SUSTAINABLE HETEROGENEOUS CATALYSIS FOR C-C/C-N COUPLING USING METHANOL AND TRIGLYCERIDE

DOCTORAL THESIS

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Dedicated to

My daughter

Ashmira Shehreen Jamil

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Abstract

Sustainable synthesis of useful chemicals is of the major concerns in the scientific community. To address the issues the areas of catalytic synthesis have dynamically grown over the decades and still in rise. Enormous works have been carried out employing both homogenous and heterogeneous catalysis and these are now advanced viable methods of useful chemical synthesis. Despite sufficient developments in conventional catalysis some challenges still remain unaddressed specially catalysts reusability and easy catalyst/product separation. Besides, expensive ligands are necessary in most of the homogeneous catalysis. In contrast, heterogeneous catalytic systems offer advantages in easy catalysts/products separation and catalysts reusability. From practical point of view, this is highly beneficial and reduces the industrial production cost to a great extent. This is where remains the main focus of this thesis i.e. developing sustainable heterogeneous system for important chemicals synthesis. Heterogeneous methods for methylation of various functional chemicals with methanol using carbon supported Pt-nanoparticle catalyst (Chapter 2&3) comprises one major part of the thesis. The methylation protocols follow transition metal catalyzed borrowing hydrogen methodology. The other part focuses on the research of biomass derived platform molecules, more precisely transformation of renewable triglycerides to various functional chemicals (Chapter 4&5). High-silica Hbeta zeolite was effective catalyst for amidation, nitrillation and methanolysis of triglycerides. For reductive amination of triglycerides into fatty amines with ammonia, Pt-loaded zirconia was developed as the catalyst. Details of all the methods along with studies on structure-activity relationship and reaction mechanism are extensively discussed in the thesis with a view to design new heterogeneous catalysts for sustainable organic synthesis. A brief summary of each title works is presented in the following sections.

The thesis starts with a general introduction followed by five individual chapters. Chapter 2 presents a highly versatile, selective, and recyclable heterogeneous catalytic processes for three types of *C*-methylation reactions using methanol as a sustainable C1 source. The methods are the beta-methylation of primary alcohols, the alpha-methylation of ketones, and the *C3*-methylation of indoles. These catalytic systems are driven by a borrowing-hydrogen mechanism, wherein the Pt-nanoparticles-catalyzed dehydrogenation of methanol (and alcohols) to aldehydes is followed by a condensation of formaldehyde with the corresponding nucleophile (aldehyde, ketone, or indole) to yield unsaturated intermediates, which are subsequently hydrogenated by Pt-H species on the catalyst. Compared to previous catalytic methods of borrowing-hydrogen-type *C*-methylation reactions, this method presents several

advantages: (1) easy catalyst/product separation, (2) catalyst recyclability, (3) excellent TONs (up to two orders of magnitude higher than those previously reported), and (4) wide substrate scope. Furthermore, DFT calculations have shown that the adsorption energy of hydrogen correlates well with the catalytic activity of various active metals employed in these reactions. These results should be helpful to rationalize the properties of catalytic systems and serve as a practical guide for future catalyst design.

Chapter 3 demonstrates a general heterogeneous catalytic method for the selective *N*-methylation of amines and nitroarenes with methanol using Pt/C and base (NaOH or KOtBu). The presented catalyst system is exclusively effective for four types of *N*-methylation reactions: dimethylation of aliphatic amines, selective monomethylation of aliphatic and aromatic amines, and monomethylation of nitroarenes. The same Pt/C catalyst is effective for all types of reactions depending only on tuning the reaction conditions such as temperature and atmosphere. Compared to the previously reported methods with homogeneous and heterogeneous catalysts, all these reactions under the same catalytic system showed high yields of the corresponding methylamines for a wide range of substrates, high turnover number (TON), and good catalyst reusability. Mechanistic studies suggested that the reaction proceeded via a borrowing hydrogen methodology. Kinetic results combined with density functional theory (DFT) calculations revealed that the high performance of Pt/C was ascribed to the moderate metal–hydrogen bond strength of Pt.

Chapter 4 describes three heterogeneous catalytic methods for the selective one-pot transformation of triglycerides to value-added chemicals: (i) a reductive amination of triglycerides into fatty amines with aqueous ammonia under hydrogen using Pt metal nanoparticles-loaded zirconia, (ii) an amidation of triglycerides under gaseous ammonia using a high-silica Hbeta zeolite, and (iii) a direct synthesis of nitriles from triglycerides and gaseous ammonia using a high-silica Hbeta zeolite at higher temperature. These methods selectively transform a wide variety of triglycerides (C4-C18) into the corresponding amines, amides, and nitriles, and thus represent a milestone in chemical transformation of triglycerides. A systematic analysis of reaction (ii) and (iii) reveals that the acidity and hydrophobicity of the zeolites are two important factors that affect the catalytic activity of the Hbeta catalysts. Specifically, increasing the number of acid sites and increasing the hydrophobicity may lead to higher reaction rates per weight of the catalyst. Hydrophobicity and acidity of different zeolites were studied by various characterization methods, including NH_3-TPD, adsorption experiments in water, and IR spectroscopy.

Chapter 5 shows a simple method for the transesterification of triglycerides with methanol to fatty methyl esters using Hbeta-75 with Si/Al = 75 as an active and reusable catalyst. The fatty acid methyl ester (FAME) is also popular as a biofuel. The developed catalytic system was applicable to the transformation of various triglycerides having C4-C18 frames. Considering the commercial availability and high durability of the Hbeta-75 catalyst, the method could be applicable to a practical process for the conversion of biomass-derived triglycerides into biofuel. The number of Brønsted acid sites and hydrophobicity are two dominant factors that influence the catalytic activity of the presented catalytic system. Quantitative relationships between acidity, hydrophobicity, and reaction rates versus Si/Al ratio of Hbeta zeolite catalysts show that a low affinity to glycerol, which arises from the hydrophobicity of the high-silica zeolites, is an important parameter for controlling the catalytic activity.

Chapter 6 is the general conclusion that summarizes the highlights of this thesis. To reiterate, the key points in two major areas of development i.e. methods in 1) *C*- and *N*-methylation using methanol by Pt/C catalyst, and 2) catalytic transformation of biomass derived platform molecule (triglyceride) to valuable chemicals are summarized. All the described methods are highly selective heterogenous systems with reusable catalysts having wide substrate scopes and excellent TONs.

List of Publications

Chapters 2-5 of this thesis are based on the contents of the following publications:

- **Chapter 2**: *C*-Methylation of alcohols, ketones, and indoles with methanol using heterogeneous platinum catalysts; S. M. A. Hakim Siddiki, Abeda S. Touchy, **Md. A. R. Jamil**, Takashi Toyao, Ken-ichi Shimizu.

  ACS Catal. **2018**, 8, 3091-3103 ***(highlighted in the supplementary cover)***

- **Chapter 3**: *N*-Methylation of Amines and Nitroarenes with Methanol Using Heterogeneous Platinum Catalysts; **Md. A. R. Jamil**, Abeda S Touchy, Md. Numobi Rashed, Kah Wei Ting, S.M.A. Hakim Siddiki, Takashi Toyao, Zen Maeno, Ken-ichi Shimizu.

  Journal of Catalysis, **2019**, 371, 47-56.

- **Chapter 4**: Selective Transformations of Triglycerides into Fatty Amines, Amides, and Nitriles using Heterogeneous Catalysts; **Md. A. R. Jamil**, S.M.A. Hakim Siddiki, Abeda S. Touchy, Md. Nurnobi Rashed, Sharmin S. Poly, Yuan Jing, Kah Wei Ting, Takashi Toyao, Zen Maeno, Ken-ichi Shimizu.

  ChemSusChem, **2019**, 12, 3115 – 3125. (***Selected for front cover***)

- **Chapter 5**: High-silica Hβ zeolite catalyzed methanolysis of triglycerides to form fatty acid methyl esters (FAMEs); **Md. A. R. Jamil**, Abeda Sultana Touchy, Sharmin Sultana Poly, Md. Nurnobi Rashed, S. M. A. Hakim Siddiki, Takashi Toyao, Zen Maeno, and Ken-ichi Shimizu.

  Fuel Processing Technology, **2020**, 197, 106204

The contents of the following publications were **NOT** used directly in this thesis:

- Acetalization of glycerol with ketones and aldehydes catalyzed by high silica Hβ zeolite; Sharmin Sultana Poly, **Md. A. R. Jamil**, Abeda S. Touchy, Shunsaku Yasumura, S. M. A. Hakim Siddiki, Takashi Toyao, Zen Maeno, and Ken-ichi Shimizu.

  Molecular Catalysis, **2019**, 479,110608.

- Direct Phenolysis Reactions of Unactivated Amides into Phenolic Esters Promoted by a Heterogeneous CeO_2 Catalyst; Md. Nurnobi Rashed, S.M.A.Hakim Siddiki, Abeda S. Touchy, **Md. A. R. Jamil**, Sharmin S. Poly, Takashi Toyao, Zen Maeno, Ken-ichi Shimizu.

  Chem. Eur. J., **2019**, 25, 10594 – 10605. IF = 5.317. (***Selected for front cover***)

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Chapter One

General Introduction

1. Introduction

The advent of 'green chemistry' and 'sustainable technology' have revolutionized the world of chemical synthesis in both academia and industry.[1] The major cutting-edge research in green chemical syntheses that reduce or eliminate the use and generation of hazardous substances are introducing meaningful ways to face one of the major challenges of our time which is to find efficient new solutions beyond our waning fossil resources (oil, natural gas, coal) and the severe environmental consequences of excessive combustion of carbon-containing fuels and their products. In terms of strategies, utilization of renewable biomass and activation of small molecules by catalytic reactions to realize the critical chemical synthesis are growing. Catalysis, one of the vital principles in green chemistry, is also known as "the pillar of green chemistry" and a powerful tool to design efficient synthesis protocols that can minimize the energy consumption, waste generation and production costs.[1,2] In the recent years, incorporation of machine learning technologies and catalysis for new chemical design is adding innovative dimensions in the field.[3,4] In this quest, developing robust methods in heterogenous catalysis for useful chemical synthesis from renewable resources is the main challenging goal of this thesis. As an overview, catalytic formation of C-C and C-N bonds involving borrowing hydrogen methodology, and transformation of bio-based raw materials (e.g. methanol, triglycerides) are investigated where transition metal catalyzed borrowing hydrogen methodology for methylation using methanol as C1 source is prominent.

1.1 Supported metal nanoparticles as heterogeneous catalysts

Generally, the organic reactions are carrying out in catalytic condition. In the classical catalytic systems, the catalysts are in either homogeneous or heterogeneous states of the reactions. The main features of the frequently used homogeneous transition metal catalysts are having great activity and selectivity since they work in the same reaction phase.[5] However, they have some serious disadvantages owing from the requirements of specific reaction conditions i.e. inert atmosphere, water free solvents and expensive ligands.[5-8] Also, some of them are unstable thereby strongly integrated to the reaction system or unable to separate from the reaction mixture thus make it impossible to reuse.[5-8] Overall, the sustainability of the methods is not satisfied from the green chemistry point of view. Structures of some commonly used typical homogeneous catalysts are shown in the **Figure 1**.

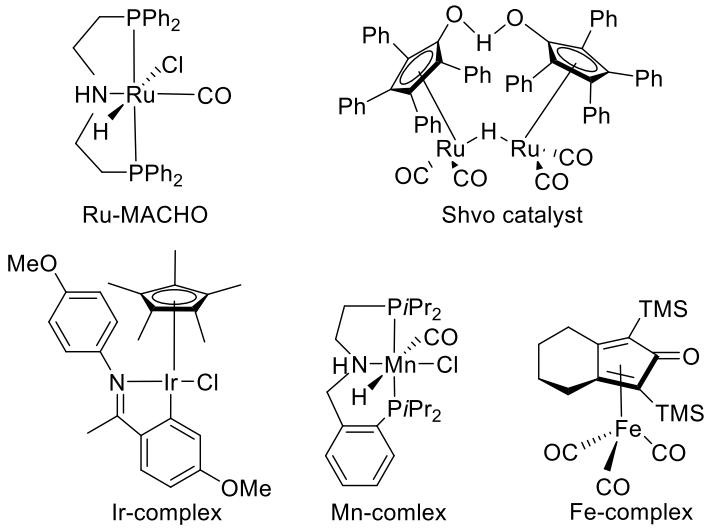


Figure 1. Examples of typical transition metal complexes used as homogeneous catalysts.

On the other hand, heterogenous catalysts such as supported metal nanoparticles of Pt, Ru, Ir, Rh, etc., different Lewis acid-base metal oxides, solid acids, polymers, MOFs, zeolites with Brønsted acidity having specific Si/Al ratio and porosity work in the reactions as solid catalysts maintaining a different phase than the reactions. Thus, the heterogenization of the catalysts can eliminate the disadvantages associated with the homogeneous methods in many ways. Because, the heterogeneous catalysts can be easily removed from the reaction mixture by simple separation techniques such as filtration or centrifugation and make it easy for the catalysts to regenerate and recycle into a new reaction.[5] Additionally, the sensitive homogeneous transition metal catalysts are stable or do not require special storage and reaction conditions when used as heterogeneous catalysts.

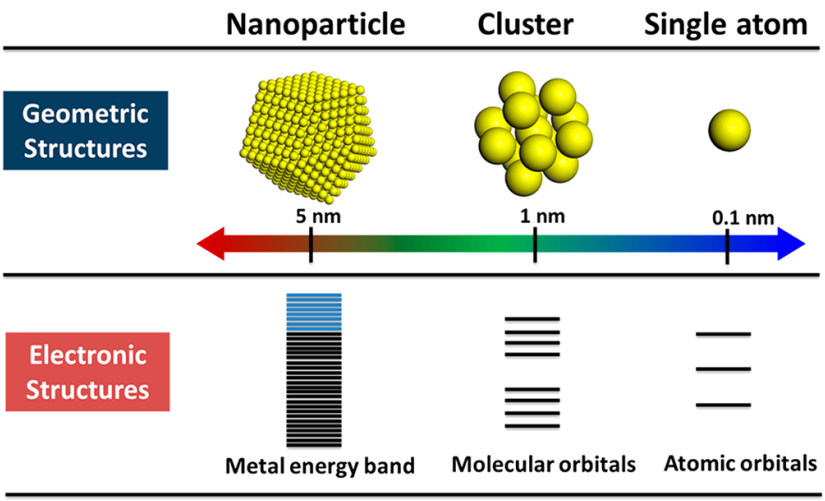


Figure 2. Schematic representation of the single atom formation. Geometric and electronic structures of single atom, clusters, and nanoparticles.[6]

Several competitive homogeneous and heterogeneous catalysts have been introduced ranging from a single atom to combination of complex molecular systems by many research groups. Various metal oxides, zeolites, supported metals catalysts are studied by both academic and industrial chemists. As presented in **Figure 2**, with the advancement of the analytical techniques and spectroscopic methods for surface analysis, for example using X-ray absorption spectroscopy such as EXAFS (Extended X-ray Absorption Fine Structure), XANES (X-ray Absorption Near Edge Structure) etc., now it is possible to observe the catalysts at the atomic levels to describe the core fundamental properties and make it possible to design target-oriented catalysts. Formation of single atom to defined clusters of metal species with different size extending from single atom to larger nanoclusters, and nanoparticles as shown in **Figure 2** have different catalytic behaviors for various heterogeneous catalytic reactions. It has also been shown in the literature that many factors including the particle size, shape, chemical composition, metal–support interaction, and metal–reactant/solvent interaction can have significant influences on the catalytic properties of metal catalysts.[6] In addition to that, the recent developments of well-controlled synthesis methodologies and advanced characterization tools allow one to correlate the relationships of the catalytic feature at the molecular level.

1.2 Transition metal catalyzed borrowing hydrogen reaction

The borrowing hydrogen (BH) principle also known as hydrogen auto-transfer is the most studied strategy for new bond forming (carbon–carbon and carbon–heteroatom) reactions employing the transition metal catalysts in the recent years.[5,7,16,17,8–15] The BH methodology is applicable to a broad range of areas in chemistry using both homogenous and heterogenous catalysis (**Figure 3**).[18] It is a powerful approach which combines transfer hydrogen (without the direct use of molecular hydrogen or external hydrogen source) followed by one or more intermediate reactions to synthesize more complex molecules without the need for tedious separation or isolation processes. The strategy usually follows three steps, (i) dehydrogenation, (ii) intermediate reaction, and (iii) hydrogenation, is an excellent and well-recognized process from the synthetic, economic, and environmental point of view.[5] This is simple and straightforward process for enabling the catalytic formation of not only C–C bonds but also of many other types of linkages, including C–N coupling with various coupling partners, and are thus regarded as highly atom economic manufacturing process for bulk and fine chemicals in industries.[19–25]

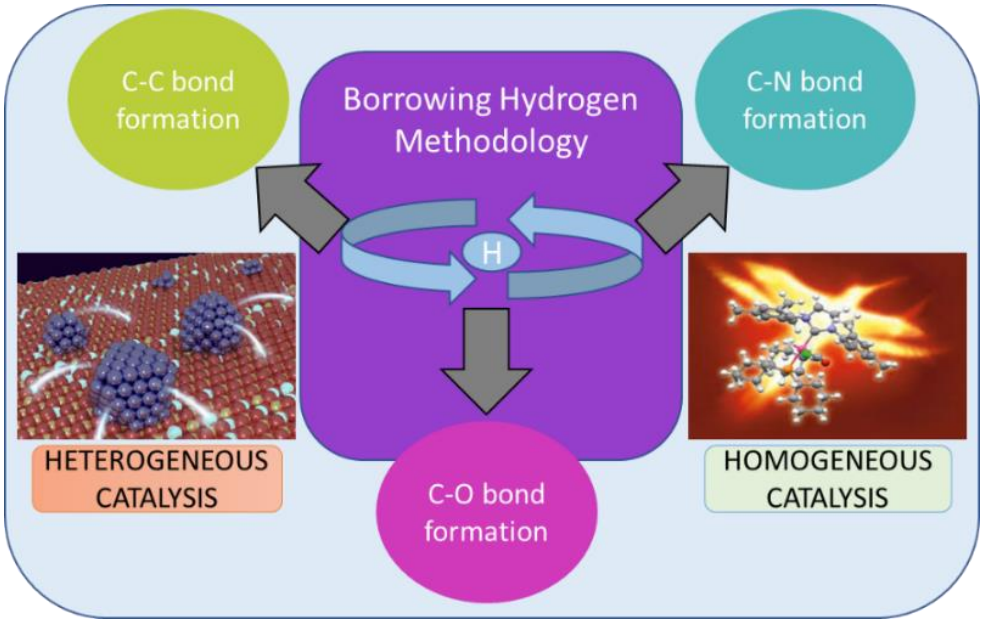
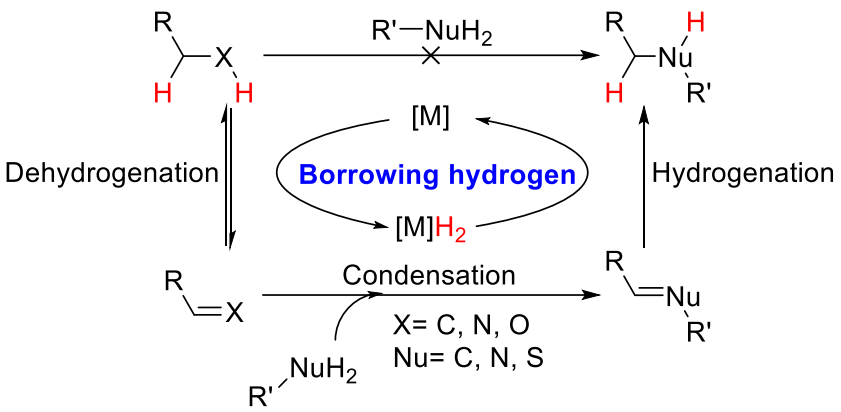


Figure 3. Scope of BH methodology using homo and heterogeneous catalysis.

A basic scheme of this BH concept is shown in **Scheme 1**. The name itself describe the key concept of borrowing hydrogen which is the hydrogen from a donor molecule will be stored by a catalytic metal fragment to be released in a final hydrogenation step. Therefore, the development of catalytic systems in borrowing hydrogen catalysis involves metal complexes or supported metal particles in which H_2 dissociation and recombination is simple, preferably without requiring severe reaction conditions. Unfortunately, most of the metal hydrides that may form during hydrogen activation processes are too stable to easily give back the activated hydrogen, being therefore inactive for the BH methodology.[26] For example, among several metals ruthenium (Ru),[27,28] iridium (Ir),[29,30] rhodium (Rh),[30] Iron (Fe) and manganese (Mn)[31] complexes are typical homogeneous complexes that have been reported for BH reactions. In the reaction settings borrowing hydrogen strategy begins with a metal catalyzed dehydrogenation, as an effect of which a usually less reactive donor molecule is temporarily converted into a more reactive substrate (e.g., an alkane transforms into an alkene, an alcohol into an aldehyde or a ketone and an amine into an imine).[18] The more activated intermediate can undergo further transformations to give an unsaturated compound that wsill be reduced by the borrowed hydrogen on the metal hydrides species generated during the first dehydrogenation step.



Scheme 1. Basic scheme of borrowing hydrogen methodology.

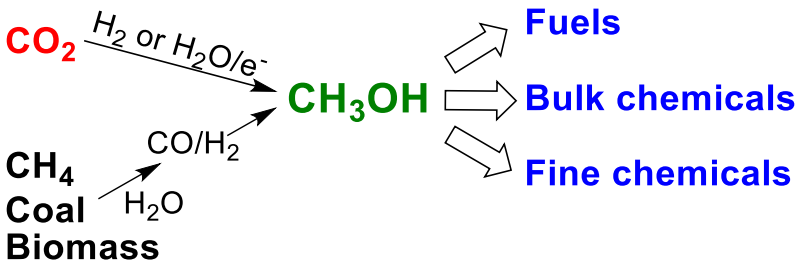
With several established homogeneous transition metal catalytic methods in organic synthesis, new synthetic techniques are continuously advancing in the industries. However, owing to the difficulties associated with the homogeneous methods, alternative highly atom efficient and benign methods are in high demand that can be realized from heterogeneous systems. Thus, from the viewpoints of sustainability, developing reusable new heterogeneous methods in catalysis are crucial.

1.3 Sustainable carbon source and renewable biomass

Statistically, the world's population currently exceeds 7 billion and this number is expected to rise to 10 billion by the year 2050.[32] The rapid growth of population and development in economies will eventually increase the demand for supplies in all trades of life. As of feeding, industrialisation, manufacturing process, infrastructures development is hiking, surprisingly, however, almost everything depending on the natural fossil base. In contrast, the supply of the resources is restricted and diminishing, and this growing demand along with the concomitant increase in CO_2 emissions and their adverse environmental effects is of major concern politically, economically and academically. Considering these facts, there has been increased interest in the development of a green, sustainable and cost-effective alternative to petroleum fuels and platform chemicals derived specially from crude oil. Renewable resources of energy, such as hydroelectric, wind and solar power have the potential to meet some of the energy requirements, but the replacement of chemicals derived from petroleum is vital to have carbon atoms in them. As the sustainable alternative, renewable biomass provides both a viable and attractive solution to all these problems. Two major sustainable renewable sources which are connected to this thesis are discussed in the following sections.

1.3.1 Methanol–a greener C1 source

One of the great challenges of our time is to find the best alternative to use renewable resources to lower the dependence on the limited fossil sources. Atmospheric carbon dioxide is considered as a sustainable carbon source - an alternative to the fossil resources. In other words, for which currently we rely on oil, can be replaced by the use of CO_2.[33]



Scheme 2. Route to fine chemicals using atmospheric carbon dioxide.

As shown in **Scheme 2**, capturing the atmospheric CO_2 and transforming them to valuable chemicals specially to methanol can reduce the greenhouse gas effect in one hand and can act as a source of carbon feedstock on the other hand. This sustainable methanol as it is used today for the bulk chemicals and fuels syntheses, can be a building block for the synthesis of fine chemicals too. Hence, much attention has been given in the recent years to transform CO_2 to methanol and its derivatives to obtain materials in energy carriers and other forms from CO_2. Transforming CO_2 to useful consumables has several benefits from the environmental perspective. The foremost one is the impact on reducing greenhouse gas and global warming.[34] As a matter of fact, nowadays most of the production companies around the world use methanol as a raw material to produce different products. From the idea of green chemistry, methanol from CO_2 is a promising sustainable carbon source which presumably would act as an alternative source material to replace the natural fossil sources on which we depend almost for everything. Another benign property of methanol is the biodegradability and relatively less toxic than the other chemicals such as formaldehyde, formic acid, methyl halides etc. that are widely used C1 sources.

1.3.2 Triglycerides – a low cost renewable feedstock

Oil, natural gas and coal are the main fossil fuels of the world. They are not only our major energy sources, they are also the feedstocks for a great variety of manmade materials and products. The products range from gasoline and diesel oil to varied petrochemical and chemical products, including synthetic materials, plastics, and pharmaceuticals. Owing to the

multipurpose application, fossil resources continue to be significantly depleted and eventually will impose higher cost on the supply chain in near future. Thus, we need to search for new sources and sustainable solutions.

Lignocellulosic biomass and food wastes constitute inexpensive and sustainable renewable carbon sources that can be upgraded into high-quality diesel fuels and chemicals using catalysts.[35–39] The catalytic conversion of lignocellulosic biomass to diesel fuel-range alkanes has been reported for long, but involves several steps.[40–42] In contrast, the conversion of vegetable and waste cooking oils (WCO), consisting of triglycerides and free fatty acids as the main components, to renewable diesel fuels and other chemicals involve fewer processing steps and can be more energy efficient.[43–48] Currently, first generation biofuels are produced from vegetable oils, starches and sugars. However, a potentially more sustainable, more abundant and cheaper alternative can be targeted renewables such as triglyceride and convert them to not only biofuels, but also to other valuable chemicals that are widely used in chemical and pharmaceutical industries. A potential triglyceride source is the massive waste stream from food industries and non-food plant biomass (**Figure 4**). Valorisation of this massive waste materials can incredibly boost the economic development by adding valuable chemicals in the industries, saving money from the waste management cost and overall save the environment from unwanted pollution.

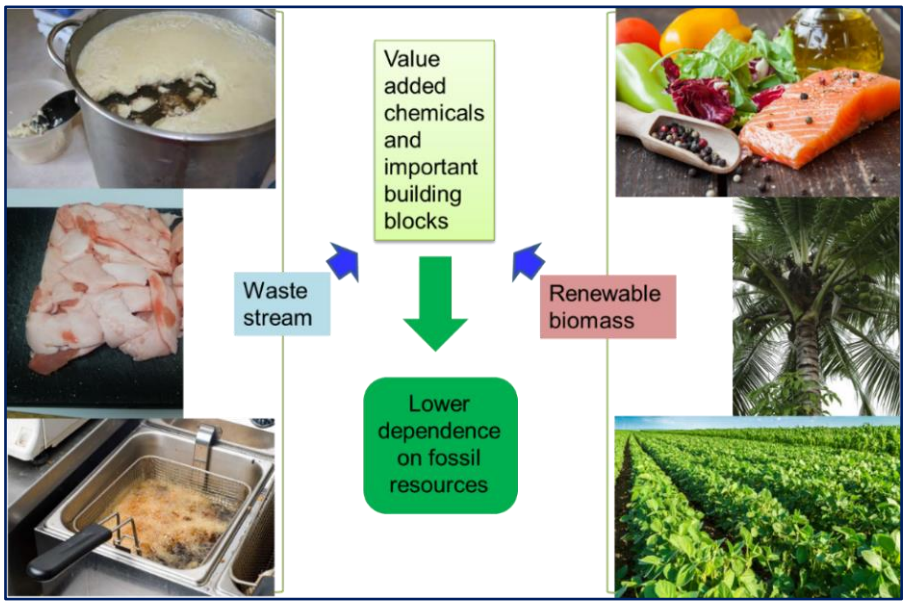


Figure 4. Potential renewable biomass from food industry waste stream and plants.

1.4 Objective of the thesis

In light with the above contextual discussion and the necessity of more benign, viable and greener chemical synthesis methods, my concentration centers in the sustainable heterogeneous synthesis. In other words, the main target of my thesis is to address the sustainability issues in chemical synthesis by introducing new methods to utilize renewable biomass for useful chemical synthesis. Broadly two major concerns in sustainable synthesis have been addressed, which are:

- developing methylation protocols using methanol as a carbon (C1) source employing borrowing hydrogen strategy; and
- transforming renewable biomass to valuable chemicals.

1.4.1 Selective methylation using methanol

Generally, alkylation is the process for extending molecular structure applying BH strategy. The activation of alcohols in this borrowing process has been extensively studied in the recent years in form of a varied combination of BH reactions. Incorporating alkyl segments through C-C or C-N coupling can potentially to generate a Markush structure of useful chemicals having a diverse range of physical and chemical properties. It is noteworthy to mention that inserting specially a methyl moiety into organic structures give novel properties to the compound which are useful for designing new chemicals having biological and pharmaceutical importance. This also give directions towards the design and formulation of new chemicals or drugs.

In the first part of my thesis, I focused in developing methods for methylation i.e. inserting methyl moieties from methanol into the backbone as well as onto the functional groups of various substrates. Methanol, the simplest aliphatic alcohol, is an abundant, biodegradable liquid and an alternative fuel for internal combustion.[49] For simplicity, I have subdivided this part of the work into two categories which are i) *C*-methylation: addition of methyl group through C-C bond formation, and ii) *N*-methylation that resembles the incorporation of methyl group through C-N bond formation.

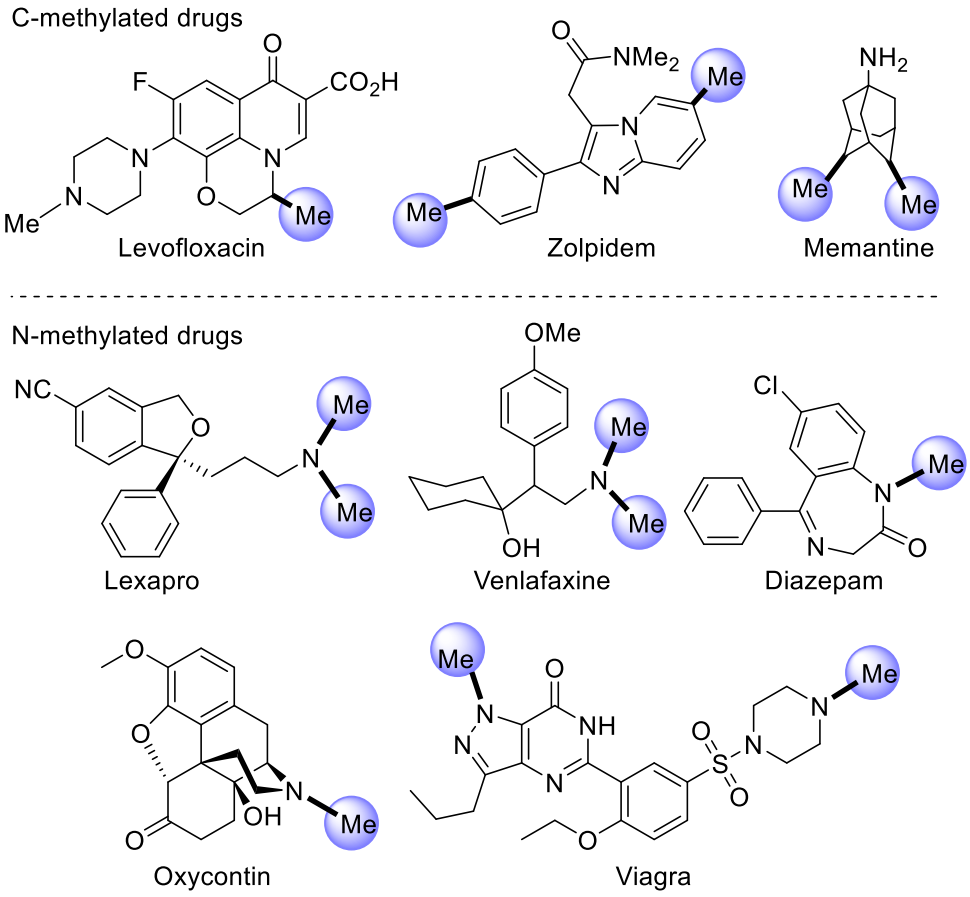


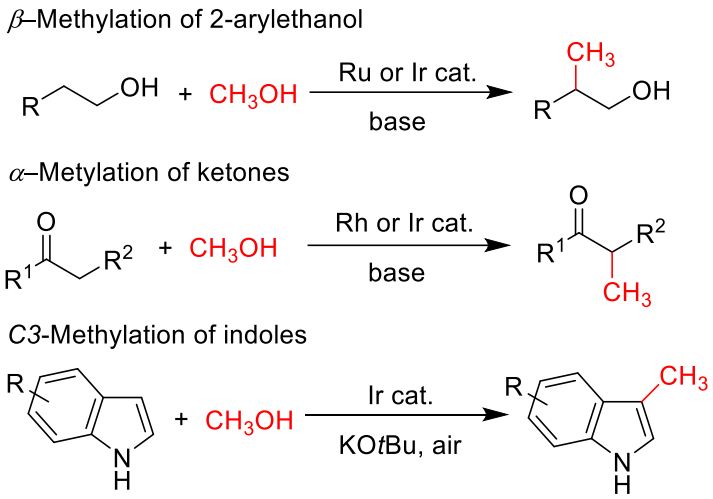
Figure 5. Selected world's top selling drugs containing methyl groups.[49]

C-methylation: formation of C-C bonds

The C-C bond forming reactions have given much attention in the recent years, particularly in C-methylation, which is highly important since the methyl moiety is present in several widely used leading pharmaceutical drugs (**Figure 5**). Many research groups have reported various coupling partners such as alcohol, aldehyde, alkyl halide etc. for this C-C bond forming reactions.[9,17,50,51] However, a benign method is yet to achieved. With this thought, I focused on developing methods for C-C bond formation reactions using sustainable methanol as a greener coupling partner employing borrowing hydrogen methodology.

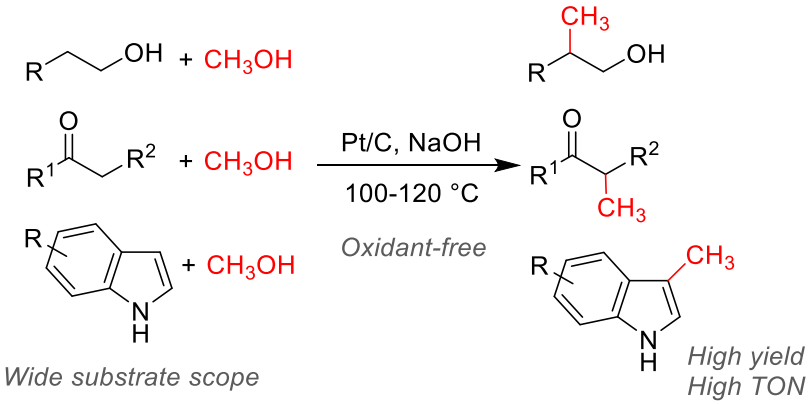
Out of many alcohols used as alkylating reagents, methanol is of particular interest owing to its great potential as a sustainable resource.[52] Methanol is currently obtained from natural gas, coal, and biomass. However, in the near future, methanol from CO_2 and sustainable H_2 will provide a sustainable C1 feedstock for a "methanol economy", in which methanol will serve as the source material for a wide range of chemical intermediates and products.[49,53–55] For many decades, great efforts have been devoted to the synthesis of H_2, other fuels, and

bulk chemicals from methanol.[56] However, selective organic transformations of methanol into fine chemicals remain in their early stages, mostly due to the fact that the reactivity of methanol is relatively low compared to that of other conventional methylation reagents such as methyl iodide, dimethyl sulfone, diazomethane, and formaldehyde, which are all considered genotoxic impurities in pharmaceutical manufacturing.[57] In addition, the use of methanol as a synthetic building block requires its selective activation for further transformation. This is particularly difficult for heterogeneous catalysts and, therefore, only very few methylation reactions employing methanol for synthetic applications have been reported so far (**Scheme 3**).[5,16,24,58–62]



Scheme 3. Previous homogenous methods for C-methylation using methanol.

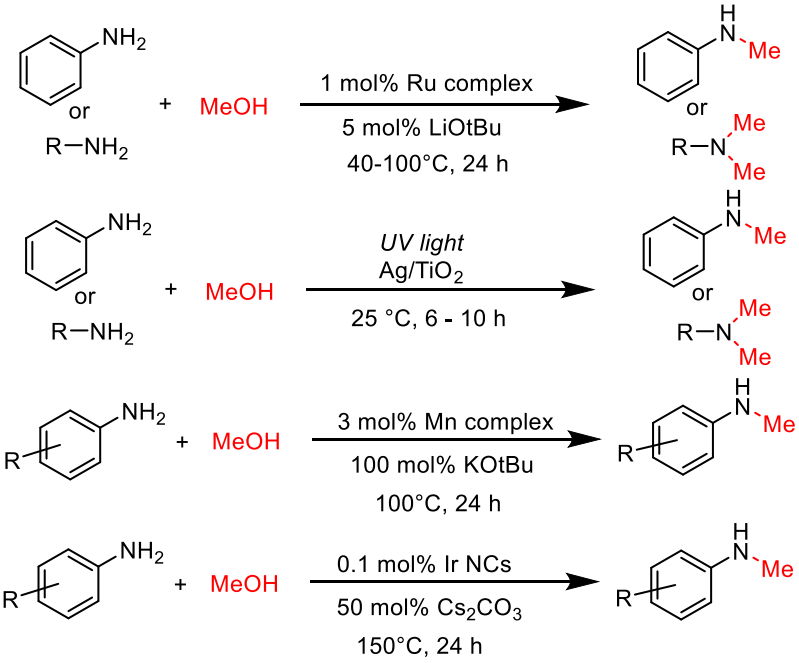
Like the above, I have developed three types of heterogeneous C-methylation reactions using methanol as the methylating agent: (1) the *β*-methylation of alcohols, (2) the *α*-methylation of ketones, and (3) the *C3*-methylation of indoles. The synthesis is carried out using Pt nanoparticles loaded on carbon (Pt/C) in the presence of NaOH (**Scheme 4**). This is a highly versatile catalytic methylation system that proceeds via a borrowing-hydrogen mechanism. In addition to the development of this catalytic system, the rationalization of the catalytic properties based on density functional theory (DFT) calculations has also been described in the Chapter 2 of this thesis.



Scheme 4. Heterogenous C-methylation of alcohols, ketones and indoles with methanol by Pt/C catalyst.

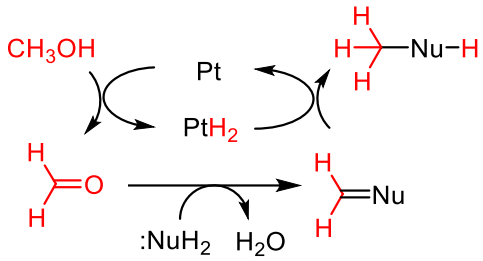
N-methylation: formation of C-N bonds

Amines are important compounds for the chemical industry as intermediate products in the preparation of dyes, polymers, as well as for the synthesis of new pharmaceuticals, food additives, etc.[63] The amine-type functionality is also included in compounds with biological or pharmacological activity (e.g., nucleotides, amino acids, alkaloids, etc.). Many world leading pharmaceutical drugs (e.g. olanzapine, oxycodone, imatinib, viagra and venlafaxine) contain amine functionality more specifically N-methyl moiety as presented in **Figure 5**.[49,64]



Scheme 5. Previous *N*-methylation methods using homogeneous, photocatalytic and heterogenous catalysis.

Towards this direction, I targeted to develop methods for inserting methyl moiety onto the amine functionality in different degrees which have application in the industrial production of fine chemicals including surfactants, polymers, dyes, pharmaceuticals, agrochemicals and pesticides.[65] In industries the reductive amination of toxic formaldehyde still constitutes a major approach in both homogeneous and heterogeneous systems.[66] As a greener alternative method, I have developed catalytic *N*-methylation of amines with methanol as a robust heterogeneous system in comparison to the previously reported methods (**Scheme 5**).[23–25,67]

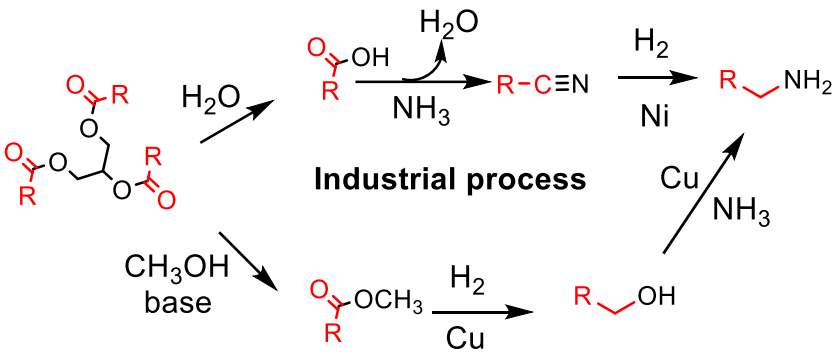


Scheme 6. Hydrogen-borrowing type methylation using methanol as methylating agent.

The developed catalytic system, Pt/C with base, driven by borrowing hydrogen mechanism (**Scheme 6**) was demonstrated for selective *N*,*N*-dimethylation of aliphatic amines and *N*-monomethylation of anilines under N_2 atmosphere. While an unprecedented method for the selective *N*-monomethylation of aliphatic primary amines under the same catalytic system was developed using pressurized H_2.[68] Moreover, the one-pot synthesis of *N*-methylanilines from nitroarenes and methanol was carried out under H_2 atmosphere.[25] Kinetic and computational studies were conducted to discuss the catalytic pathway and the factors controlling the catalytic activity of transition-metal nanoparticles for the *N*-methylation of amines by methanol.

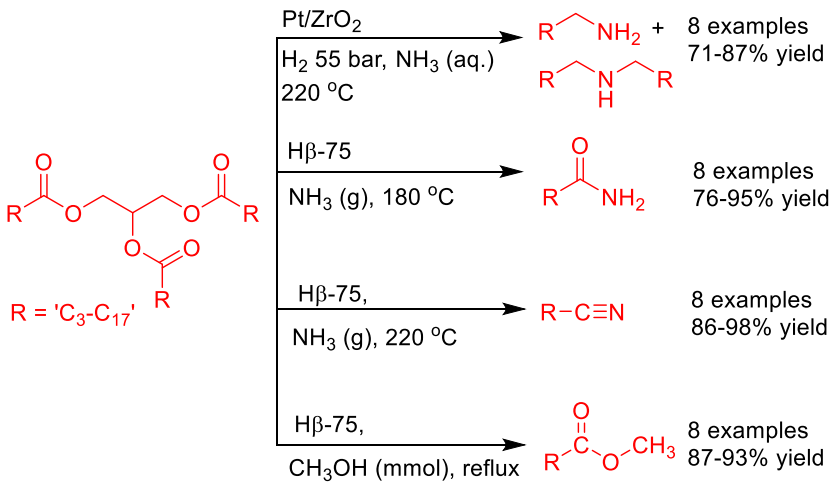
1.4.2 Triglycerides to amines, amides, nitriles and fatty ester

In general, benign manufacturing processes for the direct transformation of triglycerides into fatty amines, amides, nitriles, and fatty methyl ester are relatively rare.[69] Most of the methods in practice suffer from serious drawbacks, which include harsh reaction conditions for example high temperature (200-400 °C) and high pressure (50-400 bar H_2) and requirement of sub-stoichiometric amounts of catalysts (**Scheme 7**).[70–73] Some other catalytic methods for triglyceride conversion are reported in homogeneous fashion which also involve several steps.[73] Overall, these energy extensive processes compel the industries to pay high production costs even though some methods use renewable biomass resources.



Scheme 7. Energy extensive multistep industrial process for triglyceride conversion in the temperature range between 200-400 °C and a H_2 pressure of 50-400 bar.[74–76]

In this section, I have reported four types of selective heterogeneous catalytic methods for the direct transformation of triglycerides into amines, amides, nitriles and fatty acid methyl esters (FAMEs) as shown in (**Scheme 8**). First, I have shown the direct synthesis of amines from triglycerides and aqueous NH_3 under H_2 using a Pt-loaded ZrO_2 (Pt/ZrO_2) catalyst. Then, the direct conversion of triglycerides with gaseous NH_3 in to the corresponding amides or nitriles using a commercially available H-beta zeolite (Hβ) catalyst are demonstrated. With the same H-beta zeolite (Hβ) catalyst, fatty acid methyl esters (FAMEs) have been synthesized using methanol as the coupling partner. Which means the developed methods are robust heterogenous catalyst systems since the same catalyst works for several transformation simply by tuning the reaction conditions or the coupling partners.



Scheme 8. Catalytic conversion of triglycerides to fatty amines, amides, nitriles and FAMEs.

1.5 Conclusion

In the first part of this thesis, I reported highly selective methylation reactions of various substrates including alcohols, ketones, indoles, amines and nitroarenes by supported solid Pt/C catalyst. All these methods are versatile and tunable to the synthesis of controlled *C*- and *N*-methylated products in both aliphatic and aromatic series. While the previous methods are restricted to either aliphatic or aromatic substrates and degree of methylation is not controllable. Certainly, this is a new dimension in methylation reactions using sustainable methanol to avoid the highly toxic conventional methylating agents. Mechanistic studies suggested that the reaction proceeded via a borrowing hydrogen methodology. Kinetic results combined with density functional theory (DFT) calculations revealed that the high performance of Pt/C is credited to the moderate metal–hydrogen bond strength of Pt. The final part of the thesis presented four types of direct process for conversion of triglycerides selectively to amines, amides, nitriles and fatty acid methyl esters (FAMEs) by heterogeneous catalysts. The survival acidity and hydrophobicity of the catalysts are two important parameters for the effective catalytic activity in these reactions. These methods show the effective uses of low-cost biomass resources and one pot transformation selectively to valuable products which are widely used in the industries. All the developed catalysts are reusable, and methods gave high yields and high TONs than the previously reported methods in gram scale synthesis applicable to range of substrates. Thus, industrialization of the above methylation as well as triglyceride conversion methods have potential to replace the less effective and energy extensive conventional methods for the synthesis of valuable chemicals targeted in my research.

1.6 Outline of the thesis

This thesis endeavors to developing heterogeneous methods for sustainable synthesis of chemicals from biomass raw materials. Two major areas are 1) methylation protocols using methanol, and 2) transformation of triglycerides to valuable chemicals where new catalytic methods are developed. The detailed discussions of the methods are presented in four main chapters followed by a general conclusion at the end.

Chapter 2 presents a highly versatile, selective, and recyclable heterogeneous catalytic processes for three types of *C*-methylation reactions using methanol as a sustainable C1 source on the beta-methylation of primary alcohols, the alpha-methylation of ketones, and the C3-methylation of indoles. These catalytic systems are driven by a borrowing-hydrogen mechanism, wherein the Pt-nanoparticles-catalyzed dehydrogenation of methanol (and

alcohols) to aldehydes is followed by a condensation of formaldehyde with the corresponding nucleophile (aldehyde, ketone, or indole) to yield unsaturated intermediates, which are subsequently hydrogenated by Pt-H species on the catalyst. Compared to previous catalytic methods for borrowing-hydrogen-type *C*-methylation reactions, this method presents several advantages: (1) easy catalyst/product separation, (2) catalyst recyclability, (3) excellent TONs (up to two orders of magnitude higher than those previously reported), and (4) wide substrate scope. Furthermore, DFT calculations have shown that the adsorption energy of hydrogen correlates well with the catalytic activity of various active metals employed in these reactions. These results should be helpful to rationalize the properties of catalytic systems and serve as a practical guide for future catalyst design.

Chapter 3 demonstrates a general heterogeneous catalytic method for the selective N-methylation of amines and nitroarenes with methanol using Pt/C and base (NaOH or KO*t*Bu). The presented catalyst system is exclusively effective for four types of *N*-methylation reactions: dimethylation of aliphatic amines, monomethylation of aliphatic and aromatic amines, and monomethylation of nitroarenes on tuning the reaction conditions such as temperature and reaction atmosphere. Compared to the previously reported methods with homogeneous and heterogeneous catalysts, all these reactions under the same catalytic system showed high yields of the corresponding methylamines for a wide range of substrates, high turnover number (TON), and good catalyst reusability. Mechanistic studies suggested that the reaction proceeded via a borrowing hydrogen methodology. Kinetic results combined with density functional theory (DFT) calculations revealed that the high performance of Pt/C was ascribed to the moderate metal–hydrogen bond strength of Pt.

Chapter 4 describes three heterogeneous catalytic methods for the selective one-pot transformation of triglycerides to value-added chemicals: (i) a reductive amination of triglycerides into fatty amines with aqueous ammonia under hydrogen using Pt metal nanoparticles-loaded zirconia, (ii) an amidation of triglycerides with gaseous ammonia using a high-silica Hbeta zeolite, and (iii) a direct synthesis of nitriles from triglycerides and gaseous ammonia using a high-silica Hbeta zeolite at higher temperature. These methods selectively transform a wide variety of triglycerides (C4-C18) into the corresponding amines, amides, and nitriles, and thus represent a milestone in chemical transformation of triglycerides. In case of (i) the reductive amination of TG to amine highly dispersed Pt/ZrO_2 was effective catalyst where the zirconia support is important probably due to the intrinsic nature and active Lewis acidity of ZrO_2 in the reaction condition. A systematic analysis of reaction (ii) and (iii) reveals

that the acidity and hydrophobicity of the zeolites are two important factors that affect the catalytic activity of the Hbeta catalysts. Specifically, increasing the number of acid sites and increasing the hydrophobicity may lead to higher reaction rates per weight of the catalyst. Hydrophobicity and acidity of different zeolites were studied by various characterization methods, including NH_3-TPD, adsorption experiments in water, and IR spectroscopy.

Chapter 5 shows a simple method for the transesterification of triglycerides with methanol to fatty methyl esters using Hbeta-75 with Si/Al = 75 as an efficient and reusable catalyst. The developed catalytic system is applicable to the transformation of various triglycerides having C4-C18 frames. Considering the commercial availability and high durability of the Hbeta-75 catalyst, the method could be applicable to a practical process for the conversion of biomass-derived triglycerides into biofuel. The number of Brønsted acid sites and hydrophobicity are two dominant factors that influence the catalytic activity of the presented catalytic system. Quantitative relationships between acidity, hydrophobicity, and reaction rates versus Si/Al ratio of Hbeta zeolite catalysts show that a low affinity to glycerol, which arises from the hydrophobicity of the high-silica zeolites, is an important parameter for controlling the catalytic activity.

Chapter 6 is the general conclusion that summarizes the highlights of this thesis. To reiterate, the key points in two major areas of development i.e. methods in 1) *C*- and *N*-methylation using methanol by Pt/C catalyst, and 2) transformation of triglyceride to valuable chemicals are summarized. All the described methods are highly selective heterogenous systems with reusable catalysts having wide substrate scope and excellent TONs. The catalyst Pt/C and Pt/ZrO_2 were prepared in the laboratory by simple thermal impregnation method and characterized by using the advanced analytical techniques such as EXAFS, XPS, TEM, ABF- and HAADF-STEM and EDX etc. Mechanistic studies suggested that the catalytic methylation systems are driven by borrowing hydrogen methodology. Kinetic results combined with density functional theory (DFT) calculations revealed that the high performance of Pt/C was attributed to the moderate metal–hydrogen bond strength of Pt. In case of the reductive amination of TG to amine by Pt/ZrO_2, the presence of zirconia support is important probably due to the intrinsic nature and reactive acidic properties of ZrO_2 in the reaction condition. While the H-beta (Hβ) zeolite was commercially available and an in-depth insight of the catalytic behavior suggests that the number of Brønsted acid sites and hydrophobicity are dominant factors that influence the catalytic activity of the presented Hbeta zeolite catalyst systems for triglycerides conversions.

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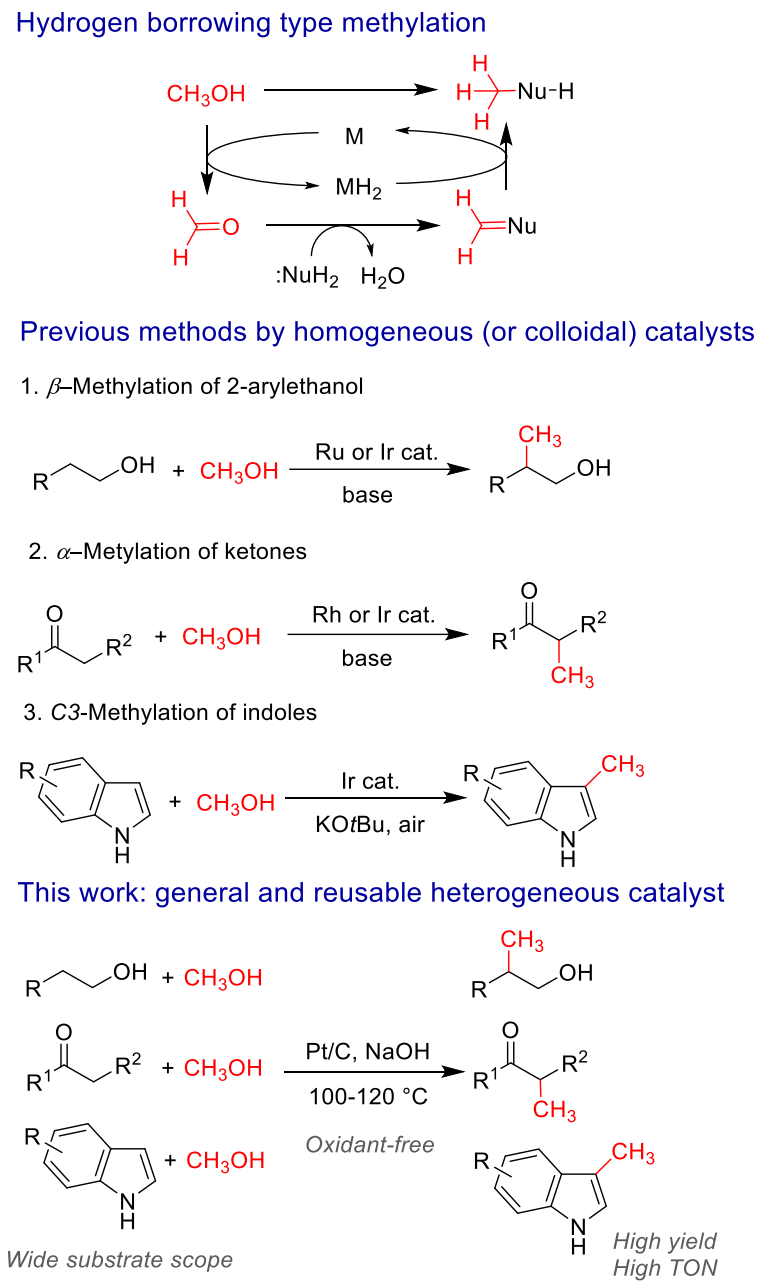
Chapter Two

C-Methylation of Alcohols, Ketones, and Indoles with Methanol Using Heterogeneous Platinum Catalysts

2.1 Introduction

C–C bond formation reactions are of great interest and importance in organic chemistry. Much effort has been devoted especially to the development of atom-efficient and environmentally friendly processes owing to their economic importance and significance in the industrial and academic context.[1–4] Nevertheless, many processes still rely on conventional methods that involve cation–anion-based nucleophilic substitution reactions between organometallic reagents and organohalides.[5,6] Although these conventional systems are very important, the inevitable workup procedures, which include hazardous quenching steps, filtrations, and repeated extractions, as well as the concomitant formation of undesirable waste, are problematic, especially on an industrial scale. Another shortcoming of these systems is the use of organometallic agents as homogeneous catalysts. The organometallic agents are often air- and moisture-sensitive, and can thus be difficult to handle.[7] From the viewpoint of green and sustainable chemistry, it is highly desirable to develop new processes that do not rely on these toxic and hazardous materials, with the aim to eventually realize ideal yet practical processes.[8]

Toward this aim, borrowing-hydrogen reactions have attracted much attention in recent years.[9–17] These reactions enable the catalytic formation of not only C–C bonds but also of many other types of linkages, including C–N bonds, using alcohols as the alkylating reagents, and are thus regarded as an atom-economical manufacturing approach for bulk and fine chemicals.[18–24] Among the variety of alcohols used as alkylating reagents, methanol is of particular interest owing to its great potential as a sustainable resource.[25] Methanol is currently obtained from natural gas, coal, and biomass. However, in the near future, methanol from CO_2 and sustainable H_2 will provide a sustainable C1 feedstock for a "methanol economy", in which methanol will serve as the source material for a wide range of chemical intermediates and products.[26–29] It is therefore hardly surprising that great efforts have been devoted to the synthesis of H_2, other fuels, and bulk chemicals from methanol.[30] However, selective organic transformations of methanol into fine chemicals remain in their infancy, mostly due to the fact that the reactivity of methanol is relatively low compared to that of other conventional methylation reagents such as methyl iodide, dimethyl sulfone, diazomethane, and formaldehyde, which are all considered genotoxic impurities in pharmaceutical manufacturing.[31] In addition, the use of methanol as a synthetic building block requires its selective activation for further transformation. This is particularly difficult for heterogeneous catalysts and, therefore, only very few methylation reactions employing methanol for synthetic applications have been reported so far.



Scheme 1. *C*-methylation reactions employing methanol as the methylating agent. The three types of *C*-methylation reactions are successfully realized by a Pt-nanoparticles-loaded carbon catalyst (Pt/C).

Recently, substantial progress has been made in borrowing-hydrogen-type catalytic methylation reactions using homogeneous transition-metal catalysts.[27,32,41–45,33–40] Borrowing-hydrogen-type *C*-methylation methods are classified into the following three reaction types: (1) the *β*-methylation of alcohols,[32–34] (2) the *α*-methylation of ketones,[35–40] and (3) the methylation of phenols[41,42] and heterocycles,[43–45] which includes the *C3*-methylation of indoles. Methylation methods typically employ homogeneous (or colloidal) Ru, Ir, or Rh catalysts, although all of these suffer from low turnover numbers (TONs) and difficulties associated with the catalyst/product separation and the recycling of the catalyst. Another drawback of these methods is their limited synthetic scope. Most methods are applicable only to activated (aromatic) substrates, and a single catalyst that is generally applicable to all the aforementioned *C*-methylation reactions has not yet been reported.

Herein, we report a heterogeneous catalytic system for the three *C*-methylation processes mentioned above, employing methanol as the methylating agent (**Scheme 1**). The synthesis is carried out using Pt nanoparticles loaded on carbon (Pt/C) in the presence of NaOH. This is a highly versatile catalytic methylation system that proceeds via a borrowing-hydrogen mechanism. In addition to the development of this catalytic system, we describe the rationalization of the catalytic properties based on density functional theory (DFT) calculations. The observed catalytic activity of a variety of transition-metal catalysts correlates well with the adsorption energy of hydrogen on different metal surfaces. Our results suggest that the adsorption energy of hydrogen can be effectively used as a simple descriptor for C–C bond formation reactions.

2.2 Experimental Section

2.2.1 General

Commercially available organic and inorganic chemicals (Tokyo Chemical Industry, Wako Pure Chemical Industries, Kishida Chemical, or Mitsuwa Chemicals) were used without further purification. Methanol-d_3 (CD_3OH; 99.8 atom% D) was purchased from Sigma-Aldrich. GC (Shimadzu GC-2014) and GCMS (Shimadzu GCMS-QP2010) analyses were carried out using an Ultra ALLOY capillary column UA^+-1 (Frontier Laboratories Ltd.) with N_2 or He as the carrier gas. ^1H and ^{13}C NMR spectra were recorded at ambient temperature on a JEOL-ECX 600 spectrometer operating at 600.17 and 150.92 MHz, respectively, with tetramethylsilane as the internal standard. HAADF-STEM images were taken on a JEM-ARM200F microscope equipped with a JED-2300 EDX spectrometer (JEOL) at an acceleration voltage of 200 kV.

The Cs-corrector CESCOR (CEOS) was used in the STEM mode. The samples were prepared by dropping ethanol suspensions of the catalysts on carbon-supported copper grids.

2.2.2 Catalyst Preparation

Standard carbon (296 m^2 g^{-1}, Kishida Chemical) and SiO_2 (Q-10, 300 m^2 g^{-1}, Fuji Silysia Chemical Ltd.) supports were obtained commercially. CeO_2 (JRC-CEO3, 81 m^2 g^{-1}), MgO (JRC-MGO-3), TiO_2 (JRC-TIO-4), and H^+-exchanged β zeolite (Hβ, SiO_2/Al_2O_3 = 25±5, JRC-Z-HB25) were supplied by the Catalysis Society of Japan. γ-Al_2O_3 was prepared by calcination of γ-AlOOH (Catapal B Alumina, Sasol) at 900 °C for 3 h. ZrO_2 was prepared by hydrolysis of zirconium oxynitrate 2-hydrate in an aqueous solution of NH_4OH, followed by filtration, washing with distilled water, drying at 100 °C for 12 h, and finally calcination at 500 °C for 3 h. Nb_2O_5 was prepared by calcination of $Nb_2O_5 \cdot nH_2O$ (CBMM) at 500 °C for 3 h. The Pt/C precursor was prepared by the following impregnation method: a mixture of carbon (10 g) and an aqueous HNO_3 solution of $Pt(NH_3)_2(NO_3)_2$ that contained 4.96 wt% of Pt (10.62 g) and 50 mL of ion-exchanged water was added to a round-bottom flask (500 mL). The mixture was then stirred (200 rpm) for 15 min at room temperature. Subsequently, the reaction mixture was evaporated to dryness at 50 °C, followed by drying at 90 °C under ambient pressure for 12 h. Prior to each catalytic experiment, a Pt/C sample with 5 wt% Pt loading was prepared by pre-reduction of the precursor in a Pyrex tube under a H_2 flow (20 cm^3 min^{-1}) at 300 °C for 0.5 h. Other supported Pt catalysts (5 wt% Pt loadings) were prepared by the same method. M/C (M = Rh, Ir, Ru, Pd, Re, Cu, Ni) catalysts with 5 wt% metal loadings were prepared in a similar manner using aqueous HNO_3 solutions of $Rh(NO_3)_3$ or $Pd(NH_3)_2(NO_3)_2$, or aqueous solutions of metal nitrates (for Ni, Cu), $IrCl_3 \cdot nH_2O$, $RuCl_3$, or NH_4ReO_4.

2.2.3 Typical Procedure for the Catalytic Reactions

Pt/C (39 mg; 1 mol% Pt with respect to 1 mmol of substrate) reduced at 300 °C was used as the standard catalyst.[46,47] After the reduction, the catalyst was placed in a closed glass tube sealed with a septum inlet and cooled to room temperature under H_2. Methanol (10 or 20 mmol) was injected through the septum inlet into the glass tube containing the pre-reduced catalyst. Next, the septum was removed under air, and 1 mmol of the substrate (alcohol, ketone, or indol), NaOH (0.1 or 1.5 mmol), *n*-dodecane (0.25 mmol), and a magnetic stirring bar were added to the tube, which was then introduced in a stainless steel autoclave (28 cm^3). After sealing, the autoclave was charged with 1 bar N_2 and heated at 100 or 120 °C under stirring (500 rpm). After the reaction, the reactor was cooled to room temperature, before the catalyst was removed

by filtration. For the optimization studies (**Tables 1** and **2**) and the kinetic experiments, the conversions and yields of the products were determined by GC using *n*-dodecane as the internal standard, while the GC-sensitivity was estimated from commercial compounds or the isolated products. For the substrate scope studies, the products were isolated by column chromatography on silica gel 60 (spherical, 40–100 μm, Kanto Chemical Co. Ltd.) using hexane/ethyl acetate (9:1, v/v) as the eluent, and the yields of the isolated products were determined. The products were identified by ^{1}H and ^{13}C NMR spectroscopy in combination with GCMS, whereby the mass spectrometer was equipped with the same column as that used for the GC analyses.

For the recycling experiments, after each catalytic cycle, 2-propanol (3 mL) was added to the mixture. The catalyst was separated by centrifugation and washed with water (3 mL) and acetone (6 mL). The catalyst was then dried at 100 °C for 3 h and reduced at 300 °C for 0.5 h under an atmosphere of H_2. Subsequently, the reactor was charged with a mixture of the substrate and NaOH and the recovered Pt/C catalyst. It should be noted that the initial formation rates for reactions with yields below 30% were obtained on the basis of the product yield after a reaction time of 2 h for *β*-methylation of 2-phenylethanol and 1 h for methylation *α*-methylation of propiophenone and *C3*-methylation of indole.

2.2.4 Computational Methods

All calculations were performed with the Vienna *ab-initio* simulation package (VASP)[48,49] using projector-augmented wave potentials[50] and the Perdew–Burke–Ernzerhof (PBE) functional.[51] The dispersion-corrected DFT-D2 method was employed to account for van der Waals interactions.[52] The lattice constants of the bulk structures were calculated with an energy cut-off of 400 eV and a 15 × 15 × 15 k-point mesh and used in all subsequent calculations. The Ni(111), Cu(111), Rh(111), Pd(111), Ir(111), Pt(111), Ru(0001), and Re(0001) surfaces were modeled by a supercell slab consisting of a 3 × 3 surface unit cell with four atomic layers. It should be noted that the most stable and common planes were used for each metal. The (111) surface (Ni, Cu, Rh, Pd, Ir, and Pt) presents a face-centered-cubic (fcc) structure, while the (0001) surface (Ru and Re) has a hexagonal-close-packed (hcp) structure. The slab was separated in the vertical direction by a vacuum void (height: 15 Å). An energy cut-off of 400 eV and a 5 × 5 × 1 point mesh were used for the slab model calculations. The energy of the isolated H atom was obtained using the same parameters as those in the free-surface slab calculations. The geometry-convergence criterion was set at $F_{max} < 0.03$ eV Å^{-1}, where F_{max} is the maximum force acting on a mobile atom. Spin-polarized calculations were

carried out for all systems. The adsorption energy (E_{ads}) was calculated as the difference in energy between the molecule absorbed on the surface ($E_{molecule/surface}$), the individual adsorbate molecule ($E_{molecule}$), and the surface ($E_{surface}$) according to:

$$E_{ads} = E_{molecule/surface} - E_{molecule} + E_{surface} \quad (6)$$

The location of the adsorption sites on the adsorbates was initially determined, which showed that the most stable adsorption sites for hydrogen are the 3-fold hollow sites (**Fig. S1**; fcc sites for the fcc metals). The adsorption energies employed in this study were calculated for the structures where hydrogen was more strongly adsorbed.

2.3 Results and discussion

2.3.1 Catalyst Characterization

A carbon-supported Pt nanoparticles catalyst (Pt/C) was obtained from a facile impregnation method, followed by H_2 reduction at 300 °C, according to a previous study using the same Pt/C catalyst.[46] **Figure 1** shows the annular bright field scanning transmission electron microscopy (ABF-STEM) image and high-angle annular dark-field STEM (HAADF-STEM) images of the Pt/C catalyst together with the corresponding energy-dispersive X-ray spectrometry (EDX) elemental mapping. The Pt nanoparticles are highly dispersed over the entire carbon support. The additional characterization data for Pt/C, e.g., temperature-programmed H_2-reduction (H_2-TPR) and X-ray absorption fine structure (XAFS) analyses, which have been provided in our previous study, confirmed that the deposited Pt nanoparticles are in the metallic state.[46]

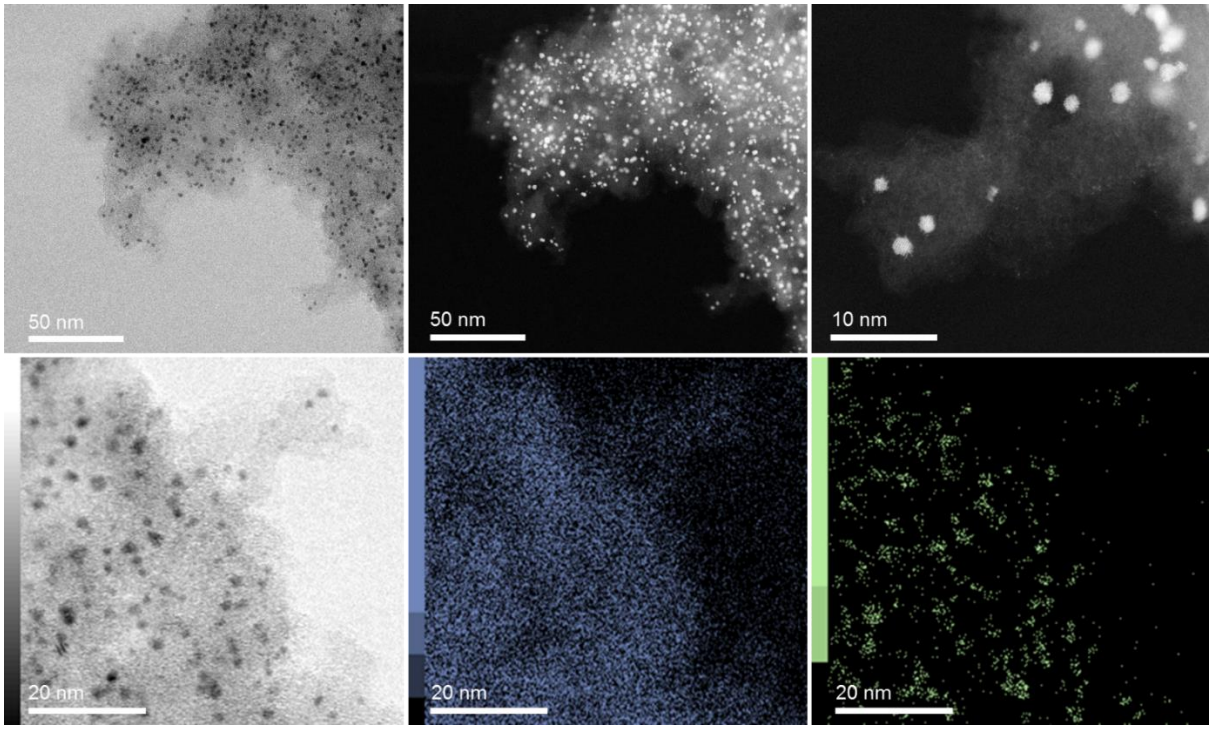
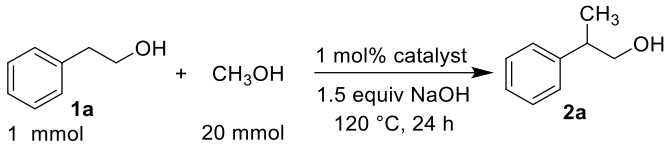


Figure 1. ABF- and HAADF-STEM images and EDX mapping for Pt/C.

2.3.2 *β*-Methylation of Alcohols

The *β*-methylation of 2-phenylethanol (**1a**) was selected as the benchmark reaction for the *β*-methylation of alcohols with different heterogeneous catalysts. A catalyst screening was carried out for the reaction of **1a** (1 mmol) and methanol (20 mmol) with NaOH (1.5 mmol) at 120 °C for 24 h. It should be noted that the reaction was carried out in a glass reactor that was inserted in a stainless steel autoclave, in which the reactor was heated to temperatures beyond the boiling point of methanol. Initially, we tested a series of Pt-loaded (5 wt%) heterogeneous catalysts (39 mg in total; 1 mol% Pt with respect to **1a**). **Table 1** lists the yields obtained for 2-phenyl-1-propanol (**2a**) as the desired product. The reaction did not occur in the absence of a transition-metal catalyst (entry 1), and carbon-supported platinum oxide (PtO_x/C) afforded **2a** in merely 2% yield (entry 2). The results show that the combination of a base (NaOH) and platinum oxide does not catalyze the reaction. In contrast, carbon loaded with metallic Pt nanoparticles (Pt/C, entry 3) afforded **2a** in 91% yield. Exposure of the as-reduced Pt/C catalyst to air at room temperature for 0.5 h resulted in a lower yield of **2a** (42%, entry 4), most likely due to air-oxidation of the superficial Pt^0 sites, i.e., the active sites of Pt/C. Thus, metal-loaded catalysts reduced under H_2 at 300 °C were used for the subsequent reactions in the absence of air (entries 5–19). Pt-metal particles supported on different metal oxides (entries 5–12)

Table 1. Catalyst screening for the *β*-methylation of 2-phenylethanol (**1a**)



Entry	Catalyst	Yield (%)[a]
1	None	0
2	PtO_X/C	2
3	Pt/C	91
4	Pt/C-air	42
5	Pt/Al_2O_3	14
6	Pt/CeO_2	32
7	Pt/MgO	11
8	Pt/ZrO_2	12
9	Pt/Nb_2O_5	9
10	Pt/TiO_2	8
11	Pt/SiO_2	7
12	Pt/Hβ	13
13	Rh/C	28
14	Ir/C	31
15	Ru/C	13
16	Pd/C	10
17	Re/C	8
18	Cu/C	2
19	Ni/C	11

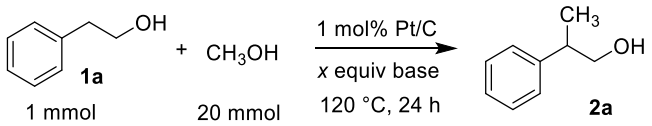
[a] GC yield.

generated lower yields of **2a** (7–32%) than Pt/C. Subsequently, we compared the activity of various transition metal nanoparticles on the same support (carbon; entries 13–19), whereby the catalytic performance followed the order: Pt > Ir > Rh > Ru > Ni > Pd > Re > Cu. The results in **Table 1** indicate that Pt/C (entry 3) is the most suitable catalyst for the *β*-methylation of **1a** in the presence of 1.5 equiv NaOH. The effect of the Pt loading in the Pt/C catalyst was investigated by employing a Pt/C catalyst with 1 wt% of Pt (**Table S1**). The results show that the Pt/C catalyst with 5 wt% Pt loading exhibited better catalytic performance.

With the best catalyst in hand, we examined further potential optimizations of the reaction conditions (**Table 2**). The reaction did not proceed in the absence of a base (entry 1), which indicates that Pt/C alone does not promote the reaction, and that the addition of a base is essential. The results with different additives (entries 2–11) revealed that the efficacy of the base follows the order NaOH > NaOMe > NaO*t*Bu > KO*t*Bu > KOH > NaOEt > Cs_2CO_3 > Na_2CO_3 > K_2CO_3 > Et_3N. Catalytic runs with different loadings (0.5–2.0 mmol) of NaOH (entries 2, 12–14) confirmed that 1.5 equiv of NaOH afford the highest yield of **2a**. Finally, varying the methanol loading (5–60 mmol, entries 2, 15–18) revealed the optimal amount of methanol (20 mmol).

Under the optimized conditions, we studied the catalytic performance of the Pt/C-catalyzed *β*-methylation of various alcohols with methanol. **Table 3** shows the scope of primary alcohols for the present catalytic *β*-methylation system. For all the substrates except the linear aliphatic alcohols (entries 14 and 15), full conversion of the alcohol was observed. The yields of the isolated *β*-methylation products are listed in **Table 3**. 2-Phenylethanol (entry 1) and its derivatives with electron-donating (entries 2–4) and electron-withdrawing (entry 5) groups at the *para*-position were successfully methylated to give the corresponding *β*-methylated alcohols in good to high isolated yield (76–87%). 2-Naphthalene-1-yl ethanol (entry 6), 3-phenylpropan-1-ol (entry 7), and 3-(4-bromophenyl)propan-1-ol (entry 8) afforded methylated alcohols in good to high yield. Heteroaromatic alcohols with indole-3-propyl (entry 9), pyridinyl (entry 10), and thienyl (entry 11) groups, or with a 2-(benzyloxy)ethan-1-ol moiety (entry 12) were well tolerated and furnished the corresponding *β*-methylated alcohols in high yield (83–95%). Aliphatic primary alcohols (entries 13–15) also underwent this *β*-methylation reaction to afford the corresponding products in good yield (73–85%), thus demonstrating the high versatility of this heterogeneous catalytic system for the *β*-methylation of aliphatic alcohols with methanol.

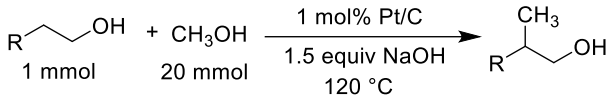
Table 2. Optimization of the reaction conditions for the *β*-methylation of 2-phenylethanol

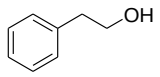
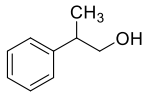
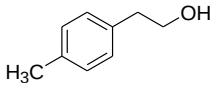
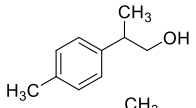
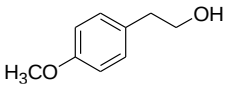
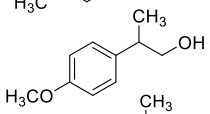
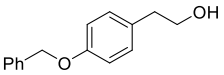
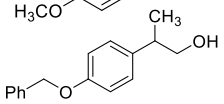
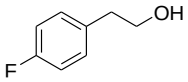
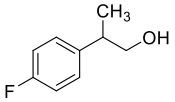
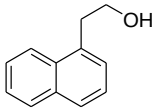
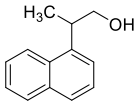
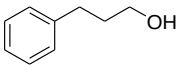
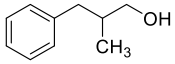
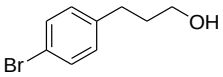
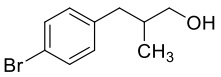
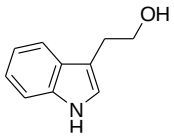
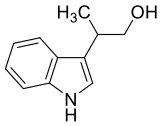
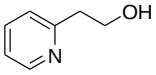
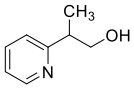
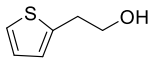
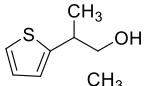
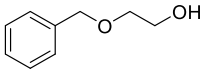
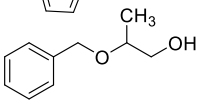
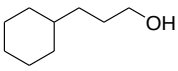
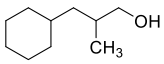
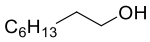
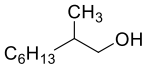
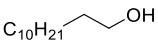
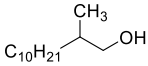


Entry	CH_3OH (mmol)	Base (*x*)	Yield (%)[a]
1	20	None	0
2	20	NaOH (1.5)	91
3	20	KOH (1.5)	54
4	20	Na_2CO_3 (1.5)	17
5	20	K_2CO_3 (1.5)	13
6	20	Cs_2CO_3 (1.5)	34
7	20	NaO*t*Bu (1.5)	64
8	20	KO*t*Bu (1.5)	67
9	20	NaOMe (1.5)	70
10	20	NaOEt (1.5)	49
11	20	Et_3N (1.5)	0
12	20	NaOH (0.5)	28
13	20	NaOH (1.0)	74
14	20	NaOH (2.0)	85
15	5	NaOH (1.5)	74
16	10	NaOH (1.5)	83
17	40	NaOH (1.5)	90
18	60	NaOH (1.5)	52

[a] GC yield.

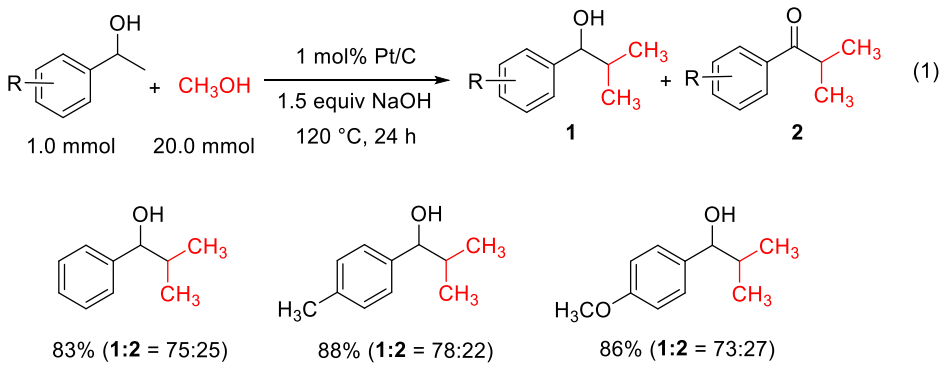
Table 3. Pt/C-catalyzed *β*-methylation of primary alcohols



Entry	Alcohol	Product	*t* (h)	Yield (%)[a]
1			24	87
2			24	78
3			24	81
4			30	78
5			24	76
6			36	88
7			24	92
8			24	73
9			12	95
10			24	83
11			24	88
12			24	86
13			24	85
14			30	77
15			30	73

[a] Isolated yield.

Recently, Obora and co-workers have reported the first example of the *β*-methylation of secondary alcohols with methanol.[33] Equation (1) shows the results for the *β*-methylation of secondary alcohols by our method using 1 mol% of Pt/C catalyst with 1.5 equiv of NaOH at 120 °C for 24 h. 1-Phenylethanol and its derivatives with electron-donating (methyl, methoxy) groups at the *para*-position were converted into bis-methylated products (alcohols and ketones) in 83–88% yield. In the literature, only one homogeneous catalyst [33], i.e., a combination of carbonylchlorohydrido{bis[2(diphenylphosphinomethyl)ethyl]amino}ethyl]amino}Ru(II) (Ru-MACHO) and Shvo's diruthenium complex, and one heterogeneous catalyst,[33] i.e., colloidal Ir nanoclusters, have been reported to catalyze the *β*-methylation of a variety of alcohols with methanol. **Table 4** compares the catalytic performance of our system to that of these previously reported catalysts. While the previous methods are effective only for activated substrates, i.e., aromatic alcohols, our method is effective for aromatic and aliphatic (non-activated) alcohols. As shown in equation (2), a gram-scale reaction of **1a** (5 mmol) with 20 equiv of methanol and 1.5 equiv of NaOH using 0.025 mol% of the Pt/C catalyst for 90 h afforded **2a** in high yield (82%). This value corresponds to a TON of 3280, which is one order of magnitude higher than those of the previous methods for the *β*-methylation of **1a**.[33,34]



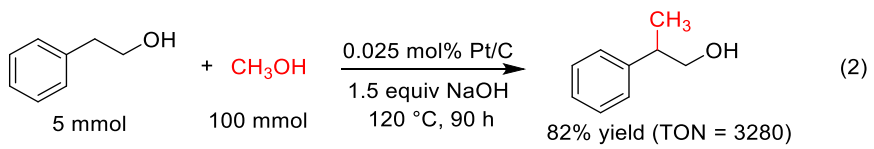


Table 4. β-Methylation of alcohols with methanol using different catalysts

Catalyst	Substrate scope	TON[a]	Catalyst reuse	Ref.
Pt/C	2-Arylethanols 3-Arylpropanols Aliphatic alcohols 1-Phenylethanol	3280	5 runs	This work
Ru complex	2-Arylethanols	435	No	[32]
Ir nanocluster	2-Arylethanols 1-Phenylethanol	356	No	[33]

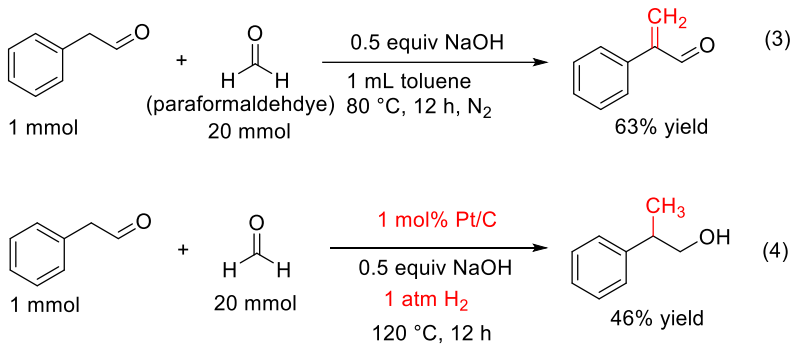
[a] TON per number of total metal atoms in the catalysts for the β-methylation of 2-phenylethanol.

Next, we examined the heterogeneous nature and reusability of the Pt/C catalyst. After a standard reaction (entry 1 in **Table 3**), 2-propanol (3 mL) was added to the mixture and Pt/C was removed by filtration, followed by inductively coupled plasma atomic emission spectrometry (ICP-AES) analysis of the reaction mixture, which showed that the content of Pt in the solution was below the detection limit (10 ppb). After a standard workup and catalyst recovery,[54] the spent catalyst was reused four times, whereby a significant loss of activity was not observed (**Fig. 2**). In addition to the final yield, the initial product formation rates were investigated for each cycle, and the results are shown in **Fig. S2** in the Supporting Information. These results do not show a significant decrease in activity, which confirms the high durability of the catalyst. The necessity of H_2 reduction prior to each recycling test was examined (**Table S2**). The yield for the second run decreased when the catalyst was used without prior H_2 reduction, which indicates that H_2 reduction is indispensable for the recycling the catalyst. These results unequivocally demonstrate that Pt/C is a reusable heterogeneous catalyst for this reaction.

Considering the previously proposed mechanisms for such reactions,[33,34] our β-methylation method may likely follow a borrowing-hydrogen mechanism (**Scheme 2**). To examine this hypothesis, we carried out the following kinetic and mechanistic experiments. **Figure 3** shows the time course of the products (GC analysis) for the Pt/C-catalyzed β-methylation of 2-naphthalene-1-yl ethanol (**1b**). Initially (t < 5 h), 2-(naphthalen-1-yl)acetaldehyde (**4b**) is generated, although its content decreases with time. For 5 h < t < 35 h, the molar fraction of 2-(naphthalen-1-yl)acrylaldehyde (**3b**) initially increases, and then decreases. Finally (t > 35 h), the amount of 2-naphthalene-1-yl propanol (**2b**) reaches its highest

value. This is a time course typical for consecutive reactions. Aldehyde **4b** represents the initial intermediate, which is subsequently transformed into the *α*,*β*-unsaturated aldehyde intermediate **3b**, which serves as the precursor for the hydrogenated product **2b**.

Figure 4 shows the results of the kinetic isotope effect (KIE) analysis for the *β*-methylation reaction of the standard substrate 2-phenylethanol (**1a**). The zero-order rate constant for CH_3OH (k_{CH}), estimated from the initial slope of the plot, is larger than that for CD_3OH (k_{CD}), and a moderate KIE (k_{CH}/k_{CD}) value of 1.8 was obtained. This suggests that the catalytic cycle involves the dissociation of a C–H bond in methanol as a kinetically important step. As shown in eqn (3), the cross-aldol condensation of the dehydrogenated intermediates (formaldehyde and phenylacetaldehyde) was catalyzed by 0.5 equiv of NaOH (in the absence of Pt/C) under N_2 at a relatively low temperature (80 °C). In the presence of Pt/C and NaOH at 120 °C, the reaction of formaldehyde and phenylacetaldehyde under H_2 furnished 2-phenyl-1-propanol (**2a**), the final product for the standard *β*-methylation of 2-phenylethanol (**1a**) with methanol.



Based on these mechanistic results, we conclude that this catalytic system is driven by a borrowing-hydrogen mechanism (**Scheme 2**). Both alcohols, i.e., the starting reagent and methanol are dehydrogenated to give the corresponding aldehydes and four atoms of hydrogen on the catalyst surface. The aldehydes undergo a cross-aldol condensation to generate an *α*,*β*-unsaturated aldehyde intermediate, which is then reduced by the four hydrogen atoms on the Pt surface.

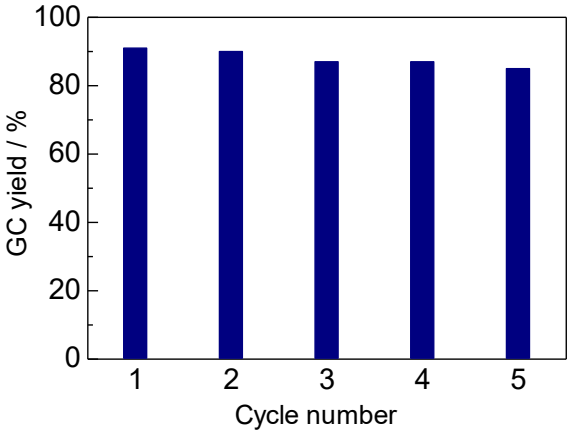


Figure 2. Catalyst recyclability for the *β*-methylation of 2-phenylethanol (**1a**) with methanol and the Pt/C catalyst. The conditions used are those of entry 1 in Table 3.

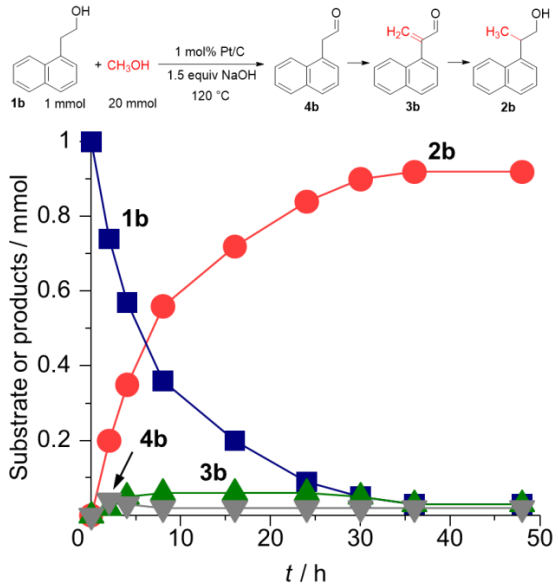
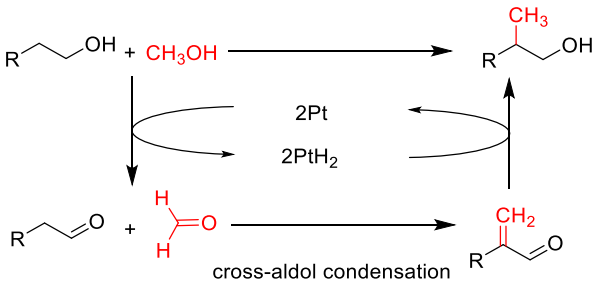


Figure 3. Reaction course for (**1b**) 2-naphthalene-1-yl ethanol, (**2b**) 2-naphthalene-1-yl propanol, (**3b**) 2(naphthalen-1-yl)acrylaldehyde, and (**4b**) 2-(naphthalen-1-yl)acetaldehyde.



Scheme 2. Proposed catalytic cycle for the *β*-methylation of alcohols.

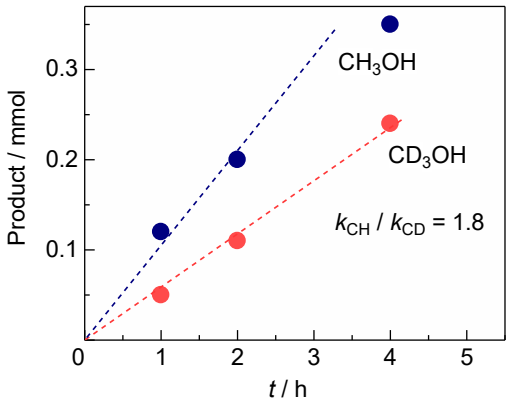


Figure 4. Kinetic isotopic effect analysis for the Pt/C-catalyzed β-methylation of **1b** under the conditions shown in Fig. 3. The KIE (k_{CH}/k_{CD}) value estimated from the zero-order rate constants (the slope of the lines) is shown.

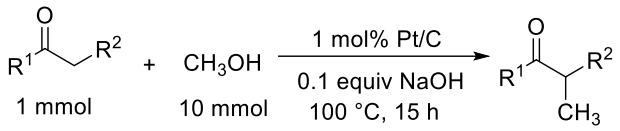
2.3.3 α-Methylation of Ketones

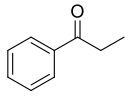
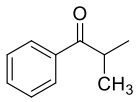
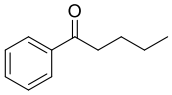
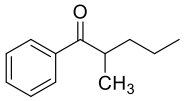
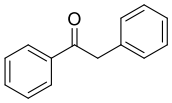
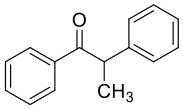
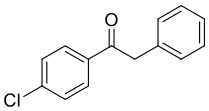
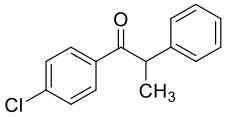
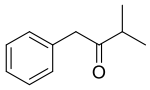
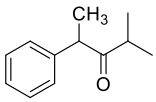
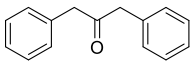
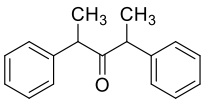
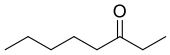
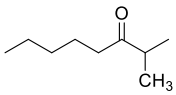
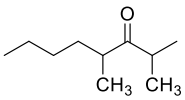
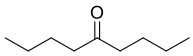
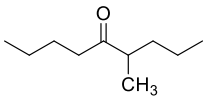
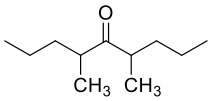
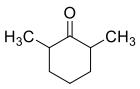
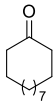
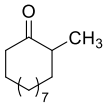
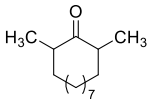
The same catalytic system, i.e., Pt/C and NaOH, is also effective for the α-methylation of ketones with methanol. In the literature, several homogeneous catalysts have been reported to catalyze this reaction, but the known methods suffer from drawbacks, usually associated with scope limitations and/or low TONs.[35–40] Here, we present a reusable catalyst with wide scope and high TONs. Initially, we carried out the optimization of the catalyst and reaction conditions for the α-methylation of propiophenone. Based on the results (not shown), we adopted the following optimized reaction conditions: ketone (1 mmol), methanol (10 mmol), 1 mol% of Pt/C, 10 mol% NaOH, 100 °C, and 15 h. **Table 5** summarizes the general applicability of the present system for the α-methylation of aromatic ketones. The examined aromatic and aliphatic ketones are mainly mono-methylated at the α-position. Propiophenone (entry 1), butyrophenone (entry 2), benzyl phenyl ketones (entries 3 and 4), other benzyl ketones (entries 5 and 6), and linear and cyclic aliphatic ketones (entries 7–10) can be converted into the corresponding α-methylation products in good to high yield (73–94%). Note that doubly methylated compounds were observed as minor products for entries 7, 8, and 10. **Figure 5** shows the results for the catalyst recyclability in the α-methylation of propiophenone under the standard conditions shown in **Table 5** (entry 1). Using the standard method for the catalyst separation and regeneration [54], the Pt/C catalyst was reused four times, demonstrating that Pt/C is a robust heterogeneous catalyst for this reaction. The examination of the initial product formation rates for each cycle confirms the high durability of the catalyst (**Figure S3**).

Table 6 lists the results for the α-methylation of methyl ketones and aliphatic ketones with methanol. Acetophenone (entry 1) and its derivatives with electron-donating (entries 2 and 3) and electron-withdrawing (entry 4) groups were selectively bis-methylated, while mono-

methylated products were not observed by GC analysis. Aliphatic ketones (entries 5 and 6), including linear and branched ketones, were predominantly mono-methylated at the terminal position, albeit that minor amounts of 1,3-dimethylated (14% and 18%) and 1,1,3-trimethylated (8% and 7%) products were also obtained.

Table 5. Pt/C-catalyzed *α*-methylation of aromatic and aliphatic ketones.



Entry	Ketone	Methylated product(s)	Yield (%)[a]
1			90
2			88
3			94
4			85
5			89
6			87
7		 	73[b], 19[b]
8		 	74[b], 16[b]
9			88[b]
10		 	93, 3[b]

[a] Isolated yield, [b] GC yield.

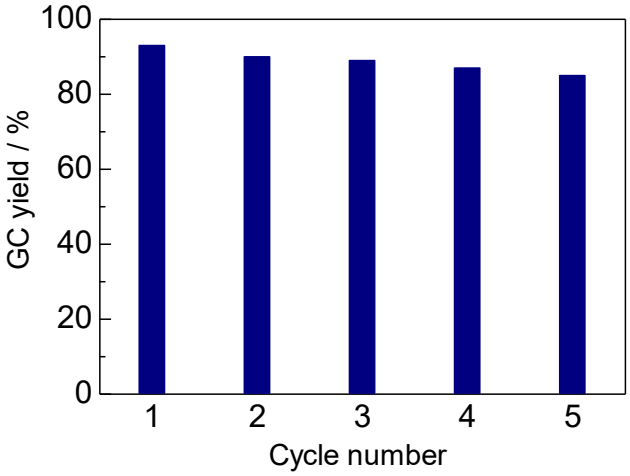
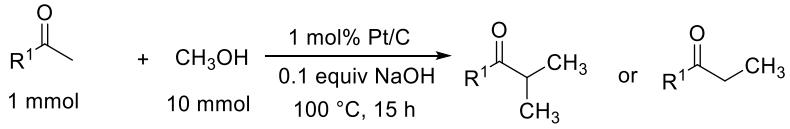
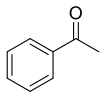
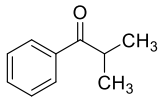
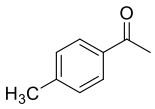
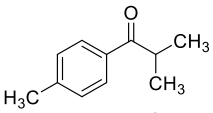
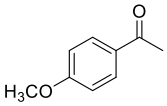
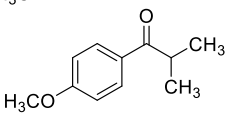
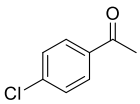
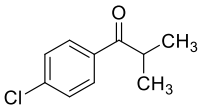
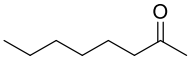
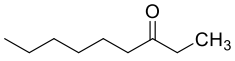
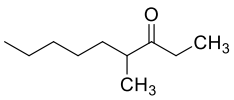
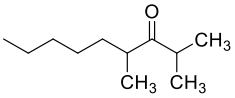
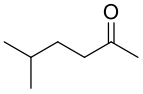
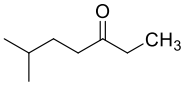
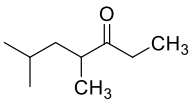
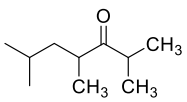


Figure 5. Catalyst recyclability for the α-methylation of propiophenone with methanol and the Pt/C catalyst. The conditions used are those described in Table 5 (entry 1).

Table 6. Pt/C-catalyzed α-methylation of methyl ketones and aliphatic ketones.

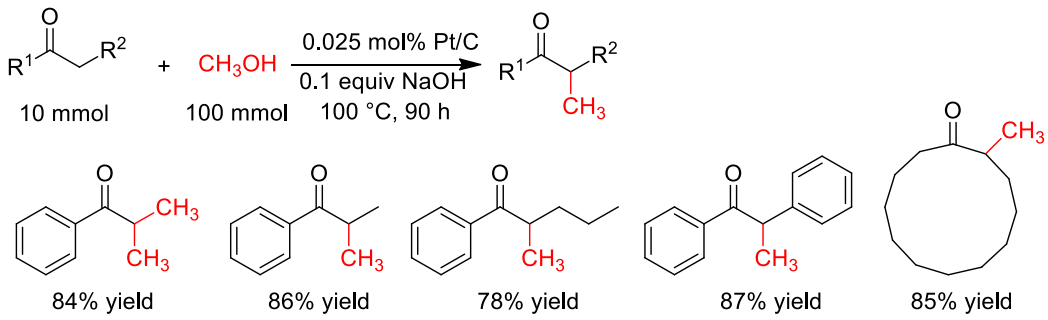


Entry	Ketone	Methylated product(s)	Yield (%)[a]
1			91
2			93
3			88
4			79
5		  	76[b], 14[b], 8[b]
6		  	71[b], 18[b], 7[b]

[a] Isolated yield, [b] GC yield.

The method was also successfully applied to the gram-scale methylation of several ketones. **Scheme 3** summarizes the isolated yields of the products for the α-methylation of 10 mmol of

various ketones for 90 h using only 0.025 mol% of the Pt/C catalyst. Acetophenone was transformed into isobutyrophenone in 84% yield. A variety of aromatic and aliphatic ketones were converted into the corresponding mono-methylated products in 78–86% yield. The TON values for these reactions were >3000. Several homogeneous catalysts, such as $[Cp^*RhCl_2]_2$, $[Cp^*RuCl_2]_2$, and $[Cp^*IrCl_2]_2$ catalyze the α-methylation of ketones with methanol.[35–40] **Table 7** compares the performance of our method to that of the representative catalysts $[Cp^*RhCl_2]_2$ and $[Cp^*IrCl_2]_2$ in the α-methylation of ketones. Again, these homogeneous catalytic systems are only effective for activated (aromatic) ketones, while our method is effective for aromatic and aliphatic (non-activated) ketones. In the α-methylation of 2-propiophenone, the TON of the Pt/C catalyst (3440) is two orders of magnitude higher than those of the previous methods for the same reaction.[38,39] Based on the mechanistic results for the β-methylation of alcohols, a reasonable catalytic cycle for this reaction is proposed in **Scheme 4**. Methanol is dehydrogenated to give formaldehyde and two atoms of hydrogen on the catalyst surface. Formaldehyde and the ketone substrate then undergo a cross-aldol condensation reaction to give an α,β-unsaturated intermediate, which is finally reduced by the two hydrogen atoms on the Pt surface.

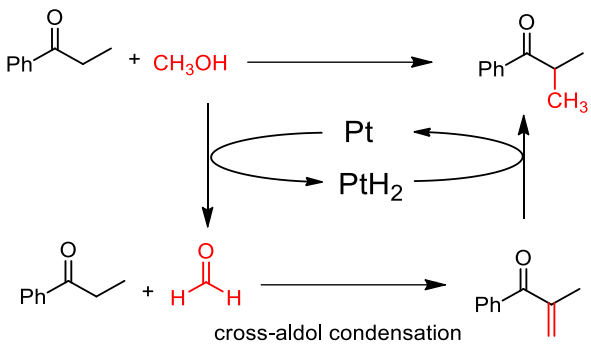


Scheme 3. Gram-scale α-methylation of ketones.

Table 7. α-Methylation of ketones with methanol using different catalysts

Catalyst	Additives	TON [a]	Catalyst reuse	Ref.
Pt/C	0.1 equiv NaOH	3440	5 runs	This work
Rh complex	5 equiv Cs_2CO_3, O_2	15	No	[35]
Ir complex	4 equiv Cs_2CO_3	95	No	[39]

[a] TON per number of total metal atoms in the catalysts for the α-methylation of 2-propiophenone.



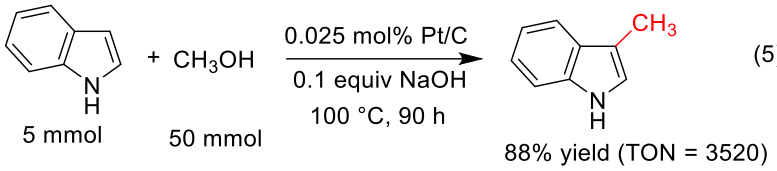
Scheme 4. Proposed catalytic cycle for the *α*-methylation of ketones.

2.3.4 *C3*-Methylation of Indoles

The developed catalytic system (Pt/C and NaOH) was furthermore applied to the *C3*-methylation of indoles with methanol. Only one homogeneous catalytic method has so far been reported for this reaction, but the method suffers from low TONs as well as difficulties associated with the removal and recycling of the catalyst.[44] Thus, the development of more efficient and reusable heterogeneous catalysts is highly desirable. Preliminary experiments for the optimization of this reaction revealed the optimum conditions: indole (1 mmol), methanol (10 mmol), Pt/C (1 mol%), NaOH (10 mol%), 100 °C, and 14 h. Under these optimized conditions, the *C3*-methylation of a variety of indoles afforded the desired products (**Table 8**). The reactions of indole (entry 1), *C5*-substituted indoles with electron-donating and electron-withdrawing groups (entries 2–5), 2,5-dimethylindole (entry 6), and 2-methyl-indole (entry 7) proceeded smoothly to give the corresponding *C3*-methylated products in high yield (81–95%). 3-Methyl indole (entry 8) and *N*-methyl indole (entry 9) did not undergo such a *C3*-methylation. This result is consistent with a proposed reaction route (**Scheme 5**) that involves a nucleophilic attack of the *C3*-carbon of the indole to the formaldehyde molecule. It should be noted that neither 3,3'-bisindolylmethane nor its derivatives are generated by this method, which supports the borrowing-hydrogen mechanism depicted in **Scheme 5**.

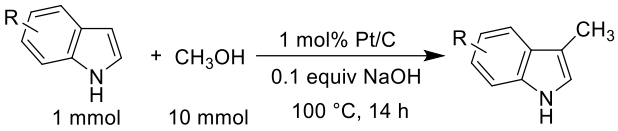
Catalyst recycling tests were carried out for the *C3*-methylation of indole using the standard method for catalyst separation and regeneration.[54] As shown in **Figure 6**, the spent Pt/C catalyst was reused at least four times, which demonstrates that Pt/C is a robust heterogeneous catalyst for this reaction. The initial product formation rates were examined for each cycle in addition to the final yields (**Fig. S4**). A significant loss of the initial rate was not observed, which suggests that Pt/C is a robust heterogeneous catalyst. Using a low Pt/C loading (0.025 mol%), a gram-scale reaction of 5 mmol indole with 50 mmol methanol at 100 °C for 90 h resulted in a high isolated yield of the product (88%), corresponding to a TON of 3520 (eqn (5)). **Table 9** compares the main features of the present method with those of the

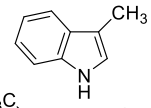
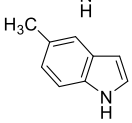
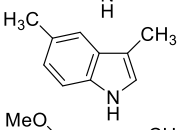
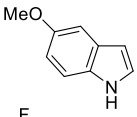
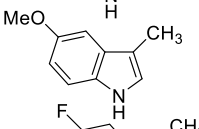
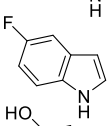
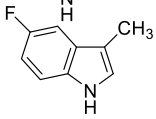
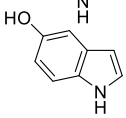
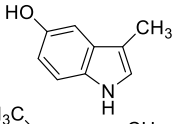
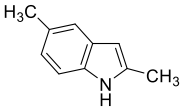
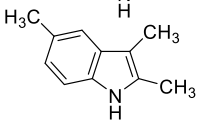
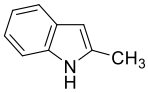
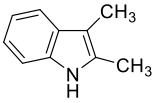
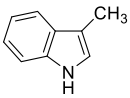
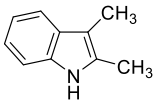
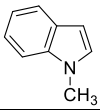
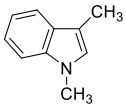
previously reported system with a homogeneous $[Cp^*IrCl_2]_2$ catalyst for the *C3*-methylation of indole. Our method is superior to the reported one in terms of the TON (two orders of magnitude higher) and catalyst reusability. These results demonstrate that this heterogeneous catalytic system, which is based on Pt/C and NaOH, is highly versatile for *C*-methylation transformations, including the *β*-methylation of primary alcohols, the *α*-methylation of ketones, and the *C3*-methylation of indoles. Importantly, all these reactions use methanol as a sustainable C1 source, and additional hydrogen sources are not required.



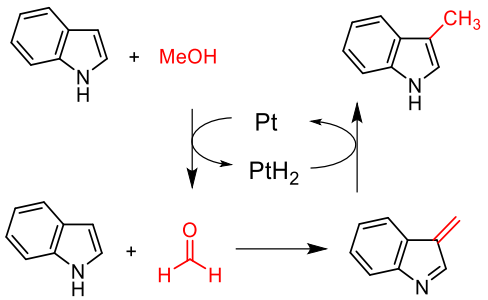
(5)

Table 8. Pt/C-catalyzed *C3*-methylation of indoles



Entry	Indole	Product	Yield (%)[a]
1			95
2			88
3			85
4			83
5			81[b]
6			86
7			93
8			0
9			0

[a] Isolated yield, [b]GC yield



Scheme 5. Proposed catalytic cycle for the *C3*-methylation of indole.

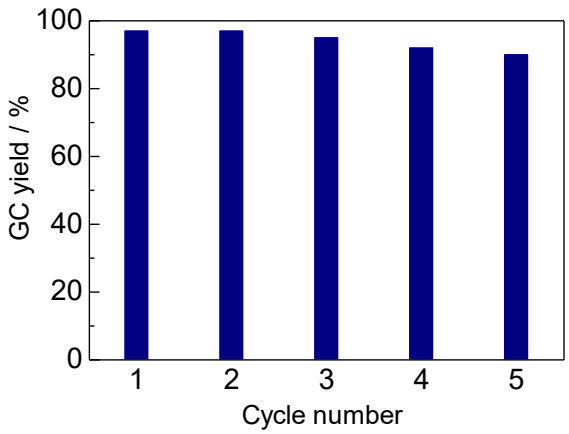


Figure 6. Catalyst recyclability for the *C3*-methylation of indole with methanol and the Pt/C catalyst. The conditions used are those described in Table 8 (entry 1).

Table 9. Catalyst comparison for the *C3*-methylation of indole

Catalyst	Additives	TON [a]	Catalyst reuse	Ref.
Pt/C	0.1 equiv NaOH	3520	5 runs	This work
Ir complex	1 equiv KO*t*Bu	24	No	[44]

[a] TON per number of total metal atoms in the catalysts.

2.3.5 Relationship between the catalytic activity and the adsorption energy of hydrogen: Volcano plots

Rationalizing the properties of catalysts and establishing theories for heterogeneous catalysis are challenging but inevitable tasks in order to understand the underlying phenomena and ultimately develop improved catalysts.[55,56] Recent findings in this area, obtained from density functional theory (DFT) calculations, have shown that the adsorption energy of atoms, molecules, and related species can serve as a simple descriptor to rationalize the activity and selectivity of heterogeneous catalysts. [57-60] This is based on the knowledge that adsorption

is a fundamental step for surface-catalyzed reactions following the Brønsted–Evans–Polanyi (BEP) relation.[61,62] It is also well-known that a Sabatier-type trade-off exists between the adsorption of reactants and the desorption of products, so that catalysts that exhibit optimal adsorption energies afford maximal catalytic activities.[63,64] Therefore, volcano plots are usually obtained for catalytic processes. This rationalization has been applied to relatively simple catalytic reactions involving gas molecules as products, but not extensively to organic transformation reactions.[65] Here, we disclose that the adsorption energy of hydrogen on different metal surfaces correlates well with the catalytic activity of the metals in methylation reactions. Atomic hydrogen was chosen as the adsorbate, as methylation reactions are considered to typically proceed via a hydrogen-borrowing mechanism, implying that adsorbed hydrogen species are involved in the catalytic cycle. The adsorption energy of H on Ni(111), Cu(111), Rh(111), Pd(111), Ir(111), Pt(111), Ru(0001), and Re(0001) surfaces was initially determined theoretically by means of DFT calculations, and subsequently employed as descriptors to explain the catalytic activity of different catalysts (see the experimental section for computational details and the Supporting Information for the optimized structures). **Figure 7** plots the reaction rates (per number of total metal atoms in the catalyst) for the *β*-methylation of 2-phenylethanol, the *α*-methylation of 2-propiophenone, and the *C3*-methylation of indole, over a series of metal-loaded carbon catalysts as a function of the hydrogen adsorption energy. Platinum, which is the most active metal tested, displays a moderate hydrogen adsorption energy, and volcano-type correlations are observed for all three reactions. These observations indicate that the adsorption energy of hydrogen on metal surfaces serves as a good descriptor to explain the activity of a catalyst in certain organic transformation processes. This finding should thus contribute to the rationalization of the catalytic activity of metals in hydrogen-borrowing reactions and to the future design of catalysts without the need for extensive trial-and-error experimental testing.

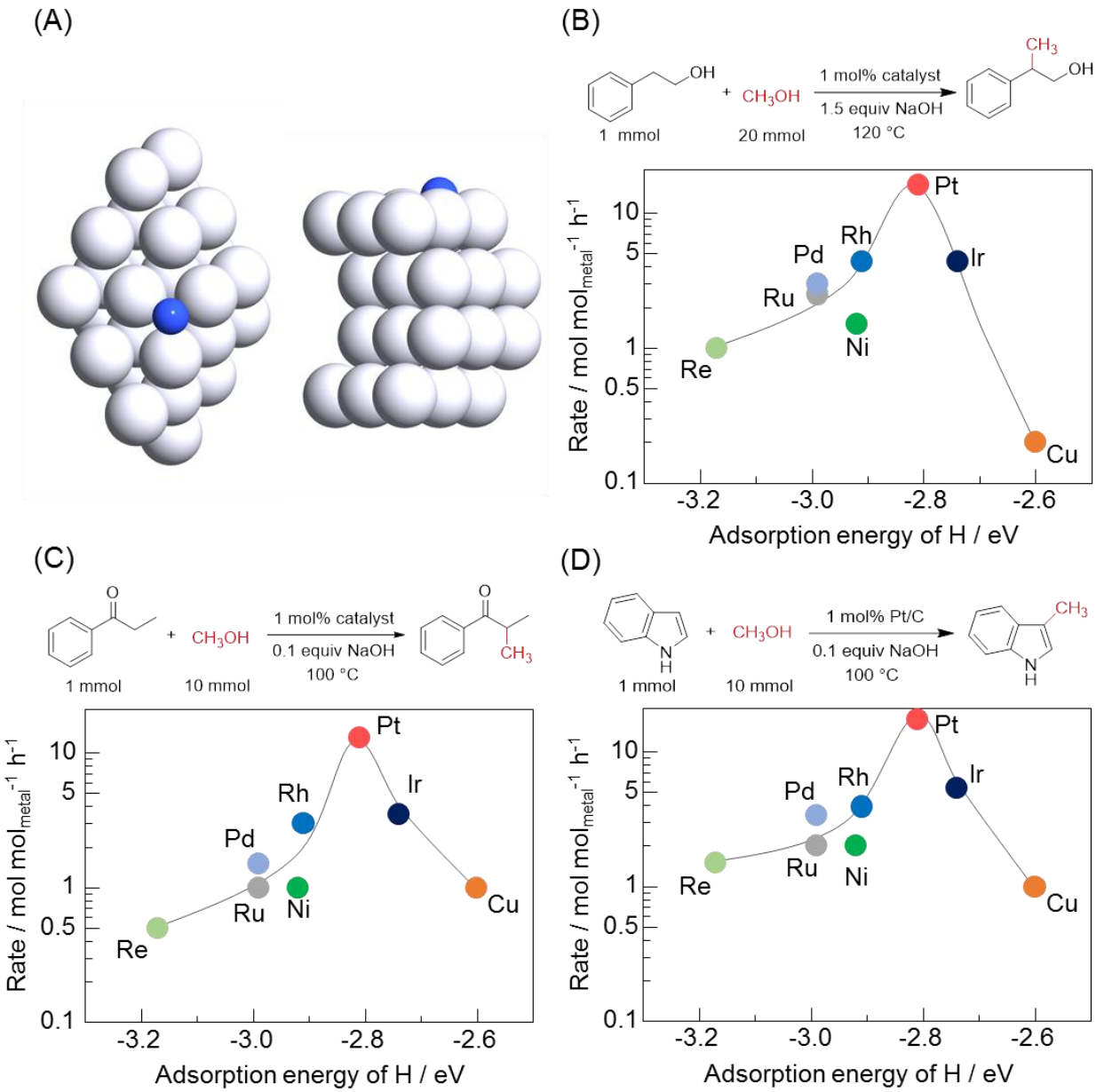


Figure 7. (A) Adsorption models for H on the Pt(111) surface; top (left) and side (right) view. Reaction rates (based on the total number of metal atoms in the catalyst) for (B) the *β*-methylation of 2-phenylethanol, (C) the *α*-methylation of 2-propiophenone, and (D) the *C3*-methylation of indole by metal(M)-loaded carbon catalysts as a function of the adsorption energy of hydrogen on the metal surface.

2.4 Conclusion

Highly versatile, selective, and recyclable heterogeneous catalytic processes were developed for three *C*-methylation reactions using methanol as a sustainable C1 source: (1) the *β*-methylation of primary alcohols, (2) the *α*-methylation of ketones, and (3) the *C3*-methylation of indoles. These catalytic systems are driven by a borrowing-hydrogen mechanism, wherein the Pt-nanoparticles-catalyzed dehydrogenation of methanol (and alcohols) to aldehydes is followed by a condensation of formaldehyde with the corresponding nucleophile (aldehyde, ketone, or indole) to yield unsaturated intermediates, which are subsequently hydrogenated by Pt–H species on the catalyst. Compared to previous catalytic methods for borrowing-hydrogen-type *C*-methylation reactions, our method presents the following advantages: (1) easy catalyst/product separation, (2) catalyst recyclability, (3) excellent TONs (up to two orders of magnitude higher than those previously reported), and (4) wide substrate scope. Furthermore, DFT calculations have shown that the adsorption energy of hydrogen correlates well with the catalytic activity of various active metals employed in these reactions. These results should be helpful to rationalize the properties of catalytic systems and serve as a practical guide for future catalyst design.

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Chapter Three

N-Methylation of Amines and Nitroarenes with Methanol Using Heterogeneous Platinum Catalysts

3.1 Introduction

Methanol is primarily produced from natural gas or coal. Methanol from CO_2 and solar hydrogen could be a promising candidate as a sustainable carbon feedstock for the production of a variety of chemicals [1-3]. In previous catalytic studies on methanol conversion, fuels and bulk chemicals have been the main target products rather than fine chemicals. Potentially, methanol can be a C1 source in fine chemical synthesis as an alternative to the conventional toxic methylation reagents (methyl iodide, dimethyl sulfone, diazomethane, and formaldehyde), which can be sources of genotoxic impurities in pharmaceutical manufacturing [4]. In this context, borrowing hydrogen (or hydrogen auto-transfer) reactions [5-11] for construction of C−N [12-46], C−C [44-51] and C−O bonds [52] by methanol have attracted recent attention in catalysis and organic synthesis since it can be applied to the atom-economic manufacture of fine chemicals from methanol.

N-Methylation of amines is one of the most important transformations in the industrial production of fine chemicals including surfactants, polymers, dyes, pharmaceuticals, agrochemicals and pesticides [52], where reductive amination of toxic formaldehyde still constitutes a major approach [3]. As a greener alternative method, catalytic *N*-methylation of amines with methanol has been investigated mainly using homogeneous catalysts including Ir [12-14], Ru [15-21], Mn [22-24], Fe [25,26] or Re [27] catalysts, in which *N*-monomethylation of aromatic primary amines (aniline derivatives) was mainly investigated. Recently, Seayad et al. reported that a Ru complex catalyst, which was effective for *N*-methylation of aromatic amines, promoted *N*,*N*-dimethylation of primary aliphatic amines [17]. The tandem transformation of nitro compounds into *N*-methylated amines was demonstrated by Kundu et al. where *in situ* generated amines by reduction of nitro compounds reacted with methanol in a borrowing hydrogen manner [19]. Very recently, Hong's group reported the selective *N*-monomethylation of aliphatic primary amines by methanol using a homogeneous Ru catalyst. The key to achieving high selectivity was the use of H_2 as a reducing agent in combination with a relatively low reaction temperature, which can retard the dehydrogenation steps of methanol [37]. Although various kinds of *N*-methylation reactions have been achieved by metal complex catalysts, these methods principally suffer from difficulties in catalyst product separation and catalyst reuse.

In contrast, heterogeneous catalysts have advantages in terms of simplicity in handling, catalyst product separation and reuse. However, only a few heterogeneous systems using solid acid/base [28-30] and photocatalysts (Pt, Ag, or Pd-loaded TiO_2) [31-33] for *N*-methylation of amines with methanol have been reported to date. Additionally, these systems require high

temperatures (230-425 °C) [28-30] or photo-irradiation [31-33] and still have problems such as low selectivity for di- or mono-methylated amines [29,31,34] and limited substrate scopes [30,31,34,35], which are disadvantageous from a practical viewpoint. Accordingly, a heterogeneous catalytic system that can selectively promote various kinds of *N*-methylations of aromatic and aliphatic amines under milder reaction conditions is strongly required.

Herein, we report a simple and versatile heterogeneous catalytic method for various types of *N*-methylation reactions with methanol. The developed catalytic system, Pt/C with base, was demonstrated for selective *N*,*N*-dimethylation of aliphatic amines and *N*-monomethylation of anilines under N_2 atmosphere. Inspired by Hong's method [37], the selective *N*-monomethylation of aliphatic primary amines under the same catalytic system was developed using pressurized H_2. Moreover, the one-pot synthesis of *N*-methylanilines from nitroarenes and methanol [19] was carried out under H_2 atmosphere. Kinetic and computational studies were conducted to discuss the catalytic pathway and the factors controlling the catalytic activity of transition-metal nanoparticles for the *N*-methylation of amines by methanol.

3.2 Experimental

3.2.1 General

We used commercial chemicals (Tokyo Chemical Industry, Wako Pure Chemical Industries, Kishida Chemical, or Mitsuwa Chemicals) without purification. GC-FID (Shimadzu GC-2014) and GC-MS (Shimadzu GCMS-QP2010) analyses were performed using an Ultra ALLOY capillary column UA^+-1 (Frontier Laboratories, Ltd.) with N_2 or He as the carrier gas. ^1H and ^{13}C NMR measurements were conducted using a JEOL-ECX 600 spectrometer operating at 600.17 and 150.92 MHz, or JEOL-ECX 400 operating at 399.78 and 100.52 MHz, respectively, with tetramethylsilane as the internal standard.

3.2.2 Catalyst preparation

The carbon support (296 $m^2\ g^{-1}$, Kishida Chemical) was commercially obtained. γ-Al_2O_3 was prepared by calcining γ-AlOOH (Catapal B Alumina kindly supplied by Sasol) at 900 °C (3 h). CeO_2 (JRC-CEO3, 81 $m^2\ g^{-1}$), MgO (JRC-MGO-3), and TiO_2 (JRC-TIO-4) were supplied by the Catalysis Society of Japan. ZrO_2 was prepared by calcination of hydrous zirconia at 500 °C (3 h) [51]. Nb_2O_5 was prepared by calcination of $Nb_2O_5{\cdot}nH_2O$ (kindly supplied by CBMM) at 500 °C (3 h). SiO_2 (Q-10, 300 $m^2\ g^{-1}$) was kindly supplied by Fuji Silysia Chemical, Ltd.

The Pt/C catalyst with Pt loading of 5 wt% was prepared by the same wet impregnation

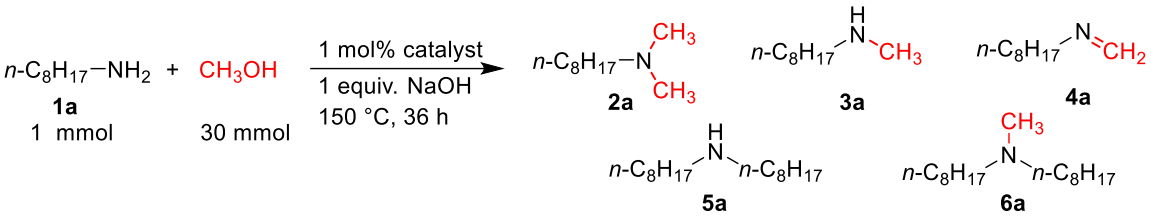
method as reported in our earlier paper [51]: a mixture of carbon (10 g), a 10.62 g of an aqueous HNO_3 solution of $Pt(NH_3)_2(NO_3)_2$ that contained 4.96 wt % of Pt (Furuya Metal Co., LTD.), and 50 mL of deionized water was added to a round-bottom flask (500 mL). The mixture was then stirred (200 rpm) for 30 min at 50 °C, followed by subsequent evaporation to dryness at 50 °C at reduced pressure and finally dried in an oven at 100 °C under ambient pressure for 12 h. The obtained powder was reduced in a Pyrex tube under a flow of H_2 (20 cm^3 min^{-1}) at 300 °C for 0.5 h and then used for the reaction.

Other supported Pt catalysts with Pt loading of 5 wt% were also prepared by the same method. M/C (M = Rh, Ir, Ru, Pd, Re, Cu, Ni) catalysts with metal loading of 5 wt% [51] were prepared by a similar method as that for Pt/C using an aqueous HNO_3 solution of $Rh(NO_3)_3$ or $Pd(NH_3)_2(NO_3)_2$ or an aqueous solution of metal nitrates (for Ni, Cu), $IrCl_3 \cdot nH_2O$, $RuCl_3$ or NH_4ReO_4.

3.2.3 Characterization

Transmission electron microscopy (TEM) observations were conducted using a JEOL JEM-2100F TEM (200 kV). Pt L_3-edge X-ray absorption near-edge structures (XANES) and extended X-ray absorption fine structure (EXAFS) experiments were carried out in transmittance mode at the BL14B2 with a Si(111) double crystal monochromator in SPring-8 operated at 8 GeV. The Pt/C catalyst pre-reduced in a flow of H_2 (20 cm^3 min^{-1}) for 0.5 h at 300 °C was cooled to room temperature under a flow of H_2 and was sealed in cells made of polyethylene under N_2, and then the EXAFS spectrum was taken at room temperature. The spectra of Pt foil and the Pt/C catalyst just after the 5th reaction cycle was recorded without the pre-reduction treatment. The EXAFS analysis was performed using the REX ver. 2.5 program (RIGAKU) using the parameters for Pt–O and Pt–Pt shells provided by the FEFF6.

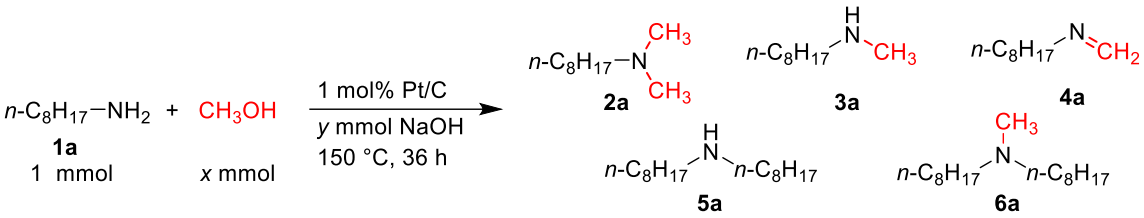
Table 1 Catalysts screening for *N,N*-dimethylation of *n*-octylamine by methanol.



entry	catalysts	**1a** conv. (%)[a]	GC yield (%)[a]				
			2a	**3a**	**4a**	**5a**	**6a**
1	blank	0	0	0	0	0	0
2	PtO_X/C	3	0	0	0	0	0
3	Pt/C	100	96	2	0	0	2
4	Pt/C-air	65	58	3	0	0	2
5	Pt/Al_2O_3	85	9	44	4	7	18
6	Pt/CeO_2	86	7	39	0	12	29
7	Pt/MgO	96	56	18	12	10	0
8	Pt/ZrO_2	96	18	35	1	0	20
9	Pt/Nb_2O_5	85	0	7	33	22	9
10	Pt/TiO_2	94	27	36	13	7	1
11	Pt/SiO_2	73	3	8	22	9	1
12	Pd/C	97	69	7	0	3	10
13	Rh/C	98	62	11	1	5	1
14	Ir/C	94	55	14	0	6	12
15	Ni/C	92	14	42	0	3	31
16	Ru/C	84	10	43	0	2	16
17	Re/C	49	7	39	0	0	1
18	Cu/C	5	1	2	2	0	0

[a] Conv. and yields were determined by GC analyses.

Table 2 Optimization of the conditions for Pt/C-catalyzed *N,N*-dimethylation of *n*-octylamine.



entry	*x* (mmol)	base (*y*)	**1a** conv. (%)[a]	GC yield (%)[a]				
				2a	**3a**	**4a**	**5a**	**6a**
1	30	None	33	0	3	0	0	0
2	**30**	**NaOH (1.0)**	**100**	**96**	**2**	**0**	**0**	**2**
3	30	KOH (1.0)	96	82	12	0	0	2
4	30	Na_2CO_3 (1.0)	68	16	23	19	1	0
5	30	K_2CO_3 (1.0)	56	12	14	18	0	0
6	30	Cs_2CO_3 (1.0)	70	32	13	7	3	0
7	30	NaO*t*Bu (1.0)	86	61	21	0	0	1
8	30	KO*t*Bu (1.0)	91	78	12	0	0	1
9	30	NaOMe (1.0)	94	67	23	0	1	2
10	30	NaOEt (1.0)	76	30	19	16	0	0
11	30	Et_3N (1.0)	41	0	4	21	0	0
12	30	DBU (1.0)	36	4	9	17	0	0
13	30	NaOH (0.25)	83	74	5	0	0	1
14	30	NaOH (0.5)	92	78	13	0	0	1
15	30	NaOH (1.5)	100	68	24	0	2	3
16	5	NaOH (1.0)	92	27	31	23	0	0
17	10	NaOH (1.0)	95	76	15	4	0	0
18	20	NaOH (1.0)	97	90	5	0	0	1
19	40	NaOH (1.0)	100	64	23	0	3	1
20	60	NaOH (1.0)	100	47	29	12	2	0

[a] Yields were determined by GC analyses.

3.2.4 Typical procedures of catalytic reactions

After the reduction under a flow of H_2 at 300 °C for 0.5 h, we carried out catalytic tests without exposing the catalyst to air as follows. Methanol (30 mmol) was injected to the reduced

catalyst inside the glass tube through a septum inlet, thus the catalyst was covered with a layer of methanol to restrict it from air exposure. After removal of the septum under air, amine (1 mmol), solid NaOH (1 mmol), *n*-dodecane (0.25 mmol) and a magnetic stirrer bar were placed in the tube. The tube was inserted into a stainless-steel autoclave (28 cm^3) and purged with N_2 gas. Finally, the resulting mixture was heated at 150 °C and stirred under 1 bar N_2. For the model reaction of *n*-octylamine, the catalyst screening, optimization of reaction conditions, kinetic studies and control reactions, the conversion of *n*-octylamine and yields of products were determined by GC analyses, using *n*-dodecane as an internal standard by applying the GC sensitivity of the isolated or commercial products. For the substrate scope study, the products were isolated by column chromatography with silica gel 60 (spherical, 60-100 μm, Kanto Chemical Co., Ltd.) using hexane/ethyl acetate or ethyl acetate/methanol as the eluting solvent. The yields of the isolated amine derivatives were determined and identified by ^1H and ^{13}C NMR and GC-MS methods.

3.2.5 Computational Methods

Adsorption energies of a H atom on various metal surfaces reported in our recent study were used to rationalize the catalytic performance in the *N*-methylation reaction. [51] Brief computational methods are described as follows. All the calculations were performed with the Vienna *ab-initio* simulation package (VASP) [54,55] using projector-augmented wave potentials [56] and the Perdew–Burke–Ernzerhof (PBE) functional. [57] The dispersion-corrected DFT-D2 method was employed to account for van der Waals interactions. [58] The Ni(111), Cu(111), Rh(111), Pd(111), Ir(111), Pt(111), Ru(0001), and Re(0001) surfaces were modeled by a supercell slab consisting of a 3 × 3 surface unit cell with four atomic layers. It should be noted that the most stable and common planes were used for each metal. The (111) surface (Ni, Cu, Rh, Pd, Ir, and Pt) presents a face-centered-cubic (fcc) structure, while the (0001) surface (Ru and Re) has a hexagonal-close-packed (hcp) structure. The slab was separated in the vertical direction by a vacuum void (height: 15 Å). An energy cut-off of 400 eV and a 5 × 5 × 1 point mesh were used for the slab model calculations. The energy of the isolated H atom was obtained using the same parameters as those in the free-surface slab calculations. The geometry-convergence criterion was set at $F_{max} < 0.03$ eV $Å^{-1}$, where F_{max} is the maximum force acting on a mobile atom. The adsorption energy (E_{ads}) was calculated as the difference in energy between the molecule absorbed on the surface ($E_{molecule/surface}$), the individual adsorbate molecule ($E_{molecule}$), and the surface ($E_{surface}$) according to:

$$E_{ads} = E_{molecule/surface} - E_{molecule} + E_{surface} \quad (1)$$

3.3 Results and discussion

3.3.1 *N,N*-Dimethylation of aliphatic amines

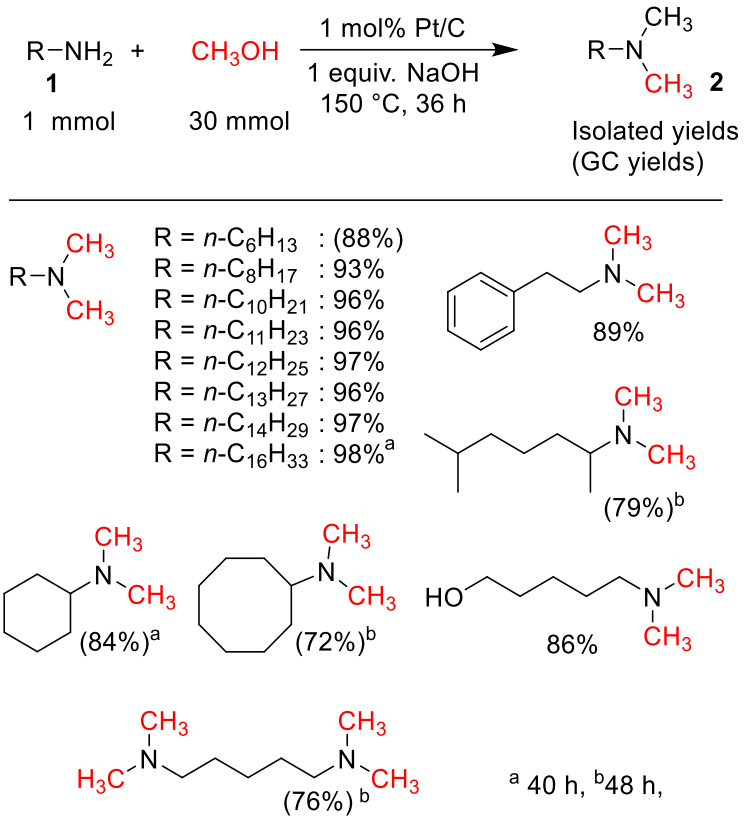
We selected the *N*-methylation of *n*-octylamine (**1a**) in methanol as a model reaction to optimize various parameters, including catalyst composition and reaction conditions. First, catalyst screening was carried out for the reaction of **1a** (1 mmol) and methanol (30 mmol) with NaOH (1 mmol) at a temperature of 150 °C for 36 h. Since the reaction was tested in a closed stainless-steel autoclave, the temperature of the reaction mixture could be higher than the boiling point of methanol. We screened a series of Pt-loaded (5 wt%) heterogeneous catalysts (39 mg in total; 1 mol% Pt with respect to **1a**). **Table 1** lists the yields of *N,N*-dimethyloctylamine (**2a**) as the main product, together with the yields of minor products, i.e., *N*-methyl-*n*-octylamine (**3a**), *n*-octylmethanimine (**4a**), dioctylamine (**5a**) and *N*-methyl-dioctylamine (**6a**). The substrate **1a** was not consumed in the absence of a transition-metal catalyst (entry 1). Platinum oxide did not catalyze the reaction; the product yields were negligible in the presence of carbon-supported platinum oxide, PtO_x/C (entry 2). In contrast, carbon-supported Pt metal nanoparticles (Pt/C, entry 3) gave **2a** in 96% yield. Exposure of the as-reduced Pt/C catalyst to air at room temperature for 0.5 h decreased the yield of **2a** to 58% (entry 4), possibly due to oxidation of the surface Pt^0 species. Under the standard conditions (entries 3,5–18), supported metal nanoparticle catalysts reduced under H_2 at 300 °C (for Pd, Rh, Ir, Ru, and Cu) or 500 °C (for Ni and Re) were used for the subsequent reactions without exposing them to air. The reactions with metal oxides-supported Pt catalysts (entries 5–11) gave mixtures of **2a**, **3a**, **4a**, **5a** and **6a** and the yields of **2a** (0–56%) were lower than that of Pt/C. Note that the kind of carbon support did not affect the catalysis as revealed by control experiments using several Pt/C catalysts (See Table S1). We also tested various transition-metal nanoparticles loaded on the carbon support (entries 3,12–18). Unlike Pt/C, other metal catalysts gave a mixture of various products. The yield of **2a** decreased in the following order: Pt > Pd > Rh> Ir > Ni > Ru > Re > Cu. In summary, the results in **Table 1** show that Pt/C (entry 3) is the most suitable catalyst for the selective *N,N*-dimethylation of **1a** with methanol into **2a** in the presence of 1 equiv. NaOH.

Using the most effective catalyst (Pt/C), we optimized the reaction conditions (**Table 2**). The *N*-methylation reaction did not occur in the absence of a base (entry 1). This indicates that Pt/C alone does not catalyze the reaction and the presence of a base is crucial. The results with different bases (entries 2–12) indicate that the yield of **2a** depends strongly on the base and changes in the order of NaOH > KOH > KO*t*Bu > NaOMe > NaO*t*Bu > Cs_2CO_3 > NaOEt > Na_2CO_3 > K_2CO_3 > DBU > Et_3N. The yield of **2a** also depends on the amount of NaOH (entries

2, 13–15); the yield increases with the amount of NaOH up to 1 equiv. with respect to **1a**, but further addition of base gives lower yields. The yield of **2a** also depends on the amount of methanol (5-60 mmol, entries 2, 16-20); the optimal amount of methanol is 30 mmol (entry 2). The lowest amount of methanol (entry 16) results in the highest yield of the imine intermediate **4a**, which suggests that methanol acts as a hydrogen source as well as a methylation reagent. The reaction with too much methanol (60 mmol) results in a low yield of **2a** (27%), which may be due to the lower concentration of the substrate **1a** than the standard conditions, leading to lower reaction rates.

Under the optimized conditions, we studied the performance of the Pt/C-catalyzed *N,N*-dimethylation of aliphatic amines with methanol. **Scheme 1** shows the scope of various aliphatic amines. Linear aliphatic primary amines with different chain lengths (C_6–C_{16}) were selectively methylated to give the corresponding *N,N*-dimethyl amines in excellent isolated yields (88-98%). It is noteworthy that the products, *N,N*-dimethylated aliphatic amines, are an important class of chemicals for the industrial production of surfactants, germicides, and softeners [53]. 2-Phenylethylamine, a branched aliphatic primary amine, 1,5-dimethyl hexylamine, and cyclic aliphatic amines were converted to the corresponding *N,N*-dimethylated amines in 72-89% yields. A typical diamine, 1,5-pentanediamine, was transformed to the tetramethylated product in 76% yield. A hydroxyl group in 5-aminopentan-1-ol was tolerated, with the *N,N*-dimethylated product obtained in 86% yield. These results demonstrate the wide applicability of this heterogeneous catalytic method for the *N,N*-dimethylation of the $-NH_2$ group in various aliphatic amines.

Among the previous reports on the *N*-methylation of amines by methanol [12-36] by homogeneous and heterogeneous catalysts, the *N,N*-dimethylation of aliphatic amines by methanol is rare [12,17,18,28,32]. One of the most successful methods was reported by Seayad and co-workers [17] in which the 0.5 mol% Ru-complex-catalyzed reaction of undecylamine amines with methanol gave the *N,N*-dimethylated amine in 83% yield, corresponding to a TON of 166. We tested gram scale reactions of C_8, C_{11} and C_{12} linear aliphatic amines with methanol using 10 mg of Pt/C containing 0.0025 mmol (0.025 mol%) of Pt (**Table 3**). The yields of *N,N*-dimethylated amines from C_8, C_{11} and C_{12} amines were 91%, 88% and 92% respectively, corresponding to TONs of 3640 (C_8), 3520 (C_{11}) and 3680 (C_{12}). For the *N,N*-dimethylation of *n*-octylamine, the TON of our method is one order of magnitude higher than that of the previous method [17].



Scheme 1 Pt/C-catalyzed *N,N*-dimethylation of aliphatic amines by methanol.

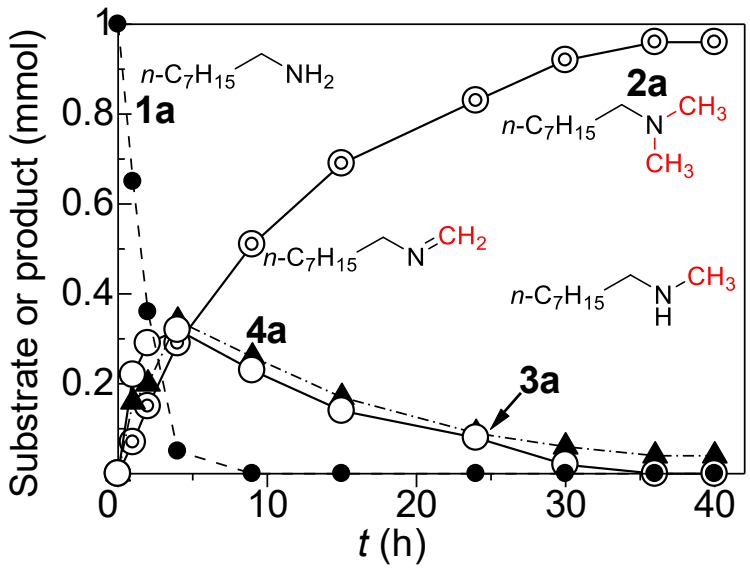
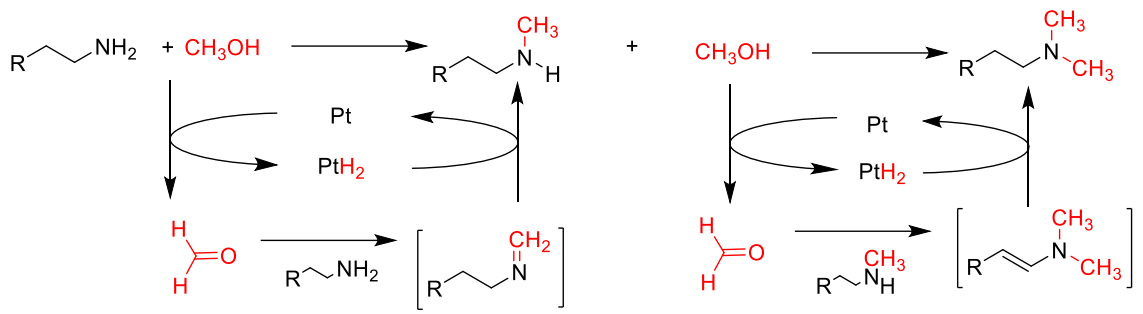


Fig. 1. Time course for methylation of **1a** with methanol: conditions are shown in Scheme 1.



Scheme 2 Proposed catalytic cycle for the *N,N*-dimethylation of amines.

According to the previously proposed mechanism for this type of reaction [17], the present reaction proceeds via the borrowing hydrogen mechanism (**Scheme 2**). **Figure 1** shows the time course of the products, analyzed by GC, for the standard reaction of **1a**. During the initial period (t < 5 h), *n*-octylamine (**1a**) is consumed, accompanied by the formation of *n*-octylmethanimine (**4a**) and *N*-methyl-*n*-octylamine (**3a**) as the main products. Next, **4a** and **3a** are consumed, accompanied by an increase in the amount of the final product, *N,N*-dimethyloctylamine (**2a**). This indicates that **2a** is produced by consecutive reactions via **4a** and **3a**. Based on this result, we proposed a reasonable mechanism as shown in **Scheme 2**. Methanol is first dehydrogenated to give two hydrogen atoms on the Pt surface and formaldehyde, which reacts with the amine to afford an imine. NaOH would assist this dehydrogenation through deprotonation [61]. Next, the imine intermediate is hydrogenated by the hydrogen atoms on the catalyst to yield monomethyl amine. Consecutive borrowing hydrogen methylation of the monomethyl amine with methanol, probably via an enamine intermediate [12], gives the *N,N*-dimethyl amine. Intermediacy of the enamine is supported by a control experiment shown in eqn. (1). We synthesized the enamine, (*E*)-*N,N*-dimethyl-2-phenylethen-1-amine, which was isolated and used for transfer hydrogenation by methanol as a hydrogen donor in the presence of Pt/C and NaOH. The C=C bond of the enamine underwent transfer hydrogenation with methanol, affording *N,N*-dimethyl-2-phenylethan-1-amine in 95% yield.

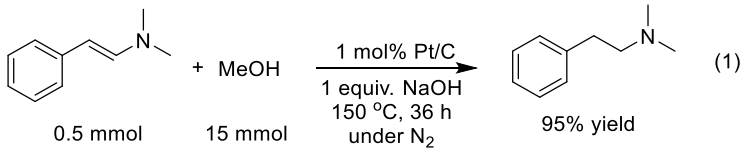
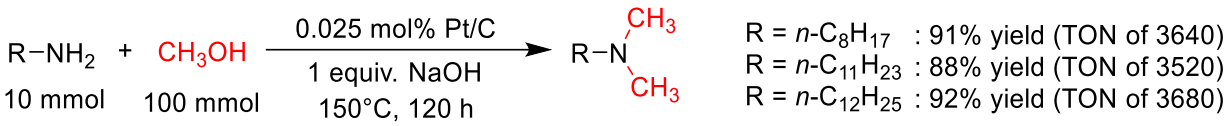


Table 3 Comparison of TON of Pt/C with a previous catalyst.



catalyst	R	TON[a]	ref.
Pt/C	C_8H_{17}	3640	This work
	$C_{11}H_{23}$	3520	
	$C_{12}H_{25}$	3680	
Ru complex	$C_{11}H_{23}$	166	[17]

[a] TON per number of total metal atoms in the catalyst.

3.3.2 *N*-Monomethylation of aliphatic amines

The selective synthesis of *N*-monomethyl amines provides various functional chemicals but has been a challenging target in organic synthesis due to the difficulties in preventing over-methylation. Classical and less atom-efficient methods are still utilized for the synthesis of *N*-monomethyl amines with a conventional methylating agent such as methyl halides [59,60], generally by a protection/deprotection methodology [59]. Heterogeneous catalysis for the selective monomethylation of aliphatic primary amines by methanol has not been achieved previously. Our results shown above also indicate that the reactions of aliphatic primary amines with methanol under N_2 afforded dimethyl amines. This may be due to the higher nucleophilicity of secondary amines than primary amines, which results in over-methylation of the monomethyl amines. Inspired by the first report by Hong's group [37] for the selective monomethylation of aliphatic primary amines by a homogeneous Ru catalyst under 40 bar H_2, we studied the selective monomethylation of aliphatic primary amines by the heterogeneous Pt/C catalyst.

First, we optimized the conditions by changing the reaction temperature (120-180 °C), reaction time (12-40 h), H_2 pressure (2.5-40 bar) and catalyst loading (0.5-5 mol%) for the reaction of the model primary amine **1a** with methanol using Pt/C and 1 mmol of NaOH (**Fig. 2**). The reactions under 40 bar H_2 (36 h) at different temperatures (**Fig. 2A**) show that a moderate temperature (130 °C) is suitable for selective monomethylation; higher temperatures resulted in higher yields of dimethyl amine **2a**. **Fig. 2B** shows the time dependence of the reaction under 40 bar H_2 at the optimal temperature (130 °C). A reaction time of 36 h gives the highest yield of monomethyl amine **3a**. After 36 h, the monomethyl amine **3a** was converted

to the dimethyl amine **2a**. We next optimized the H_2 pressure (**Fig. 2C**). It is shown that higher H_2 pressure results in a higher yield of monomethyl amine **3a**. Finally, the catalyst loading was optimized (**Fig. 2D**). The use of 1 mol% Pt/C was found to be optimal, and higher catalyst loading resulted in a drastic decrease of the yield of **3a**. These results indicate that we can maximize the yield of monomethyl amine **3a** by kinetic control of the reaction. The best conditions for the selective monomethylation of **1a** are as follows: 130 °C for 36 h under 40 bar H_2 with 1 mol% of Pt/C.

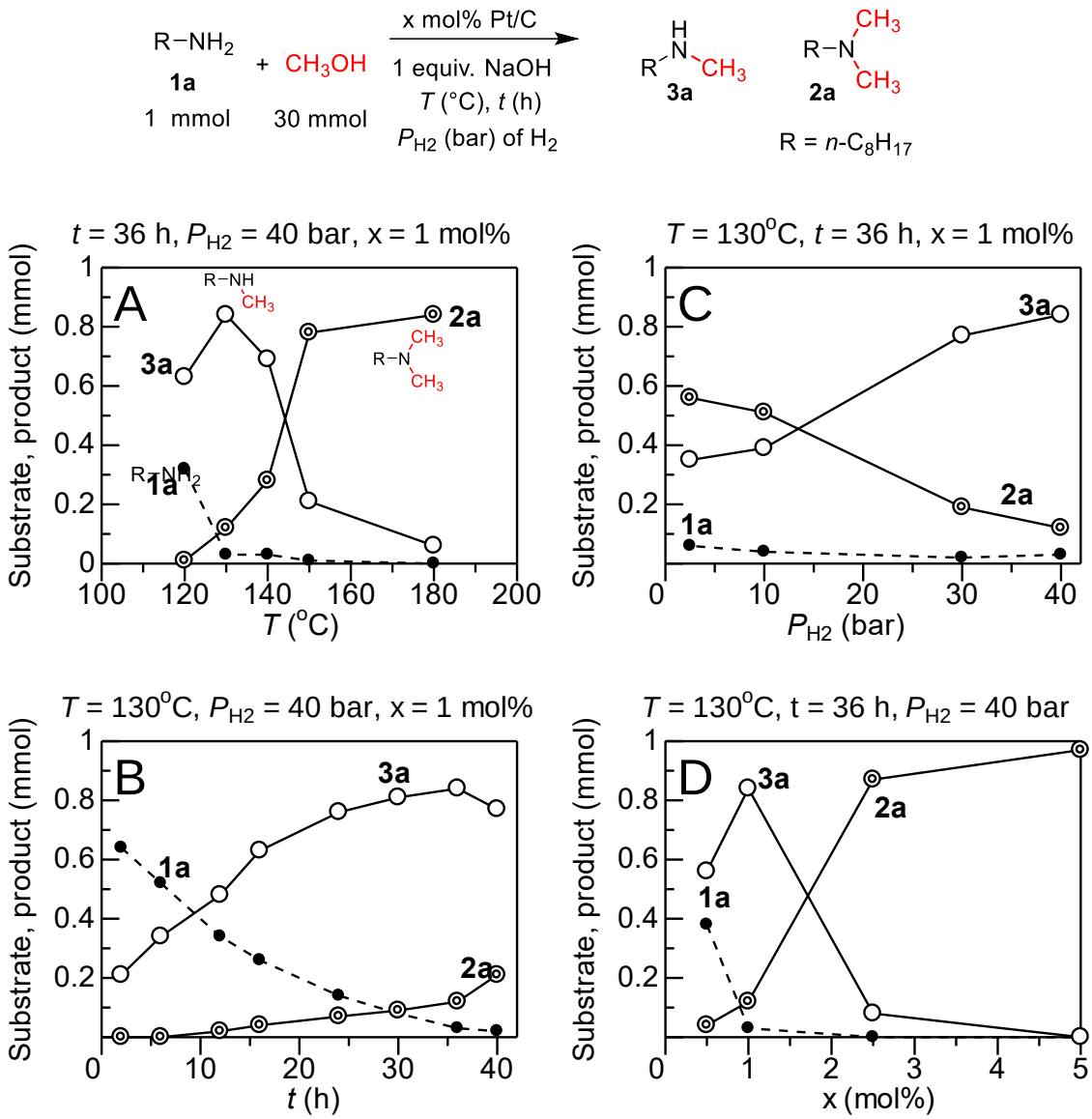
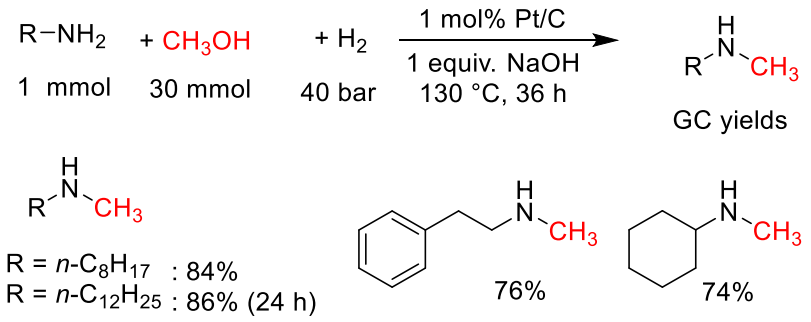


Fig. 2. Optimization of the conditions for monomethylation of **1a** under H_2.

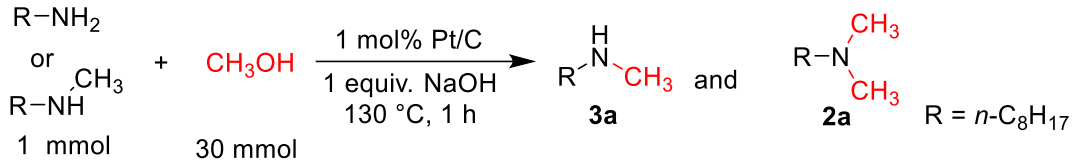
With the optimized conditions in hand, we tested the substrate scope of this method (**Scheme 3**). Linear aliphatic primary amines with different chain lengths (C_8, C_{12}) were selectively transformed to the corresponding monomethyl amines in high yields (84-86%). 2-Phenylethylamine and cyclohexyl amine were converted to the corresponding monomethyl amines in good yields.



Scheme 3 Pt/C-catalyzed *N*-monomethylation of aliphatic amines by methanol.

The question arises as to how H_2 addition increases the selectivity for monomethyl amine **3a**. As shown in **Scheme 2**, dehydrogenation of methanol to formaldehyde is the key step of this reaction. It is reasonable to assume that H_2 addition decreases the amount of the formaldehyde intermediate [37], which in turn decreases the formation rates of the imine and enamine intermediates. We studied controlled kinetic experiments for methylation of the primary amine **1a** and monomethyl amine **3a** under the same conditions. **Table 4** compares the initial formation rates of monomethyl amine **3a** (V_{3a}) and dimethyl amine **2a** (V_{2a}) under 1 bar N_2 and 40 bar H_2 at 130 °C. Regarding the methylation of the primary amine **1a**, the V_{3a} value under H_2 (12.7 mol mol_{Pt}^{-1} h^{-1}) is higher than that under N_2 (5.6 mol mol_{Pt}^{-1} h^{-1}), which indicates that H_2 addition promotes the monomethylation of the primary amine **1a**. Considering the fact that the imine **4a** was not detected under H_2 atmosphere, it is suggested that the promotion of the monomethylation of the primary amine is caused by hydrogenation of the imine **4a** by H_2 to give **3a**. On the other hand, for the methylation of the monomethyl amine **3a**, the V_{2a} value under H_2 (2.0 mol mol_{Pt}^{-1} h^{-1}) is lower than that under N_2 (10.0 mol mol_{Pt}^{-1} h^{-1}), which indicates that H_2 addition suppresses the methylation of the monomethyl amine **3a**. The reason for the opposite impact of H_2 on the methylation rates of primary and monomethyl amines is not clear.

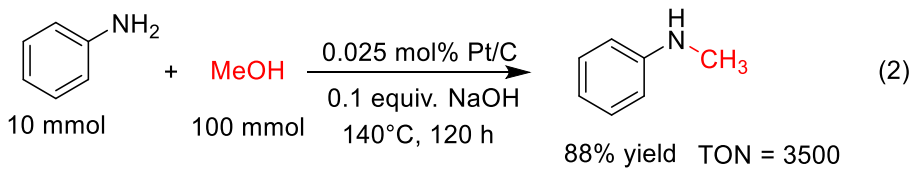
Table 4 Initial formation rates (mol mol_{Pt}^{-1} h^{-1}) of **3a** (V_{3a}) and **2a** (V_{2a}).



amine	under 1 bar N_2		under 40 bar H_2	
	V_{3a}	V_{2a}	V_{3a}	V_{2a}
R-NH_2	5.6	0.9	12.7	0
R-NH-CH_3	-	10	-	2

3.3.3 *N*-Monomethylation of aromatic amines

Similar to the reported results [12-36], the *N*-methylation of aromatic amines under N_2 with Pt/C and NaOH resulted in *N*-monomethylation. We initially optimized the catalyst and reaction conditions for the *N*-monomethylation of aniline **1b**. Based on the results (not shown), we standardized the following optimized reaction conditions: amine (1 mmol), methanol (10 mmol), 1 mol% Pt/C, 10 mol% NaOH, 140 °C, and 15 h. **Scheme 4** summarizes the substrate scope of our catalytic method for the *N*-monomethylation of aromatic amines. Aniline and its derivatives with electron-donating and electron-withdrawing groups, aminopyridines, 6-methyl-1,2,3,4-tetrahydroquinoline, and indoline were converted to the corresponding *N*-monomethylated products in high yields (81–98%). A gram scale reaction of aniline (10 mmol) with methanol (100 mmol) using 0.025 mol% of the Pt/C catalyst gave *N*-methylaniline in 88% yield, corresponding to a TON of 3500 (eqn. (2)).



(2)

Reusability of the Pt/C catalyst was tested for the reaction of aniline **1b**. After the reaction of **1b** for 15 h, 2-propanol (3 mL) was added to the reaction mixture, and the Pt/C catalyst was collected by filtration and was washed with acetone (3 mL), water (3 mL) and acetone (3 mL). After drying at 110 °C (12 h), the catalyst underwent H_2 reduction (300 °C, 0.5 h) in a test tube.

The tube was then charged with the reaction mixture according to the standard procedure. Applying this recycling procedure, the spent catalyst was reused four times, maintaining high **2b** yields (81-92%) as shown in **Fig. 3**. In a separate series of catalyst recycling experiments, the initial rate of **2b** formation was estimated for each cycle. The result (black bars in **Fig. 3**) indicates that the Pt/C catalyst is a reusable catalyst for this reaction.

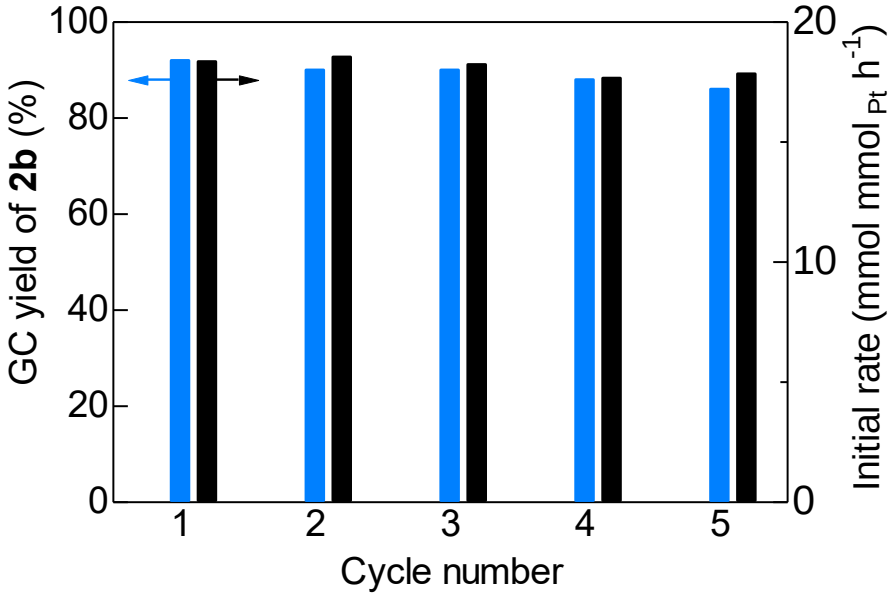
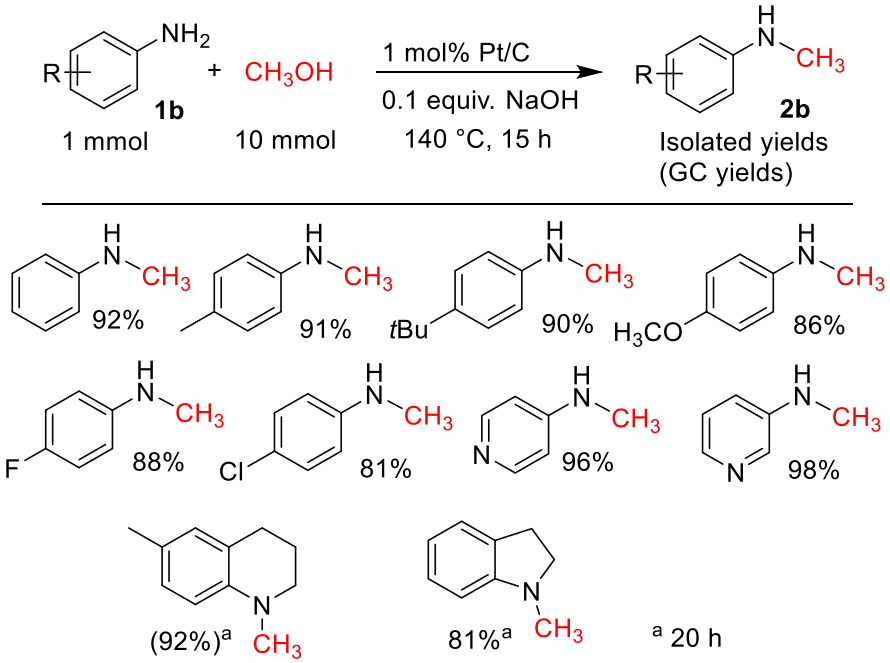


Fig. 3. Catalyst reuse for the *N*-monomethylation of aniline with methanol using Pt/C catalyst with NaOH under the standard conditions shown in Scheme 4: (blue bars) **2b** yields after 15 h and (black bars) initial rates of **2b** formation.



Scheme 4 Pt/C-catalyzed *N*-methylation of aromatic amines by methanol.

The structure of the fresh and the 5th cycled Pt/C catalysts were characterized by TEM (**Fig. 4**) and Pt L_3-edge XANES/EXAFS (**Fig. 5**). The characterization results for the fresh Pt/C were reported in our previous study [61,62]. The particle size distribution, estimated by TEM analysis (**Fig. 4**), shows that the volume-area mean diameter (*D*) of Pt particles in the 5th cycled Pt/C (5.2 ± 1.1 nm) is close to that in the fresh Pt/C (4.7 ± 1.0 nm) [61] within experimental error. The XANES result (**Fig. 5A**) shows the metallic state of the fresh Pt/C [62]. The white line intensity for Pt/C was increased by the catalyst recycling treatment, indicating that Pt is partly oxidized. However, after reduction of the recycled Pt/C sample under H_2 at 300 °C, its white line intensity was again close to that of the fresh Pt/C. The EXAFS results (**Fig. 5B**) were used for the curve fitting analysis to give the structural data in **Table 5**. After the reduction treatment (under H_2 at 300 °C), the EXAFS features of the recycled Pt/C sample (10.9 Pt–Pt bonds at 2.74 Å) were close to those of fresh Pt/C (9.9 Pt–Pt bonds at 2.75 Å). Based on the TEM and XANES/EXAFS results, we can conclude that the structure of the Pt species in the recycled catalyst is essentially unchanged after the 5th cycle, but the recovered catalyst should be re-reduced in order to regenerate the metallic state of the Pt nanoparticles.

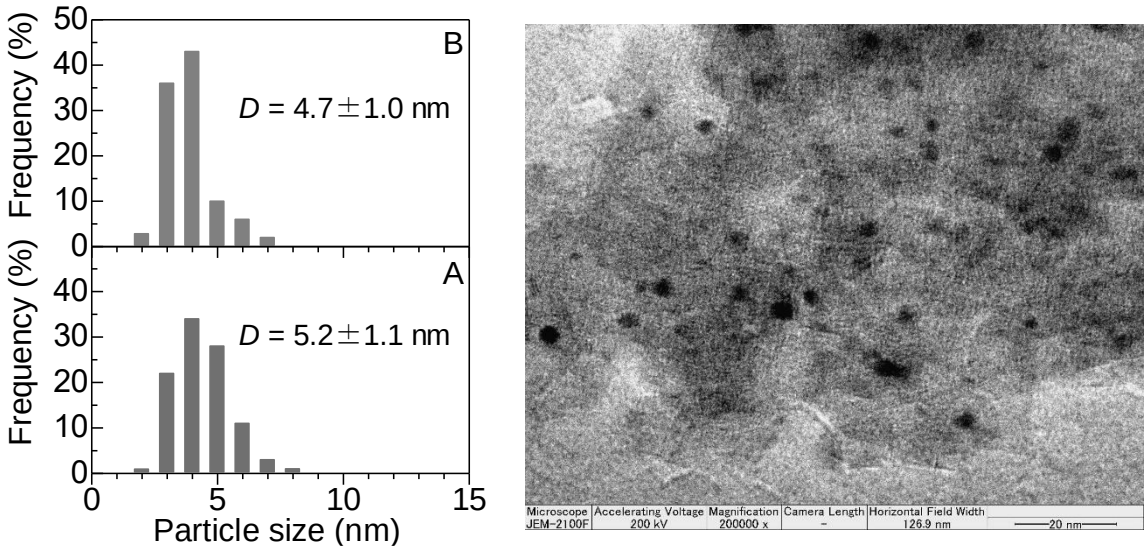


Fig. 4. Pt particle size distributions of Pt/C (B) before and (A) after the recycling test in Fig. 3. A typical TEM image for Pt/C after the recycling test is also shown.

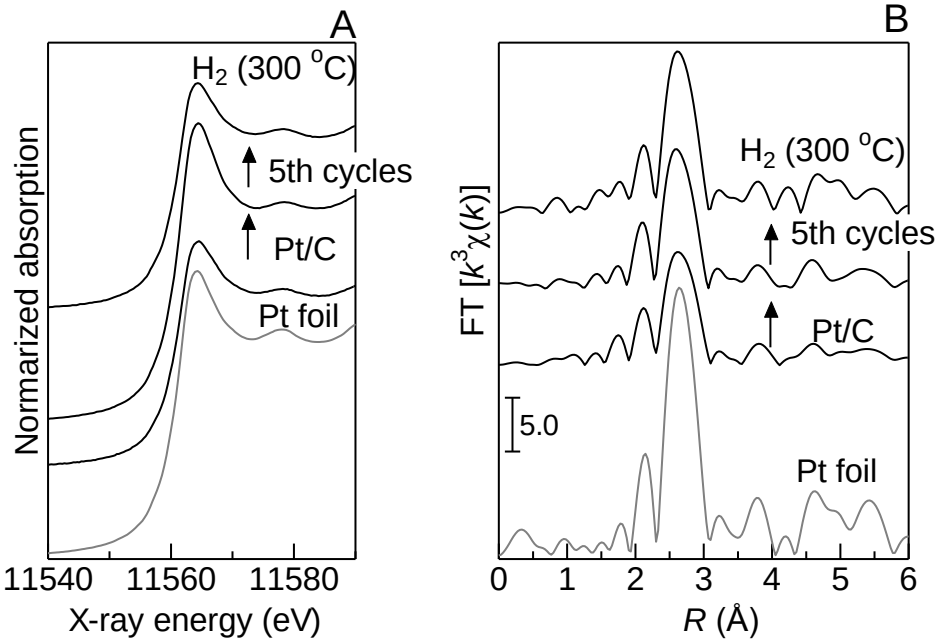


Fig. 5. Pt L_3-edge (A) XANES spectra and (B) EXAFS Fourier transforms of Pt/C before and after the recycling test in Fig. 3. Spectra of a reference compound (Pt foil) are shown as gray lines.

Table 5 Curve-fitting analysis of Pt L_3-edge EXAFS of Pt/C.

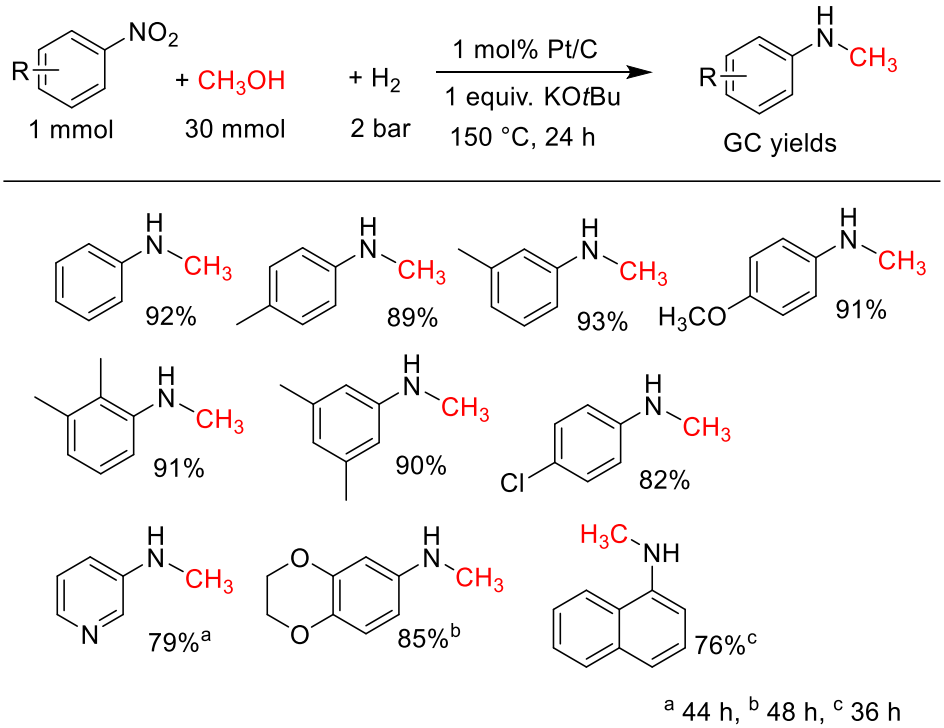
sample	shell	N [a]	*R* (Å) [b]	σ (Å) [c]	R_f (%) [d]
Pt/C	Pt	9.9	2.75	0.079	3.9
Pt/C (after 5th cycles)	Pt	9.0	2.73	0.069	2.1
Pt/C (H_2 at 300 °C)	Pt	10.9	2.74	0.071	2.7

[a] Coordination numbers. [b] Bond distance. [c] Debye-Waller factor. [d] Residual factor.

3.3.4 Synthesis of *N*-methylanilines from nitroarenes

Recently, Kundu et al. reported the first example of the tandem transformation of nitro compounds into *N*-methylated amines by methanol under H_2 [19]. Upon successful development of the selective *N*-methylation protocols for anilines, we aimed to extend the scope of our method to the tandem synthesis of methyl anilines from nitroarenes under H_2. Optimization studies (not shown) on a model substrate, nitrobenzene, produced the following conditions: nitrobenzene (1 mmol), methanol (30 mmol), 1 mol% Pt/C, 1 equiv. KO*t*Bu, 150 °C, under 2 bar H_2. **Scheme 5** shows the substrate scope for the conversion of nitroarenes to *N*-methyl amines. Nitrobenzene and its derivatives with electron-donating and electron-withdrawing groups, 3-nitropyridine, 3,4-ethylenedioxynitrobenzene, and 1-nitronaphthalene

were transformed to the corresponding *N*-methylated amines in good to high yields (76-93%). The detailed mechanism of this one-pot reaction is not clear. Considering the recent report on the Pd nanoparticle-catalyzed tandem transformation of nitroarenes into *N*-methylated amines by formaldehyde under H_2 [63], it is most likely that the *in situ* formed formaldehyde and anilines are the key intermediates in this tandem reaction of nitroarenes.



Scheme 5. Pt/C-catalyzed synthesis of *N*-methylanilines from nitroarenes and methanol under H_2.

3.3.5 Factors affecting the catalytic activity

Finally, we discuss an essential factor affecting the catalytic activity of different metals supported on carbon. We carried out kinetic experiments for *N*-monomethylation of aniline **1b** by methanol under the conditions in **Scheme 4** using various metal-loaded carbon catalysts. By controlling the reaction time, the initial rates of *N*-methylaniline (**2b**) formation (V_0) were measured under the conditions where conversions of **1b** were below 30% (**Table 6**). In our previous work, we estimated the number of the surface metal atoms by using the volume-area mean diameter of the metal particles, assuming the (111) surface for fcc structures (Cu, Ir, Pt, Rh, Ni, Pd) and the (0001) surface for hcp structures (Ru and Re) [64]. The initial rates were divided by the number of the surface metal atoms to give the turnover frequency (TOF) per surface metal atom. We also reported the adsorption energies of a H atom on Pt(111), Ir(111), Pd(111), Rh(111), Cu(111), Ni(111), Ru(0001), and Re(0001) surfaces obtained by DFT

calculations [50]. The TOF per surface metal atom was plotted as a function of the adsorption energy of the H atom in **Fig. 6**. The result shows the metal species with favorable absorption energy exhibit higher TOF values. It is reasonable that metals with moderate metal–hydrogen bond strength are suitable for this *N*-methylation reaction because it proceeds through a borrowing hydrogen mechanism where the catalysts should dehydrogenate the substrate and formally transfer the H atoms to an unsaturated intermediate. The high performance of Pt/C over other metal catalysts is ascribed to its moderate metal–hydrogen bond strength.

Table 6. TOF calculations for carbon-supported metal catalysts and DFT calculations.

Metal	D^{a} (nm)	N^{b} (nm^{-2})	N_S/N_T [c]	V_0 [d] (mol h^{-1} mol_{metal}^{-1})	TOF [e] (h^{-1})	E_{Had} [f] (eV)
Cu	9.3	17.7	0.14	0.12	0.9	-2.60
Ir	4.9	14.6	0.26	6.31	24.2	-2.74
Pt	4.4	14.6	0.31	18.25	58.3	-2.81
Rh	3.8	15.6	0.35	6.99	19.9	-2.91
Ni	7.0	18.8	0.17	8.45	48.7	-2.92
Pd	8.3	14.8	0.17	9.51	57.6	-2.99
Ru	6.4	16.3	0.21	3.98	18.7	-2.99
Re	3.9	15.1	0.35	1.17	3.3	-3.17

[a] Volume mean diameter of supported metal particles estimated by TEM analysis.

[b] Number of metal atoms per unit area (nm^2) on the assumed surface.

[c] Dispersion of supported metals, N_S/N_T, where N_S is the number of surface metal atoms and N_T is the total number of metal atoms in the supported metals.

[d] Initial rate of **2b** formation per total metal atoms in the catalyst.

[e] TOF per surface metal atom defined as TOF = V_0 (mol h^{-1} mol^{-1}) × N_S/N_T.

[f] Adsorption energy of a H atom on the assumed metal surface [50].

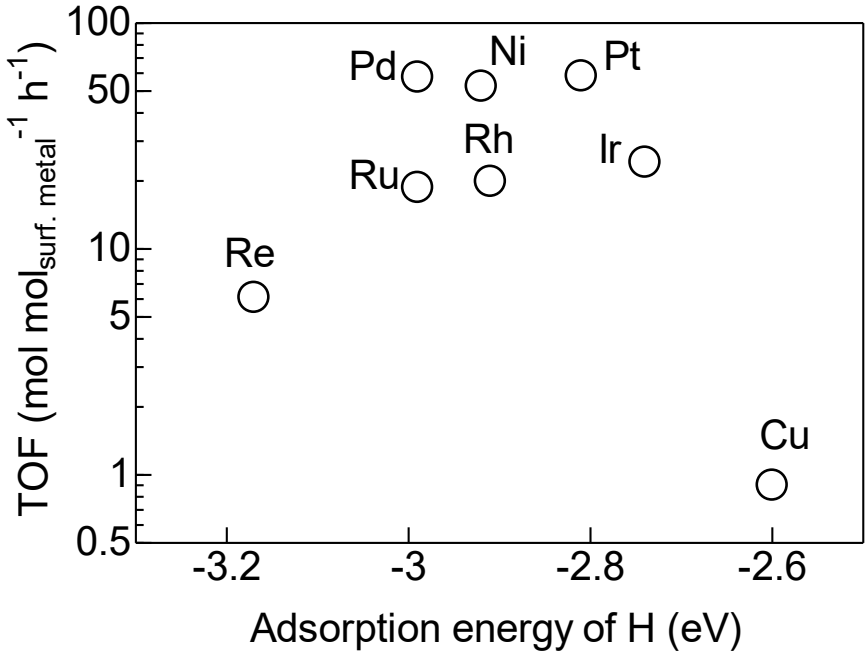


Fig. 6. TOF (per surface metal atoms) for *N*-monomethylation of aniline by metal-loaded carbon catalysts as a function of the adsorption energy of hydrogen on the metal surfaces (**Table 6**).

3.4 Conclusion

We have developed a general heterogeneous catalytic method for the selective *N*-methylation of amines and nitroarenes with methanol using Pt/C and base (NaOH or KO*t*Bu). The present catalyst system is effective for four types of *N*-methylation reactions: dimethylation of aliphatic amines, monomethylation of aliphatic and aromatic amines, and monomethylation of nitroarenes by tuning the reaction conditions such as temperature and atmosphere. Compared to the previously reported methods with homogeneous and heterogeneous catalysts, our method has the following advantages: (1) easy catalyst/product separation, (2) catalyst reusability, (3) high TON, and (4) broad applicability. Kinetic studies show the moderate metal–hydrogen bond strength of Pt is the main reason for its high for its high performance over other carbon supported metal catalysts.

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Chapter Four

Selective Transformations of Triglycerides into Fatty Amines, Amides, and Nitriles using Heterogeneous Catalysts

4.1 Introduction

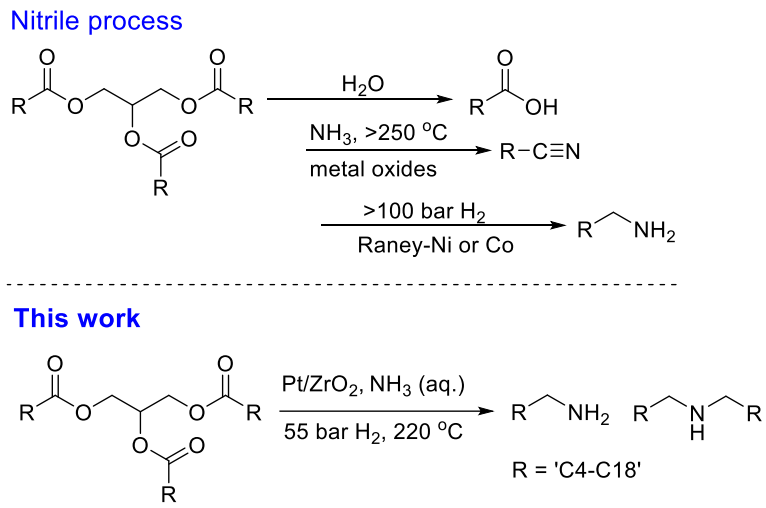
The alarming predictions for the rapid depletion of fossil-fuel resources have inspired researchers to develop alternative technologies that exploit renewable energy sources.[1-13] Many studies have focused on the conversion of lignocellulosic biomass[14-21] and triglycerides[14,22,23] into various platforms of value-added chemicals.[24-33] Industrially, triglycerides in oils and fats have been used as feedstocks for the synthesis of fatty amines, amides, nitriles, and alcohols, which in turn are used for the production of surfactants, polymers, and other useful commodity chemicals.[34]

Currently, fatty amines are produced industrially from triglycerides via fatty nitriles or fatty alcohols.[1,34] In the former method ('nitrile process' in **Scheme 1**), triglycerides extracted from oilseeds undergo hydrolysis to afford fatty acids, which are then treated with NH_3 in the presence of metal-oxide catalysts at high temperature to yield fatty nitriles; a subsequent metal-catalyzed high-temperature hydrogenation of the nitriles under high pressure of H_2 furnishes the targeted fatty amines.[14,34,35] In the latter method, fatty acids or their methyl esters are hydrogenated to generate fatty alcohols, which are then treated with NH_3 to produce fatty amines.[36] Henkel & Co Ltd. have reported a direct conversion of triglycerides into amines using Zn-Al_2O_3 or Zn-Cr_2O_3 catalysts with NH_3 or short-chained alkyl amines. However, this method suffers from serious drawbacks, which include harsh reaction conditions (200-400 °C; 50-400 bar H_2) and the use of sub-stoichiometric amounts of catalysts.[37] Recently, Beller and co-workers have reported the first homogenous catalytic method for the direct synthesis of *N*-alkylated amines from triglycerides and amines under a H_2 pressure of 60 bar,[38] which employs the [Ru(acac)$_3$]/Triphos/HNTf$_2$ catalytic system (acac = acetylacetonate; Triphos = 1,1,1-tris(diphenylphosphinomethyl)-ethane; HNTf$_2$ = triflimide). Although this study represents a significant step forward in this area, this catalytic system still requires additives and suffers from difficulties associated with catalyst/product separation. In addition, the use of NH_3 as a nitrogen source was not addressed in this report.

Fatty amides are widely used as/in surfactants, lubricants, cosmetics, shampoos, foam-control agents, fungicides, corrosion inhibitors, water repellents, detergents, and anti-blocking agents in the plastics-processing industry.[39-41] Industrially, fatty amides are currently produced using a two-step process (**Scheme 2**): the conversion of triglycerides into fatty acid esters, followed by a high-temperature aminolysis to produce fatty amides.[42] Several studies have reported the direct amidation of triglycerides with amino alcohols or isopropylamine using basic promoters such as methoxides,[43] NaOH/CaO,[44] Na-doped Ca(OH)$_2$,[45] and

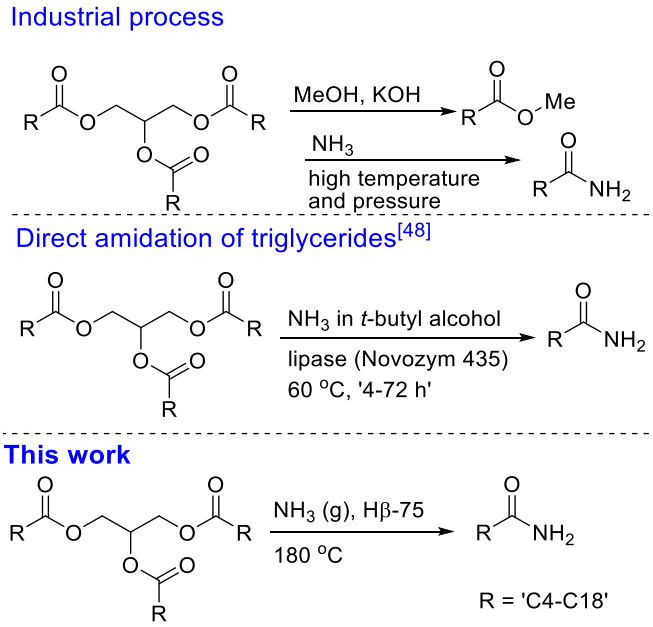
Li-doped CaO,[46] or using solid acid or biocatalysts.[47] However, reports on the direct amidation of triglycerides with NH_3 remain scarce. To the best of our knowledge, only one report discusses the direct amidation of triglycerides to amides using NH_3-saturated *t*-butyl alcohol and lipase (Novozym 435).[48] An environmentally benign method for the synthesis of fatty amides based on reusable heterogeneous catalysts thus represents an attractive research target.

Reports on the direct synthesis of fatty nitriles from triglycerides and NH_3 remain equally scarce. As summarized by Corma,[1] fatty nitriles are generally obtained from triglycerides via fatty acids or their esters (**Scheme 3**).[1,49,50] Even though the direct synthesis of nitriles from renewable triglycerides is highly desirable, only one method has been reported so far, and that method requires high temperatures (400 °C).[51] Thus, the development of more viable catalytic methods for the direct synthesis of nitriles from triglycerides is also desirable.

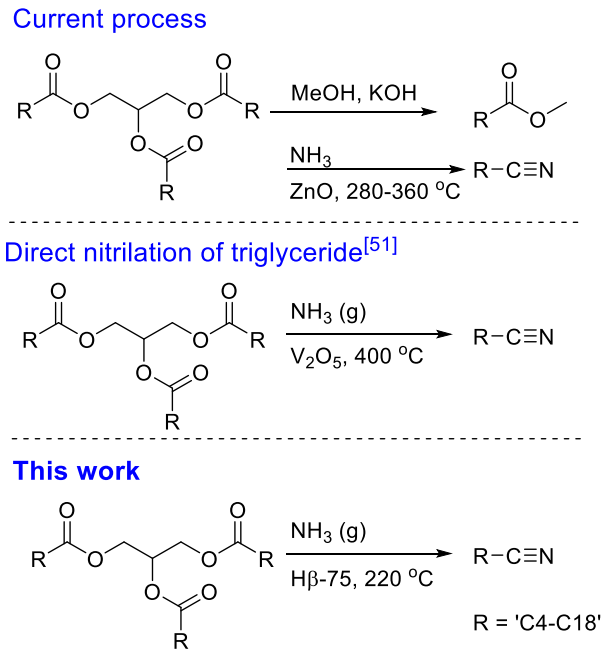


Scheme 1. The currently used multi-step industrial pathway to fatty amines (nitrile process) and the direct route presented in this study.

In general, benign manufacturing processes for the direct transformation of triglycerides into fatty amines, amides, and nitriles are relatively rare.[1] Herein, we report three types of selective heterogeneous catalytic methods for the direct transformation of triglycerides into amines, amides, and nitriles. First, we show the direct synthesis of amines from triglycerides and aqueous NH_3 under H_2 using a Pt-loaded ZrO_2 (Pt/ZrO_2) catalyst. Then, we demonstrate the direct conversion of triglycerides with gaseous NH_3 in to the corresponding amides or nitriles using a commercially available H-beta zeolite (Hβ) catalyst.



Scheme 2. Comparison of the amidation of triglycerides: the currently favored industrial multistep process, the direct lipase (Novozym 435) catalyzed amidation using ammonia-saturated *t*-butyl alcohol, and the Hβ-75-catalyzed direct amidation with gaseous NH_3 (this work).



Scheme 3. Comparison of different nitrilation processes and this work (Hβ-75-promoted one-pot nitrilation with NH_3).

4.2 Results and Discussion

4.2.1 Characterization of Pt/ZrO_2

Figure 1 shows the results of the X-ray absorption near-edge structure (XANES) and extended X-ray absorption fine structure (EXAFS) measurements for pre-oxidized PtO_X/ZrO_2, pre-reduced Pt/ZrO_2, and the corresponding reference compounds (Pt foil and PtO_2). The distances and coordination numbers for the Pt–O and Pt–Pt shells were determined by a curve-fitting analysis of the EXAFS data (**Table 1**). The XANES spectrum of PtO_X/ZrO_2 shows an intense white-line peak that is quite similar to that of PtO_2. The EXAFS spectrum of PtO_X/ZrO_2 consists of a single Pt–O contribution at 2.02 Å with a coordination number of 5.5. The XANES and EXAFS results show that the Pt species in PtO_X/ZrO_2 are platinum oxides. The XANES spectrum of the reduced Pt/ZrO_2 is basically identical to that of Pt foil. The EXAFS analysis of Pt/ZrO_2 shows 4.5 Pt–Pt bonds at 2.65 Å. This distance is shorter than the Pt–Pt distance in bulk Pt metal (2.76 Å), and the Pt–Pt coordination number (4.5) is lower than that of bulk Pt metal (12). These features are similar to those of previously reported small Pt metal clusters. [52]

Figure 2 shows the annular bright field scanning transmission electron microscopy (ABF-STEM) image and high-angle annular dark-field STEM (HAADF-STEM) images of Pt/ZrO_2, which show small Pt particles (diameter < 2 nm). In their entirety, the characterization data of the unreduced precursor (PtO_X/ZrO_2) and of reduced Pt/ZrO_2 suggest that the former is composed of platinum oxides on ZrO_2, while the latter consists of small Pt nanoparticles on ZrO_2.

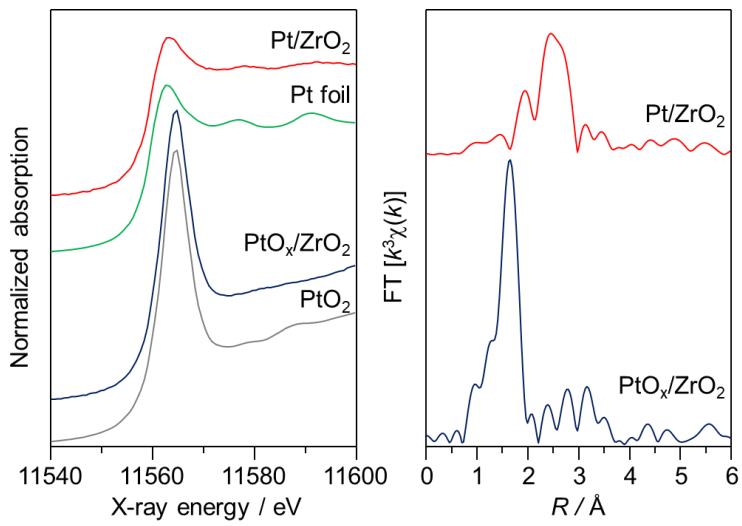


Figure 1. Pt L_3-edge XANES (left) and EXAFS Fourier transforms (right) of the Pt catalysts and the reference compounds.

Table 1. Curve-fitting analysis of the Pt L_3-edge EXAFS of the supported Pt catalysts.

Sample	Shell	N [a]	*R* (Å) [b]	σ (Å) [c]	R_f (%) [d]
PtO_X/ZrO_2	O	5.5	2.02	0.061	0.8
Pt/ZrO_2	Pt	4.5	2.65	0.078	0.3

[a] Coordination number. [b] Bond distance. [c] Debye-Waller factor. [d] Residual factor.

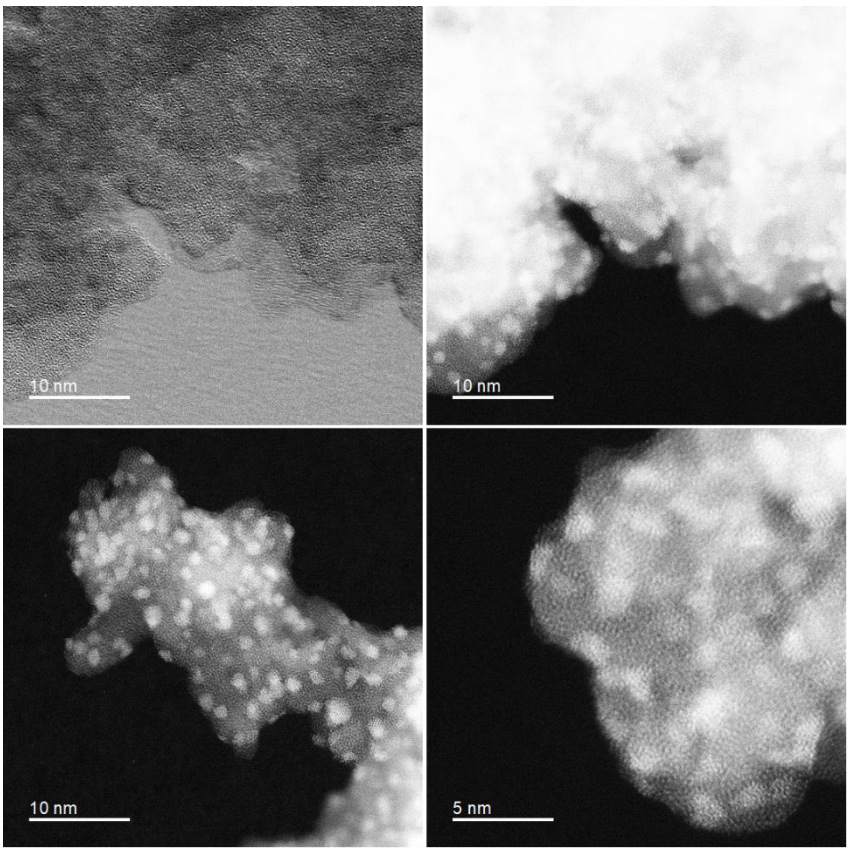


Figure 2. ABF- and HAADF-STEM images for Pt/ZrO_2.

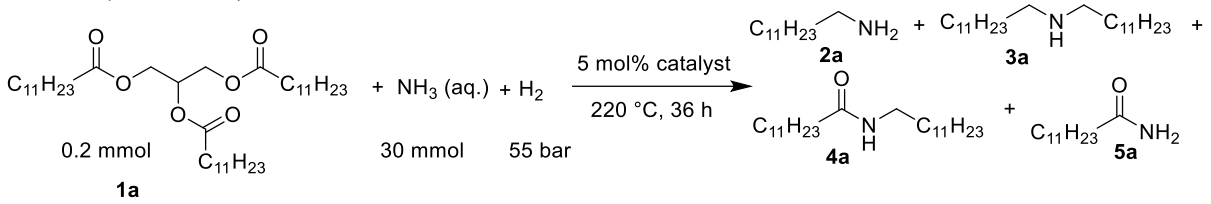
4.2.2 Transformation of triglycerides into amines

To optimize the catalysts and reaction conditions for the reductive amination of triglycerides, we carried out a benchmark reaction, in which trilaurin (**1a**) was treated with aqueous ammonia under H_2 in a stainless-steel autoclave (dead space: 9.7 cm^3). Catalyst screening tests (**Table 2**) were carried out using a series of supported metal nanoparticle catalysts that were pre-reduced under a flow of H_2 at 300 °C: a mixture of **1a** (0.2 mmol), 28% aqueous ammonia (30 mmol NH_3), and the catalyst containing 0.01 mmol of Pt (5 mol% with respect to **1a**) was stirred for 36 h at 220 °C under 55 bar H_2. **Table 2** summarizes the yields of dodecylamine (**2a**) and *N,N*-didodecylamine (**3a**) together with those of the undesired side products *N*-dodecyldodecanamide (**4a**) and dodecylamide (**5a**). In the first screening tests (entries 2-10), we tested 5 wt% Pt on various support materials. In the absence of a catalyst

(entry 1), only **5a** was obtained in 72% yield. Using PtO_x/ZrO_2 also furnished only **5a** (80% yield) as an unreduced side product (entry 2). However, when using the pre-reduced metallic catalyst Pt/ZrO_2 (entry 3), amines were observed as the major products (**2a**: 43% yield; **3a**: 20%), together with unreduced side products (**4a**: 18%; **5a**: 17%). These results indicate that metallic Pt is the active species for the present reductive amination, while Pt oxides are inactive. Exposure of the reduced Pt/ZrO_2 catalyst to air at room temperature for 0.5 h (entry 4) resulted in lower amine yields (**2a**: 17%; **3a**: 3%). The lower yields could potentially be attributed to a decrease in the superficial amount of Pt^0 species due to a re-oxidation by O_2. The reactions using metallic Pt on carbon (entry 5) and various other metal oxides (Al_2O_3, CeO_2, TiO_2, Nb_2O_5, and MgO; entries 6–10) afforded mixtures of **2a**, **3a**, **4a**, and **5a**, and the yields of amines **2a** and **3a** were lower than those obtained from Pt/ZrO_2. Interestingly, the yields of the amines increased upon decreasing the Pt load from 5 wt% to 1 wt% (entries 12-20). The yield of **2a** obtained from using 1 wt% Pt on ZrO_2 (entry 12) was higher than those obtained from other transition-metal-loaded ZrO_2 catalysts (entries 13-20), which furnished the unreduced amides **4a** and **5a** as the major products. The yield of **2a** decreased in the order Pt > Pd > Ru > Rh > Ni > Ir > Re > Cu > Ag. Based on the screening results, we identified 1 wt% Pt/ZrO_2 (entry 12) as the most suitable catalyst for the selective amination of **1a** to amines (**2a** and **3a**).

In separate catalytic experiments using Pt/ZrO_2 catalysts with different Pt loadings (1, 3, and 5 wt%), we estimated the initial formation rates for the conversion of **1a** into amines **2a** and **3a** under those conditions where the conversion of **1a** was < 40%, and we calculated the rates per total number of Pt atoms in the catalysts. We also carried out CO-adsorption experiments for the Pt/ZrO_2 catalysts in order to estimate the number of superficial Pt^0 sites. The reaction rates per total number of Pt atoms and the fraction of surface Pt^0 sites per total number of Pt atoms in Pt/ZrO_2 (**Figure 3**) show similar trends as a function of the Pt loading, and the catalyst with the lowest loading exhibits the highest conversion rate and the highest fraction of superficial Pt^0 sites. These results show that the high activity of the 1 wt% Pt/ZrO_2 catalyst is due to the high dispersion of Pt^0 in the catalyst.

Table 2. Catalyst screening for the amination of triglyceride **1a** into amines (**2a** and **3a**) and amides (**4a** and **5a**).



Entry	Catalyst	**2a** Yield [%] [a]	**3a** Yield [%] [a]	**4a** Yield [%] [a]	**5a** Yield [%] [a]
1	none	0	0	0	72
2	PtO_x/ZrO_2	0	0	0	80
3	Pt/ZrO_2	43	20	18	17
4	Pt/ZrO_2 -air [b]	17	3	1	77
5	Pt/C	3	0	5	79
6	Pt/Al_2O_3	6	2	7	82
7	Pt/CeO_2	14	26	11	46
8	Pt/TiO_2	21	8	7	60
9	Pt/Nb_2O_5	9	6	4	79
10	Pt/MgO	6	1	1	87
11	Pt/ZrO_2	48	24	17	9
12	Pt/ZrO_2	59	32	7	2
13	Pd/ZrO_2	28	9	7	45
14	Rh/ZrO_2	19	6	2	57
15	Ir/ZrO_2	11	7	1	69
16	Ni/ZrO_2	13	5	3	71
17	Ru/ZrO_2	21	8	5	53
18	Re/ZrO_2	9	6	2	73
19	Cu/ZrO_2	1	2	1	86
20	Ag/ZrO_2	0	0	0	85

[a] Yields were determined by GC (error range ±1.5%) Metal loading: 5 wt% for entries 2-10; 3 wt% for entry 11; 1 wt% for entries 12-20. [b] A pre-reduced Pt/ZrO_2 catalyst was exposed to air for 0.5 h at room temperature prior to use.

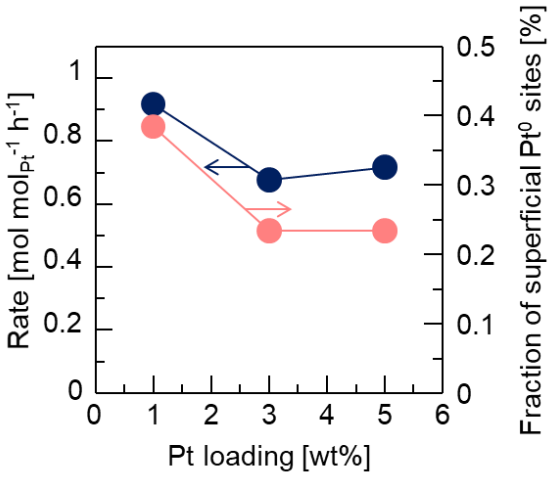
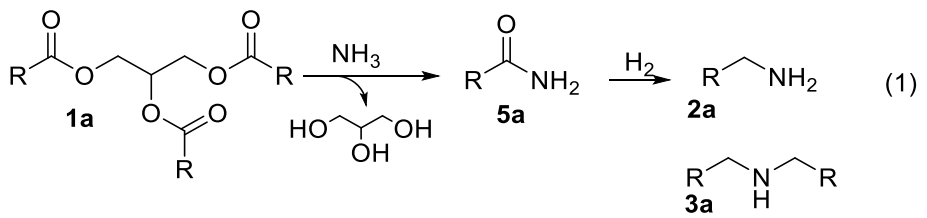
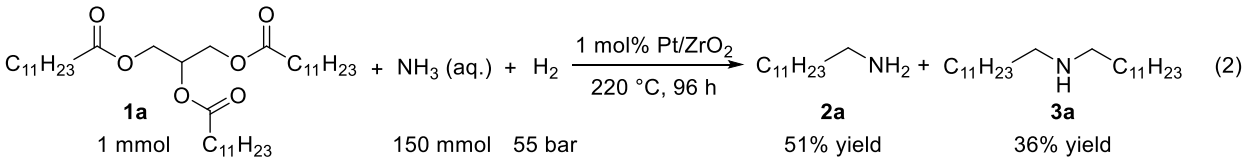


Figure 3. Conversion rate for the amination of **1a** into **2a** and **3a** per total number of Pt atoms in the catalyst and fraction of the superficial Pt^0 sites per total number of Pt atoms in Pt/ZrO_2 as a function of the Pt loading in the catalyst.

Using the most effective catalyst, 1wt% Pt/ZrO_2, we then optimized the reaction conditions. **Figure 4** shows plots of the yields of amines **2a** and **3a** and amides **4a** and **5a** as a function of (A) the reaction temperature (150-240 °C), (B) the H_2 pressure (10-55 bar), (C) the amount of catalyst (0.5-5.0 mol%), and the reaction time (0-36 h) for the Pt/ZrO_2-catalyzed reductive amination of **1a** with aqueous NH_3. The temperature dependence of the yields under otherwise optimized conditions (55 bar H_2, 36 h, 5 mol% catalyst) in **Figure 4A** shows that increasing the temperature (up to 220 °C) results in a decreased yield of dodecylamide (**5a**) and an increased yield of amines (**2a** and **3a**); accordingly, 220 °C was identified as the optimal temperature. The effect of the H_2 pressure on the yields under otherwise optimized conditions (220 °C, 36 h, 5 mol% catalyst) in **Figure 4B** shows that increasing the H_2 pressure leads to a decreased yield of amide **5a**, while the yield of the amines (**2a** and **3a**) is increased; accordingly, 55 bar was identified as the most suitable pressure. The effect of the amount of catalyst on the yields under otherwise optimized conditions (220 °C, 55 bar H_2, 36 h) in **Figure 4C** shows that increasing the amount of catalyst decreases the yield of amide **5a** and increases that of the amines (**2a** and **3a**); accordingly, 5 mol% of the catalyst affords the highest yield of the amines (**2a** and **3a**). The time course of the reaction under the optimal conditions (**Figure 4D**) shows the typical kinetic pattern of a consecutive reaction. In the early stages of the reaction ($t < 5$ h), the amount of unreacted trilaurin (**1a**) decreases with time, accompanied by the formation of dodecylamide (**5a**) and then *N*-dodecyldodecanamide (**4a**). The yields of **5a** and **4a** reach a maximum at 5 h and 8 h, respectively, before they decrease with time, accompanied by the formation of the amines (**2a** and **3a**). After 36 h, the yields of the amines do not increase anymore. It should be noted that, no glycerol was observed during the time course analyses of the amination reaction. The kinetic results indicate that **2a** and **3a** are produced via the consecutive pathways shown in eqn. (1): **1a** undergoes a direct amidation with NH_3 to give **5a**, which is then hydrogenated to give **2a**; part of **2a** can react with free lauric acid to give the *N*-dodecyldodecanamide **4a**. Dodecylamine **2a** partly can also undergo a self-coupling reaction to form *N,N*-didodecylamine **3a**, which could also partly be produced by the hydrogenation of *N*-dodecyldodecanamide **4a**.



As the attempt to gram scale synthesis of amine (eqn. 2), we demonstrated the reaction of 1 mmol of **1a**, 150 mmol of NH_3 (aq.) and 55 bar of hydrogen using 1 mol% of Pt/ZrO_2 catalysts for 96 h and obtained yields of amines are 51% for dodecylamine and 36% for *N,N*-didodecylamine. This implies that the developed catalytic method, is also applicable for higher scale conversion of triglyceride to corresponding amines.



Under the optimized reaction conditions (220 °C, 36 h, 55 bar H_2, 5 mol% of 1 wt% Pt/ZrO_2), we examined the substrate scope for the reductive amination of triglycerides with ammonia (**Scheme 4**). A series of triglycerides with different chain lengths (C4-C18) were converted into the corresponding primary and secondary fatty amines, whereby the yield of the former was moderate to good (48-59%). It is noteworthy that thus obtained fatty amines are an important class of chemicals for the industrial production of surfactants, germicides, and softeners. Although reductive amination of relatively reactive carbonyl compounds such as ketones and aldehydes to give amines has been studied extensively,[53-59] reports on reductive amination of carboxylic acids and esters including triglycerides are still relatively rare.[33,38,60-63] Our heterogeneous catalytic system using H_2 and NH_3 as a nitrogen source without any additives would serve as an effective method for the direct transformation of triglycerides into fatty amines.

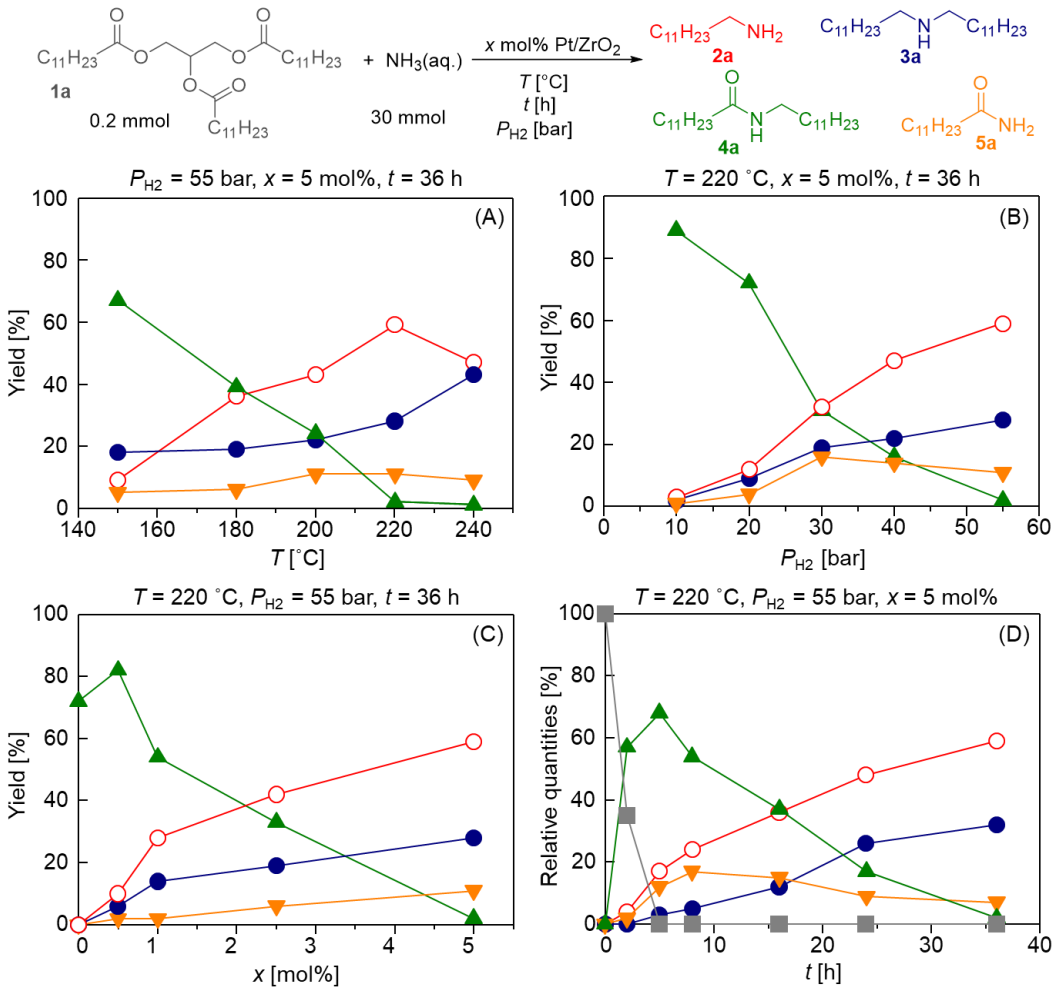
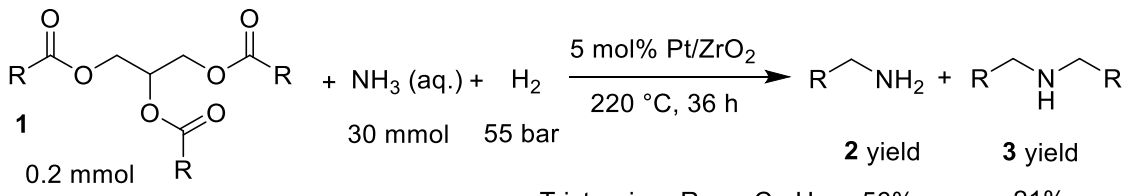


Figure 4. Optimization of the reaction conditions for the reductive amination of trilaurin **1a**.



		2 yield	**3** yield
Tristearin,	R = n-$C_{17}H_{35}$	: 56%	21%
Tripalmitin,	R = n-$C_{15}H_{31}$	: 54%	19%
Trimyristin,	R = n-$C_{13}H_{27}$	: 53%	18%
Trilaurin,	R = n-$C_{11}H_{23}$	: 59%	28%
Tricaprin,	R = n-C_9H_{19}	: 51%	30%
Tricaprylin,	R = n-C_7H_{15}	: 49%	31%
Tricaproin,	R = n-C_5H_{11}	: 48%	33%
Tributyrin,	R = n-C_3H_7	: 52%	31%

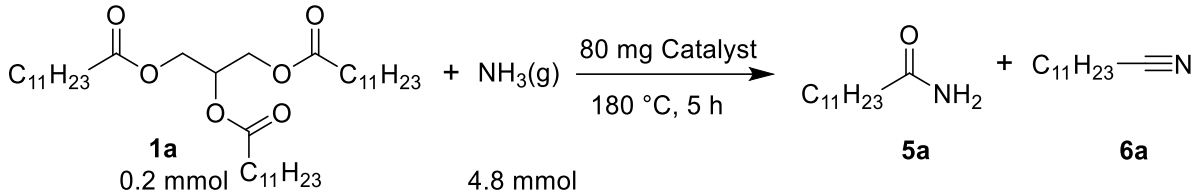
Scheme 4. Examination of the substrate scope for the reductive amination of various triglycerides using 5 mol% of 1 wt% Pt/ZrO_2.

4.2.3 Transformation of triglycerides into amides and nitriles

Potentially, the reactions of triglycerides with NH_3 could also represent useful synthetic routes to fatty amides and nitriles. However, catalytic methods that afford fatty amides and nitriles in high yield remain rare, mostly due to the low reactivity of triglycerides and the difficulties associated with controlling the selectivity, i.e., the difficulties associated with preventing an over-dehydration to nitriles. Classically, multi-step methods with low atom efficiency are used for the synthesis of fatty amides and nitriles.[12] Thus, an operationally simple heterogeneous catalytic method for the selective synthesis of primary fatty amides from triglycerides and ammonia represents an attractive research target.

To establish high-yield catalytic methods for the transformation of triglycerides into fatty amides and nitriles, we carried out a catalyst screening on the model substrate trilaurin **1a** (4 bar/ 4.8 mmol NH_3; 180 °C; 5 h). **Table 3** summarizes the yields of dodecylamide **5a** and dodecanenitrile **6a**. Under the applied conditions and in the absence of any catalyst, **5a** and **6a** were not obtained (entry 1). Various acid or base catalysts, including various types of heterogeneous catalysts (entries 2-17) and three types of homogeneous catalysts (entries 18-20) were also tested for this reaction. Among various single-metal oxides, ZrO_2 (entry 6) and SiO_2 (entry 8) afforded **5a** in relatively high yield (67-68%). We also screened Hbeta (Hβ) zeolites with different Si/Al ratios; Hβ-75, a zeolite with an intermediate Si:Al ratio of 75:1, furnished the highest yield of **5a** (95%). Among commercially available acidic resins, Amberlyst-15 afforded **5a** in higher yield (82%) than a *Nafion*/SiO_2 composite (32%). The water-tolerant homogeneous Lewis acid $Sc(OTf)_3$ and the homogeneous Brønsted acids p-toluenesulfonic acid (PTSA) and H_2SO_4 furnished **5a** in moderate to low yields (8-41%). Thus, Hβ-75 was identified as the best catalyst for the selective synthesis of amide **5a** from trilaurin **1a** and NH_3.

Table 3. Catalyst screening for the selective amidation of trilaurin (**1a**) to dodecylamide (**5a**).



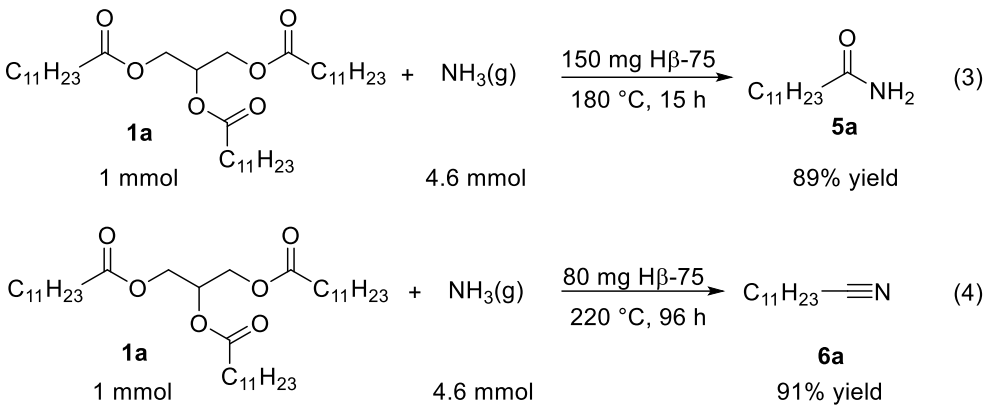
Entry	Catalysts	**5a** Yield [%] [a]	**6a** Yield [%] [a]
1	none	0	0
2	Nb_2O_5	28	10
3	TiO_2	19	6
4	CeO_2	16	3
5	Al_2O_3	24	4
6	ZrO_2	67	5
7	MgO	9	4
8	SiO_2	68	7
9	Hβ-12.5	62	5
10	Hβ-20	66	6
11	Hβ-75	95	4
12	Hβ-255	78	4
13	HZSM5-75	52	3
14	HY-50	61	5
15	HMOR-45	59	2
16	Amberlyst-15	82	7
17	Nafion/SiO_2	32	5
18	$Sc(OTf)_3$	41	7
19	PTSA	32	3
20	H_2SO_4	8	1

[a] Yields were determined by GC (error range ±1.5%)

Subsequently, we tested the effect of various reaction parameters on the yields of **5a** and **6a** for this reaction (**Figure 5**). The effect of the reaction temperature on the yields of **5a** and **6a** shows that the yield of **5a** is highest at 180 °C (**Figure 5A**). The effect of the initial NH_3 pressure on the yields of **5a** and **6a** were tested by carrying out the reaction at 180 °C using different initial amounts of NH_3 (mmol) in the reactor. The results (**Figure 5B**) show that increasing amounts of NH_3 afford higher yields of **5a**. The time course of the reaction under 4 bar NH_3 (4.8 mmol NH_3) at 180 °C (**Figure 5C**) shows that the yield of **5a** reaches a maximum after 5 h. Based on these results, the optimal conditions for the selective synthesis of fatty amides were determined as: 4 bar NH_3, 180 °C, 5 h, Hβ-75 (80 mg).

Hβ-75 catalyzed reaction of triglyceride with gaseous ammonia is time dependent and it produces nitrile under prolong reaction time. For the gram scale synthesis of dodecanamide

(eqn. 3) the reaction of 1 mmol of trilaurin **1a**, 4.6 mmol (considering 29.3 cm^3 of dead space) of NH_3(g) using 150 mg of Hβ-75 catalyst was performed for 15 h (optimized at complete conversion of trilaurin with minimum yield of nitrile), which produces 89% yield of dodecanamide and 5% dodecanenitrile respectively. We have also conducted the gram scale reaction for nitrile synthesis from trilaurin (eqn. 4). Using 80 mg of Hβ-75 catalyst, reaction of trilaurin (1 mmol) with NH_3(g) 4.6 mmol (considering 29.3 cm^3 of dead space) was resulted in 91% yield of dodecanenitrile and 3% dodecanamide at 220 ºC in 96 h.



Under the optimized conditions, we examined the substrate scope of this catalytic amidation using various triglycerides (**Scheme 5**). Triglycerides with different chain lengths (C4-C18) were selectively transformed into the corresponding fatty amides in high yield (82-95%). A slightly longer time (6 h) was required for the optimal transformation of the long-chain triglycerides (C13, C15, and C17).

The time course data at 180 °C (**Figure 5C**) after 5 h shows that amide **5a** is converted into **6a** in up to 78% yield (after 36 h). This indicates that **5a** undergoes dehydration to form dodecanenitrile **6a**. This result motivated us to investigate the optimal conditions for the selective conversion of triglycerides into nitriles using Hβ-75 as a catalyst. **Figure 5D** shows the time course of the same reaction at higher temperature (220 °C). The formation rate of **6a** and the final yield of **6a** were higher than those at 180 °C, i.e., the yield of nitrile **6a** reached 96% after 40 h. It is interesting to note that only by tuning the reaction conditions, the same zeolite works as a catalyst for the selective synthesis of amides and nitriles.

Under the conditions stipulated in **Figure 5D** (40 h), we studied the substrate scope of the direct nitrile synthesis using various triglycerides (**Scheme 6**). The C4-C18 triglycerides were transformed into the corresponding fatty nitriles in high yield (86-98%). Conventionally, fatty nitriles are produced from triglycerides via methyl esterification, followed by amidation

with ammonia and dehydration of the amides to the corresponding fatty nitriles. [1,49,50] This reaction represents a rare example of a direct catalytic reductive nitrilation of various triglycerides with NH_3.

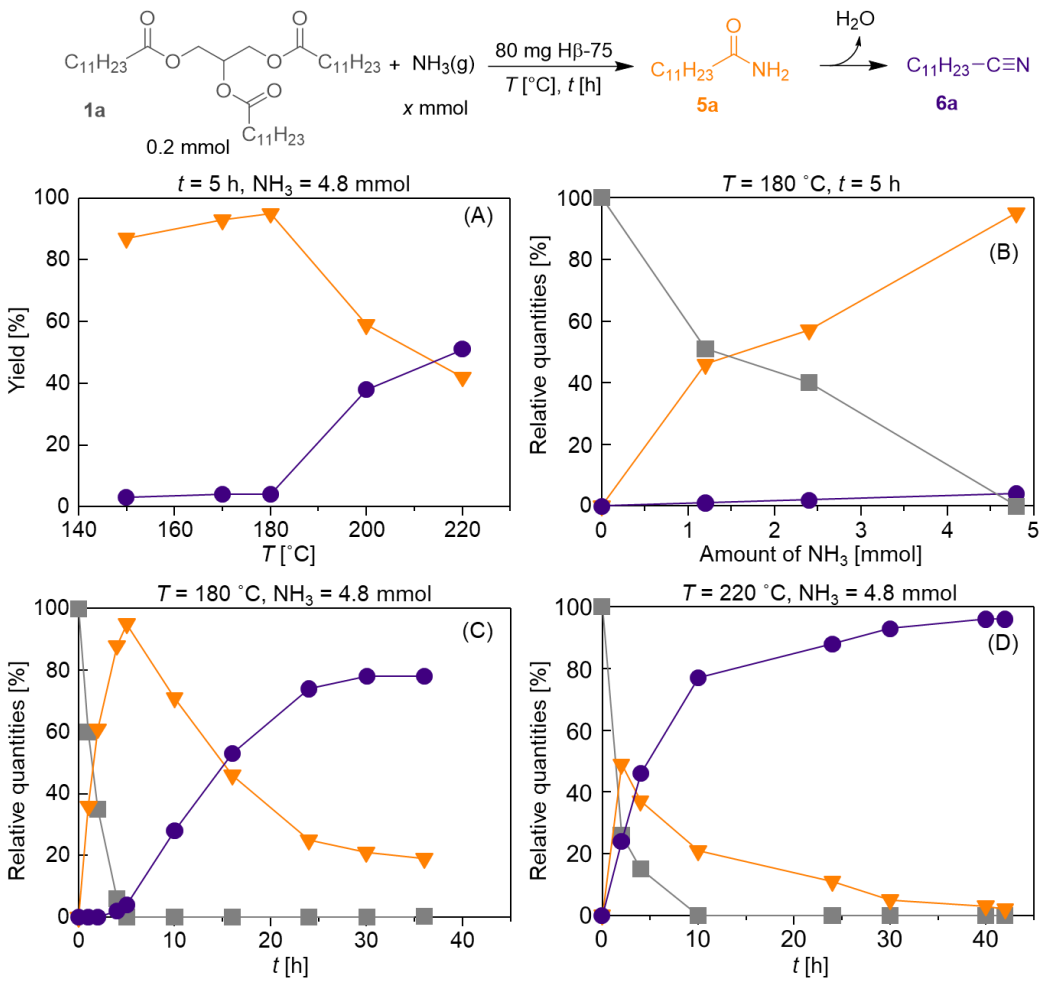
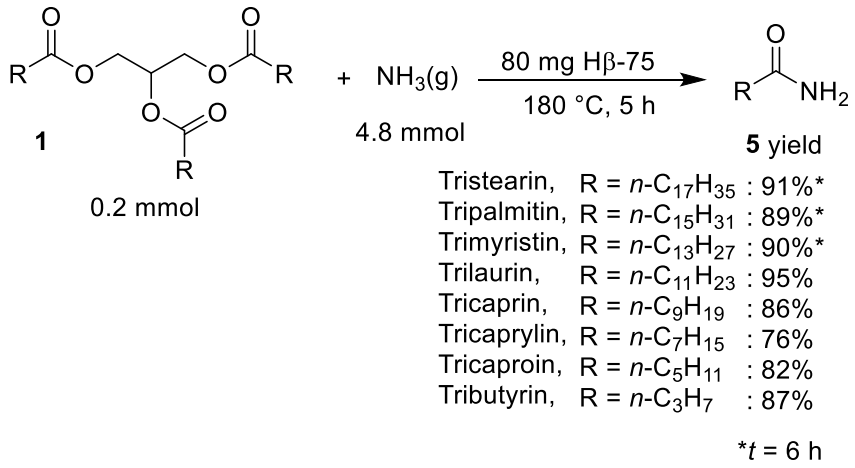


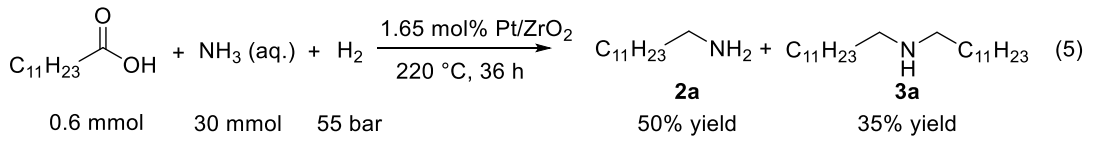
Figure 5. Optimization of the reaction conditions for the selective amidation of trilaurin (**1a**) to dodecylamide (**5a**) and dodecylnitrile (**6a**).



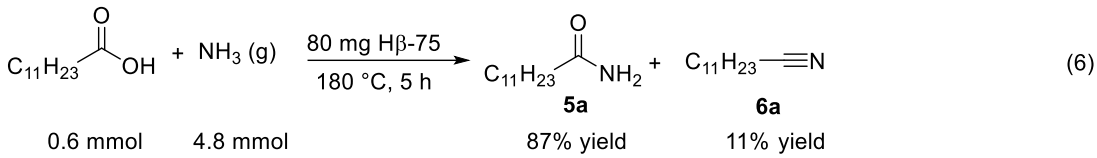
Scheme 5. Hβ-75 catalyzed direct amidation of triglycerides with NH_3.

We have also demonstrated the applicability of our catalytic systems to the lauric acid as a model of fatty acids. In this aspect, three types of reactions including amination, amidation and nitrilation of lauric acid were performed using Pt/ZrO_2 catalyst in eqn. (5) and Hβ-75 catalyst in eqn. (6) and (7) respectively. The reactions were designed with the same amount of lauric acid (0.6 mmol) as supposed to be generated from trilaurin (0.2 mmol) used in the model reactions of the above three catalytic systems keeping the other parameters of the reactions same as the standard model reaction conditions accordingly. Reductive amination of lauric acid produces dodecylamine **2a** and *N,N*-didocecylamine in 50% and 35% yields respectively. Amidation and nitrilation of lauric acid also resulted with high yields of corresponding amide and nitrile as shown in eqn. (6) and (7).

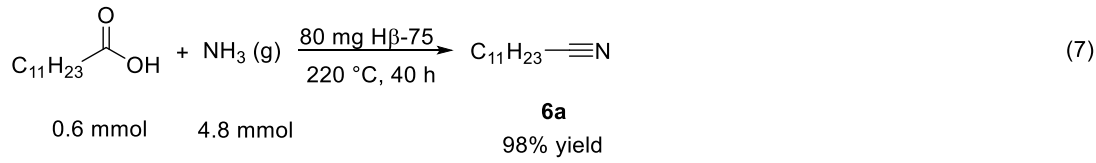
Amination of lauric acid



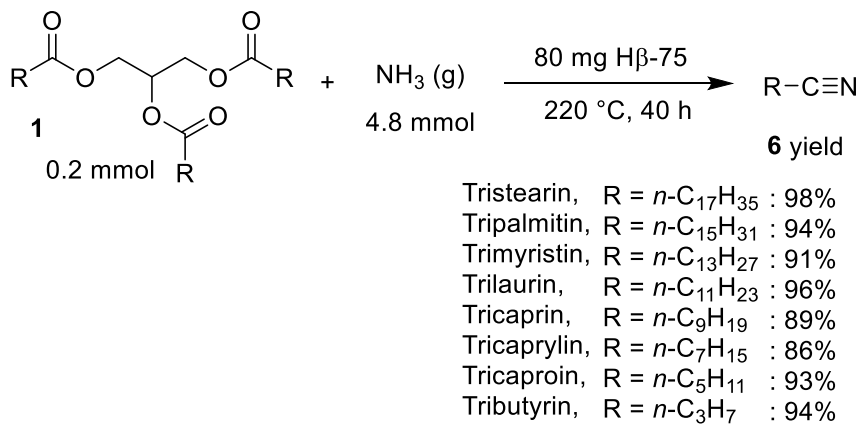
Amidtion of lauric acid



Nitrilation of lauric acid



Finally, we would like to discuss the factors affecting the catalytic activity of Hβ for the direct conversion of triglyceride **1a** into amides and nitriles using NH_3. Employing Hβ catalysts with different Si/Al ratios, we estimated the initial formation rates of amide **5a** and nitrile **6a** at 180 °C and 220 °C, respectively, under conditions where the conversion of **1a** was < 40%. As shown in **Figure 6**, the reaction rate per catalyst weight shows a volcano type dependence on the Si/Al ratio, in which Hβ with a moderate Si/Al ratio (Hβ-75) gives the highest rate.



Scheme 6. Hβ-75 catalyzed direct nitrilation of triglycerides with NH_3.

Recently, we have studied the hydrophilicity and acidity of such Hβ catalysts; [64-65] the number of acid sites was estimated by NH_3-TPD (temperature programmed desorption) and the hydrophobicity was estimated by the number of *n*-dodecane adsorbed on Hβ in water. The number of acid sites decreases with increasing Si/Al ratio, while the hydrophobicity of Hβ increases with the Si/Al ratio (**Figure 6**). Using the number of the acid sites, we calculated the turnover frequency (TOF) per acid site. The TOF for the formation of amides and nitriles increases with increasing Si/Al ratio, i.e., similar to the trend observed for the hydrophobicity of the zeolites.[66] These results indicate that the acidity and hydrophobicity are two important factors affecting the activity of the Hβ catalysts in this direct and selective catalytic reductive amidation/nitrilation of various triglycerides with NH_3. A larger number of acid sites and high hydrophobicity can increase the reaction rates (relative to the weight of the catalyst), which is the reason why the Hβ catalyst with a moderate Si/Al ratio (Hβ-75) exhibits the highest catalytic activity.

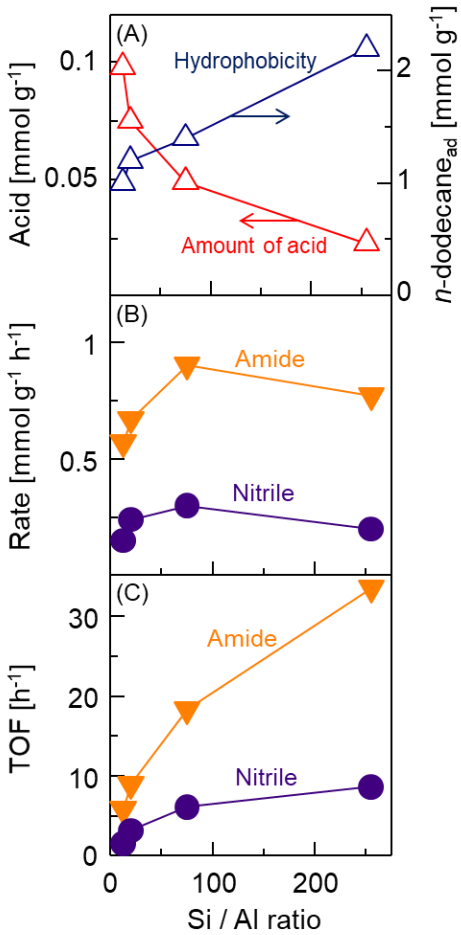


Figure 6. (A) Number of acid sites and amount of *n*-dodecane adsorbed in Hβ (hydrophobicity); (B) formation rates of amide **5a** and nitrile **6a** in the reactions of **1a** with NH_3 at 180 °C and 220 °C, respectively; (C) TOF per number of acid sites for the formation of amide **5a** and nitrile **6a** as a function of the Si/Al ratio in Hβ.

4.3 Experimental

4.3.1 General

Chemical reagents were purchased from common commercial suppliers (Tokyo Chemical Industry, Wako Pure Chemical Industries, Kishida Chemical, or Mitsuwa Chemicals) and used as received. GC-FID (Shimadzu GC-2014) and GC-MS (Shimadzu GCMS-QP2010) analyses were performed using an Ultra ALLOY capillary column UA$^+$-1 (Frontier Laboratories Ltd.) with N_2 or He as the carrier gas. ^{1}H and ^{13}C NMR measurements were conducted on a JEOL-ECX 600 spectrometer operating at 600.17 (^{1}H) and 150.92 MHz (^{13}C), or on a JEOL-ECX 400 spectrometer operating at 399.78 (^{1}H) and 100.52 MHz (^{13}C), using tetramethylsilane as the internal standard.

4.3.2 Catalyst preparation

In the zeolites Hβ-x, x denotes the Si/Al ratio. The catalysts Hβ-75 (JRC-Z-HB150; originally supplied from Clariant), Hβ-12.5 (JRC-Z-HB25), HMOR-45 (JRC-Z-HM90; originally supplied from Clariant), ZrO_2 (JRC-ZRO-5; 193.7 m^2 g^{-1}), TiO_2 (JRC-TIO-4), CeO_2 (JRC-CEO-3), and MgO (JRC-MGO-3) were supplied by the Catalysis Society of Japan. Nb_2O_5 was prepared by calcination (500 °C; 3 h) of $Nb_2O_5 \cdot nH_2O$ (kindly supplied by CBMM). SiO_2 (Q-10; 300 m^2 g^{-1}) was kindly supplied by Fuji Silysia Chemical Ltd. The carbon support (296 m^2 g^{-1}; Kishida Chemical) was commercially obtained. γ-Al_2O_3 was prepared by calcination of γ-AlOOH (Catapal B Alumina kindly supplied by Sasol; 900 °C; 3 h). Hβ-20 (HSZ-940HOA), Hβ-255 (HSZ-980HOA) and HY-50 (HSZ-385HUA) were purchased from Tosoh Co. HZSM5-75 was supplied from N.E. CHEMCAT Co.

Pt/ZrO_2 catalysts with a Pt loading of 1, 3, and 5 wt% were prepared by evaporating a mixture of ZrO_2 and an aqueous HNO_3 solution of $Pt(NH_3)_2(NO_3)_2$ at 50 °C, followed by consecutive drying (110 °C; 12 h) and reduction in a Pyrex tube under a flow of H_2 (20 cm^3 min^{-1}) at 300 °C (0.5 h). Other supported Pt catalysts with Pt loadings of 5 wt% were prepared by the same method. M/ZrO_2 (M = Rh, Ir, Ru, Pd, Re, Cu, Ni, Ag) catalysts with a metal loading of 1 wt% were prepared by a similar method as for Pt/ZrO_2 using aqueous HNO_3 solutions of $Rh(NO_3)_3$ or $Pd(NH_3)_2(NO_3)_2$, aqueous solutions of metal nitrates (Ni, Cu, Ag), $IrCl_3 \cdot nH_2O$, $RuCl_3$, or NH_4ReO_4. Platinum-oxide-loaded ZrO_2 (PtO_x/ZrO_2) was prepared by calcination of the $Pt(NH_3)_2(NO_3)_2$-loaded ZrO_2 (300 °C; 0.5 h; in air).

4.3.3 Characterization

ABF- and HAADF-STEM images for 1 wt% Pt/ZrO_2 were recorded on a JEM-ARM200F microscope (JEOL) using an acceleration voltage of 200 kV. The Cs-corrector CESCOR (CEOS) was used in the STEM mode. The pre-reduced catalyst powder that was exposed to air at room temperature, was mixed with ethanol, and this ethanolic suspension of the sample was dropped on a carbon-supported copper grid.

Pt L_3-edge X-ray absorption near-edge structures (XANES) and extended X-ray absorption fine structure (EXAFS) measurements were carried out in transmittance mode at the BL14B2 beamline of SPring-8 (8 GeV), using a Si(311) double crystal monochromator. The Pt/ZrO_2 catalyst, pre-reduced under a flow of H_2 (20 cm^3 min^{-1}) for 0.5 h at 300 °C, was cooled to room temperature under the flow of H_2 and sealed in a polyethylene-cell under N_2, before the EXAFS spectrum was recorded at room temperature. The curve-fitting EXAFS analysis was carried out using the REX ver. 2.5 program (RIGAKU) and the parameters for the

Pt–O and Pt–Pt shells provided by FEFF6.

4.3.4 Catalytic reactions

Before the catalytic tests for the amine synthesis, the metal catalysts were deposited in a glass tube (6.5 cm^3) and reduced for 0.5 h under a flow of H_2 at 300 °C. Catalytic experiments were carried out without exposing the reduced catalyst to air. Hexadecane (1 mmol) was added to the reduced catalyst via a septum inlet; thus, the catalyst was covered with the hexadecane layer to avoid exposure to air. After removal of the septum in air, triglycerides (0.2 mmol), an aqueous solution of 28 wt% NH_3 (30 mmol) and a magnetic stirrer bar were added to the tube. The tube was then inserted into a stainless-steel autoclave (dead space: 9.7 cm^3) and pressurized with H_2 (55 bar), followed by heating the autoclave to 220 °C for 36 h.

For the syntheses of amides and nitriles, triglycerides (0.2 mmol), *n*-hexadecane (0.25 mmol), and a magnetic stirrer bar were deposited in a reaction tube (30 cm^3) in air. The glass tube was then inserted in a low-pressure autoclave (dead space: 30 cm^3). Then, NH_3 (gas; 4.8 mmol) was added into the closed autoclave, which was subsequently heated for 5 h to 180 °C to yield the amide, and for 40 h to 220 °C to yield the nitriles.

After completion of the reaction ethylacetate (3 mL) was added and the products were analyzed by GC (Shimadzu GC-14B with Ultra ALLOY capillary column UA^+-1 of Frontier Laboratories Ltd., N_2) and GC-MS (SHIMADZU GCMS-QP2010 with Ultra ALLOY capillary column UA^+-1 of Frontier Laboratories Ltd., He). Product isolation was carried out by using column chromatography on silica gel 60 (spherical, 50-100 μm, Kanto Chemical Co. Ltd.) with hexane/ethylacetate (75/25) as the eluting solvent. The isolated products were then analyzed by using GC, GC-MS, ^1H and ^{13}C NMR. Isolated yields were determined relative to the starting triglycerides. Product yields (based on the amount of ester groups in triglycerides) were determined by GC analysis, where GC-sensitivities were estimated in comparison to the isolated products or to the commercial products applying *n*-hexadecane as an internal standard. Further careful analyses of GC conversions and yields were also estimated in an error range (±1.5) by exploiting the duplicated yields or conversions of same reaction. In substrate scope studies (**Schemes 4-6**), products yields are based on GC analysis and identified by GCMS in which the mass spectrometer was equipped with the same column as that used for GC analysis.

To ensure the presence of glycerol in the reaction mixture of all three types of the reaction systems, we work-up each model reactions by adding ethylacetate (3 mL) and D_2O (2 mL). Then aqueous layer was analyzed by ^1H NMR. Amination reaction doesn't show presence of glycerol under this reductive catalytic system whereas, glycerol was confirmed in the amidation

and nitrilation reaction mixture, which could be separated out from the desired products by simple water wash.

4.4 Conclusion

This study presents three heterogeneous catalytic methods for the selective one-pot transformation of triglycerides to value-added chemicals: (i) a reductive amination of triglycerides into fatty amines with aqueous NH_3 under an atmosphere of H_2 using ZrO_2-supported Pt metal nanoparticles, (ii) an amidation of triglycerides under gaseous NH_3 using a high-silica Hβ zeolite at 180 °C, and (iii) a direct synthesis of nitriles from triglycerides and gaseous NH_3 using a high-silica Hβ zeolite at 220 °C. These methods selectively transform a wide variety of triglycerides (C4-C18) into the corresponding amines, amides, and nitriles, and thus represent a milestone in chemical transformation of triglycerides. A systematic analysis of reaction (ii) and (iii) reveals that the acidity and hydrophobicity of the zeolites are two important factors that affect the catalytic activity of the Hβ catalysts. Specifically, increasing the number of acid sites and increasing the hydrophobicity may lead to higher reaction rates per weight of the catalyst.

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Chapter Five

High-silica Hβ zeolite catalyzed methanolysis of triglycerides to form fatty acid methyl esters (FAMEs)

5.1 Introduction

The concept of alternative energy sources has been recognized for decades and has become a core research area in chemical industries to address the growing demand for energy, rapid decline in fossil fuels, and necessity to lower the discharge of greenhouse gases and environmental pollution [1–8]. In this quest, biodiesel has become an inevitable alternative in the sector of fuel energy. Fatty acid methyl esters (FAMEs) are one of the most promising components of biodiesels [9–11]. They are currently produced by transesterification of triglycerides (plants oil or waste oil) with methanol using excess amounts of Na- or K-containing bases [12]. Although the current industrial methods provide a good productivity of FAMEs, the methods have the serious problem of a complicated catalyst removal process, which causes co-production of a large amount of wastes as well as a decrease in the yields and quality of the products. Mineral acids can catalyze the reaction, but in the presence of a small amount of water, free fatty acids are produced, which lead to soap formation that can inhibit separation of the biodiesel from glycerol [1,13].

To develop alternatives of the current method, various catalysts have been studied for transesterification of triglycerides using a wide range of homogeneous and heterogeneous catalysts. Homogeneous Brønsted base catalysts (such as carbenes [14]) and Lewis acid catalysts [15–18], including $Sc(OTf)_3$, have been developed, though these catalytic systems suffer from difficulties in catalysts/product separation and catalyst reuse. To overcome these drawbacks, metal oxides (sulfated zirconia [19], $MnTiO_3$ [20], hydrotalcite [21,22], heteropoly acids [23], solid base [24], bifunctional acid-base catalysts [25–27], zeolites [28–30] and metal–organic framework (MOF)-based catalysts [31–35]) have been developed as heterogeneous catalysts for the reaction. However, these catalysts suffer from low yields or catalyst deactivations during reuse tests, possibly arising from leaching of the catalytically active components. Among the reported heterogeneous catalysts, acidic [13,36–39] or basic [40–42] functional groups covalently immobilized to polymer supports show high yields of the methyl ester (75–99%) and good catalyst reusability. Especially, polymer-based organocatalysts with a hydrophobic nature [36,41] show excellent yields owing to their high affinity to triglycerides (lipophilicity) and low affinity to glycerol, which suggests that hydrophobicity is an important factor affecting the catalytic activity of heterogeneous catalysts for the methanolysis of triglycerides. So far, only a few studies have been devoted to the quantitative relationship between hydrophobicity and activity of heterogeneous catalysts for this reaction.

Recently, we demonstrated that a beta zeolite with a relatively high Si/Al ratio of 75 (Hβ-

75) is a highly active catalyst for one-pot amidation or nitrilization of triglycerides with NH_3 [43], hydration of alkynes and epoxides [44], and hydrolysis of esters [45]. Based on the quantitative relationship between acidity/hydrophobicity and the reaction rates for these reactions, we concluded that the high activity of Hβ-75 is caused by hydrophobicity and Bronsted acidity of the high-silica Hβ zeolite. Herein, we report that Hβ-75, a readily available commercial zeolite, shows higher yields of FAMEs for the methanolysis of triglycerides than various other catalysts including metal oxides, other zeolites, acidic resigns, and homogeneous catalysts. The importance of hydrophobicity is discussed on the basis of the quantitative relationship between acidity/hydrophobicity and reaction rates. It should be noted that zeolites (La^{3+}-exchanged beta [28] and beta zeolite with KOH [29] or with NaOH [30]) were studied for the methanolysis of vegetable oils, but the previous methods showed low yields of methyl esters (49–59%) and the quantitative analysis of effects of acidity/hydrophobicity was not discussed [30].

5.2 Material and methods

5.2.1 Catalysts preparation

Chemical reagents were purchased from known commercial suppliers (Tokyo Chemical Industry, Wako Pure Chemical Industries, Kishida Chemical, or Mitsuwa Chemicals) and used as received unless otherwise stated. The zeolites catalysts, commercially purchased, are named Hβ-x, where x denotes the Si/Al ratio. Hβ-75 (JRC-Z-HB150; originally supplied from Clariant), Hβ-12.5 (JRC-Z-HB25), HMOR-45 (JRC-Z-HM90; originally supplied from Clariant), HY-2.7 (JRC-Z-HY5.5), ZrO_2 (JRC-ZRO-5), TiO_2 (JRC-TIO-4), CeO_2 (JRC-CEO-3) were supplied by the Catalysis Society of Japan. Hβ-20 (HSZ-940HOA), Hβ-255 (HSZ-980HOA) and HY-50 (HSZ-385HUA), HY250 (HSZ-390HUA) were purchased from Tosoh Co. HZSM5-75, HZSM5-150 was supplied from N.E. CHEMCAT Co. Nb_2O_5 was prepared by calcination (500 °C, 3 h) of $Nb_2O_5 \cdot nH_2O$ (CBMM). γ-Al_2O_3 was prepared by calcination of γ-AlOOH (900 °C, 3 h; Catapal B Alumina, Sasol). SiO_2 (Q-10; 300 m^2 g^{-1}) was supplied by Fuji Silysia Chemical. Montmorillonite K10 clay and Amberlyst-15 were purchased from Sigma-Aldrich. Scandium(III) trifluoromethanesulfonate ($Sc(OTf)_3$) and *p*-toluenesulfonic acid (PTSA) were purchased from Tokyo Chemical Industry.

5.2.2 Catalytic reactions

For methanolysis of triglycerides, triglyceride **1a** (0.2 mmol), *n*-hexadecane (0.25 mmol), methanol (20 mmol), and a magnetic stirrer bar were charged in a reflux reaction tube (17 cm^3) in air. The glass tube was then secured with a cap, purged with N_2 to attain an inert atmosphere, and subsequently heated at 80 °C for 16 h under reflux; the upper part of the reaction tube was surrounded by a condenser. After completion of the reaction, 2-propanol (3 mL) was added to the reaction tube. The products were identified by gas chromatography (GC; Shimadzu GC-14B with Ultra ALLOY capillary column UA^+-1 of Frontier Laboratories Ltd., N_2) and gas chromatography–mass spectrometry (GC-MS; SHIMADZU GCMS-QP2010 with Ultra ALLOY capillary column UA^+-1 of Frontier Laboratories Ltd., He). Product yields (based on the amount of ester groups in triglycerides) were determined by GC applying *n*-hexadecane as an internal standard; GC sensitivities of methyl esters were estimated using the commercial products or the isolated methyl esters synthesized.

For the recycling reaction, the Hβ-75 catalyst was separated from the reaction mixture by simple centrifugation. The recovered catalyst was washed with H_2O (3 mL) several times to remove glycerol and then with ethyl acetate (3 mL) for several times, followed by drying at 110 °C for 3 h, and reused for the next reaction according to the standard procedure described above.

5.2.3 Adsorption experiments

For the liquid phase adsorption of glycerol, glycerol (2 mmol) in methanol (1 mL) was stirred with Hβ (0.1 g) for 12 h at room temperature, followed by centrifugation to separate the Hβ powder from the liquid. After evaporation of methanol from the liquid, D_2O (2 mL) and sodium acetate (0.2 mmol; internal standard) were added. The amount of glycerol in the liquid was analyzed by proton nuclear magnetic resonance (^{1}H NMR; JEOL-ECX 600).

NH_3-TPD measurement was examined using BELCAT (BEL Japan, Inc). Hβ-75 (50 mg) was heated in a flow of He (20 mL min^{-1}) at 500 °C for 10 min, followed by cooling to 200 °C. Then, the zeolite was exposed to a flow of 5% NH_3/He (20 mL min^{-1}) for 30 min. After purged in He for 30 min, the catalyst was heated linearly at 10 °C min^{-1} until 700 °C in a flow of He, and outlet gas (m/e = 16) was measured by the mass spectrometer (BEL Mass, BEL Japan, Inc.). Based on the result of NH_3-TPD (**Fig. S1**) in this study and the spectrum of IR measurement obtained our previous paper [44], the integrated molar extinction coefficient of the NH^{4+} in zeolites was obtained (0.013 cm μmol^{-1}). Using this coefficient value, the acidities of Hβ were re-evaluated based on the IR spectra of NH_3 adsorption.

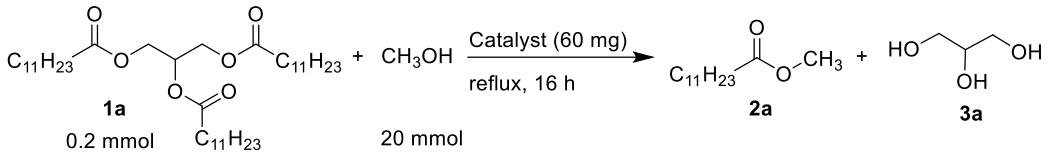
5.3 Results and discussion

5.3.1 Screening of Hβ zeolites and comparison with other catalysts

First, we employed a series of potential catalysts (**Table 1**) to the transesterification reaction of the model triglyceride, trilaurin **1a**, with methanol to obtain methyl laurate **2a**. For the test reaction, a mixture of **1a** (0.2 mmol), methanol (20 mmol), and the catalyst (60 mg) was stirred for 16 h under reflux conditions. Without catalyst (entry 1), **2a** was not observed. In the first screening tests (entries 2–12), we checked a series of proton-exchanged zeolites with different structures and Si/Al ratios. For the Hβ catalysts of Hβ-75 with different Si/Al ratio (entries 2–5), Hβ-75 having an intermediate Si/Al ratio of 75:1 gave the highest yield of **2a** (92%). An Si/Al ratio other than 75:1 gave a lower yield. That is, the Si/Al ratio of Hβ affected the yield of **2a**. The Hβ catalysts with a high Al content (Hβ-12.5) and low Al content (Hβ-255) both gave lower yields than Hβ-75. Similar trends were observed in the case of proton-exchanged HZSM5 (entries 6–8) and HY (entries 9–11) with different Si/Al ratios, where HZSM5 and HY with intermediate values of the Si/Al ratio gave the highest yields. Among the zeolites, Hβ-75 gave the highest yield of **2a** (92%).

Then, we compared the performance of Hβ-75 with other heterogeneous catalysts. Commercially available solid acids (montmorillonite K10 clay and Amberlyst-15) and metal oxides (SiO_2, Al_2O_3, ZrO_2, TiO_2, SnO_2, CeO_2, and Nb_2O_5) gave poor yields (1–16%) of **2a** (entries 13–21). We tested the reaction with typical homogeneous catalysts (entries 22–25), including Brønsted acids (H_2SO_4, PTSA), a Lewis acid ($Sc(OTf)_3$), and a base (KOH). The reaction with 10 mol% (with respect to the ester group in **1a**) of these homogeneous catalysts gave **2a** in low to moderate yields (15–64%). Based on the above results, it was concluded that Hβ-75 is the most effective catalyst for the methanolysis of trilaurin **1a** to methyl laurate **2a**.

Table 1. Catalyst screening for methanolysis of trilaurin to methyl laurate.



Entry	Catalysts	Yield **2a** (%)[a]
1	blank	0
2	Hβ-12.5	51
3	Hβ-20	65
4	Hβ-75	92
5	Hβ-255	68
6	HZSM5-20	39
7	HZSM5-75	64
8	HZSM5-150	56
9	HY-2.7	53
10	HY-50	78
11	HY-250	67
12	HMOR-45	22
13	Montmorillonite K10	1
14	Amberlyst-15	13
15	SiO_2	7
16	Al_2O_3	6
17	ZrO_2	12
18	TiO_2	4
19	SnO_2	1
20	CeO_2	8
21	Nb_2O_5	16
22[b]	$Sc(OTf)_3$	61
23[b]	H_2SO_4	15
24[b]	PTSA	64
25[b]	KOH	19

[a] Yields were determined by GC. [b] 0.06 mmol of the catalysts were used.

5.3.2 Optimization of reaction conditions

Having the best catalyst Hβ-75 in hand, we optimized the reaction conditions for the conversion of triglyceride **1a** (0.2 mmol) to the methyl laurate **2a**. We tested the effect of various parameters on the yields of **2a** for this reaction. **Figure 1** plots of the yields of the methyl ester **2a** versus (A) the heating temperature, (B) catalyst amount, (C) amount of methanol (5–60 mmol), and (D) reaction time for the Hβ-75 catalyzed reaction of **1a** with methanol. The results with different heating temperatures (50–100 °C) showed that temperatures higher than the boiling point of methanol (64.7 °C) were suitable (**Fig. 1A**). The reaction under reflux conditions (at a heating temperature of 80 °C) with different amounts of Hβ-75 (25–80 mg, **Fig. 1B**) and methanol (5–60 mmol, **Fig. 1C**) showed that 60 mg of Hβ-75 and 20 mmol of methanol were sufficient to obtain high yields. Finally, the time course of the reaction using 60 mg of catalyst and 20 mmol of methanol under reflux conditions (**Fig. 1D**) showed that the yield of **2a** reached a maximum value after 16 h. Based on these results, the optimal conditions were determined as follows; 60 mg of Hβ-75, 20 mmol of methanol, and 16 h under reflux conditions.

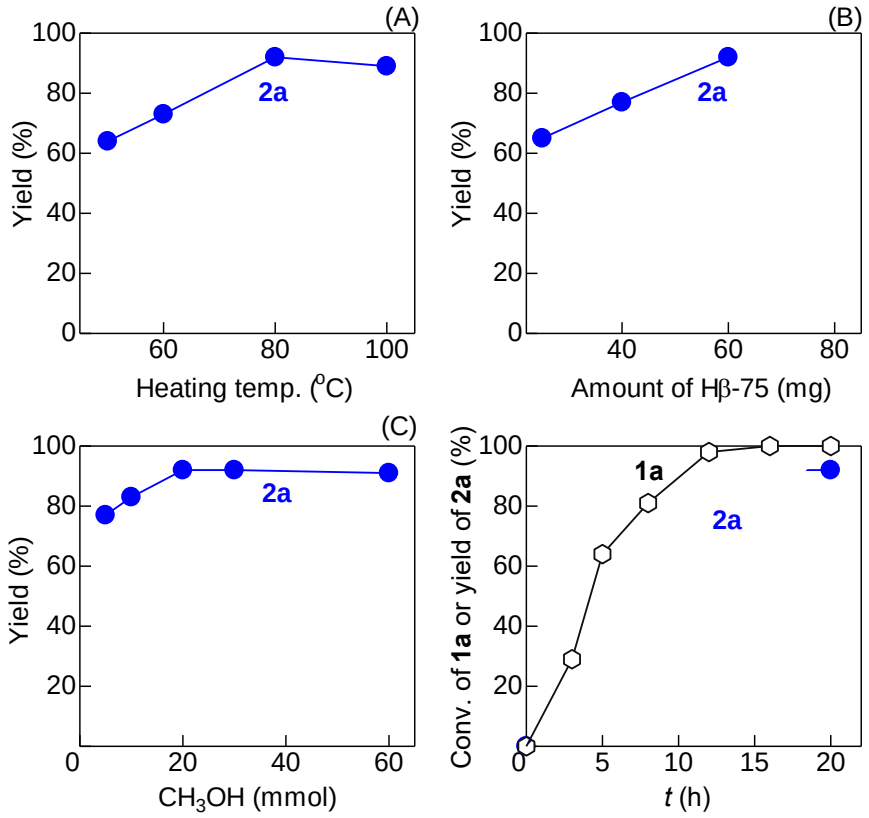
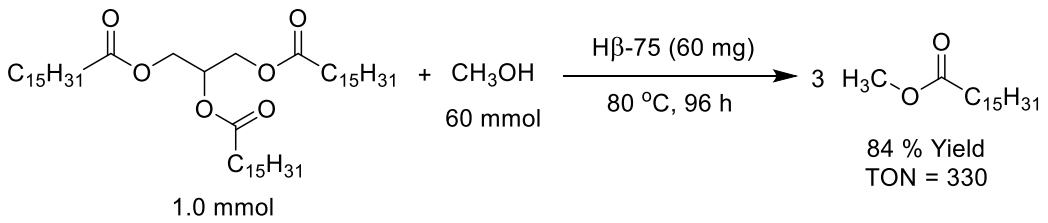


Fig. 1. Optimization of the reaction conditions for transesterification of **1a** to **2a** in methanol: (A) heating temperature, (B) amount of Hβ-75, (C) amount of methanol, (D) reaction time.

5.3.3 Application of the method and reusability of Hβ-75 catalyst

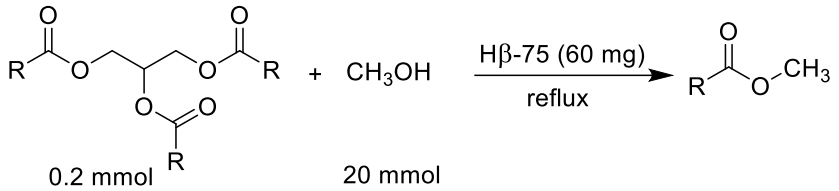
Under the optimized reaction conditions, we examined the substrate scope for the transesterification of various triglycerides with methanol (**Table 2**). Our method was successfully applied to a series of triglycerides with a different carbon backbone (C4-C18), which produced the corresponding methyl esters in high yields (87–93%). It is noteworthy that the thus obtained methyl esters are an important class of chemicals, which is best known as biodiesel and an obvious alternative to the conventional fossil fuels.

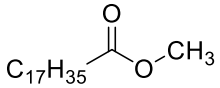
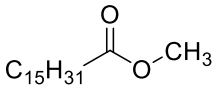
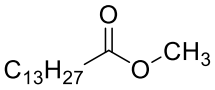
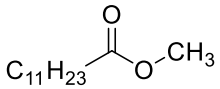
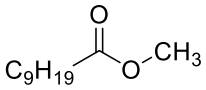
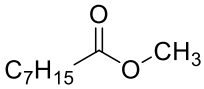
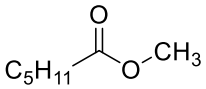
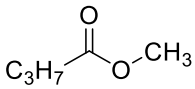
Next, we tested the reusability of the Hβ-75 catalyst for the standard reaction of **1a**. After the reaction, the Hβ-75 catalyst was recovered from the reaction mixture by simple centrifugation and regenerated (cf. Material and methods section). The spent catalysts were reused six times and maintained high yields of **2a** (85–92%), as shown in **Figure 2**. Turnover number for the first cycle was 121, based on the number of Brønsted acid sites (0.127 mmol g^{-1}) (**Table 3**) and total turnover number was 815. In a separate set of catalyst recycling experiments, the initial rate of **2a** formation was estimated for each cycle. The results (grey bars in **Figure 2**) indicated that the Hβ-75 catalyst was reusable for several cycles for this biodiesel synthesis reaction. Furthermore, we carried out the 1.0 mmol-scale reaction in methanolysis of tripalmitin, as shown in **Scheme 1**, where an 86% yield of product was obtained. The TON value reached to 330, which is higher than those in previous reported catalyst systems [37-39, 41, 42]. Our heterogeneous catalytic system using methanol does not require any additives and could serve as an effective method for the direct transformation of triglycerides into biodiesel.



Scheme 1. 1.0 mmol-scale methanolysis of tripalmitin using Hβ-75.

Table 2. Hβ-75 catalyzed transformation of triglycerides to methyl esters.



Entry	Triglycerides	Products	*t* (h)	Yield (%)[a]
1	Tristearin (R = $C_{17}H_{35}$)		22	89
2	Tripalmitin (R = $C_{15}H_{31}$)		20	93
3	Trimyristin (R = $C_{13}H_{27}$)		20	90
4	Trilaurin (R = $C_{11}H_{23}$)		16	92
5	Tricaprin (R = C_9H_{19})		16	91
6	Tricaprylin (R = C_7H_{15})		16	88
7	Tricaproin (R = C_5H_{11})		12	89
8	Tributyrin (R = C_3H_7)		12	87

[a] Yields were determined by GC.

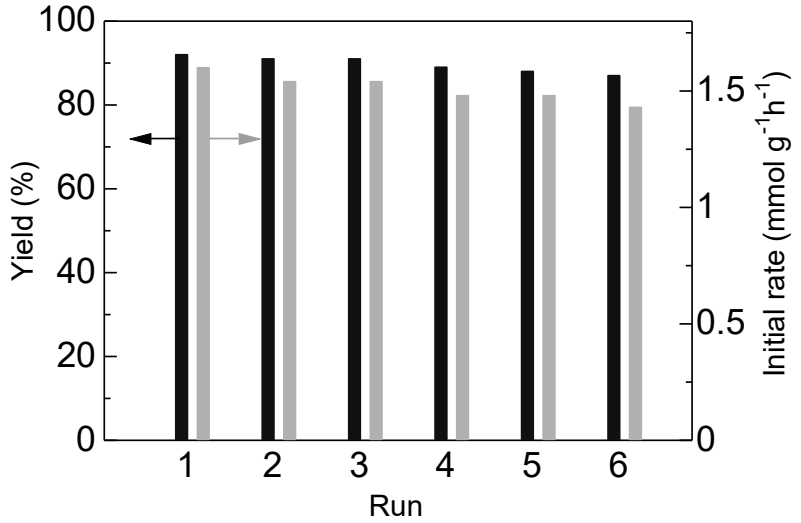


Fig. 2. Recycling of the catalyst for the methanolysis of trilaurin **1a** to methyl ester **2a** under the reflux conditions shown in Table 1 (entry 4): (grey bars) initial rates of **2a** formation (3 h) and (black bars) **2a** yields after 16 h.

5.3.4 Hydrophobicity effect

It has been demonstrated that the construction of a hydrophobic nature surrounding the catalytically active component could facilitate effective reaction environments for industrially important catalytic reactions including hydrolysis and hydration [44–46]. In our previous studies, we reported the characterization results on hydrophobicity and acidity of the Hβ catalysts [44,45]. Using these results, combined with the kinetic and adsorption results in this study, we will discuss the dominant factors affecting the catalytic activity of Hβ zeolites for methanolysis of **1a** as a function of Si/Al ratio.

First, we compared the molecular sizes of substrate and possible products in methanolysis of trilaurin with the pore size of Hβ zeolite. The minimum cross-diameters of trilaurin **1a** and dilaurates, such as 3-hydroxypropan-1,2-diyl laurate and 2-hydroxypropan-1,3-diyl laurate, are 9.9 Å × 9.1 Å, 9.5 Å × 8.6 Å, and 9.5 Å × 8.6 Å, respectively (**Fig. S2**). These values are slightly larger than the pore size of Hβ (7.6 Å × 7.3 Å). The minimum cross-diameters of monolaurates, such as 1,3-dihydroxypropan-2-yl laurate (6.3 Å × 6.0 Å) and 2,3-dihydroxypropan-1-yl laurate (7.3 Å × 6.6 Å), and methyl laurate **2a** (5.7 Å × 5.6 Å) are comparable with or smaller than the pore size of Hβ. Therefore, it is considered that methanolysis of triglycerides can occur in the pore of Hβ-75 although tri- and di-glycerides less smoothly access into the Hβ pore compared to monoglycerides.

For the kinetic study using Hβ catalysts with different Si/Al ratios, the initial rates of **2a** formation were measured under conditions where the conversions of **1a** were below 40%. As shown in **Fig. 3A**, the reaction rate per catalyst weight showed a volcano-type dependence on the Si/Al ratio; the Hβ catalyst with a moderate Si/Al ratio (Hβ-75) exhibited the highest rate. **Table 3** lists the number of Brønsted acid sites and the amount of *n*-dodecane adsorbed on Hβ zeolites in water (a hydrophobicity index) that was reported in our previous study [44]. Considering that the glycerol produced as a by-product of the methanolysis of **1a** is the most polar molecule in the reaction mixture, we carried out an adsorption experiment of glycerol in methanol at room temperature. **Table 3** shows the amount of glycerol adsorbed on Hβ zeolites in water. The reaction rates per catalyst weight were divided by the number of Brønsted acid sites to give the turnover frequency (TOF) for the present catalytic system. As shown in **Fig. 3B**, the TOF monotonically increased with the Si/Al ratio of the Hβ catalyst. The hydrophobicity monotonically increased with the Si/Al ratio (**Table 3**), while the amount of glycerol adsorbed decreased with the Si/Al ratio (**Fig. 3C**). Combined with the fact that the less polar substrates, triglycerides, should approach the Brønsted acid sites (polar sites), which are surrounded by polar molecules (glycerol and methanol), the high TOF of the high silica zeolite indicated that TOF (per Brønsted acid sites) increases with the hydrophobicity of the zeolite because of its low interaction with the polar by-product, glycerol, produced during the reaction. The volcano type dependence of the reaction rate (per catalyst weight) on the Si/Al ratio (**Fig. 3A**) was interpreted as follows. As the Si/Al ratio increases from 12.5 to 75, the interaction of zeolite pore surfaces with glycerol as a catalyst poison is weakened, leading to the higher reaction rate. Although the increase of Si/Al ratio from 75 to 255 further weakens the interaction between zeolite and glycerol, the number of Brønsted acid site as catalytically active sites decreases, resulting in the decrease of reaction rate. This result indicates that a balance between the hydrophobicity of zeolite pore surfaces and the number of Brønsted acid sites should be adjusted to achieve the efficient progression of the reactions.

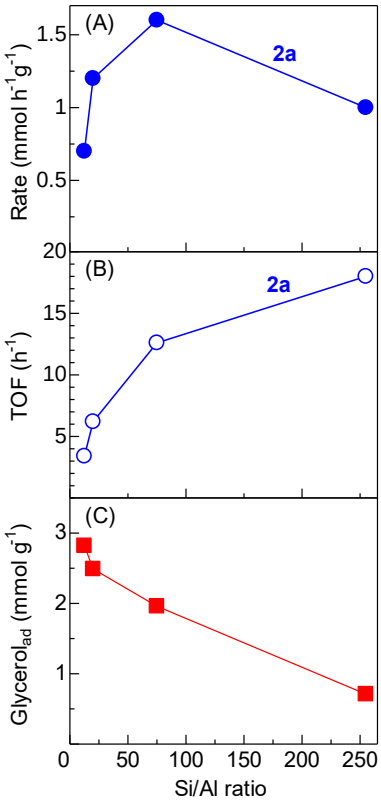


Fig. 3. Effect of the Si/Al ratios of Hβ on (A) the initial rates of the methanolysis of **1a** under the standard conditions, (B) TOF per number of Brønsted acid sites and (C) the amount of glycerol adsorbed on the Hβ samples.

Table 3. Acidity, hydrophobicity, and glycerol adsorption capacity of Hβ zeolites.

catalyst	$[H^+]^a$ (mmol g^{-1})	$Dodecane_{ad}$ [b] (mmol g^{-1})	$Glycerol_{ad}$ [c] (mmol g^{-1})
Hβ-12.5	0.208	1.0	2.82
Hβ-20	0.192	1.2	2.49
Hβ-75	0.127	1.4	1.96
Hβ-255	0.056	2.2	0.71

[a] Number of Brønsted acid sites estimated by IR measurement and NH_3-TPD (see experimental).

[b] Amount of *n*-dodecane adsorbed in Hβ at room temperature[44].

[c] Amount of glycerol adsorbed in Hβ at room temperature.

5.4 Conclusion

We report a simple method for the transesterification of triglycerides with methanol to fatty methyl esters using Hβ-75 with Si/Al = 75 as an active and reusable catalyst. The developed catalytic system can be applicable to the transformation of various triglycerides having C4-C18 frames. The number of Brønsted acid sites and hydrophobicity are dominant factors that influence the catalytic activity of the present catalytic system. Considering the commercial availability and high durability of the Hβ-75 catalyst, the method could be applicable to a practical process for the conversion of biomass-derived triglycerides into biofuel.

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Chapter Six

General Conclusion

General Conclusion

This thesis highlights our future challenges in resource, environment, economy, and societal sustainability that demand more efficient and benign scientific technologies for working with chemical processes and products. Sustainable syntheses as the concept of green chemistry address challenges by inventing novel reactions that can maximize the desired products and minimize by-products, designing new synthetic schemes that can simplify operations in chemical productions, and seeking chemicals that are inherently benign environmentally and ecologically. Driven with these hypotheses this thesis strived fundamental innovations in chemical sciences towards a new generation of chemical syntheses where renewable biomass can be used as the source materials. It has introduced several high atoms efficient and easy to operate synthetic methods for useful chemical synthesis utilizing benign chemicals and renewable resources to reflect the goals of sustainability in chemistry.

The Chapter 1 of this thesis is a general introduction where the background and motivation of this research due to some crucial concerns in the catalytic syntheses or challenges in sustainability are highlighted. The discussion focused on the depleting fossil resources and importance of finding alternative renewable sources, and recent discoveries in the field. Concerns raised on the necessity of replacing conventional multi-steps chemical processes by highly atom efficient one pot sustainable methods that uses renewable biomass. Indeed, catalysis has been recognized as the paramount strategy in chemical synthesis and heterogenization of chemical methods can lead the paradigm shift towards a greener world.

To realize the thought, Chapter 2 & 3 presented the heterogeneous methylation methods by Pt/C catalyst that placed the works in alternative synthesis of chemicals using sustainable methanol. A reusable catalytic method for *C*-methylation and *N*-methylation is reported which is highly versatile, selective, and recyclable. The heterogeneous catalytic processes can be applied to various families of compounds. Three types of *C*-methylation reactions using methanol as a sustainable C1 source: (1) the *β*-methylation of primary alcohols, (2) the *α*-methylation of ketones, and (3) the *C3*-methylation of indoles are reported. In addition, similar unique heterogeneous catalytic processes were developed for four types of *N*-methylation reactions: (1) *N,N*-dimethylation of aliphatic amines under N_2, (2) *N*-monomethylation of aliphatic amines under 40 bar H_2, (3) *N*-monomethylation of aromatic amines under N_2, and (4) tandem synthesis of *N*-methyl anilines from nitroarenes and methanol under 2 bar H_2. All these

reactions under the same catalytic system showed high yields of the corresponding methylated products for a wide range of substrates, high turnover number (TON), and good catalyst reusability. The catalyst Pt/C was prepared in the laboratory by simple thermal impregnation method and characterized using the advanced analytical techniques such as EXAFS, XPS, TEM, ABF- and HAADF-STEM and EDX etc. Mechanistic studies suggested that these catalytic systems are driven by borrowing hydrogen methodology. Kinetic results combined with density functional theory (DFT) calculations revealed that the high performance of Pt/C was attributed to the moderate metal–hydrogen bond strength of Pt.

In chapter 4 & 5, methods for sustainable synthesis of various functional chemicals from triglyceride - a renewable biomass feedstock has been described. Four types of heterogeneous catalytic methods have been developed for the selective one-pot transformation of triglycerides into value-added chemicals. The methods are: (i) the reductive amination of triglycerides to fatty amines with aqueous NH_3 under H_2 promoted by ZrO_2-supported Pt clusters, (ii) the amidation of triglycerides under gaseous NH_3 catalyzed by high-silica H-beta (Hβ) zeolite at 180 °C, (iii) the Hβ-promoted synthesis of nitriles from triglycerides and gaseous NH_3 at 220 °C and (iv) transesterification of biomass-derived triglycerides with methanol (methanolysis of triglycerides) to fatty acid methyl esters (FAMEs) catalyzed by high-silica H-beta (Hβ) zeolite. These methods are widely applicable to the transformation of various triglycerides (C4-C18 skeletons) into the corresponding amines, amides, nitriles and FAMEs. The used catalyst Pt/ZrO_2 is homemade, but H-beta (Hβ) zeolite is commercially available. For the reductive amination of TG to amine, high dispersion of Pt catalyst having smaller particle size and the intrinsic nature of ZrO_2 maintaining reactive Lewis acidity in the reaction condition probably the reason for high activity. In-depth studies on the reaction pathways and the catalytic features revealed that the number of Brønsted acid sites and hydrophobicity of the H-beta (Hβ) zeolite are dominant factors that influence the catalytic activity of the presented catalytic system. Particularly the quantitative relationships between acidity, hydrophobicity, and reaction rates versus Si/Al ratio of Hβ zeolite catalysts show that a low affinity to glycerol, which arises from the hydrophobicity of the high-silica zeolites, is an important factor for controlling the catalytic activity specially in case of fatty acid methyl ester synthesis.

==The End==