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Direct Synthesis of Chemicals by Acceptorless Dehydrogenation of Alcohols and Cyclic Amines with supported Pt Catalysts

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Hokkaido University

ABSTRACT

According to the concept of green chemistry, catalysis is an important key for ideal synthesis to prevent waste materials and increase atom economy. This concept urges chemist to develop new methodology to sustainable production of chemicals. Acceptorless catalytic dehydrogenation of alcohols and amines is regarded as one of the most important reactions for sustainable production of chemicals, because the reaction can give industrially important chemicals, carbonyl compounds and imines, without additional reagents. However, most of the reports used homogeneous catalysts, which have serious drawbacks of difficulties in product/catalyst separation and catalyst reuse and needs of additives including expensive ligands. Also, dehydrogenation of alcohols can be a key reaction in one-pot bond formation reaction from alcohols as an atom-efficient synthetic method, but most of the reports have used homogeneous catalysts. Development of heterogeneous catalysts for these reactions addresses the issues of homogeneous catalysts and consequently will provide practical methods for sustainable production of chemicals in industry. The objective of this thesis is to develop new heterogeneous catalysts for acceptorless dehydrogenation of amines and dehydrogenative one-pot bond formation reactions of alcohols. The thesis will show supported Pt nanoparticles are efficient and reusable heterogeneous catalysts for these reactions under additive-free conditions. Characterization of catalysts and model reactions are also studied to discuss catalyst design concept.

In chapter 2, the author investigated various metal loaded carbon catalysts and various supported Pt catalysts for acceptorless dehydrogenation of *N*-heterocycles under additive-free conditions under N_2. Pt metal nanoparticles-loaded carbon (Pt/C) was the best catalyst for the dehydrogenation of 6-methyl-1,2,3,4-tetrahydro-quinoline to 6-methyl-quinoline, and Pt/C was reusable. Various *N*-heterocycles, derivatives of tetrahydroquinoline and indoline, were converted to quinolines and indole with high yields. For the dehydrogenation of 1,2,3,4-tetrahydroquinoline, turnover number (TON) of Pt/C was more than one order of magnitude higher than those of the previous homogeneous and heterogeneous catalysts. Additionally, the same catalyst was effective

for the reverse reaction, hydrogenation of quinoline under 3 bar H_2. Thus, this catalytic method may be useful for a organic halide–based hydrogen storage system.

In chapter 3, a series of transition metal-loaded metal oxide catalysts were examined for the synthesis of indoles via acceptorless dehydrogenative cyclization of 2-(2-aminophenyl) ethanol. Pt/Nb_2O_5 and Pt/HBEA were found to be effective heterogeneous catalysts for the reaction. These catalysts showed higher TON than previously reported catalysts, and the Pt/Nb_2O_5 catalyst was reusable. The reaction consists of dehydrogenation and cyclodehydration steps with elimination of water as byproduct.

In chapter 4, the author examined various metal loaded-SnO_2 and supported Pt catalysts for acceptorless dehydrogenative coupling of primary alcohols to esters under additive-free and solvent-free conditions. Among screened catalysts, Pt/SnO_2 was most active. The method was effective for various primary alcohols under additive-free and solvent-free conditions, and the catalyst was reusable. IR study show that activation of carbonyl groups in aldehydes is the primary important role of the SnO_2 support. Combined with other mechanistic study a reaction pathway is proposed; the reaction of alcohol with the aldehyde coordinated to Sn^{4+} Lewis acid site to give a hemiacetal intermediate followed by its dehydrogenation to the ester. This catalytic system is the first example of heterogeneous catalyst for this reaction, which provides one of the most atom-efficient and step-efficient catalytic routes to esters from readily available starting materials, alcohols.

Chapter 5 is the general conclusion. Chapter 2-4 show systematic examples of new heterogeneous catalysts for acceptorless dehydrogenation reactions of amines (*N*-heterocycles) and alcohols for the synthesis of chemicals under additive-free conditions with liberation of H_2 as a byproduct. The heterogeneous catalysts developed in this work have advantages over the previous homogeneous catalysts, including good catalyst reusability and high TON, and hence will provide practical methods for sustainable production of chemicals.

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Chapter 1

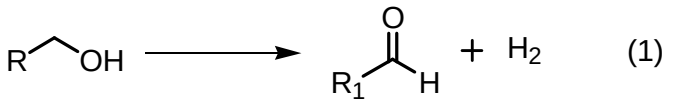
General Introduction

1. Introduction

Green chemistry is also known as sustainable chemistry, is an area of chemistry and chemical engineering focused on the design of products and processes that minimize the use and generation of hazardous substances.[1] The principle of green chemistry provide the concept of an ideal synthesis in terms of catalytic activity, selectivity, atom efficiency, step-efficiency and toxicity.[2,3] Researchers get inspiration from this concept to develop new atom-economical, environmentally benign synthetic methodology.

1.1. Catalytic Acceptorless Dehydrogenation of alcohols and cyclic amines

The dehydrogenation of alcohols (eqn.-1) and cyclic amines (eqn.-2) is of predominant importance in organic synthesis because of wide applications of carbonyl compounds and nitriles as important intermediates in medicines, agricultural chemicals and fragrances.[4-7]



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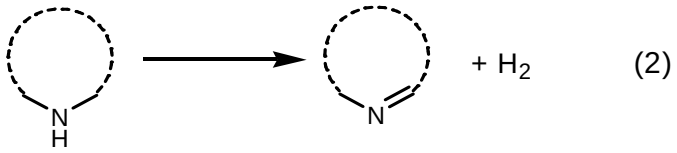

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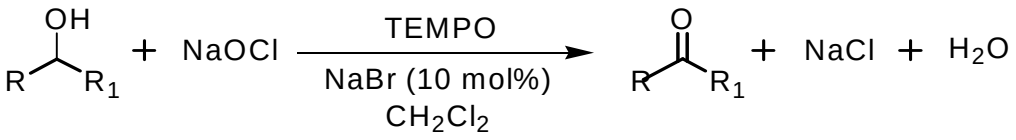
Catalytic dehydrogenation (CDH) is a very important reaction in the manufacturing of vendible chemicals.[8] Although CDH offers considerable benefits with respect to atom economy and environmental impact because of the avoidance of stoichiometric oxidants, it has been much less used in the synthesis of fine chemicals, pharmaceuticals, and agrochemicals. Inspite of sacrificial hydrogen acceptors and additives are frequently used, CDH of amines and alcohols has been realized with metal complexes in recent years.[9] More recently, Fujita and Yamaguchi reported the first example of homogeneous

dehydrogenation of tetrahydroquinolines using a [Cp*Ir(2-hydroxypyridine)] catalyst.[10] The limitation of this method is only a few examples of 1,2,3,4-tetrahydroquinolines were demonstrated and the reaction conditions were relatively forcing [2 mol% catalyst for 20 h in refluxing *p*-xylene (bp 138 °C) or 5 h in mesitylene (bp 165 °C)].

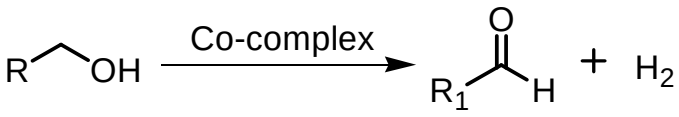
Acceptorless Dehydrogenation (AD) reactions can result not only in simple removal of hydrogen gas from various substrates but also, importantly, in surprisingly efficient and environmentally benign ("green") synthetic methodologies when intermediates resulting from the initial dehydrogenation process undergo further reactions. Conventionally, metal-based oxidants such as dichromate,[11] permanganate ions[12] in the presence of strong mineral acids, silver oxide,[13] and lead tetraacetate[14] in stoichiometric amounts[6,15] are used for dehydrogenations of alcohols and amines. On the contrary, in some cases precious metals have been used as efficient catalysts with molecular oxygen as main oxidant to effect this transformation.[16] A few reports are found by using organic oxidants such as TEMPO (scheme 1), which is applied for the purpose of dehydrogenation reaction.[17] For the above processes where acceptor[18] is used, the reactions generate excessive amounts of toxic metal salts waste[19] which is undesirable from both economical and environmental points of view or have difficulties to recover the expensive metal catalysts.



Scheme 1: Acceptorless dehydrogenation of alcohols using acceptor.[17]

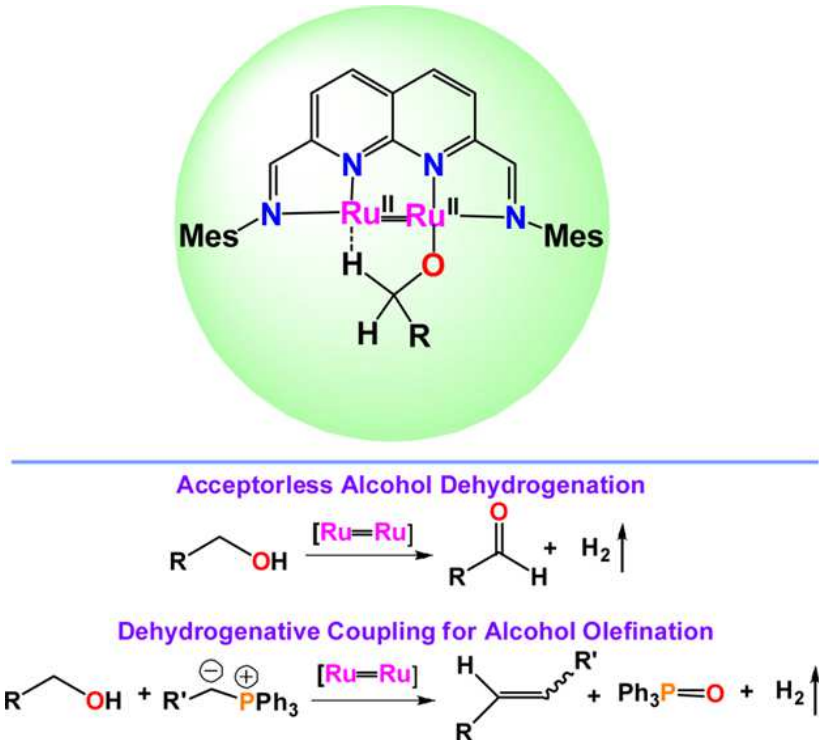
To overcome the drawbacks of the dehydrogenation method using acceptor, acceptorless method are also developed. The acceptorless dehydrogenation of alcohols is an efficient and atom-economical method for the convertion of alcohols into carbonyl compounds and other derivatives.[20,21] Alcohol dehydrogenation are used in hydrogen

storage and production, as a selective and low-temperature route to generate hydrogen from biomass-derived alcohols and carbohydrates.[22] G. Zhang et al. reported Co-complex[23] (scheme 2) catalyzed acceptorless dehydrogenation of alcohols, where no oxidant was used and no byproduct were produced. But the reported method is homogeneous, additives were used and showed lower turnover number.



Scheme 2: Co-complex catalyzed acceptorless dehydrogenation of alcohols.[23]

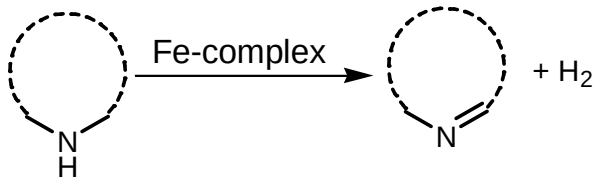
J. K. Bera et al. reported diruthenium-complex[24] catalyzed acceptorless dehydrogenation of alcohols (scheme 3). They have synthesized a diruthenium (II,II) complex incorporating a naphthyridine−diimine ligand. The ligand structure offers accessible sites trans to the naphthyridine unit. They showed that the title compound was an excellent catalyst for acceptorless dehydrogenation of alcohols to the corresponding carbonyl compounds. That diruthenium assembly was surprisingly effective for the clean conversion of primary alcohols to the corresponding aldehydes and no ester product was found as side products. They give a possible explanation for the above mechanism, that is, the generated aldehyde is rapidly extruded from the [Ru-Ru] core and hence the hemiacetalyzation is hindered. The same catalyst was also used for catalytic olefination of alcohols using ylides to react with the in situ produced aldehyde. They show kinetic experiments, isotope labeling studies, and DFT calculations point to a bimetallic cooperative mechanism that operates on the equatorial platform. A low-energy bimetallic β-hydride elimination makes dehydrogenation process the rate-limiting step.



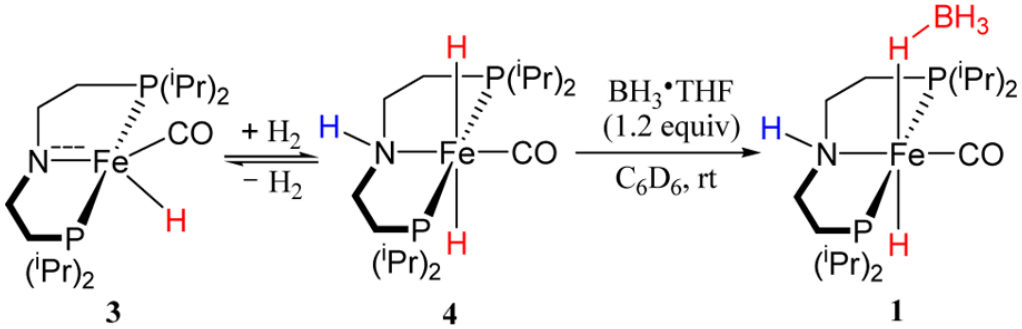
Scheme 3: [Ru=Ru] catalyzed acceptorless dehydrogenation of alcohols.[24]

Recently William D. Jones et al. reported the acceptorless dehydrogenation and hydrogenation of *N*-heterocycles (scheme 4) with a single molecular iron catalyst.[25] They have demonstrated reversible dehydrogenation−hydrogenation of *N*-heterocycles with earth-abundant iron-based molecular catalysts. Products from both the dehydrogenation and hydrogenation reactions were isolated in good yields. They demonstrated that penta-coordinated iron hydride species 3 (Scheme 5) and the proposed dehydrogenation intermediate, was isolated by an independent route, which was directly involved in the catalysis. The initial amine dehydrogenation step was supported by substrate-driven mechanistic studies and provide evidence against direct alkane dehydrogenation from the partially oxidized *N*-heterocycles. They found that presence of the N atom in the

molecule was critical for a successful catalytic dehydrogenation. On the contrary, a trans-dihydride species 4 (Scheme 5) was acted as the active catalyst for the hydrogenation of *N*-heterocycles. The formation of such a catalyst species was supported by NMR and trapping experiments. These homogeneous catalytic methods suffer from drawbacks of difficulties in product/catalyst separation and no reusability of the catalyst, lower turnover number and in some cases use of additive.



Scheme 4: Fe-complex catalyzed acceptorless dehydrogenation of *N*-heterocycles.[25]



Scheme 5: NMR and Trapping Experiments to Support the Formation of the trans-Dihydride Intermediate.[25]

Now a days, several heterogeneous catalysts have been developed for dehydrogenation of amines and alcohols into their corresponding dehydrogenated products using various oxidizing agents.[26] However the previous reported methodologies were mostly involved in over oxidation of the dehydrogenated product and other functional groups on the substrate due to high reaction temperatures which inhibit its

utility for a wide substrate scope.[27] Moreover, the formation of byproduct water, produced during dehydrogenation could lead to catalyst deactivation and reusability problems. Alternatively, several precious metal-based heterogeneous catalysts have been developed to overcome these drawbacks and to achieve an efficient oxidant-free dehydrogenation of wide range of alcohols and amines.[28]

1.2. Acceptorless dehydrogenation of alcohols by heterogeneous catalyst

Our group reported heterogeneous supported metal catalyzed dehydrogenation of alcohols (scheme 6).[29,30,31] Pt nanocluster-loaded metal oxides, in situ pre-reduced under H_2 at 500 °C, were tested for the dehydrogenation of aliphatic secondary alcohols in the liquid phase. According to the report, activity for dehydrogenation of 2-octanol depended strongly on the acid–base character of the support oxide, and amphoteric oxides, especially γ-Al_2O_3,[29] which gave high activity for this reaction. Al_2O_3 supported Pt acted as reusable heterogeneous catalyst for dehydrogenation of aliphatic secondary alcohols to the corresponding ketones. Pt/Al_2O_3 showed higher activity than other M/Al_2O_3 (Co, Ni, Cu, Ru, Rh, Pd, Ag, Re, Ir, Au) catalysts and showed two orders of magnitude higher turnover number (TON) than previously reported Pt catalysts for dehydrogenation of alcohol to kitones.

Another report by our group showed that a series of transition metal(M)-loaded TiO_2 catalysts (M/TiO_2) and Co-loaded catalysts on various support materials were prepared by an impregnation method, followed by in situ H_2-reduction at 400 °C and tested for the acceptorless oxidation of cyclododecanol in the liquid phase. Among several supported metal catalysts including noble metal catalysts, Co/TiO_2[30] showed the highest activity for acceptorless dehydrogenation of cyclododecanol.

For the oxidation of secondary alcohols,[31] acceptorless dehydrogenation were studied by alumina-supported Ni metal nano particles as a heterogeneous and reusable catalyst. nickel-nanoparticle-loaded θ-Al_2O_3 (Ni/θ-Al_2O_3) was prepared by H_2-reduction of NiO/θ-Al_2O_3, acts as an effective and reusable heterogeneous catalyst for acceptorless dehydrogenation of alcohols in a liquid phase. Among various supports, amphoteric supports (such as θ-Al_2O_3), having both acidic and basic sites, gave higher activity than

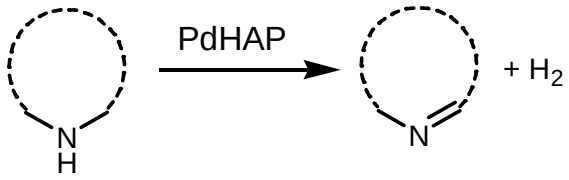
acidic or basic supports for this dehydrogenation reaction.

Scheme 6: Dehydrogenation of alcohols by heterogeneous catalyst.[29,30,31]

1.3. Acceptorless dehydrogenation of cyclic amines by heterogeneous catalyst

Kaneda et al. showed that hydroxyapatite-bound palladium[32] was found as an effective catalyst for the dehydrogenation of various types of indolines to give the corresponding indoles. The catalyst was easy recoverable from the reaction mixture, and was reusable without any loss of its catalytic activity. They showed that the dehydrogenation of various indolines in the presence of PdHAP (scheme 7) can also proceed efficiently. In addition to advantages such as simple work-up procedures and the ability to recycle the catalyst, the catalytic system described herein exhibits high catalytic activities as compared to other reported methods. However the method shows low turnover number and substrate scope is limited.

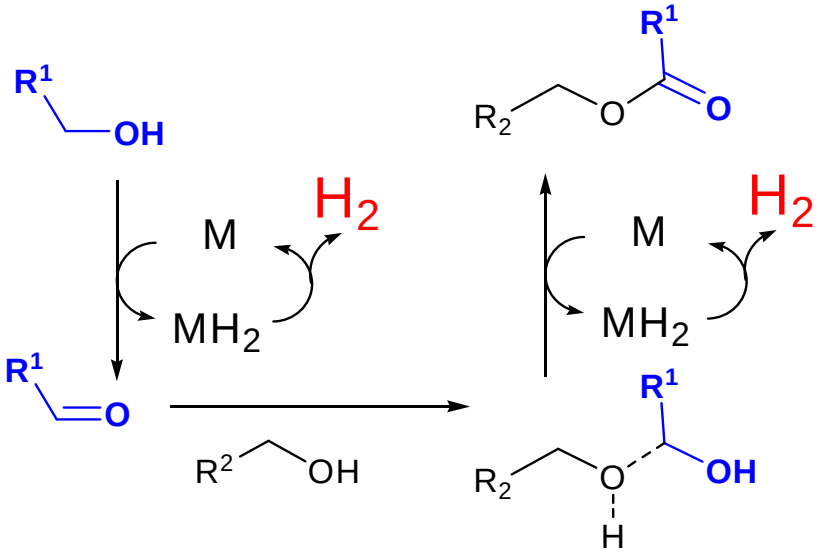
Pravin R. Likhar et al. developed a simple and convenient process for the synthesis of monodispersed and highly stable nanocopper(0)[33] on alumina from copper aluminum hydrotalcite by a chemical reduction method for the dehydrogenation of amines to imines/nitriles and alcohols to carbonyl compounds. The scope of the dehydrogenation reactions were available for several amines such as benzylamines, long-chain alkylamines, heterocyclic amines and alcohols using $Cu(0)/Al_2O_3$ as an efficient catalyst. The stability of $Cu(0)/Al_2O_3$ was demonstrated by studying its recovery and reuse properties in the dehydrogenation of amines and alcohols. Thus, $Cu(0)/Al_2O_3$ constitutes a unique catalytic system and opens up an attractive alternative to expensive noble metal-based catalysts for the acceptorless and oxidant-free dehydrogenation of amines and alcohols.



Scheme 7: Acceptorless dehydrogenation of cyclic amines.[32]

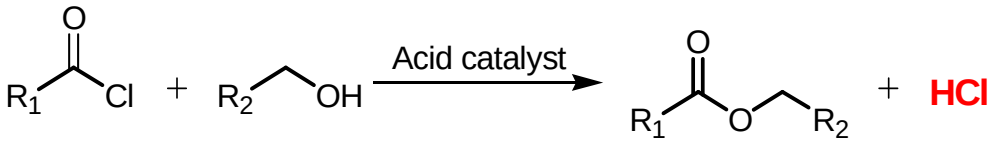
1.4. Acceptorless Dehydrogenative Coupling of Alcohols

Ester can be synthesized by acceptorless dehydrogenative coupling of alcohols. First, metal accept hydrogen from alcohols and convert it to aldehyde. Then another molecule of alcohol combine with aldehyde and a intermediate is formed. This intermediate convert to ester by losing another molecule of hydrogen (scheme 9).



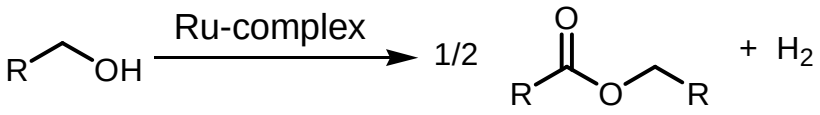
Scheme 9: Catalytic acceptorless dehydrogenetive coupling of alcohols to esters.

Alcohols react with acyl chlorides and acid anhydrides to give esters (scheme 10).[34] The reactions are irreversible simplifying work-up. Since derivatives of carboxylic acids such as acyl chlorides and acid anhydrides also react with water, anhydrous conditions are preferable for this reaction. This traditional method suffers from drawbacks of stoichiometric amount of toxic reagents and/or promoters generation of waste, separation and purification of intermediates.



Scheme 10: Acid catalyzed ester synthesis from alcohols acid derivatives.[34]

To overcome the drawbacks of traditional multisteps synthesis, several one-pot acceptorless synthetic methods are developed. Literature showed that the acceptorless catalytic dehydrogenation reactions are one-pot synthesis and most of the methods are homogeneous. Ru-complex[35] catalyzed acceptorless dehydrogenetion of alcohols to esters are reported by Milstein group. Recently, D. G. Gusev et al. also reported Ru-complex[36] catalyzed acceptorless dehydrogenetion of alcohols to esters (scheme 11). These one pot catalytic method have several advantages such as this method is environmentally green, no hazardous byproduct or waste is produced and the procedure is relatively safe. But still one-pot synthesis have some problems such as this homogeneous catalytic system suffers from difficulties in catalyst/product separation and no reusibility of the catalyst. In some cases the method also shows low TON.



Scheme 11: Acceptorless dehydrogenetion of alcohols to esters.[36]

1.5. Concluding remarks

There is a need to develop heterogeneous catalysts for direct synthesis of chemicals from alcohols and cyclic amines under additive-free and acceptorless dehydrogenation methodology. The reusable heterogeneous catalyst will provide practical methods for sustainable production of chemicals with substrate scope and high TON.

1.6. Outlines of thesis

This thesis focuses on direct synthesis of chemicals from alcohols and cyclic amines under additive-free and acceptorless dehydrogenation methodology. The objective of this thesis is to develop new heterogeneous catalysts for acceptorless dehydrogenation of cyclic amines and dehydrogenative one-pot bond formation reactions of alcohols. The thesis will show supported Pt nanoparticles are efficient and reusable heterogeneous catalysts for these reactions under additive-free conditions. Characterization of catalysts and model reactions are also studied to discuss catalyst design concept.

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Chapter 5 is the general conclusion. Chapter 2-4 show systematic examples of new heterogeneous catalysts for acceptorless dehydrogenation reactions of amines (*N*-heterocycles) and alcohols by for the synthesis of chemicals under additive-free conditions with liberation of H_2 as a byproduct. The heterogeneous catalysts developed in this work have advantages over the previous homogeneous catalysts, including good catalyst reusability and high TON, and hence will provide practical methods for sustainable production of chemicals.

References :

1. *"Green Chemistry". United States Environmental Protection Agency. 2006-06-28*. Retrieved 2011-03-23.
2. R. A. Sheldon, I. W. C. E. Arends and U. Hanefeld, *Green Chemistry and Catalysis.* Wiley-VCH. WEinheim, 2007.
3. P. T. Anatas and J. C. Warner, *Green chemistry: Theory and Practice, ed.* Oxford University Press. Oxford, 1988.
4. a) T. M. Harris, C. M. Harris, T. A. Oster Jr, L. E. Brown and J. Y. C. Lee, *J. Am. Chem. Soc*., 1988, **110**, 6180–6186; b) G. K. Jnaneshwara, V. H. Deshpande, M. Lali-thambika, T. Ravindranathan and A. V. Bedekar, *Tetrahedron Lett.*, 1998, **39**, 459–462.
5. a) K. Yamaguchi, M. Matsushita and N. Mizuno, *Angew. Chem*., 2004, **116**, 1602–1606; *Angew. Chem. Int. Ed*., 2004, **43**, 1576–1580; b) V. V. Grushin and H. Alper, *Chem. Rev*., 1994, **94**, 1047–1062; c) J. N. Moorthy and N. Singhal, *J. Org. Chem*., 2005, **70**, 1926–1929.
6. R. A. Sheldon and J. K. Kochi, in: Metal Catalyzed Oxidations of Organic Compounds, Academic Press, New York, 1981.
7. a) S. V. Ley and A. Madin, in: Comprehensive Organic Synthesis, Vol. 7, (Eds.: B. M.Trost, I. Fleming, S. V. Ley), Pergamon Press, Oxford, 1991; 251–289; b) M. Hudlicky, in: Oxidations in Organic Chemistry, ACS Monograph Series, American Chemical Society, Washington DC, 1990.
8. H. J. Arpe, *Industrial Organic Chemistry*, Wiley-VCH, Weinheim, **2010**.
9. a) G. E. Dobereiner and R. H. Crabtree, *Chem. Rev*., 2010, **110**, 681- 703; b) J. Choi, A. H. R. MacArthur, M. Brookhart and A. S. Goldman, *Chem. Rev*., 2011, **111**, 1761-1779.
10. R. Yamaguchi, C. Ikeda, Y. Takahashi and K. Fujita, *J. Am. Chem. Soc*., 2009, **131**, 8410-8412.
11. a) J. R. Holum, *J. Org. Chem*., 1961, **26**, 4814–4816; b) D. G. Lee and U. A. Spitzer, *J. Org. Chem*., 1970, **35**, 3589–3590; c) G. Cainelli and G. Cardillo, in: Chromium Oxidants in Organic Chemistry, Springer, Berlin, 1984; d) J. Muzart, *Chem. Rev*., 1992, **92**, 113–140.

12. a) F. M. Menger and C. Lee, *Tetrahedron Lett*., 1981, **22**, 1655–1656; b) S. L. Regen and C. Koteel, *J. Am. Chem. Soc*., 1977, **99**, 3837–3838; c) S. Dash, S. Patel and B. K. Mishra, *Tetrahedron*, 2009, **65**, 707–739; d) W. A. Waters, *Trans. Faraday Soc*., 1946, **42**, 184–190.
13. a) M. Fleischmann, K. Korinek and D. Pletcher, *J. Chem. Soc*., Perkin Trans. 2, 1972, 1396–1403; b) R. G. R. Bacon, W. J. W. Hanna and D. Stewart, J. Chem. Soc. C, 1966, 1388–1389.
14. A. Stojiljkovic, V. Andrejwic and M. L. J. Mihailovi, *Tetrahedron*, 1967, **23**, 721–732.
15. C. L. Hill, in: Advances in Oxygenated Processes, Vol. 1, (Ed.: A. L. Baumstark), JAI Press, Inc., London, 1988, 1–30.
16. a) B. Karimi and F. Kabiri Esfahani, *Chem. Commun*., 2009, 5555–5557; b) M. Kotani, T. Koike, K. Yamaguchi and N. Mizuno, *Green Chem*., 2006, **8**, 735–741; c) F. Li, J. Chen, Q. Zhang and Y. Wang, *Green Chem*., 2008, **10**, 553–562; d) S. Yamazaki and Y. Yamazaki, *Bull. Chem. Soc. Jpn*., 1990, **63**, 301–303; e) K. Yamaguchi, J. W. Kim, J. He and N. Mizuno, *J. Catal*., 2009, **268**, 343–349; f) S. Cenini, F. Porta and M. Pizzottio, *J. Mol. Catal*., 1982, **15**, 297–308.
17. a) R. A. Sheldon and I. W. C. E. Arends, *Adv. Synth. Catal*., 2004, **346**, 1051–1071; b) Z. Hu and F. M. Kerton, *Org. Biomol. Chem*., 2012, **10**, 1618–1624; c) L. Cheng, J. Wang, M. Wang and Z. Wu, *Inorg. Chem*., 2010, **49**, 9392–9399; d) W. Yin, C. Wang and Y. Huang, *Org. Lett*., 2013, **15**, 1850–1853; e) J. U. Ahmad, Thesis Dissertation, University of Helsinki, 2012, ISBN 978-952-10-7925–2; f) S. Coseri, *Eur. J. Org. Chem*., 2007, 1725–1729.
18. R. A. Sheldon, I. W. C. E. Arends, G. T. Brink and A. Dijksman, *Acc. Chem. Res*., 2002, **35**, 774-781.
19. M. B. Smith, March's Advanced Organic Chemistry, 5th Ed., Wiley, New York, 2001, 1509–1514.
20. (a) A. J. Watson and J. M. J. Williams, *Science*, 2010, **329**, 635–636. (b) M. H. S. A. Hamid, P. A. Slatford, J. M. J. Williams, *Adv. Synth. Catal*., 2007, **349**, 1555–1575. (c) G. Guillena, D. J. Ramon, M. Yus, *Chem. Rev.*, 2010, **110**, 1611–1641.
21. A. Dobson and S. D. Robinson, *Inorg. Chem*., 1977, **16**, 137–142.

22. (a) H. Junge, B. Loges and M. Beller, *Chem. Commun*., 2007, 522–524. (b) M. Nielsen, A. Kammer, D. Cozzula, H. Junge, S. Gladiali and M. Beller, *Angew. Chem., Int. Ed*., 2011, **50**, 9593–9597.
23. G. Zhang and S. K. Hanson, *Org. Lett.*, 2013, **15**, 650–653.
24. I. Dutta, A. Sarbajna, P. Pandey, S. M. W. Rahaman, K. Singh and J. K. Bera, *Organometallics*, 2016.
25. S. Chakraborty, W. W. Brennessel and W. D. Jones, *J. Am. Chem. Soc*., 2014, **136**, 8564–8567.
26. a) K. Yamaguchi and N. Mizuno, *Angew. Chem*., 2003, **115**, 1518–1521; *Angew. Chem. Int. Ed*., 2003, **42**, 1480–1483; b) M. Kotani, T. Koike, K. Yamaguchi and N. Mizuno, *Green Chem*., 2006, **8**, 735–741; c) F. Li, J. Chen, Q. Zhang and Y. Wang, *Green Chem*., 2008, **10**, 553–562; d) W. Fang, Q. Zhang, J. Chen, W. Deng and Y. Wang, *Chem. Commun*., 2010, **46**, 1547–1549; e) K. Yamaguchi and N. Mizuno, *Angew. Chem*., 2002, 114, 4720–4724; *Angew. Chem. Int. Ed*., 2002, **41**, 4538–4542.
27. a) M. Isamu, (Nippon Shokubai Kagaku Kogyo), Japanese Patent 11,335,315, 1999; Chem. Abstr. 2000, 132, 12155m; b) J. Thorsten, L. Oliver, B. E. Johannes, E. Klaus, H. Klaus, W. Christian (BASF), U.S. Patent 0,191,644, 2007; Chem. Abstr. 2005, 143, 305930q; c) H. L. Slaugh (Shell), U.S. Patent 4,891,446, 1990; Chem. Abstr. 1990, 112, 216231e.
28. a) W.-H. Kim, I. S. Park and J. Park, *Org. Lett*., 2006, **8**, 2543–2545; b) T. Mitsudome, Y. Mikami, H. Funai, T. Mizugaki, K. Jitsukawa and K. Kaneda, *Angew. Chem*., 2008, **120**, 144–147; c) T. Hara, K. Mori, T. Mizugaki, K. Ebitani and K. Kaneda, *Tetrahedron Lett*., 2003, **44**, 6207–6210.
29. K. Kon, S. M. A. H. Siddiki and K. Shimizu, *J. Catal*., 2013, **304**, 63-71.
30. K. Shimizu, K. Kon, M. Seto, K. Shimura, H. Yamazaki and J. N. Kondo, *Green Chem.*, 2013, **15**, 418-424.
31. K. Shimizu, K. Kon, K. Shimura and S. M. A. H. Siddiki, *J. Catal.*, 2013, **300**, 242-250.
32. T. Hara, K. Mori, T. Mizugaki, K. Ebitani and K. Kaneda, *Tetrahedron Lett*., 2003, **44**, 6207-6210.
33. D. Damodara, R. Arundhathi and P. R. Likhar, *Adv. Synth. Catal*., 2014, **356**,

189–198.

34. "Esters, Organic" ***Ullmann's Encyclopedia of Industrial Chemistry***, 2005, Wiley-VCH, Weinheim.
35. J. Zhang, G. Leitus, Y. Ben-Devid and D. Milstein, *J. Am. Chem. Soc*., 2005, **127**, 10840-10841.
36. D. Spasyuk and D. G. Gusev, *Organometallics*, 2012, **31**, 5239-5242.

Chapter 2

Acceptorless Dehydrogenation of *N*-heterocycles by supported Pt catalysts

2.1. Introduction

Catalytic dehydrogenation[1-9] and oxidation[10-21] of saturated *N*-heterocycles are of fundamental importance in the synthesis of nitrogen-containing aromatics. Previous methods[10-21] are based on the catalytic oxidation of *N*-heterocycles using an external oxidant such as O_2 and stoichiometric oxidants, but use of the oxidant potentially limits selectivity and functional group tolerance. An alternative method is the catalytic dehydrogenation of *N*-heterocycles in the absence of oxidants.[1-9] Recently reported homogeneous catalytic methods with Ir,[4,5,7] Ru,[8] Co[6] and Fe[9] catalysts were effective for the reaction, but most of these methods have drawbacks such as low turnover number (TON) and difficulties in catalyst/product separation and reuse of the homogeneous catalyst.[5-9] A few reports showed acceptorless dehydrogenation of *N*-heterocycles with heterogeneous catalysts.[1-3] For example, Kaneda et al. developed Pd[1] and Cu catalysts[2] for dehydrogenation of indolines and tetrahydroquinoline, respectively. For a model dehydrogenation of 1,2,3,4-tetrahydroquinoline, the previous homogeneous[4,7,8,6,9] and heterogeneous[2,3] catalysts showed limited turnover number (TON) in a range of 3.3-87. Among these examples, a few studies have succeeded in the reversible dehydrogenation-hydrogenation reactions of *N*-heterocycles with a single catalyst.[2,4-6,9] This reversible transformation is of particular importance from a viewpoint of organic hydrides for hydrogen storage system. As a part of our continuous studies in heterogeneous catalysis for oxidant-free dehydrogenation reactions,[22] we report herein dehydrogenation of saturated *N*-heterocycles by a Pt/C catalyst, which shows higher TON for dehydrogenation of tetrahydroquinoline than previous catalytic systems. Additionally, Pt/C is effective for the reverse reaction, that is hydrogenation of quinoline into tetrahydroquinoline under 3 bar H_2.

2.2. Experimental

2.2.1. Catalyst Preparation

Commercially available organic and inorganic compounds (Tokyo Chemical Industry, Kanto Chemical) were used without further purification. The standard carbon support, Vulcan XC72 (210 m^2 g^{-1}), was commercially supplied. γ-Al_2O_3 (124 m^2 g^{-1}) was

prepared by calcination of γ-AlOOH (Catapal B Alumina from Sasol) at 900 °C for 3 h. SiO_2 (Q-10, 300 m^2 g^{-1}) was supplied from Fuji Silysia Chemical Ltd. TiO_2 (JRC-TIO-4, 50 m^2 g^{-1}), MgO (JRC-MGO-3, 19 m^2 g^{-1}), SiO_2-Al_2O_3 (JRC-SAL-2, Al_2O_3 = 13.75 wt%, 560 m^2 g^{-1}) and HBEA zeolite (SiO_2/Al_2O_3 = 25±5, JRC-Z-HB25) were supplied from Catalysis Society of Japan. Nb_2O_5 (54 m^2 g^{-1}), ZrO_2 and SnO_2 were prepared by calcination of $Nb_2O_5.nH_2O$ (CBMM), $ZrO_2.nH_2O$ and H_2SnO_3 (Kojundo Chemical Laboratory Co., Ltd.), respectively, at 500 °C for 3 h.

A precursor of the 5 wt% Pt/C catalyst was prepared by impregnation method; a mixture of carbon (Vulcan-XC72) and aqueous HNO_3 solution of $Pt(NH_3)_2(NO_3)_2$ (Furuya Metal Co., Ltd.) was evaporated at 50 °C, followed by drying at 90 °C for 12 h. The reduced Pt/C catalyst, designated as Pt/C, was prepared by reduction of the precursor ($Pt(NH_3)_2(NO_3)_2$-loaded carbon) in a pyrex tube under H_2 flow (20 cm^3 min^{-1}) at 300 °C for 0.5 h. The other Pt catalysts were prepared by the same method as Pt/C. Carbon-supported metal catalysts, designated as M/C (M = Rh, Pd, Ir, Ru, Ni, Cu, Co, Ag), with metal loading of 5 wt% were prepared by impregnation method by the similar manner as Pt/C using aqueous solution of metal nitrates (for Ni, Cu, Co, Ag) or $IrCl_3.nH_2O$ or aqueous HNO_3 solution of $Rh(NO_3)_3$ (Furuya Metal Co., Ltd.) or $Pd(NH_3)_2(NO_3)_2$ (Kojima Chemicals Co., Ltd.). These catalysts were reduced under H_2 flow at 300 °C for 0.5 h. Platinum oxides-loaded carbon (PtOx/C) was prepared by calcination of the $Pt(NH_3)_2(NO_3)_2$-loaded C in air at 300 °C for 0.5 h.

2.2.2. Catalyst Characterization

Temperature programmed reduction by H_2 (H_2-TPR) was carried out by BELCAT (MicrotracBEL). PtOx/C (20 mg) in a quartz tube was heated with a temperature ramp-rate of 10 °C min^{-1} in a flow of 5% H_2/Ar (20 cm^3 min^{-1}). The effluent gas was passed through a trap containing MS4Å to remove water, then through the thermal conductivity detector, which detected the amount of H_2 consumed during the experiment. The number of surface Pt^0 atoms on Pt/C, pre-reduced in H_2 at 300 °C for 0.5 h, was estimated from the CO uptake of the samples at room temperature using the pulse-adsorption of CO in a flow of He by BELCAT (MicrotracBEL). The average Pt

particle size was calculated from the CO uptake assuming that CO was adsorbed on the surface of spherical Pt particles at a stoichiometry of CO/(surface Pt atom) = 1/1. Transmission electron microscopy (TEM) observation of Pt/C was carried out by a JEOL JEM-2100F TEM operated at 200 kV.

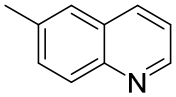
2.2.3. Catalytic tests

Typically, 5 wt% Pt/C was used as the standard catalyst. After the H_2-reduction of the catalyst at 300 °C, catalytic tests were carried out using a batch-type reactor without exposing the catalyst to air as follows. A mixture of 6-methyl 1,2,3,4-tetrahydroquinoline (1.0 mmol) and *n*-dodecane (0.29 mmol) in *o*-xylene (1.5 mL) was injected to the pre-reduced catalyst inside the reactor (cylindrical glass tube) through a septum inlet, followed by filling N_2. Then, the resulting mixture in a 15 mL of closed reflux system under 1 atm N_2 was magnetically stirred and was heated to reflux temperature; the bath temperature was 160 °C and reaction temperature was *ca.* 144 °C. The yield of 6-methyl-quinoline was determined by GC (Shimadzu GC-14B with Ultra ALLOY capillary column UA$^+$-1 of Frontier Laboratories Ltd., N_2) using *n*-dodecane as an internal standard. Typically, the error in the yield determined by GC was ±1.5%. To determine the isolated yield of 6-methyl-quinoline, 6-methyl-quinoline was isolated by column chromatography using silica gel 60 (spherical, 63-210 μm, Kanto Chemical Co. Ltd.) with hexane/ethylacetate (90/10) as the eluting solvent, followed by analyses by GCMS and ^{1}H and ^{13}C NMR. The hydrogenation of quinoline was carried out by a stainless autoclave (28 cm^3) at 160 °C under 3 bar H_2.

2.2.4. NMR and GCMS analysis

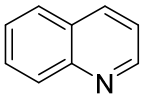
^{1}H and ^{13}C NMR spectra were recorded at ambient temperature by JEOL-ECX 600 operating at 600.17 and 150.92 MHz, respectively with tetramethylsilane as an internal standard. All chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. All chemical shifts are reported relative to tetramethylsilane and *d*-solvent peaks (77.00 ppm, chloroform), respectively. Abbreviations used in the NMR experiments: s, singlet d, doublet; t, triplet; m, multiplet. GC-MS spectra were recorded by SHIMADZU QP2010.

2.2.4.1. 6-Methyl-quinoline (Table 2.3, entry 1)[18]



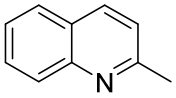
^{1}H NMR (600.17 MHz, $CDCl_3$), TMS: δ 8.51 (d, *J* = 2.70 Hz, 1H), 7.73 (d, *J* = 8.94 Hz, 1H), 7.54 (d, *J* = 7.56 Hz, 1H), 7.12 (d, *J* = 8.22 Hz, 1H), 7.05 (s, 1H), 6.98-6.87 (m, 1H), 2.09 (s, 3H); ^{13}C NMR (150.91 MHz, $CDCl_3$) δ 148.63, 146.11, 135.36, 134.39, 130.82, 128.27, 127.44, 125.79, 120.17, 20.66; MS m/e 143.07.

2.2.4.2. Quinoline (Table 2.3, entry 2)[16]



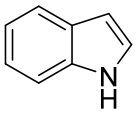
^{1}H NMR (600.17 MHz, $CDCl_3$), TMS: δ 8.89 (d, *J* = 2.76 Hz, 1H), 8.12-8.07 (m, 2H), 7.76 (d, *J* = 8.22 Hz, 1H), 7.68 (t, *J* = 7.56 Hz, 1H), 7.50 (t, *J* = 7.56 Hz, 1H), 7.33-7.32 (m, 1H); ^{13}C NMR (150.91 MHz, $CDCl_3$) δ 150.15, 148.02, 135.81, 129.22, 129.19, 128.03, 127.57, 126.30, 120.83; MS m/e 129.04.

2.2.4.3. 2-Methyl-quinoline (Table 2.3, entry 3)[23]



^{1}H NMR (600.17 MHz, $CDCl_3$), TMS: δ 8.03 (d, *J* = 8.28 Hz, 1H), 7.80 (d, *J* = 8.28 Hz, 1H), 7.59 (d, *J* = 7.56 Hz, 2H), 7.34 (t, *J* = 6.90 Hz, 1H), 7.05 (t, *J* = 6.18Hz, 1H), 2.64 (s, 3H); ^{13}C NMR (150.91 MHz, $CDCl_3$) δ 158.13, 147.18, 135.35, 128.68, 127.95, 126.82, 125.77, 124.93, 121.22, 24.65; MS m/e 143.07.

2.2.4.4 Indole (Table 2.3, entry 4)[14]



^{1}H NMR (600.17 MHz, $CDCl_3$), TMS: δ 8.09 (s, NH, 1H), 7.65 (d, *J* = 8.28 Hz, 1H), 7.38 (d, *J*= 8.28 Hz, 1H), 7.19 (m, 2H), 7.12 (t, *J* = 7.20 Hz, 1H), 6.55 (s, 1H); ^{13}C NMR

(150.91 MHz, $CDCl_3$) δ 135.74, 127.82, 124.10, 121.96, 120.71, 119.79, 111.00, 102.60; MS m/e 117.10.

2.3. Result and discussion

2.3.1. Catalyst characterization

Fig. 2.1 shows temperature programmed H_2-reduction (H_2-TPR) profile of $Pt(NH_3)_2(NO_3)_2$-loaded carbon as the precursor of Pt/C. The H_2-TPR profile shows H_2 consumption peaks below 250 °C assignable to the reduction of Pt(II) to metallic Pt. This indicates that the standard Pt/C catalyst pre-reduced at 300 °C contains metallic Pt. Fig. 2.2 shows a representative TEM image and Pt size distribution of Pt/C. The average diameter of Pt particles for 98 particles was 2.9 ± 0.8 nm, and the volume-area mean diameter of Pt particles was 3.5 ± 0.8 nm. The volume-area mean diameter (TEM analysis) was consistent with the mean diameter estimated by the CO adsorption experiment (3.2 nm) within the experimental error of TEM analysis, which supprted the TEM reults. Summarizing the above characterization results, we conclude that Pt species in the standard Pt/C catalyst are present as 3.5 nm sized Pt metal nanoparticles.

2.3.2. Catalytic tests

In order to optimize catalyst compositions and reaction conditions, we carried out dehydrogenation of 6-methyl-1,2,3,4-tetrahydroquinoline (**1a**) into 6-methyl-quinoline (**1b**) under refluxing of *o*-xylene in 1 atm N_2 for 6 h in the presence of 1 mol% of Pt. Table 2.1 shows the results of the Pt catalysts on various supports pre-reduced at 300 °C. Among the catalysts tested, Pt/C (entry 1) showed the highest yield (81%). Pt/SiO_2 and Pt/HBEA (entries 4,5) showed 25% yields, and Pt/Al_2O_3, Pt/MgO, Pt/TiO_2, Pt/Nb_2O_5, Pt/ZrO_2 and Pt/SnO_2 gave low yields of 6-19%. The platinum oxides-loaded carbon (PtOx/C) catalyst showed no activity (entry 3). When the pre-reduced Pt/C was exposed to air at room temperature for 0.5 h, the air-exposed catalyst (Pt/C-air in entry 2) showed lower yield (58%) than the as-reduced Pt/C catalyst (81%) possibly due to the oxidation of some of the surface Pt^0 species. These results indicates that metallic Pt^0 is the active species in this catalytic system.

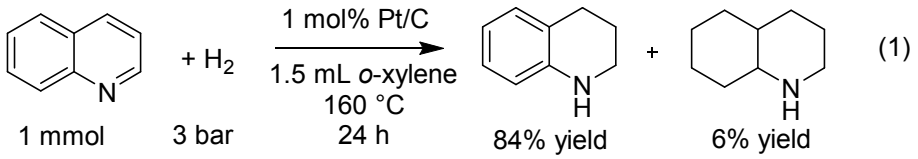
Adopting carbon as the most effective support material, we next screened various metal-loaded carbon (M/C) catalysts for the model dehydrogenation of **1a** (1 mmol) using only 0.1 mol% (0.001 mmol) of active metals (Pt, Ir, Ag, Pd, Rh, Ru, Cu, Ni, Co). Table 2.2 lists the yield of **1b** for the catalysts in the initial period of the reaction (6 h). The yields changed in the order of Co/C < Ag/C < Cu/C < Ni/C < Ru/C < Ir/C < Pd/C < Rh/C < Pt/C. Fig. 2.3 (left) compares the time course of the reaction for representative catalysts. Among the catalysts, Pt/C catalyst showed the highest activity in terms of the initial rate and the final yield (96%) after 50 h. The final yields for Ir/C (83 %), Pd/C (72%) and Ru/C (70%) were moderately high, while the other catalysts showed low yields (< 40%) after 50 h. For the standard Pt/C catalyst, the time course profile in Fig. 2.3 (right) shows that the conversions of **1a** and the yields of **1b** were nearly close to each other during the reaction, which indicates that **1a** is selectively transformed to **1b**.

Fig. 2.4 shows the results of catalyst reusability of Pt/C for the dehydrogenation of **1a**. After the first cycle, 2-propanol (1 mL) was added to the reaction mixture and the catalyst was separated by centrifugation. Then, 6-methyl-quinoline (**1b**) in the solution was isolated by column chromatography. The yield of the isolated 6-methyl-quinoline (94%) was close to the yield determined by GC (98%). The separated Pt/C catalyst was washed with acetone three times, followed by centrifugation and drying in oven (under air) at 90 °C for 12 h and by reduction in H_2 at 300 °C for 0.5 h. After the treatment, the recovered Pt/C catalyst showed 96-98% GC yields of **1b** during the next four recycle tests. In a separate experiment, ICP-AES analysis of the filtrate after the first reaction with Pt/C showed that the content of Pt in the solution was 0.35 ppm, corresponding to 0.024% of Pt in the catalyst used.

Table 2.3 shows the substrate scope for dehydrogenation of various *N*-heterocycles (1 mmol) in the presence of 0.1 mol% (0.001 mmol) of Pt/C. Derivatives of tetrahydroquinoline, including 6-methyl-1,2,3,4-tetrahydroquinoline (entry 1), 1,2,3,4-tetrahydroquinoline (entry 2) and 2-methyl-1,2,3,4-tetrahydroquinoline (entry 3) were transformed to 6-methyl-quinoline, quinoline and 2-methyl-quinoline, respectively, with high yields (91-96%). Indoline (entry 4) was also converted to indole with high yield

(97%). For the dehydrogenation of 1,2,3,4-tetrahydroquinoline (entry 2), 91% yield of quinoline corresponds to TON of 910, which is higher than those of the previous homogeneous[4,7,8,6,9] and heterogeneous[2,3] catalysts (TON = 3.3-87). These results show that the method is effective for the oxidant-free dehydrogenation of various *N*-heterocycles.

Under 3 bar H_2, the same catalytic system was effective for hydrogenation of quinoline. As shown in eqn. (1), the hydrogenation reaction of quinoline by 1 mol% of the Pt/C catalyst under 3 bar H_2 in an autoclave reactor at 160 ˚C gave 1,2,3,4-tetrahydroquinoline in 84% yield together with 6% yield of *trans*-decahydroquinoline as an undesirable side product.



Finally, we study the relationship between the electronic properties of various metals and the catalytic activity of various metals loaded on carbon for the dehydrogenation of **1a** and discuss a possible reason why Pt/C gave higher activity than the other metals (Table 2.2). Fig. 2.5 plots the initial rate of the dehydrogenation (from Table 2.2[24]) as a function of the d-band center (ε_d) relative to the Fermi energy (E_F), ε_d - E_F, for the clean metal surface calculated by Hammer and Nørskov using DFT method.[25] The d-band center has been used as a descriptor of activity trends in various transition metal surfaces.[25-27] The result in Fig. 2.5 shows a typical volcano-type dependence of the catalytic activity on the d-band center; the platinum-group-metals (Pt, Ir, Pd, Rh, Ru) having intermediate d-band center show higher catalytic activity than the metals with a deep ε_d levels (Ag, Cu) and the metals with d-band centers close to E_F (Ni, Co). Taking into account a general tendency that the bond strength between a metal surface (M) and a hydrogen atom (H) is weaker for a metal with deeper ε_d level[26] and that the catalytic dehydrogenation of *N*-heterocycles can include the formation and dissociation of M-H bonds, the result suggests that a moderate M-H bond strength is favorable for this

catalytic system. The metals with a deep ε_d levels (Ag, Cu) may show low activity for the C-H dissociation step than platinum-group-metals, while strong M-H bonds on the metals with d-band centers close to E_F (Ni, Co) may show low activity for the M-H dissociation step (H_2 desorption step). Similar volcano-type dependence has been observed for several catalytic systems.[26,27]

2.4. Conclusions

We found that Pt metal nanoparticles-loaded carbon (Pt/C) was effective and reusable heterogeneous catalyst for oxidant-free dehydrogenation of *N*-heterocycles. Derivatives of tetrahydroquinoline and indoline were converted to quinolines and indole with high yields. For the dehydrogenation of 1,2,3,4-tetrahydroquinoline, TON of Pt/C was more than one order of magnitude higher than those of the previous homogeneous and heterogeneous catalysts. Additionally, the same catalyst was effective for the reverse reaction, hydrogenation of quinoline under 3 bar H_2. Thus, this catalytic method may be useful for a organic halide–based hydrogen storage system.

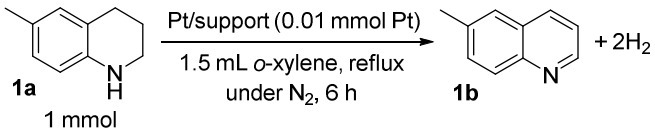
References

1. T. Hara, K. Mori, T. Mizugaki, K. Ebitani and K. Kaneda, *Tetrahedron Lett*., 2003, **44**, 6207–6210.
2. Y. Mikami, K. Ebata, T. Mitsudome, T. Mizugaki, K. Jitsukawa and K. Kaneda, *Heterocycles*, 2011, **82**, 1371–1377.
3. D. Damodara, R. Arundhathi and P. R. Likhar, *Adv. Synth. Catal*., 2014, **356**, 189–198.
4. R. Yamaguchi, C. Ikeda, Y. Takahashi and K. Fujita, *J. Am. Chem. Soc*., 2009, **131**, 8410–8412.
5. K. Fujita, Y. Tanaka, M. Kobayashi and R. Yamaguchi, *J. Am. Chem. Soc*., 2014, **136**, 4829–4832.
6. R. Xu, S. Chakraborty, H. Yuan and W.D. Jones, *ACS Catal*., 2015, **5**, 6350−6354.
7. J. Wu, D. Talwar, S. Johnston, M. Yan and J. Xiao, *Angew. Chem., Int. Ed*., 2013, 52, 6983–6987.
8. K.T. Tseng, A.M. Rizzi and N.K. Szymczak, *J. Am. Chem. Soc*., 2013, 135, 16352–16355.
9. S. Chakraborty, W.W. Brennessel and W.D. Jones, *J. Am. Chem. Soc*., 2014, **136**, 8564–8567.
10. K. Yamaguchi and N. Mizuno, *Angew. Chem. Int. Ed*., 2003, **42**, 1480–1483.
11. K. Kamata, J. Kasai, K. Yamaguchi and N. Mizuno, *Org. Lett*., 2004, **6**, 3577–3580.
12. T. Tanaka, K. Okunaga and M. Hayashi, *Tetrahedron Lett.*, 2010, **51**, 4633–4635.
13. D. Dean, B. Davis and P.G. Jessop, *New J. Chem*., 2011, **35**, 417–422.
14. S. Venkatesan, A.S. Kumar, J.-F. Lee, T.-S. Chan and J.-M. Zen, *Chem. Eur. J*., 2012, **18**, 6147–6151.
15. D. Ge, L. Hu, J. Wang, X. Li, F. Qi, J. Lu, X. Cao and H. Gu, *ChemCatChem*, 2013, **5**, 2183–2186.
16. S. Furukawa, A. Suga and T. Komatsu, *Chem. Commun*.,2014, **50** , 3277–3280.
17. D.V. Jawale, E. Gravel, N. Shah, V. Dauvois, H. Li, I.N.N. Namboothiri and E. Doris, *Chem. Eur. J*., 2015, **21**, 7039–7042.
18. A.V. Iosub and S. S. Stahl, *Org. Lett*., 2015, **17**, 4404−4407.
19. S.-I. Murahashi, T. Naota and T.H. Taki, *J. Chem. Soc., Chem. Commun.*, 1985,

613–614.

20. P. Müller and D.M. Gilabert, *Tetrahedron*, 1988, **44**, 7171–7175.
21. A.E. Wendlandt and S.S. Stahl, *J. Am. Chem. Soc*., 2014, **136**, 11910–11913.
22. S.K. Moromi, A.S. Touchy, S.M.A.H. Siddiki, M.A. Ali and K. Shimizu, *RSC Adv*., 2015 **5**, 1059–1062.
23. The Aldrich Library of ^{13}C and ^{1}H FT NMR Spectra, 1st ed., Vol. 3; C.J. Pouchert, J. Behnke, Aldrich Chemical Company Inc., Milwaukee, 1993, 421B.
24. H_2-TPR showed that the precursors of Ni/C and Co/C catalysts were reduced to metallic states by reduction at 500 ^{o}C. The catalytic tests of Ni/C and Co/C catalysts after reduction at 500 ^{o}C are shown in parentheses of Table 2, and the results are converted to the reaction rates in Fig. 5.
25. B. Hammer and J.K. Norskov, *Adv. Catal*., 2000, **45**, 71–129.
26. H. Toulhoat and P. Raybaud, *J. Catal.*, 2003, **216**, 63–72.
27. M. Tamura, K. Kenichi, A. Satsuma and K. Shimizu, *ACS Catal*., 2012, **2**, 1904–1909.

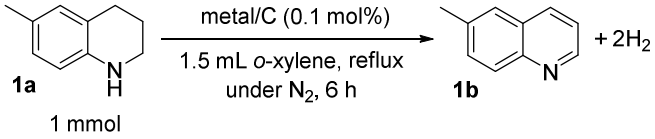
Table 2.1. Dehydrogenation of **1a** by supported Pt catalysts reduced at 300 °C.



Entry	Catalyst	Yield (%)
1	Pt/C	81
2	Pt/C-air	58
3	PtOx/C	0
4	Pt/SiO_2	25
5	Pt/HBEA	25
6	Pt/SiO_2-Al_2O_3	19
7	Pt/Al_2O_3	19
8	Pt/MgO	18
9	Pt/TiO_2	12
10	Pt/Nb_2O_5	16
11	Pt/ZrO_2	9
12	Pt/SnO_2	6

a PtOx/C was not reduced before the reaction.

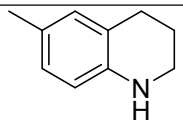
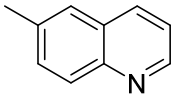
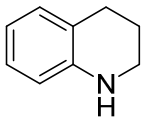
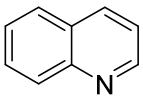
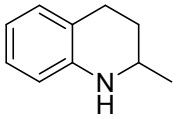
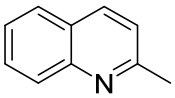
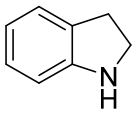
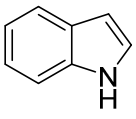
Table 2.2. Dehydrogenation of **1a** by carbon-supported metal catalysts reduced at 300 °C.



Entry	Catalyst	Yield (%)
1	Pt/C	36
2	Rh/C	28
3	Pd/C	26
4	Ir/C	22
5	Ru/C	17
6	Ni/C	11 (7) [a]
7	Cu/C	10
8	Ag/C	6
9	Co/C	5 (7) [a]

a Catalyst reduction temperature was 500 °C.

Table 2.3. Dehydrogenation of saturated *N*-heterocycles by Pt/C.[a]

Entry	Substrate	Product	*t* (h)	Conv. (%)	Yield (%)
1			50	100	96
2			65	100	91
3			60	100	93
4			45	100	97

[b] Conditions: 1 mmol *N*-heterocycles in 1.5 mL *o*-xylene, reflux, 0.1 mol% Pt/C

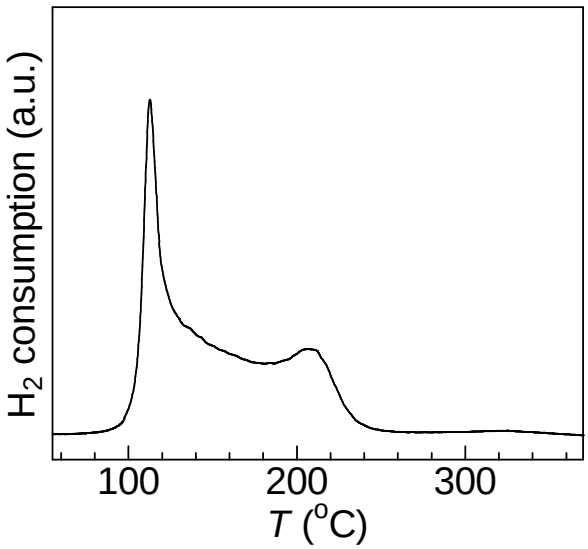


Fig. 2.1 H_2-TPR profile of $Pt(NH_3)_2(NO_3)_2$-loaded carbon.

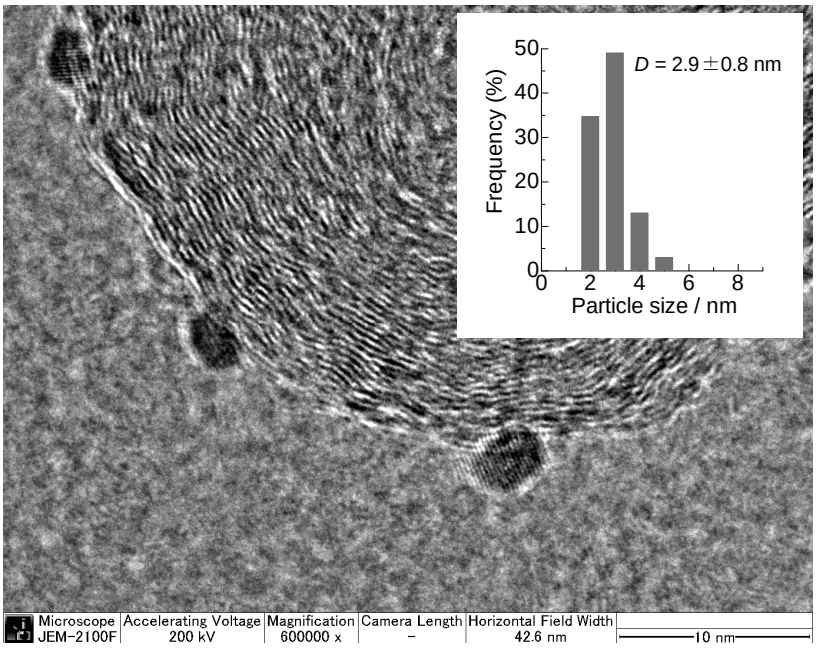


Fig. 2.2 A representative TEM image and Pt particle size distribution of Pt/C (pre-reduced at 300 °C). The mean diameter of Pt particle was 2.9 ± 0.8 nm, and the volume-area mean diameter was 3.5 ± 0.8 nm.

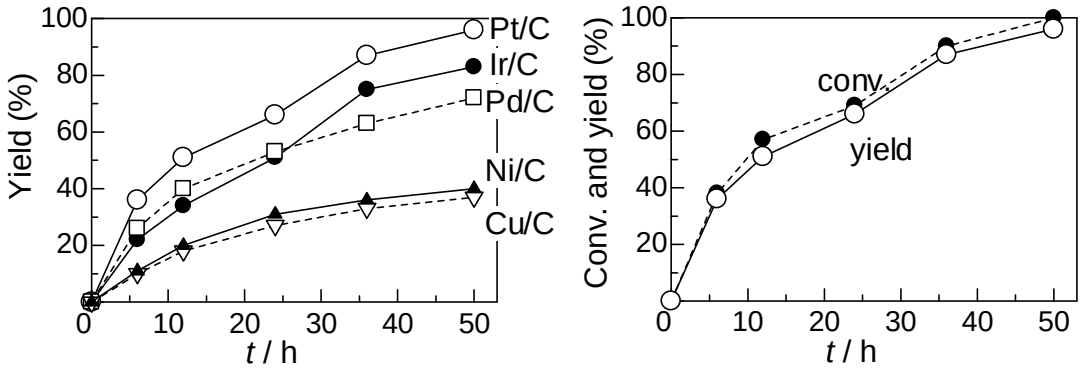


Fig. 2.3 Time-yield profiles for various metal-loaded carbon catalysts (left) and time course of the reaction for the standard Pt/C catalyst (right). Conditions are shown in Table 2.2.

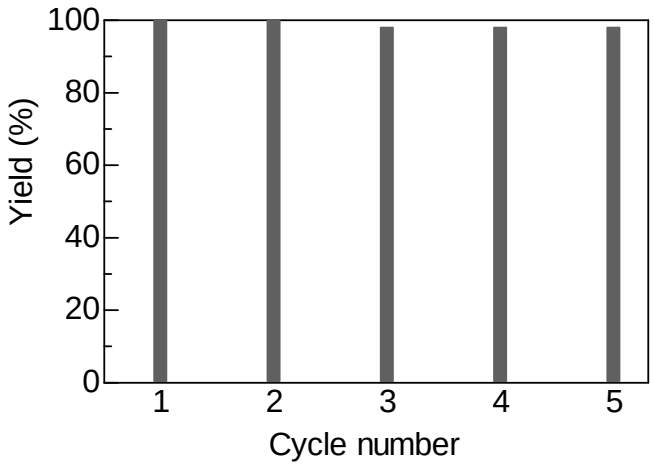


Fig. 2.4. Catalyst reuse for dehydrogenation of **1a** (1 mmol) under N_2 in refluxing *o*-xylene (1.5 mL) for 11 h using Pt/C (1 mol% Pt with respect to **1a**).

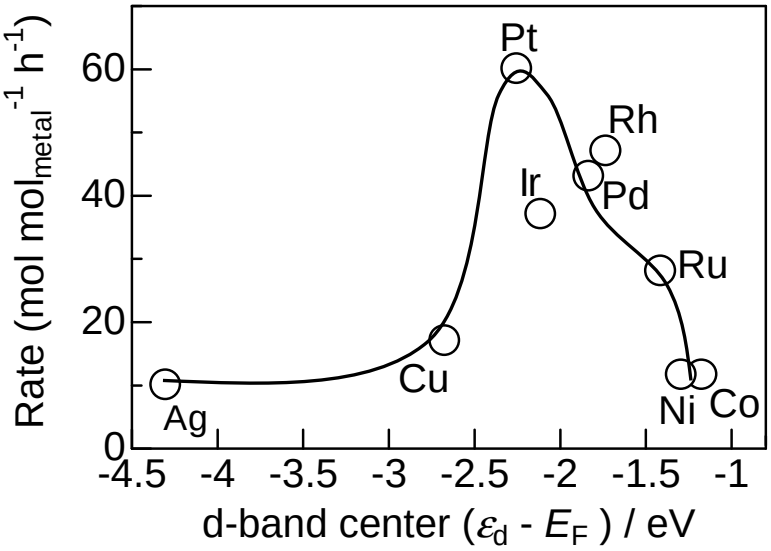


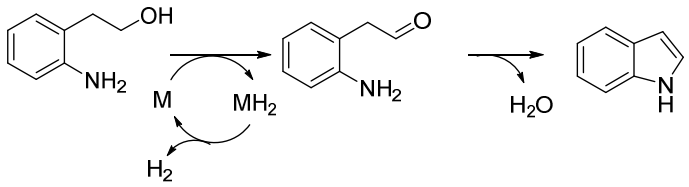
Fig. 2.5. Effect of the d-band center of the metals relative to the Fermi energy[25] on the initial rate of **1b** formation for dehydrogenation of **1a** by carbon-supported metal catalysts (from Table 2.2).

Chapter 3

Synthesis of indoles *via* dehydrogenative *N*-heterocyclization by supported Pt catalysts

3.1. Introduction

Indoles are important organic compounds, which are widely used for the syntheses of pharmaceuticals and agrochemicals.[1–4] Various methods to prepare indoles were reported.[1–6] Oxidative or dehydrogenative *N*-heterocyclization of 2-(2-aminophenyl) ethanol alcohols is one of the most promising protocols,[7-17] since the starting alcohol is easily prepared by the condensation of 2-nitrotoluene with formaldehyde in the presence of bases, followed by the reduction of a nitro functionality to an amino one.[8] Heterogeneous copper catalysts were reported to catalyze the reaction at high temperatures (> 200 °C).[7] Homogeneous transition metal catalysts, such as ruthenium[8-10] and iridium[11-14] complexes and a copper/TEMPO system[15] catalyzed the reaction at lower temperatures but have problems such as difficulties in catalyst/product separation and catalyst reuse and needs of additives such as base or acceptor. A supported Au catalyst also required basic additives (200 mol% of NaO*t*Bu) and oxidant (O_2).[16] From a viewpoint of sustainable chemistry, acceptorless dehydrogenative coupling methodology[5,6,18-20] under neutral conditions using a reusable catalyst is most attractive. Recently, Wada and co-workers[17] developed a new heterogeneous catalyst, Ru/CeO_2, that was effective for acceptorless dehydrogenative synthesis of indole from 2-(2-aminophenyl)ethanol in the absence of any additives. As discussed in the previous studies on this reaction, the reaction can proceeds via the following two step pathway :



where dehydrogenation of 2-(2-aminophenyl)ethanol by a metal (M) catalyst is followed by condensation of the amino aldehyde intermediate to give indole. As a part of our continuing interest in heterogeneous Pt catalysts for acceptorless dehydrogenation of alcohols[21] and acceptorless dehydrogenative coupling reactions of alcohols,[22,23] we report herein the synthesis of indoles via acceptorless dehydrogenative *N*-heterocyclization 2-(2-aminophenyl)ethanol under additive-free conditions by heterogeneous Pt catalysts, which show higher TON than previous catalytic systems.

3.2. Experimental

General

Commercially available organic compounds (from Tokyo Chemical Industry) were used without further purification. The GC (Shimadzu GC-14B) and GCMS (Shimadzu GCMS-QP2010) analyses were carried out with Ultra ALLOY capillary column UA^{+}-1 (Frontier Laboratories Ltd.) using nitrogen and helium as the carrier gas.

Catalyst preparation

H^{+}-type BEA zeolite (HBEA, SiO_2/Al_2O_3 = 25±5, JRC-Z-HB25), CeO_2 (JRC-CEO-3), MgO (JRC-MGO-3), TiO_2 (JRC-TIO-4) and SiO_2-Al_2O_3 (JRC-SAL-2, Al_2O_3 = 13.75 wt%) were supplied from Catalysis Society of Japan. Nb_2O_5 was prepared by calcination of niobic acid (CBMMI) at 500 °C for 3 h. SnO_2 was prepared by calcination of H_2SnO_3 (Kojundo Chemical Laboratory Co., Ltd.) at 500 °C for 3 h. ZrO_2 was prepared by calcination of a hydroxide of Zr at 500 °C for 3 h.[23] γ-Al_2O_3 was prepared by calcination of γ-AlOOH (Catapal B Alumina purchased from Sasol) at 900 °C for 3 h. Precursor of 5 wt% Pt/Nb_2O_5 was prepared by an impregnation method; a mixture of Nb_2O_5 and an aqueous HNO_3 solution of $Pt(NH_3)_2(NO_3)_2$ was evaporated at 50 °C, followed by drying at 90 °C for 12 h. A pre-reduced catalyst, named Pt/Nb_2O_5, was prepared by pre-reduction of the precursor in a pyrex tube under a flow of H_2 (20 cm^3 min^{-1}) at 300 °C for 0.5 h. Platinum oxides-loaded Nb_2O_5 (PtO_x/Nb_2O_5), as a comparative catalyst, was prepared by calcination of the precursor in air at 300 °C for 3 h. By using various supports, several pre-reduced Pt catalysts were prepared by the same method as Pt/Nb_2O_5. Nb_2O_5-supported metal catalysts, M/Nb_2O_5 (M = Co, Cu, Ru, Pd, Ag, Re, Ir) with metal loading of 5 wt% were prepared by impregnation method in a similar manner as Pt/Nb_2O_5 using an aqueous solution of metal nitrates (for Co, Cu, Ag), $RuCl_3$, $IrCl_3$, NH_4ReO_4 or an aqueous HNO_3 solution of $Pd(NO_3)_2$.

Catalytic tests

Typically, 5 wt% Pt/Nb_2O_5 (39 mg, 0.01 mmol of Pt) was used as a standard catalyst. After the pre-reduction at 300 °C, we carried out catalytic tests using a batch-type reactor

without exposing the catalyst to air as follows. A mixture of 2-(2-aminophenyl)ethanol (1.0 mmol) and *n*-dodecane (0.2 mmol) in *o*-xylene (1 mL) was injected to the pre-reduced catalyst inside the reactor (cylindrical glass tube) through a septum inlet, followed by filling N_2. Then, the resulting mixture was magnetically stirred for 5 h under reflux condition; the bath temperature was 155 °C and reaction temperature was *ca.* 144 °C. The yield of indole was determined by GC using *n*-dodecane as an internal standard. The analysis of the gas phase product (H_2) was carried out by the mass spectrometer (BELMASS). To determine the isolated yield of indole, indole was isolated by column chromatography using silica gel 60 (spherical, 63-210 μm, Kanto Chemical Co. Ltd.) with hexane/ethylacetate (95/5) as the eluting solvent, followed by analyses by GCMS and ^{1}H and ^{13}C NMR (JEOL-ECX 600 operating at 600.17 and 150.92 MHz, respectively) with tetramethylsilane as an internal standard.

NMR and GC/MS analysis

^{1}H and ^{13}C NMR spectra for synthesized compounds were assigned and reproduced to the corresponding literature. ^{1}H and ^{13}C NMR specta were recorded using at ambient temperature on JEOL-ECX 600 operating at 600.17 and 150.92 MHz, respectively with tetramethylsilane as an internal standard. All chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. All chemical shifts are reported relative to tetramethylsilane and *d*-solvent ($CDCl_3$)peaks respectively. Abbreviations used in the NMR experiments: s, singlet d, doublet; t, triplet; q, quartet; m, multiplet. GC-MS spectra was taken by SHIMADZU QP2010.

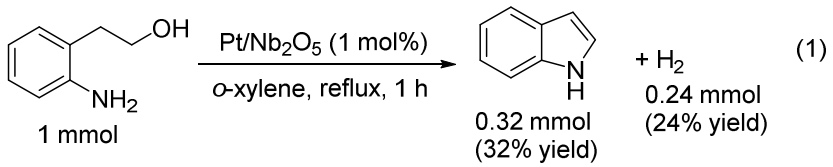
3.3. Results and discussion

Catalyst screening

We started the *N*-heterocyclization of 2-(2-aminophenyl)ethanol under *o*-xylene reflux conditions in N_2 as a model system in order to optimize catalytic conditions. Table 3.1 (entries 1–8) summarizes the results of the initial catalyst screening test under the same reaction conditions using various transition metal (Pt, Ir, Ru, Re, Pd, Co, Cu, Ag)

catalysts supported on Nb_2O_5 pre-reduced in H_2 at 300 °C. Cu and Ag catalysts (entries 7,8) showed no activity and Ru, Re, Pd and Co catalysts (entries 3–6) showed low yields. Ir/Nb_2O_5 (entry 2) gave a good yield of 68%. Among the catalysts tested, Pt/Nb_2O_5 (entry 1) showed the highest yield (82%) of indole. Entries 10–19 show the results of Pt catalysts loaded on the other supports (HBEA zeolite, CeO_2, MgO, TiO_2, ZrO_2, Al_2O_3, SnO_2,carbon, SiO_2). Pt/Nb_2O_5 (entry 1) and Pt/HBEA (entry 10) showed higher yields (82-83%) than the other supported Pt catalysts. Pt/CeO_2, Pt/MgO, Pt/TiO_2, Pt/ZrO_2, Pt/Al_2O_3, Pt/SiO_2-Al_2O_3, Pt/C and Pt/SiO_2 (entries 11–19) gave low to moderate yields (9–69%). To study the effect of the oxidation state of Pt species on the activity, we tested the activity of a pre-oxidized catalyst named PtO_x/Nb_2O_5, that is, a platinum oxides-loaded Nb_2O_5 catalyst. PtO_x/Nb_2O_5 (entry 20) showed a lower yield (10%) than with the pre-reduced catalyst, Pt/Nb_2O_5 (entry 1). Taking into account the result that the activity of the metal-unloaded Nb_2O_5 was negligible (entry 9) and the result that the activity depends strongly on the support, it is suggested that the co-presence of metallic Pt species and specific support materials (Nb_2O_5 or HBEA) is important factor of highly active catalysts. Note that indole was not produced in the absence of a catalyst (entry 21).

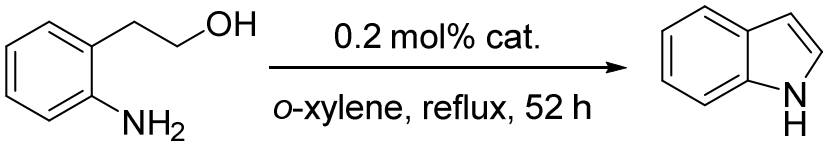
Table 3.2 shows the effect of reaction conditions on the yield of indole for the reaction of 2-(2-aminophenyl)ethanol by Pt/Nb_2O_5 under reflux conditions for 7 h. The reactions in toluene and hexane gave low yield (entries 3,4), and the reaction in mesitylene gave 78% yield (entry 2). The reaction in reflux of *o*-xylene gave the highest yield of 93% (entry 1). After the reaction, the catalyst was removed from the mixture and indole was isolated by column chromatography, resulting in high isolated yield of indoles (88%). The reaction in *o*-xylene at lower temperature (130 °C) gave low yield (29%) of indole (entry 5). The reaction under 1atm O_2 in the gas phase (entry 6) gave lower yield (82%) than that under N_2 (93%), indicating that O_2 as a hydrogen acceptor does not accelerate the catalytic reaction. For the reaction under N_2 with Pt/Nb_2O_5, we carried out mass spectrometry analysis of the gas phase products after 1 h. As shown in eqn. (1), the yields of gas phase H_2 (24%) was close to the yield of indole (32%).



(1)

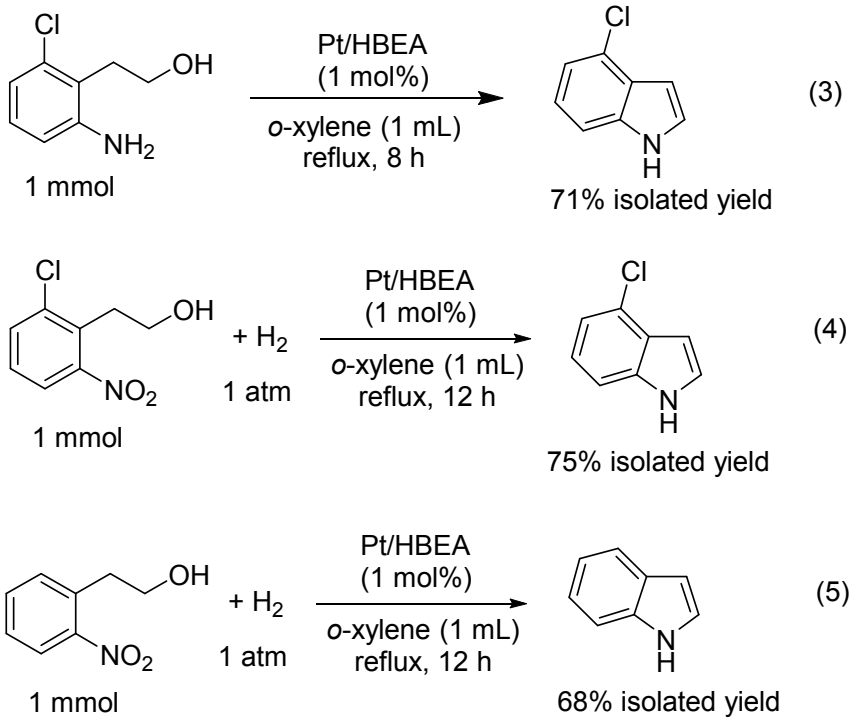
Using Pt/Nb_2O_5 and Pt/HBEA as two of the effective catalysts for this reaction, we carried out detailed catalytic studies. We checked the time course of the reaction under the standard conditions (Fig. 3.1). For Pt/Nb_2O_5, the yield of indole increased with time and reached 93% after 7 h. For Pt/HBEA, the yield of indole reached 95% after 12 h. Fig. 3.2 shows the results of catalyst reusability of Pt/Nb_2O_5 and Pt/HBEA. After completion of the reaction, 2-propanol (1 mL) was added to the reaction mixture and the catalyst was separated by centrifugation. The recovered catalyst was washed with acetone three times, followed by centrifugation and drying in an oven (under air) at 90 °C for 12 h and then H_2 reduction at 300 °C for 0.5 h. The recovered Pt/Nb_2O_5 catalyst showed high yield for the second and the third cycle. In contrast, the recovered Pt/HBEA catalyst showed low yields in the second and third cycles. Thus, Pt/Nb_2O_5 was found to be a better catalyst in terms of reusability.

In order to evaluate TON of the catalytic system, next we carried out the reaction with small amount of the catalysts. As shown in eqn. (2), the reactions with 0.2 mol% of Pt/Nb_2O_5 and Pt/HBEA for 52 h resulted in 76% and 90% yields, corresponding to TONs of 380 and 450, respectively. The TON by Pt/HBEA is 3~25 times larger than those by homogeneous[8-15] and heterogeneous[17] catalysts in the literature for the same reaction. ICP-AES analysis of the filtrate after the reaction with Pt/HBEA showed that the content of Pt in the solution was quite low (3.4 ppm).



(2)

cat.	GC yield	TON
Pt/Nb_2O_5	76%	380
Pt/HBEA	90%	450



The present method was also effective for the synthesis of a functionalized indole. As shown in eq. (3), the 2-aminophenethyl alcohol with a Cl- group on the aromatic ring was converted to the corresponding indole in 71% isolated yield by 1 mol% of Pt/HBEA.

Since supported Pt catalysts can exhibit a catalytic activity for the reduction of the nitro group to an amino group with H_2, we examined the synthesis of indoles from 2-nitrophenthyl alcohols. As shown in equations (4) and (5), Cl-functionalized 2-nitrophenthyl alcohol and 2-nitrophenthyl alcohol were selectively converted to the corresponding indole derivatives in moderate isolated yields under balloon H_2 pressure for 12 h in the presence of 1 mol% of Pt/HBEA.

3.4. Conclusion

We reported that Pt/Nb_2O_5 and Pt/HBEA acted as effective heterogeneous catalysts for the synthesis of indoles via acceptorless dehydrogenative cyclization of 2-(2-aminophenyl)ethanol. These catalysts showed higher TON than previously reported catalysts, and the Pt/Nb_2O_5 catalyst was reusable.

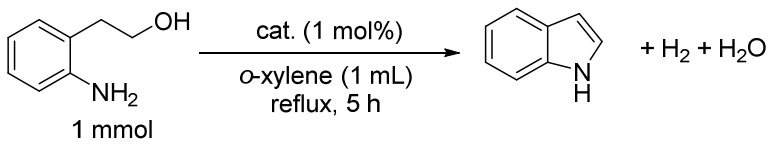
References

1. a) R. J. Sundberg, *The Chemistry of Indoles*; Academic Press: New York, 1970; b) L. S. Hegedus, *Angew. Chem., Int. Ed*., 1988, **27**, 1113–1226; c) T. L. Gilchrist, *J. Chem. Soc., Perkin Trans. 1*, **1999**, 2849–2866.
2. G. W. Gribble, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1045–1075.
3. S. Cacchi and G. Fabrizi, *Chem. Rev*., 2005, **105**, 2873–2920.
4. J. Barluenga, F. Rodríguez and F. T. Fañanás, *Chem.–Asian J*., 2009, **4**, 1036–1048.
5. M. Zhang, F. Xie, X. T. Wang, F. Yan, T. Wang, M. Chen and Y. Ding, *RSC Adv*., 2013, **3**, 6022–6029.
6. M. Tursky, L. L. R. Lorentz-Petersen, L. B. Olsen and R. Madsen, *Org. Biomol. Chem*., 2010, **8**, 5576–5582.
7. W. Hammerschmidt, A. Baiker, A. Wokaun and W. Fluhr, *Appl. Catal*., 1986, **20**, 305–312.
8. Y. Tsuji, S. Kotachi, K.-T. Huh and Y. Watanabe, *J. Org. Chem*., 1990, **55**, 580–584.
9. T. Kondo, T. Kanda, Daisuke Takagi, Kenji Wada, Yu Kimura and Akio Toshimitsu, *J. Heterocycl. Chem*., 2012, **86,** 1015–1022.
10. S. C. Ghosh and S. H. Hong, *Eur. J. Org. Chem*., 2010, 4266–4270.
11. K. Fujita, K. Yamamoto and R. Yamaguchi, *Org. Lett*., 2002, **4**, 2691–2694.
12. S. Whitney, R. Grigg, A. Derrick and A. Keep, *Org. Lett*., 2007, **9**, 3299–3302.
13. C.-F. Fu, Y.-H. Chang, Y.-H. Liu, S.-M. Peng, C. J. Elsevier, J.-T. Chen and S.-T. Liu, *Dalton Trans*., **2009**, 6991–6998.
14. G. Guisado-Barrios, J. Hiller and E. Peris, *Chem.–Eur. J*., 2013, **19**, 10405–10411.
15. J. C. A Flanagan, L. M. Dornan, M. G. McLaughlin, N. G. McCreanor, M. J. Cook and M. J. Muldoon, *Green Chem*., 2012, **14**, 1281–1283.
16. R. Bernini, S. Cacchi, G. Fabrizi, S. Niembro, A. Prastaro, A. Shafir and A. Vallribera, *ChemSusChem*, 2009, **2**, 1036–1040.
17. S. Shimura, H. Miura, K. Wada, S. Hosokawa, S. Yamazoe and M. Inoue, *Catal. Sci. Technol*., 2011, **1**, 1340–1346.
18. a) C. Gunanathan and D. Milstein, *Science*, 2013, **341**, 249–260; b) G. E. Dobereiner and R. H. Crabtree, *Chem. Rev*., 2010, **110**, 681–703; c) C. Chen and S. Hyeok Hong, *Org. Biomol. Chem*., 2011, **9**, 20–26; d) T. Hille, T. Irrgang, and R. Kempe, *Chem.*

Eur. J., 2014, **20**, 5569–5572; e) S. Michlik and R. Kempe, *Nat. Chem*. 2013, **5**, 140–144; f) F. Xie, M. Chen, X. Wang, H. Jiang and M. Zhang, *Org. Biomol. Chem*., 2014, **12** , 2761–2768.

19. H. Wang, J. Zhang, Y.-M. Cui, K.-F. Yang, Z.-J. Zheng and L.-W. Xu, *RSC Adv*., 2014, **4**, 34681–34686.
20. X. Wang, M. Chen, F. Xie and M. Zhang, *RSC Adv*., 2014, **4**, 14744–14751.
21. K. Kon, S. M. A. H. Siddiki and K. Shimizu, *J. Catal.*, 2013, **304**, 63–71.
22. S. M. A. H. Siddiki, K. Kon, A. S. Touchy and K. Shimizu, *Catal. Sci. Technol*., 2014, **4**, 1716–1719.
23. S. K. Moromi, S. M. A. H. Siddiki, Md. A. Ali, K. Kon and K. Shimizu, *Catal. Sci. Technol*., 2014, **4**, 3631–3635.

Table 3.1. Catalyst screening for indole synthesis from 2-(2-amino-phenyl)-ethanol.[a]



Entry	Catalyst	Yield[a] (%)
1	Pt/Nb_2O_5	82
2	Ir/Nb_2O_5	68
3	Ru/Nb_2O_5	9
4	Re/Nb_2O_5	2
5	Pd/Nb_2O_5	1
6	Co/Nb_2O_5	1
7	Cu/Nb_2O_5	0
8	Ag/Nb_2O_5	0
9[b]	Nb_2O_5	1
10	Pt/HBEA	77
11	Pt/CeO_2	69
12	Pt/MgO	69
13	Pt/TiO_2	47
14	Pt/ZrO_2	42
15	Pt/Al_2O_3	22
16	Pt/SiO_2-Al_2O_3	15
17	Pt/SnO_2	9
18	Pt/C	15
19	Pt/SiO_2	10
20	PtO_x/Nb_2O_5	10
21	blank	0

[a] Yield was determined by GC.

[b] Catalyst amount was 39 mg.

Table 3.2. Indole synthesis from 2-(2-amino-phenyl)-ethanol by Pt/Nb_2O_5.[a]

Entry	Solvent	Conv.(%)	Yield (%)
1	*o*-xylene	100	93
2	mesitylene	100	78
3	hexane	74	5
4	toluene	65	23
5[b]	*o*-xylene	44	29
6[c]	*o*-xylene	99	82

[a] Conditions: 1 mol% Pt/Nb_2O_5, 1.0 mmol 2-(2-amino-phenyl)-ethanol, 1 mL solvent, reflux, in N_2, 7 h. Yield was determined by GC.

[b] T = 130 °C.

[c] in 1 atm O_2.

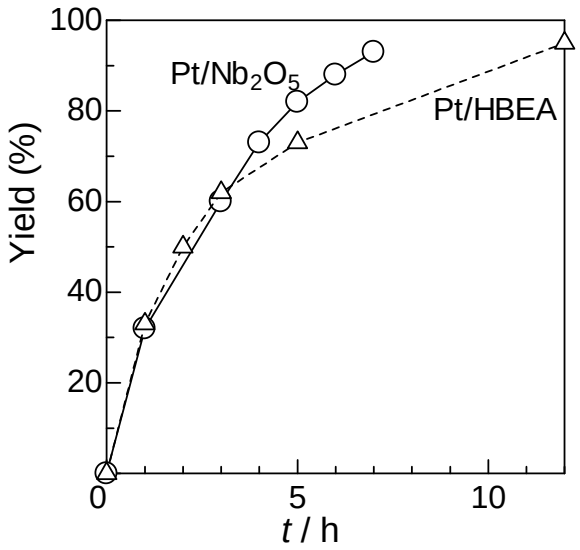


Fig. 3.1 Yields of indole *vs* time for *N*-heterocyclization of 2-(2-aminophenyl)ethanol under *o*-xylene reflux conditions in N_2 by Pt/Nb_2O_5 (ᘓ) or Pt/HBEA (ρ).

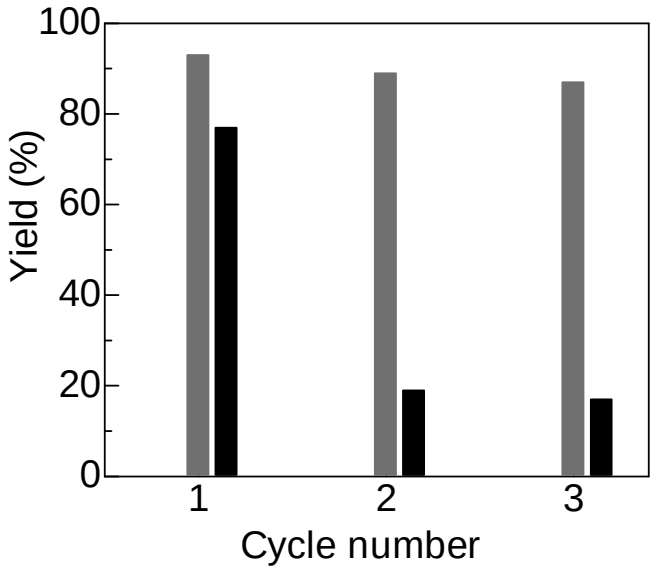
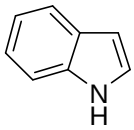


Fig. 3.2. Reuse of Pt/Nb_2O_5 (gray bars) or Pt/HBEA (black bars) for *N*-heterocyclization of 2-(2-aminophenyl)ethanol under *o*-xylene reflux conditions in N_2 for 7 h.

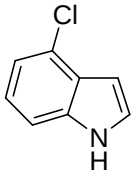
NMR and GC-MS analysis

Indole:[1]



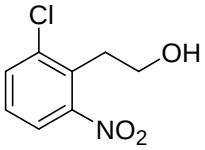
^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 7.91 (brs, 1H), 7.64 (d, *J* = 8.28 Hz, 1H), 7.31 (d, *J* = 8.22 Hz, 1H), 7.19-7.16 (m, 1H), 7.13-7.09 (m, 2H), 6.53 (d, *J* = 2.04 Hz, 1H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 135.65, 127.73, 124.12, 121.90, 120.66, 119.74, 111.01, 102.45; GC-MS m/e 117.055.

4-Chloro-1*H*-indole:[1]



^{1}H NMR (600.17 MHz, $CDCl_3$, TMS): δ 8.25 (brs, 1H), 7.29 (d, *J* = 7.56 Hz, 1H), 7.25-7.22 (m, 1H), 7.13-7.09 (m, 2H), 7.13-7.09 (m, 2H), 6.66 (t like d, *J* = 3.42 Hz, 1H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 136.42, 126.73, 126.12, 124.63, 122.57, 119.57, 109.62, 101.35; GC-MS m/e 151.020.

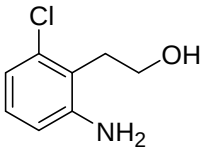
2-(2-Chloro-6-nitro-phenyl)-ethanol:[2]



A typical reaction procedure is described for the synthesis of 2-(2-Chloro-6-nitro-phenyl)-ethanol. 2-chloro-6 nitro toluene (6.3 g, 36.5 mmol), paraformaldehyde (91 mmol), DMSO (20 mL), and Triton B (Benzenetrimethylammonium hydroxide, 40% solution of MeOH, 1.0 mL), were placed in a 100-mL three necked round bottomed flask equiped with a reflux condenser. The reaction mixture was stirred for 8 h at 90 ˚C. Then the reaction mixture was quenched with saturated NH_4Cl solution, the organic compounds were extracted with ehtylacetate.

The combined organic layers were washed with brine and dried over Na_2SO4. After removal of the solvent, the residue was subjected to column chromatography (*n*-hexane:AcOEt = 4:1) to give 2-(2-Chloro-6-nitro-phenyl)-ethanol (88%). Mp 60-61 °C (*n*-hexane/AcOEt), light yellowish solid; ^{1}H NMR δ 7.70 (dd, 1H, *J* = 7.2, 1.2 Hz, 1H), 7.62 (dd, 1H, *J* = 7.2, 1.0 Hz, 1H), 7.33 (t, *J* = 8.10 Hz, 1H), 3.94 (t, *J* = 6.8 Hz, 2H), 3.27 (t, *J* = 6.8 Hz, 2H), 2.01 (brs, 1H); ^{13}C NMR δ 151.97, 136.64, 133.74, 130.99, 127.90, 122.90, 61.07, 32.62; GC-MS m/e 201.02.

2-(2-Amino-6-chloro-phenyl)-ethanol:[2]



A typical reaction procedure is described for the synthesis of 2-(2-amino-6-chloro-phenyl)-ethanol. 2-(2-Chloro-6-nitro-phenyl)-ethanol (2.016 g, 10 mmol), Pd/C (5 wt %, 1 mol%), ethylacetate (5.0 mL) were placed in a 100-mL round bottomed flask equiped with a Hydrogen balloon . The reaction mixture was stirred for 6 h at room temperature. Then the catalyst was filtered off and after removal of the solvent, the residue was purified by column chromatography (*n*-hexane:AcOEt = 3:1) to give 2-(2-amino-6-chloro-phenyl)-ethanol (90%).

References

1. K. Fujita, K. Yamamoto and R. Yamaguchi, *Org. Lett.*, 2002, **4**, 2691.

2. Y. Tsuji, S. Kotachi, K. Huh and Y. Watanabe, *J. Org. Chem.*, 1990, **55**, 580.

Chapter 4

Acceptorless Dehydrogenative Coupling of Primary Alcohols to Esters by Heterogeneous Pt Catalysts

4.1. Introduction

The synthesis of esters is one of the most fundamental and important transformations in organic synthesis.[1] Both in industry and in laboratories, esters are conventionally produced by condensation of a carboxylic acid or activated acid derivatives (acid chlorides or anhydrides) with excess amounts of an alcohol in the presence of an acid catalyst or a dehydrating agent, which results in a significant amount of waste. Recently, green catalytic methods such as condensation of an equimolar amount of carboxylic acid and alcohol[2] and esterification of aldehydes with alcohols[3-5] have been developed. However, the development of a novel catalytic system for the direct esters synthesis from stable and readily available substrates still remains a major challenge. Considering that alcohols are less corrosive and more accessible than acids or aldehydes, the direct aerobic oxidation of alcohols to esters is an important alternative, which has been accomplished with several homogeneous[6-9] and heterogeneous[10-17] catalytic systems. From a viewpoint of safety, anaerobic transformation of alcohols to esters in the presence of a stoichiometric amount of acceptor[18–20] (ketone or olefin) is more preferable. The most attractive method is the esterification of primary alcohols in the absence of an oxidant (acceptor) via acceptorless dehydrogenative coupling.[21] The most attractive methodology is the esterification of primary alcohols in the absence of an oxidant (acceptor). Homogeneous Ru,[22-33] Os,[34] Re[35] and Ir[36] catalysts were reported to be effective for this atom-efficient reaction. However, these systems suffer from difficulties in catalyst/product separation and catalyst reuse. Many of them also suffer from necessities of basic co-catalyst in the solution.[23-28,33-35] Although heterogeneous Cu catalysts are effective for gas-phase dehydrogenation of ethanol to ethyl acetate,[37-41] they suffer from low yield and need of high temperature. Cu-based heterogeneous catalyst were reported to be effective for acceptorless lactonization of diols.[42,43] Sánchez[26] first reported silica-immobilized pincer-type Ru complex as a reusable catalyst for dehydrogenation of a primary alcohol to ester, but the system required basic additive (KOH) and the substrate scope was limited only to hexanol. Herein we report the first example of reusable heterogeneous catalyst for the acceptorless dehydrogenative coupling of various primary alcohols to esters under additive-free and solvent-free conditions using SnO_2-supported Pt catalyst (Pt/SnO_2).

4.2. Experimental

General

Commercially available organic compounds (from Tokyo Chemical Industry or Kanto Chemical) were used without further purification. The GC (Shimadzu GC-14B) and GCMS (Shimadzu GCMS-QP2010) analyses were carried out with Ultra ALLOY capillary column UA$^+$-5 (Frontier Laboratories Ltd.) using nitrogen and He as the carrier gas.

Catalyst preparation

SnO_2 was prepared by calcination of H_2SnO_3 (Kojundo Chemical Laboratory Co., Ltd.) at 500 °C for 3 h. Nb_2O_5 was prepared by calcination of niobic acid (CBMMI) at 500 °C for 3 h. SiO_2 (Q-10, 300 m^2 g^{-1}) was supplied from Fuji Silysia Chemical Ltd. HBEA zeolite (JRC-Z-HB25, SiO_2/Al_2O_3= 25±5), MgO (JRC-MGO-3), TiO_2 (JRC-TIO-4), CeO_2 (JRC-CEO-3) was supplied from Catalysis Society of Japan. γ-Al_2O_3 was prepared by calcination of γ-AlOOH (Catapal B Alumina purchased from Sasol) for 3 h at 900 °C. ZrO_2 was prepared by calcination (500 °C for 3 h) of $ZrO_2.nH_2O$ prepared by hydrolysis of zirconium oxynitrate 2-hydrate in water by aqueous NH_4OH solution, followed by filtration of precipitate, washing with water three times, and drying at 100 °C for 12 h.

Precursor of Pt/SnO_2 was prepared by an impregnation method; a mixture of SnO_2 and an aqueous HNO_3 solution of $Pt(NH_3)_2(NO_3)_2$ was evaporated at 50 °C, followed by drying at 90 °C for 12 h. Before each catalytic experiment, the Pt/SnO_2 catalyst (with Pt loading of 5 wt%) was prepared by in situ pre-reduction of the precursor in a pyrex tube under a flow of H_2 (20 cm^3 min^{-1}) at 150 °C for 0.5 h. Other supported Pt catalysts (Pt = 5 wt%) were prepared by the same method. SnO_2–supported metal catalysts, M/SnO_2 (M = Ni, Cu, Co, Ag, Pd, Ru, Rh, Re, Ir) with metal loading of 5 wt% were prepared by the impregnation method in the similar manner as Pt/SnO_2 using aqueous solution of metal nitrates (for Ni, Cu, Co, Ag), $RuCl_3$, $IrCl_3.nH_2O$ or NH_4ReO_4 or aqueous HNO_3 solution of $Pd(NO_3)_2$. A commercial Pt-loaded carbon catalyst (Pt/C, Pt = 5 wt%) was purchased from N.E. Chemcat, Corporation.

Catalytic reactions

Pt/SnO_2 was used as a standard catalyst. After the pre-reduction at 150 °C, we carried out catalytic tests using a batch-type reactor without exposing the catalyst to air as follows. The mixture of alcohol (1 mmol) and n-dodecane (0.2 mmol) was injected to the pre-reduced catalyst inside the reactor (cylindrical glass tube) through a septum inlet, followed by filling 1 atm N_2. Then, the resulting mixture was stirred and heated at 180 °C. Conversion and yields of products were determined by GC using n-dodecane as an internal standard adopting the GC-sensitivity estimated using the isolated product. The products were identified by GC-MS equipped with the same column as GC. GC analysis of the gas phase product (H_2) was carried out by the mass spectrometer (BELMASS). Another sets of catalytic experiments were carried out to determine isolated yields of ester as follows. After the reaction, the catalyst was removed by filtration and the reaction mixture was concentrated under vacuum evaporator to remove the volatile compounds. Then, the esters in Table 4.3 were isolated by column chromatography using silica gel 60 (spherical, 63-210 μm, Kanto Chemical Co. Ltd.) with hexane/ethylacetate (2/98 or 5/95) as the eluting solvent, followed by analyses by ^{1}H NMR, ^{13}C NMR and GCMS.

In situ IR

In situ IR spectra were recorded at 40 °C using a JASCO FT/IR-4200 with an MCT detector. The sample was pressed into a 30 mg of self-supporting wafer (ϕ = 2 cm) and mounted into the quartz IR cell (CaF_2 windows) connected to a conventional flow reaction system. Spectra were measured accumulating 15 scans at a resolution of 4 cm^{-1}. A reference spectrum of the catalyst wafer in He taken at 40 °C was subtracted from each spectrum. Prior to the experiment the disk of SnO_2 (or SiO_2) was heated in H_2 flow (20 cm^3 min^{-1}) at 300 °C for 0.5 h, followed by cooling to 40 °C and purging with He. Then, 1 μL of benzaldehyde was injected to He flow preheated at 200 °C, which was fed to the IR cell. Then, the IR disk was purged with He for 1000 s, and IR measurement was carried out.

NMR and GCMS analysis

H and 13C NMR spectra were recorded using at ambient temperature on JEOL-ECX 600 operating at 600.17 and 150.91 MHz, respectively with tetramethylsilane as an internal standard. All chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. All chemical shifts are reported relative to tetramethylsilane and *d*-solvent peaks (77.00 ppm, chloroform), respectively. Abbreviations used in the NMR experiments: s, singlet d, doublet; t, triplet; m, multiplet. GC-MS spectra were recorded by SHIMADZU QP2010.

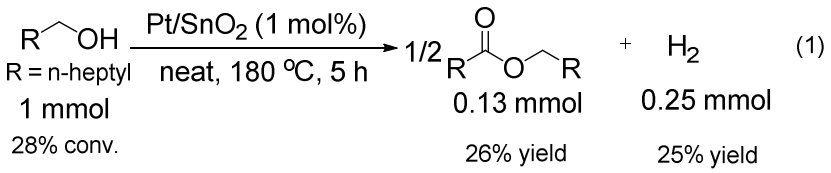
4.3. Results and discussion

Catalyst screening

We chose the esterification of 1-octanol under solvent-free conditions in N_2 at 180 °C as a model system in order to optimize catalytic conditions. Table 4.1 (entries 1-10) summarizes the results of the initial catalyst screening test under the same reaction conditions using various transition metal (Pt, Pd, Ir, Re, Ni, Rh, Cu, Ag, Co, Ru,) catalysts supported on SnO_2 pre-reduced in H_2 at 150 °C. Among the catalysts tested, Pt/SnO_2 showed the highest yield (26%) of the corresponding ester. Entries 12-21 show the results of Pt catalysts loaded on the other supports(ZrO_2, CeO_2, Nb_2O_5, TiO_2, C, Al_2O_3, SiO_2, HBEA zeolite, MgO). Pt/SnO_2 (entry 1) showed higher yield of the ester (98%) than these Pt catalysts. Pt/Nb_2O_5, Pt/CeO_2, and Pt/TiO_2 (entries 12-15) gave low yields (8-14%), and the Pt loaded on C, Al_2O_3, SiO_2, HBEA, MgO were completely inactive (entries 16-20). The ester was not produced in the absence of any catalysts (entry 21).

Using Pt/SnO_2 as the most effective catalyst for this reaction, we carried out detailed catalytic studies. We checked time course of the reaction of 1-octanol under the standard conditions at 180 °C (result not shown). During the reaction, the conversion of 1-octanol and the yield of the ester were nearly the same, and no byproducts or possible intermediates such as n-octanal were observed by GC and GCMS analyses. We also carried out mass spectrometry analysis of gas phase products after 5 h. The yields of gas

phase H_2 (25%) and the ester (26%) were nearly identical to the conversion of 1-octanol (28%), indicating that H_2 was generated quantitatively during the dehydrogenative coupling of 1-octanol to the ester (eq. 1).



(1)

After 36 h, full conversion of 1-octanol and 98% yield of the ester were observed. ICP-AES analysis of the solution confirmed that the content of Pt in the solution was below the detection limit and that of Sn was quite low (0.62 ppm, 0.006% of Sn in the catalyst used). Then, we tested reusability of Pt/SnO_2. After completion of the reaction, 2-propanol(1 g)/acetone (1 g) was added to the reaction mixture and catalyst was separated by centrifugation. For each successive use, recovered catalyst was washed by acetone three times, followed by centrifugation and drying in oven (under air) at 90 °C for 3 h, followed by H_2-reduction at 150 °C for 0.5 h. The recovered catalyst was reused at least three times without a marked loss of its catalytic activity (Figure 4.1). These results indicate that Pt/SnO_2 acts as reusable heterogeneous catalysts for this reaction.

Table 4.2 shows the effect of solvent on the yield of the ester for the standard reaction of 1-octanol for 36 h. The reaction under the solvent-free conditions gave the highest yield (98%). Reactions in a polar solvent (diglyme) and in a non-polar solvent (dodecane) were also successful, but mesitylene gave lower yield. Under the solvent-free conditions, the reaction at lower temperature (150 °C) resulted in lower conversion (result not shown). Under the optimized conditions with the most effective catalyst (Pt/SnO_2), we studied general applicability of the present catalytic system (Table 4.3). Linear and cyclic aliphatic primary alcohols (entries 1-5) were effectively converted to the corresponding ester in high yield. Benzylalcohol (entry 7) and 4-fluoro benzyl alcohol (entry 6) were also converted to the corresponding ester with moderate yields. After the reactions in Table 4.3, the catalyst was removed from the mixture and the esters were

isolated by column chromatography, resulting in moderate to high isolated yields (53-91%) of the esters.

Finally, we discuss a possible mechanism of the present catalytic system. As discussed in the previous papers on homogeneous Ru catalysts for this reaction,[23-33] dehydrogenative coupling of primary alcohols to esters by Pt/SnO_2 may, in principle, proceed through two possible pathways: (a) the dehydrogenation to aldehyde which reacts with alcohol to give hemiacetal followed by its dehydrogenation to the ester (Scheme 4.1) or (b) aldehyde disproportionation so called Tishchenko reaction. The hypothesis (a) is evidenced by the following results. The reaction of 1 mmol of *n*-octanal under the standard conditions in Table 4.3 resulted in no formation of the corresponding ester. This result rules out an aldehyde disproportionation pathway as the main route to ester. Instead, the reaction of a 1:1 mixture of *n*-octanal and 1-octanol under N_2 in the presence of Pt/SnO_2 at 150 °C gave the corresponding ester in 48% yield after 5 h.

SnO_2 is a well-known promoter on platinum-group-metal catalysts for selective hydrogenation of α,β-unsaturated aldehydes to unsaturated alcohols.[44-46] Generally, the addition of SnO_2 significantly increase the selectivity of C=O bond reduction. On the basis of the IR result that co-loading of SnO_2 on a supported Rh catalyst led to a red shift in the C=O stretching band of the adsorbed propionaldehyde species via Lewis acid-base interaction between Sn cations and oxygen atoms of carbonyl groups, Nishiyama *et al.*[45] showed that the Sn cation acted as a Lewis acid site that activate the C=O groups. Recently, they studied selective hydrogenation of unsaturated aldehyde by Sn-modified silica-coated Pt catalysts and proposed that the high selectivity in C=O bond reduction than C=C bond reduction was caused by cooperation between Pt and SnO_2, in which H_2 is dissociated by Pt and C=O bond of aldehyde is activated by SnO_2.[46] For hydrogenation of esters with SnOx-promoted Rh catalysts, Ru is believed to activate H_2 and Sn species are believed to activate carbonyl groups.[47,48] Lewis acid assisted C=O bond activation in heterogeneous metal catalysis has been also reported for various catalytic systems.[49-51] To evaluate the Lewis acid-base interaction between Sn cation and carbonyl oxygen of aldehyde, we carried out IR experiment of benzaldehyde adsorbed on SnO_2. The

spectrum in Figure 4.2 shows the C=O stretching band of the benzaldehyde at lower wavenumber (1686 cm^{-1}) than that for benzaldehyde adsorbed on non Lewis acidic oxide, SiO_2 (1693 cm^{-1}). This indicates charge transfer from the oxygen atom of carboxyl group (Lewis base) to the Sn^{4+} cation (Lewis acid site) of SnO_2. On the basis of these results, combined with the facts that H_2 was quantitatively observed (eq. 1), we propose a possible mechanism of the present catalytic system in Scheme 4.1. Note that aldehydes are not observed by GC during the catalytic reaction, suggesting that adsorbed aldehyde species can be intermediates instead of free aldehydes. The reaction begins with the Pt-catalyzed dehydrogenation of primary alcohol to adsorbed aldehyde accompanied by the generation of H_2. Then, nucleophilic attack of another alcohol to the aldehyde species coordinated to Sn^{4+} (Lewis acid site) gives hemiacetal adspecies, which undergoes Pt-catalyzed dehydrogenation to ester. Enhanced electrophilicity of the carbonyl groups in aldehydes via Lewis acid-base interaction of the Sn cation and carboxyl oxygen can be the primary important role of the SnO_2 support, which should promote the nucleophilic attack of alcohols to the adsorbed aldehyde species to Sn^{4+}.

4.4. Conclusion

We developed the first example of heterogeneous catalysts for the acceptor-free dehydrogenative coupling of various primary alcohols to esters under additive-free and solvent-free conditions using the SnO_2-supported Pt catalyst. The method was effective for various primary alcohols under additive-free and solvent-free conditions, and the catalyst was reusable. Therefore, the method provides one of the most atom-efficient and step-efficient catalytic routes to esters from readily available starting materials, alcohols. The reaction pathway can consist of the reaction of adsorbed aldehyde on SnO_2 with alcohol to give hemiacetal intermediate followed by its dehydrogenation to the ester. On the basis of the IR evidence on Lewis acid-base interaction between the surface Sn cation and carboxyl oxygen of the adsorbed aldehyde, we propose that activation of carbonyl groups in aldehydes is the primary important role of the SnO_2 support.

References

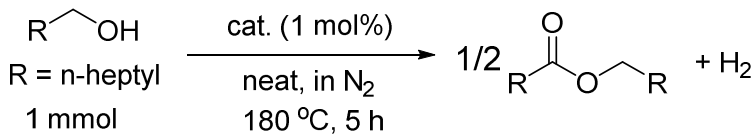
1. B. R. Davis and P. J. Garratt, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, vol. 2, p. 799.
2. K. Ishihara, S. Ohara and H. Yamamoto, *Science*, 2000, 290, 1140–1142.
3. W.-J. Yoo and C.-J. Li, *Tetrahedron Lett.*, 2007, **48**, 1033–1035.
4. T. Yasukawa, H. Miyamura and S. Kobayashi, *Chem. – Asian J*., 2011, **6**, 621–627.
5. C. Liu, S. Tang, L. Zheng, D. Liu, H. Zhang and A. Lei, *Angew. Chem., Int. Ed*., 2012, **51**, 5662–5666.
6. S. Arita, T. Koike, Y. Kayaki and T. Ikariya, *Chem. – Asian J.*, 2008, 3, 1479–1485.
7. A. Izumi, Y. Obora, S. Sakaguchi and Y. Ishii, *Tetrahedron Lett*., 2006, **47**, 9199–9201.
8. S. Gowrisankar, H. Neumann and M. Beller, *Angew. Chem., Int. Ed*., 2011, **50**, 5139–5143.
9. C. Liu, J. Wang, L. Meng, Y. Deng, Y. Li and A. Lei, *Angew. Chem., Int. Ed*., 2011, **50**, 5144–5148.
10. I. S. Nielsen, E. Taarning, K. Egeblad, R. Madsen and C. H. Christensen, *Catal. Lett*., 2007, **116**, 35–40.
11. F.-N. Su, J. Ni, H. Sun, Y. Cao, H.-Y. He and K.-N. Fan, *Chem. – Eur. J*., 2008, **14**, 7131–7135.
12. R. L. Oliveira, P. K. Kiyohara and L. M. Rossi, *Green Chem*., 2009, **11**, 1366–1370.
13. H. Miyamura, T. Yasukawa and S. Kobayashi, *Green Chem*., 2010, **12**, 776–778.
14. T. Ishida, Y. Ogihara, H. Ohashi, T. Akita, T. Honma, H. Oji and M. Haruta, *ChemSusChem*, 2012, **5**, 2243–2248.
15. K. Suzuki, T. Yamaguchi, K. Matsushita, C. Iitsuka, J. Miura, T. Akaogi and H. Ishida, *ACS Catal.*, 2013, **3**, 1845–1849.
16. R. V. Jagadeesh, H. Junge, M.-M. Pohl, J. Radnik, A. Brückner and M. Beller, *J. Am. Chem. Soc*., 2013, **135**, 10776–10782.
17. A. B. Powell and S. S. Stahl, *Org. Lett*., 2013, **15**, 5072–5075.
18. N. Yamamoto, Y. Obora and Y. Ishii, *J. Org. Chem*., 2011, **76**, 2937–2941.
19. T. Suzuki, T. Matsuo, K. Watanabe and T. Katoh, *Synlett*, 2005, 1453–1455.
20. N. A. Owston, T. D. Nixon, A. J. Parker, M. K. Whittlesey and J. M. J. Williams,

Synthesis, 2009, 1578–1581.

21. C. Gunanathan and D. Milstein, *Science*, 2013, 249–260.
22. S. Murahashi, K. Ito, T. Naota and Y. Maeda, *Tetrahedron Lett*., 1981, **22**, 5327–5330.
23. J. Zhang, G. Leitus, Y. Ben-David and D. Milstein, *J. Am. Chem. Soc*., 2005, **127**, 10840–10841.
24. S. Musa, I. Shaposhnikov, S. Cohen and D. Gelman, *Angew. Chem., Int. Ed*., 2011, **50**, 3533–3537.
25. A. Sølvhøj and R. Madsen, *Organometallics*, 2011, **30**, 6044–6048.
26. C. del Pozo, M. Iglesias and F. Sánchez, *Organometallics*, 2011, **30**, 2180–2188.
27. M. Nielsen, H. Junge, A. Kammer and M. Beller, *Angew. Chem., Int. Ed*., 2012, **51**, 5711–5713.
28. D. Spasyuk, S. Smith and D. G. Gusev, *Organometallics*, 2012, **31**, 5239–5242.
29. G. Zeng, T. Chen, L. He, T. Pinnau, Z. Lai and K.-W. Huang, *Chem. – Eur. J.*, 2012, **18**, 15940–15943.
30. M. H. G. Prechtl, K. Wobser, N. Theyssen, Y. Ben-David, D. Milstein and W. Leitner, *Catal. Sci. Technol*., 2012, **2**, 2039–2042.
31. D. Srimani, E. Balaraman, B. Gnanaprakasam, Y. Ben-David and D. Milstein, *Adv. Synth. Catal*., 2012, **354**, 2403–2406.
32. P. P. M. Schleker, R. Honeker, J. R. Klankermayer and W. Leitner, *ChemCatChem*, 2013, **5**, 1762–1764.
33. I. S. Makarov and R. Madsen, *J. Org. Chem*., 2013, **78**, 6593–6598.
34. D. Spasyuk, S. Smith and D. G. Gusev, *Angew. Chem., Int. Ed*., 2012, **51**, 2772–2775.
35. P. P. M. Schleker, R. Honeker, J. R. Klankermayer and W. Leitner, *ChemCatChem*, 2013, **5**, 1762–1764.
36. K. Fujita, W. Ito and R. Yamaguchi, *ChemCatChem*, 2014, **6**, 109–112.
37. N. Iwasa and N. Takezawa, *Bull. Chem. Soc. Jpn*., 1991, **64**, 2619–2623.
38. K. Inui, T. Kurabayashi and S. Sato, *Appl. Catal., A*, 2002, **237**, 53–61.
39. K. Inui, T. Kurabayashi and S. Sato, *J. Catal*., 2002, **212**, 207–215.
40. S. W. Colley, J. Tabatabaei and K. C. Waugh, *J. Catal*., 2005, **236**, 21–33.

41. M. H. Zhang, G. M. Li, H. X. Jiang and J. Y. Zhang, *Catal. Lett.*, 2011, **141**, 1104–1110.
42. Y. Mikami, K. Ebata, T. Mitsudome, T. Mizugaki, K. Jitsukawa and K. Kaneda, *Heterocycles*, 2010, **80**, 855–861.
43. D. W. Hwang, P. Kashinathan, J. M. Lee, J. H. Lee, U.-H. Lee, J.-S. Hwang, Y. K. Hwang and J.-S. Chang, *Green Chem*., 2011, **13**, 1672–1675.
44. S. Nishiyama, T. Kubota, K. Kimura, S. Tsuruya and M. Masai, J. Mol. *Catal. A: Chem*., 1997, **120**, 17–22.
45. S. Nishiyama, T. Hara, S. Tsuruya and M. Masai, *J. Phys. Chem. B*, 1999, **103**, 4431–4439.
46. K. Taniya, H. Jinno, M. Kishida, Y. Ichihashi and S. Nishiyama, *J. Catal*., 2012, **288**, 84–91.
47. Y. Kojima, S. Kotani, M. Sano, T. Suzuki and T. Miyake, *J. Jpn. Pet. Inst*., 2013, **56**, 133–141.
48. M. Toba, S. Tanaka, S. Niwa, F. Mizukami, Z. Koppány, L. Guczi, K. Cheah and T. Tang, *Appl. Catal., A*, 1999, **189**, 243–250.
49. A. Primo, P. Concepcion and A. Corma, *Chem. Commun*., 2011, **47**, 3613–3615.
50. A. Boffa, C. Lin, A. T. Bell and G. A. Somorjai, *J. Catal*., 1994, **149**, 149–158.
51. H. Yoshitake and Y. Iwasawa, *J. Catal*., 1990, **125**, 227–242.

Table 4.1. Catalyst screening for dehydrogenative esterification of 1-octanol.[a]



Entry	Catalyst	Yield (%) [a]
1	Pt/SnO_2	26
2	Rh/SnO_2	15
3	Ir/SnO_2	10
4	Pd/SnO_2	5
5	Re/SnO_2	1
6	Ru/SnO_2	<1
7	Ag/SnO_2	0
8	Ni/SnO_2	1
9	Co/SnO_2	0
10	Cu/SnO_2	0
11[b]	SnO_2	0
12	Pt/ZrO_2	14
13	Pt/CeO_2	8
14	Pt/Nb_2O_5	8
15	Pt/TiO_2	6
16	Pt/C	0
17	Pt/Al_2O_3	0
18	Pt/SiO_2	0
19	Pt/HBEA	0
20	Pt/MgO	0
21	blank	0

[a] Yield was determined by GC.

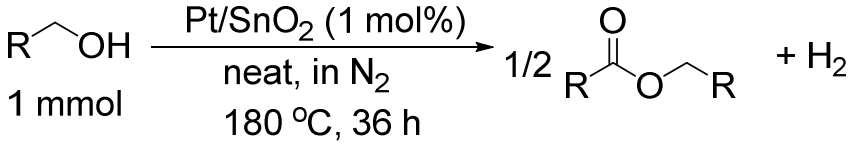
[b] Catalyst amount was 50 mg.

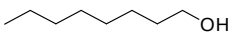
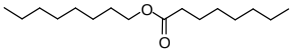
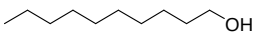
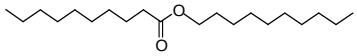
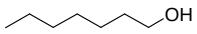
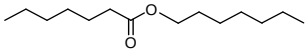
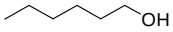
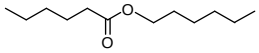
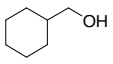
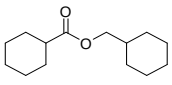
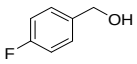
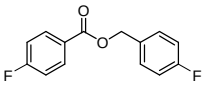
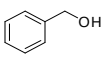
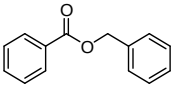
Table 4.2. Solvent screening for Pt/SnO_2.[a]

Solvent	Yield (%)
no solvent	98
diglyme	95
dodecane	90
mesitylene	70

[a] Conditions: 1 mol% Pt/SnO_2 (0.01 mmol Pt), 1 mmol 1-octanol, 0 or 1 g solvent, 180 °C, 36 h. Yield was determined by GC.

Table 4.3. Synthesis of esters from various alcohols by Pt/SnO_2.



Entry	Alcohols	Products	Yield[a] (%)
1			98 (91)
2			90 (82)
3			92 (81)
4			84 (69)
5			89 (79)
6			62 (53)
7			68 (60)

[a] GC yields. Isolated yields are in parentheses.

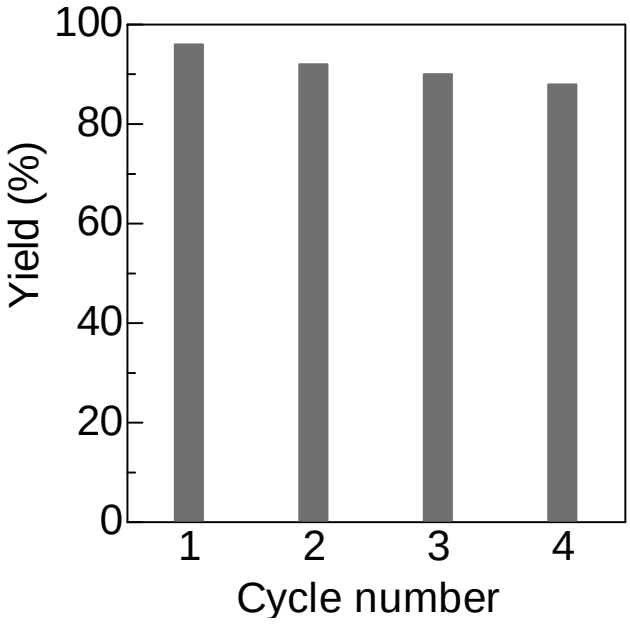


Figure 4.1. Catalyst reuse for esterification of 1-octanol by Pt/SnO_2. Conditions are shown in Table 4.3.

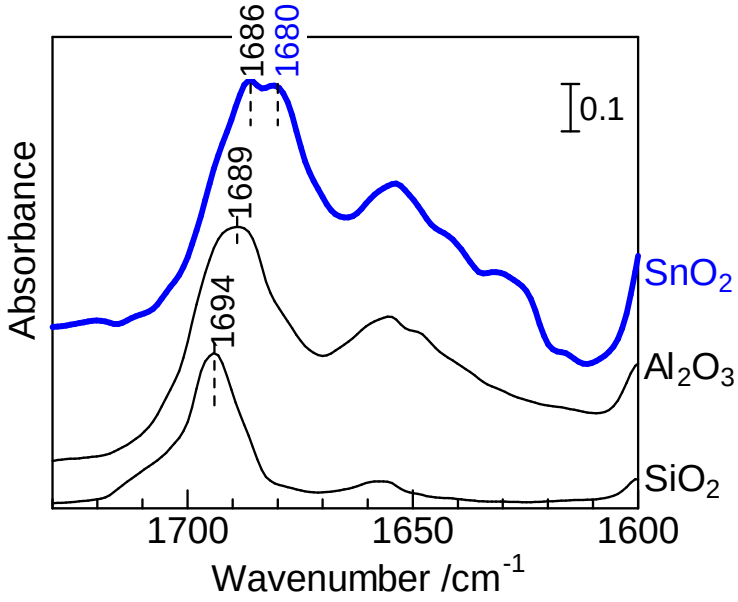
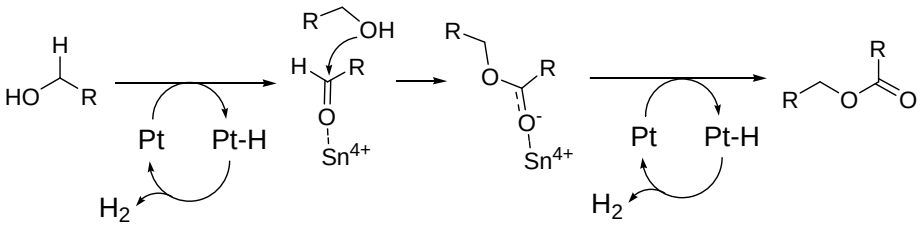


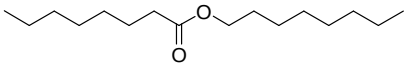
Figure 4.2. IR spectra of benzaldehyde adsorbed on SnO_2 and SiO_2 at 40 ^{o}C.



Scheme 4.1. Proposed pathway of dehydrogenative esterification of primary alcohols by Pt/SnO_2.

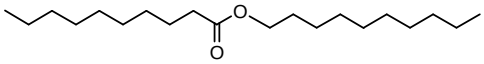
NMR and GCMS analysis

Octanoic acid octyl ester ($C_{16}H_{32}O_2$) :[1]



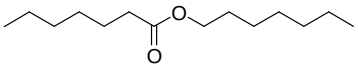
^{1}H NMR (600.17 MHz, $CDCl_3$), TMS: δ 4.04 (t, *J* = 6.84 Hz, 2H), 2.28 (t, *J* = 7.56 Hz, 2H), 1.62-1.58 (m, 4H), 1.33-1.24 (m, 18H), 0.86 (t, *J* = 6.90 Hz, 6H); ^{13}C NMR (150.91 MHz, $CDCl_3$) δ 174.37, 64.53, 34.41, 31.90, 31.76, 31.64, 29.19, 29.16, 29.08, 28.90, 28.60, 25.91, 25.00, 22.61, 22.57, 14.01; GC-MS m/e 256.24.

Decanoic acid decayl ester ($C_{20}H_{40}O_2$) :[2]



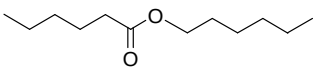
^{1}H NMR (600.17 MHz, $CDCl_3$), TMS: δ 4.05 (t, *J* = 6.84 Hz, 2H), 2.28 (t, *J* = 7.56 Hz, 2H), 1.63-1.60 (m, 4H), 1.32-1.19 (m, 26H), 0.88 (t, *J* = 6.90, 6H); ^{13}C NMR (150.91 MHz, $CDCl_3$) δ 173.91, 64.36, 34.41, 31.97, 29.75, 29.58, 29.48 (C×2), 29.35, 29.32 (C×2), 29.31, 29.20 (C×2), 28.70, 25.98, 25.06, 25.86, 22.70 (C×2); GC-MS m/e 312.41.

Heptanoic acid heptyl ester ($C_{14}H_{28}O_2$) :[3]



^{1}H NMR (600.17 MHz, $CDCl_3$), TMS: δ 4.05 (t, *J* = 6.90 Hz, 2H), 2.27 (t, *J* = 7.56 Hz, 2H), 1.64-1.57 (m, 4H), 1.34-1.24 (m, 14H), 0.98-0.85 (m, 6H); ^{13}C NMR (150.91 MHz, $CDCl_3$) δ 173.88, 64.30, 34.34, 31.69, 31.43, 28.88, 28.79, 28.63, 25.86, 24.94, 22.53, 22.45, 13.99, 13.94; GC-MS m/e 228.20.

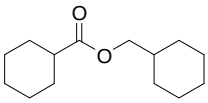
Hexanoic acid hexyl ester ($C_{12}H_{24}O_2$) :[4]



^{1}H NMR (600.17 MHz, $CDCl_3$), TMS: δ 4.05 (t, *J* = 6.90 Hz, 2H), 2.28 (t, *J* = 6.90 Hz, 2H), 1.66-1.56 (m, 4H), 1.38-1.19 (m, 10H),0.88-0.83 (m, 6H); ^{13}C NMR (150.91 MHz,

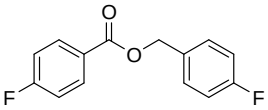
$CDCl_3$) δ 173.95, 64.33, 34.32, 31.39, 31.28, 28.57, 25.55, 24.67, 22.49, 22.28, 13.93, 13.86; GC-MS m/e 200.10.

Cyclohexane methanoic acid cyclohexane methyl ester ($C_{13}H_{22}O_2$) :[4]



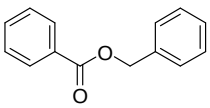
^{1}H NMR (600.17 MHz, $CDCl_3$); TMS: δ 3.86-3.84(m, 2H), 2.30-2.26 (m, 1H), 1.90-1.88 (m, 2H), 1.72-1.62 (m, 8H), 1.45-1.39 (m, 2H), 1.29-1.11 (m, 6H), 0.98-0.92 (m, 1H); ^{13}C NMR (150.91 MHz, $CDCl_3$) δ 176.18, 69.23, 43.31, 37.15, 29.65 (C×2), 29.06 (C×2), 26.36, 25.76, 25.68 (C×2), 25.46; GC-MS m/e 224.20.

4-Fluro benzoic acid 4-fluro benzyl ester ($C_{14}H_{10}F_2O_2$) :[5]



^{1}H NMR (600.17 MHz, $CDCl_3$); TMS: δ 8.11-8.06 (m, 2H), 7.42 (d, *J* = 5.52 Hz, 2H), 7.12-7.05 (m, 4H), 5.31 (s, 2H); ^{13}C NMR (150.91 MHz, $CDCl_3$) δ 165.84 (d, *J* = 254.50 Hz), 165.39, 162.70 (d, *J* = 247.58 Hz), 161.88, 132.23 (d, *J* = 9.20 Hz), 131.70 (d, *J* = 3.1 Hz), 130.27 (d, *J* = 8.07), 126.24 (d, *J* = 3 Hz), 115.56 (d, *J* = 21.88 Hz), 66.12; GC-MS m/e 248.19.

Benzoic acid benzyl ester ($C_{14}H_{12}O_2$) :[6]



^{1}H NMR (600.17 MHz, $CDCl_3$); TMS: δ 8.10-8.09 (m, 2H), 7.56 (t, *J* = 6.90 Hz, 1H), 7.47-7.44 (m, 4H), 7.40 (t, *J* = 7.50 Hz, 2H), 7.37-7.34 (m, 1H), 5.36 (s, 2H); ^{13}C NMR (150.91 MHz, $CDCl_3$) δ 166.38, 136.01, 132.98, 130.09, 129.66 (C×2), 128.55(C×2), 128.33(C×2), 128.20, 128.12(C×2), 66.64; GC-MS m/e 212.16.

References

1. M. Minakawa, H. Baek, Y. M. A Yamada, J. W Han and Y. Uozumi, *Org. Lett*., 2013, **15**, 5798.
2. J. Malineni, C. Merkens, H. Keul, M. Möller, *Catal. Commun*., 2013, **40**, 80.
3. A. Amati, G. Dosualdo, L. Zhao, A. Bravo, F. Fontana, F. Minisci and H. Bjørsvik, *Org. Proc. Res. Dev.*, 1998, **2**, 261.
4. T. Ooi, T. Miura, K. Takaya, K. Maruoka, *Tetrahedron Lett*., 1999, **40**, 7695.
5. C. Liu, S. Tang and A. Lei, *Chem. Commun*., 2013, **49**, 1324.
6. K. Ishihara, M. Niwa and Y. Kosugi, *Org. Lett*., 2008, **10**, 2187.

Chapter 5

General Conclusion

Heterogeneous Pt catalyzed direct synthesis of chemicals by acceptorless dehydrogenation of alcohols and cyclic amines give atom efficient routes under neutral conditions. Chapter 2-4 show systematic examples of new heterogeneous catalysts for acceptorless dehydrogenation reactions of amines (*N*-heterocycles) and alcohols under additive-free conditions with liberation of H_2 as a byproduct. Comparing with organometallic catalysis, heterogeneous Pt catalysts do not requires additives (ligand, acid or base) which increases atom economy. The concept of catalyst design is multifunctionality of the metal loaded acid/neutral support in which acid sites of metal oxide selectively catalyzes dehydrogenative coupling and neutral support was effective for the dehydrogenation of amines.

The heterogeneous catalysts developed in this work have advantages over the previous homogeneous catalysts, including good catalyst reusability and high TON, and hence will provide practical methods for sustainable production of chemicals. To achieve more sustainable chemical process, this work will help for the rational development of new heterogeneous catalysts for this type of multistep reactions without additives.

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Sondomoyee Konika Moromi