latter (fine

chemicals and pharmaceuticals) involves multistep syntheses and partly because stoichiometric (inorganic) reagents and solvents are used.³ The sheer magnitude of the waste management problem in the manufacture of chemicals is readily apparent from the consideration of the amount of waste produced per kg product, in different segments of the chemical industry (**Table 1.1**). The organic solvents in the amount of more than US\$ 5 billion are used for the synthesis of chemicals annually, which has significant impact on environment.⁴ With respect to Green Chemistry principles, there is a need to replace conventional organic solvents completely or at least partially to green ones.

Table 1.1 E factor in various chemical industries.

Industry segment	Product tonnage^a	kg waste^b /kg product
Oil refining	10 ⁶ –10 ⁸	<0.1
Bulk chemicals	10 ⁴ –10 ⁶	<1–5
Fine chemicals	10 ² –10 ⁴	5–>50
Pharmaceuticals	10–10 ³	25–100

^aTypically represents annual production volume of a product at one site (lower end of range) or world- wide (upper end of range).

^bDefined as everything produced except the desired product (including all inorganic salts, solvent losses, etc.)

Several attempts have been reported for the development of alternative reaction media using water⁵⁻⁸, fluoros liquids,⁹⁻¹² ionic liquids,¹³⁻¹⁵ dense phase CO₂¹⁶⁻¹⁹ and others.²⁰⁻²¹ The use of water as solvent is the most attractive option because of its cheap, abundant, non-flammable and non-toxic nature. Water can be used in several chemical reactions, in which it forms a biphasic system (aqueous-organic) with many organic liquids due to low solubility of organic liquids into aqueous phase. The fluoros liquids show immiscibility with organic liquids at room temperature, but become miscible at increasing temperature, allowing the easy separation of fluoros liquids, organic products and/or catalysts. The ionic liquids are non-flammable and highly tunable with small pressure changes. However, high cost, difficulty in purification and toxicity make fluoros and ionic liquids non-practical for reaction media. The physical and chemical properties of CO₂ are well-studied. The dense phase CO₂ has attractive advantages for a green ideal reaction medium, which will be explained in detail later.

1.3 Multiphase catalytic reaction media under pressurized CO₂

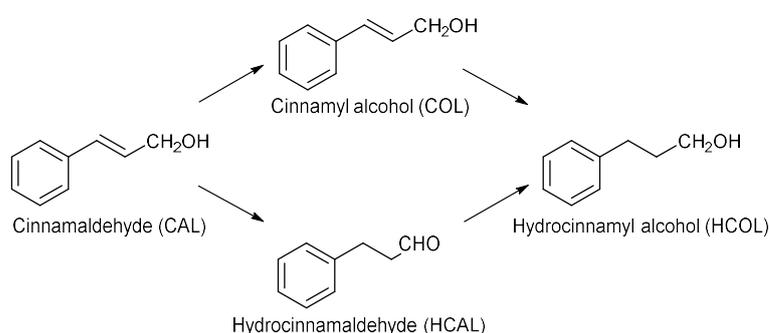
Dense phase CO₂ is a convenient and important component in green multiphase reaction and separation processes.²²⁻²⁵ The use of CO₂ as solvent gives easy separation by depressurization and CO₂ can work as a solvent at low temperature. We will examine the phase behavior of a mixture of organic liquid (substrate, solvent) and CO₂ at different pressures. When the solubility of organic liquid in CO₂ is large or the volume of organic liquid is small, the liquid - gas biphasic state will change into a single-phase state with increasing CO₂ pressure (**Figure 1.1** left). When the solubility of organic liquid in CO₂ is small or the volume of organic liquid is large, the biphasic state will remain unchanged but the organic phase will expand by the dissolution of CO₂ with increasing CO₂ pressure (**Figure 1.1** right). This expanded liquid phase is called as CO₂-dissolved expanded liquid phase (CXL). The single phase (**Figure 1.1** left) can be a reaction medium but the low solubility of reacting species (substrate, product, catalysts) is often a big problem and the reaction should be conducted at elevated CO₂ pressure. The CXL can also be a reaction medium for which the influence of CO₂ dissolution into the liquid phase should be considered. The dissolution of CO₂ may promote the dissolution of coexisting gaseous reactants (O₂, H₂, CO). In addition, the CO₂ molecules dissolved in the liquid phase may interact with substrates, intermediates, products, and/or catalysts, affecting their chemical reactivity. Several previous works demonstrate the interesting features of CXL media for various reactions such as oxidation, hydrogenation, hydroformylation, Heck coupling, and others.²⁶⁻²⁹

The dissolution of CO₂ has been reported as a phase switch to make a system of immiscible fluorinated metal complex and organic solvent into a homogeneous solution in which the complex catalyst can work as expected.³⁰⁻³⁴ The addition of gaseous CO₂ to fluorine-organic biphasic systems results in a single homogeneous liquid phase at temperatures well below the upper critical solution temperature of the binary liquid mixture.³¹ The fluorocarbons such as perfluorohexane, FC-75 (90% perfluoro-2 butyltetrahydrofuran) and FC-40 (95% perfluorotributylamine) have been used with equal volumes of organic solvents such as ethyl acetate, tetrahydrofuran, chloroform, acetone, and so on. The CO₂ pressure can tune the reaction system from heterogeneous to homogeneous one.



Figure 1.1. Phase behavior of an organic liquid phase in the presence of CO₂ at atmospheric pressure (center), at a high pressure giving a single homogeneous phase (left), and at a low pressure giving a CXL phase and a gas phase (right).

Zhao *et al.* reported the selective hydrogenation of cinnamaldehyde to cinnamyl alcohol using homogeneous Ru catalyst under CO₂ pressure (**Scheme 1.1**).³⁵ CO₂-expanded liquid phase showed a higher yield (> 98%) than obtained in scCO₂ (< 25%). The authors studied molecular interactions of CO₂ with cinnamaldehyde at different CO₂ pressures using *in situ* high pressure FTIR measurement. At ambient CO₂ pressure, the absorption band of $\nu(\text{C}=\text{O})$ of cinnamaldehyde was observed at 1740 cm⁻¹. This absorption band showed red shift from 1740 cm⁻¹ to 1690 cm⁻¹ when CO₂ pressure was increased to 8.5 MPa. In contrast, there was no change in the absorption band of $\nu(\text{C}=\text{C})$ at high CO₂ pressures. These results indicated that the reactivity of carbonyl group became increased at high CO₂ pressure while there was no effect on the reactivity of C=C, leading to the selective hydrogenation of cinnamaldehyde to hydrocinnamyl alcohol.

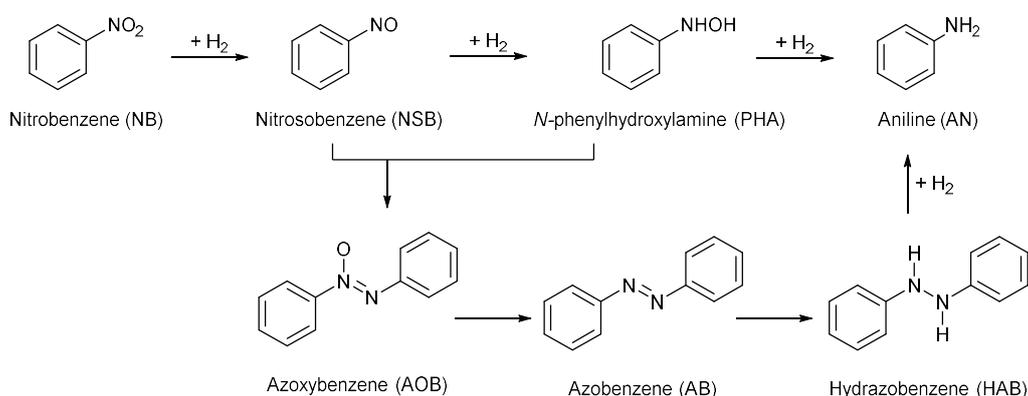


Scheme 1.1. Selective hydrogenation of cinnamaldehyde to cinnamyl alcohol

Meng *et al.* reported the selective hydrogenation of nitrobenzene to aniline by Ni/Al₂O₃ catalyst under CXL and scCO₂ conditions.³⁶ The hydrogenation of nitrobenzene mainly occurs through the direct hydrogenation route, i.e., nitrobenzene (NB) → nitrosobenzene (NSB) → *N*-phenylhydroxylamine (PHA) → aniline (AN). The conversion of nitrobenzene increased with CO₂ pressure in CXL phase. The low conversion of nitrobenzene was observed under homogeneous scCO₂ conditions (**Scheme 1.2**). It is interesting to note that the selectivity of the final product, aniline, was almost 100% in both CXLs and scCO₂; the phase behavior did not vary the product distribution in selective hydrogenation of nitrobenzene. *In situ* high pressure FTIR spectroscopy study evidenced the interaction of CO₂ with nitrobenzene and nitrosobenzene. It was revealed that the reactivity of nitrobenzene decreased in dense phase CO₂. The reactivity of nitrosobenzene and *N*-phenylhydroxylamine increased in the presence of dense phase CO₂. Dense phase CO₂ strongly interacts with NB, NSB, and PHA, modifying the reactivity of each species and contributing to positive effects on the reaction rate and the selectivity to aniline.

Meng *et al.* also examined the selective hydrogenation of chloronitrobenzene (CNB) to chloroaniline (CAN) by Ni/TiO₂ catalyst in dense phase CO₂.³⁷ The hydrogenation of chloronitrobenzene mainly occurs through the direct hydrogenation route, i.e., chloronitrobenzene (CNB) → chloronitrosobenzene (CNSB) → *N*-chlorophenylhydroxylamine (CPHA) → chloroaniline (CAN). Generally, dechlorination of chloroaniline is main difficulty

to achieve high yield of chloroaniline. The dechlorination of chloroaniline to aniline or chloronitrobenzene to nitrobenzene is another side reaction that decreases the selectivity to chloroaniline and results in the formation of hydrogen chloride. The same effect of dense phase CO₂ was again observed in selective hydrogenation of chlorobenzene to chloroaniline as observed in selective hydrogenation of nitrobenzene to aniline.³⁶ The selectivity to the desired product, chloroaniline, was >97% over the conversion range of 9-100%. The interaction of CO₂ with reacting species i.e. chloronitrobenzene, chloronitrosobenzene, and *N*-chlorophenylhydroxylamine improves the selectivity of chloroaniline. The nitro group of chloronitrobenzene interacts with CO₂ through its nitrogen and oxygen atoms.



Scheme 1.2. Possible reaction pathways for the hydrogenation of nitrobenzene

1.4 Benefits of using water with pressurized CO₂ in multiphase reaction media

From the viewpoint of green chemistry, water is gaining attention as a green solvent. The water is non-flammable and non-toxic and so it can act as an environmentally safe green solvent. It is also less costly. The organic reactions in water are a hot topic in current research field. When CO₂ dissolves in water, carbonic acid is formed by hydration of CO₂ in water, and the pH value of water is decreased by proton from carbonic acid (Eqn.(1)-(2)). It may accelerate the rate of a reaction catalyzed by an acid and modify the product selectivity therein.

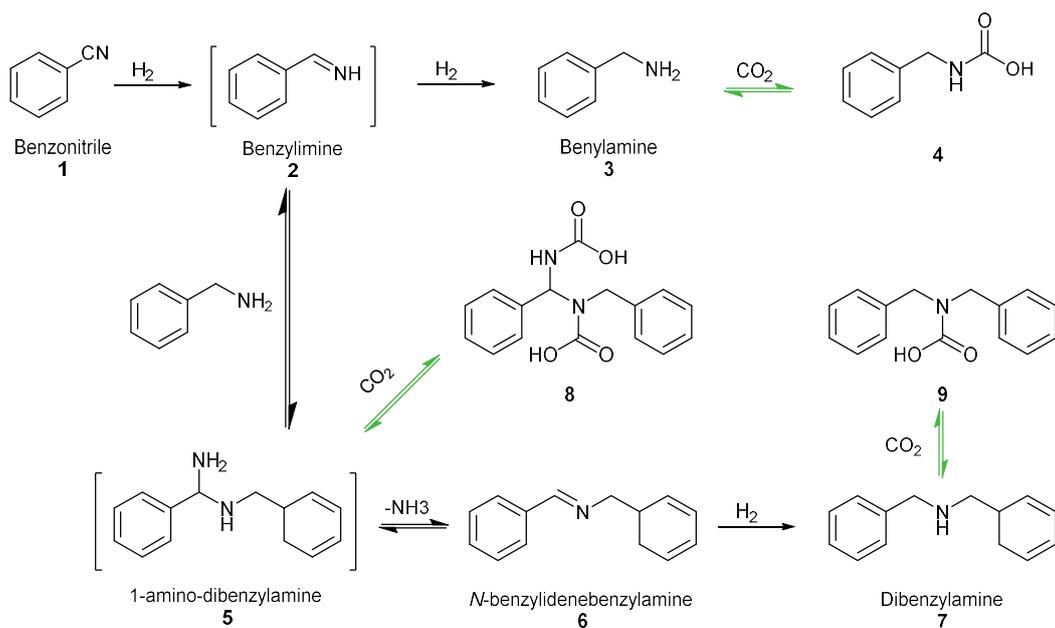


Meng *et al.* investigated the synergetic effect of water and low pressure CO₂ for selective hydrogenation of aromatic nitro compounds to aniline by Ni/Al₂O₃.³⁸ The hydrogenation of nitro aromatic compounds such as nitrobenzene, nitrosobenzene and *N*-phenylhydroxylamine showed better results in CO₂-H₂O medium than in H₂O medium alone. The conversion in hydrogenation of nitrobenzene in pure water was 21 % with 62% selectivity to aniline. In H₂O-CO₂ medium, the conversion was 55 % with 95% selectivity. The

hydrogenation of nitrosobenzene and *N*-phenylhydroxylamine showed slightly higher conversion and aniline selectivity in H₂O-CO₂ medium. The authors examined the effect of acidic nature by dissolving NaHCO₃ in H₂O and non-buffer H₂O. The enhancement in the solubility of a gaseous reactant H₂ in H₂O by dissolving CO₂ and the acidic nature of H₂O phase were main factors for the enhancement observed in conversion and selectivity.

Pd/C catalyzed hydrogenation of acetophenone in the presence of H₂O and CO₂ was reported by Hiyoshi *et al.*³⁹ The authors found that conversion of acetophenone was tripled by increasing the CO₂ pressure from 0 to 0.8 MPa with a high selectivity of 1-phenylethanol. To study the effect of acid formation in H₂O by dissolving CO₂, the reactions were carried out in the presence of acetic acid with water and the conversion of acetophenone was observed to increase, similar to that in the presence of water and CO₂. By addition of acid species in H₂O, the hydrogenation of carbonyl group of acetophenone was improved via interactions between the oxygen atom of carbonyl group and cationic species (H⁺) with Lewis acidity.

Cheng *et al.* reported selective hydrogenation of benzonitrile with Ni/Al₂O₃ catalyst. They used different multiphase reaction media such as solventless system, compressed CO₂ alone, *n*-hexane alone, *n*-hexane-CO₂ system, ethanol alone, ethanol-CO₂ system, H₂O alone and H₂O-CO₂ system.⁴⁰ The presence of compressed CO₂ retarded the rate of benzonitrile conversion in solventless, hexane and ethanol systems, but accelerated the rate in water. The desired product of benzylamine transforms to carbamates in the presence of CO₂ and precipitates out in CO₂ and hexane-CO₂ systems but dissolves in ethanol-CO₂ and H₂O-CO₂ media. The decrease in the rate of reaction observed in neat benzonitrile and hexane-CO₂ systems may be explained: benzylamine converted to carbamates, precipitated out, and covered the surface of catalyst. When a liquid solvent or substrate phase is pressurized by CO₂, it expands by dissolution of CO₂. This will facilitate the dissolution of other co-existing gases such as O₂, H₂, and CO, accelerating the reactions involved in these gaseous reactants, but at the same time, decrease the concentration of substrate and other reacting species in the reaction media (dilution effect).^{19, 26} The dilution effect was mainly responsible for retardation of the rate of reaction in ethanol-CO₂ system. The final effects of CO₂ pressurization, positive or negative, depend on the balance of those positive and negative factors. High concentration of gaseous H₂ in H₂O-CO₂ system was main reason for increased rate of reaction in H₂O-CO₂ system.



Scheme 1.3 Possible reaction pathways for the hydrogenation of benzonitrile

Yoshida *et al.* also demonstrated the superiority of water for hydrogenation of benzonitrile by Pd/Al₂O₃ catalyst.⁴¹ The transfer of water-soluble carbamates from organic phase to aqueous phase is responsible for the high selectivity of benzylamine, which can avoid the formation of undesired products such as secondary amine.

1.5 Direct synthesis of lactams through chemical trapping

1.5.1 Synthesis of Lactams from amines or nitriles

Selective catalytic transformation of nonfood biomass-derived platform compounds is a key technology in sustainable production of chemicals. In this context, levulinic acid (LA) has been identified as one of the most important platform compounds because it can be easily and economically produced from lignocellulosic materials and can be converted to various chemicals. In particular, *N*-alkyl-5-methyl-2-pyrrolidones, which can be produced by reductive amination of LA, are of importance as industrial solvents, surfactants, complexing agents, and intermediates in synthesis of functional compounds such as printing ink and fiber dyes.⁴³⁻⁴⁵ Most of the recent studies on this reaction using Ru⁴⁶ and Ir⁴⁷ complexes were use formic acid as a reductant⁴⁶⁻⁴⁹ and were reported as effective catalysts for this reaction. For a practical application, these homogeneous methods have disadvantages such as a difficulty in catalyst/product separation, inability of catalyst reuse, limited scope, and necessities of additives (ligands, t-Bu₃PHBF₄⁴⁶ or HCOONa⁴⁷), excess amount of formic acid (>13 equiv)⁴⁷ and amine (2.7 equiv).⁴⁷ Cao et al. reported a greener method using heterogeneous Au/ZrO₂ catalyst, but the method was limited in substrate scope and the catalyst reusability was not tested.⁴⁸ From economic and industrial viewpoints, use of H₂ as a less expensive reductant is important. A previous patent showed reductive amination of LA by H₂ with heterogeneous Pt and Pd catalysts, but the catalyst reusability was not tested.⁵⁰ Additionally, the catalysts suffer from disadvantages such as narrow substrate scope, low turnover number (TON), and necessities of excess amount of amine (2 equiv), high temperature (150 °C), and high H₂ pressure (6.9 MPa).⁵⁰ To our knowledge, there are no examples of a reusable and general catalytic system for reductive amination of LA by H₂. We have studied that Pt and MoO_x coloaded TiO₂ (Pt-MoO_x/TiO₂), which has been effective for reductive amination of CO₂,⁵¹ acts as heterogeneous catalyst for reductive amination of LA with a range of primary amines under solvent-free and mild (100 °C, 0.3 MPa of H₂) conditions. This is the first successful example of reusable and general catalytic system for reductive amination of LA with high TON (2150).⁵²

One pot reactions some of the nitriles⁵³⁻⁵⁵ and nitro compounds with LA and H₂ can provide a sustainable and practical route to the pyrrolidones. Recently, the first general method for one-pot synthesis of the pyrrolidones via reductive amination of ethyl levulinate with nitro compounds under 0.1 MPa H₂ reported by Corma, Iborra and co-workers⁵⁶ using Pt-loaded TiO₂ nanotube catalyst, though the method requires large amount of ethyl levulinate (3 equiv. with respect to the nitro compounds).⁵⁶ the use of nitriles instead of primary amines in the synthesis of pyrrolidones from LA and nitriles (3-penteneitrile and benzonitrile) under H₂ using Pd, Rh, Ru, or Pt loaded on carbon or Al₂O₃ catalysts was reported only by Manzer.⁵⁹ But, the method has several disadvantages such as low yields (< 43.4%), limited scope, no example of catalyst reuse, low turnover number (TON), and necessities of high H₂ pressure (5.5-6.9 MPa), high temperature (150 °C), and dioxane as solvent. In this study we have found that Pt-MoO_x/TiO₂ selectively catalyzes the direct synthesis of *N*-substituted lactams (including *N*-alkyl-5-methyl-2-pyrrolidones) from 1:1 mixture of keto acids (including LA) and nitriles

under 0.7 MPa H₂ at 110 °C in the absence of solvent. To our knowledge, this is the first example of reusable and general catalytic system for direct synthesis of *N*-substituted lactams from keto acids, nitriles, and H₂. The selective reaction of nitriles with equimolar amount of LA under H₂ is a challenging reaction, because hydrogenation of nitriles to primary amines is accompanied by the formation of secondary and tertiary amines.⁵³⁻⁵⁵

1.6 Purpose of the present work

Different types of multiphase reaction systems using dense phase CO₂ could be designed and applied for various chemical transformations. The previous works offer attractive potentialities of multiphase reactions using dense phase CO₂ and H₂O. The CO₂-H₂O medium may improve the rate of reaction and/or the selectivity to the desired product. To date, however, there are few reports on multiphase hydrogenation reactions of nitriles using organic solvent-water-CO₂ medium and heterogeneous metal catalysts.

The CO₂ molecules dissolved in a liquid phase (substrate, solvent) have an interaction with certain functional groups of substrates and/or intermediates and then alter their reactivity. The presence of CO₂ may have a positive impact on the reaction rate and the product selectivity in the reactions. The use of both CO₂ and water is interesting for multiphase catalytic reactions, in which the separation of products, catalyst, and solvent may be easy. The pressurization of CO₂ facilitates the dissolution of H₂ into the organic liquid phase including a substrate and/or a solvent and water phase, resulting in the acceleration of several multiphase reactions.

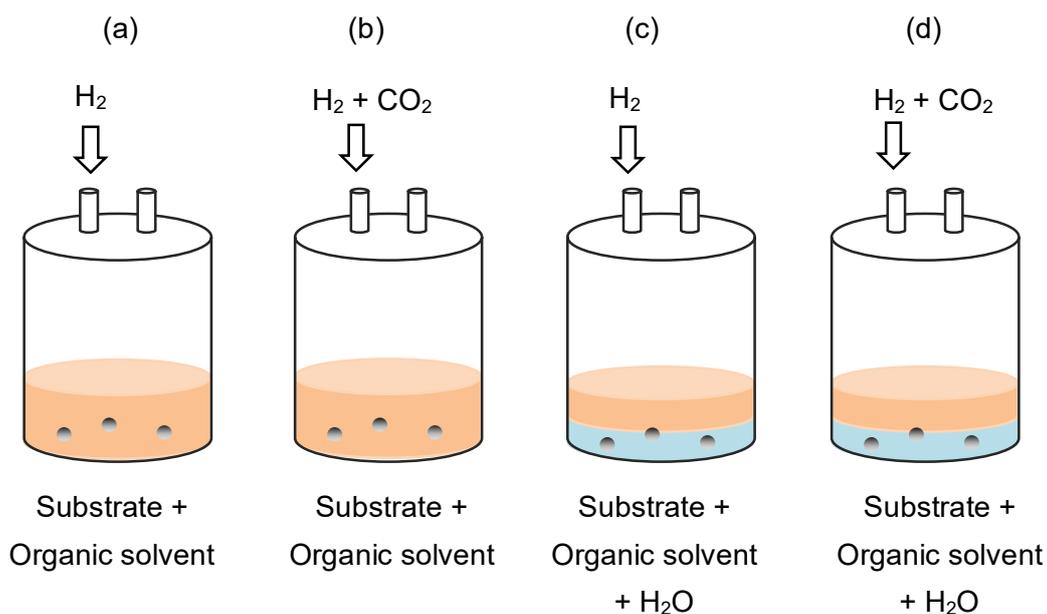
The formation of carbamate salts on supported metal catalyst is observed for several reactions when CO₂ is used in the synthesis of organic amine derivatives. Xie *et al.* reported the formation of carbamate salt in the CO₂-expanded ethanol phase and observed an enhanced benzylamine selectivity of 98%.⁵⁸ Chatterjee *et al.* also reported the formation of carbamate salt from benzylamine and CO₂ and its importance for high selectivity to benzylamine.⁵⁹ When carbamate salt formed is insoluble into the reaction media, it may cover the surface of catalyst and cause the catalyst deactivation. Such a phenomenon is observed in the selective hydrogenation of benzonitrile to benzylamine over Pd/Al₂O₃ catalyst at 323 K.⁴¹ The catalyst deactivation was observed with increasing CO₂ pressure. The carbamate salt formed is likely to accumulate on and cover the surface of Pd/Al₂O₃ catalyst during the reaction, which results in the catalyst deactivation. Such catalyst deactivation was suppressed by the addition of water to the reaction system. The conversion reached to 100% with 98% benzylamine selectivity at any conversion level. The presence of both CO₂ and water in the reaction medium gives excellent performance on the selective hydrogenation of benzonitrile without any catalyst deactivation. The primary amine is soluble into both organic and aqueous phases, whereas the carbamate salt formed from the primary amine and CO₂ is soluble only into aqueous phase. Therefore, the primary amine produced is likely to react with CO₂ and move as the carbamate salt from the organic phase to the aqueous phase. This may reduce the chance for the primary amine to go through further hydrogenation yielding the secondary amine.

When hydrogenation reactions are conducted with supported metal catalysts in the presence of pressurized H₂ and CO₂, there is a possibility of the formation and adsorption of CO through the reverse water gas shift reaction. The adsorption of CO on supported metal catalysts may change the catalytic performance or cause the catalyst deactivation. The formation and adsorption of CO from H₂ and CO₂ in the presence of water was investigated using *in situ* high-pressure FTIR measurements and CO species were observed on alumina-supported noble metal catalysts.⁶⁰ Interestingly, direct interactions of the adsorbed CO species with water molecules are unlikely to occur but water molecules may be preferentially adsorbed

on atomically rough surfaces of noble metal particles rather than CO molecules. These results indicate that the presence of water in reaction media may prevent the catalyst deactivation in the multiphase catalytic hydrogenation in the presence of pressurized H₂ and CO₂.

The present work has been undertaken to examine the effects of additional (additional to organic solvent) components of water and CO₂ for selective hydrogenation of nitriles with supported Pd catalysts in an organic solvent. Selective hydrogenation of various nitriles was studied using different multiphase systems such as organic solvent (a), organic solvent-CO₂ (b), organic solvent-H₂O (c), and organic solvent-H₂O-CO₂ (d) as illustrated in **Figure 1.2**. In addition to these reaction runs; phase behavior of reaction mixtures was examined and interactions of CO₂ and water with organic substrates were measured by *in situ* FTIR spectroscopy. On the basis of those experimental results, the usefulness and features of the multiphase medium including both CO₂ and water will be shown for the selective hydrogenation of nitrile compounds to primary amines and possible physical and/or chemical functions of CO₂ and water will be discussed.

In chapter 2, selective hydrogenation of benzyl cyanide (BC) to 2-phenylethylamine was investigated with a commercial Pd/Al₂O₃ catalyst in different multiphase reaction media including *n*-hexane, water, and/or CO₂ (**Figure 1.2**). In neat *n*-hexane, the hydrogenation of BC occurs at a large rate but no PEA was formed and the secondary amine of *N, N*-bis(2-phenylethyl)amine (BPEA) was produced as the main product. The pressurization of *n*-hexane with CO₂ decreased the rate of hydrogenation and the main product was BPEA. In this *n*-hexane – CO₂ medium, the catalyst lost its activity during the reaction. When a similar volume of water was added to *n*-hexane, the rate of hydrogenation did not change so much but a small amount of the primary amine was detected to form in addition to the main product of BPEA. In contrast to these reaction media, a high PEA selectivity of > 90% was obtained and no catalyst deactivation occurred in an *n*-hexane – water – CO₂ medium. The rate of hydrogenation was smaller than that in neat *n*-hexane but comparable to those in *n*-hexane – water and *n*-hexane – CO₂ media. Those results show that synergistic effects appear on the selective hydrogenation of BC to PEA when both water and CO₂ are included in the reaction medium. Possible roles and actions of water and CO₂ have been discussed on the basis of the results of hydrogenation runs under different conditions and *in situ* ambient and high pressure Fourier transform infrared spectroscopy measurements that give light to molecular interactions of CO₂ with reacting species.



● Supported metal catalyst

Figure 1.2. Four different multiphase reaction media including organic solvent, CO₂, and/or water for hydrogenation reactions studied in this work.

In chapter 3, the applicability of a multiphase medium including CO₂ and water was studied for the selective hydrogenation of various nitriles such as 2-phenylethyl cyanide (PEC), cinnamitrile (CN), *n*-hexanenitrile (HN) and 4-cyanobiphenyl (CBP) with the Pd/Al₂O₃ catalyst. The effectiveness of the multiphase reaction medium was different from one nitrile to another. The selective production of primary amine was achieved with 2-phenylethyl cyanide (PEC) and *n*-hexanenitrile (HN) but not with the other nitriles. In the case of cinnamitrile and 4-cyanobiphenyl (CBP), their CN groups are conjugated and this may affect their reduction, resulting in the selective hydrogenation of PEC and HN to the corresponding primary amines. The rate of nitrile conversion in this multiphase medium is smaller than that in neat organic solvents. This should result from the dilution of reacting species in the liquid phase by the dissolution of CO₂, the change of reaction locus from the organic phase to the organic - aqueous interfacial layer, and/or the decreased reactivity of nitrile group via interactions with CO₂ molecules.

As discussed in Chapter 1-3, the H₂O-CO₂ medium is effective for the selective hydrogenation of nitriles to primary amines with Pd/Al₂O₃ catalyst. Further, the effectiveness of the H₂O-CO₂ medium was examined for selective hydrogenation of benzyl cyanide (BC) and *n*-hexanenitrile (HN) using a commercial Pd/C catalyst that was different in the surface properties from the above-mentioned Pd/Al₂O₃ one. The results obtained are shown in Chapter 4. The synergistic effects of CO₂-water system was not observed in hydrogenation of benzyl cyanide and *n*-hexanenitrile over the Pd/C catalyst, in contrast to Pd/Al₂O₃. The product selectivity obtained was also different between the two catalysts even in the same H₂O-CO₂

medium and possible reasons will be discussed after considering the difference in the hydrophilicity/ hydrophobicity of their surfaces.

In Chapter 5 the first general and reusable catalytic system was studied for one-pot synthesis of lactams by reductive conversion of keto acids with nitriles and H₂ using Pt-MoO_x/TiO₂ catalyst. High selectivity to lactams (low selectivity to side product, secondary amine) is due to removal of the primary amine by its fast reaction with keto acids.

Chapter 6 will provide general summary of the present work including macroscopic and microscopic features of the multiphase hydrogenation reactions of nitriles in the presence of dense phase CO₂ and water. After considering the usefulness of the multiphase reaction medium including CO₂ and/or water in selective hydrogenation of various nitriles to primary amines, the author gives some comments on future research work to further examine the potentiality of the CO₂ - water multiphase reaction medium from practical and academic points of view.

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Chapter 2

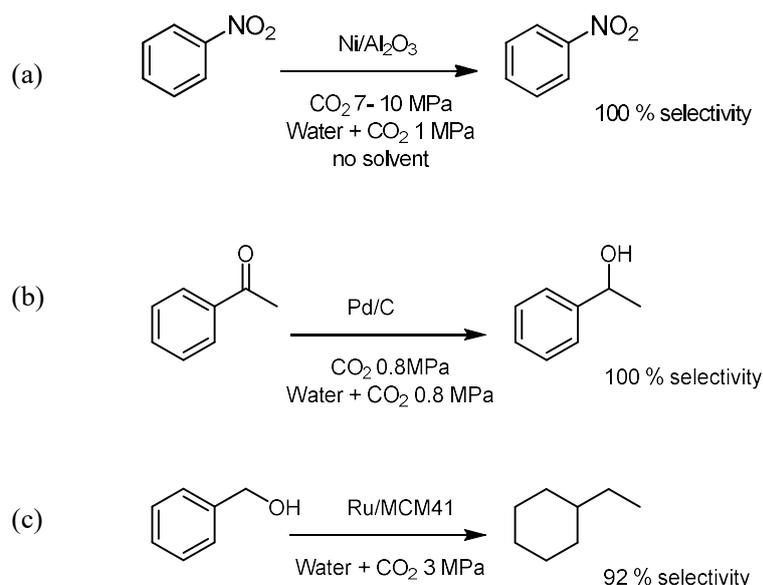
Selective Hydrogenation of Benzyl Cyanide in the Presence of Carbon Dioxide and/or Water over Pd/Al₂O₃

The selective hydrogenation of benzyl cyanide (BC) to the primary amine of 2-phenylethylamine (PEA) was investigated with a Pd/Al₂O₃ catalyst in different multiphase reaction media including *n*-hexane, water, and/or CO₂. In neat *n*-hexane, the hydrogenation of BC occurs at a large rate but no PEA was formed and the secondary amine of *N,N*-bis(2-phenylethyl)amine (BPEA) was produced as the main product. The pressurization of *n*-hexane with CO₂ decreased the rate of hydrogenation and the main product was BPEA. In this *n*-hexane – CO₂ medium, the catalyst lost its activity during the reaction. When a similar volume of water was added to *n*-hexane, the rate of hydrogenation did not change so much but a small amount of the primary amine was detected to form in addition to the main product of BPEA. In contrast to these reaction media, a high PEA selectivity of > 90% was obtained and no catalyst deactivation occurred in an *n*-hexane – water – CO₂ medium. The rate of hydrogenation was smaller than that in neat *n*-hexane but comparable to those in *n*-hexane – water and *n*-hexane – CO₂ media. Those results show that synergistic effects appear on the selective hydrogenation of BC to PEA when both water and CO₂ are included in the reaction medium. Possible roles and actions of water and CO₂ have been discussed on the basis of the results of hydrogenation runs under different conditions and *in situ* ambient and high pressure Fourier transform infrared spectroscopy measurements that give light to molecular interactions of CO₂ with reacting species.

2.1 Introduction

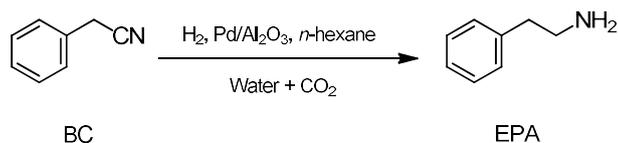
Water and carbon dioxide (CO₂) are environmentally benign fluids and can serve as interesting reaction solvents and promoters; that is, these are green components useable to design effective multiphase reaction media for organic synthetic reactions. The rate of reactions with molecular catalysts is promoted in the presence of water and the organic – aqueous interface is important for activating polar functional groups of organic substrates, as demonstrated by several examples in the literature.¹ Supercritical CO₂ is also an interesting solvent/promoter, which enhances the reaction rate and controls the product distribution of catalytic and non-catalytic reactions.² Carbon dioxide shows promotional effects even at pressures below its critical pressure (7.4 MPa).³⁻⁷ For an organic liquid substrate or solvent phase pressurized by CO₂, the dissolution of CO₂ may affect the result of an organic reaction in the liquid phase. Interesting results using such CO₂-dissolved expanded liquid phases have been reported for oxidation, hydroformylation, hydrogenation, Heck coupling, Diels-Alder reaction, and so on.³⁻⁷

It was previously shown that when a liquid phase of nitrobenzene including a supported nickel catalyst was pressurized by CO₂ at pressures of 7 – 10 MPa, the rate of nitrobenzene hydrogenation was enhanced and the selectivity to aniline was almost 100% at any conversion level ⁸⁻⁹ (**Scheme 2.1 a**). These promotional effects of CO₂ pressurization result from an increase in the dissolution of a gaseous reactant of H₂ and molecular interactions of CO₂ with reacting species in the liquid phase. The dissolution of CO₂ causes the liquid phase to take a CO₂-philic nature, increasing the dissolution of H₂. The interactions of CO₂ molecules decrease the reactivity of the nitro group of the substrate and this retards the first step of the change to the corresponding imine. In contrast, the molecular interactions of CO₂ accelerate the subsequent reaction steps toward the final desired product of aniline. As a result, aniline can be selectively obtained at a high rate of hydrogenation. It should be noted, furthermore, that the same promotional effect of CO₂ can appear at a lower pressure of around 1 MPa when another foreign phase of water is added.¹⁰ The effectiveness of multiphase reaction media including water and CO₂ was shown for hydrogenation reactions by Hiyoshi *et al.* for acetophenone with a Pd/C catalyst ¹¹ (**Scheme 2.1 b**) and by Lin *et al.* for benzyl alcohol and its derivatives with supported Ru catalysts¹² (**Scheme 2.1 c**). These results allow ones to expect interesting synergistic effects of water and CO₂ for organic synthetic reactions.



Scheme 2.1 Examples of multiphase organic reactions promoted by the presence of CO₂ and water

The present work has been undertaken to examine the effects of additional components of water and CO₂ for selective hydrogenation of benzyl cyanide with a Pd/Al₂O₃ catalyst in an organic solvent of *n*-hexane. The features of the *n*-hexane – water – CO₂ medium (**Figure 2.1**) have been compared with those of *n*-hexane, *n*-hexane – water and *n*-hexane – CO₂ media with respect to the rate of hydrogenation, the product selectivity and the catalyst deactivation. For hydrogenation reactions by H₂ over supported metal catalysts in the presence of CO₂, supported metal catalysts often lose their activity due to the formation and adsorption of CO produced through reverse water gas shift reaction (CO₂ + H₂ → CO + H₂O).^{6, 13-15} In addition to the hydrogenation runs in different reaction media, molecular interactions of CO₂ with the substrate have been examined by *in situ* Fourier transform infrared spectroscopy (FTIR) with attenuated total reflection (ATR) mode at ambient and high pressures¹⁶ to discuss possible roles and actions of CO₂ and water in the selective hydrogenation of benzyl cyanide in *n*-hexane.



Scheme 2.2 Selective hydrogenation of benzyl cyanide (BC) to 2-phenylethylamine (PEA)

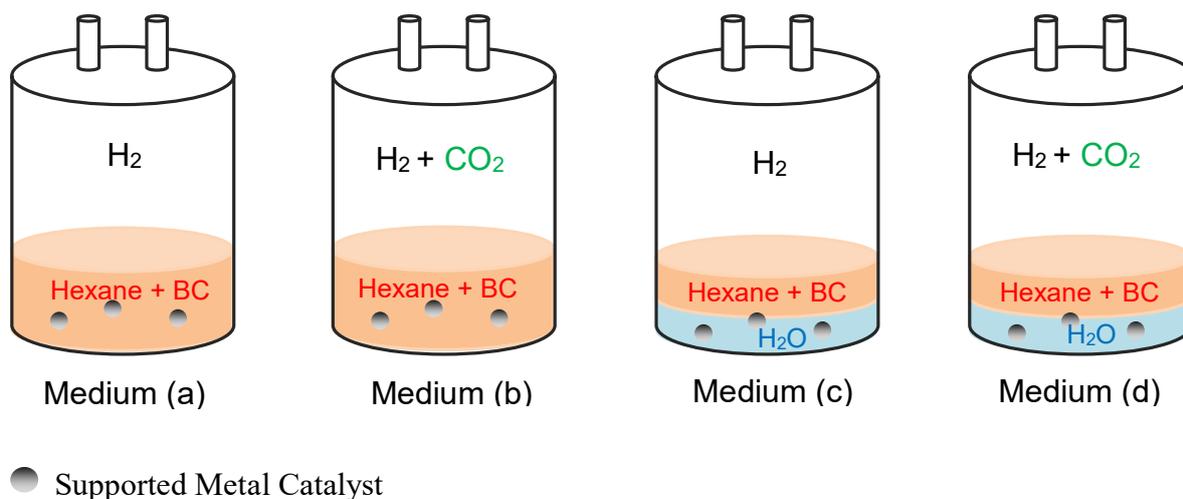


Figure 2.1 Four different multiphase reaction media including organic solvent, CO₂, and/or water for hydrogenation with H₂ investigated in the present work

Hydrogenation of nitriles to primary amines, which are important intermediates in chemical and pharmaceutical industries, is one of practically important reactions.^{17, 18} Several authors investigated the selective hydrogenation of nitriles in the presence of CO₂ and/or water. Recently, Cheng *et al.*¹⁹ and Yoshida *et al.*²⁰ investigated the hydrogenation of benzonitrile in different multiphase media using a Ni/Al₂O₃ catalyst and a Pd/Al₂O₃ one, respectively. These authors indicated the effectiveness of dense phase CO₂ on the selective production of the desired primary amine of benzylamine in the absence of water. However, the former group showed that a medium including both CO₂ and water was not effective while the latter group observed that the coexistence of CO₂ and water was more beneficial in improving the selectivity to the primary amine. One of important reasons for the high selectivity to benzylamine is the formation of water-soluble carbamate from benzylamine and CO₂ followed by its transfer from organic phase to water, which inhibits undesired further chemical changes of benzylamine to the secondary amine and others in the organic phase. Hegedűs *et al.* studied the hydrogenation of benzyl cyanide using a Pd/C catalyst in a mixture

of water and dichloromethane and in the presence of an acidic additive of NaH_2PO_4 .²¹ They reported a small selectivity to the primary amine at a complete conversion. Previously, Xie *et al.* indicated that CO_2 would act as a protecting agent for primary and secondary amines during the hydrogenation of nitriles.²² Chatterjee *et al.* reported the selective hydrogenation of benzyl cyanide and others with a Pd/MCM-41 catalyst in the presence of CO_2 at a high pressure of 10 MPa.²³ They did not mention the possibility of catalyst deactivation in the hydrogenation of benzyl cyanide.

2.2 Experimental

2.2.1 Hydrogenation

A commercially available 5 wt% Pd/ Al_2O_3 (Wako) was used as a catalyst for multiphase hydrogenation reactions of benzyl cyanide (Aldrich). The hydrogenation reactions were carried out in a 100 cm^3 Teflon-lined autoclave. The reactor was charged with 1.0 mmol (0.117 g) benzyl cyanide, 5 cm^3 *n*-hexane, 5 cm^3 water (Wako) and 58.5 mg Pd/ Al_2O_3 catalyst and it was flushed with H_2 for three times to remove the air. The reactor was heated in a heating mantle up to the desired temperature. After the reaction temperature was attained, 2 MPa H_2 (99.99%) was introduced, followed by the introduction of liquid CO_2 (99.99%) to the desired total pressure with a high pressure liquid pump (JASCO SCF-Get). The reactions were carried out at 323 K while stirring the reaction mixture with a magnetic stirrer. After the reaction, the reactor was cooled in an ice water bath and depressurized carefully to atmospheric pressure. The reaction mixture was analyzed by gas chromatograph (GL Sciences GC-390B) using a capillary column (TC 1701) and flame ionization detector. The total conversion was determined from the initial and final amounts of benzyl cyanide. The product and by-products were identified by GC-MS (Shimadzu 17A). Under the present reaction conditions, 2-phenylethylamine (PEA), *N,N*-bis(2-phenylethyl)amine (BPEA), and bis-(2-phenylethyl) diazene (BPEDA) were observed to form (as described later in **Scheme 2.3**).

2.2.2 Phase behavior observation

When a liquid solvent or substrate phase is pressurized by CO_2 , it expands by dissolution of CO_2 . This will facilitate the dissolution of other co-existing gases such as O_2 , H_2 , and CO and this may accelerate the reactions involved with these gaseous reactants.⁶ To examine the chemical reactions in the presence of CO_2 , the phase behavior study is important to check whether the reaction is occurring in a single phase homogeneously or heterogeneously in two or more phases.²⁵ A 10 cm^3 high pressure view cell with sapphire windows was used for phase behavior study. The observation was made with a similar

volumetric ratio of solvent *n*-hexane to the reactor as used in the hydrogenation reaction. A certain amount of *n*-hexane was added into the cell and it was purged with H₂ three times. The cell was heated up to 323 K (reaction temperature) by circulation of preheated water outside the cell, followed by the introduction of 2 MPa H₂. Then CO₂ was slowly introduced into the cell to the desired pressure while stirring the mixture by a magnetic stirrer. The phase behavior was visually examined by naked eyes at different CO₂ pressures.

2.2.3 *In situ* FTIR and XPS measurement

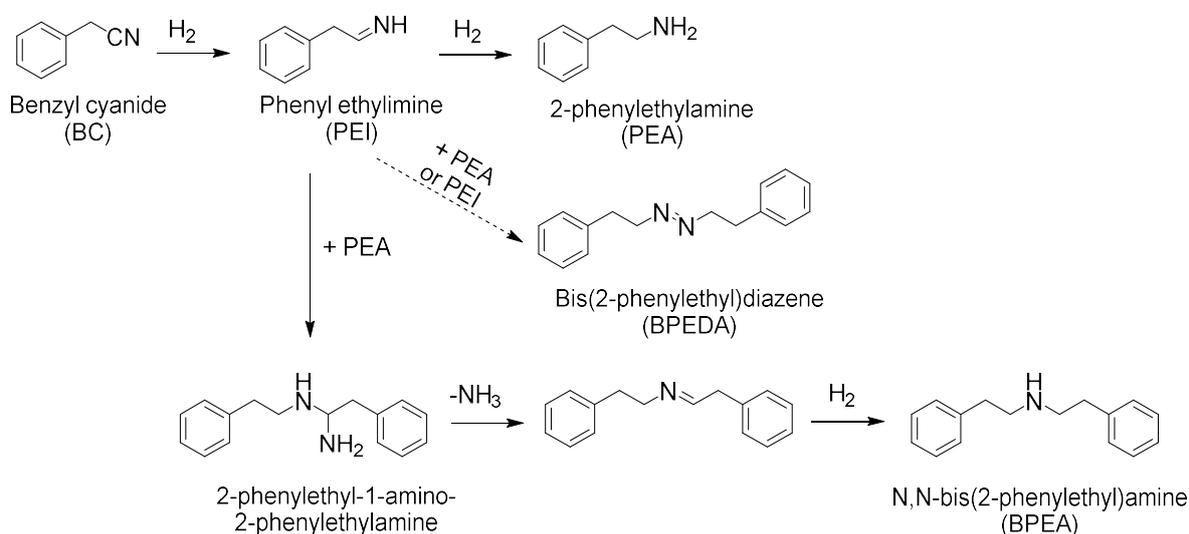
Interactions between substrate and CO₂ molecules were examined by *in situ* high-pressure FTIR measurements using a JASCO FTIR-620 spectrometer with a triglycine sulfate detector at a wavenumber resolution of 2 cm⁻¹ and at 323 K (reaction temperature). The FTIR-ATR spectra were collected in an *in situ* high-pressure ATR cell (1.18 cm³) attached with a ZnSe crystal rod. The temperature of the cell was controlled by a temperature controller and a heating jacket with rod heaters.^{20, 26} The FTIR spectra were collected for a mixture of CO₂ dissolved in liquid benzyl cyanide at different pressures.

The surface of supported Pd particles on Al₂O₃ was examined by X-ray photoelectron spectroscopy. The catalyst samples were ground in mortar, pressed onto a sample holder, and measured by a JOEL model of JPS-9200.

2.3 Results and discussion

2.3.1 Hydrogenation in different types of reaction media

The hydrogenation of benzyl cyanide (BC) was studied with a 5wt. % Pd/Al₂O₃ catalyst in different reaction media at 323 K. Under the reaction conditions employed, 2-phenylethylamine (PEA), *N,N*-bis(2-phenylethyl)amine (BPEA), and bis(2-phenylethyl)diazene (BPEDA) were observed to form. Possible reaction pathways for these products are shown in **Scheme 2.3**. The primary amine of PEA is produced through the formation of an intermediate of phenylethylimine (PEI), which can further react with the product of PEA and change to the secondary amine of BPEA.²⁴ The BC conversion and the product distribution were significantly changed depending on the reaction media used, as explained in the following.



Scheme 2.3 Possible reaction pathways in hydrogenation of benzyl cyanide. BC: benzyl cyanide, PEI: phenylethylimine, PEA: 2-phenylamine, BPEA, *N,N*-bis(2-phenylethyl)amine, BPEDA bis(2-phenylethyl)diazene.

Table 2.1 shows the reaction results obtained using four different types of reaction media. In the absence of CO₂ and water (medium a), the reaction took place very fast as compared to the others examined and almost all BC was consumed in 1 h. However, the main product was the undesired secondary amine of BPEA and no formation of the objective product of PEA was detected. In the presence of 3 MPa CO₂ (medium b), the conversion in 1 h decreased to 61% and no PEA was produced with the formation of BPEA as the main byproduct, similar to the medium (a). When water was added in the same volume as of *n*-hexane (medium c), the primary amine of PEA was formed, although its selectivity was still not high (24 %). A BC conversion of 73% was slightly larger than that (61%) obtained in the

medium (b). In contrast to those media, in the presence of both water and CO₂ (medium d), the selectivity to PEA was significantly enhanced to 93% along with a decrease in the conversion to 56%. Namely, the coexistence of water and CO₂ is indispensable for the highly selective hydrogenation of BC to PEA. Influence of CO₂ and water on the BC conversion and the PEA selectivity will be discussed later.

Table 2.1 Results of benzyl cyanide hydrogenation with Pd/Al₂O₃ catalyst in the presence and absence of CO₂ and/or water^a

Medium	Time (min)	Conversion (%)	Selectivity (%)		
			PEA	BPEA	BPEDA
(a) <i>n</i> -Hexane	5	63	0	76	24
	60	99	0	83	16
(b) <i>n</i> -Hexane - CO ₂	60	61	0	74	26
(c) <i>n</i> -Hexane - H ₂ O	60	73	24	66	10
(d) <i>n</i> -Hexane - CO ₂ -H ₂ O	60	56	93	7	< 0.5

^a Reaction conditions: benzyl cyanide 1 mmol, catalyst 58.5 mg, *n*-hexane 10 cm³ (for a, b) and 5 cm³ (for c, d), H₂O 5 cm³ (for c, d), temperature 323 K, H₂ 2 MPa, CO₂ 3 MPa.

The formation of BPEDA is unclear at present. When PEA alone (1 mmol) or a PEA – BC mixture (1 mmol each) was treated in *n*-hexane in the presence of atmospheric N₂ and Pd/Al₂O₃ at 323 K for 1 h, the formation of BPEDA was not detected. These observations suggest that, for the formation of BPEDA, the coupling of two PEA molecules and that of BC and PEA are not responsible and the presence of intermediate PEI is indispensable. BPEDA might be formed via the reaction of PEI with the reactant BC or the product PEA. As shown in **Table 2.1**, the selectivity to BPEDA was very low in the *n*-hexane – water – CO₂ medium, in which PEA formed was suggested, as discussed later, to move to the aqueous phase, resulting in decrease in the chance for PEA to react with PEI. If BPEDA is produced from PEI and BC, the selectivity to BPEDA would be high even in this medium because both PEI and BC exist in the same *n*-hexane phase. However, this was not the case; hence, BPEDA should be produced via the reaction between PEI and PEA.

For the reaction in the *n*-hexane medium, the selectivity to BPEDA was found to be about 25% at BC conversion levels of 60% - 90% but it tended to decrease slightly with the conversion, which was about 15% at the almost complete conversion. It is then possible that a part of BPEDA is reversely decomposed to PEI and PEA and those species formed are recombined to 1-amino-*N,N*-bis(2-phenylethyl)amine, which then transforms to the secondary amine of BPEA. However, the decrease in the BPEDA selectivity observed is not so large that the contribution of BPEDA to the formation of BPEA should be less significant.

It was previously indicated for hydrogenation reactions in the presence of dense phase CO₂ that supported metal catalysts often lost their activity during the reactions.^{14, 16, 20}

One important reason is the formation of CO through reverse water gas shift reaction ($\text{CO}_2 + \text{H}_2 \rightarrow \text{CO} + \text{H}_2\text{O}$) and its adsorption on the surface of supported metal particles. To examine the possibility of such a catalyst deactivation in present cases, time – conversion profiles were measured for the above-mentioned four reaction media. The results obtained are given in **Figure 2.2**, indicating that the Pd/Al₂O₃ catalyst became deactivated for the medium (b) but not for the others. It is noteworthy that the deactivation of Pd/Al₂O₃ catalyst can be hindered by the addition of water even in the presence of CO₂. Possible reasons for the influence of water will be discussed later. Previously, Chatterjee *et al.* studied the hydrogenation of nitriles with a Pd/MCM-41 catalyst in supercritical CO₂.²³ They reported its good performance for the selective hydrogenation of BC to PEA at 343 K and at a higher CO₂ pressure of 10 MPa (H₂ 2 MPa), under which a high PEA selectivity of 98% was obtained at a conversion of 82% in 4 h. No time – conversion profile was presented in their work and so they did not mention the catalyst deactivation. They noted from the results of recycling test with another substrate of benzonitrile (BN) that the Pd/MCM-41 catalyst was stable although comparison was made at relatively high conversion levels $\approx 90\%$. It is difficult at present to explain why the Pd/Al₂O₃ catalyst deactivated in the present case with BC at a low CO₂ pressure of 3 MPa but the Pd/MCM-41 catalyst did not in their case with BN (not BC) at a higher CO₂ pressure of 10 MPa.

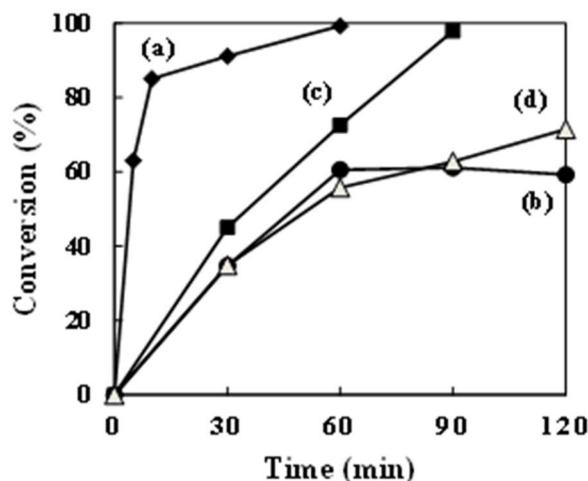


Figure 2.2 Time profiles of total conversion in hydrogenation of BC in the four different multiphase media given in **Table 2.1** such as (a) *n*-hexane, (b) *n*-hexane-CO₂, (c) *n*-hexane-H₂O and (d) *n*-hexane-CO₂-H₂O.

To examine the chemical reactions in the presence of CO₂, the phase behavior study is important to check whether the reaction is occurring in a single phase homogeneously or heterogeneously in two or more phases.²⁵ The present reaction mixture includes three phases of gas (H₂, CO₂), liquid (organic), and solid (catalyst) in the absence of water. The phase behavior of the present reaction mixture under ambient and CO₂ pressurized conditions are

displayed in **Figure 2.3**. The phase behavior of reaction mixture was examined at a reaction temperature of 323 K and at different CO₂ pressures. It was observed that the volume of liquid phase expanded when it was pressurized by CO₂ and the two-phase state (gas-liquid phase) changed to one-phase state (gas phase) at a certain pressure. The CO₂ pressure used for the hydrogenation reactions was not high, say 3 MPa, and so the reaction mixture was in the three-phase state in the absence of water and four-phase state in the presence of water. The Pd/Al₂O₃ catalyst was likely to exist in the aqueous phase in the presence of water and an organic liquid.

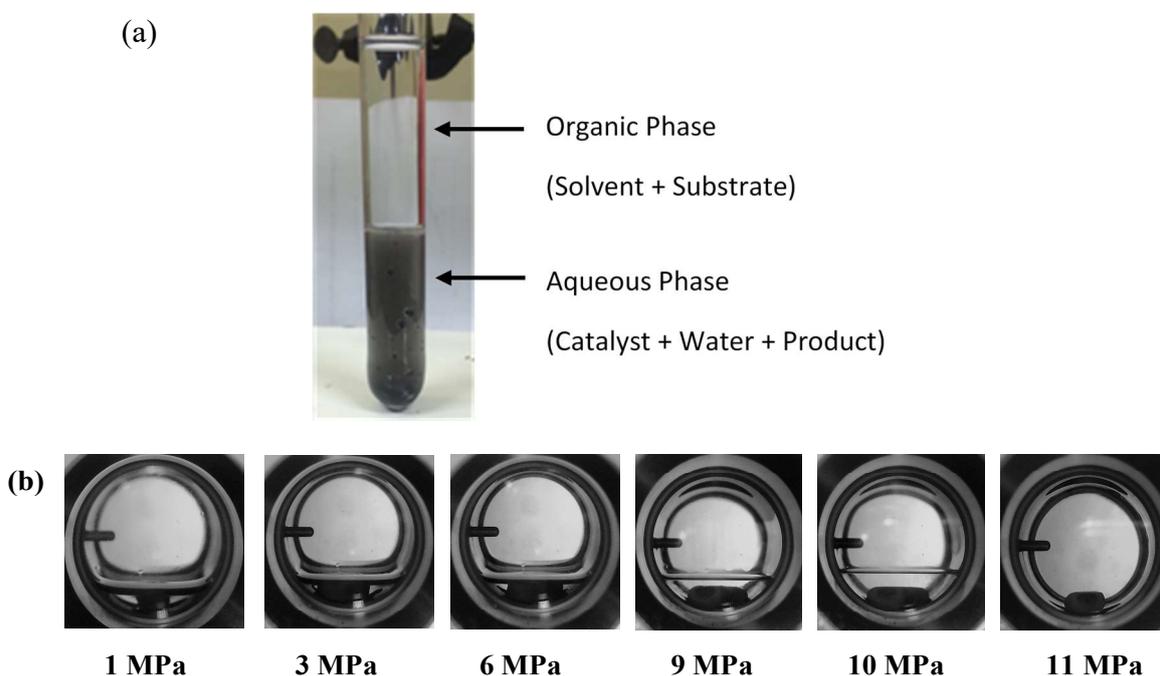


Figure 2.3 Phase behavior of the present reaction mixtures: (a) *n*-hexane – water – catalyst under ambient conditions. (b) *n*-hexane – CO₂ mixture at different CO₂ pressures given.

2.3.2 Hydrogenation in the presence of CO₂ and water

The above-mentioned results demonstrate that the multiphase reaction medium (d), including *n*-hexane, water, and CO₂, is effective for the selective hydrogenation of BC to the primary amine PEA. Further reaction experiments were carried out to examine the effects of CO₂ and H₂ pressures and pH of the aqueous phase for this medium. **Figure 2.4A** shows that the rate of BC hydrogenation obtained in the medium (d), at H₂ and CO₂ pressures of 2 MPa and 1 MPa, respectively, is smaller than that in neat *n*-hexane, medium (a), at a H₂ pressure of 4 MPa. When the CO₂ pressure is raised to 3 MPa, the rate of BC hydrogenation decreases but not so significantly. The rate of BC hydrogenation increases slightly with increase in H₂ pressure from 2 MPa through 6 MPa at 1 MPa CO₂ pressure. The PEA selectivity does not change with H₂ and CO₂ pressures so much (**Figure 2.4B**). A low CO₂ pressure of 1 MPa is sufficient for the effectiveness of medium (d) to appear in the selective hydrogenation of BC to PEA.

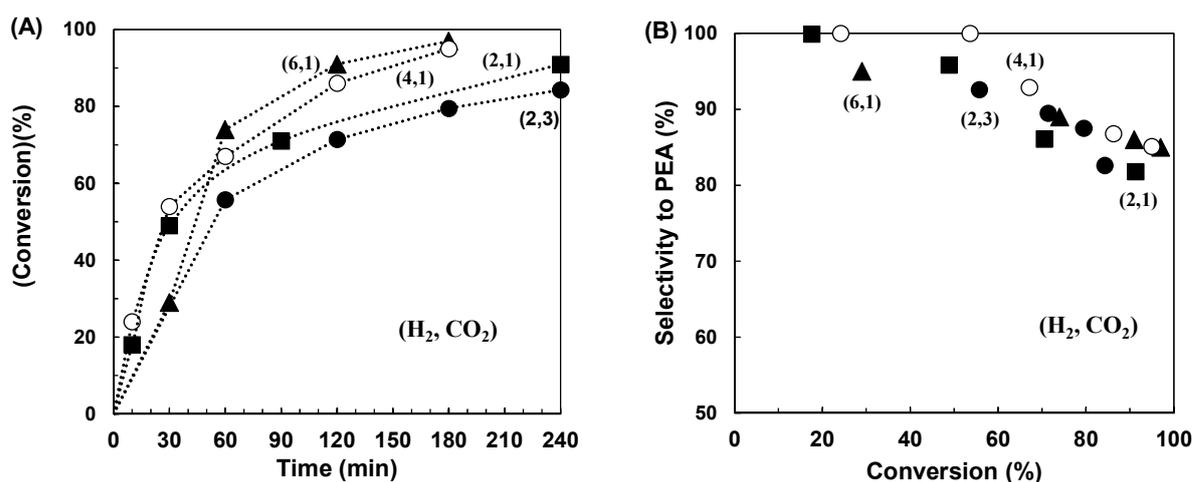


Figure 2.4 Total conversion against reaction time (A) and PEA selectivity against total conversion (B) in hydrogenation of BC in the presence of water and CO₂ (medium (d)). H₂ pressure (in MPa): 4 (a), 2 (b, c); CO₂ pressure (in MPa): 1 (a, b), 3 (c).

In addition, the reactions were conducted in a protic solvent of ethanol (**Table 2.2**). The rates of BC conversion obtained in *n*-hexane and ethanol were similar but the primary amine PEA was formed in the latter although the main product was still the secondary amine BPEA (entry 5). The protic nature of solvent might somewhat be beneficial for the rate of BC hydrogenation. When the ethanol was pressurized by CO₂ (entry 6), the PEA selectivity increased to 38% but less significantly compared to the medium including water and CO₂ (entry 4). The reaction mixture with ethanol includes three phases (gas, liquid, solid), similar to the above-mentioned mixture with *n*-hexane (**Table 2.2**).

Table 2.2 Hydrogenation of benzyl cyanide in different solvents in the presence and/or absence of pressurized CO₂^a

Entry	Medium	Conversion (%)	Selectivity (%)		
			PEA	BPEA	BPEDA
1	<i>n</i> -Hexane	99	0	83	16
2	<i>n</i> -Hexane-CO ₂	61	0	74	26
3	<i>n</i> -Hexane-H ₂ O	73	24	66	10
4	<i>n</i> -Hexane-H ₂ O-CO ₂	56	93	7	< 0.5
5	Ethanol	>99	26	73	0.8
6	Ethanol-CO ₂	63	38	58	4

^a Reaction conditions: benzyl cyanide 1 mmol, catalyst 58.5 mg, *n*-hexane 5 cm³, ethanol 10 cm³, water 5 cm³, temperature 323 K, H₂ 2 MPa, CO₂ 3 MPa, reaction time 1 h.

Previously, Hiyoshi *et al.* studied the hydrogenation of acetophenone with a Pd/C catalyst in a few different solvents in the absence and presence of CO₂.¹¹ The rate of hydrogenation was larger in an order of water > methanol > ethanol > heptane and the presence of dense phase CO₂ was effective to enhance the rate of hydrogenation in the former three solvents. They note that the increase in the conversion of acetophenone in water with the addition of CO₂ coincides with the decrease in pH of the aqueous phase, suggesting that the hydrogenation is enhanced by the protons derived from carbonic acid formed by CO₂ pressurization. Lin *et al.* investigated the ring hydrogenation of aromatic compounds such as benzyl alcohol and its derivatives in different multiphase reaction media including CO₂ and/or water over Ru/MCM-41 catalyst.¹² The presence of water resulted in a high yield of the desired product of cyclohexanemethanol of > 96% and the pressurization of CO₂ further promoted the rate of hydrogenation with no effect on the selectivity. These authors also believe that the carbonic acid should act as a promoter.

As mentioned above, the pH of water phase decreases on CO₂ pressurization and this would affect the rate of reaction and the product distribution.²⁷⁻²⁹ When the water is pressurized by CO₂ at pressures of 1–8 MPa, the pH value decreases to about 3.²⁷ So, an acetic acid solution of about pH 3 was used instead of pure water for the BC hydrogenation. **Table 2.3** indicates that the acidic medium is more effective for the total conversion and the PEA selectivity (entry 2), as compared to the reaction with pure water alone (entry 1). Although the PEA selectivity levels were very similar between the reactions in the acidic media (entries 2 and 3), the conversion obtained in the presence of 3 MPa CO₂ was smaller than that in the acetic acid. The dissolution of CO₂ into the aqueous and organic phases causes a dilution of reacting species (negative effect). The solubility of H₂ (in mole fraction) is 1.35×10^{-5} in pure water³⁰ while it increases to 1.75×10^{-4} in acetic acid³¹ (positive effect). These may be responsible for the larger conversion in the presence of acetic acid instead of pure

water (entries 1 and 2). Furthermore, the primary amine PEA is a strong base with a $pK_b = 4.17$ ($pK_a = 9.83$)³² and it is more stabilized in an acidic environment. This may contribute to the high PEA selectivity in the presence of either acetic acid or CO₂ (entries 2 and 3).

Table 2.3 Hydrogenation of benzyl cyanide in *n*-hexane using different aqueous media in the absence and presence of pressurized CO₂^a

Entry	CO ₂ (MPa)	Aqueous Media	Conversion (%)	Selectivity (%)		
				PEA	BPEA	BPEDA
1	0	Water	73	24	66	10
2	0	Acetic acid ^b	93	90	9	1
3	3	Water	56	93	7	< 0.5

^a Reaction conditions: benzyl cyanide 1 mmol, catalyst 58.5 mg, *n*-hexane 5 cm³, aqueous phase 5 cm³, temperature 323 K, H₂ 2 MPa, CO₂ 3 MPa, reaction time 1h.

^b 0.1 mole-% acetic acid solution (pH 2.79)

2.3.3 Molecular Interactions of CO₂ with benzyl cyanide

To discuss the possible roles and actions of CO₂ and water in the selective hydrogenation of benzyl cyanide in *n*-hexane, the molecular interactions of BC with the solvents and CO₂ were investigated by *in situ* FTIR-ATR measurements. **Figure 2.5** shows the FTIR spectra of BC in different solvents under ambient conditions in the range of absorption band due to C≡N stretching vibration of the nitrile group in 2260-2210 cm⁻¹. The absorption band is centered at 2251 cm⁻¹ for neat BC and also for BC in either water or acetic acid but it is a little blue-shifted to 2253 cm⁻¹ for ethanol. It is thus assumed that the reactivity of the nitrile group does not change with interactions with neutral water and acidic water.

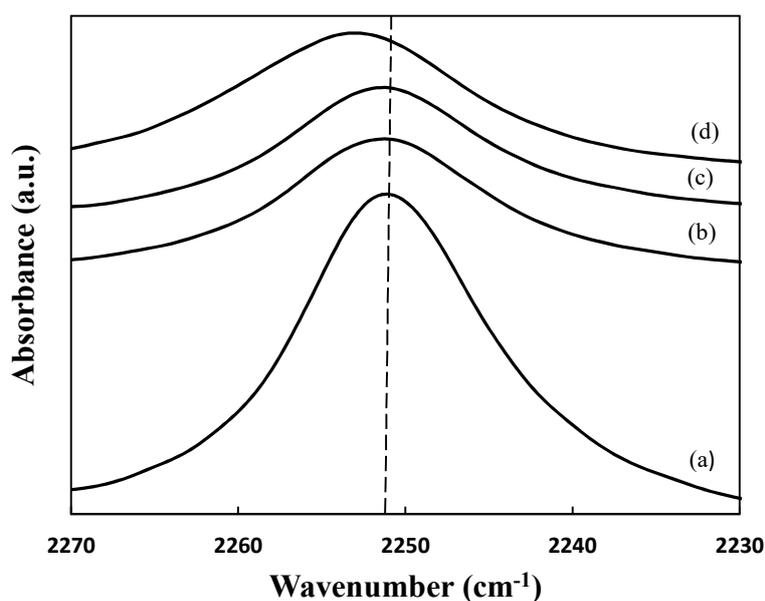


Figure 2.5 *In situ* high pressure FTIR-ATR spectra collected at 323 K for (a) neat BC (b) BC in acetic acid (c) BC in water (d) BC in ethanol at ambient conditions.

Further, *in situ* FTIR-ATR spectra were collected in the presence of CO₂ at different pressures. **Figure 2.6** displays the spectra of neat BC and BC in either water or ethanol. The CO₂ pressurization weakened the absorption band of the nitrile group and made the absorption band shifted to a higher frequency region. When the liquid phase (neat BC, water, or ethanol) was pressurized by CO₂, the concentration of BC was lowered. This is responsible for the decrease in the intensity of the absorption band of the nitrile group with CO₂ pressure. Careful examination of those spectra shows that the absorption band of the nitrile group is blue-shifted with increasing CO₂ pressure for the BC in water; the extent of the blue-shift was 4.8 cm⁻¹ at 6 MPa, indicating that the CN bond was likely to become stronger and its reactivity became lowered. In contrast, the blue-shift was marginal for the neat BC and the BC in ethanol, which was 1.5 cm⁻¹ for the former at 10 MPa and 1.4 cm⁻¹ for the latter at 6 MPa. The chemical impact of CO₂ molecules on the CN bond is stronger in the presence of water compared to that for the neat BC and BC in ethanol. A low CO₂ pressure of 3 MPa was used in the present hydrogenation of BC but a similar impact of CO₂ should also appear. In

addition, because of the stronger interactions of CO₂ with the nitrile group in the presence of water, for the BC-water-CO₂ mixture, the absorption band of hydroxyl group in the frequency of 3950 – 2800 cm⁻¹ was examined. **Figure 2.7** indicates that the absorption band for OH group of water did not significantly vary with CO₂ pressure, probably due to the low concentration of BC. The interface between the organic and aqueous phases might be significant for the CO₂-BC interactions to occur.

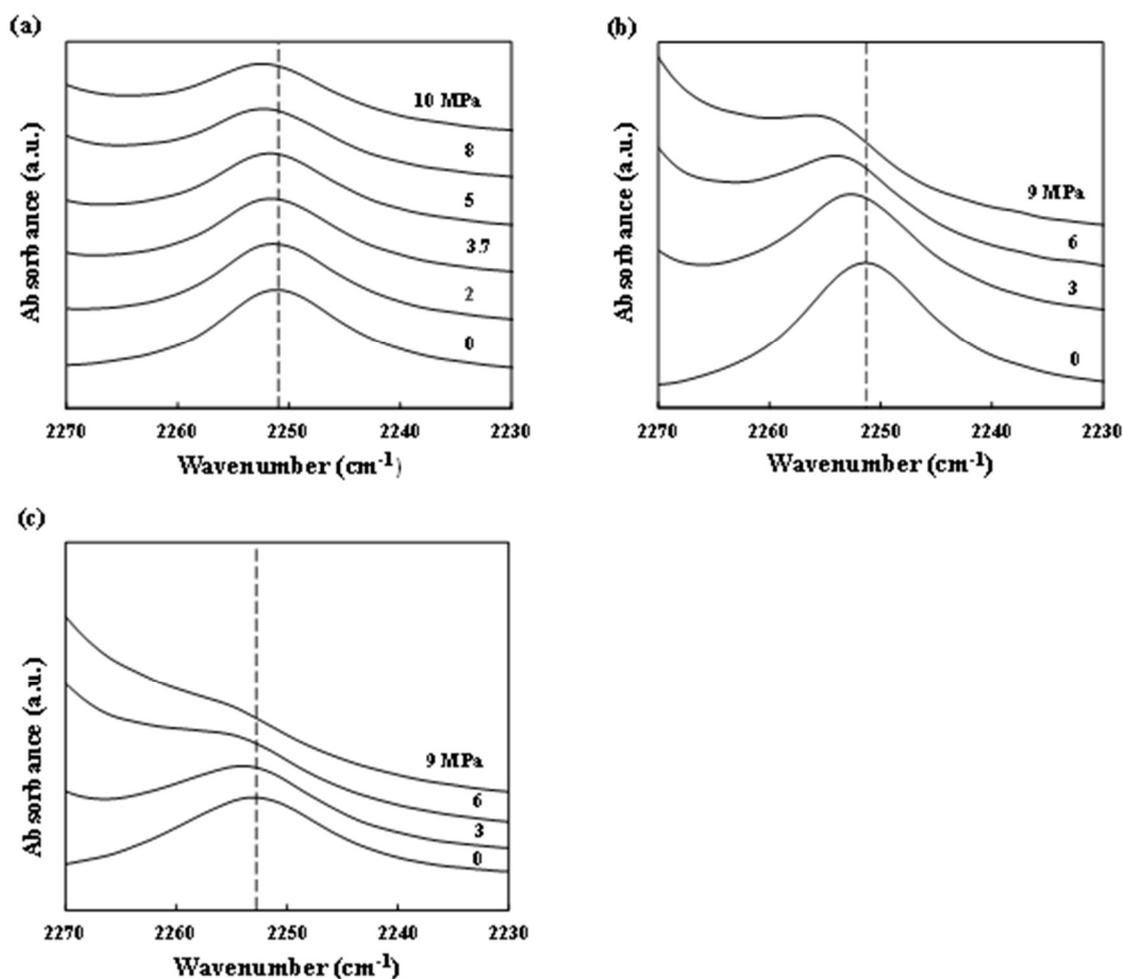


Figure 2.6 *In situ* high pressure FTIR-ATR spectra collected at 323 K for (a) neat BC (b) BC in water (c) BC in ethanol under compressed CO₂ at pressures given.

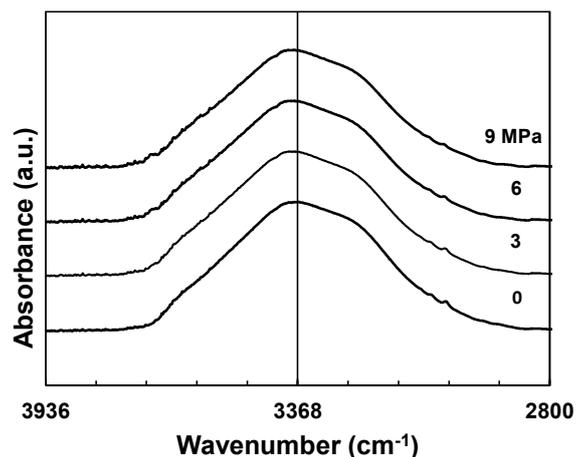


Figure 2.7 *In situ* high pressure FTIR-ATR spectra collected at 323 K for OH group for BC in water under compressed CO₂ at pressures given.

2.3.4 Catalyst recyclability in the CO₂ and water multiphase medium

Finally, the catalyst recyclability was tested in the multiphase medium including both water and CO₂. The catalyst was separated by simple filtration and washed by distilled water and ethanol for 4-5 times. The reactor was loaded with the recovered catalyst, BC, *n*-hexane, and water and the next reaction was conducted in the same manners as used in the first run. The reaction was repeated four times (three recycling tests) with the same catalyst sample. The results obtained are presented in **Table 2.4**, including the weight of catalyst that was separated and recovered by the above-mentioned procedures, which caused some loss in the catalyst weight. The conversion was found to decrease on the recycling and the extent of decrease in the conversion was larger than expected from the decrease in the weight of catalyst recovered and used for the repeated runs. Namely, catalyst deactivation occurred to some extent on the recycling.

Table 2.4 Recycling test of Pd/Al₂O₃ catalyst for hydrogenation of BC in CO₂-H₂O medium^a

Run No.	Catalyst weight (mg)	Conversion (%)	Selectivity (%)		
			PEA	BPEA	BPEDA
1	59	71	90	10	<0.5
2	49	49	89	10	1
3	41	27	90	7	3
4	38	22	87	12	1

^a Reaction conditions: benzyl cyanide 1 mmol, catalyst- 58.5 mg, *n*-hexane 5 cm³, aqueous phase 5 cm³, temperature 323 K, H₂ 2 MPa, CO₂ 3 MPa, reaction time 2 h.

Figure 2.8 displays Pd 3d XPS spectra for the fresh and recycled (three runs) catalyst samples, indicating no difference in the binding energy between the two samples. The surface of Pd particles was unlikely to change during the reaction, separation, and recovery procedures. The atom concentration of Pd/Al/O in % was found to be 5.3/36/59 for the fresh catalyst but 3.7/39/57 for the recycled one; the Pd/Al (Pd/O) ratio decreased from 0.15 (0.090) to 0.095 (0.065) after the three repeated runs. That is, the number of exposed Pd atoms on the Pd/Al₂O₃ catalyst was reduced by the recycling. A possible reason for this reduction is the leaching of Pd species from the solid catalyst into the acidic water caused by the dissolution of CO₂. Yoshida *et al.* previously pointed out the possibility of metal leaching from a Pd/Al₂O₃ catalyst for hydrogenation of phenol in the water – CO₂ medium.³⁵ Another possibility is the dissolution and re-deposition of Al species on the surface of Pd particles. The aqueous phase is acidic and so the leaching of Al species, as well as Pd, from the catalyst could happen during the reaction and the subsequent re-deposition on the Pd particles during the post-separation (filtration, washing, drying).

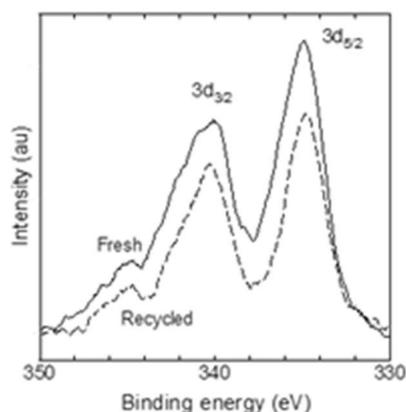


Figure 2.8 XPS Pd 3d spectra for fresh and recycled (three times) Pd/Al₂O₃ catalyst samples. Charge-up corrections of binding energy (BE) was made by reference to Al 2p BE at 74.7 eV for γ -Al₂O₃.²⁸

2.3.5 Possible roles/functions of CO₂ and water

The present results demonstrate that the multiphase medium including both water and CO₂ is promising for the selective hydrogenation of BC to the primary amine PEA. A CO₂ pressure of 3 MPa or lower is sufficient and no such a high pressure as the critical pressure of CO₂ (7.4 MPa) is needed. Note, furthermore, that the catalyst deactivation can be suppressed in this medium, which often occurs in the presence of CO₂ alone. That is, synergistic effects will appear when water and CO₂ coexist in the reaction medium. In the following, possible explanations for the effects of water and CO₂ will be considered.

The rates of BC hydrogenation observed in the media including water and/or CO₂ are smaller than that in neat *n*-hexane (**Table 2.1**). When the organic phase including *n*-hexane, BC, and Pd/Al₂O₃ catalyst is pressurized by CO₂, the concentration of the reacting

species is lowered by the dissolution of CO₂ molecules and this should result in the decrease in the conversion of BC hydrogenation. In addition, some BC molecules may be dissolved in the dense phase CO₂ gas phase and this would also reduce its concentration in the organic phase. However, the CO₂ pressure applied is not high (3 MPa) and so the dissolution of BC into the CO₂ gas phase would be less significant, as suggested by the results of phase behavior observation for *n*-hexane (**Figure 2.3b**) and others.^{15, 33} For the *n*-hexane – water medium, the catalyst is dispersed mainly in the aqueous phase (**Figure 2.3b**) and the reaction should occur at the organic – aqueous interface. The chance of contacting of the catalyst with the organic substrate should be more difficult in the *n*-hexane – water medium than in the homogeneous organic phase. The rate of BC hydrogenation at the interface is therefore assumed to be smaller than that in the homogeneous organic phase of *n*-hexane (excluding the solid catalyst). When this *n*-hexane – water medium is pressurized by CO₂, the above-mentioned negative dilution effect by the CO₂ dissolution also appears on one hand. The dissolution of CO₂ into the organic phase may assist the dissolution of H₂ on the other hand but not so significantly in the present case, judging from the phase behavior observations (**Figure 2.3b**). The water phase becomes acidic by the dissolution of CO₂²⁸ but the solubility of BC in water does not change with the pH value so much.³⁴ Furthermore, another negative effect is induced through interactions of BC with CO₂ in the aqueous phase, which decrease the reactivity of its nitrile group (**Figure 2.6**). The interactions of CO₂ molecules with the BC substrate should be significant at the organic – aqueous interface than those in either *n*-hexane or ethanol, in which CO₂ and BC exist in the same phase, as indicated by FTIR results (**Figure 2.6**). It is speculated that the interactions of the polar nitrile group of BC with CO₂ molecules are promoted at the organic – aqueous interface with some assistance of water. Importance of the organic – aqueous interface is noted for water-assisted/promoted organic synthetic reactions using homogeneous molecular catalysts .¹

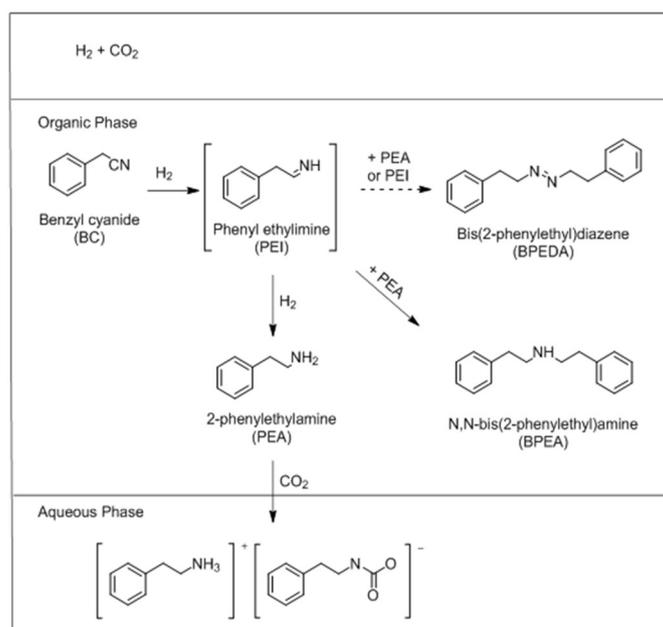


Figure 2.9 Illustration of hydrogenation of BC in medium (d); in the presence of both CO₂ and water.

The most important feature of the *n*-hexane – water – CO₂ medium is the highly selective hydrogenation of BC to the primary amine of PEA in a selectivity of > 90%. For the *n*-hexane – water medium, the selectivity to PEA is small (< 25%) but it does form. It is a water-soluble organic compound; a part of PEA formed, probably near the organic – aqueous interface, is dissolved in the water phase and so it becomes unlikely to further react with an intermediate of 2-phenylethylamine (PEI) yielding the secondary amine in the organic phase (**Figure 2.9**).³⁻⁷ Such a further hydrogenation to the secondary amine BPEA cannot be avoided in the neat *n*-hexane and *n*-hexane – CO₂ media. Also, PEA molecules produced are likely to react with CO₂ and move as carbamate salt from organic to aqueous phase (**Figure 2.9**). This may reduce the chance for PEA to react with PEI yielding the secondary amine. The carbamate salt is insoluble in BC organic phase, resulting in high selectivity to PEA. The formation of the carbamate salt from benzylamine and CO₂ was reported by Chatterjee *et al.*²³ and Yoshida *et al.*²⁰ The formation of carbamate salt in hydrogenation of BN using NiCl₂/NaBH₄ in CO₂ expanded ethanol at 303K was shown by Xie *et al.* and they also observed an enhanced benzylamine selectivity.²² For the high PEA selectivity obtained in the presence of water and CO₂ (**Table 2.1**), the acidic character of aqueous phase is also an important factor; the basic PEA molecules may be more stabilized compared to neutral water (**Table 2.3**).

On the hydrogenation of BC in *n*-hexane pressurized by CO₂, the Pd/Al₂O₃ catalyst loses its activity during the reaction (**Figure 2.2**). In the presence of H₂ and CO₂, CO is formed through reverse water gas shift reaction and adsorbed on the surface of supported metal particles.^{14, 16} On the Pd catalyst, bridged type CO is adsorbed and should cause its deactivation. The presence of water influences the adsorption of CO as evidenced by *in situ*

high pressure FTIR measurements with Al₂O₃-supported Pd and other noble metal catalysts.¹⁶ The CO molecules adsorbed on the rough surface (high Miller index planes) of supported Pd particles are removed by water molecules. These water molecules would be replaced by the substrate BC molecules or assist the contacting of the BC molecules to the Pd surface, and so the rough Pd surface should serve as active sites for the BC hydrogenation. Hence, the catalyst deactivation can be avoided but some CO molecules exist on and cover a certain partial area of Pd particles, resulting in the reduction of the overall rate of BC hydrogenation as compared to the reactions in the absence of CO₂.

2.4 Conclusions

The multiphase medium including both water and CO₂ in addition to an organic solvent of *n*-hexane is effective for the selective hydrogenation of BC to the primary amine of PEA over a Pd/Al₂O₃ catalyst. The rate of BC hydrogenation in this multiphase medium is smaller than that obtained in a homogeneous phase of neat *n*-hexane but comparable to those obtained in *n*-hexane added with either water or CO₂. In neat *n*-hexane and *n*-hexane – CO₂ media, PEA is not obtained and the secondary amine is mainly produced. In the latter medium, the catalyst loses its activity during reaction due to the formation and adsorption of CO via reverse water gas shift reaction. In contrast to these three media, the desired product of PEA is obtained in a selectivity of > 90% and no catalyst deactivation occurs in the *n*-hexane – water – CO₂ medium. The water-soluble PEA molecules produced are likely to react with CO₂ and move as a carbamate salt from organic phase to water. This may reduce the chance for PEA to react with the intermediate of PEI yielding the secondary amine in the organic phase, resulting in the highly selective production of PEA. The aqueous phase takes acidic nature by the dissolution of CO₂, which is also important for the high selectivity to PEA. It is likely that CO is also formed and adsorbed on the surface of supported Pd particles in this medium. However, some adsorbed CO molecules may be removed by water molecules, which allows some Pd sites to serve as active ones for the hydrogenation and then causes no perfect catalyst deactivation. The use of green components of water and CO₂ can significantly contribute to the design of effective media for organic synthetic reactions. The separation of water and CO₂ from organic phases is easy and this is also advantageous for practical application. In the present water – CO₂ medium, however, the total rate of hydrogenation of BC tends to decrease to some extent on the repeated runs, for which an acidic nature of water caused by the dissolution of CO₂ should be responsible. The leaching of Pd species may cause by acidic water and this may decrease the rate of hydrogenation of BC on repeated runs. Also, another possibility is the dissolution and re-deposition of Al species on the surface of Pd particles. The aqueous phase is acidic and so the leaching of Al species, as well as Pd, from the catalyst could happen during the reaction and the subsequent re-deposition on the Pd particles during the post-separation (filtration, washing, drying). The pH of water phase decreases on CO₂ pressurization and this pH change could affect the rate of reaction (activity decay) on the repeated runs. Overall it is interesting to further investigate the potential features of multiphase reaction medium and synergistic effect of the green components of CO₂ and H₂O for selective hydrogenation of other nitriles using heterogeneous catalysts.

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Chapter 3

Selective Hydrogenation of Different Nitriles in the Presence of Carbon Dioxide and/or Water over Pd/Al₂O₃

The effectiveness of a multiphase medium including CO₂ and water was studied for the selective hydrogenation of various nitriles of 2-phenylethyl cyanide (PEC), cinnamionitrile (CN), *n*-hexanenitrile (HN) and 4-cyanobiphenyl (CBP) with a conventional Pd/Al₂O₃ catalyst. Such a multiphase reaction medium was observed to have different impacts changing from one nitrile to another and the selective production of primary amine was achieved with PEC and HN but not with the other nitriles. Possible reasons for the substrate-dependent effects of CO₂ and water were discussed.

3.1 Introduction

The multiphase medium including both water and CO₂ in addition to an organic solvent of *n*-hexane is effective for the selective hydrogenation of benzyl cyanide (BC) to the primary amine of 2-phenylethylamine (PEA) over a Pd/Al₂O₃ catalyst as mentioned in **Chapter 2**, which results from synergistic effects of CO₂ and water. The use of CO₂ and/or water as components of multiphase reaction media has an interesting effect on organic synthetic reactions therein, which may increase the rate of reaction, modify the product selectivity, and/or improve the catalyst life.^{1,2} When a liquid reaction mixture is pressurized by CO₂ at a certain pressure, CO₂ molecules can be dissolved in the liquid phase, interact with aldehyde, carbonyl, nitro, nitrile, and other polar groups of substrates and/or intermediates, and then change their reactivity.³⁻⁷ As a result, CO₂ can act as a reaction promoter/modifier for several synthetic reactions although CO₂ is not involved as a reactant in the reactions at all.¹⁻⁸ The pressurization is needed for the dissolution of some amount of CO₂ into the organic liquid phase but at not so high pressure (< its critical pressure 7.1 MPa). The hydrogenation of phenylacetone nitrile and benzonitrile was carried out in CO₂-expanded ethanol (3 MPa) with NiCl₂/NaBH₄.⁸ The corresponding primary amines of 2-phenylethylamine and benzylamine were produced in 97% and 98% selectivity, respectively. The impact of dense phase CO₂ is also effective for the selective hydrogenation of nitrile compounds, in which further hydrogenation to secondary and tertiary amines can be suppressed. CO₂ acts as a temporary protecting group for primary and secondary amines during the hydrogenation in supercritical CO₂;^{11,12} that is, CO₂ reacts with amines just after being produced and yields carbamate salts, which thus inhibits the undesired side reactions. The addition of water also has interesting effects on organic reactions using homogeneous catalysts⁹⁻¹⁰ and the presence of water - organic interface is one of important factors

responsible for the effects. It was reported previously that the presence of high pressure CO₂ promotes the selective hydrogenation of cinnamaldehyde (CAL) to cinnamyl alcohol (COL) with homogeneous Ru-complex catalyst using a phosphine ligand.⁹ The homogeneous hydrogenation of CAL in aqueous phase was also examined under similar conditions as used for several types of multiphase reaction systems using Ru-phosphine complex catalyst in the presence of high pressure CO₂. The high COL selectivity can be achieved when the interface between the water and organic phases is the main reaction locus at low CO₂ pressures as well as at higher CO₂ pressures.

We recently indicated the usefulness of both CO₂ and water for a few multiphase reactions with heterogeneous catalysts.¹³⁻¹⁵ For hydrogenation of nitrobenzene with a Ni/Al₂O₃ catalyst, the rate of hydrogenation is enhanced and the selectivity to the desired product of aniline is 100% at any conversion level in the presence of CO₂.¹³ On the addition of water into this multiphase medium, the effect of CO₂ pressurization can appear at a low pressure of about 1 MPa.¹⁴ Another example is the selective hydrogenation of benzonitrile to the corresponding primary amine with a Pd/Al₂O₃ catalyst.¹⁵ In the hydrogenation of benzonitrile the synergetic effects of CO₂ and water give a high selectivity to the desired primary amine, in which benzylamine (BA) can be obtained with a selectivity > 95% at any conversion level with no catalyst deactivation. In the present work, therefore, the potentiality of the multiphase medium including both CO₂ and water has further been investigated for the selective hydrogenation of various nitrile substrates, in addition to benzyl cyanide (BC) as described in **Chapter 2**, with the same commercial Pd/Al₂O₃ catalyst as used for BC. The nitrile substrates examined are 2-phenylethyl cyanide (PEC), cinnamionitrile (CN), *n*-hexanenitrile (HN), and 4-cyanobiphenyl (CBP).

3.2 Experimental

3.2.1 Hydrogenation

A commercially available 5 wt. % Pd/Al₂O₃ catalyst (Wako) was used for hydrogenation of various nitriles. A Teflon lined autoclave (100 cm³) was charged with a certain amount of substrate, 5 cm³ solvent (toluene or *n*-hexane), 5 cm³ water, and a weighed amount of Pd/Al₂O₃ catalyst. Then, the reactor was flushed with H₂ (99.99%) three times to remove the air, closed, and heated in a heating mantle to a reaction temperature of 323 K. After the reaction temperature was attained, 4 MPa H₂ (99.99%) was introduced, followed by the introduction of CO₂ (99.99%) to the desired total pressure with a high-pressure liquid pump (JASCO SGF-GET). The reactions were carried out while stirring the reaction mixture with a magnetic stirrer. After the reaction, the reactor was cooled in an ice water bath and depressurized carefully to atmospheric pressure. The reaction mixture was analyzed by gas chromatography (GL Sciences GC-390B) using a capillary column (GL Sciences TC 1701) and a flame ionization detector. The total conversion was determined from the initial and

final amounts of substrate measured. The products were identified by GC-MS (Shimadzu 17A).

3.2.2 *In situ* FTIR measurement

Interactions between substrate and CO₂ molecules in the liquid phase were examined by *in situ* high-pressure FTIR measurements using a JASCO FTIR-620 spectrometer with a triglycine sulfate detector at a wavenumber resolution of 2 cm⁻¹ and at 323 K (reaction temperature). The FTIR-ATR spectra were collected in an *in situ* high-pressure ATR cell (1.18 cm³) attached with a ZnSe crystal rod. The temperature of the cell was controlled by a temperature controller and a heating jacket with rod heaters.^{4, 15} The FTIR spectra were collected for a mixture of CO₂ dissolved in liquid nitrile substrates at different pressures.

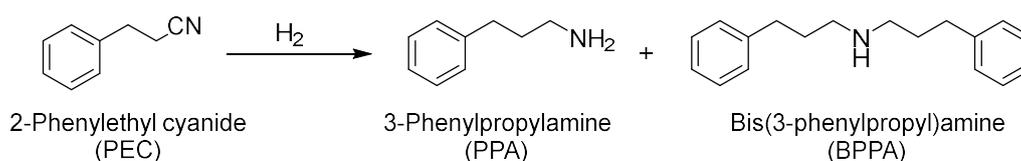
3.3 Results and discussion

3.3.1 Hydrogenation of phenylethyl cyanide (PEC) in four different reaction media

Table 3.1 gives the results of PEC hydrogenation in different reaction media. Under the reaction conditions used, the products detected were 3-phenylpropylamine (PPA) and bis(3-phenylpropyl)amine (BPPA). The secondary amine, BPPA, was selectively obtained in a conventional organic solvent of toluene, toluene + CO₂, and toluene + H₂O irrespective of conversion levels under the conditions used (entries 1 - 12). In contrast, the primary amine, PPA, was produced in a larger selectivity of 82%-87% when both CO₂ and H₂O were included in the reaction medium (entries 13-16). The presence of CO₂ and/or H₂O decreased the conversion of PEC, which may be explained as follows: when the liquid reaction mixture (toluene, PEC) is pressurized by CO₂, a certain amount of CO₂ molecules is dissolved into the liquid phase and CO₂ acts as a diluent, causing the dilution of reacting species. The reaction occurs in organic phase in the absence of H₂O but, when H₂O is used, the main reaction locus changes from the organic phase to the interfacial layer between the organic and aqueous phases, which include the substrate and the catalyst of hydrophilic nature, respectively. Those impacts of CO₂ and H₂O should result in a decrease in the conversion. However, the desired product of PPA was obtained in a larger selectivity in medium (d) including both CO₂ and H₂O (entries 13-16), which may be explained by considering a few factors. The PPA molecule is soluble in H₂O and exists in the form of stable carbamate salt with CO₂ in the aqueous phase. The acidic nature of H₂O caused by the dissolution of CO₂ should also contribute to stabilize the carbamate species. When water is pressurized by CO₂ at pressures of 1–8 MPa, the pH value decreases to about 3.^{16, 17} The transfer of PPA molecules into the aqueous phase may reduce the chance of PPA to react with intermediate species in

the organic phase yielding the secondary amine. The formation of such carbamate species with CO₂ was indicated for several amines in the literature.^{15, 18, 19} However, in the presence of toluene + CO₂ (medium (b)), toluene + H₂O (medium (c)), and toluene + CO₂ + H₂O (medium (d)), the reaction stopped after a certain period of reaction time; namely, the catalyst deactivation occurred. This will be discussed later (Section 3.3.5 and 3.3.7).

Table 3.1 Results of PEC hydrogenation in different reaction media including CO₂ and/or H₂O

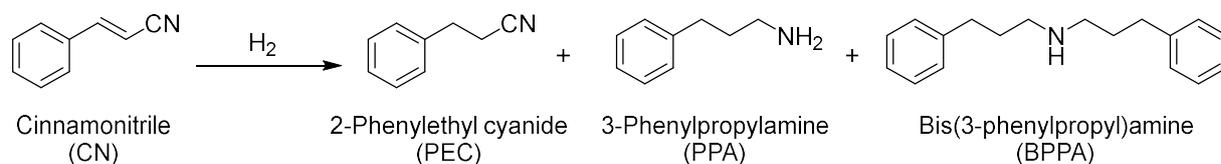


Entry	Time (min)	Conversion (%)	Selectivity (%)	
			PPA	BPPA
Medium (a) including toluene				
1	30	56	0	>99
2	60	71	0	>99
3	120	83	0	>99
4	210	90	0	>99
Medium (b) including toluene, CO ₂				
5	60	48	0	>99
6	120	54	0	>99
7	300	56	0	>99
8	360	56	0	>99
Medium (c) including toluene, H ₂ O				
9	60	6	0	>99
10	180	12	0	>99
11	300	31	34	67
12	24h	33	35	66
Medium (d) including toluene, H ₂ O, CO ₂				
13	60	32	82	18
14	120	46	84	16
15	180	48	88	12
16	300	48	87	13

Reaction conditions: PEC 1 mmol (0.131 g), 5 wt.-% Pd/Al₂O₃ catalyst 65.6 mg, toluene 10 cm³ (for 1, 2) and 5 cm³ (for 3, 4), H₂O 5 cm³ (for 3, 4), 323 K, H₂ 4 MPa, CO₂ 1 MPa

3.3.2 Hydrogenation of cinnamionitrile (CN) in four different reaction media

The results of CN hydrogenation are presented in **Table 3.2**, indicating that H₂ was selectively added to C-C double bond but not to C-N bond and so 2-phenylethyl cyanide (PEC) was exclusively obtained in four different reaction media (entries 1 - 17) under the conditions used. The rate of hydrogenation of C-C bond is larger than that of C- N bond. It is expected, for the toluene - CO₂ - H₂O medium, that the product of PEC would further be hydrogenated to PPA for a longer reaction time, according to the results of **Table 3.1** in which PEC is the starting substrate. The presence of H₂O has a negative impact on the rate of CN conversion (entries 1, 8), similar to the reaction of PEC (**Table 3.1**). The rate of CN conversion in medium (d) is larger than that in medium (c) (entries 8, 12); the positive effect of CO₂ dissolution may increase the rate of reaction in medium (d). The catalyst deactivation was not observed for CN hydrogenation in the four-reaction media (a) - (d) examined. In medium (a) only, BPPA (secondary amine) was formed at a later stage of reaction. The reaction medium (a) shows the positive effect on further hydrogenation of PEC to BPPA. Namely, the hydrogenation of PEC formed was inhibited by CO₂ and/or H₂O.

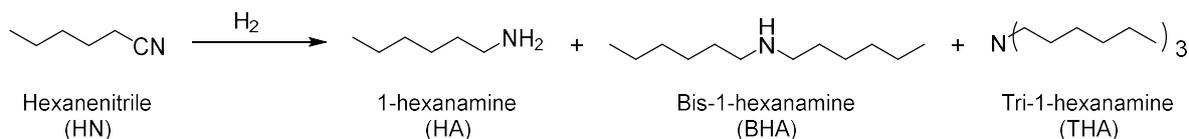
Table 3.2 Results of CN hydrogenation in different reaction media including CO₂ and/or H₂O

Entry	Time (min)	Conversion (%)	Selectivity (%)		
			PEC	PPA	BPPA
Medium (a) including toluene					
1	30	>99	>99	0	0
2	60	>99	82	0	18
3	120	>99	71	0	29
Medium (b) including toluene, CO ₂					
4	30	>99	>99	0	0
5	60	>99	>99	0	0
6	120	>99	>99	0	0
Medium (c) including toluene, H ₂ O					
7	10	35	>99	0	0
8	30	56	>99	0	0
9	60	>99	>99	0	0
10	120	>99	>99	0	0
Medium (d) including toluene, H ₂ O, CO ₂					
11	10	44	>99	0	0
12	30	87	>99	0	0
13	60	97	>99	0	0
14	120	>99	>99	0	0
15	180	>99	>99	0	0
16	240	>99	>99	0	0
17	360	>99	>99	0	0

Reaction conditions: CN 1 mmol (0.129 g), 5 wt.-% Pd/Al₂O₃ catalyst 64.5 mg, toluene 10 cm³ (for 1, 2) and 5 cm³ (for 3, 4), H₂O 5 cm³ (for 3, 4), 323 K, H₂ 4 MPa, CO₂ 1 MPa

3.3.3 Hydrogenation of *n*-hexanenitrile (HN) in four different reaction media

An aliphatic nitrile of HN was also examined, for which *n*-hexane was used instead of toluene due to its solubility. Under the reaction conditions used, the products detected were 1-hexanamine (HA), bis-1-hexanamine (BHA), and tri-1-hexanamine (THA). The results obtained in different reaction media are presented in **Table 3.3**. The primary amine of HA was not detected to form in *n*-hexane (entries 1-3) and *n*-hexane - CO₂ (entries 4-7) and the conversion of HN in *n*-hexane - H₂O was very small (entries 8-10) under the conditions used. Although the rate of HN conversion was small, the primary amine of HA was selectively formed in *n*-hexane - CO₂ - H₂O medium (entries 11, 12). In this medium (d), HA was observed to change to BHA and THA for a longer reaction time although HN was little consumed (entries 11, 12). The formation of BHA, which is produced via condensation between HA produced and the intermediate of hexylideneimine may responsible for the decrease in HA selectivity. The rate of HN conversion in *n*-hexane - CO₂ - H₂O is larger than that in *n*-hexane - H₂O (entries 10, 11). This may be ascribed to the increased acidic nature of H₂O by the dissolution of CO₂,^{16, 17} which should be beneficial for hydrogenation reactions. The catalyst deactivation occurred in medium (b) and medium (d). The reasons for the catalyst deactivation will be discussed later in section 3.3.5 and 3.3.7.

Table 3.3 Results of HN hydrogenation in different reaction media including CO₂ and/or H₂O

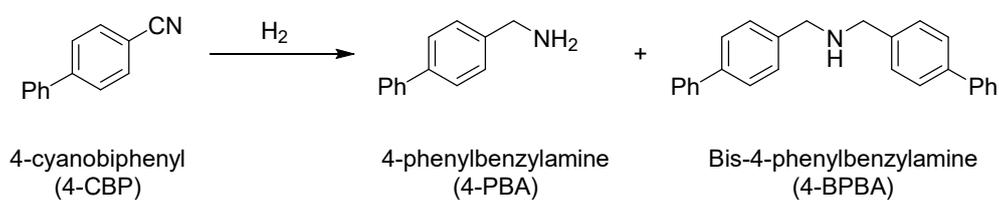
Entry	Time (min)	Conversion (%)	Selectivity (%)		
			HA	BHA	THA
Medium (a) including <i>n</i> -hexane					
1	30	72	0	34	66
2	60	87	0	18	82
3	90	92	0	15	85
Medium (b) including <i>n</i> -hexane, CO ₂					
4	30	43	0	42	58
5	60	52	0	38	62
6	90	53	0	37	63
7	120	54	0	38	62
Medium (c) including <i>n</i> -hexane, H ₂ O					
8	30	<0.1	0	0	0
9	60	<0.1	0	0	0
10	300	<0.1	0	0	0
Medium (d) including <i>n</i> -hexane, H ₂ O, CO ₂					
11	300	32	>99	0	0
12	24h	34	62	29	9

Reaction conditions: HN 1 mmol (0.0972 g), 5 wt.-% Pd/Al₂O₃ catalyst 48.6 mg, *n*-hexane 10 cm³ (for 1, 2) and 5 cm³ (for 3, 4), H₂O 5 cm³ (for 3, 4), 323 K, H₂ 4 MPa, CO₂ 1 MPa

3.3.4 Hydrogenation of 4-cyanobiphenyl (CBP) in four different reaction media

Finally, a large aromatic nitrile of CBP was tested and the results obtained are given in **Table 3.4**. The primary amine, 4-phenylbenzylamine (PBA), was exclusively formed in toluene, toluene - CO₂, and toluene - H₂O (entries 1 - 11). In this hydrogenation, the primary amine of PBA is less soluble in H₂O and so it stays in the organic phase; however, its selectivity is high at relatively high conversion levels, suggesting that the second step of PBA transformation to the secondary amine (bis-4-phenylbenzylamine, BPBA) is slower compared to the first one of hydrogenation of CBP to PBA. This may be due to difference in the structure between CBP and PBA molecules; CN group is bonded to the phenyl ring in a large conjugated system in the former but not NH₂ group in the latter. The differences in the rate of CBP conversion among these four media were not so large as compared to the results of PEC (**Table 3.1**) and HN (**Table 3.3**). The dissolution of CO₂ causes the dilution of reacting species in the organic phase (toluene) as above-mentioned but, concurrently, it assists the dissolution of a gaseous reactant of H₂. That is, the pressurization with CO₂ has positive and negative impacts depending on the type and nature of reactions and reaction conditions. The rate in medium (c) is smaller than those in media (a) and (b) and reason for this will be discussed later. For the toluene - CO₂ - H₂O medium (entries 12-15), CBP was observed to give a conversion of 34% in 60 min but PBA and BPBA were not detected to form and products were unable to identify at present. The catalyst deactivation occurs in media (a)-(d) and the reasons of the catalyst deactivation will be discussed later in section 3.3.5 and 3.3.7.

Table 3.4 Results of CBP hydrogenation in different reaction media including CO₂ and/or H₂O



Entry	Time (min)	Conversion (%)	Selectivity (%)	
			PBA	BPBA
Medium (a) including toluene				
1	30	45	>99	0
2	60	70	>99	0
3	120	78	>99	0
4	180	80	>99	0
Medium (b) including toluene, CO ₂				
5	30	40	>99	0
6	60	76	>99	0
7	120	80	>99	0
Medium (c) including toluene, H ₂ O				
8	30	30	>99	0
9	60	61	>99	0
10	120	70	>99	0
11	300	88	>99	0
Medium (d) including toluene, H ₂ O, CO ₂				
12	60	34	0	0
13	120	46	0	0
14	300	48	0	0
15	360	48	0	0

Reaction conditions: CBP 0.5 mmol (0.0895 g), 5 wt.-% Pd/Al₂O₃ catalyst 44.8 mg, toluene 10 cm³, H₂O 5 cm³ (for 3, 4), 323 K, H₂ 4 MPa, CO₂ 1 MPa

3.3.5 Time profiles of hydrogenation reactions in four different media

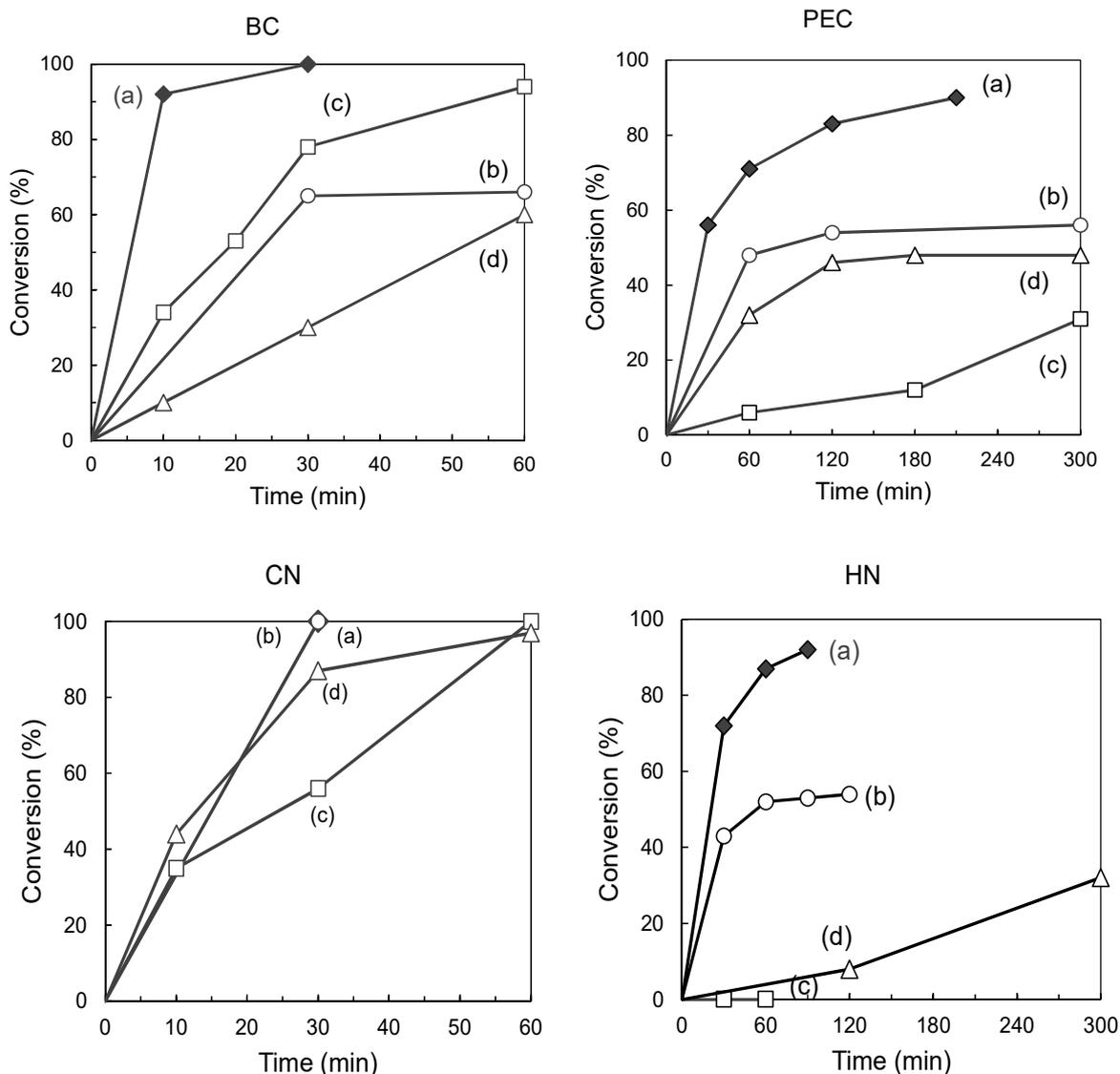
The selective hydrogenation of benzyl cyanide (BC) using multiphase reaction medium including CO₂ and/or water is described in **Chapter 2**. The time-conversion profiles of BC hydrogenation reactions using four different multiphase reaction media at H₂ 4 MPa and CO₂ 1 MPa are shown in **Figure 3.1**. The products formed in the BC hydrogenation were 2-phenylethylamine (PEA), *N,N*-bis(2-phenylethyl)amine (BPEA), and bis(2-phenylethyl)diazene (BPEDA), as shown in **Scheme 2.3**. As shown in **Figure 3.1**, in the absence of CO₂ and water (medium a) the reaction went smoothly and almost 100% conversion was obtained within 30 min under the reaction conditions used. The deactivation of Pd/Al₂O₃ catalyst was observed in the presence of 1 MPa CO₂ and in the absence of H₂O (medium b). The reason for this catalyst deactivation will be discussed in detail later. In the presence of water (medium c), the reaction went smoothly and a BC conversion of > 90% was observed in 1 h. In the presence of both CO₂ and water (medium d), the conversion was lowered to nearly 60% in 1 h, but no catalyst deactivation occurred in this multiphase reaction medium, in which nearly 95% BC conversion was obtained in 180 min (as described later in **Table 4.2**, entry 14). The primary amine of PEA was observed to form in the reaction medium (d) and the product distribution was shown to depend on the reaction media employed. The medium-dependent product formation and selectivity will be discussed later in **Section 3.3.7**.

In the hydrogenation of 2-phenylethyl cyanide (PEC) the time-conversion profile in **Figure 3.1** and **Table 3.1** show that the catalyst became deactivated for the three-reaction media (b), (c), and (d). In neat organic solvent, toluene (medium a) nearly 90% PEC conversion was obtained in 3.5 h. In the presence of CO₂ (media b and d) the reaction stopped in 2 h. In the presence of water (medium c), the reaction proceeded very slowly and a smaller PEC conversion of 30% was obtained in 5 h after which the conversion little increased in 24 h (**Table 3.1**). The initial rate of hydrogenation in the presence of both CO₂ and water (medium (d)) was larger than that in medium (c) but the rate became leveled off at a smaller conversion. Although the rate of PEC hydrogenation in medium (d) was smaller than those in media (a) and (b), the desired product of the primary amine, 3-phenylpropyl amine, was produced in a high selectivity of > 80% (**Table 3.1**). The influence of reaction media on the product selectivity will be discussed later.

Figure 3.1 shows that the hydrogenation of cinnamionitrile (CN) proceeded smoothly in four different multiphase reaction media. The media of neat toluene (medium a) and toluene-CO₂ (medium d) gave almost 100% CN conversion in 30 min. In toluene-H₂O (medium c) and toluene-CO₂-H₂O (medium d), conversion values of >99% and 97% were obtained in 60 min, respectively. In all four different reaction media examined, the reduction of C=C bond of the side chain occurred exclusively, yielding 2-phenylethyl cyanide (PEC) in a high selectivity. **Table 3.2** shows that in medium (a) only BPPA was formed at a later stage of reaction. The reaction medium (a) shows the positive effect on further hydrogenation of PEC to BPPA.

The time-conversion profiles for HN hydrogenation in **Figure 3.1** indicate that in neat solvent of *n*-hexane (medium a) the reaction goes smoothly but, in *n*-hexane-CO₂ (medium b) the reaction stops in 30 min. No reaction occurred in *n*-hexane-H₂O (medium c). The rate of HN hydrogenation in the presence of *n*-hexane-CO₂-H₂O (medium (d)) was even smaller than those in media (a) and (b). The catalyst deactivation was observed to occur in *n*-hexane – CO₂ (medium b) and *n*-hexane – CO₂-H₂O (medium d) (also see **Table 3.3**).

The selective hydrogenation of 4-cyanobiphenyl (CBP) was carried out using four different types of reaction media. The time-conversion profiles presented in **Figure 3.1** shows that a CBP conversion of >75 % was obtained in 120 min in either neat solvent toluene (medium a) or toluene-CO₂ (medium b). The conversion was decreased to 70% and 46% in toluene-H₂O (medium c) and toluene-CO₂-H₂O (medium d) in 120 min, respectively. For the medium (a) and (b) catalyst deactivation occurs after 120 min. The catalyst deactivation occurs in CBP hydrogenation in the medium (a)-(d) and the reasons of catalyst deactivation will be discussed later (**Table 3.4**).



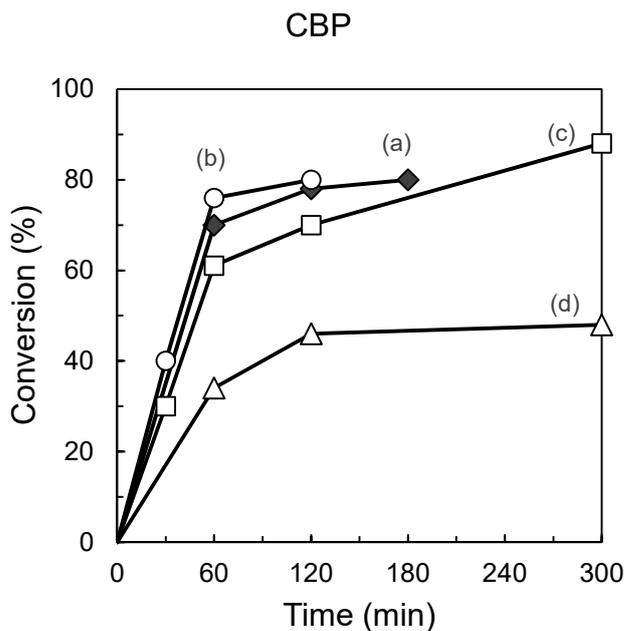


Figure 3.1 Total conversion against reaction time for hydrogenation reactions of five substrates including BC, PEC, CN, HN and CBP in the four different multiphase reaction media at H₂ 4 MPa and CO₂ 1 MPa. See **Tables 2.1, 3.1 -3.4** for other reaction conditions. Where, reaction medium: (a) neat solvent *n*-hexane/Toluene; (b) *n*-hexane/Toluene-CO₂; (c) *n*-hexane/Toluene-H₂O; and (d) *n*-hexane/Toluene-CO₂-H₂O.

Note: For CN the total conversion against reaction time profiles for media (a) and (b) are similar (overlapped in the graph; see **Table 3.2**).

3.3.6 Substrate - CO₂ interactions and phase behavior

Furthermore, molecular interactions of CO₂ with the substrates, 2-phenylethyl cyanide (PEC), cinnamitrile (CN), hexanenitrile (HN), and 4-cyanobiphenyl (CBP), were measured by *in situ* high-pressure FTIR in attenuated total reflection mode (ATR) at a reaction temperature of 323 K.^{20,21} **Figure 3.2** shows FTIR spectra collected at different CO₂ pressures. The peaks of the absorption bands of stretching vibration of nitrile group were located at 2220 - 2350 cm⁻¹ (Characteristic IR absorption frequency range) depending on the structure of substrates examined. The absorption peak was blue-shifted with increasing CO₂ pressure for all substrates in common although the extent of blue-shift depended on the substrates examined (**Table 3.5**). Those results indicate that C-N bond becomes stronger through interactions with CO₂ and its reactivity is likely to be reduced to some extent. At low CO₂ pressure of 1 MPa used in the present reaction runs, however, such an effect of CO₂ should not be taken into consideration.

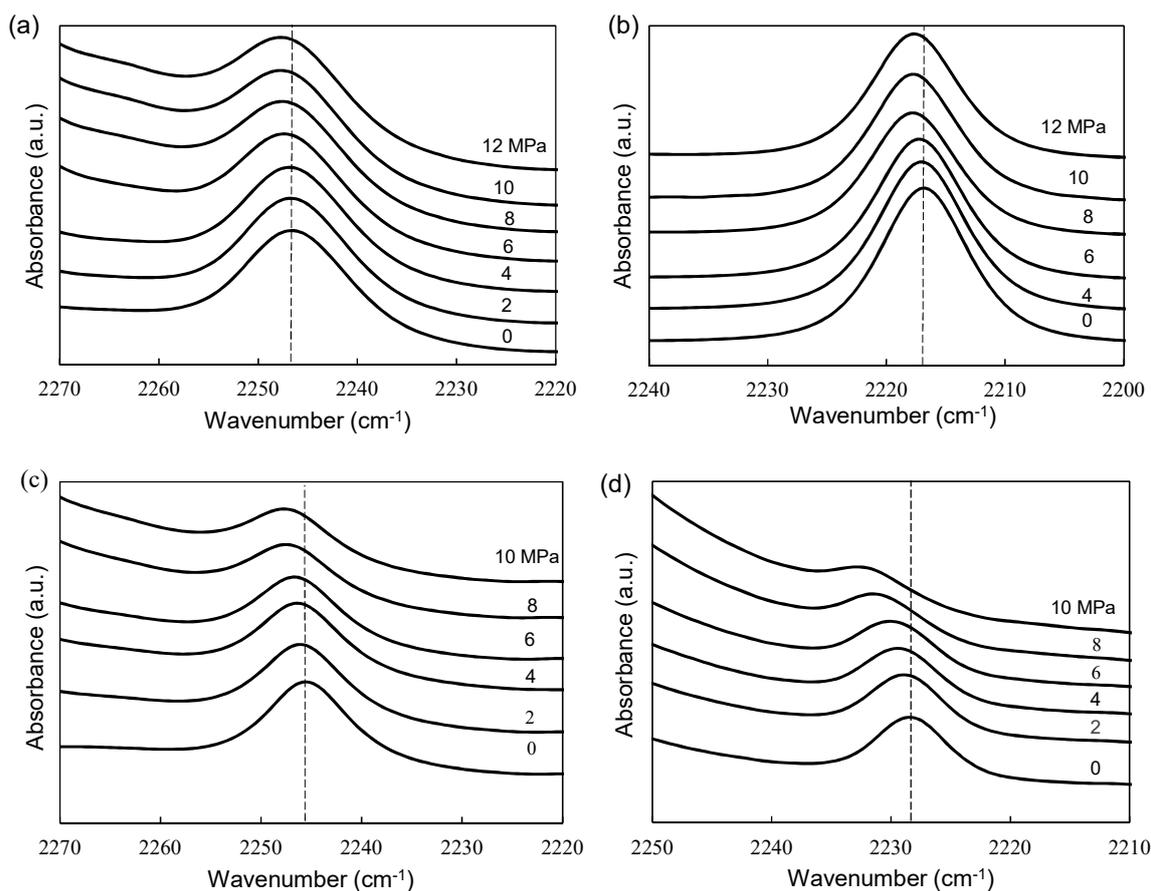


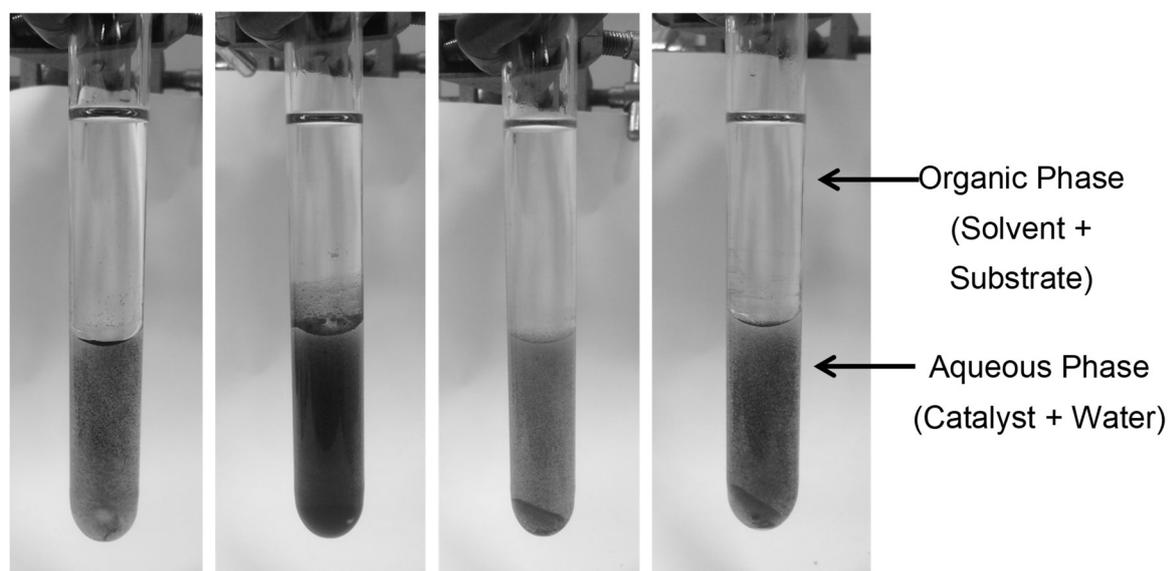
Figure. 3.2 *In-situ* high pressure FTIR-ATR spectra collected at 323 K for (a) neat PEC, (b) neat CN, (c) neat HN and (d) CBP in toluene under compressed CO₂ at pressures given.

Table 3.5 Interactions between substrate and CO₂ by FTIR at 323 K

Entry	Substrate	$\nu(\text{CN})$ observed at 0 MPa (cm ⁻¹)	CO ₂ pressure used (MPa)	$\Delta\nu$ (CN) observed (cm ⁻¹)
1	PEC	2246	0-12	1
2	CN	2217	0-12	< 1
3	HN	2245	0-10	2
4	CBP	2227	0-10	3

Interactions of organic substrates with another component of H₂O would have impacts on the reaction. In hydrogenation of nitrobenzene with a Ni/Al₂O₃ catalyst, the reactivity of nitro group of the substrate is lowered by interactions with CO₂ while that of an intermediate of phenylhydroxylamine is enhanced.⁴ In addition, interactions with H₂O also have an impact of enhancing the reactivity of the intermediate, as indicated by FTIR-ATR.⁴ This results in the complete (100%) selectivity to the desired product of aniline at any conversion level. For the present H₂O - nitrile substrates, unfortunately, it is difficult to make similar FTIR-ATR measurements with homogeneous aqueous solutions because of their low solubility in H₂O.

The present reaction system is multiphasic and it is important to see where (in which phase) the Pd/Al₂O₃ catalyst exists. It was difficult to examine the state of catalyst dispersion under reaction conditions and so it was examined in a simple way under ambient conditions. A glass tube was added with 5 cm³ water and a magnetic stirrer and then with an organic solution of 5 cm³ solvent and 1 mmol of nitrile substrate. It was further added with the same amount of Pd/Al₂O₃ catalyst as used in the reaction runs (see **Tables 3.1 - 3.4**). Then reaction mixture was mixed for 2-3 min and allowed to stand for 1-2 min. Then, the photographs of the reaction mixtures were taken. **Figure 3.3** gives pictures for the mixtures of substrate, organic solvent, water, and catalyst. For all mixtures examined the catalyst powder was observed to exist in an aqueous phase and then completely settle down at the bottom of glass tube within 5 min probably due to hydrophilic nature of its support material and the density of the catalyst.



(a) PEC/toluene (b) CN/toluene (c) HN/hexane (d) CBP/toluene

Figure 3.3 Phase behavior of organic solvent-water systems including nitrile substrates under ambient conditions.

3.3.7 Possible roles/functions of CO₂ and water

The present results demonstrate that the multiphase medium (d) including both water and CO₂ is promising for the selective hydrogenation of PEC and HN to the primary amines, in addition to the substrate of BC (**Chapter 2**), but not for the other substrates of CN and CBP. No primary amine has been observed to form in CN and CBP hydrogenation. The presence of CO₂ and/or water influences the rate of reaction, the product selectivity, and the catalyst life (deactivation). In the following, possible roles/functions of CO₂ and water in those effects observed will be discussed.

(a) Reaction rate

The present work used five different nitrile substrates of benzyl cyanide (BC), 2-phenylethyl cyanide (PEC), cinnamitrile (CN), hexanenitrile (HN), and 4-cyanobiphenyl (CBP). For the substrates of BC, PEC, and HN, the rate of hydrogenation in conventional medium (a) (in neat organic solvent) was the largest as compared to the other multiphase media. The order of the rate of hydrogenation at small conversion levels is medium (a) > medium (b) > medium (d) >> medium (c). When CO₂ co-exists in medium (a), the conversion was lowered by the addition of CO₂ as compared to medium (a), the decrease in conversion may be ascribed to the formation of CO through water gas shift reaction ($\text{CO}_2 + \text{H}_2 \rightarrow \text{CO} + \text{H}_2\text{O}$) and adsorbed on the surface of supported metal particles.²⁴⁻²⁵ As mentioned above, medium (c) also shows decrease in rate of conversion for BC, PEC (except HN). This may ascribe to the reason that is for the *n*-hexane/toluene – water medium (medium C), the catalyst is dispersed mainly in the aqueous phase (**Figure 3.3**) and the reaction should occur at the organic – aqueous interface. The chance of contacting of the catalyst with the organic substrate should be more difficult in the *n*-hexane/toluene – water medium than in the homogeneous organic phase. The rate of nitrile hydrogenation at the interface is therefore assumed to be smaller than that in the homogeneous organic phase of *n*-hexane/toluene (excluding the solid catalyst). The hydrogenation reaction not proceeded for HN in medium (c) and reason for this is unknown. When this *n*-hexane/toluene – water medium is pressurized by CO₂ (medium d), the above mentioned negative dilution effect by the CO₂ dissolution also appears on one hand in this nitriles hydrogenation (BC, PEC, HN). The interactions of nitrile substrate with CO₂ in the aqueous phase may decrease the reactivity of its nitrile group (**Figure 3.2**). It is speculated that the interactions of the polar nitrile group with CO₂ molecules are promoted at the organic – aqueous interface with some assistance of water. Importance of the organic – aqueous interface is noted for organic synthetic reactions assisted by water.²³

For the other substrates of CN and CBP, in contrast, the initial rate of hydrogenation was larger in the order of medium (a) \approx medium (b) > medium (d) > medium (c) for the former and medium (a) \geq medium (b) > medium (c) > medium (d) for the latter. Substrate CN shows the same conversion in both the medium (a) and (b). CBP also shows almost

similar conversion in medium (a)-(c) (nearly 80% CBP conversion). This may be due to difference in the structure, in CBP and CN substrate; $C\equiv N$ group is in a large conjugated system; due to this structural effect CN substrate selectively hydrogenated to saturated nitrile, PEC and CBP hydrogenated to PBA. As mentioned above, the dissolution of CO_2 causes the dilution of reacting species in the organic phase (*n*-hexane/toluene), concurrently, it assists the dissolution of a gaseous reactant of H_2 . That is, the pressurization with CO_2 has positive effect in CN and CBP hydrogenation in medium (b). Medium (c) shows smaller decrease in the initial rate of hydrogenation of CN and CBP as compared to initial hydrogenation rates of CN and CBP in medium (a) and (b). As mentioned above (for BC, PEC and HN), when this *n*-hexane/toluene – water medium is pressurized by CO_2 (medium d), the negative dilution effect by the CO_2 dissolution appears on one hand in this nitriles hydrogenation (CN and CBP). The interactions of nitrile substrate with CO_2 in the aqueous phase may decrease the reactivity of its nitrile group (**Figure 3.2**).

(b) Product selectivity

The most important feature of the *n*-hexane/toluene – water – CO_2 medium (d) is the highly selective hydrogenation of PEC and HN to the primary amine, similar to the substrate of BC. In the hydrogenation of PEC and HN, the primary amines of 3-phenylpropyl amine and 1-hexanamine were produced in >80% selectively (**Table 3.1**, entries 13-16) and >99% selectivity (**Table 3.3**, entries 11, 12), respectively. When liquid solvent or substrate phase is pressurized by CO_2 , it expands by dissolution of CO_2 . The dissolved CO_2 interacts with the primary amines and produces the water-soluble carbamate species, which may transfer from the organic phase to the aqueous phase. This transfer of primary amines from organic phase to aqueous phase may reduce the chance of further hydrogenation to secondary amine or byproducts. The acidic nature of water caused by dissolution of CO_2 should also contribute to stabilize the carbamate species. Such synergistic effects of CO_2 and water were not observed in CN and CBP hydrogenation reactions. The 2-phenylethyl cyanide is the only product in the former hydrogenation. The carbon-carbon double bond of the side chain is more selectively reduced than the carbon-nitrogen triple bond. The conjugation of the nitrile group, the $C=C$ bond, and the aromatic ring does not assist nitrile reduction in this case. In the case of the CBP hydrogenation, in medium (c) including water and organic phases, 4-phenylbenzylamine (PBA) was formed in 100% selectivity and detected in the organic phase only because its solubility in water is low. In medium (d), no products were detected in the organic phase as well as in aqueous phase. In medium (d), CO_2 may have negative influence on the production of PBA. Due to positive effect of dilution of CO_2 , CO_2 may interact with $C\equiv N$ group of CBP and promote the formation of PBA in medium (b).

In the case of CN hydrogenation, medium (a) shows the formation of BPPA (**Table 3.2**, entries 1-3) at a later stage of reaction; PEC may further have hydrogenated to the

secondary amine. The same effect was observed in HN hydrogenation in medium (d) in which the product of HA was further hydrogenated to BHA and THA (secondary and tertiary amines) (**Table 3.3**, entries 11-12) with increasing reaction time (24 h). The condensation between HA produced and the intermediate of hexylideneimine may be responsible for the formation of BHA and THA.

(c) Catalyst life

As mentioned in section 3.3.5, the nitrile hydrogenation was observed to stop after a certain period of reaction time; namely, catalyst deactivation occurred in some cases (**Tables 3.1, 3.3, 3.4, Figure 3.1**). In **Table 3.6**, conversion values were listed at which the activity decay became significant. The occurrence of catalysts deactivation depends on the substrate and the medium examined. Possible reasons for the catalyst deactivation will be discussed in the following.

Table 3.6 Results of catalyst deactivation with various substrates in different reaction media^a

Substrate	Medium (a)	Medium (b)	Medium (c)	Medium (d)
BC	-	× (65%)	-	-
PEC	-	× (60%)	× (30%)	× (50%)
CN	-	-	-	-
HN	-	× (55%)	- ^b	× (35%)
CBP	× (80%)	× (80%)	-	× (50%)

^a CO₂ 1 MPa, H₂ 4 MPa ^b The reaction hardly took place.

× means the occurrence of Pd/Al₂O₃ catalyst deactivation during reaction.

The catalyst deactivation was not observed for CN hydrogenation (**Table 3.3** and **Figure 3.1**). As mentioned below, the C=C bond, and the aromatic ring does not assist nitrile reduction in this case. **Table 3.5** also shows less interaction between C≡N group of substrate CN and CO₂. **Table 3.2** shows that the C=C was selectively hydrogenated and PEC was exclusively obtained in four reaction media (a)-(d). That is the C=C bond, and the aromatic ring does not assist nitrile reduction in this case. **Table 3.5** also shows less interaction between C≡N group of substrate CN and CO₂. The catalyst deactivation was not observed for CN hydrogenation. So CN hydrogenation cannot be related to catalyst deactivation here.

Table 3.6 demonstrate that the multiphase reaction medium and conversion values at which the reaction stooped. The reasons for this catalyst deactivation for all substrate will be discussed here in common with respect to multiphase reaction medium used. The catalyst deactivation observed in medium (b) and (d) may ascribe to formation and adsorption CO species on catalyst, when *n*-hexane/toluene pressurized by CO₂, the Pd/Al₂O₃ catalyst loses its activity during the reaction. In the presence of H₂ and CO₂, CO is formed through reverse water gas shift reaction and adsorbed on the surface of supported metal particles.^{24, 25} On the Pd catalyst, bridged type CO is adsorbed and should cause its deactivation. The presence of water influences the adsorption of CO as evidenced by *in situ* high pressure FTIR measurements with Al₂O₃-supported Pd and other noble metal catalysts.²⁵ The CO molecules adsorbed on the rough surface (high Miller index planes) of supported Pd particles are removed by water molecules. These water molecules would be replaced by the substrate

molecules or assist the contacting of the substrate molecules to the Pd surface, and so the rough Pd surface should serve as active sites for the nitrile hydrogenation. Hence, the catalyst deactivation can be avoided but some CO molecules exist on and cover a certain partial area of Pd particles, resulting in the reduction of the overall rate of nitrile hydrogenation as compared to the reactions in the absence of CO₂.

In all the nitrile hydrogenation mass balance of reaction was > 95% except PEC hydrogenation. In PEC hydrogenation, catalyst deactivation occurs in medium (a)-(d) (**Table 3.6, Figure 3.1**); mass balance (GC analysis) was not good (average 94%). So used catalyst samples were washed by organic solvent and water, filtrate samples were collected and analyzed by GC and GC-MS and PPA detected as a major product and BPPA as a minor product. Thus, some product should exist on the catalyst and cause its deactivation. To examine the possibility, FTIR was used to measure the adsorption of product on the Pd/Al₂O₃ catalyst. **Figure 3.4 A** shows that the absorption bands of the aromatic C–H stretching vibration appear at 3081, 3062 and 3025 cm⁻¹ (Characteristic IR absorption frequency range, 3100-3000 cm⁻¹); the absorption bands of aliphatic C–H stretching vibration appear at 2937 and 2860 cm⁻¹ (Characteristic IR absorption frequency range, 3000-2850 cm⁻¹). The absorption band of C–N stretching vibration appear at 1154 cm⁻¹ (**Figure 3.4 B**). These results suggest that PPA and BPPA molecules can be adsorbed on the Pd metal and/or support. Unfortunately, the absorption band of N–H stretching vibration was not observed at 3500-3400 cm⁻¹ due to weak absorption (**Figure 3.4 C**). In CBP hydrogenation, catalyst deactivation occurred in medium (a) also (**Figure 3.1**), this may ascribe to the large conjugated system of CBP.

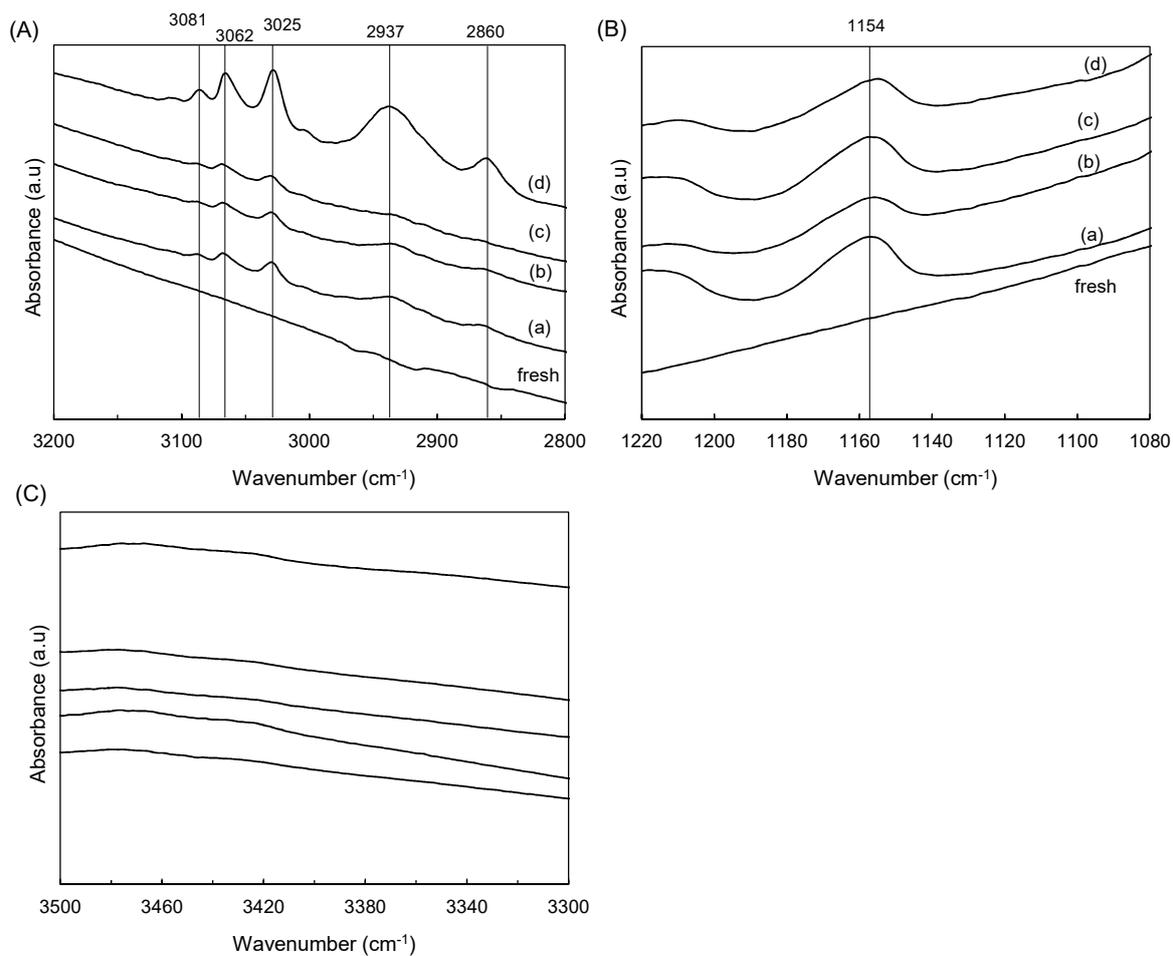


Figure 3.4 The FTIR spectra of used catalyst Pd/Al₂O₃ in hydrogenation of PEC in different reaction media. (a) Toluene (b) Toluene-CO₂ (c) Toluene-H₂O and (d) Toluene-CO₂-H₂O

3.4 Conclusions

The organic solvent (toluene, *n*-hexane) - CO₂ - H₂O medium (d) has been demonstrated to be effective for the selective hydrogenation of nitriles to corresponding primary amines with aromatic and aliphatic nitriles of PEC and HN, similar to BC, but, unfortunately, not for CN and CBP. The rate of nitrile conversion in this multiphase medium is smaller than that in neat organic solvents. This should result from the dilution of reacting species in the liquid phase by the dissolution of CO₂, the change of reaction locus from the organic phase to the organic - aqueous interfacial layer, and the decreased reactivity of nitrile group via interactions with CO₂ molecules. Unfortunately, the catalyst deactivation occurred with PEC, HN and CBP substrates in medium (b) and (d). and possible reason is formation and adsorption of CO through the through reverse water gas shift reaction ($\text{CO}_2 + \text{H}_2 \rightarrow \text{CO} + \text{H}_2\text{O}$), when hydrogenation reactions are conducted with supported metal catalysts in the presence of pressurized H₂ and CO₂.for all nitrile substrates used (except cinnamionitrile) with Pd/Al₂O₃ catalyst. In PEC hydrogenation, the products were adsorbed on catalyst and this may also deactivate the catalyst. For other substrates > 95% mass balance was obtained so there is no possibility of adsorption of products or substrate on catalyst. The catalyst is deactivated in CBP hydrogenation may ascribable to its large conjugated system. It is interesting to apply the multiphase reaction medium including CO₂ and H₂O for other synthetic reactions.

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Chapter 4

Selective Hydrogenation of Different Nitriles in the Presence of Carbon Dioxide and/or Water over Pd/C

The selective hydrogenation of benzyl cyanide (BC) and *n*-hexanenitrile (HN) has been carried out with a commercial 5 wt% Pd/C catalyst in different multiphase reaction media including CO₂ and/or water. The effectiveness of the medium including both CO₂ and water for the selective hydrogenation to primary amines has been investigated. The results with Pd/C have been compared with those with Pd/Al₂O₃ to examine the functions of CO₂ and water, similar or different, among these two Pd catalysts on different supports.

4.1 Introduction

The multiphase medium including both water and CO₂ in addition to an organic solvent of *n*-hexane is effective for the selective hydrogenation of BC to the primary amine of PEA over a Pd/Al₂O₃ catalyst as mentioned in **Chapter 2**, which results from synergistic effects of CO₂ and water when both are included in the reaction medium. The effectiveness of the multiphase medium including CO₂ and water was studied with the same Pd/Al₂O₃ catalyst for the selective hydrogenation of various nitriles of 2-phenylethyl cyanide (PEC), cinnamitrile (CN), *n*-hexanenitrile (HN) and 4-cyanobiphenyl (CBP) as mentioned in **Chapter 3**. Such a multiphase reaction medium was observed to have different impacts changing from one nitrile to another. The selective production of primary amine was achieved with PEC and HN. Then, the multiphase medium including CO₂ and water has further been applied for the selective hydrogenation of the two nitriles, BC and HN, using a commercial Pd/C catalyst. The properties (for example, surface hydrophilicity/hydrophobicity) of Pd/C catalyst may be different from those of Pd/Al₂O₃ one and so the multiphase medium would have different impacts on the selective hydrogenation of BC and HN. In the multiphase reactions using a solid catalyst, interface among organic liquid, water, and catalyst would be important for determining the reaction rate, the product selectivity, and/or the catalyst life. The importance of the interface between aqueous and organic phase is noted for promotional effects caused by the presence of water, which is believed to interact with organic substrates through hydrogen bonding at the interface and accordingly modify their reactivity.¹⁻³ Shirai *et al.* reported the multiphase hydrogenation of acetophenone over an activated carbon-supported Pd catalyst.³ The conversion of acetophenone was only 2% in the absence and presence of such organic solvents as heptane, ethanol and methanol. However, the conversion was enhanced to 27% in the presence of water alone. The conversion of acetophenone was tripled (70%) by the addition of 0.8 MPa CO₂ with high selectivity to 1-phenylethanol. The

addition of CO₂ and water effectively enhances the rate of acetophenone hydrogenation under the conditions of two-liquid systems.

A previous work reported that in the liquid phase hydrogenation of benzonitrile over a Pd/C catalyst, a very high selectivity to benzylamine (95%) was obtained at complete benzonitrile conversion and that the surface acidity exhibited by Pd/C contributed to the activation of the nitrile or amine and then to higher reaction rate.⁵ The activity of Pd catalyst was influenced by supports used (activated carbon, titania or γ -alumina). Sodium dihydrogen phosphate (NaH₂PO₄) was used as an acidic additive in benzonitrile hydrogenation. Its function is to form a salt with benzylamine and to keep the primary amine in the aqueous phase in order to avoid its further conversion. A recent work on hydrogenation of benzonitrile over a 5% Pd/Al₂O₃ catalyst highlighted the importance of reaction pathways, where toluene was observed as a by-product.⁶ At higher hydrogen pressure, the formation of β -palladium hydrides was observed at the catalyst surface. The formation of β -palladium hydrides results in selective formation of benzylamine on the catalyst surface due to the larger adsorption strength. The β -palladium hydrides prevent the hydrogenolysis reaction that gives toluene and increases the formation of the coupling product, dibenzylamine. Hence, β -palladium hydrides are effective for the formation of primary and secondary amines by preventing the hydrogenolysis reaction.

Maschmeyer and co-workers studied the hydrogenolysis of various nitriles, imines and amines over Pd/C.⁷ A high yield of toluene was obtained with a high catalyst loading promoting the unexpected hydrogenolysis of various nitriles, imines and amines, rather than their hydrogenation. They also examined the hydrogenation and hydrogenolysis of benzonitrile over a carbon-supported Pd catalyst under mild conditions (80°C, 0.1 MPa H₂).⁸ The authors reported the benzylamine to be strongly bound to the catalyst surface and to be capable of reversibly poisoning its hydrogenolysis function. Thus, the production of the hydrogenolysis product (toluene) is prevented at low catalyst loadings.⁸

Hao and co-workers studied the support effects in the gas phase hydrogenation of butyronitrile over Pd/Al₂O₃ and Pd/C catalysts.⁹ Authors reported that Pd/Al₂O₃ and Pd/C catalysts generated distinct product distributions, giving secondary amine over the former catalyst and tertiary amine over the latter. Hao and co-workers also studied the gas phase hydrogenation of benzonitrile over 1.2% Pd/Al₂O₃ and 1% Pd/C catalysts for selective production of benzylamine.¹⁰ Toluene was generated as a principal product over Pd/C (mean Pd particle size = 2.5 nm) and benzylamine over Pd/Al₂O₃ (Pd particle size = 3.0 nm). The 1% Pd/C catalyst exhibits a higher rate of nitrile consumption than 1.2% Pd/Al₂O₃ and this is ascribed to its smaller particle size (a larger amount of exposed Pd sites). Hydrogen desorption from Pd/C was significantly greater (by a factor of over 30) than expected from the chemisorption on Pd sites only, which suggests spillover that is migration of atomic hydrogen to the support following dissociation at Pd sites and greater specific surface area (Pd/C 870 m²/g, compared to Pd/Al₂O₃ 145 m²/g) can accommodate more spillover. The Pd/C delivered a significantly higher nitrile consumption rate than Pd/Al₂O₃, which can be linked to greater available surface reactive hydrogen.^{9, 10}

4.2 Experimental

4.2.1 Hydrogenation

Commercially available 5 wt% Pd/Al₂O₃ (Wako) and 5 wt% Pd/C (Aldrich) catalysts were used for multiphase hydrogenation reactions of benzyl cyanide (Aldrich) and *n*-hexanenitrile (TCI). The hydrogenation reactions were carried out in a 100 cm³ Teflon-lined autoclave. The reactor was charged with 1.0 mmol substrate, 5 cm³ *n*-hexane (Wako), 5 cm³ water (Wako) and 58.5 mg Pd/Al₂O₃ or 58.5 mg Pd/C catalyst and it was flushed with H₂ for three times to remove the air. The reactor was heated in a heating mantle up to the desired temperature. After the reaction temperature was attained, 4 MPa H₂ (99.99%) was introduced, followed by the introduction of liquid CO₂ (99.99%) to the desired total pressure with a high-pressure liquid pump (JASCO SCF-Get). The reactions were carried out at 323 K while stirring the reaction mixture with a magnetic stirrer. After the reaction, the reactor was cooled in an ice water bath and depressurized carefully to atmospheric pressure. The reaction mixture was analyzed by a gas chromatograph (GL Sciences GC-390B) using capillary column (TC 1701) and flame ionization detector. The total conversion was determined from the initial and final amounts of benzyl cyanide and *n*-hexanenitrile. The product was identified by GC-MS (Shimadzu 17A).

The present hydrogenation reactions of benzyl cyanide (BC) and *n*-hexanenitrile (HN) were conducted under different conditions as used in the runs described in **Chapters 2 and 3**. In **Chapter 2** the selective hydrogenation of benzyl cyanide in the presence of CO₂ and water over Pd/Al₂O₃ catalyst has been carried out at different H₂ (2 and 4 MPa) and CO₂ (0, 1 and 3 MPa) pressures (**Figure 2.4**). The hydrogenation runs with benzyl cyanide and *n*-hexanenitrile over Pd/C and Pd/Al₂O₃ catalysts described in this chapter were conducted at H₂ 4 MPa and CO₂ 1 MPa.

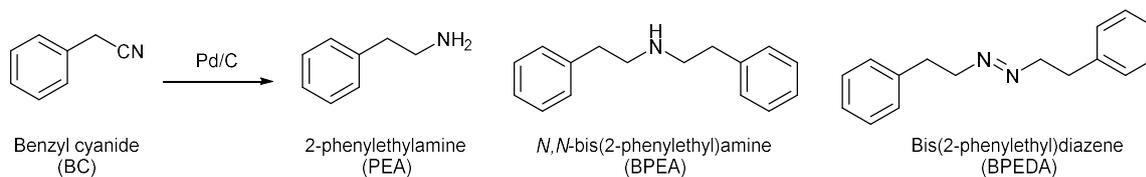
4.3 Results and discussion

4.3.1 Hydrogenation of benzyl cyanide in four different reaction media

(a) Reaction results

The selective hydrogenation of benzyl cyanide was carried out using 5 wt% Pd/C and 5 wt% Pd/Al₂O₃ catalysts in four different reaction media at 323 K, which were medium (a) including *n*-hexane alone, medium (b) including *n*-hexane and CO₂, medium (c) including *n*-hexane and water, and medium (d) including *n*-hexane, water, and CO₂. The results obtained with Pd/C and Pd/Al₂O₃ catalysts are shown in **Table 4.1** and **Table 4.2**, respectively. Under the reaction conditions employed, 2-phenylethylamine (PEA), *N,N*-bis(2-phenylethyl)amine (BPEA), and bis(2-phenylethyl)diazene (BPEDA) were observed to form. Possible reaction pathways for these products are shown in **Scheme 4.1**. The primary amine of PEA is produced through the formation of an intermediate of phenylethylimine (PEI), which can further react with the product of PEA and be converted to the secondary amine of BPEA. The BC conversion and the product distribution were significantly changed depending on the reaction media and the catalysts used, as explained in the following.

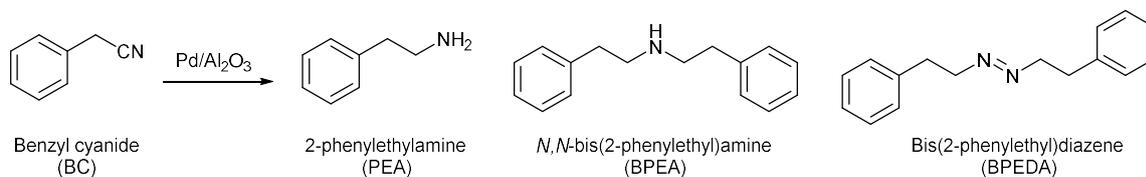
Table 4.1 Results of hydrogenation of benzyl cyanide with Pd/C catalyst in four different reaction media



Entry	Time (min)	Conversion (%)	Selectivity (%)		
			PEA	BPEA	BPEDA
Medium (a) including <i>n</i> -hexane					
1	10	60	0	22	78
2	30	85	0	4	96
3	60	98	0	3	97
Medium (b) including <i>n</i> -hexane, CO ₂					
4	10	63	0	6	94
5	30	73	0	10	90
6	60	80	0	10	89
7	90	80	0	10	90
Medium (c) including <i>n</i> -hexane, H ₂ O					
8	10	45	0	1	99
9	30	49	0	1	99
10	60	98	0	3	97
Medium (d) including <i>n</i> -hexane, H ₂ O, CO ₂					
11	30	53	0	4	96
12	60	97	0	1	99
13	180	> 99	0	< 0.5	> 99

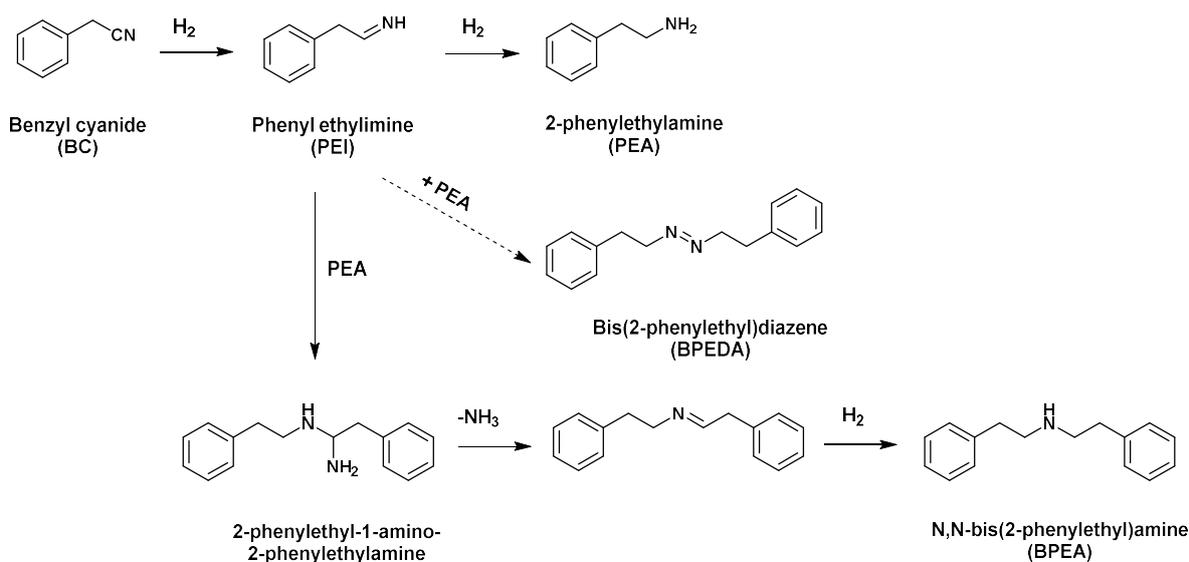
Reaction conditions: substrate 1 mmol; catalyst 58.5 mg, temperature 323 K, *n*-hexane 10 cm³ (for a, b) and 5 cm³ (for c, d), H₂O 5 cm³ (for c, d), H₂ 4 MPa, CO₂ 1 MPa

Table 4.2 Results of hydrogenation of benzyl cyanide with Pd/Al₂O₃ catalyst in four different reaction media



Entry	Time (min)	Conversion (%)	Selectivity (%)		
			PEA	BPEA	BPEDA
Medium (a) including <i>n</i> -hexane					
1	5	71	0	98	2
2	10	92	0	89	11
3	30	>99	0	73	27
Medium (b) including <i>n</i> -hexane, CO ₂					
4	10	63	0	34	66
5	30	65	0	91	9
6	60	66	0	69	31
Medium (c) including <i>n</i> -hexane, H ₂ O					
7	10	34	0	94	6
8	30	78	0	89	11
9	60	94	0	78	22
Medium (d) including <i>n</i> -hexane, H ₂ O, CO ₂					
10	10	24	>99	0	0
11	30	54	>99	0	0
12	60	67	93	7	0
13	120	86	87	12	1
14	180	95	85	14	1

Reaction conditions: substrate 1 mmol; catalyst 58.5 mg, temperature 323 K, *n*-hexane 10 cm³ (for a, b) and 5 cm³ (for c, d), H₂O 5 cm³ (for c, d), H₂ 4 MPa, CO₂ 1 MPa



Scheme 4.1 Possible reaction pathways in hydrogenation of benzyl cyanide. BC: benzyl cyanide, PEI: phenylethylimine, PEA: 2-phenylamine, BPEA: *N,N*-bis(2-phenylethyl)amine, BPEDA : bis(2-phenylethyl)diazene.

Table 4.1 and **Table 4.2** show that in reaction medium (a), the reaction took place very fast with both the catalysts and almost all BC was consumed in 60 min for Pd/C (**Table 4.1**, entry 3) and 30 min for Pd/Al₂O₃ (**Table 4.2**, entry 3). Undesired bis-(2-phenylethyl)diazene (BPEDA) was obtained as a main product with Pd/C catalyst while undesired bis-(2-phenylethyl) amine (BPEA) with Pd/Al₂O₃ catalyst. No formation of the objective product of 2-phenylethyl amine (PEA) was detected with the two catalysts in reaction medium (a). In the presence of CO₂ (medium b), the conversion in 1 h decreased to 80% for Pd/C (**Table 4.1**, entry 6) and 66% for Pd/Al₂O₃ (**Table 4.2**, entry 6) as compared to medium (a). The product distribution was not so different between the media (a) and (b) for either Pd/C or Pd/Al₂O₃. The objective product of the primary amine of PEA was not detected in these two media. In medium (b), the hydrogenation stopped for Pd/C (**Table 4.1**, entries 6-7) and for Pd/Al₂O₃ (**Table 4.2**, entries 5-6) after a certain period of reaction time; that is, catalyst deactivation occurred. In the medium (c) as well, no primary amine was formed with the two Pd catalysts and the product distribution patterns were similar to those obtained in the media (a) and (b). Namely, the presence of water alone had no impact on the product selectivity. However, the rates of BC consumption in medium (c) and medium (a) are almost similar and higher than that in medium (b) for either Pd catalyst. Also, the product distribution was not so different among the media (a), (b) and (c) for either Pd/C or Pd/Al₂O₃ catalyst. As already reported in **Chapter 2**, the medium (d) including both water and CO₂ is effective for the selective formation of primary amine, PEA, in the BC hydrogenation with Pd/Al₂O₃ (**Table 4.2**, entries 10-14). With the other catalyst, Pd/C, however, no primary

amine was detected to form, similar to the results in the other media (a), (b), and (c). A BC conversion of 97 % in 1 h with Pd/C catalyst (**Table 4.1**, entry 12) is larger than that of 67 % in 1 h with Pd/Al₂O₃ one (**Table 4.2**, entry 12). The reasons for the differences in conversion, selectivity, and catalyst deactivation in BC hydrogenation among the four media with the two Pd catalysts will be discussed later.

(b) Reaction rate

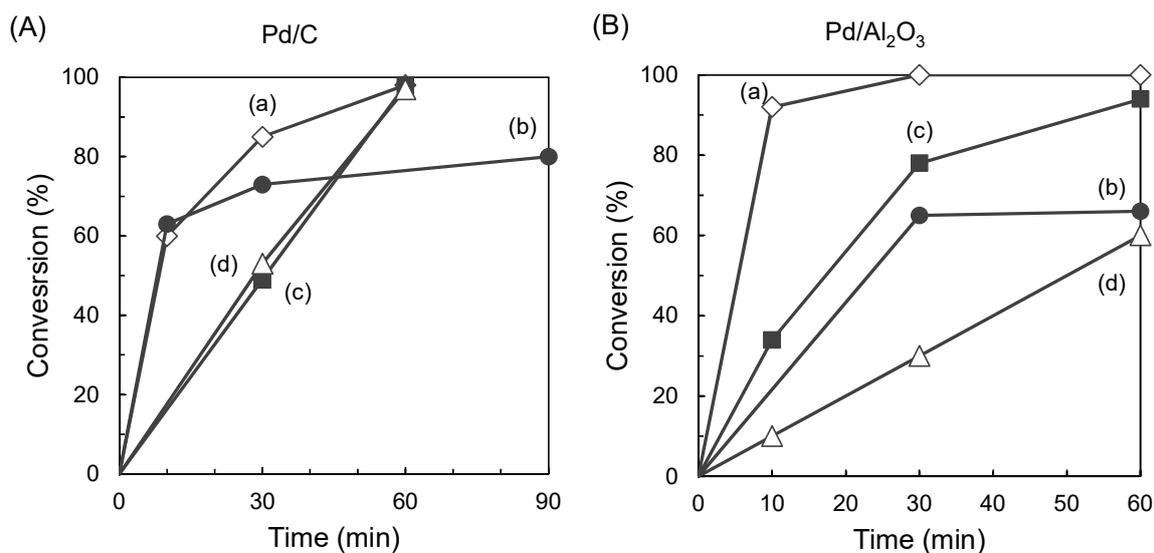


Figure 4.1 Time profiles of total conversion in hydrogenation of benzyl cyanide in the four different multiphase reaction media given in **Table 4.1** and **Table 4.2** such as (a) *n*-hexane, (b) *n*-hexane-CO₂, (c) *n*-hexane-H₂O and (d) *n*-hexane-CO₂-H₂O with (A) Pd/C catalyst and (B) Pd/Al₂O₃ catalyst at H₂ 4 MPa and CO₂ 1 MPa.

The rate of hydrogenation with the two catalysts in four reaction media will be discussed (**Figure 4.1**). In the presence of neat solvent *n*-hexane (medium (a)); the reaction proceeded smoothly and almost complete conversion of BC was obtained with the two catalysts. However, the reaction became stooped after a certain period of time, when 1 MPa CO₂ was added to medium (a). The reason for this catalyst deactivation may be ascribed to the formation of CO through a reverse water gas shift reaction ($\text{CO}_2 + \text{H}_2 \rightarrow \text{CO} + \text{H}_2\text{O}$) and its adsorption on the surface of supported metal particles with the Pd/Al₂O₃ catalyst.^{12, 14} When water was added in the same volume as that of *n*-hexane (medium (c)), the rate of BC hydrogenation is slightly smaller than as that in *n*-hexane alone with both the catalysts. The reaction occurs in organic phase in the absence of water but, when water is used, the main reaction locus changes from the organic phase to interfacial layer between the organic and aqueous phases because Pd/Al₂O₃ is dispersed in aqueous phase (as described later in **Figure 4.2**). This may have a negative impact on the rate of BC conversion with the two Pd catalysts. Though the catalyst Pd/C was dispersed in organic phase (**Figure 4.2**), the rate of BC

hydrogenation was influenced by the presence of water (**Table 4.1**). When medium (c) was pressurized by CO₂ (medium (d)), a larger decrease in the rate of BC conversion was observed as compared to medium (a) and almost complete conversion of BC was obtained within a longer reaction time of 3 h with the two catalysts.

(c) Product selectivity

As already reported in **Chapter 2**, medium (d) including both water and CO₂ is effective for the selective formation of primary amine, PEA, in the BC hydrogenation with Pd/Al₂O₃ (**Table 4.2**, entries 10-14). With the other catalyst, Pd/C, however, no primary amine was detected to form, similar to the results in the other media (a), (b), and (c). As mentioned above, the product selectivity pattern was not observed to depend on the reaction medium used for the BC hydrogenation over Pd/C catalyst (**Table 4.1**), in contrast to the results over Pd/Al₂O₃ catalyst (**Table 4.2**). The undesired product of BPEDA was selectively obtained with Pd/C catalyst in all reaction media. With Pd/Al₂O₃ the desired primary amine of PEA was formed in a high selectivity in medium (d) but not in the other three media.

The presence of both CO₂ and water is essential for the formation of PEA molecules in the reaction medium (as seen in Chapter 2) for Pd/Al₂O₃ catalyst. When water is pressurized by CO₂ at 1-8 MPa, the pH of water decreases to 3. The PEA is a strong base with pK_b = 4.17 (pK_a = 9.83) and it is more stabilized in an acidic environment. This may contribute to the high PEA selectivity in the presence of CO₂ and water. Such an effect for the formation of PEA was not expected in the medium (b) and (c) including CO₂ and water, respectively, but PEA does form means secondary or tertiary amine formed via the reaction of imine intermediate with the primary amine. **Scheme 4.1** represents the detail mechanism of formation of secondary and tertiary amine. The formation of BPEA and BPDEA was observed in the media (b) and (c), which are produced by the reaction between intermediate PEI and PEA molecules (**Scheme 4.1**). PEA is a water-soluble organic compound and so PEA formed probably near the organic – aqueous interface with Pd/Al₂O₃ catalyst; it is dissolved in the water phase and so it becomes unlikely to further react with an intermediate of 2-phenylethylimine (PEI) yielding the secondary amine in the organic phase (**Figure 2.9**). Such a further hydrogenation to the secondary amine BPEA cannot be avoided in the medium (b). In medium (d) PEA molecules produced are likely to react with CO₂ and move as carbamate salt from organic to aqueous phase (**Figure 2.9**). This may reduce the chance for PEA to react with PEI yielding the secondary amine. The carbamate salt is insoluble in BC organic phase, resulting in high selectivity to PEA. The Pd/C catalyst is dispersed mainly in organic phase and so the reaction should occur in the organic phase; therefore, the chance for the catalyst with organic substrate is easy. The primary amine, PEA, produced in the BC hydrogenation may readily interact with imine intermediate and the reaction may proceed further, giving secondary amine, BPEA, and bis(2-phenylethyl)diazine, BPDEA, in the presence and absence of CO₂ and/or water. Due to these differences in the surfaces of the two catalysts, the product selectivity is different between them.

The formation of PEA with the catalyst Pd/Al₂O₃ (medium d) in high selectivity may also be ascribed to possibility of adsorption of PEA molecules on the surface of Pd/Al₂O₃ catalyst. In the presence of CO₂ and water, PEA forms carbamate species (see **Figure 2.9**), which may be adsorbed on Al₂O₃ through interactions with the surface hydroxyl group of the support, suppressing its further hydrogenation to BPEA or byproduct BPEDA. In contrast, such significant adsorption of PEA does not occur on the surface of C and so it can be further hydrogenated to BPEDA. That is, the adsorption of PEA should be difficult on the surface of Pd/C catalyst and so the PEA molecules formed may easily desorb into the liquid phase. So, the synergistic effects of CO₂ and water in multiphase reaction medium were observed for BC hydrogenation with Pd/Al₂O₃ catalyst but not with Pd/C catalyst.

The present reaction system is multiphasic and it is important to see where (in which phase) the Pd/Al₂O₃ or Pd/C catalyst exists. It was difficult to examine the state of catalyst dispersion under reaction conditions and so it was examined in a simple way under ambient conditions. The state of catalyst dispersion in the biphasic medium (d) was examined in a simple way and shown in **Figure 4.2**. A two different glass tubes were added with 5 cm³ water and a magnetic stirrer and then with an organic solution of 5 cm³ solvent *n*-hexane and 1 mmol of nitrile substrate. It was further added with the same amount of Pd/C or Pd/Al₂O₃ catalyst as used in the reaction runs (see **Tables 4.1 – 4.2**). The reaction mixture was mixed for 2-3 min and allowed to stand for 1-2 min. Then, the photographs of reaction mixtures were taken. **Figure 4.2** gives pictures for the mixtures of organic solvent, water, and catalyst. For the two mixtures, Pd/C catalyst was observed to be dispersed in the organic phase while Pd/Al₂O₃ was dispersed in the aqueous phase and then Pd/Al₂O₃ completely settled down at the bottom of glass tube within 5 min probably due to hydrophilic nature of its support material and the density of the catalyst. The differences in the product selectivity between the two Pd catalysts will be explained in the following paragraph.

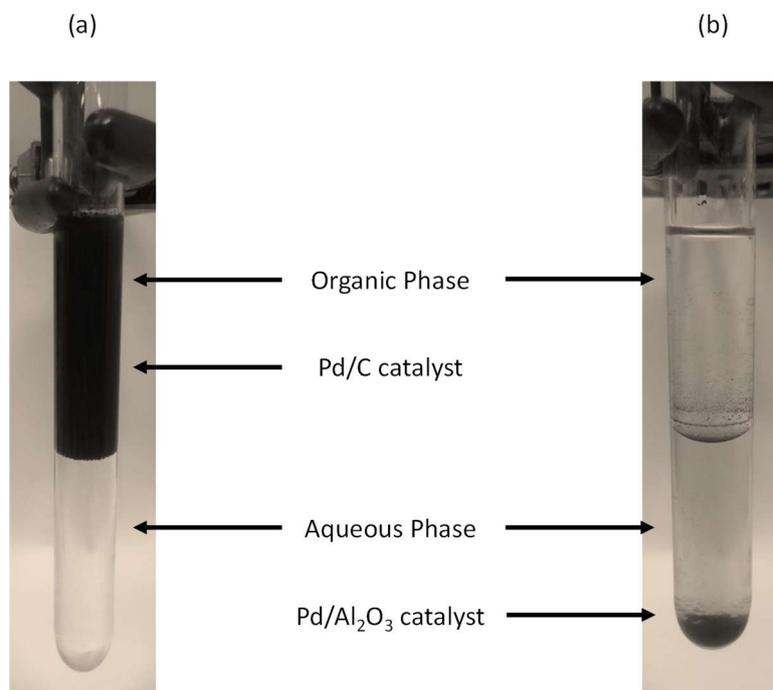


Figure 4.2 Photographs of the mixture of solvent *n*-hexane-water with catalyst (a) Pd/C and (b) Pd/Al₂O₃.

(d) Catalyst deactivation

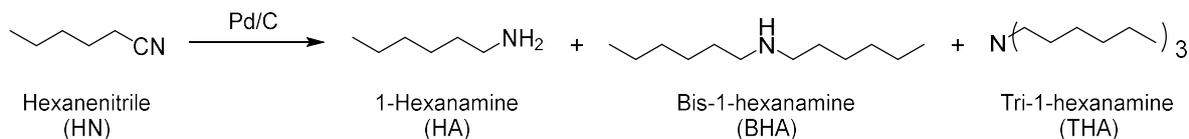
The catalyst deactivation was observed in medium (b) with the two Pd catalysts (**Figure 4.1**); the hydrogenation stopped after a certain period of time. Carbon dioxide interacts with the C-N group of the substrate in medium (b) and (d), may decreasing reactivity of BC (**Figure 2.6**). **Figure 4.1** indicates that the Pd/C and Pd/Al₂O₃ catalysts became deactivated for medium (b) but not for others. The possibility for the deactivation of Pd/Al₂O₃ catalyst may be ascribed to the formation of CO through a reverse water gas shift reaction ($\text{CO}_2 + \text{H}_2 \rightarrow \text{CO} + \text{H}_2\text{O}$) and its adsorption on the surface of supported metal particles with the Pd/Al₂O₃ catalyst. This deactivation of catalyst can be hindered by the addition of water even in the presence of CO₂.¹¹⁻¹⁵

4.3.2 Hydrogenation of *n*-hexanenitrile in four different types of reaction media

(a) Reaction results

As mentioned above (see section 4.2.1), similar to benzyl cyanide hydrogenation, the selective hydrogenation of *n*-hexanenitrile has been carried out over Pd/Al₂O₃ (**Chapter 3, Table 3.3**) and compared with hydrogenation results obtained over Pd/C (**Table 4.3**). Under the reaction conditions employed, 1-hexanamine (HA), bis-1-hexanamine (BHA), and tri-1-hexanamine (THA) were observed to form (**Scheme 4.2**). The HN conversion and the product distribution were significantly changed depending on the reaction media used, as explained in the following.

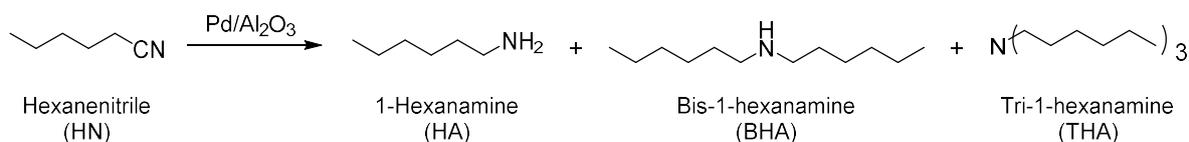
Table 4.3 Results of hydrogenation of *n*-hexanenitrile with Pd/C catalyst in four different reaction media



Entry	Time (min)	Conversion (%)	Selectivity (%)		
			HA	BHA	THA
Medium (a) including <i>n</i> -hexane					
1	10	64	0	20	80
2	30	73	0	15	85
3	60	87	0	12	88
4	120	95	0	07	93
Medium (b) including <i>n</i> -hexane, CO ₂					
5	30	56	0	0	>99
6	60	64	0	0	>99
7	120	65	0	0	>99
Medium (c) including <i>n</i> -hexane, H ₂ O					
8	30	64	0	16	84
9	60	87	0	12	88
10	120	99	0	11	89
Medium (d) including <i>n</i> -hexane, H ₂ O, CO ₂					
11	10	30	0	29	71
12	30	33	0	20	80
13	60	36	0	25	75
14	120	55	0	15	85
15	180	55	0	15	85
16	360	55	0	16	84

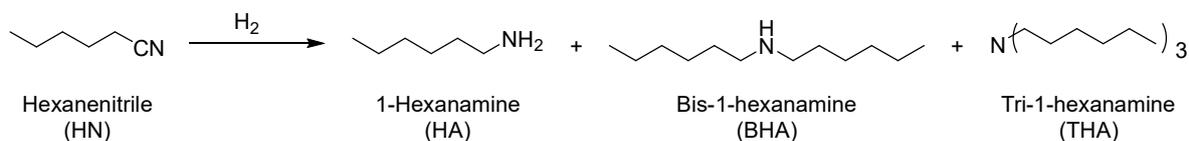
Reaction conditions: substrate 1 mmol; catalyst 58.5 mg, temperature 323 K, *n*-hexane 10 cm³ (for a, b) and 5 cm³ (for c, d), H₂O 5 cm³ (for c, d), H₂ 4 MPa, CO₂ 1 MPa

Table 4.4 Results of hydrogenation of *n*-hexanenitrile with Pd/Al₂O₃ catalyst in four different reaction media



Entry	Time (min)	Conversion (%)	Selectivity (%)		
			HA	BHA	THA
Medium (a) including <i>n</i> -hexane					
1	30	72	0	34	66
2	60	87	0	18	82
3	90	92	0	15	85
Medium (b) including <i>n</i> -hexane, CO ₂					
4	30	43	0	42	58
5	60	52	0	38	62
6	90	53	0	37	63
7	120	54	0	38	62
Medium (c) including <i>n</i> -hexane, H ₂ O					
8	30	<0.1	0	0	0
9	60	<0.1	0	0	0
10	300	<0.1	0	0	0
Medium (d) including <i>n</i> -hexane, H ₂ O, CO ₂					
11	300	32	>99	0	0
12	24h	34	62	29	9

Reaction conditions: substrate 1 mmol; catalyst 58.5 mg, temperature 323 K, *n*-hexane 10 cm³ (for a, b) and 5 cm³ (for c, d), H₂O 5 cm³ (for c, d), H₂ 4 MPa, CO₂ 1 MPa



Scheme 4.2 The products observed in hydrogenation of *n*-hexanenitrile. HN: *n*-hexanenitrile, HA: 1-Hexanamine, BHA: Bis-1-Hexanamine, THA: Tri-1-Hexanamine.

In neat solvent, 95% (**Table 4.3**, entry 4) and 92% (**Table 4.4**, entry 3) conversion values were obtained in 120 min and 90 min respectively. THA was obtained as a main product with the two Pd catalysts. The addition of CO₂ decreased the total conversion and catalyst deactivation will be discussed later. THA was obtained in a high selectivity of >99% with the Pd/C catalyst (**Table 4.3**, entries 6-7) and of nearly 60% with the Pd/Al₂O₃ catalyst (**Table 4.4**, entries 5-7). The addition of water shows >99% conversion of HN with Pd/C in 120 min (**Table 4.3**, entries 8-10) and a very small of HN conversion (<0.1%) with Pd/Al₂O₃ 300 min (**Table 4.4**, entries 8-10). The primary amine, HA, was not detected to form with the two Pd catalyst in the above multiphase reaction media (a), (b), and (c). When both CO₂ and water were added, the conversion was also lowered to 55% in 120-360 min, the reaction stopped after a certain period of time, THA was obtained as a main product, and HA was not detected to form with the Pd/C catalyst (**Table 4.3**, entry 14). The co-existence of both CO₂ and water also lowered HN conversion to 32% in 300 min but, interestingly, the HA was produced in a high selectivity of >99% in a reaction time of 5 h (**Table 4.4**, entry 11) with Pd/Al₂O₃ catalyst. However, the reaction hardly proceeded during the next 19 h and HA selectivity decreased to nearly 60%; BHA and THA were obtained as undesired side products. These results show that the catalyst deactivation also occurred in the presence of CO₂ and water with the two Pd catalysts. From those results obtained, possible roles of CO₂ and H₂O in hydrogenation of HN with respect to the total conversion, the product selectivity, and the catalyst deactivation will be discussed in detail in the following.

(b) Reaction rate

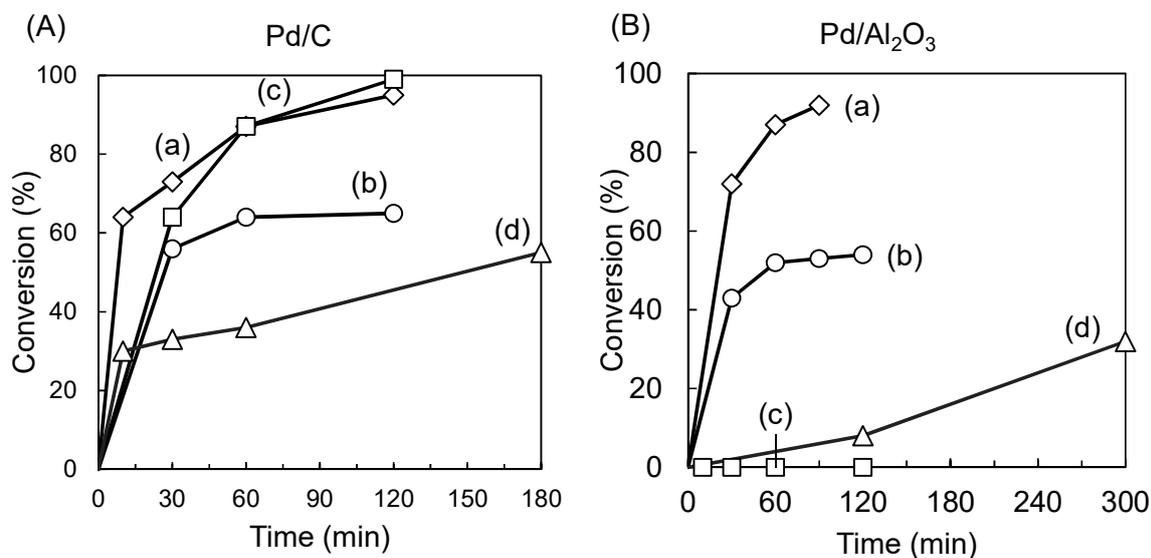


Figure 4.3 Time Profiles of total conversion in hydrogenation of *n*-hexanenitrile in the four different multiphase reaction media given in **Table 4.3** and **Table 4.4** such as (a) *n*-hexane, (b) *n*-hexane-CO₂, (c) *n*-hexane-H₂O and (d) *n*-hexane-CO₂-H₂O with (A) Pd/C catalyst and (B) Pd/Al₂O₃ catalyst at H₂ 4 MPa and CO₂ 1 MPa.

An aliphatic nitrile, HN was hydrogenated in four different reaction media with the two Pd catalysts. **Figure 4.3** shows that the reaction goes smoothly in the presence of neat solvent (medium (a)) and almost complete conversion of HN was obtained with the two Pd catalysts. When medium (a) was pressurized by 1 MPa CO₂ (medium (b)), the rate of HN conversion decreased and the reaction stopped after a certain period of time with the two Pd catalysts. The dissolution CO₂ may cause the decrease in HN conversion, the dissolved CO₂ molecules may interact with CN group of HN (**Figure 3.2**), and this may responsible for the smaller rate in medium (b) than medium (a). In medium (c), the reaction conversion was so small with Pd/Al₂O₃ catalyst, whereas, complete conversion of HN was obtained with Pd/C catalyst. Unfortunately, reason for the small rate of HN conversion with Pd/Al₂O₃ is unknown. In the presence of both CO₂-water system (medium (d)), the reaction took place very slowly and stopped after a certain period of time; namely catalyst deactivation occurs with the two Pd catalysts. As mentioned above, the simple dilution effect of CO₂ into the liquid substrate phase under pressurized conditions would promote the dissolution of H₂ but, at the same time, decrease the concentration of the substrate in the reaction medium. This negative, dilution effect should be responsible for decrease in conversion of reaction in medium (d) with the two Pd catalysts.

(c) Product selectivity

Table 4.3 and **4.4** show that the tertiary amine, THA, forms selectively with Pd/C catalyst in all reaction media while HA forms with Pd/Al₂O₃ catalyst medium (d). The difference in the surface properties between the catalyst supports may be responsible for the differences in the selectivity of products in medium (d). The HA formation with the Pd/Al₂O₃ catalyst with a high selectivity may be ascribed to possibility of adsorption of HA molecules on the surface of Pd/Al₂O₃ catalyst.¹⁶ In the presence of CO₂ and water, HA forms carbamate species, which may be adsorbed on Al₂O₃ through interactions with the surface hydroxyl group of the support and suppress its further hydrogenation to bis-1-hexanamine or tri-1-hexanamine. In contrast, such significant adsorption of HA does not occur on the surface of C and so it can be further hydrogenated to tri-1-hexanamine. The adsorption of HA should be difficult on surface of Pd/C catalyst and the HA molecules formed may desorb into the liquid phase. So the synergistic effects of CO₂ and water in multiphase reaction medium were observed for HN hydrogenation with Pd/Al₂O₃ catalyst but not with Pd/C catalyst. As mentioned previously, the highly selective PEA (primary amine) formation was obtained in medium (d) with Pd/Al₂O₃ catalyst, due to synergistic effects of CO₂ and water. That is, the same effects may also appear in the selective hydrogenation of HN to HA with the Pd/Al₂O₃ catalyst. The selective hydrogenation of *n*-hexanenitrile under scCO₂ has been reported previously with Pd/MCM-41 catalyst.¹⁶ Authors proposed a plausible mechanism of formation of carbamate species.

(d) Catalyst deactivation

Figure 4.3 represents that catalyst is deactivated in the presence of CO₂ (medium (b) and (d)) with the two Pd catalysts. As mentioned previously, the reasons for the catalyst deactivation are same as for BC hydrogenation, the catalyst deactivation with the Pd/Al₂O₃ catalyst may be ascribable to formation of CO through a reverse water gas shift reaction ($\text{CO}_2 + \text{H}_2 \rightarrow \text{CO} + \text{H}_2\text{O}$) and its adsorption on the surface of supported metal particles.¹³⁻¹⁷ On the Pd catalyst, bridged type CO is adsorbed and should cause its deactivation. The presence of water influences the adsorption of CO as evidenced by *in situ* high pressure FTIR measurements with Al₂O₃-supported Pd and other noble metal catalysts. The CO molecules adsorbed on the rough surface (high Miller index planes) of supported Pd particles are removed by water molecules. These water molecules would be replaced by the substrate molecules or assist the contacting of the substrate molecules to the Pd surface, and so the rough Pd surface should serve as active sites for the nitrile hydrogenation. Hence, the catalyst deactivation can be avoided but some CO molecules exist on and cover a certain partial area of Pd particles, resulting in the reduction of the overall rate of nitrile hydrogenation as compared to the reactions in the absence of CO₂. **Figure 4.3** (B) shows that conversion of

HN was very small in medium (c), so the formation of products was not detected. Unfortunately, the reason for small conversion rate of HN with Pd/Al₂O₃ is unknown.

4.4 Conclusions

The effectiveness of the CO₂ and water medium was examined for selective hydrogenation of benzyl cyanide (BC) and n-hexanenitrile (HN) using a commercial Pd/C which was different in the surface properties from the Pd/Al₂O₃ catalyst. The synergetic effects of CO₂-water system were not observed in hydrogenation of benzyl cyanide and n-hexanenitrile over the Pd/C catalyst, in contrast to Pd/Al₂O₃. The product selectivity obtained was different between the two catalysts even in the same CO₂ and water medium. The possible reasons will be the difference in the hydrophilicity/ hydrophobicity of their surfaces. The catalyst Pd/C is mainly present in the organic phase, so the primary amine, such as PEA and HA may form and further hydrogenated to form secondary or tertiary amine.

4.5 References

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Chapter 5

Direct Synthesis of *N*-Substituted-5-Methyl-2-Pyrrolidones from Levulinic Acid, Nitriles and H₂ by Heterogeneous Pt Catalysts

We report herein the first general and reusable catalytic system for direct synthesis of *N*-substituted lactams (including *N*-alkyl-5-methyl-2-pyrrolidones) by reductive conversion of keto acids (including levulinic acid) with nitriles and H₂ under mild conditions (0.7 MPa H₂, 110 °C, solvent-free). The most effective catalyst, Pt and MoO_x co-loaded TiO₂ (Pt-MoO_x/TiO₂), shows a wide scope for nitriles, high turnover number (TON), and good reusability.

5.1 Introduction

Sustainable use of biomass is a major challenge in chemistry. Selective catalytic transformation of lignocellulose to chemicals via platform compounds plays a key role in this research area.¹ Levulinic acid (LA) is a key platform compound, because it can be easily and economically obtained by acid-catalyzed dehydration of lignocellulosic biomass and can be converted to various chemicals.¹ Among the chemicals, *N*-alkyl-5-methyl-2-pyrrolidones, which can be produced by reductive amination of LA, are industrially used as solvents, surfactants, complexing agents, and intermediates for fine chemicals.^{2,3} Previous non-catalytic⁴ and catalytic⁵⁻¹⁰ methods for this reaction used formic acid⁴⁻¹¹ or a hydrosilane⁹ as a reductant. Most of the methods used homogeneous systems which suffer from difficulties in catalyst/product separation and catalyst reuse and needs of additives, expensive reductants, or a toxic solvent (dichloromethane)⁴ for separation of the products from DMSO. The method can be more economical, if one uses a reusable heterogeneous catalyst and molecular H₂ as a reductant.¹¹ Recently, we have reported a new heterogeneous catalyst, Pt and MoO_x co-loaded TiO₂ (Pt-MoO_x/TiO₂), for the direct synthesis of *N*-alkyl-5-methyl-2-pyrrolidones from LA, primary amines and H₂,¹² which is more efficient than the pioneering method in the patent by Manzer¹¹ in terms of yields, substrate scope, catalyst reusability and mild conditions. Later, several heterogeneous catalytic systems (Pt/TiO₂,¹³ FeNi nanoparticles¹⁴) were reported to be effective for this type of transformation.

Considering that some of the nitriles¹⁵⁻¹⁷ and nitro compounds are the intermediates of primary amines, one-pot reactions of them with LA and H₂ can provide a sustainable and practical route to the pyrrolidones. Very recently, Corma, Iborra and co-workers¹⁸ have reported the first general method for one-pot synthesis of the pyrrolidones via reductive amination of ethyl levulinate with nitro compounds under 0.1 MPa H₂ using Pt-loaded TiO₂ nanotube catalyst, though the method requires large amount of ethyl levulinate (3 equiv. with respect to the nitro compounds).¹⁸ As for the use of nitriles alternative to primary amines, to our knowledge, only one patent by Manzer¹⁹ reported the synthesis of the pyrrolidones from LA and nitriles (3-penteneitrile and benzonitrile) under H₂ using Pd, Rh, Ru, or Pt loaded on carbon or Al₂O₃ catalysts. However, the method has several disadvantages such as low yields (< 43.4%), limited scope, no example of catalyst reuse, low turnover number (TON), and necessities of high H₂ pressure (5.5-6.9 MPa), high temperature (150 °C), and dioxane

as solvent. During our efforts on the hydrogenation reactions by Pt-MoO_x/TiO₂,^{12,20,21} inspired by previous efforts on the utilization of nitriles as primary amine surrogate,^{19,22} we have found that Pt-MoO_x/TiO₂ selectively catalyzes the direct synthesis of *N*-substituted lactams (including *N*-alkyl-5-methyl-2-pyrrolidones) from 1:1 mixture of keto acids (including LA) and nitriles under 0.7 MPa H₂ at 110 °C in the absence of solvent. To our knowledge, this is the first example of reusable and general catalytic system for direct synthesis of *N*-substituted lactams from keto acids, nitriles, and H₂. Note that the selective reaction of nitriles with equimolar amount of LA under H₂ is a challenging reaction, because hydrogenation of nitriles to primary amines is accompanied by the formation of secondary and tertiary amines.¹⁵⁻¹⁷

5.2 Experimental

5.2.1 General

Commercially available organic compounds (from Tokyo Chemical Industry or Kanto Chemical Co. Ltd.) were used without further purification. The GC (Shimadzu GC-2014) and GCMS (Shimadzu GCMS-QP2010) analyses were carried out with Ultra ALLOY capillary column UA⁺-1 (Frontier Laboratories Ltd.) using nitrogen and He as the carrier gas.

5.2.2 Catalyst preparation

TiO₂ (JRC-TIO-4, 50 m² g⁻¹) and CeO₂ (JRC-CEO-3) were supplied from Catalysis Society of Japan. SiO₂ (Q-10, 300 m² g⁻¹) was supplied by Fuji Silysia Chemical Ltd. γ -Al₂O₃ was prepared by calcination (900 °C, 3 h) of boehmite (Catapal B Alumina, Sasol). Nb₂O₅ was prepared by calcination (500 °C, 3 h) of Nb₂O₅·*n*H₂O supplied by CBMM.

The M-MoO_x/TiO₂ catalysts (M = 5 wt% Pt, Ir, Ru, Rh, Pd, Re, Ni, Co, Cu; 7 or 15 wt% Mo) were prepared by a sequential impregnation method as follows. Metal sources were aqueous HNO₃ solutions of Pt(NH₃)₂(NO₃)₂, Rh(NO₃)₃, and Pd(NH₃)₂(NO₃)₂ and aqueous solution of RuCl₃, NH₄ReO₄, nitrates (Ni, Co, Cu), and (NH₄)₆Mo₇O₂₄·4H₂O. MoO₃-loaded TiO₂ (MoO₃/TiO₂) was prepared by mixing TiO₂ powder with aqueous solution of (NH₄)₆Mo₇O₂₄·4H₂O (50 mL), followed by evaporation of the mixture at 50 °C, drying the solid at 90 °C (12 h), and by its calcination in air at 500 °C (3 h). Then, MoO₃/TiO₂ (or other supports) and aqueous HNO₃ solution of Pt(NH₃)₂(NO₃)₂ were mixed, evaporated, dried at 90 °C to yield a Pt(II)-loaded precursor. Before the catalytic experiment, the catalysts were prepared by reduction of the precursor in a Pyrex tube under flowing H₂ (20 cm³ min⁻¹) at 300 °C for 0.5 h.

5.2.3 Catalyst characterization

Transmission electron microscopy (TEM) and high-angle annular dark-field scanning transmission electron microscopy (HAADF-STEM), in conjunction with energy dispersive X-ray spectroscopy (EDS) mapping images were taken on a JEM-2100F (JEOL)

operated at 200 kV accelerating voltage. The samples for TEM, STEM and EDS analyses were prepared by putting drops of a methanol solution onto a carbon-coated copper grid.

5.2.4 Typical procedures of catalytic reactions

The catalytic reactions were carried out as follows. After the reduction, the as-prepared catalyst in the closed Pyrex tube sealed with a septum inlet was cooled to room temperature under H₂, followed injection of mixture of 1 mmol levulinic acid (LA), 1 mmol nitriles, and 0.2 mmol *n*-dodecane. Then, the septum was removed under air, a magnetic stirrer bar was put in the tube, followed by inserting the tube inside stainless autoclave (28 cm³). After being sealed, the reactor was charged with 0.8 MPa H₂ and heated at 110 °C under stirring (500 rpm). After a certain period of time, the reactor was cooled followed by adding 2-propanol (6 cm³) to the mixture, followed by removal of the catalyst by filtration, conversions and yields of products were determined by GC using *n*-dodecane as an internal standard using the GC-sensitivity estimated by the commercial compounds (nitriles) or isolated products. The mixture after the reaction was concentrated under vacuum evaporator to remove the volatile compounds, and then *N*-alkyl-5-methyl-2-pyrrolidones were isolated by column chromatography using silica gel 60 (spherical, 63-210 μm, Kanto Chemical Co. Ltd.) with hexane/ethylacetate (7/3) as the eluting solvent, followed by analyses by ¹H NMR, ¹³C NMR and GCMS.

5.2.5 NMR and GC/MS analysis

¹H and ¹³C NMR spectra for *N*-substituted-5-methyl-2-pyrrolidones of **Table 5.3** were assigned and reproduced to the corresponding literature. ¹H and ¹³C NMR spectra were recorded using at ambient temperature on JEOL-ECX 600 operating at 600.17 and 150.92 MHz, respectively with tetramethylsilane as an internal standard. All chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. All chemical shifts are reported relative to tetramethylsilane and *d*-solvent peaks 77.00 ppm chloroform. Abbreviations used in the NMR experiments: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. GC-MS spectra was taken by SHIMADZU QP2010.

Previously,²⁰ we reported detailed characterization of Pt-MoO_x/TiO₂ (with Mo loading of 7 wt%) by temperature programmed reduction in H₂, X-ray absorption spectroscopy, CO adsorption, and TEM and the structural model was proposed as follows. Thin layer (or small clusters) of MoO_x species covers the surface of TiO₂, and Pt metal nanoparticles with mean diameter of 4.7 nm are supported on the Mo oxides-covered TiO₂. Exposed Mo cations on the surface MoO_x species act as Lewis acid sites, while Pt sites act as H₂ dissociation sites. The MoO_x-covering model was based on the indirect evidences. Hence, we carried out the microscope studies to obtain the direct evidence on the model. **Figure 5.1** shows TEM images of Pt-MoO_x/TiO₂ (Pt = 5 wt%, Mo = 15 wt%). Pt metal particles with size in a range of 3-5 nm are observed on the support surface, while MoO_x

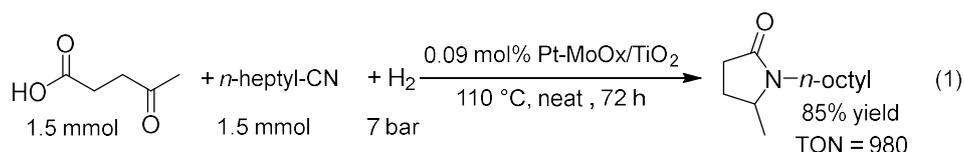
particles are not observed. To achieve elemental mapping over a catalyst particle, we carried out high-angle annular dark-field scanning transmission electron microscopy (HAADF-STEM),²³ in conjunction with EDX analysis in **Figure 5.2**. Yellow pixels (Pt) are observed on the 2-5 nm sized white particles. Red pixels (Mo) are not aggregated but highly dispersed over the TiO₂ particle (cyan pixels). These results give direct evidence on the structural model of Pt-MoO_x/TiO₂ proposed in our previous study;²⁰ thin layer (or small clusters) of MoO_x species covers the surface of TiO₂, and Pt metal nanoparticles are supported on the MoO_x-covered TiO₂.

5.3 Results and Discussion

Table 5.1 summarizes the results for catalyst screening using 5 wt% metal-loaded metal oxides containing 0.01 mmol (1 mol%) of the active metals with respect to LA. Reaction of neat LA (**1a**, 1 mmol) with *n*-octanenitrile (**2a**, 1 mmol) under 0.7 MPa H₂ at 110 °C for 24 h was used as a model reaction. No reaction occurred in the catalyst-free conditions (entry 1). The metal-free MoO_x/TiO₂ support showed only 2% yield of the desired product, 5-methyl-1-octyl-pyrrolidin-2-one (**3a**). Among the MoO_x/TiO₂-supported metal catalysts (entries 3-10), Pt-MoO_x/TiO₂ (entry 3) showed the highest yield (85%) of **3a**. For Pt-MoO_x/TiO₂, increasing the Mo content from 7 wt% (entry 3) to 15 wt% (entry 11) resulted in higher yield (92%) of **3a**. The other Pt catalysts (entries 12-16) such as Pt/TiO₂ and Pt/Al₂O₃ showed lower yields than Pt-MoO_x/TiO₂. The most effective catalyst, Pt-MoO_x/TiO₂ with 15 wt% loading of Mo (entry 11), is hereafter used as the standard catalyst. Noted that the yields of byproducts, di-*n*-octylamine (**4a**) and tri-*n*-octylamine (**5a**), for this catalyst are relatively low compared to the other catalysts.

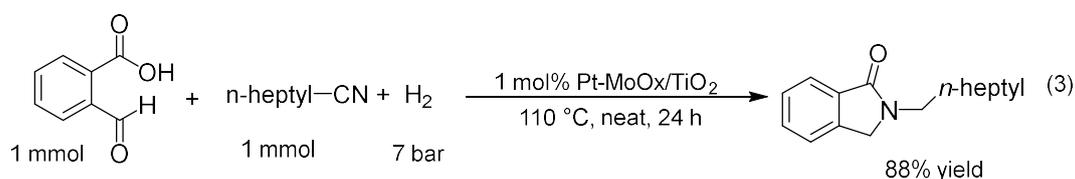
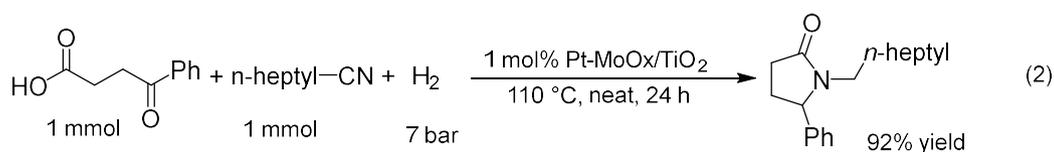
Next, we studied the effect of various reaction conditions on the catalytic properties of Pt-MoO_x/TiO₂ for the reaction of LA (**1a**) with *n*-octanenitrile (**2a**) for 24 h. The results are listed in **Table 5.2**. The reactions of 1 mmol **2a** with various amount of **1a** at 100 °C under the solvent-free conditions (entries 1-3) showed that the **2a** conversion and the **3a** yield (based on **2a**) did not increase with increase in the amount of **1a**. The reactions of 1 mmol **1a** with various amount (1-1.5 mmol) of **2a** (results not shown) showed that the excess amount of **2a** gave lower amount of **3a** and higher amount of byproducts (**4a**, **5a**) than the stoichiometric condition. Thus, we adopted the reaction of 1 mmol **1a** with 1 mmol **2a** as the standard conditions. With increase in the H₂ pressure from 0.3 MPa (entry 1) to 5 and 0.7 MPa (entries 4,5), the conversion of **2a** and the yield of **3a** increased. Under 0.7 MPa H₂, the yield of **3a** increased with the temperature upto 110 °C (entry 6), but further increase in the temperature (entries 7,8) resulted in decrease in the yield of **3a** and increase in the yields of byproducts (**4a**, **5a**). At the optimal temperature (110 °C) and H₂ pressure (0.7 MPa), the reaction in various solvent showed that the solvent-free conditions (entry 6) gave higher yield of **3a** than the reactions in the solvent, such as toluene, *o*-xylene, *n*-decane, and dioxane (entries 9-12). Summarizing these results, we determined the standard conditions: **1a** / **2a** = 1/1, 110 °C, 0.7 MPa H₂, without solvent.

ICP-AES analysis of the filtrate showed that the Pt content in the solution was below the detection limit. These results confirm that the reaction is attributed to the heterogeneous catalysis of Pt-MoO_x/TiO₂. **Figure 5.1** shows the result of catalyst recycle test. After the standard reaction, followed by adding 3 mL 2-propanol to the mixture, the catalyst separation from the mixture by filtration, washing the catalyst with 6 mL acetone, drying the catalyst at 90 °C (12 h), and by reduction of it at 300 °C (0.5 h), the recovered catalyst showed high yields of **3a** (90-84%) during the following 4 cycles. As shown eqn. (1), the standard reaction with 0.09 mol% of Pt-MoO_x/TiO₂ (5.3 mg) gave 85% yield of **3a**. This value corresponds to TON of 980.

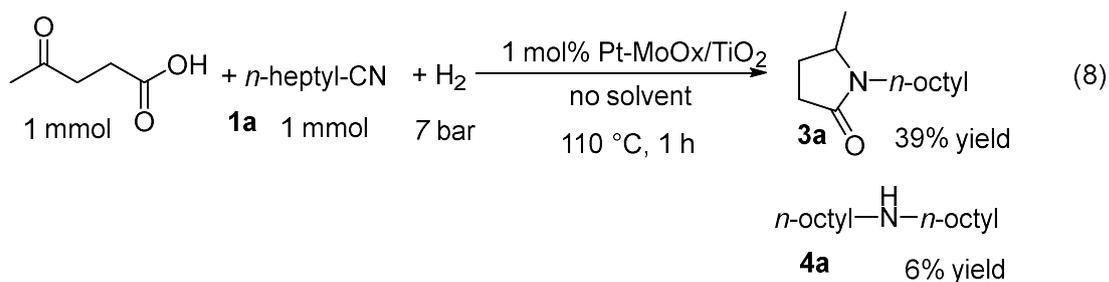
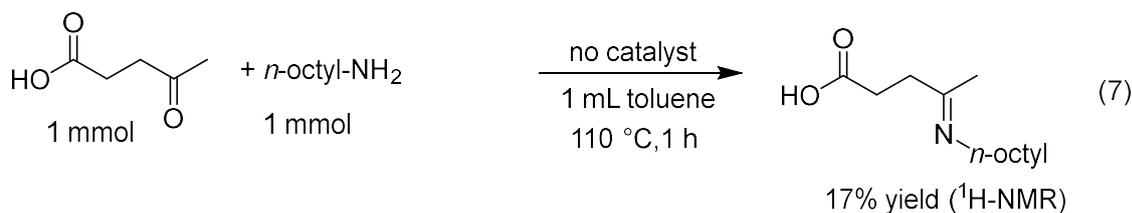
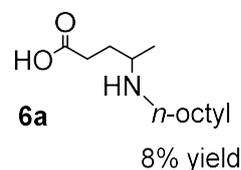
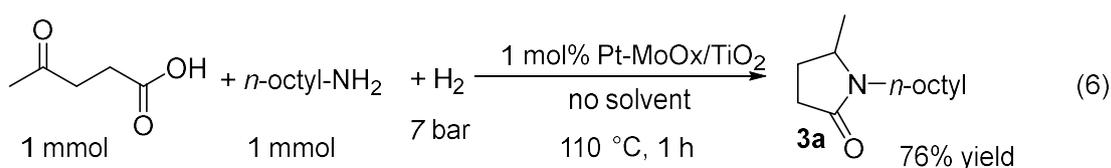
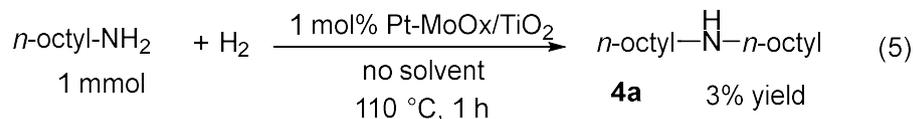
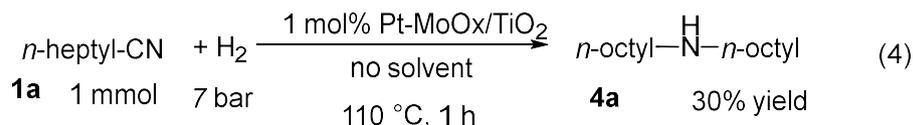


Then, we studied the scope of nitriles for the catalytic reaction. **Table 5.3** shows the yields of N-substituted-5-methyl-2-pyrrolidones from LA and various nitriles under 0.7MPa H₂ by 1 mol% Pt-MoO_x/TiO₂. Aliphatic nitriles (entries 1,2), dimethylaminopropionitrile (entry 3), ethyl cyanoacetate (entry 4), benzonitrile (entry 5), its derivatives with electron-donating (entries 6,7) and electron-withdrawing substituents (entry 8), 2-naphthonitrile (entry 9), phenylacetone nitrile (entry 10), its derivatives with electron-donating (entries 11,12) and electron-withdrawing substituents (entries 13), and 2-naphthylacetone nitrile were selectively converted to the corresponding pyrrolidones in good to high yields (72-92%). The preceding patent by Manzer¹¹ reported the same catalytic reaction. However, the method showed low yields (<43.4%) only for limited substrates under high H₂ pressure (5.5-6.9 MPa) at high temperature (150 °C) and catalyst reusability was not tested. Considering the superior catalytic performance of our method in terms of yields, substrate scope, and catalyst reusability under mild conditions, this is the first general catalytic method for direct synthesis of pyrrolidinones from LA and various nitriles.

As shown in equations (2) and (3), the method is applicable to direct synthesis of γ -lactams from keto acid or 2-carboxybenzaldehyde.



Scheme 5.1 shows a reaction pathway which is supported by the results of the control reactions in equations (4) - (8) at 110 °C for 1 h. First, we studied the side reaction pathways from nitrile (**2**) to secondary amine (**4**). Under 0.7 MPa H₂, *n*-octanenitrile **1a** was hydrogenated to give di-*n*-octylamine **4a** in 30% yield. Self-coupling of *n*-octylamine (under the same conditions) resulted in lower yield (3%) of **4a**. The most probable route from nitriles to secondary amines¹⁷ is shown in Scheme 5.1. The nitrile **2** is hydrogenated to give imine **2'** and primary amine **2''**. The imine **2'** reacts with the primary amine **2''** to give the secondary imine **3** which is hydrogenated to secondary amine **4**.¹⁷ Our results, the equations (4) and (5), are consistent with this scheme; the secondary amine (**4a**) is not produced by self-coupling of the primary amine but by the hydrogenation of the nitrile possibly via the imine intermediate **2'**. If the reaction of the primary amine **2''** with LA under H₂ (target reaction) is faster than the reaction of the primary amine with the imine intermediate **2'** (side reaction), the pyrrolidone **8** could be selectively obtained. This assumption is verified by the higher yield of the pyrrolidone **3a** (76%) by the reaction of LA and *n*-octylamine under H₂ in the equation (6) than that of secondary amine **4a** (30%) in the equation (4). Thermal condensation of the primary amine with LA, equation (7), was also fast; it gave the imine intermediate **6** in 17% yield even under the catalyst-free conditions. The C=N bond in the intermediate **6** can be hydrogenated to give the final intermediate **7**, which undergoes intramolecular amidation to give the pyrrolidone **8** and H₂O. We observed the intermediate **7** as a byproduct of the reaction of LA, *n*-octylamine and H₂ in the equation (4). The yield of the pyrrolidone **3a** from *n*-octanenitrile (39%) in the equation (8) is lower than that from *n*-octylamine (76%) in the equation (6), which indicates that hydrogenation of the nitrile is a relatively slow step in the present one-pot reaction.



5.4 Conclusions

We have found the first general and reusable catalytic system for one-pot synthesis of N-substituted lactams (including N-alkyl-5-methyl-2-pyrrolidones) by reductive conversion of keto acids (including levulinic acid) with nitriles and H₂ under mild conditions (0.7 MPa H₂, 110 °C, solvent-free) using the Pt-MoOx/TiO₂ catalyst. This method can be a sustainable route to N-alkyl-5-methyl-2-pyrrolidones from biomass-derived LA.

5.5 References

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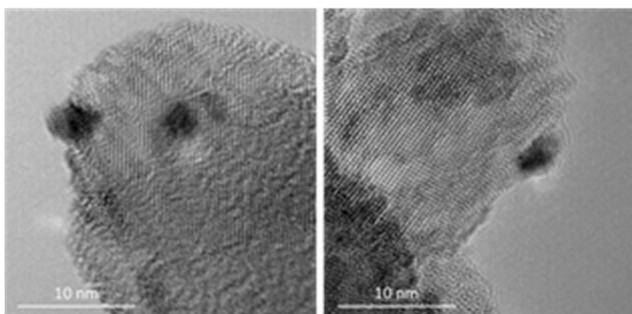


Figure 5.1 Representative TEM images of Pt-MoOx/TiO₂.

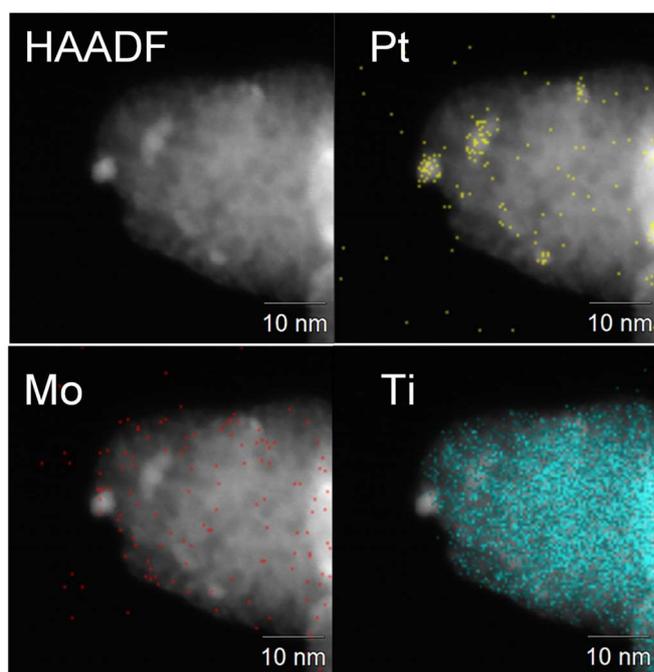
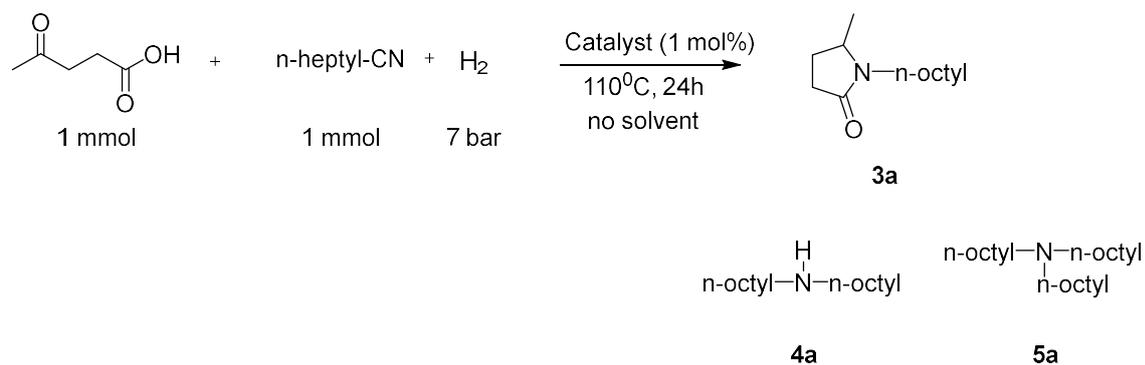


Figure 5.2 HAADF-STEM images superimposed with EDX elements mapping of Pt-MoOx/TiO₂. The yellow, red, and cyan pixels in the mapping correspond to Pt, Mo, and Ti, respectively.

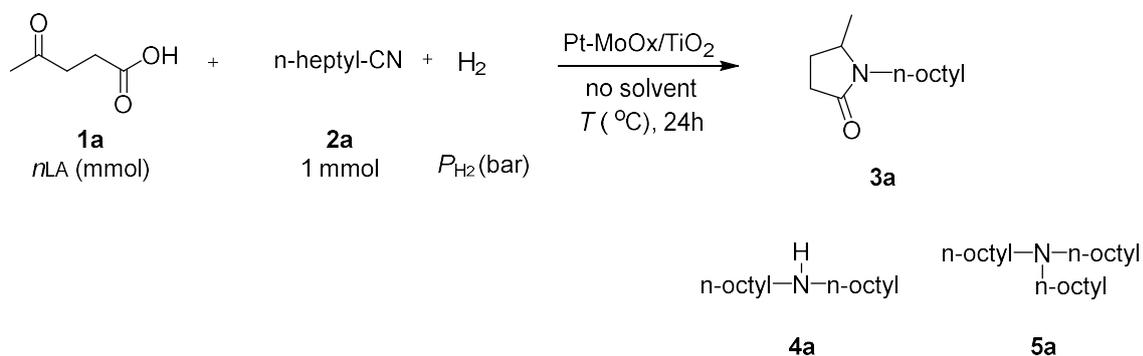
Table 5.1 Reaction of **1a** with **2a** under H₂ by various catalysts. ^a

Entry	Catalyst	Conversion, %	Yield, %		
			3a	4a	5a
1	blank	0	0	0	0
2	MoO _x /TiO ₂	4	2	0	0
3	Pt- MoO _x /TiO ₂	100	85	6	9
4	Ir- MoO _x /TiO ₂	10	6	1	1
5	Ru- MoO _x /TiO ₂	6	3	0	0
6	Rh- MoO _x /TiO ₂	68	28	17	21
7	Pd- MoO _x /TiO ₂	85	51	9	23
7	Re- MoO _x /TiO ₂	9	7	0	0
8	Ni- MoO _x /TiO ₂	8	6	0	0
9	Co- MoO _x /TiO ₂	6	2	0	0
10	Cu- MoO _x /TiO ₂	5	2	0	0
11^b	Pt- MoO_x/TiO₂	100	92	3	5
12	Pt/TiO ₂	61	34	11	15
13	Pt/SiO ₂	56	27	14	11
14	Pt/Al ₂ O ₃	77	52	10	13
15	Pt/Nb ₂ O ₅	18	9	3	4
16	Pt/CeO ₂	64	45	8	11

^a Conversion of **2a** and yields were determined by GC. Mo loading is 7 wt% for entries 2-10.

^b Mo =15 wt%

Table 5.2 Reaction of **1a** with **2a** and H₂ by 1 mol% Pt-MoO_x/TiO₂ under various conditions.^a



Entry	n_{LA}	P_{H_2}	T, °C	Solvent	Conversion, %	Yield/%		
						3a	4a	5a
1	1	3	100	no	78	69	3	6
2	1.2	3	100	no	78	70	3	5
3	1.5	3	100	no	76	67	3	5
4	1	5	100	no	88	80	3	5
5	1	7	100	no	96	86	4	6
6	1	7	110	no	100	92	3	5
7	1	7	120	no	100	85	5	10
8	1	7	140	no	100	78	7	15
9	1	7	110	toluene	65	45	9	11
10	1	7	110	<i>o</i> -xylene	53	38	6	9
11	1	7	110	<i>n</i> -decane	26	16	4	6
12	1	7	110	dioxane	17	8	4	5

^a Conversion of **2a** and yields were determined by GC

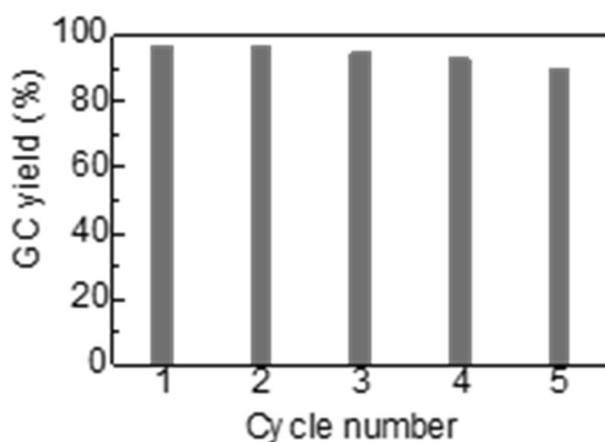
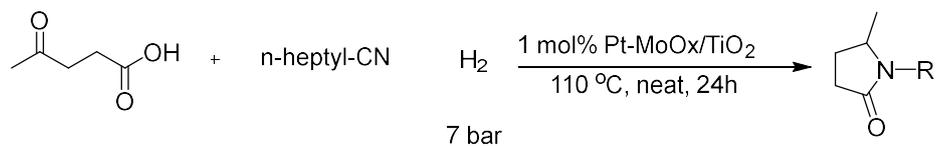
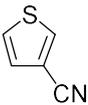
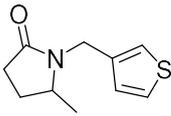
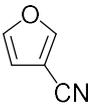
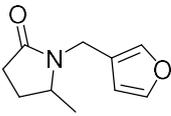
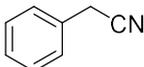
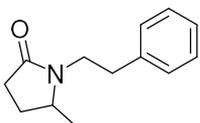
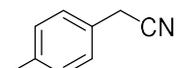
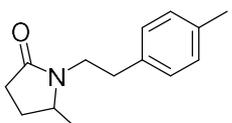
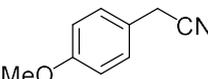
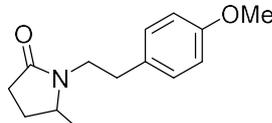
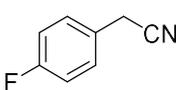
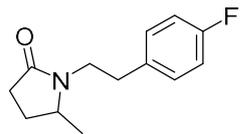
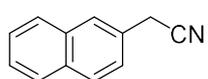
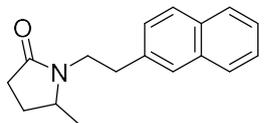


Figure 5.3 Reuse of Pt-MoO_x/TiO₂ for the reaction of **1a** with **2a** under 0.7 MPa H₂ by. Conditions are the same as in **Table 5.1**.

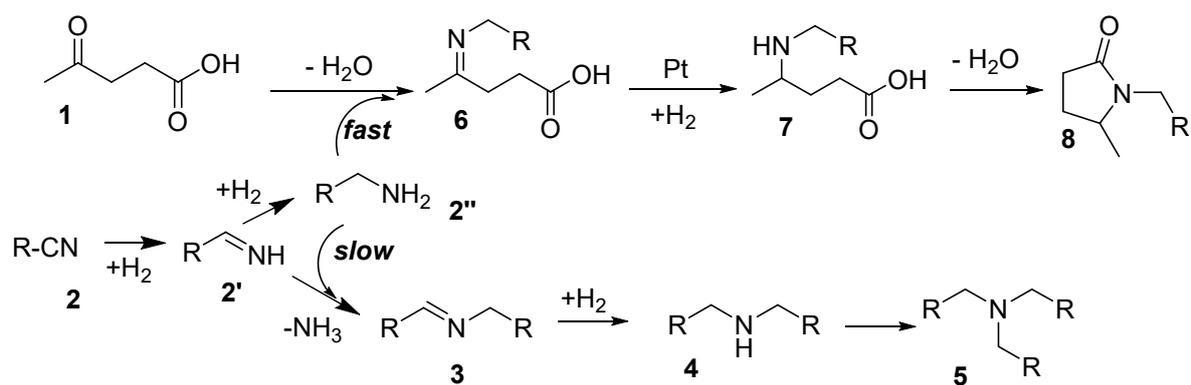
Table 5.3 Reaction of LA with nitriles under H₂ by Pt-MoO_x/TiO₂.^a



Entry	Nitriles	Products	Yield,%
1	<i>n</i> -heptyl-CN		92
2	<i>n</i> -nonyl-CN		90
3			(88)
4			(85)
5			(73)
6			82
7			88
8			87
9			72
10			91
11			(76)

12			(68)
13			(65)
14			84
15			76
16			75
17			72
18			88

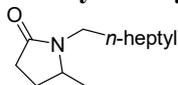
^a Yields were determined by GC. Isolated yields are parentheses.



Scheme 5.1 A possible reaction pathway of Pt-MoO_x/TiO₂-catalyzed reductive amination of LA with amines under H₂.

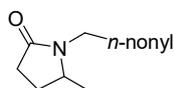
NMR and GCMS analysis

5-Methyl-1-octyl-pyrrolidin-2-one:¹



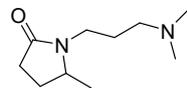
¹H NMR (600.17 MHz, CDCl₃, TMS): δ 3.69-3.67 (m, 1H), 3.58-3.55 (m, 1H), 2.93-2.89 (m, 1H), 2.39-2.37 (m, 2H), 2.34-2.30 (m, 1H), 2.20-2.17 (m, 1H), 1.57-1.54 (m, 2H), 1.45-1.42 (m, 1H), 1.31-1.27 (m, 10 H), 1.22-1.20 (m, 3H), 0.88-0.86 (m, 3H); ¹³C NMR (150.92 MHz, CDCl₃) δ 174.29, 52.94, 39.71, 31.50, 30.08, 29.03, 28.92, 27.15, 26.70, 26.53, 22.34, 19.51, 14.79; GC-MS m/e 211.20.

5-Methyl-1-decyl-pyrrolidin-2-one:¹



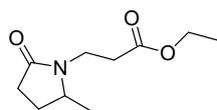
¹H NMR (600.17 MHz, CDCl₃, TMS): δ 3.69-3.67 (m, 1H), 3.58-3.56 (m, 1H), 2.92-2.89 (m, 1H), 2.42-2.37 (m, 1H), 2.35-2.30 (m, 1H), 2.19-2.17 (m, 1H), 1.57-1.54 (m, 2H), 1.45-1.40 (m, 1H), 1.31-1.25 (m, 14H), 1.20-1.19 (m, 3H), 0.89-0.86 (m, 3H); ¹³C NMR (150.92 MHz, CDCl₃) δ 174.54, 53.15, 39.95, 31.82, 30.32, 29.49, 29.48, 29.30, 29.24, 27.39, 26.94, 26.76, 22.61, 19.74, 14.05; GC-MS m/e 239.30.

1-(3-Dimethylamino-propyl)-5-methyl-pyrrolidin-2-one:



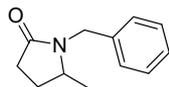
GC-MS m/e 184.20.

3-(2-Methyl-5-oxo-pyrrolidin-1-yl)-propionic acid ethyl ester:



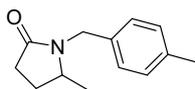
GC-MS m/e 199.15.

1-Benzyl-5-methyl-pyrrolidin-2-one:¹



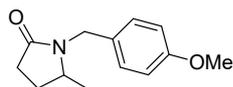
¹H NMR (600.17 MHz, CDCl₃, TMS): δ 7.32-7.28 (m, 2H), 7.26-7.21 (m, 3H), 4.94 (d, *J* = 15.12 Hz, 1H), 3.97 (d, *J* = 15.12 Hz, 1H), 3.51-3.49 (m, 1H), 2.51-2.45 (m, 1H), 2.42-2.35 (m, 1H), 2.15-2.10 (m, 1H), 1.62-1.54 (m, 1H), 1.14 (d, *J* = 6.18 Hz, 3H); ¹³C NMR (150.92 MHz, CDCl₃) δ 174.89, 136.76, 128.53 (C×2), 127.89 (C×2), 127.32, 52.71, 43.79, 30.21, 26.57, 19.52; GC-MS m/e 189.15.

5-Methyl-1-(4-methyl-benzyl)-pyrrolidin-2-one:¹



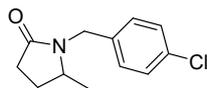
^1H NMR (600.17 MHz, CDCl_3 , TMS): δ 7.12-7.11 (m, 4H), 4.94 (d, $J = 14.40$ Hz, 1H), 3.92 (d, $J = 14.40$ Hz, 1H), 3.52-3.50 (m, 1H), 2.49-2.45 (m, 1H), 2.41-2.38 (m, 1H), 2.35 (s, 3H), 2.14-2.12 (m, 1H), 1.59-1.57 (m, 1H), 1.15 (d, $J = 6.18$ Hz, 3H); ^{13}C NMR (150.92 MHz, CDCl_3) δ 174.84, 136.99, 133.67, 129.22 (C \times 2), 127.92 (C \times 2), 52.62, 43.49, 30.27, 26.56, 21.04, 19.52; GC-MS m/e 203.15.

1-(4-Methoxy-benzyl)-5-methyl-pyrrolidin-2-one:¹



^1H NMR (600.17 MHz, CDCl_3 , TMS): δ 7.24-7.21 (m, 1H), 7.19-7.17 (m, 1H), 6.91-6.88 (m, 1H), 6.86-6.85 (m, 1H), 4.81 (d, $J = 15.12$ Hz, 1H), 4.20 (d, $J = 15.12$ Hz, 1H), 3.82 (s, 3H), 3.55-3.52 (m, 1H), 2.49-2.45 (m, 1H), 2.39-2.35 (m, 1H), 2.15-2.13 (m, 1H), 1.59-1.57 (m, 1H), 1.17 (d, $J = 6.18$ Hz, 3H); ^{13}C NMR (150.92 MHz, CDCl_3) δ 174.92, 157.22, 129.32, 128.39, 124.84, 120.52, 110.18, 55.22, 53.15, 38.18, 30.19, 26.58, 19.55; GC-MS m/e 219.15.

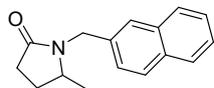
5-Methyl-1-(4-chloro-benzyl)-pyrrolidin-2-one:¹



^1H NMR (600.17 MHz, CDCl_3 , TMS): δ 7.29 (d, $J = 8.28$ Hz, 2H), 7.18 (d, $J = 8.28$ Hz, 2H), 4.87 (d, $J = 15.12$ Hz, 1H), 4.01 (d, $J = 15.12$ Hz, 1H), 3.52 (m, 1H), 2.52-2.47 (m, 1H), 2.42-2.39 (m, 1H), 2.19-2.15 (m, 1H), 1.63-1.58 (m, 1H), 1.15 (d, $J = 6.18$ Hz, 3H); ^{13}C NMR (150.92 MHz, CDCl_3) δ 175.03, 135.42, 133.17, 129.28 (C \times 2), 128.73 (C \times 2), 52.90, 43.28, 30.15, 26.63, 19.61; GC-MS m/e 223.09

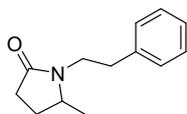
Note: 17% yield of chlorine detached pyrrolidinone (1-Benzyl-5-methyl-pyrrolidin-2-one) was observed by NMR and GCMS analysis. Under standard reaction condition 8% and during isolation 9% of chlorine detached pyrrolidinone was observed.

5-Methyl-1-naphthalene-2-yl-methyl-pyrrolidin-2-one:



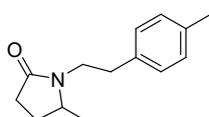
^1H NMR (600.17 MHz, CDCl_3 , TMS): δ 7.82-7.79 (m, 3H), 7.67 (s, 1H), 7.48-7.44 (m, 2H), 7.35 (d, $J = 8.22$ Hz, 1H), 5.12 (d, $J = 15.06$ Hz, 1H), 4.14 (d, $J = 15.06$ Hz, 1H), 3.58-3.50 (m, 1H), 2.52-2.50 (m, 1H), 2.45-2.43 (m, 1H), 2.15-2.13 (m, 1H), 1.60-1.58 (m, 1H), 1.15 (d, $J = 6.90$ Hz, 3H); ^{13}C NMR (150.92 MHz, CDCl_3) δ 175.02, 134.33, 133.23, 132.70, 128.47, 127.62 (C \times 2), 126.65, 126.17, 125.99, 125.84, 52.83, 44.05, 30.26, 26.60, 19.59; GC-MS m/e 239.15.

5-Methyl-1-phenylethyl-pyrrolidin-2-one:¹



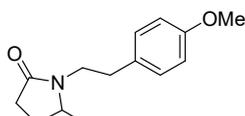
¹H NMR (600.17 MHz, CDCl₃, TMS): δ 7.30-7.26 (m, 3H), 7.22-7.21 (m, 2H), 3.83-3.81 (m, 1H), 3.53-3.51 (m, 1H), 3.15-3.13 (m, 1H), 2.87-2.86 (m, 1H), 2.77-2.76 (m, 1H), 2.38-2.36 (m, 1H), 2.30-2.27 (m, 1H), 2.12-2.10 (m, 1H), 1.54-1.52 (m, 1H), 1.13 (d, *J* = 6.18 Hz, 3H); ¹³C NMR (150.92 MHz, CDCl₃) δ 174.72, 138.87, 128.81, 128.73, 128.64, 128.40, 126.23, 53.64, 41.64, 33.81, 30.15, 27.99, 19.63; GC-MS *m/e* 203.10.

5-Methyl-1-(2-*p*-tolyl-ethyl)-pyrrolidin-2-one:



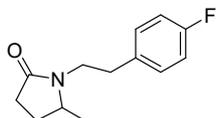
¹H NMR (600.17 MHz, CDCl₃, TMS): δ 7.12-7.06 (m, 4H), 3.81-3.79 (m, 1H), 3.56-3.52 (m, 1H), 3.13-3.10 (m, 1H), 2.83-2.80 (m, 1H), 2.74-2.72 (m, 1H), 2.42-2.36 (m, 1H), 2.31-2.25 (m, 4H), 2.13-2.11 (m, 1H), 1.54-1.52 (m, 1H), 1.15 (d, *J* = 6.18 Hz, 3H); ¹³C NMR (150.92 MHz, CDCl₃) δ 174.62, 135.79, 135.75, 129.07 (C×2), 128.05 (C×2), 53.58, 41.68, 33.36, 30.18, 26.73, 20.94, 19.65; GC-MS *m/e* 217.10.

1-[2-(4-methoxy-phenyl)-ethyl]-5-methyl-pyrrolidin-2-one:



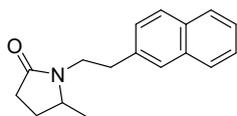
¹H NMR (600.17 MHz, CDCl₃, TMS): δ 7.13 (d, *J* = 8.14 Hz, 2H), 6.83 (d, *J* = 8.28 Hz, 2H), 3.80-3.77 (m, 4H), 3.54-3.51 (m, 1H), 3.12-3.09 (m, 1H), 2.82-2.79 (m, 1H), 2.73-2.69 (m, 1H), 2.40-2.36 (m, 1H), 2.32-2.25 (m, 1H), 2.15-2.08 (m, 1H), 1.56-1.52 (m, 1H), 1.15 (d, *J* = 6.18 Hz, 3H); ¹³C NMR (150.92 MHz, CDCl₃) δ 174.69, 158.05, 130.83, 129.53 (C×2), 113.75 (C×2), 55.09, 53.59, 41.73, 32.84, 30.12, 26.68, 19.59; GC-MS *m/e* 233.15.

1-[2-(4-fluoro-phenyl)-ethyl]-5-methyl-pyrrolidin-2-one:



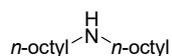
¹H NMR (600.17 MHz, CDCl₃, TMS): δ 7.18-7.16 (m, 2H), 6.99-6.96 (m, 2H), 3.80-3.76 (m, 1H), 3.54-3.51 (m, 1H), 3.14-3.11 (m, 1H), 2.86-2.83 (m, 1H), 2.77-2.73 (m, 1H), 2.42-2.37 (m, 1H), 2.31-2.26 (m, 1H), 2.14-2.10 (m, 1H), 1.56-1.53 (m, 1H), 1.15 (d, *J* = 6.82 Hz, 3H); ¹³C NMR (150.92 MHz, CDCl₃) δ 174.84, 161.52 (d, *J* = 248.55 Hz, 4-F-C), 134.56 (d, *J* = 2.89 Hz, *para* to 4-F), 130.11 (d, *J* = 7.23 Hz, *meta* to 4-F, C×2), 115.27 (d, *J* = 21.67 Hz, *ortho* to 4-F, C×2), 53.72, 41.69, 33.06, 30.17, 26.79, 19.72; GC-MS *m/e* 221.27.

5-Methyl-1-(2-naphthalene-2-yl-ethyl)-pyrrolidin-2-one:



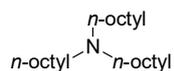
^1H NMR (600.17 MHz, CDCl_3 , TMS): δ 7.82-7.79 (m, 3H), 7.67 (s, 1H), 7.48-7.44 (m, 2H), 7.35 (d, $J = 8.22$ Hz, 1H), 5.12 (d, $J = 15.06$ Hz, 1H), 4.14 (d, $J = 15.06$ Hz, 1H), 3.58-3.50 (m, 1H), 2.52-2.50 (m, 1H), 2.45-2.43 (m, 1H), 2.15-2.13 (m, 1H), 1.60-1.58 (m, 1H), 1.15 (d, $J = 6.90$ Hz, 3H); ^{13}C NMR (150.92 MHz, CDCl_3) δ 175.02, 134.33, 133.23, 132.70, 128.47, 127.62 (C \times 2), 126.65 (C \times 2), 126.17, 125.99, 125.84, 52.83, 44.05, 30.26, 26.60, 19.59; GC-MS m/e 253.25.

Diethyl-amine:



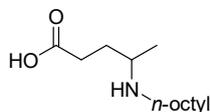
GC-MS m/e 241.30.

Triethyl-amine:



GC-MS m/e 353.45.

4-Octylamino-pentanoic acid:



GC-MS m/e 229.25.

References

1. A. S. Touchy, S. M. A. H. Siddiki, K. Kon, K. Shimizu, *ACS Catal.* 2014, **4**, 3045–3050.

Chapter 6

Conclusions

The present work exhibits the effectiveness of multiphase reaction media including the use of water and CO₂ with organic solvent *n*-hexane/toluene for hydrogenation of nitriles over supported Pd catalysts. These works would help to the development of greener reaction medium which allow easy catalyst-substrate separation process. The hydrogenation of various nitriles and *in situ* high-pressure FTIR measurements were examined to study the role of water and CO₂ in the multiphase reaction media. The synergetic effect of *n*-hexane/toluene-CO₂-H₂O affects the rate of hydrogenation, the product selectivity, and the catalyst life/deactivation. The interesting results obtained are summarized in the following.

Chapter 1 provides the general introduction to the properties and usefulness of CO₂ and water in multiphase reaction media. It consists literature of multiphase reactions carried out in the presence of CO₂ and CO₂-water system. It summarizes the research work included in **Chapter 2-5**.

Chapter 2 shows the usefulness of multiphase medium using *n*-hexane-CO₂-H₂O for selective hydrogenation of benzyl cyanide (BC) to 2-phenylethylamine (PEA) with Pd/Al₂O₃. The rate of BC hydrogenation in *n*-hexane-CO₂-H₂O system was smaller than those in neat *n*-hexane, *n*-hexane-CO₂ and *n*-hexane-H₂O systems. The secondary amine was obtained as a major product in neat *n*-hexane and *n*-hexane-CO₂ systems instead of the desired primary amine of PEA. However, PEA was formed in *n*-hexane-H₂O system with less selectivity. The catalyst deactivation was found in *n*-hexane-CO₂ system due to formation and adsorption of CO via reverse water gas shift reaction. The *n*-hexane-CO₂-H₂O system gave a high selectivity to the desired product of primary amine without deactivation of catalyst. Water-soluble PEA formed carbamate salts with CO₂ (CO₂ is dissolved in both organic and aqueous phases) which avoided its further change to undesired products. CO was also formed and adsorbed on the surface of supported Pd particles in *n*-hexane-CO₂-H₂O system but no catalyst deactivation was found. Probably, adsorbed CO molecules were removed by water.

Chapter 3 demonstrated the effectiveness of organic solvent (toluene, *n*-hexane) with CO₂ and H₂O for the selective hydrogenation of aliphatic and aromatic nitriles to corresponding primary amines with Pd/Al₂O₃, but, unfortunately, not for CN and CBP. The rate of nitrile conversion in H₂O-CO₂-hexane system was smaller than in neat organic solvent, organic solvent-CO₂ and organic solvent-H₂O systems. The dilution of reacting species in the liquid phase by the dissolution of CO₂, the change of reaction locus from the organic phase to the organic - aqueous interfacial layer, and interaction of nitrile group with CO₂ molecules may be responsible for the decreased in activity.

Chapter 4 the effectiveness of the CO₂ and water medium was examined for selective hydrogenation of benzyl cyanide (BC) and *n*-hexanenitrile (HN) using a commercial Pd/C catalyst that was different in the surface properties from the above-mentioned Pd/Al₂O₃ one. The synergetic effects of CO₂-water system were not observed in hydrogenation of benzyl cyanide and *n*-hexanenitrile over the Pd/C catalyst, in contrast to Pd/Al₂O₃. The product selectivity obtained was also different between the two catalysts even in the same CO₂ and water medium and possible reason may be the difference in the hydrophilicity/hydrophobicity of their surfaces.

Chapter 5, shows the first general and reusable catalytic system for one-pot synthesis of lactams by reductive conversion of keto acids with nitriles and H₂ using Pt-MoO_x/TiO₂ catalyst. High selectivity to lactams (low selectivity to side product, secondary amine) is due to removal of the primary amine by its fast reaction with keto acids.

In conclusion, this work clarifies the usefulness of two concepts, (1) physical (phase) separation using *n*-hexane/CO₂/water solvent and (2) chemical separation using condensation of reactive intermediate (primary amine) with keto acids, in selective reductive transformation of nitriles by supported noble metal catalysts.