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Author(s)	CHAUDHARI, CHANDAN SUBHASH
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Heterogeneous Pt Catalysts for Direct Synthesis of Chemicals from Alcohols by Borrowing-hydrogen and Acceptorless Dehydrogenation Reactions

Chandan Chaudhari

2015

Graduate school of chemical sciences and engineering

Hokkaido University

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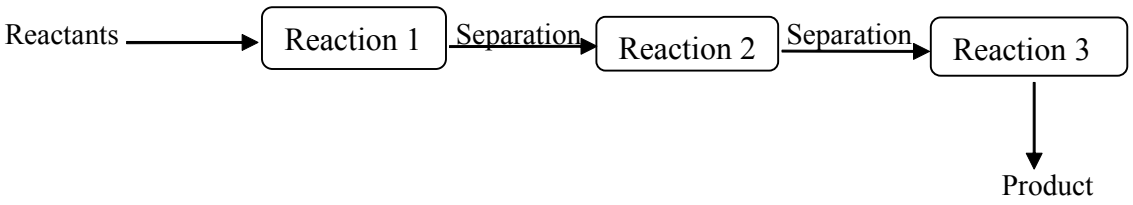
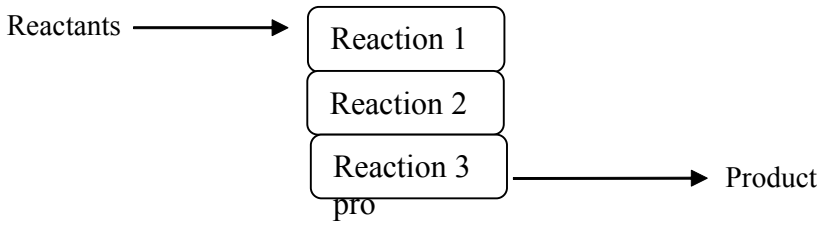
Chapter 1. General introduction

The principles of green chemistry provide the concept of ideal synthesis in term of catalytic activity, selectivity, atom-efficiency, step-efficiency and toxicity.[1,2] This concept inspires researchers to develope new atom-economical, environmentally benign synthetic methodology. Recently, several attempts have been reported for the multiple catalytic transformation in same vessel which are known as one-pot or tandem or domino or cascade synthesis. One-pot synthesis is the combination of multistep catalytic synthesis which reduces energy consuming steps such as separation and purification of intermediate. The simple and benign molecules are usually stable therefore it should be transformed to activated intermediates *in situ* without using sacrificial promoters. Using heterogeneous catalyst, one pot methodology plays vital role in synthetic organic methodology because of easy separation and recycling of catalyst.[3-8]

Multistep synthesis



One-pot synthesis



In heterogeneous catalysis, active site with different functions can be prepared on the same solid and different sites can work cooperatively or separatively in different steps. In bifunctional metal and metal oxide support catalyst, metal acts as redox center and the surface of metal oxide acts as acidic or basic sites.

The construction of C-C and C-N bonds

The carbon-carbon(C-C) and carbon-nitrogen(C-N) are most abundant bonds in

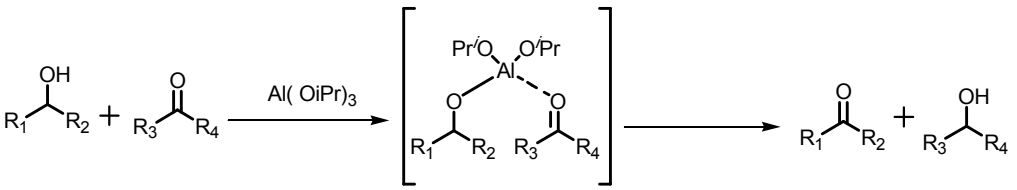
organic chemistry and useful for the construction of organic compounds in pharmaceutical and fine chemical industries. The classical method for the synthesis of C-C and C-N bonds is based on activated substrate such as alkyl halide which produces large of amount salt wastes (Scheme 1.1).

$$\text{R-H} + \text{R`-Cl} \xrightarrow{\text{Classical method}} \text{R-R`} + \text{HCl}$$

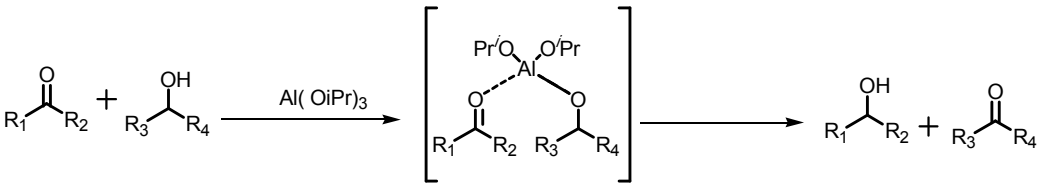
$$\text{R-H} + \text{R`-OH} \xrightarrow{\text{Emerging method}} \text{R-R`} + \text{H}_2\text{O}$$

Scheme 1.1 Methods for the synthesis of C-C and C-N bond formation.

With respect to the principles of green chemistry, the biomass derived alcohols can be attractive option for alkyl halides for the formation of C-C and C-N bonds because it generates water as byproduct. In the lights of literature, the earliest example of C-C bonds formation using alcohol is Guerbet reaction. In these reaction, alcohol dehydrogenate to aldehydes which undergo aldol condensation and give α,β-unsaturated carbonyl compound. Finally, hydrogenation of α,β-unsaturated carbonyl compound transform to β-alkylated alcohol. The Oppenauer oxidation and Meerwein-Pondorf-Verley reduction were the earliest example of transfer hydrogenation (Scheme 1.2 and 1.3). Both reactions used aluminum isopropoxide reagent and proceed via cyclic transition state.[14,15] However, use of stoichiometric amount of reagents and formation of byproduct were major drawbacks of this methodology.



Scheme 1.2 Oppenauer oxidation of alcohol to ketone.

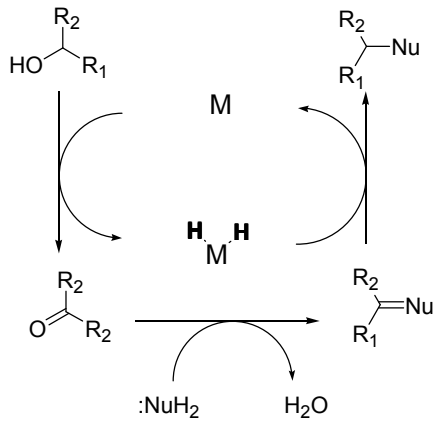


Scheme 1.3 Meerwein-Pondorf-Verley reduction of ketone to alcohol.

Recently, several attempts have been reported using alcohol as green alkylating agent for synthesis of chemicals via borrowing hydrogen and acceptorless dehydrogenation methodology.[9-13]

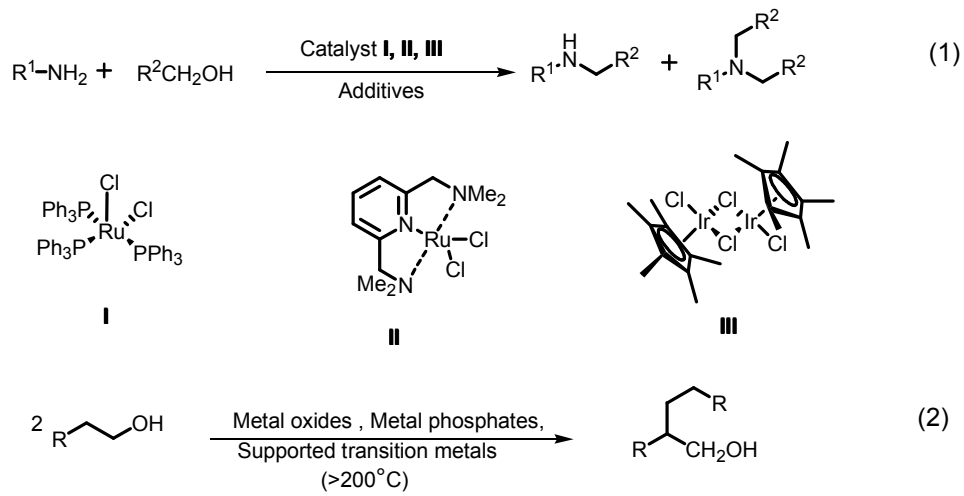
Borrowing-hydrogen methodology

The borrowing hydrogen or hydrogen auto-transfer consist of dehydrogenation of alcohols to carbonyl compounds, condensation of carbonyl compounds and nucleophile which give C=C bond formation and reduction of C=C bond by metal hydride (Scheme 1.4). This method shows greener and cleaner way to form C-C and C-N bond formation without using stoichiometric oxidants or reductants and prefunctionalized substrate.



Scheme 1.4 Borrowing hydrogen methodology.

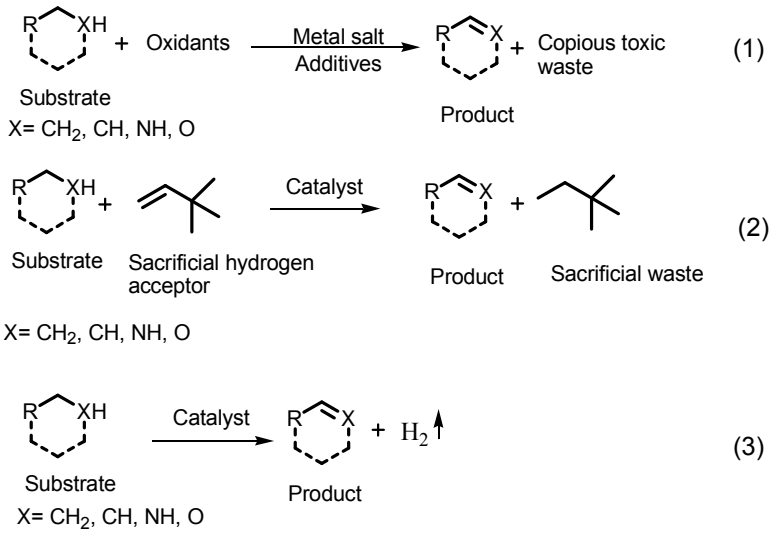
In early reports by Grigg *et al*,[16] Watanabe *et al* [17] and as summarized in recent reviews,[9-13] effective C-C and C-N bond formation have been studied using Ru or Ir complex catalysts under mild conditions (Scheme 1.5 eq.1). However this method suffers from use of additives, catalyst reuse, catalyst separation from reaction mixture. In early reports,[18-20] the heterogeneous catalysts showed limited scope, low selectivity, high temperature (>200ºC) and use of H_2 (Scheme 1.5 eq. 2). Recently, the heterogeneous catalysts have been reported under mild reaction conditions for the synthesis of C-C bonds formation via borrowing hydrogen methodology but still need of additives.[21-23]



Scheme 1.5 Typical catalysts for borrowing-hydrogen methodology.

Acceptorless dehydrogenation methodology

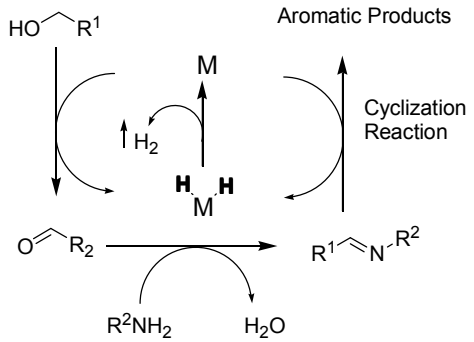
Generally, oxidation/dehydrogenation reactions carried out with the help of stoichiometric amount of toxic oxidants or pressurized oxygen or peroxide or sacrificial hydrogen acceptor. The toxic oxidant and sacrificial acceptor produce stoichiometric amount of wastes. The pressurized oxygen or peroxide may cause explosion hazard. The acceptor-free dehydrogenation of alcohols to carbonyl compounds under anaerobic conditions is simple and attractive route. Acceptorless dehydrogenation have great importance in catalytic synthetic chemistry which liberate hydrogen as byproduct.



Scheme 1.6 Classification of dehydrogenation reactions.

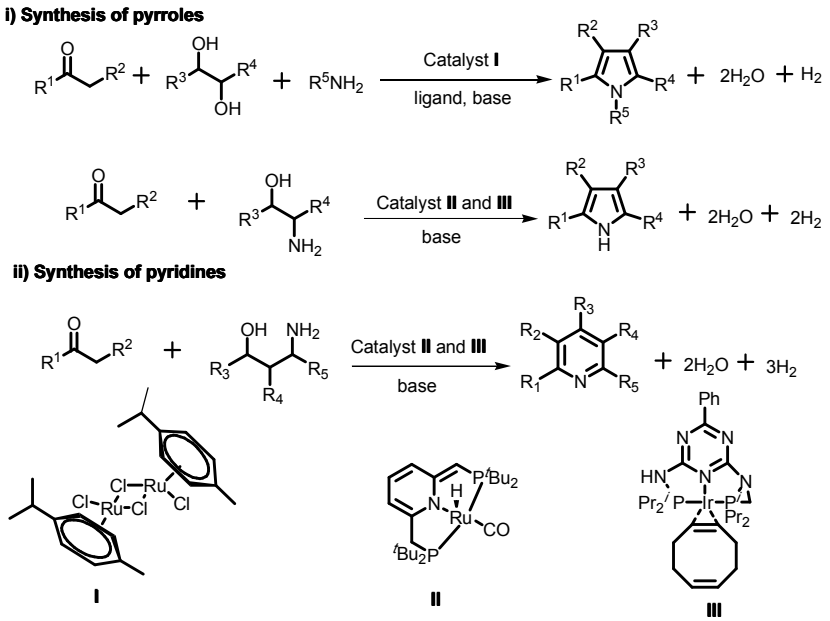
The acceptorless dehydrogenative coupling reactions are attractive version of

acceptorless dehydrogenation. It is combination of dehydrogenation of alcohols to carbonyl compounds, condensation of carbonyl compounds and nucleophiles followed by cyclization and aromatization with elimination of water and liberation of hydrogen (Scheme 1.7).



Scheme 1.7 Acceptorless dehydrogenative coupling reaction.

Recently, Ir complex catalyst and Ru complex catalyst have been developed for acceptorless dehydrogenative coupling of alcohol and/or diols and amines or amino alcohols to synthesis N-heteroaromatic compounds such as pyrroles and pyridines (Scheme 1.8).[24-27] However, these methods suffer from use of stoichiometric amount of ligand and additives and low efficiency.



Scheme 1.8 Synthesis of N-heterocycles via acceptorless dehydrogenative coupling reactions.

Concluding remarks

There is a need to develop heterogeneous catalysts for synthesis of chemicals from alcohols under additive-free conditions via borrowing hydrogen and acceptorless dehydrogenation methodology. The reusable heterogeneous catalyst with wide scope is promising way for industries.

Outlines of thesis

This thesis focuses on direct C-C and C-N bonds formation using alcohols as green alkylating reagents via borrowing hydrogen and acceptorless dehydrogenation methodology. The objectives of this work is the development of efficient and reusable heterogeneous catalyst for the synthesis of chemicals under neutral conditions which include the preparation of various metals supported and Pt-loaded catalysts and characterization of catalysts using XANES, EXAFS and XPS spectra.

In chapter 2, I examined various metal loaded-Al_2O_3 and supported Pt catalysts for alkylation of 2-methylquinoline with benzyl alcohol under additive-free condition. Among screened catalysts, Pt/Al_2O_3 was found to be the most effective catalyst for the alkylation of 2-methylquinoline with benzyl alcohol. The catalyst was reusable and showed good to moderate yield of for the alkylation of 2-methylquinoline with various alcohols. Mechanistic study show that the reaction was driven by the borrowing hydrogen pathway which showed a sequence of dehydrogenation-condensation-dhydrogenation reactions. This results demonstrate the first heterogenous catalytic system for this reaction.

In chapter 3, I investigated various metal loaded-CeO_2 and supported Pt catalysts for alkylation of oxindole with alcohols under additive free condition. I found that Pt/CeO_2 was the best catalyst for alkylation for oxindole with 1-octanol. The catalyst was reusable and showed good to moderate yield of for the alkylation of oxindoles with various alcohols. Mechanistic study show that the reaction was driven by the borrowing hydrogen pathway which showed a sequence of dehydrogenation-condensation-hydrogenation reactions. This results demonstrate the first additive-free catalytic system for this reaction.

In chapter 4, a series of transition metal-loaded metal oxide catalysts examined for self coupling of 2-octanol. Pt/CeO_2 showed the highest activity among various various metal loaded-CeO_2 and supported Pt catalysts for self-coupling of 2-octanol. This results

demonstrated that Pt/CeO_2 was the most effective catalyst for self-coupling of aliphatic alcohols. Pt/CeO_2 was also effective for α-alkylation of methyl ketone.

In chapter 5, I demonstrated the first acceptorless method for synthesize of 2-quinazoline from 2-aminobenzylamine with primary alcohols or aldehydes under additive-free condition. CeO_2-supported Pt nanoparticle catalysts showed high activity among various metal supported and Pt loaded catalysts. I investigated the reusability of catalyst and general applicability of the present catalytic system. Mechanistic study show that the reaction was driven by the acceptorless dehydrogenation pathway which include dehydrogenation -condensation and cyclization-dehydrogenation steps.

In chapter 6, Pt/Al_2O_3 and Pt/TiO_2 were effective catalysts for the synthesis of 2-substituted benzothiazoles and benzimidazoles from 2-aminothiophenol and 1,2-phenylenediamine with alcohols or aldehydes under acceptor-free and additive-free conditions. With optimized Pt/TiO_2 and Pt/Al_2O_3 catalysts, I investigated the general applicability of present catalytic system using various alcohols for the synthesis of 2-substituted benzothiazole and 2-substituted benzimidazole respectively.

Chapter 7 is the general summary. Chapters 2-6 show the first examples of heterogeneous catalysis for the synthesis of chemicals via alkylation of nucleophiles by alcohols under additive-free conditions. Contrary to organometallic catalysis, heterogeneous Pt catalysts does not requires additive (ligand, acid or base) which increases atom economy. The borrowing hydrogen methodology includes dehydrogenation-condensation-hydrogenation steps with elimination of water as byproduct. The acceptorless dehydrogenation methodology include dehydrogenation-condensation and cyclization-dehydrogenation steps with elimination of water and liberation of H_2 as byproduct.

References

1. R. A. Sheldon, I. W. C. E. Arends, U. Hanefeld, *Green Chemistry and Catalysis*. Wiley-VCH. WEinheim, **2007**.
2. Green chemistry: Theory and Practice, ed. P.T. Anatas, J.C. Warner, Oxford University Press. Oxford, **1998**.
3. K. Kaneda, K. Ebitani, T. Mizugaki and K. Mori, *Bull. Chem. Soc. Jpn.*, 2006, **79**, 981-1016.
4. F. Felpin and E. Fouquest, *ChemSusChem.*, 2008, **1**, 718-724.
5. K. Yamaguchi and N. Mizuno, *Synlett.*, 2010, 2365-2381.
6. M. J. Climent, A. Corma and S.Iborra, *Chem. Rev.*, 2011, **111**, 1072-1133.
7. M. Tamura, K. Shimizu and A. Satsuma, *Chem. Lett.*, 2012, **41**, 1397-1405.
8. X. Liu, L. He, Y. M. Liu and Y. Cao, *Acc. Chem. Res.*, 2014, **47**, 793-804.
9. T. D. Nixon, M. K. Whittlesey and J. M. J. William, *Dalton Trans.*, 2009, 753-762.
10. K. I. Fujita and R. Yamaguchi, *Synlett.*, 2005, 560-571.
11. Y. Obara, *ACS Catal.*, 2014, **4**, 3972-3981.
12. C. Gunanathan, D. Milstein, *Science*, 2013, **341**, 1229712-10.
13. C. Gunanathan, D. Milstein, *Acc. Chem.,* 2011, **44**, 588-602.
14. R. V. Oppenauer, *Rav. Trav. Chim.*, 1937, **56**, 137-144.
15. H. Meerwein and R. Schmidt, *Leibigs Ann. Chem.*, 1925, **44**, 221-238.
16. R. Grigg, T.R. B. Mitchell, S, Sutthivaiyakit and N. Tongpenyai, *Tetrahedron Lett.*, 1981, **22**, 4107-4110.
17. Y. Watanabe, Y. Tsuji and Y. Ohsugi, *Tetrahedron Lett.*, 1981, **22**, 2667-2670.
18. G. Guillena, D. J. Ramon and M. Yus, *Chem. Rev.*, 2010, **110**, 1611-1641.
19. A. Baiker, *Catal. Rev.:Sci. Eng.*, 1985, **27**, 653-697.
20. J. T. Kozlowski and R. J. Davis, *ACS Catal.*, 2013, **3**, 1588-1600.
21. S. Kima, S. W. Baeb, J. S. Leeb and J. Park *Tetrahedron*, 2009, **65**, 1461-1466.
22. C.S. Cho, W. X. Ren, and S. C. Shim, *Bull. Korean. Chem. Soc.*, 2005, **26**, 1611-1613.
23. R. Cano, M. Yus and D. J. Ramón, *Chem. Commun.*, 2012, **48**, 7628-7630.
24. S. Michlik and R. Kempe, *Nat. Chem.*, 2013, **5**, 140-144; *Angew. Chem. Int. Ed.,* 2013, **125**, 6450-6454.
25. D. Srimani, Y. Ben-David and D. Milstein, *Angew. Chem. Int. Ed.,* 2013, **52**, 4012-4015; *Chem. Comm.*, 2013, **49**, 6632-6634.
26. M. Zhang, X. Fang, H. Neumann and M. Beller, *J. Am. Chem. Soc.*, 2013, **135**, 11384-11388.
27. J. Schranck, A. Tlili and M. Beller, *Angew. Chem. Int. Ed.*, 2013, **52**, 7642-7644.

Chapter 2. Alkylation of 2-methylquinoline under additive-free conditions by Al_2O_3-supported Pt catalyst

2.1 Introduction

Quinolines and their derivatives have great importance in pharmaceutical and agricultural industries.[1,2] Among various methods for synthesizing quinolines,[3] the introduction of alkyl-chain moieties into benzoquinones using methylquinolines as a starting material is of particular importance,[4,5] because methylquinolines are easily accessible. In the classical synthetic method of alkylquinolines is the reaction of a 2-methylquinoline with *n*-BuLi, followed by reaction with an alkyl halide. However, the main drawback of this method is the formation of stoichiometric amount of waste salts and use of hazardous reagent.

In recent years, much attention has focused on the alkylation reactions using alcohols as alkylating agent driven by the borrowing-hydrogen[6] or hydrogen-autotransfer[7] mechanism. It provides excellent protocols for selective C-C bond formations such as α-alkylation of ketones,[8] β-alkylation of secondary alcohols,[9-12] and Guerbet-type dimerizations of alcohols.[13-16] In these protocols, alcohol is initially dehydrogenated, then undergoes a functionalization reaction, and finally, re-hydrogenated by in-situ formed hydride species. Recently, this methodology has been used for alkylation of more challenging substrates. Kempe and co-workers reported the catalytic alkylation of methyl-N-heteroaromatics by alcohols in the presence of homogeneous catalyst $[IrCl(cod)]_2$ with $Py_2NP(i\text{-}Pr)_2$ ligand under basic condition.[18] Recently, Obora and co-worker developed a selective alkylation of methylquinolines by alcohols using the $[Ir(OH)(cod)]_2$ complex combined with a phosphine ligand and a base. The reaction provides a simple and atom-economical direct route to alkylquinolines, as the exclusive products, in good to excellent yields. However, this method suffers such as low turnover number (TON), necessity of substoichiometric amount (50 mol%) of base and difficulties in catalysts-product separation and catalyst reuse. As a part of our continuing interest in the heterogeneous catalysis for hydrogen-transfer reactions,[17,20,21] we report herein the first heterogeneous catalytic system for selective alkylation of methylquinolines by alcohols using Pt nanocluster-loaded $\gamma\text{-}Al_2O_3$ catalyst. This method has advantages over the previous homogeneous system in terms of higher TON, catalyst reusability and greener (additive-free) conditions.

2. 2 Experimental

General

γ-Al_2O_3 was prepared by calcination of γ-AlOOH (Catapal B Alumina purchased from Sasol) at 900°C for 3h. CeO_2 (JRC-CEO-2), TiO_2 (JRC-TIO-4), MgO (JRC-MGO-3) and Na-BEA zeolite (JRC-Z-B25) were supplied from catalysis society of Japan. $Zr(OH)_2$ was prepared by hydrolysis of zirconium oxynitrate 2-hydrate in distilled water by gradually adding an aqueous NH_4OH solution (1.0 mol dm^{-3}), followed by filtration of precipitate, washing with distilled water three times, drying at 100 °C for 12 h. $Nb_2O_5 \cdot nH_2O$ was commercially supplied (CBMM). ZrO_2 and Nb_2O_5 were prepared by calcination of these hydroxides at 500°C for 3h. Active carbon (296 m^2 g^{-1}) was purchased from Kishida Chemical.

Catalyst preparation

A precursor of Pt/Al_2O_3 (Pt = 1 wt%) was prepared by an impregnation method; a mixture of γ-Al_2O_3 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, a pre-reduced catalyst was prepared by in situ pre-reduction of the precursor in a glass (pyrex or quartz) tube under a flow of H_2 (20 cm^3 min^{-1}) at 500 °C for 0.5 h. The catalyst is designated as Pt/Al_2O_3. Other supported Pt catalysts (Pt = 1 wt%) were prepared by the same method. γ-Al_2O_3–supported metal catalysts, M/Al_2O_3 (M = Ir, Re, Rh, Pd, Ag, Ni, Co and Cu) with metal loading of 1 wt% were prepared by impregnation method in the similar manner as Pt/Al_2O_3 using aqueous solution of metal nitrates (for Co, Ni, Cu and Ag), $RuCl_3$, $IrCl_3 \cdot nH_2O$, NH_4ReO_4 or aqueous HNO_3 solution of $Rh(NO_3)_3$ or $Pd(NO_3)_2$.

Catalyst characterization

Pt L_3-edge measurement was carried out at BL01B1 of SPring-8 (Hyogo, Japan, Proposal No. 2011B1137). The storage ring was operated at 8 GeV. A Si(111) single crystal was used to obtain a monochromatic X-ray beam. The Pt/Al_2O_3 catalyst pre-reduced in a flow of 100% H_2 (20 cm^3 min^{-1}) for 0.5 h at 500 °C was cooled to room temperature in the flow of H_2 and was sealed in cells made of polyethylene under N_2, and then the EXAFS spectrum was taken at room temperature. The analyses of the extended X-ray absorption fine structure (EXAFS) and X-ray absorption near-edge structures (XANES) were performed using the REX version 2.5 program (RIGAKU). For the

EXAFS analysis, we used the parameters from FEFF6.

The number of surface metal atoms in Pt/Al_2O_3, pre-reduced in H_2 at 500°C 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 (BELL Japan Inc.). The average particle size was calculated from the CO uptake assuming that CO was adsorbed on the surface of spherical Pt particles at CO/(surface Pt atom) = 1/1 stoichiometry. Transmission electron microscopy (TEM) measurements were carried out by using a JEOL JEM-2100F TEM operated at 200 kV.

Typical procedures of catalytic reactions

After the pre-reduction, we carried out catalytic tests without exposing the catalyst to air as follows. The mixture of mesitylene (1.0 mL), alcohol (1.1 mmol), and 2-methylquinoline (1.0 mmol) was injected to the pre-reduced catalyst inside a reactor (cylindrical glass tube) through a septum inlet, followed by filling N_2. Then, the resulting mixture was stirred under reflux condition; bath temperature was 170°C and reaction temperature was ca. 164°C. Conversion and yields of products were determined by GC using *n*-dodecane as an internal standard and isolated yield after purifying by column chromatography. The products were identified by H-NMR as well as by GC-MS equipped with the same column as GC.

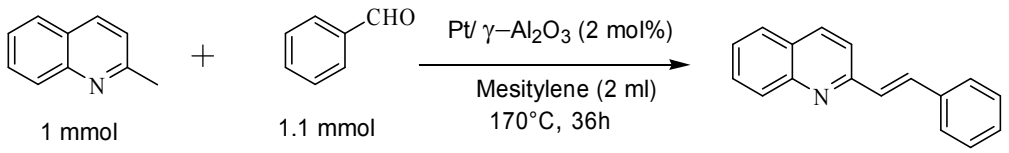
NMR and GCMS analysis

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

2.3 Results and discussion

The structure of Pt species in the standard catalyst, Pt/Al_2O_3, was examined by Pt L_3-edge XANES (Figure 2.1A) and EXAFS (Figure 2.1B). XANES features of Pt/Al_2O_3 are close to those of Pt foil. The EXAFS curve-fitting analysis (Table 2.1) showed that

the EXAFS of Pt/Al_2O_3 mainly consists of a Pt-Pt bond at of 2.70 Å with coordination number of 6.4. The Pt-Pt distance shorter than that of bulk Pt (2.76 Å) and Pt-Pt coordination number lower than that of bulk Pt (12) are characteristic features of small Pt metal clusters.[22] These features are consistent to with the average diameter of Pt metal estimated by CO adsorption experiment (2.3 nm). From these results, it is revealed that dominant Pt species in Pt/Al_2O_3 is the metallic Pt nanocluster. The catalyst named Pt/Al_2O_3–air was prepared by exposing the as-reduced Pt/Al_2O_3 catalyst to the ambient conditions for 0.5 h. The EXAFS result of Pt/Al_2O_3–air (Table 2.1) showed that air-exposure of Pt/Al_2O_3 resulted in an appearance of the Pt-O shell with coordination number of 1.6 and a decrease in the Pt-Pt coordination number from 6.4 to 3.9. The XANES result showed that air-exposure of Pt/Al_2O_3 resulted in an increase in the white line intensity. These results indicate that the metallic Pt was partially re-oxidized in air. First, we carried out catalysts screening study. We adopted the alkylation of 2-methylquinoline (1 mmol) with benzyl alcohol (1.1 mmol) in mesitylene (1 g) under reflux conditions in the presence of 2 mol% of the metal catalyst as a model reaction. Table 2.2 shows the effect of metal species on the activity of various metal-loaded Al_2O_3. Among various transition metals (Pt, Ir, Re, Rh, Pd, Ag, Ni, Co and Cu), the Pt catalyst showed the highest yield (82%) of the alkylated product. Table 2.3 shows the effect of support on the activity of Pt-loaded catalysts. Among various support materials, Al_2O_3 was found to be the best support. From these results, Pt/Al_2O_3 was found to be the most effective catalyst for the alkylation of 2-methylquinolinewith benzyl alcohol.



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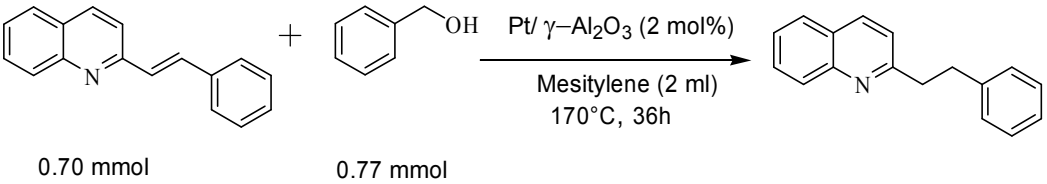


(2)

Next we studied the scope of substrates for alkylation of 2-methylquinoline (1 mmol)

with various alcohols (1.1 mmol) in mesitylene (1 g) under reflux conditions in the presence of 2 mol% Pt/Al_2O_3 (Table 2.3). The substituted benzyl alcohols with electron donating groups (entries 2, 3) and that with electron withdrawing group (entry 4) gave good yields (70-75%). 4-Fluorobenzyl alcohol (entry 5) resulted in a moderate yield (50%). Aliphatic alcohols such as octanol and hexanol (entries 6 and 7) also resulted in moderate yields (60-63%). Note that, unlike the homogeneous Ir catalyst reported by Obora,[19] our system does not require additives and excess molar amount of 2-methylquinoline.

We studied leaching test and reusability study for the Pt/Al_2O_3-catalyzed alkylation of 2-methylquinoline with benzyl alcohol. The reaction was completely terminated by removal of the catalyst from the reaction mixture after 4 h; further heating of the filtrate for 36 h under the reflux condition did not increase the yield. ICP-AES analysis of the filtrate confirmed that the content of Pt in the solution was below the detection limit. These results confirm that the reaction is attributed to the heterogeneous catalysis of Pt/Al_2O_3. Figure 2.3 shows the results of catalyst reuse. After the reaction of cycle 1 (entry 1, Table 2.4), we separated catalyst from reaction mixture by centrifuge. The separated catalyst was dried at 90ºC at 12 h and then reduced in H_2 at 500ºC for 0.5h. The recovered catalyst was reused at least four times without marked indication of catalyst deactivation. The total TON for the five cycles was 195. This value is 2.2 times higher than that of the homogeneous Ir (TON = 18.4 for the same reaction).[19]

In analogy to the proposed mechanism for the C-3 alkylation of indole with alcohols, [19] the present reaction may proceed through the hydrogen-borrowing pathway (Figure 2.3). The time course of the reaction (Figure 2.4) shows a profile characteristic to a consecutive reaction mechanism via the unreduced intermediate, phenylethenylquinoline, detected and confirmed by GC-MS analysis; the intermediate formed at an initial induction period was consumed to give the hydrogenated product. The reaction of benzaldehyde and 2-methylquinoline with 2 mol% of Pt/Al_2O_3 under N_2 resulted in the formation of the unreduced intermediate, phenylethenylquinoline, in 70 % yield (GC-MS analysis). From these considerations, we propose a tentative catalytic cycle shown in Fig. 4. First, hydrogen transfer from alcohol to a Pt^0 site on a Pt metal cluster, giving aldehyde and Pt-H species. Then, Al_2O_3-catalyzed aldol condensation of aldehyde and

2-methylquinoline give alkenylquinoline, which is hydrogenated by the Pt-H species to give alkylated quinoline.

2.4 Conclusion

In summary we have shown that γ-Al_2O_3 supported Pt cluster catalyze the alkylation reaction of 2-methylquinoline with various alcohols under additive free conditions. Considering the fact that the previous system using $[Ir(OH)(cod)]_2$ catalyst with 50 mol% t-BuOK and 20 mol% Ph_3P is the only successful catalytic method of the title reaction, our method provides the most effective and environmentally benign catalytic system for 2-methylquinoline with alcohols because of the following advantages: (1) high TON, (2) easy catalyst/product separation, (3) catalyst reuse, (4) no needs of additives and excess molar amount of 2-methylquinoline.

References

1. T. Wang, L.-G. Zhuo, Z. Li, F. Chen, Z. Ding, Y. He, Q.-H. Fan, J. Xiang, Z.-X. Yu and A. S. C. Chan, *J. Am. Chem. Soc.*, 2011, **133**, 9878-9891.
2. A. R.Katritzky, S. Rachwal and B. Rachwal, *Tetrahedron,* 1996, **52**, 15031-15070.
3. B. Robinson, *Chem. Rev.*, 1963, **63**, 373-401.
4. V. S.Robert and W. C. Jimmy, *J. Org. Chem.*, 1990, **55**, 2237-2240.
5. P. Vimal, A. R. James and W. Martin, *Tetrahedron: Asymmetry,* 2010, **21**, 1549-1556.
6. M. H. S. A. Hamid, P. A. Slatford and J. M. J. Williams, *Adv. Synth. Catal.,* 2007, **349**, 1555–1575.
7. G. Guillena, D.J. Ramón and M. Yus, *Angew. Chem. Int. Ed.*, 2007, **46**, 2358–2364.
8. K. Taguchi, H. Nakagawa, T. Hirabayashi, S. Sakaguchi, and Y. Ishii, *J. Am. Chem. Soc.,* 2004, **126**, 72–73.
9. C.S. Cho, B.T. Kim, H.S. Kim, T.J. Kim and S.C. Shim, *Organometallics,* 2003, **22**, 3608–3610.
10. R. Martinez, D.J. Ramón and M. Yus, *Tetrahedron,* 2006, **62**, 8982–8987.
11. K. Fujita, C. Asai, T. Yamaguchi, F. Hanasaka and R. Yamaguchi, *Org. Lett.,* 2005, **7**, 4017–4019.
12. O. Kose and S. Saito, *Org. Biomol. Chem.,* 2010, **8**, 896–900.
13. T. Matsu-ura, S. Sakaguchi, Y. Obora and Y. Ishii, *J. Org. Chem.,* 2006, **71**, 8306–8308.
14. K. Koda, T. Matsu-ura, Y. Obora and Y. Ishii, *Chem. Lett.,* 2009, **38**, 838–839.
15. Y. Obora, Y. Anno, R. Okamoto, T. Matsu-ura and Y. Ishii, *Angew. Chem. Int. Ed.,* 2011, **50**, 8618–8622.
16. S. Ogo, A. Onda and K. Yanagisawa, *Appl. Catal. A,* 2011, **402**, 188–195.
17. K. Shimizu, R. Sato and A. Satsuma, *Angew. Chem. Int. Ed.,* 2009, **48**, 3982–3986.
18. B. Blank and R. Kempe, *J. Am. Chem. Soc.,* 2010, **132**, 924-925.
19. Y. Obora, S. Ogawa and N. Yamamoto, *J. Org. Chem.,* 2012, **77,** 9429-9433.
20. K. Shimizu, K. Kon, W. Onodera, H. Yamazaki and J.N. Kondo, *ACS Catal.,* 2013, 112–117.
21. K. Shimizu, K. Sawabe and A. Satsuma, *Catal. Sci. Technol.,* 2011, **1**, 331-341.

22. A. I. Frenkel, C. W. Hills and R. G. Nuzzo, *J. Phys. Chem. B,* 2001, **105**, 12689–12703.

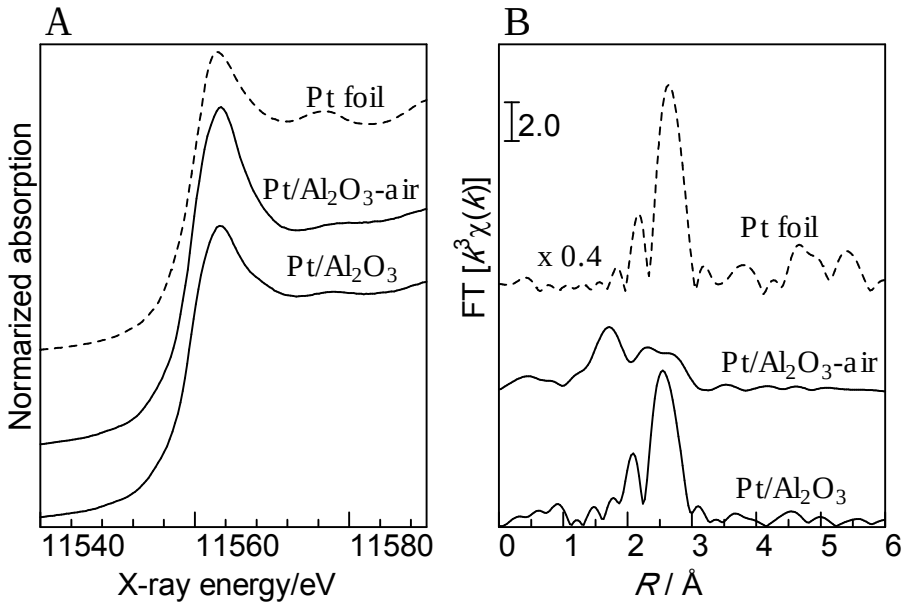


Figure 2.1 (A) XANES spectra and (B) EXAFS Fourier transforms at Pt L_3-edge for Pt catalysts and a reference compounds (Pt foil).

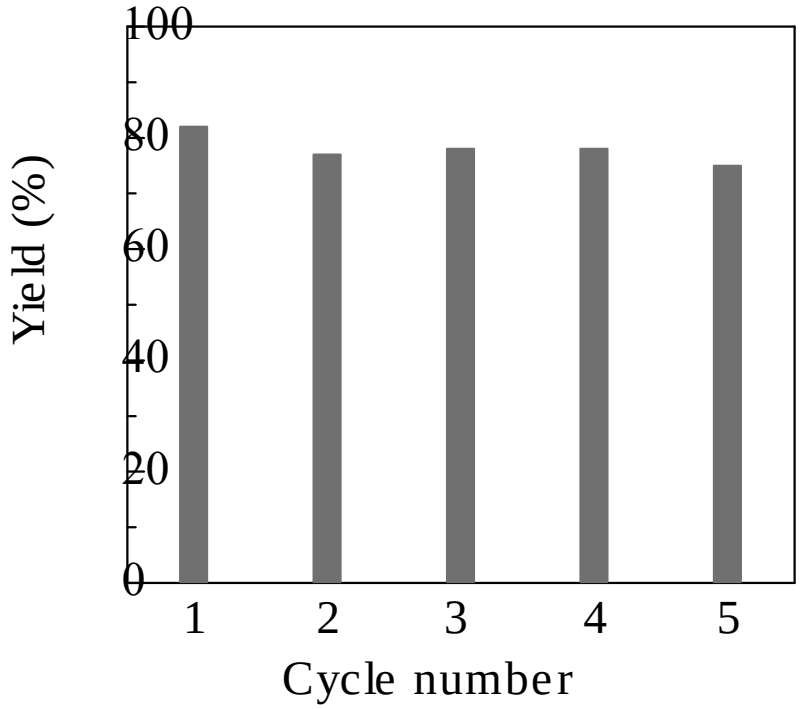


Figure 2.2 Recycle study for alkylation of 2-methylquinoline with alcohols with Pt/Al_2O_3.

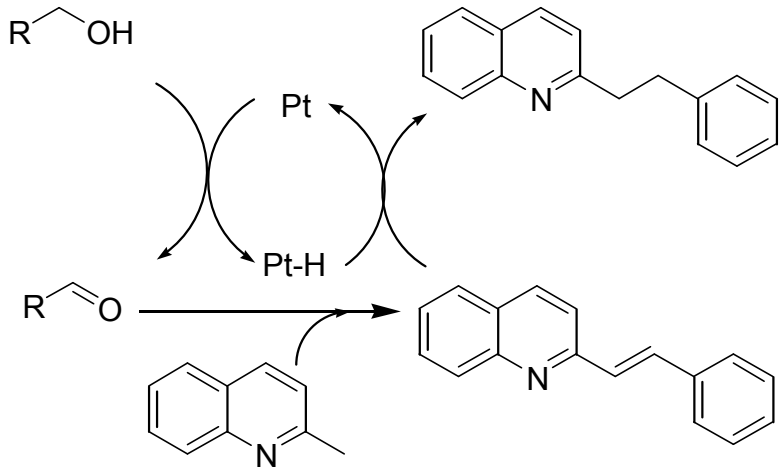


Figure 2.3 Presumable catalytic cycle for Pt/Al_2O_3-catalyzed alkylation of 2-methylquinoline with alcohols.

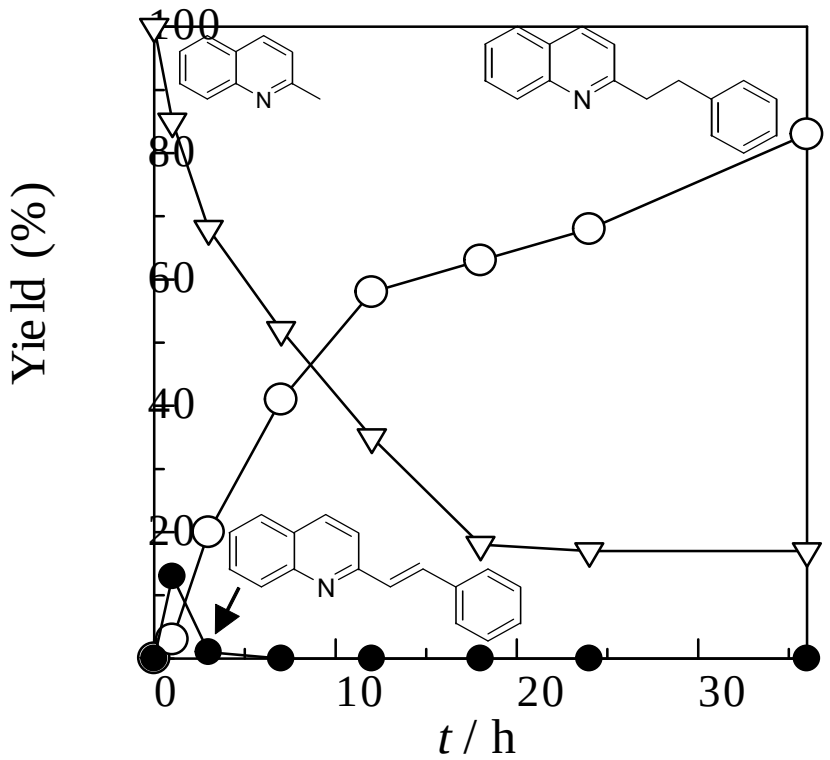


Figure 2.4 Time-yield profile for the alkylation of 2-methylquinoline (1 mmol) with benzyl alcohol (1.1 mmol) in mesitylene (1 g) under reflux conditions in the presence of 1 mol% of Pt/Al_2O_3: yields of unreacted 2-methylquinoline (♦), 2-phenethyl-quinoline (○), and phenylethenylquinoline (●).

Table 2.1 Curve-fitting analysis of Pt L_3-edge EXAFS of Pt (1 wt%)-loaded Al_2O_3.

Sample	Shell	N [a]	R /Å [b]	σ /Å [c]	R_f /% [d]
$PtOx/Al_2O_3$	O	5.3	2.01	0.068	4.5
	Pt	2.8	3.02	0.090	
Pt/Al_2O_3	Pt	6.4	2.70	0.080	1.6
Pt/Al_2O_3-air	O	1.6	2.03	0.071	2.1
	Pt	3.9	2.68	0.094	
Pt foil	Pt	(12)	(2.76)	-	-

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

Table 2.2 Alkylation of 2-methylquinoline with benzyl alcohol with 1 wt% metal-loaded Al_2O_3.[a]

Entry	Catalysts	Conv. (%)	Yield (%)
1	Pt/Al_2O_3	82	80
2	Ir/Al_2O_3	79	53
3	Re/Al_2O_3	47	6
4	Rh/Al_2O_3	39	31
5	Pd/Al_2O_3	29	32
6	Ag/Al_2O_3	15	5
7	Ni/Al_2O_3	7	4
8	Co/Al_2O_3	0	0
9	Cu/Al_2O_3	0	0

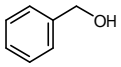
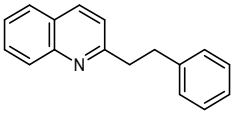
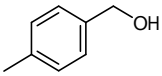
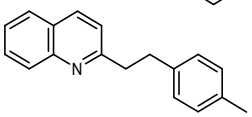
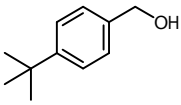
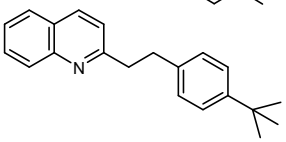
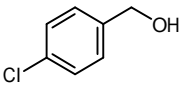
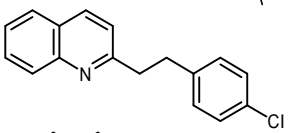
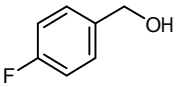
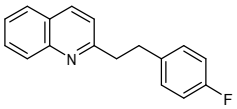
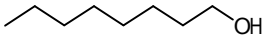
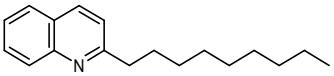
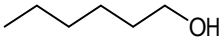
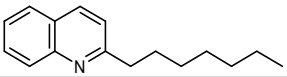
[a]Conditions: 2-methylquinoline (1mmol), benzyl alcohol (1.1 mmol), metal (0.02 mmol), mesitylene (1 g), 170ºC, 36 h.

Table 2.3 Alkylation of 2-methylquinoline with benzyl alcohol with 1 wt% Pt-loaded catalysts.[a]

Entry	Catalysts	Conv. (%)	Yield (%)
1	Pt/Al_2O_3	83	82
2	Pt/Nb_2O_5	50	20
3	Pt/C	12	7
4	Pt/BEA	5	1
5	Pt/ZrO_2	15	1
6	Pt/CeO_2	10	0
7	Pt/MgO	8	0
8	$PtOx/Al_2O_3$	45	40
9	Pt/Al_2O_3-air	18	5

[a] Conditions: 2-methylquinoline (1mmol), benzyl alcohol (1.1 mmol), Pt (0.02 mmol), mesitylene (1 g), 170ºC, 36 h.

Table 2.4 Alkylation of 2-methylquinoline with alcohols with 1 wt% Pt/Al_2O_3.[a]

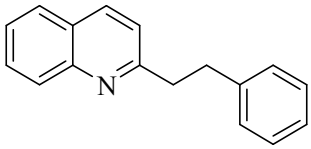
Entry	Alcohol	Product	Isolated yield (%)
1			82
2			72
3			70
4			75
5			50
6[b]			63
7[b]			60

[a] Conditions: 2-methylquinoline (1 mmol), alcohol (1.1 mmol) , Pt (0.02 mmol), mesitylene (1g), 170 ºC, 36 h.

[b] Undecane (1 g) as solvent, 200º C, 36 h.

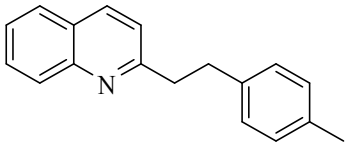
NMR and GCMS analysis

2-Phenethyl-quinoline [1] **(Table 2.4, entry 1)**



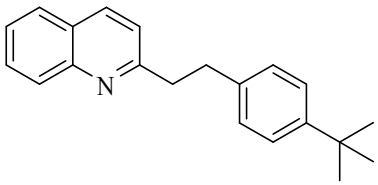
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.07 (d, *J* = 8.4 Hz, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.68-7.66 (m, 1H), 7.47-7.45 (m, 1H), 7.26-7.16 (m, 6H), 3.28-3.26(m, 2H), 3.15-3.12 (m, 2H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.7, 147.9, 141.4, 136.1, 129.3, 128.7, 128.4, 128.3, 127.4, 126.8, 126.7, 125.9, 121.5, 40.9, 35.8 ppm. MS (EI) (*m/z*) (relative intensity) 233 (M^+, 80), 232 (100), 156(60).

2-(2-*p*-Tolyl-ethyl)-quinoline [2] **(Table 2.4, entry 2)**



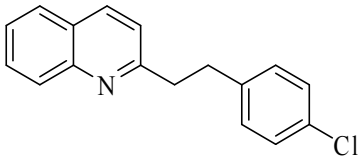
^{1}H NMR (600 MHz, $CDCl_3$):δ 7.98 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.60-7.58 (m, 1H), 7.39-7.37 (m, 1H), 7.14 (d, 1H), 7.06 (d, 1H), 7.00 (d, 1H), 3.19-3.16(m, 2H), 3.03-3.00 (m, 2H), 2.22 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.8, 147.8, 138.3, 136.1, 135.3, 129.3, 129.0, 128.7, 128.3, 127.4, 126.7, 125.6, 121.5, 41.0, 35.4, 20.9. MS (EI) (*m/z*) (relative intensity) 247 (M^+, 85), 246 (100), 156(40).

2-[2-(4-*tert*-Butyl-phenyl)-ethyl]-quinoline [3] **(Table 2.4, entry 3)**



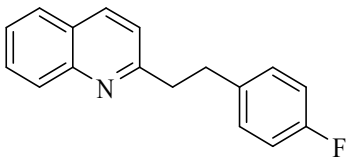
^{1}H NMR (600 MHz, $CDCl_3$):δ 8.01-7.98 (m, 2H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.64-7.61 (m, 1H), 7.44-7.41 (m, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.21 (d, 1H), 7.15 (d, 1H), 3.23-3.20(m, 2H), 3.06-3.04 (m, 2H), 1.24 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.0, 148.7, 147.9, 138.4, 136.2, 129.3, 128.8, 128.1, 127.5, 126.7, 125.5, 125.2, 121.5, 41.2, 35.4, 34.3, 31.3. MS (EI) (*m/z*) (relative intensity) 289 (M^+, 80), 288 (100), 274(25), 156(25).

2-[2-(4-Chloro-phenyl)-ethyl]-quinoline [3] **(Table 2.4, entry 4)**



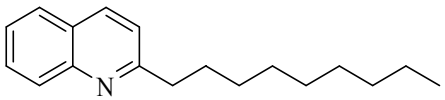
^{1}H NMR (600 MHz, $CDCl_3$):δ 8.10-8.09 (m, 2H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.70-7.68 (m, 1H), 7.51-7.48 (m, 1H), 7.18 (d *J* = 8.0 Hz,1H), 7.11-7.09 (m, 2H), 6.89-6.86 (m, 2H), 3.28-3.25(m, 2H), 3.08-3.06 (m, 2H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.1, 145.9, 138.4, 136.4, 130.5, 129.9, 129.8, 127.6, 127.3, 126.8, 126.6, 121.6, 40.0, 34.9 ppm. MS (EI) (*m/z*) (relative intensity) 267 (M^+, 90), 266 (100), 156(60).

2-[2-(4-Fluoro-phenyl)-ethyl]-quinoline (Table 2.4, entry 5)



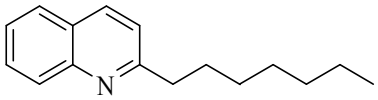
^{1}H NMR (600 MHz, $CDCl_3$):δ 8.49 (d, *J* = 8.4 Hz, 1H), 8.42 (d, *J* = 8.4 Hz, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.95-7.93 (m, 1H), 7.76-7.74 (m, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.25 (d, 1H), 7.23 (d, 1H), 3.56-3.53(m, 2H), 3.21-3.18 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.1, 148.9, 133.2, 132.4, 129.8, 128.8, 128.5, 127.9, 127.0, 123.3, 122.0, 37.5, 35.0 ppm. MS (EI) (*m/z*) (relative intensity) 251 (M^+, 95), 250 (100), 156(50).

2-Heptyl-quinoline [4] **(Table 2.4, entry 6)**



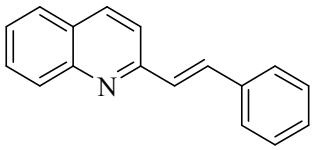
^{1}H NMR (600 MHz, $CDCl_3$):δ 8.07-8.05 (m, 2H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.70-7.67 (m, 1H), 7.50-7.47 (m, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 2.99-2.96(m, 2H), 1.84-1.79 (m, 2H), 1.44-1.41 (m, 2H),1.36-1.27 (m, 10H),0.89-0.85 (m, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.1, 147.8, 136.1, 129.2, 128.7, 127.4, 126.6, 125.5, 121.3, 39.3, 31.8, 30.0, 29.56, 29.5, 29.0, 29.2, 22.6, 14.1 ppm. MS (EI) (*m/z*) (relative intensity) 255 (M^+, 90), 156(25), 143(100),

2-Nonyl-quinoline [3] **(Table 2.4, entry 7)**



^{1}H NMR (600 MHz, $CDCl_3$):δ 8.07-8.05 (m, 2H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.70-7.67 (m, 1H), 7.50-7.47 (m, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 2.99-2.96(m, 2H), 1.84-1.79 (m, 2H), 1.44-1.41 (m, 2H),1.36-1.27 (m, 6H),0.89-0.85 (m, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.1, 147.8, 136.1, 129.2, 128.7, 127.4, 125.5, 121.3, 39.3, 31.7, 30.0, 29.4, 29.1, 22.5, 14.0 ppm. MS (EI) (*m/z*) (relative intensity) 227 (M^+, 80), 156 (20), 143(100).

2-Styryl-quinoline



MS (EI) (*m/z*) (relative intensity) 231 (M^+, 40), 230(100).

References

1. C. Ramesh, V. Kavala, C. W. Kuo and C. F. Yao, *Tetrahedron Lett.* 2010, **51**, 5234-5237.
2. M. Rueping, and R. M. Koenigs, *Chem. Commun.,* 2011, **47**, 304-306.
3. Y. Obora, S. Ogawa and N. Yamamoto, *J. Org. Chem.,* 2012, **77,** 9429-9433.
4. Fakhfakh, M. A.; Franck, X.; Fournet, A.; Hocquemiller, R.; Figadere, B. Tetrahedron Lett. 2001, **42**, 3847-3850.

Chapter 3. C-3 alkylation of oxindole with alcohols by Pt/CeO_2 catalyst in additive-free conditions

3.1 Introduction

Oxindole and their derivatives, particularly C-3 functionalized oxindoles, are important intermediates in pharmaceutical industry due to their biological activity. These include the antiinflammatory Tenidap[1] and anti-cancer kinase inhibitor Sunitinib.[2] The conventional C-3 alkylation of oxindoles with alkyl halides has serious drawbacks such as poor regioselectivity, the formation of dialkylated products, formation of salt wastes and use of hazardous reagents. Recently, much attention has been focused on the use of alcohols as economic and environmentally benign alkylating reagents in indirect C–C bond formation reactions[3–10] so-called borrowing hydrogen[3] (or hydrogen-autotransfer4) methodology, where alcohol is initially dehydrogenated, then undergoes a functionalization reaction, and finally, re-hydrogenated. Wenkert and Bringi have first described the C-3 alkylation of oxindole with alcohols in the presence of excess amount of RANEY® nickel.[11] Simig and co-workers reported the C-3 alkylation of oxindole with alcohols at 150–220 °C with relatively less amount of RANEY® Ni, but the system was still non-catalytic; substrate/catalyst molar ratio was 10:17[12]. Recently, Madsen and a co-worker[13] and Grigg et al.[14] independently reported the first catalytic C-3 alkylation of oxindole with alcohols at 110 °C by homogeneous catalysts (2 mol% $RuCl_3/PPh_3$;[13] 2.5 mol% $[IrCp^*Cl2]_2$ [14]) in the presence of strong base (10–20 mol% of KOH or NaOH). Liu et al.[15] developed a support-immobilized Ir complex as reusable catalysts for this reaction. However, the system has drawbacks such as narrow scope and needs of sub-stoichiometric amount of strong base (KOH) and an organic ligand. As a part of our continuing interest in the heterogeneous catalysis for hydrogen-transfer reactions[16–19] (such as Pt-catalyzed C-3 alkylation of indoles with alcohols[19]), we report herein the first additive-free catalytic system for C-3 selective alkylation of indole with alcohols by Pt-loaded CeO_2 as a reusable heterogeneous catalyst.

3.2 Experimental

General

Commercially available organic and inorganic compounds (from Tokyo Chemical Industry, Wako Pure Chemical Industries, Kishida Chemical, or Mitsuwa Chemicals) 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 or helium as the carrier gas.

Catalyst preparation

CeO_2 (JRC-CEO-1, 157 m^2 g^{-1}), MgO (JRC-MGO-3), TiO_2 (JRC-TIO-4) and SiO_2–Al2O_3 (JRC-SAL-2) were supplied from Catalysis Society of Japan. ZrO_2 was prepared by hydrolysis of zirconium oxynitrate 2-hydrate by an aqueous NH_4OH solution, followed by filtration, washing with distilled water, drying at 100 °C for 12 h, and by calcination at 500 °C for 3 h. 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 1 wt% Pt/CeO_2 catalyst was prepared by an impregnation method; a mixture of CeO_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. A pre-reduced catalyst (named Pt/CeO_2) was prepared by pre-reduction of the precursor in a pyrex tube under a flow of H_2 (20 cm^3 min^{-1}) at 500 °C for 0.5 h. Platinum oxides-loaded CeO_2 (PtOx/CeO_2), as a comparative catalyst, was prepared by calcination of the precursor at 300 °C for 3 h. By using various supports, several pre-reduced Pt catalysts were prepared by the same method as Pt/CeO_2. CeO_2-supported metal catalysts, M/CeO_2 (M = Co, Ni, Cu, Ru, Rh, Pd, Ag and Ir) with metal loading of 1 wt% were prepared by impregnation method in a similar manner as Pt/CeO_2 using an aqueous solution of metal nitrates (for Co, Ni, Cu and Ag), $RuCl_3$, $IrCl_3$, or an aqueous HNO_3 solution of $Rh(NO_3)_3$ or $Pd(NO_3)_2$.

XANES and EXAFS

X-ray absorption near-edge structures (XANES) and X-ray absorption fine structure (EXAFS) at Pt L_3-edge were measured at the BL14B2 in the Spring-8 (proposal no. 2012A1734). The storage ring was operated at 8 GeV. A Si(111) single crystal was used to obtain a monochromatic X-ray beam. The spectra of Pt/CeO_2 and PtO_x/CeO_2 were obtained in the fluorescent mode using a Lytle detector, and that of Pt foil was obtained in a transmittance mode. The Pt/CeO_2 catalyst pre-reduced in a flow of 100% H_2 (20 cm^3 min^{-1}) for 0.5 h at 500 °C was cooled to room temperature in the flow of H_2 and was sealed in cells made of polyethylene under N_2, and then the EXAFS spectrum was taken at room temperature. The spectra of Pt foil and PtO_x/CeO_2 were recorded without the pre-reduction treatment. The EXAFS analysis was performed using the REX version 2.5

program (RIGAKU). The parameters for the Pt–O and Pt–Pt shells were provided byFEFF6.

***In situ* IR**

In situ IR (infrared) spectra were recorded at 40 °C using a JASCO FT/IR-4200 equipped with a quartz IR cell connected to a conventional flow reaction system. The sample was pressed into a 40 mg of self-supporting wafer (ϕ = 2 cm) and mounted into the quartz IR cell with CaF_2 windows. Spectra were measured accumulating 30 scans at a resolution of 4 cm^{-1}. A reference spectrum of the catalyst wafer in He taken at the measurement temperature was subtracted from each spectrum. Prior to the experiment the disk of Pt/CeO_2 was heated in H_2 flow (20 cm^3 min^{-1}) at 500 °C for 0.5 h, followed by cooling to 40 °C and purging with He. Then, the catalyst was exposed to a flow of CO(5%)/He(20 cm^3 min^{-1}) for 180 s, followed by purging with He (40 cm^3 min^{-1}) for 600 s.

Typical procedures of the catalytic test

Pt/CeO_2 was used as a standard catalyst. After the pre-reduction at 500 °C, we carried out catalytic tests using a batch-type reactor without exposing the catalyst to air as follows. Typically, the mixture of oxindole (1.0 mmol) and 1-octanol (1.1 mmol) in mesitylene (1.5 g) 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 24 h under reflux condition; the bath temperature was 170 °C and reaction temperature was ca. 165 °C. After cooling the mixture, followed by removal of the catalyst, the mixture was purified with column chromatography and analyzed by ^1H and ^{13}C NMR and GCMS. For the screening and catalyst recycle studies, conversion of indole and yield of C-3 alkylated product were determined by GC using *n*-dodecane as an internal standard.

NMR and GCMS analysis

^1H and ^{13}C NMR spectra were recorded using at ambient temperature on JEOL-ECX 600 operating at 600.17 and 150.92 MHz, respectively with tetramethylsilane as an internal standard. All chemical shifts (δ) are reported in ppm and coupling constants (J) in Hz. All chemical shifts are reported relative to tetramethylsilane and d-solvent peaks (77.00 ppm, chloroform), respectively. Abbreviations used in the NMR experiments: s,

singlet d, doublet; t, triplet; q, quartet; m, multiplet. GC-MS spectra were recorded by SHIMADZU QP2010.

3.3 Results and discussion

We chose the alkylation of oxindole (1 mmol) with 1-octanol (1.1 mmol) as a model reaction for optimization of catalysts and conditions. Table 3.1 summarizes the results of the initial catalyst screening test under the same reaction conditions (reflux in mesitylene under N_2 for 24 h) using 1 mol% of transition metal-loaded CeO_2. The Ru and Ir-loaded CeO_2 and CeO_2 itself were completely inactive. Co, Ni, Cu, Rh, Re, Ir, and Au catalysts showed low yield of the C-3 alkylated oxindole (2–16%). In contrast, Pt-loaded CeO_2 (Pt/CeO_2) showed 99% yield of the C-3 alkylated oxindole. Then, we studied the support effect on the activity of Pt-loaded catalysts. Pt/MgO and Pt/CeO_2 gave higher yield (99%) than the other catalysts. Especially, $Pt/SiO_2–Al_2O_3$ and Pt/Al_2O_3 gave low yields (12%, 27%). Combined with a well known classification on acid–base character of metal oxides,[20] it is suggested that the basic oxides (MgO and CeO_2) are more effective than acidic oxides (Al_2O_3 and $SiO_2–Al_2O_3$). On the basis of the fact that Pt/CeO_2 showed higher yield (96%) after 6 h than Pt/MgO (73%), we adopted Pt/CeO_2 as the standard catalyst.

To discuss the relationship between the structure of Pt species and catalytic activity, we carried out spectroscopic characterizations of these catalysts. Figures 3.1A and 3.1B show XANES and EXAFS spectra of Pt/CeO_2, platinum oxides-loaded CeO_2 (PtO_x/CeO_2) and a reference compound (Pt foil). The values of the coordination numbers for Pt–O and Pt–Pt shells as well as the distances derived from the EXAFS analysis are shown in Table 3.2 The XANES spectrum of PtO_x/CeO_2 shows a strong white line peak at 11564 eV, which is generally observed for platinum oxides. The EXAFS of PtO_x/CeO_2 consists of a Pt–O contribution (4.9 Pt–O bonds at the distance of 2.00 Å). The EXAFS result indicates that the dominant Pt species in PtO_x/CeO_2 is a cationic (oxidic) Pt species highly dispersed on the support, which is consistent with the XANES results. In contrast, the XANES spectrum of Pt/CeO_2 is nearly identical to that of Pt foil, which indicates that the electronic state of the Pt species in Pt/CeO_2 is metallic. The EXAFS of Pt/CeO_2 consists of a Pt–Pt contribution (7.7 Pt–Pt bonds at the distance of 2.73 Å). The Pt–Pt

distance less than that of bulk Pt (2.76 Å) and the Pt–Pt coordination number lower than that of bulk Pt (12) are characteristic features of a few nm-sized Pt metal clusters.[21] As shown in Table 1, PtOx/CeO_2 was inactive for the reaction (entry 11), while Pt metal clusters on CeO_2 showed 99% yield. Combined with the structural results, it is concluded that oxidic Pt species are inactive and Pt metal clusters are active species.

The catalyst named Pt/CeO_2–air, prepared by exposing Pt/CeO_2 to the ambient conditions for 0.5 h, showed lower yield than the as-reduced Pt/CeO_2. This suggests that the metallic Pt^0 species on the surface of Pt nanoparticles are the active species and re-oxidation of them by O_2 under ambient conditions results in the catalyst deactivation. This hypothesis is confirmed by the following results. IR spectroscopy with CO as a probe molecule allows monitoring of the changes in the electronic states of Pt surface. As shown in Figure 3.2, the IR spectra of CO adsorbed on Pt/CeO_2 showed a band at 2064 cm^{-1} assignable to linearly coordinated CO on metallic Pt.[18] Upon exposure to air at room temperature for 0.5 h, the intensity of the band due to CO–Pt^0 decreased. Combined with the result of the catalytic test, it is clarified that the surface metallic Pt^0 sites are the catalytically active species. Summarizing the above results, we conclude that co-presence of surface Pt^0 species on Pt metal clusters and basic support are indispensable elements in this catalytic system.

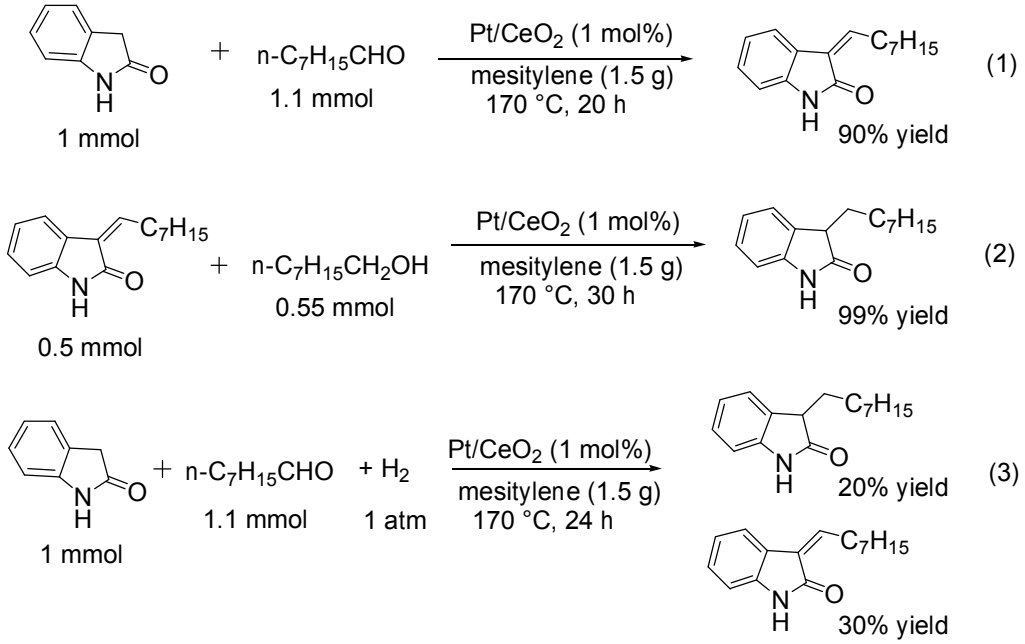
With the most effective catalyst, Pt/CeO_2, we investigated general applicability of the present catalytic system. Table 3.3 shows the scope of C-3 alkylation of oxindole with different alcohols using 1 mol% of the catalyst. Various aliphatic primary alcohols including linear and branched aliphatic alcohols (entries 1–6) were tolerated, giving 100% conversion of oxindole and good to high yield of the corresponding C-3 alkylated oxindoles. The reactions of oxindole and benzylalcohols with an electron-donating or an electron-withdrawing substituent proceeded in moderate to excellent yield (entries 7–12). This method was also applicable for the alcohol with a less stable substituent, o-substituted benzylic alcohol (entry 8). The catalyst was applicable to a heterocyclic alcohol containing nitrogen atoms (entry 13). The reactions of a N-alkylated oxindole with benzyl and aliphatic primary alcohols resulted in excellent yield (entries 14 and15). Note that the turnover number (TON) for the alkylation of oxindole with benzylalcohol (entry 7) was 95, which is higher than those obtained in the previous homogeneous

systems: TON of 45 for $RuCl_3/PPh_3/KOH$[13] and TON of 36 for $[IrCp^*Cl_2]_2/KOH$.[14]

The reaction of oxindole with 1-octanol was completely terminated by removal of the catalyst from the reaction mixture after 1.5 h; further heating of the filtrate for 24 h under the reflux condition did not increase the yield. ICP-AES analysis of the filtrate confirmed that the content of Pt in the solution was below the detection limit. These results confirm that the reaction is attributed to the heterogeneous catalysis of Pt/CeO_2. Figure 3.4 shows the results of catalyst reuse. After the reaction of cycle 1 (entry 1, Table 3.2), the catalyst was separated from the reaction mixture by centrifugation and was dried at 90 °C at 12 h and then reduced in H_2 at 500 °C for 0.5 h. The recovered catalyst showed nearly quantitative yield at least two times (Figure 3.4).

As proposed in the previous papers on the C-3 alkylation of oxindole with alcohols,[13,14] the present reaction can proceed through the hydrogen-borrowing pathway, which is evidenced by the following results. The reaction of n-octanal and indole with Pt/CeO_2 under N_2 resulted in the formation of the aldol condensation product, alkenyl–oxindole, in a quantitative yield (eqn 1). The same reaction was catalyzed by CeO_2 with higher reaction rate than Pt/CeO_2 (result not shown). Considering that solid base catalysts catalyze the aldol condensation reaction,[17] the result indicates that basic site of the CeO_2 support can be the active site for the aldol condensation of aldehyde and oxindole. Then, the aldol condensation product was isolated and underwent the transfer hydrogenation with 1-octanol (1.1 equiv) as a hydrogen donor in the presence of Pt/CeO_2 under N_2. As shown in eqn 2, the C=C bond in the aldol condensation product was hydrogenated to give the C-3 alkylated oxindole in a quantitative yield. Molecular hydrogen, which can be produced during the alkylation of oxindole with alcohols, might hydrogenate the alkenyl–oxindole, but the following result excludes this possibility. The reaction of n-octanal and indole with Pt/CeO_2 under 1 atm H_2 resulted in only 20% yield of the hydrogenated product accompanying alkenyl–oxindole in 30% yield (eqn 3). Based on the above results, we propose the mechanism for Pt/CeO_2-catalyzed alkylation of oxindole in Fig. 3.4. The reaction begins with the dehydrogenation of alcohol to carbonyl compound accompanied by the generation of Pt–H species. Then, CeO_2-catalysed aldol condensation between aldehyde and oxindole occurs to give the aldol condensation product, alkenyl–oxindole. Finally, hydrogen transfer from Pt–H species to the C=C bond

of the alkenyloxindole gives the alkylated oxindole.



3.4 Conclusions

We have developed the first additive-free method for catalytic C3 alkylation of oxindole with various alcohols by Pt-loaded CeO_2 catalyst driven by the borrowing-hydrogen pathway. Considering the fact that the previous catalytic systems need sub-stoichiometric amount of strong base and expensive organic ligands, our method provides a more environmentally benign catalytic system for C-3-alkylated oxindoles from oxindoles and alcohols because of the following advantages: (1) no need of basic co-catalyst and organic ligands, (2) easy catalyst/product separation, (3) catalyst reuse, (4) wide scope including aliphatic alcohols and N-substituted oxindole, and (5) high TON. Structure–activity relationship studies show that both surface Pt^0 species on Pt metal clusters and basic support are indispensable elements in this catalytic system.

References

1. H. Wang, M. Chen and L. Wang, *Chem. Pharm. Bull.*, 2007, **55**, 1439-1441.
2. A. Nimal, M. Benoit-Guyod and G. Leclerc, *Eur. J. Med. Chem.*, 1995, **30**, 973-981.
3. M. H. S. A. Hamid, P. A. Slatford and J. M. J. Williams, *Adv. Synth. Catal.*, 2007, **349**, 1555-1575.
4. G. Guillena, D. J. Ramón and M. Yus, *Angew. Chem., Int. Ed.*, 2007, **46**, 2358-2364.
5. R. Yamaguchi, K.-I. Fujita and M. Zhu, *Heterocycles*, 2010, **81**, 1093-1140.
6. Y. Obora and Y. Ishii, *Synlett*, 2011, 30-51.
7. S. Bähn, S. Imm, L. Neubert, M. Zhang, H. Neumann and M. Beller, *ChemCatChem*, 2011, **3**, 1853-1864.
8. C. Gunanathan and D. Milstein, *Science*, 2013, **341**, 1229712.
9. L. Guo, Y. Liu, W. Yao, X. Leng and Z. Huang, *Org. Lett.*, 2013, **15**, 1144-1147.
10. T. Kuwahara, T. Fukuyama and I. Ryu, *RSC Adv.*, 2013, **3**, 13702-13704.
11. E. Wenkert and N. V. Bringi, *J. Am. Chem. Soc.*, 1958, **80**, 5575-5576.
12. B. Volk, T. Mezei and G. Simig, *Synthesis*, 2002, **5**, 595-597.
13. T. Jensen and R. Madsen, *J. Org. Chem.*, 2009, **74**, 3990-3992.
14. R. Grigg, S. Whitney, V. Sridharan, A. Keep and A. Derrick, *Tetrahedron*, 2009, **65**, 4375-4383.
15. G. H. Liu, T. Z. Huang, Y. L. Zhang, X. H. Liang, Y. S. Li and H. X. Li, *Catal. Commun.*, 2011, **12**, 655-659.
16. K. Shimizu, K. Sawabe and A. Satsuma, *Catal. Sci. Technol.*, 2011, **1**, 331-341.
17. K. Shimura, K. Kon, S. M. A. H. Siddiki and K. Shimizu, *Appl. Catal., A*, 2013, **462**, 137-142.
18. K. Shimizu, K. Ohshima, Y. Tai, M. Tamura and A. Satsuma, *Catal. Sci. Technol.*, 2012, **2**, 730-738.
19. S. M. A. H. Siddiki, K. Kon and K. Shimizu, *Chem.–Eur. J.*, 2013, **19**, 14416-14419 .
20. M. Tamura, K. Shimizu and A. Satsuma, *Appl. Catal., A*, 2012, **433–434**, 135-145.
21. A. I. Frenkel, C. W. Hills and R. G. Nuzzo, *J. Phys. Chem. B*, 2001, **105**, 12689-12703.

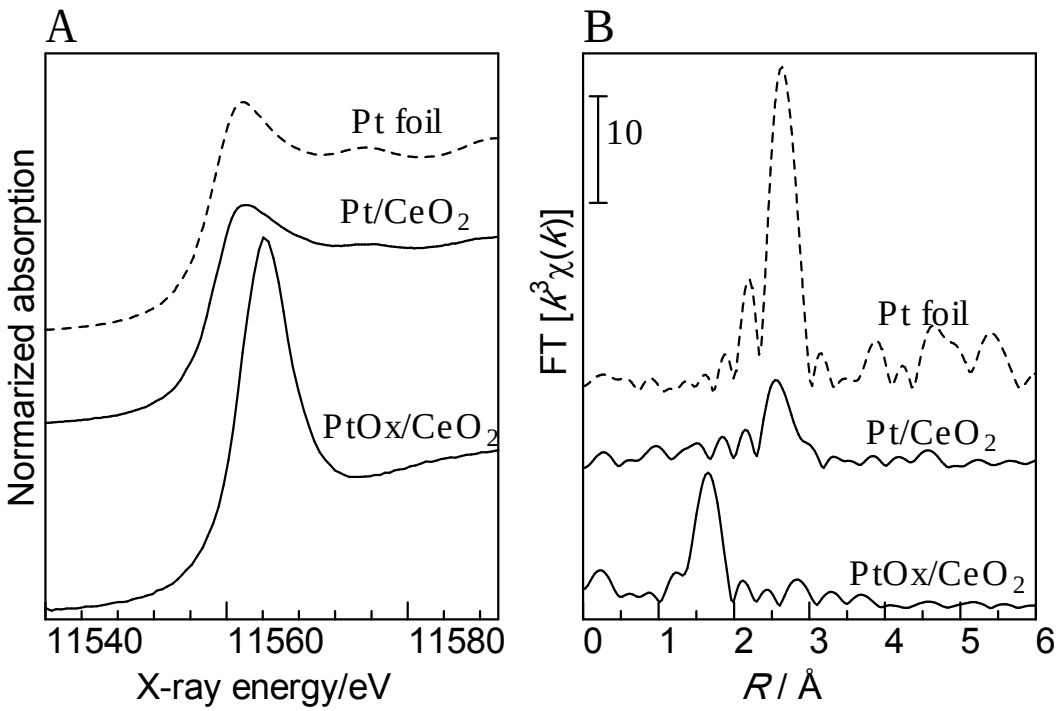


Figure 3.1 Pt L_3-edge XANES spectra (A) and EXAFS Fourier transforms (B).

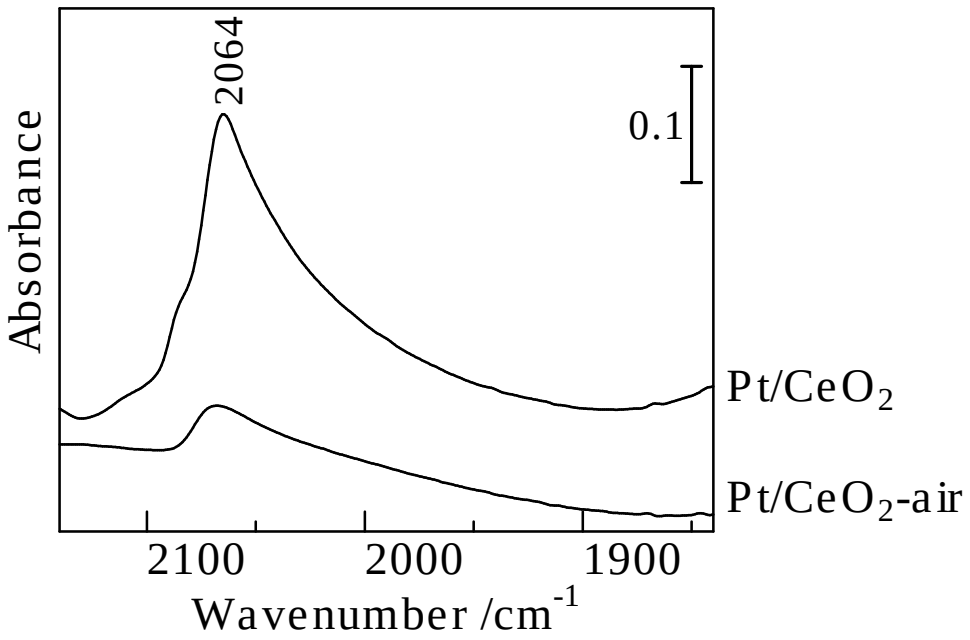


Figure 3.2 IR spectra of CO adsorbed on Pt/CeO_2 (after H_2-reduction at 500 °C for 0.5 h) and Pt/CeO_2-air (after re-oxidation of Pt/CeO_2 under air at room temperature for 0.5 h) at 40 °C.

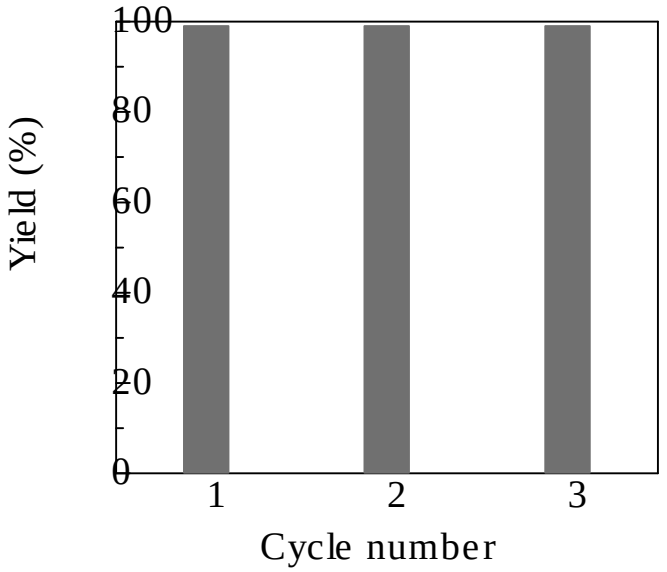


Figure 3.3 Catalyst reuse for alkylation of oxindole by 1-octanol with by Pt/CeO_2. Conditions are the same as those in Table 3 (entry 1).

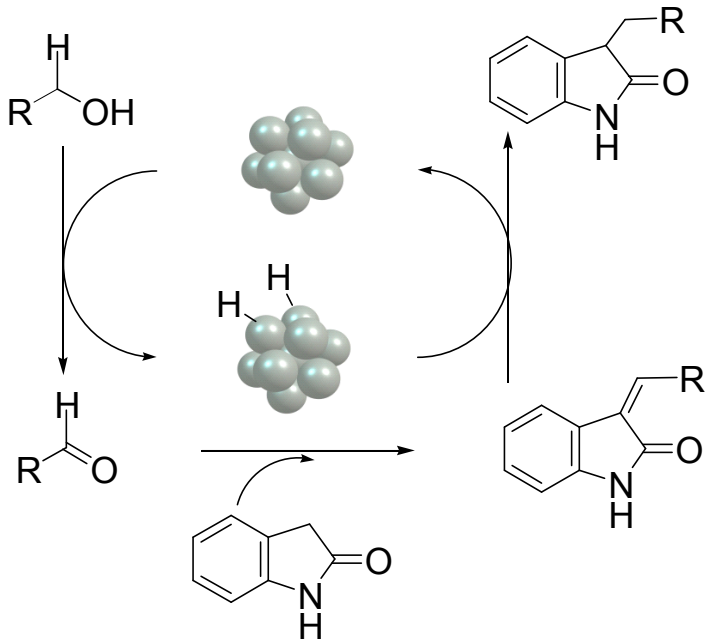
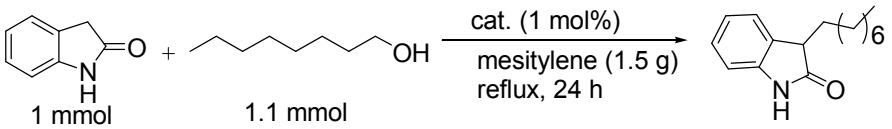


Figure 3.4 Possible mechanism for C-3 alkylation of oxindole with alcohols by Pt/CeO_2.

Table 3.1 Alkylation of oxindole by 1-octanol with 1 wt% metal (M)-loaded CeO_2 catalysts.



entry	catalyst	conv.(%)	yield (%)
1	Co/CeO_2	13	8
2	Ni/CeO_2	20	2
3	Cu/CeO_2	30	21
4	Ru/CeO_2	0	0
5	Rh/CeO_2	8	5
6	Pd/CeO_2	88	40
7	Ag/CeO_2	14	10
8	Ir/CeO_2	0	0
9	Pt/CeO_2	99	99
10[a]	Pt/CeO_2-air	99	75
11[b]	$PtOx/CeO_2$	10	0
12[c]	CeO_2	10	0
13	Pt/MgO	99	99
14	Pt/TiO_2	99	94
15	Pt/ZrO_2	99	71
16	Pt/Al_2O_3	99	27
17	Pt/SiO_2-Al_2O_3	84	12

[a] Pre-reduced Pt/CeO_2 was exposed to air at room temperature for 0.5 h.

[b] Tested without pre-reduction.

[c] Catalyst amount was 50 mg.

Table 3.2 Curve-fitting analysis of Pt L_3-edge EXAFS.

Sample	Shell	N [a]	R /Å [b]	σ /Å [c]	R_f /% [d]
$PtOx/CeO_2$	O	4.9	2.00	0.044	3.5
Pt/CeO_2	Pt	7.7	2.73	0.084	2.3
Pt foil	Pt	(12)	(2.76)	-	-

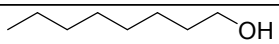
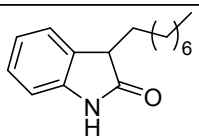
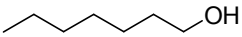
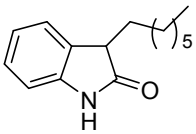
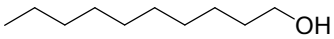
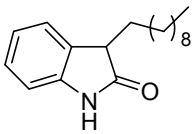
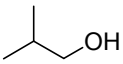
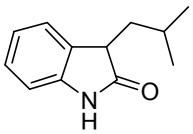
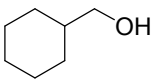
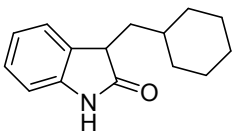
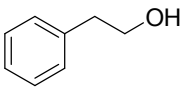
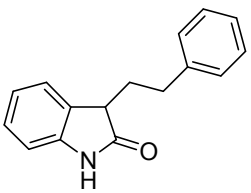
[a] Coordination numbers.

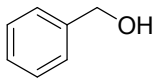
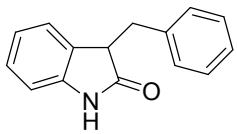
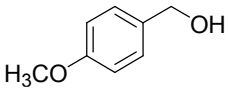
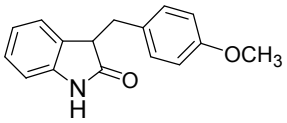
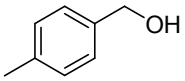
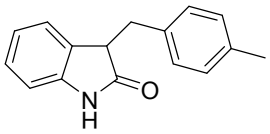
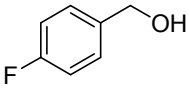
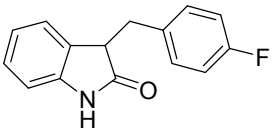
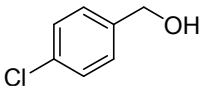
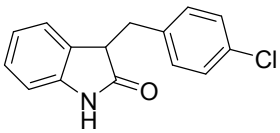
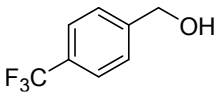
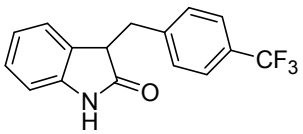
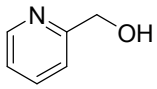
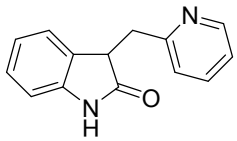
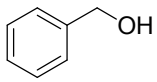
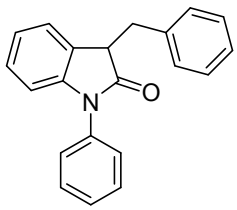
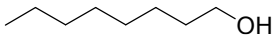
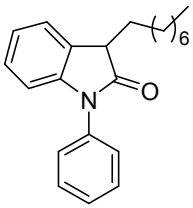
[b] Bond distance.

[c] Debye-Waller factor.

[d] Residual factor.

Table 3.3 Alkylation of oxindole with different alcohols using Pt/CeO_2.[a]

entry	alcohols	products	yield (%)[b]
1			99 (95)
2			99 (90)
3			90 (82)
4			90 (79)
5			99 (92)
6			99 (90)

7			99 (95)
8[c]			79
9			60 (54)
10			99 (89)
11			99 (92)
12			99 (85)
13			70 (58)
14			99 (92)
15			99 (94)

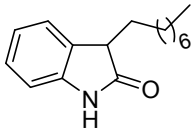
[a] 0.01 mmol Pt, 1 mmol oxindole, 1.1 mmol alcohol, 1.5 g mesitylene, 170 ºC, 24 h, in N_2.

[b] GC yield. Isolated yield is in the parentheses.

[c] 1 mmol oxindole, 1.5 mmol alcohol, 1.5 g mesitylene, 155 ºC, 24 h

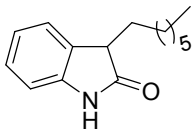
NMR and GCMS analysis

3-Octyl-1,3-dihydro-indol-2-one[1] (Table 3.3, entry 1)



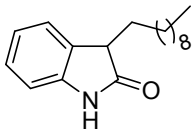
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.57 (br s, 1H), 7.16-7.13 (m, 2H), 6.98 (t, *J* = 7.6 Hz, 1H), 6.92 (d, *J* = 7.6 Hz, 1H), 3.48 (t, *J* = 6.2 Hz, 1H), 1.96-1.86 (m, 2H), 1.23-1.16 (m, 12 H), 0.88 (t, *J* = 7.56 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 180.6, 141.6, 129.9, 127.7, 124.1, 122.2, 109.6, 46.0, 31.8, 30.5, 29.5, 29.3, 29.2, 25.7, 22.6, 14.0 ppm. MS (EI) (*m/z*) (relative intensity) 245 (M^+, 35), 146 (100), 133 (80).

3-Heptyl-1,3-dihydro-indol-2-one[1] (Table 3.3, entry 2)



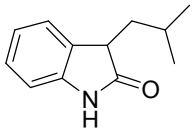
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.99 (br s, 1H), 7.18-7.12 (m, 2H), 6.93 (t, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 7.6 Hz, 1H), 3.40 (t, *J* = 6.2 Hz,1H), 1.92-1.82 (m, 2H), 1.35-1.13 (m, 10 H), 0.78 (t, *J* = 7.56 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 180.9, 141.6, 129.9, 127.7, 124.0, 122.1, 109.7, 46.1, 31.7, 30.5, 29.5, 29.0, 25.7, 22.5, 14.0 ppm. MS (EI) (*m/z*) (relative intensity) 231 (M^+, 35), 146 (100), 133 (100).

3-Decyl-1,3-dihydro-indol-2-one (Table 3.3, entry 3)



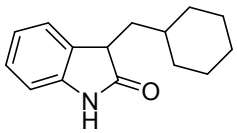
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 (br s, 1H), 7.17-7.13 (m, 2H), 6.95(t, 1H), 6.82 (d, *J* = 7.6 Hz, 1H), 3.39 (t, *J* = 5.8 Hz, 1H), 1.95-1.82 (m, 2H), 1.23-1.16 (m, 16 H), 0.81 (t, *J* = 7.56 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.9, 141.1, 129.8, 127.5, 123.9, 122.0, 109.2, 45.7, 31.6, 31.3, 30.3, 29.3, 29.3, 29.1, 29.0, 25.6, 22.4, 13.9 ppm. MS (EI) (*m/z*) (relative intensity) 273 (M^+, 35), 146 (100), 133 (90).

3-Isobutyl-1,3-dihydro-indol-2-one[3] **(Table 3.3, entry 4)**



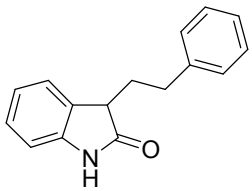
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.51 (br s, 1H), 7.14-7.11 (m, 2H), 6.91 (t, *J* = 7.56 Hz, 1H), 6.86 (d, *J* = 7.56 Hz, 1H), 3.39 (t, *J* = 6.9 Hz, 1H), 1.99–1.93 (m, 1H), 1.81–1.77 (m, 1H), 1.64–1.59 (m, 1H), 0.91 (d, *J* = 7.56 Hz, 3H), 0.88 (d, *J* = 7.56 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 181.7, 141.5, 130.2, 127.6, 124.2, 122.0, 109.9, 44.3, 39.8, 25.2, 22.9, 22.0 ppm. MS (EI) (*m/z*) (relative intensity) 189 (M^+, 60), 133 (100).

3-Cyclohexylmethyl-1,3-dihydro-indol-2-one[4] **(Table 3.3, entry 5)**



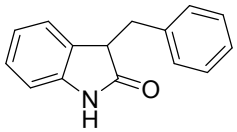
^{1}H NMR (600 MHz, $CDCl_3$) δ 9.06 (br s, 1H), 7.22-7.19 (m, 2H), 7.01 (t, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 7.6 Hz, 1H), 3.51 (t, *J* = 6.9 Hz, 1H), 1.99–1.93 (m, 1H), 1.90–1.82 (m, 2H), 1.73–1.66 (m, 6H), 1.18-1.28 (m, 2H), 1.02-0.98 (d, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 181.4, 141.4, 130.3, 127.6, 124.3, 122.0, 109.7, 43.5, 38.4, 34.5, 33.6, 32.6, 26.4, 26.1, 26.1 ppm. MS (EI) (*m/z*) (relative intensity) 229 (M^+, 20), 146 (40), 133 (100).

3-Phenethyl-1,3-dihydro-indol-2-one[6] **(Table 3.3, entry 6)**



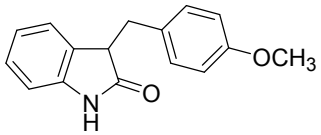
^{1}H NMR (600 MHz, $CDCl_3$) δ 9.60 (br s, 1H), 7.16-7.04 (m,7H), 6.93 (t, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 7.6 Hz, 1H), 3.41 (t, *J* = 6.2 Hz, 1H), 2.67–2.65 (m, 1H), 2.58–2.54 (m, 1H), 2.19–2.16 (m, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 180.9, 141.8, 141.1, 129.4, 128.4, 128.3, 127.8, 125.9, 123.9, 122.2, 109.9, 45.5, 32.1, 31.7 ppm. MS (EI) (*m/z*) (relative intensity) 237 (M^+, 75), 207 (100), 133 (75).

3-Benzyl-1,3-dihydroindol-2-one[2] **(Table 3.3, entry 7)** [2]



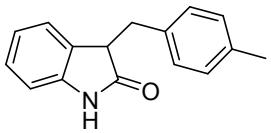
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.57 (br s, 1H), 7.19-7.08 (m, 6H), 6.82(t, *J* = 7.6 Hz, 1H), 6.83 (d, *J* = 7.6 Hz, 1H), 6.66 (d, *J* = 7.6 Hz, 1H), 3.68 (m, 1H), 3.50 (dd, *J* = 13.7, 8.9 Hz, 1H), 2.85 (dd, *J* = 13.7, 8.9 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.5, 141.3, 137.7, 129.4, 128.9, 128.3, 127.9, 126.6, 124.8, 122.0, 109.6, 47.4, 36.5 ppm. MS (EI) (*m/z*) (relative intensity) 223 (M^+, 35), 132 (20), 91 (90).

3-(4-Methoxy-benzyl)-1,3-dihydroindol-2-one[2] **(Table 3.3, entry 8)**



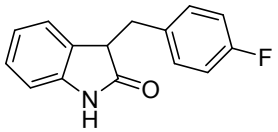
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.66 (br s, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 7.08 (d, *J* = 8.2 Hz, 2H), 6.92 (t, *J* = 7.6 Hz, 1H), 6.85 (d, 1H), 6.81-6.78 (m, 3H), 3.77 (s, 3H), 3.72 (dd, J = 8.9,4.8 Hz, 1H), 3.43 (dd, *J* = 13.7, 4.8 Hz, 1H), 2.91 (dd, *J* = 13.7, 8.9 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 180.0, 158.4, 141.7, 130.5, 129.9, 129.2, 128.0, 124.9, 122.1, 113.8, 109.9, 55.3, 47.9, 35.9 ppm. MS (EI) (m/z) (relative intensity) 253 (M+ , 5), 208(30), 144(20)

3-(4-Methyl-benzyl)-1,3-dihydroindol-2-one[3] **(Table 3.3, entry 9)**



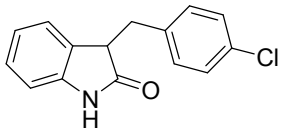
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 (br s, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 7.06 (br s, 4H), 6.91 (t, *J* = 7.6 Hz, 1H), 6.80-6.78 (m, 2H), 3.72 (dd, *J* = 8.9, 4.8 Hz, 1H), 3.43 (dd, *J* = 13.7, 4.8 Hz, 1H), 2.91 (dd, *J* = 13.7, 8.9 Hz, 1H), 2.32 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.6, 141.0, 136.1, 134.5, 129.2, 129.1, 129.0, 127.8, 124.9, 122.0, 109.3, 47.3, 36.1, 21.0 ppm. MS (EI) (*m/z*) (relative intensity) 237 (M^+, 20), 105 (100).

3-(4-Fluoro-benzyl)-1,3-dihydroindol-2-one[5] (Table 3.3, entry 10)



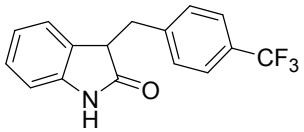
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.93 (br s, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.03-7.01 (m, 2H), 6.86-6.80 (m, 3H), 6.77-6.73 (m, 2H), 3.63 (dd, *J* = 8.6, 4.5 Hz, 1H), 3.32 (dd, *J* = 14.1, 4.5 Hz 1H), 2.89 (dd, *J* = 13.7, 8.9 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.6, 162.4, 160.8 (d, *J* = 249.98 Hz, 4-F-C), 141.4, 133.1, 130.8, 130.8, 128.6, 128.0, 124.6, 122.0, 115.1, 114.9, 109.8, 47.5, 35.6 ppm. MS (EI) (*m/z*) (relative intensity) 241 (M^+, 100), 213 (75), 159 (70), 33 (85).

3-(4-Chloro-benzyl)-1,3-dihydroindol-2-one[5] (Table 3.3, entry 11)



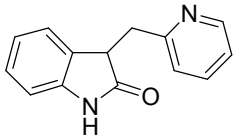
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.25 (bs, 1H), 7.22-7.17 (m, 3H), 7.08 (d, *J* = 8.2 Hz, 2H), 6.95 (t, *J* = 7.6 Hz, 1H), 6.82 (d, *J* = 7.6 Hz, 2H), 3.73 (dd, *J* = 8.9, 4.8 Hz,1H), 3.40 (dd, *J* = 13.7, 4.8 Hz, 1H), 3.00 (dd, *J* = 13.7, 8.9 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.0, 141.0, 135.7, 132.3, 130.5, 128.5, 128.2, 127.9, 124.4, 121.9, 109.5, 47.3, 35.5 ppm. MS (EI) (*m/z*) (relative intensity) 257 (M^+, 25), 132 (25), 125 (100).

3-(4-Trifluoromethyl-benzyl)-1,3-dihydroindol-2-one[5] (Table 3.3, entry 12)



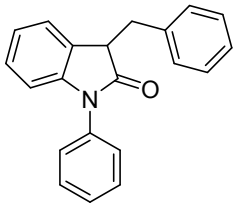
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.28 (br s, 1H), 7.41 (d, *J* = 8.2 Hz, 2H), 7.19 (d, *J* = 8.2 Hz, 2H), 7.11 (t, 1H), 6.95 (t, *J* = 7.6 Hz, 1H), 6.78-6.75 (m, 2H), 3.69 (dd, *J* = 8.9, 4.8 Hz, 1H), 3.40 (dd, *J* = 13.7, 4.8 Hz, 1H), 3.01 (dd, *J* = 13.9, 8.6 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.0, 141.8, 141.4, 129.9, 128.4, 125.4, 124.8, 122.4, 110.0, 47.2, 36.3 ppm. MS (EI) (*m/z*) (relative intensity) 291 (M^+, 40), 133 (100).

3-Pyridin-2-ylmethyl-1,3-dihydro-indol-2-one[6] (Table 3.3, entry 13)



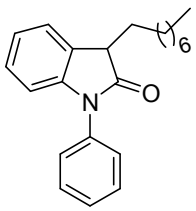
^{1}H NMR (600 MHz, $CDCl_3$) δ 9.02 (br s, 1H), 8.57 (d, *J* = 7.56 Hz, 1H), 7.60 (t, *J* = 7.56 Hz, 1H), 7.15 (m, 3H), 6.85 (m, 2H), 6.7 (d, *J* = 8.9 Hz,1H), 4.13 (dd, *J* = 8.6, 5.2 Hz, 1H), 3.60 (dd, *J* = 14.4, 5.5, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 180.1, 158.0, 149.2, 148.1, 136.3, 129.2, 127.8, 123.9, 121.9, 121.7, 109.7, 45.5, 38.5 ppm. MS (EI) (*m/z*) (relative intensity) 224 (M^+, 100), 180 (50), 146 (25).

3-Benzyl-1-phenyl-1,3-dihydro-indol-2-one[7] (Table 3.3, entry 14)



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 (t, 2H), 7.28 (t, *J* = 7.56 Hz, 1H), 7.15-7.10 (m, 5H), 7.06-7.02 (m, 3H), 6.90-6.86 (m, 2H), 6.55 (d, *J* = 7.6, 1H), 381 (dd, *J* = 8.2, 4.1, 1H), 3.41 (dd, *J* = 13.4, 4.5, 1H), 3.06 (dd, *J* = 13.7, 8.2, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.1, 144.0, 136.9, 134.1, 129.2, 127.8, 127.7, 127.5, 126.4, 126.3, 124.4, 122.2, 108.8, 46.9, 36.8 ppm. MS (EI) (*m/z*) (relative intensity) 299 (M^+, 85), 208 (90), 180 (50), 91 (100).

3-Octyl-1-phenyl-1,3-dihydro-indol-2-one (Table 3.3, entry 15)



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (t, *J* = 7.56 Hz, 2H) 7.30-7.27 (m, 3H), 7.20 (d, 1H), 7.08 (t, *J* = 7.56 Hz, 1H), 6.97 (t, *J* = 7.6 Hz,1H), 6.70 (d, *J* = 7.6 Hz, 1H), 3.52 (t, *J* = 5.8 Hz, 1H), 2.00-1.90 (m, 2H), 1.40-1.15 (m, 12 H), 0.77 (t, *J* = 7.56 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 180.6, 141.6, 129.9, 127.7, 124.1, 122.2, 109.6, 46.0, 31.8, 30.5, 29.5, 29.3, 29.2, 25.7, 22.6, 14.0 ppm. MS (EI) (*m/z*) (relative intensity) 321 (M^+, 50), 222 (100), 209 (80), 180 (30).

References

1. G. H. Liu, T. Z. Huang, Y. L. Zhang, X. H. Liang, Y. S. Li and H. X. Li, *Catal. Commun.*, 2011, **12**, 655-659.
2. R. Grigg, S. Whitney, V. Sridharan, A. Keep and A. Derrick, *Tetrahedron*, 2009, **65**, 4375-4383.
3. P. Thanigaimalai, K. C. Lee, V. K. Sharma, N. Sharma, E. Roh, Y. Kim and S. H. Sang, *Chem. Pharm. Bull. (Tokyo)*, 2011, **59**,1285-1288.
4. F. X. Smitha, B. D. Williamsa and E. G. Judy, *Synth. Commun.*, 2006 , **36**, 765 - 769.
5. T. Jensen and R. Madsen, *J. Org. Chem.*, 2009, **74**, 3990-3992.
6. I. W. Elliott , P. Rivers, *J. Org. Chem.*, 1964, **29**, 2438–2440.
7. Klasek, Antonin; Lycka, Antonin; Rouchal, Michal; Rudolf, Ondrej; Ruzicka, Ales *Helv. Chim. Acta*, 2014 , **97**, 595 - 612.

Chapter 4. Self-coupling of secondary alcohols and α-alkylation of methyl ketones with secondary alcohols by Pt/CeO_2 catalyst

4.1 Introduction

Catalytic C–C bond formation reactions are important for the construction of organic compound. Recently, much attention has been paid to the alkylation reactions using alcohols as environmentally benign alkylating agents driven by the borrowing-hydrogen[1] (hydrogen-autotransfer[2]) mechanism, because it can be a catalytic method to produce chemicals and fuels from bio-alcohols. For example, hydrogen-borrowing type coupling reactions of alcohols consist of (1) dehydrogenation of alcohols to the corresponding carbonyl compounds, (2) aldol condensation of them to form α,β-unsaturated carbonyl compounds, and (3) hydrogenation of the C=C (and C=O) bonds using the borrowed hydrogen atoms from alcohols. Only water is produced as byproducts, and the atom efficiency of this system is high. Several systems were reported to be effective for the this type of C–C bond formations (such as α-alkylation of ketones [3–11] and Guerbet-type cross- or self-coupling of alcohols[12–55]) using homogeneous (Ru,[4–6,12–20] Ir ,[3, 19–28] Pd, [29–31] Cu,[32, 33] Ni [34] and Fe[35]) and heterogeneous (Pd, [7–9, 30, 31, 36], Ir, [37] Au,[10] Ag, [38] Cu,[31,39–43] Ru,[44] Rh,[44, 45] and Ni[11, 44, 45]) catalysts and acid-basic bifunctional metal oxides [46–54]. However, these methods suffer from drawbacks such as high temperature (>200 °C), [30, 31, 38–54] high pressure (30–38 atm), [30, 31, 39, 40, 44, 45] reusability and needs of additives in the reaction mixture. [3–40, 44] Generally, the reported catalysts for the coupling of alcohols were not effective under additive free condition at low temperature. Importantly, previous reports on the self-coupling of secondary alcohols are limited. 29, 41–43 Cu-based heterogeneous catalysts for self-coupling of 2-propanol to give methyl isobutyl ketone [41–43] are known, but these examples suffer from high temperature (>200 °C) and low selectivity. A homogeneous Pd catalyst for self-coupling of an aromatic secondary alcohol (1-phenyethanol) at low temperatures 29 was reported, but this system suffers from difficulties in separation and recycle of the catalyst. Recently, we reported the first heterogeneous catalytic system for self-coupling of various aliphatic alcohols under relatively mild reaction conditions using CeO_2–supported nickel (Ni/CeO_2) catalysts. 55 In this paper, we show that CeO_2–supported Pt catalyst (Pt/CeO_2) shows 54 times higher turnover number (TON) than Ni/CeO_2. We also report detailed catalytic properties of Pt/CeO_2 for the self-coupling of various aliphatic secondary alcohols and α-alkylation of methyl ketones with aliphatic secondary alcohols.

4.2 Experimental

Catalyst Preparation

CeO_2 (JRC-CEO-3), MgO (JRC-MGO-3) and TiO_2 (JRC-TIO-4) were supplied from Catalysis Society of Japan. γ-Al_2O_3 was prepared by calcination of γ-AlOOH (Catapal B Alumina from Sasol) at 900 °C for 3 h. ZrO_2 was prepared by hydrolysis of zirconium oxynitrate 2-hydrate in distilled water by gradually adding an aqueous NH_4OH solution (1.0 mol dm^{-3}), filtration of precipitate, washing with distilled water three times, drying at 100 °C, and calcining at 500 °C. SiO_2 (Q-10) was supplied from Fuji Silysia Chemical Ltd. C (active carbon) was purchased from Kishida Chemical Co., Ltd.

A precursor of Pt/CeO_2 (with Pt loading of 1 wt%) was prepared by an impregnation method; a mixture of CeO_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 and calcining at 300 °C for 3 h. Before each catalytic experiment, a pre-reduced catalyst was prepared by 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. Other supported Pt catalysts (Pt = 1 wt%) were prepared by the same method. CeO_2–supported metal catalysts, M/CeO_2 (M = Ir, Pd, Ru, Ni and Co) with metal loading of 1 wt% were prepared by impregnation method in the similar manner as Pt/CeO_2 using aqueous solution of metal nitrates (for Co and Ni), $RuCl_3$, $IrCl_3 \cdot nH_2O$, or aqueous HNO_3 solution of $Pd(NO_3)_2$.

Typical Procedures of Catalytic Reactions

Commercially available organic compounds were used without further purification. Typically, Pt/CeO_2 was used in catalytic experiments. After the pre-reduction in H2 at 300 °C for 0.5 h, we carried out catalytic tests without exposing the catalyst to air as follows. For the self-coupling of various aliphatic secondary alcohols, the mixture of alcohol (1 mmol) and *n*-dodecane (0.5 mmol) in *o*-xylene (2 ml) was injected to the pre-reduced catalyst inside a reactor (cylindrical glass tube) through a septum inlet. Then, the reactor was purged by N_2 and set in a reaction vessel equipped with a condenser. The resulting mixture was stirred at 140 °C. For the α-alkylation of aliphatic ketones with aliphatic secondary alcohols, the mixture of ketone (1 mmol), alcohol (1 mmol) and n-dodecane (0.5 mmol) in o-xylene (2 ml) was heated at 130 °C. Conversion and yields of products were determined by GC (Shimadzu GC-14B with Ultra ALLOY capillary column UA+-5

using nitrogen as the carrier gas) using n-dodecane as an internal standard. After removal of the catalyst, the product was purified with column chromatography and analyzed by ^{1}H NMR, ^{13}C NMR (JEOL-ECX 600) and GCMS (Shimadzu GCMS-QP2010 with Ultra ALLOY capillary column UA+-5).

NMR and GCMS Analysis

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

4.3 Results and Discussion

First, we carried out catalyst screening test adopting the self-coupling of 2-octanol as a model reaction in the presence of 0.2 mol% of various 1 wt % metal-loaded catalysts pre-reduced at 300 °C. As shown in Table 4.1, Pt/CeO_2 showed higher yield of a dimer product (ketone 1a) than other Pt catalysts loaded on MgO, ZrO_2, Al_2O_3, TiO_2, SiO_2 and active carbon. The latter catalysts mainly catalyzed the dehydrogenation of 2-octanol to give 2-octanone as the main product (entries 2–7). Among various 1 wt% metal-loaded CeO_2 catalysts (entries 1, 9–13), Pt/CeO_2 showed the highest yield of the dimer product. Ir/CeO_2 and Pd/CeO_2 showed low yield (41 and 12 %) of the dimer product, and Ru/CeO_2, Co/CeO_2 and Ni/CeO_2 catalysts were inactive. Bare CeO_2 showed no yield of the self-coupling products. In our recent report, [55] 3 wt% Ni/CeO_2 was found to be the best catalyst for the self coupling of 2-octanol in a high catalyst loading conditions (3 mol%) as shown in entry 15. However, in a low catalyst loading conditions (0.2 mol%) 3 wt% Ni/CeO_2 was inactive (entry 14). From these results, Pt/CeO_2 was found to be the optimum catalyst for this reaction.

Table 4.2 shows the results of catalyst reuse and the scope of substrates for the self-coupling of secondary alcohols by using 0.2 mol% of Pt/CeO_2 pre-reduced at 300 °C. Reaction of 2-octanol at 140 °C for 20 h resulted in 93 % yield of the dimer product

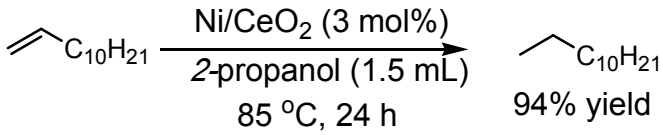
(entry 1). After the reaction, Pt/CeO_2 was easily separated from the reaction mixture by a centrifugation. The separated catalyst was washed with acetone, followed by reduction in H_2 at 300 °C for 0.5 h. As shown in Table 2 (entries 2, 3), the recovered catalyst was reused at least two times without any indication of catalyst deactivation. We also analyzed the solution after reaction by using ICP and confirmed that no Pt species were dissolved in the solution (under the detection limit less than 0.1 ppm). These results show that Pt/CeO_2 is a recyclable catalyst for the self-coupling of secondary alcohols. The reaction with less amount of the Pt/CeO_2 catalyst (0.05 mol%) for 70 h resulted in 84 % yield of the dimer product, corresponding to turnover number (TON) of 1,680. This value is 54 times higher than that of Ni/CeO_2 catalyst (TON of 31) reported in our previous study. [55]

As shown in Table 4.2 (entries 5–10), self-coupling of various liner and branched aliphatic alcohols proceeded in moderate to good yield of the corresponding dimer products, ketones. In the dimer products, alcohols which might be produced by reduction of the ketone were not observed in GC and GCMS analyses.

As shown in Table 4.3, Pt/CeO_2 was also effective for the α-alkylation of methyl ketones with secondary alcohols. Various liner and branched aliphatic ketones and alcohols were tolerated, and moderate to excellent yields (65–99 %) of the corresponding α-alkylated ketones were obtained. Reaction of 2-heptanone with 2-heptanol gave 99 % yield of α-alkylated product (entry 3).

As previously proposed [55], the self-coupling of secondary alcohols could proceed through so called hydrogen-borrowing pathway, which consists of dehydrogenation of secondary alcohols to ketones, aldol condensation of them to form α,β-unsaturated ketone, and hydrogenation of the C=C bonds using the borrowed hydrogen atoms from alcohols. Figure 4.1 shows the time course of the product yield for self-coupling of 2-octanol by Pt/CeO_2. A time-conversion profile characteristic to a consecutive reaction mechanism was observed; 2-octanone formed at an initial induction period was consumed after 2 h to give the dimer product. Thus, the initial stage of the reaction should be the oxidation of alcohols to the ketone intermediates possibly accompanied by the transitory generation of Pt–H species. Previously, we showed that bare CeO_2 was active for aldol condensation of ketones to form α,β-unsaturated ketone. We tested transfer hydrogenation of 1-dodecene

using 2-propanol as hydrogen donor by Pt/CeO_2 (Eq. 1) as a model reaction.



(1)

It was found that the catalyst was effective for the transfer hydrogenation of the C=C bond. Thus, in the self-coupling of alcohols, hydride transfer from the alcohol to the C=C bond of α,β-unsaturated ketone could occur by this catalyst. Taking into account the fact that this catalyst is effective for the α-alkylation of methyl ketones with secondary alcohols (Table 4.3), we proposed a plausible mechanism as shown in Fig. 4.2. The reaction begins with the dehydrogenation of alcohols to the corresponding ketones with the generation of Pt–H species (step 1). Then, aldol condensation between these ketones occurs to give the α,β-unsaturated ketone (step 2). Finally, hydrogen transfer from Pt–H species to the C=C bond of the α,β-unsaturated ketone gives the ketone product (step 3).

4.4 Conclusions

Transition metal-loaded metal oxides, pre-reduced in H_2 at 300 °C, were tested for C–C self coupling of aliphatic secondary alcohols under N_2 in liquid phase. Among Pt catalysts loaded on various supports (CeO_2, MgO, ZrO_2, Al_2O_3, TiO_2, SiO_2 and C) and various metal (Pt, Ir, Pd, Ru, Co and Ni)-loaded CeO_2 catalysts, Pt/CeO_2 showed the highest yield (93 %) of a dimer product (a higher ketone) for the self-coupling of 2-octanol at 140 °C. Pt/CeO_2 showed good reusability and higher turnover number (TON) than previous catalysts for self-coupling of secondary alcohols. Pt/CeO_2 was effective for self-coupling of various aliphatic secondary alcohols and α-alkylation of methyl ketones with aliphatic secondary alcohols. The self-coupling reaction could be driven by the borrowing-hydrogen pathway, in which ketone formed by dehydrogenation of alcohol undergoes aldol condensation to give α,β-unsaturated ketone which is finally hydrogenated by in situ formed Pt–H species.

References

1. M. H. S. A. Hamid, P. A. Slatford and J. M. J. Williams, *Adv. Synth. Catal.*, 2007, **349**, 1555-1575.
2. G. Guillena, D. J. Ramón and M. Yus, *Angew. Chem. Int. Ed.*, 2007, **46**, 2358-2364.
3. K. Taguchi, H. Nakagawa, T. Hirabayashi, S. Sakaguchi and Y. Ishii, *J. Am. Chem. Soc.*, 2004, **126**, 72-73.
4. C. S. Cho, B. T. Kim, T. J. Kim and S. C. Shim, *J. Org. Chem.*, 2001, **66**, 9020-9022.
5. R. Martinez, G. J. Brand, D. J. Ramon and M.Yus, *Tetrahedron Lett.*, 2005 **46**, 3683-3686.
6. T. Kuwahara, T. Fukuyama and I. Ryu, *Org Lett.*, 2012, **14**, 4703-4705.
7. C. S. Cho, *J. Mol. Catal. A*, 2005, **240**, 55-60.
8. M. S. Kwon, N. Kim, S. H. Seo, I. S. Park, R. K. Cheedrala and J. Park, *Angew. Chem. Int. Ed.*, 2005, **44**, 6913-6915.
9. Y. M. A. Yamada and Y. Uozumi, *Org. Lett.*, 2006, **8**, 1375-1378.
10. S. Kim, S. W. Bae, J. S. Lee and J. Park, *Tetrahedron*, 2009, **65**, 1461-1466.
11. F. Alonso, P. Riente and M.Yus, *Acc. Chem. Res.*, 2011, **44**, 379-391.
12. C. S. Cho, *Organometallics*, 2003, **22**, 3608-3610.
13. R. Martinez, D. J. Ramón and M. Yus, *Tetrahedron*, 2006, **62**, 8982-8987.
14. M. Viciano, M. Sanau and E. Peris, *Organometallics*, 2007, **26**, 6050-6054.
15. A. Prades, M. Viciano, M. Sanau and E. Peris, (2008) *Organometallics*, 2008, **27**, 4254-4259.
16. X. Chang, L. W. Chuan, L.Yongxin and S. A. Pullarka,t (2012) *Tetrahedron Lett.*, 2012, **53**, 1450-1455.
17. G. R. A. Adair and J. M. J. Williams, *Tetrahedron Lett.*, 2005, **46**, 8233-8235.
18. H. W. Cheung, T. Y. Lee, H. Y. Lui, C. H. Yeung and C.P. Lau, *Adv. Synth. Catal.*, 2008, **350**, 2975-2983.
19. D. Gnanamgari, C. H. Leung, N. D. Schley, S. T. Hilton and R. H. Crabtree, *Org. Biomol. Chem.*, 2008, **6**, 4442-4445.
20. D. Gnanamgari, E. L. O. Sauer, N. D. Schley, C. Butler, C. D. Incarvito and R. H. Crabtree, Organometallics, 2009, **28**, 321-325.
21. K. Fujita, C. Asai, T. Yamaguchi, F. Hanasaka and R. Yamaguchi, *Org. Lett.*, 2005, **7**,

4017-4019.

22. A. P. da Costa, M. Viciano, M. Sanaú, S. Merino, J. Tejeda, E. Peris and B. Royo, (2008) *Organometallics*, 2008, **27**, 1305-1309.
23. A.P. da Costa, M. Sanau, E. Peris and B. Royo, *Dalton Trans.*, 2009, **38**, 6960-6966.
24. X. Gong, H. Zhang and X. Li, *Tetrahedron Lett.*, 2011, **52**, 5596-5600.
25. C. Xu, L. Y. Goh and S. A. Pullarkat, *Organometallics*, 2011, **30**, 6499-6502.
26. T. Matsu-ura, S. Sakaguchi, Y. Obora and Y. Ishii, *J. Org. Chem.*, 2006, **71**, 8306-8308.
27. K. Koda, T. Matsu-ura, Y. Obora and Y. Ishii, *Chem. Lett.*, 2009, **38**, 838-839.
28. Y. Obora, Y. Anno, R. Okamoto, T. Matsu-ura and Y. Ishii, *Angew. Chem. Int. Ed.*, 2011, **50**, 8618-8622.
29. O. Kose and S. Saito, *Org. Biomol. Chem.*, 2010, **8**, 896-900.
30. C. Carlini, M. D. Girolamo, A. Macinai, M. Marchionna, M. Noviello, A. M. R. Galletti and G. Sbrana, *J. Mol. Catal. A*, 2003, **204–205**,721-728.
31. C. Carlini, A. Macinai, A. M. R. Galletti and G. Sbrana, *J. Mol. Catal. A*, 2004, **212**, 65-70.
32. T. Miura, O. Kose, F. Li, S. Kai and S. Saito, *Chem. Eur. J.*, 2011, **17**, 11146-11151
33. S. Liao, K. Yu, Q. Li, H.Tian, Z. Zhang, X. Yu and Q. Xu, *Org. Biomol. Chem.*, 2012, **10**, 2973-2978.
34. G. Tang and C. H. Cheng, *Adv. Synth. Catal.*, 2011, **353**, 1918-1922.
35. J. Yang, X. Liu, D. L. Meng, H. Y. Chen, Z. H. Zong, T. T. Feng and K. Sun, *Adv. Synth. Catal.*, 2012, **354**, 328-334.
36. C. S. Cho, W. X. Ren and S.C.Shim, *Bull. Korean. Chem. Soc.*, 2005, **26**, 1611-1613.
37. R. Cano, M. Yus and D. J. Ramón, *Chem. Commun.*, 2012, **48**, 7628-7630.
38. K. Shimizu, R. Sato and A. Satsuma, *Angew Chem Int Ed.*, 2009, **48**, 3982-3986.
39. C. Carlini, M. D. Girolamo, M. Marchionna, M. Noviello, A. M. R. Galletti and G. Sbrana, *J. Mol. Catal. A*, 2002, **184**, 273-280.
40. C. Carlini, M. D. Girolamo, A. Macinai, M. Marchionna, M. Noviello, A. M. R. Galletti and G. Sbrana *J. Mol. Catal. A*, 2003, **200**, 137-146.
41. J. I. D. Cosimo, G. Torres and C.R. Apesteguia, (2002) *J. Catal.*, 2002, **208**, 114-123.
42. S. A. El-Molla, *Appl. Catal. A*, 2006, **298**, 103-108.

43. G. Torres, C. R. Apesteguia and J. I. D. Cosimom, *Appl. Catal. A*, 2007, **317**, 161-170.
44. C. Carlini, A. Macinai, M. Marchionna, M. Noviello, A. M. R. Galletti and G. Sbrana, *J. Mol. Catal. A*, 2003, **206**, 409-418.
45. C. Carlini, M. Marchionna, M. Noviello, A. M. R. Galletti, G. Sbranaa, F. Basiled and A. Vaccarid, *J. Mol. Catal. A,* 2005, **232**, 13-20.
46. J. I. D. Cosimo, C. R. Apesteguia, M. J. L. Gines and E. Iglesia, *J. Catal.*, 2000, **190**, 261-275.
47. A.S. Ndou, N. Plint and N.J. Coville, *Appl. Catal. A*, 2003, **251**, 337-345.
48. A.S. Ndou, and N.J. Coville, *Appl. Catal. A* , 2004, **275**, 103-110.
49. T. Tsuchida, S. Sakuma, T. Takeguchi and W. Ueda, *Ind. Eng. Chem. Res.*, 2006, **45**, 8634-8642.
50. T. Tsuchida, J. Kubo, T. Yoshioka, S. Sakuma, T. Takeguchi and W. Ueda, *J. Catal.*, 2008, **259**, 183-189.
51. S. Ogo, A. Onda and K. Yanagisawa, *Appl. Catal. A*, 2011, **402**, 188-195.
52. S. Ogo, A. Onda, Y. Iwasa, K. Hara, A. Fukuoka and K. Yanagisawa, *J. Catal.*, 2012 **296**, 24-30.
53. M. Leon, E. Diaz and S. Ordonez, *Catal. Today*, 2011, **164**, 436-442.
54. M. Leon, E. Diaz, A.Vega, S. Ordonez and A. Auroux, *Appl. Catal. B*, 2011, **102**, 590-599.
55. K. Shimura, K. Kon, S. M. A. H. Siddiki and K. Shimizu , *Appl. Catal. A*, 2013, **462**, 137-142.

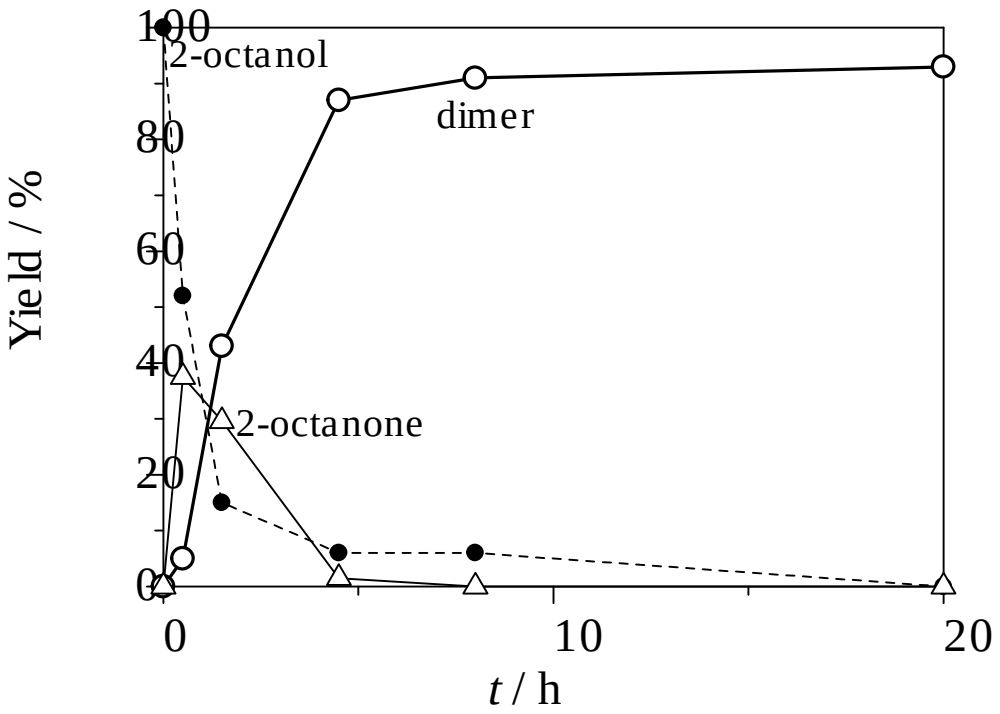


Figure 4.1 Time course of the product yield for self-coupling of 2-octanol at 130 ºC by Pt/CeO_2 reduced at 300 ºC

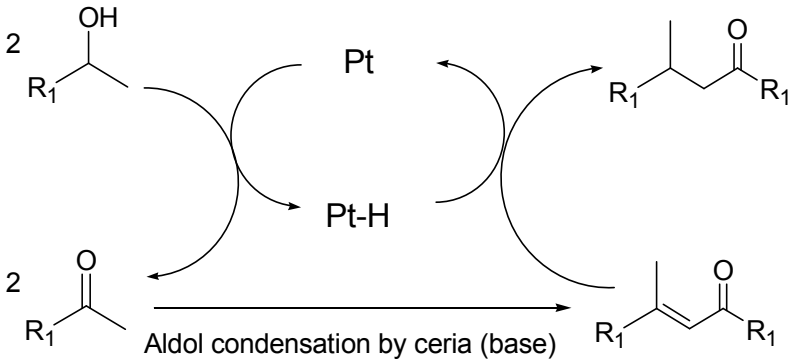
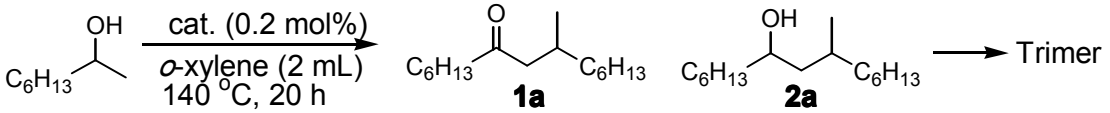


Figure 4.2 A possible catalytic cycle of self-coupling of secondary alcohols by Pt/CeO_2.

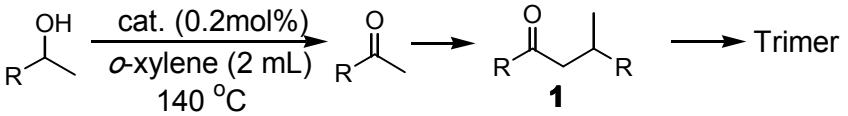
Table 4.1 Self-coupling of 2-octanol by 1 wt% metal-loaded catalysts reduced at 300 °C.



Entry	Catalyst	Conv. (%)	Yield (%)		
			2-Octanone	Dimer **1a** (**2a**)	Trimer
1	Pt/CeO_2	100	0	93	0
2	Pt/MgO	53	44	3	0
3	Pt/ZrO_2	81	54	17	0
4	Pt/Al_2O_3	69	71	4	0
5	Pt/TiO_2	98	58	24	0
6	Pt/SiO_2	2	0	0	0
7	Pt/C	15	2	0	0
8[a]	CeO_2	8	2	0	0
9	Ir/CeO_2	86	18	41	0
10	Pd/CeO_2	55	35	12	0
11	Ru/CeO_2	45	42	0	0
12	Co/CeO_2	8	3	0	0
13	Ni/CeO_2	6	5	0	1
14[b]	$Ni3/CeO_2$	5	1	0	0
15 [b, c]	$Ni3/CeO_2$	100	0	93	2

[a] CeO_2 = 35 mg. [b] Ni loading is 3 wt% [c] Ni = 3 mol%.

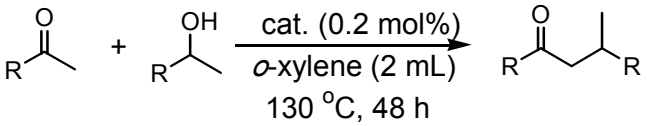
Table 4.2 Self-coupling of secondary alcohols by Pt/CeO_2.



Entry	Substrate	*t* / h	Conv. (%)	Yield (%)		
				Ketone	Dimer	Trimer
1	2-Octanol	20	100	0	93	0
2 [a]		20	100	0	90	0
3 [b]		20	100	0	90	0
4 [c]		70	100	2	84	0
5	2-Pentanol	15	100	0	84	3
6	2-Hexanol	2.5	99	1	80	0
7	2-Heptanol	15	100	0	85	0
8	2-Undecanol	15	100	0	78	4
9	3-Methyl-2-butanol	24	100	16	75	0
10	5-Methyl-2-hexanol	17	100	3	85	0

[a] Result of catalyst reuse after entry 1.
[b] Result of catalyst reuse after entry 2.
[c] Pt = 0.05 mol%.

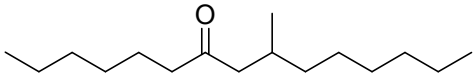
Table 4.3 α-Alkylation of ketones with secondary alcohols by 1 wt% Pt/CeO_2 pre-reduced at 300 ºC.



Entry	Ketones	Alcohols	*t* / h	Yield (%)
1	2-Butanone	2-Butanol	24	70
2	2-Hexanone	2-Hexanol	48	74
3	2-Heptanone	2-Heptanol	24	99
4	2-Octanone	2-Octanol	12	85
5	2-Undecanone	2-Undecanol	48	73
6	3-Methyl-2-butanol	3-Methyl-2-butanone	24	65
7	5-Methyl-2-hexanol	5-Methyl-2-hexanone	24	83

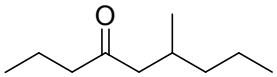
NMR and GCMS analysis

9-Methyl-pentadecan-7-one[1] (Table 4.2, entry 1 and Table 4.3, entry 4)



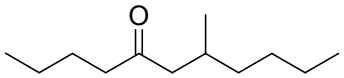
^{1}H NMR (600 MHz, $CDCl_3$) δ 2.31–2.28 (m, 3H), 2.11 (dd, *J* = 15.8, 8.2 Hz, 1H), 1.94–1.89 (m, 1H), 1.51–1.46 (m, 2H), 1.24–1.18 (m, 16H), 0.83–0.80 (m, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 211.4, 50.2, 43.3, 36.9, 31.8, 31.5, 29.4, 29.2, 28.8, 26.9, 23.7, 22.6, 22.4, 19.8, 14.0, 13.9 ppm. MS (EI) (m/z) (relative intensity) 240 (M+, 12), 129 (50), 71 (50), 57 (70), 43 (100).

6-Methyl-nonan-4-one (Table 4.2, entry 5)



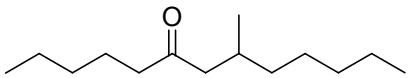
^{1}H NMR (600 MHz, $CDCl_3$) δ 2.30–2.26 (m, 3H), 2.10 (dd, *J* = 15.8, 8.2 Hz, 1H), 1.96–1.90 (m, 1H), 1.52–1.49 (m, 2H), 1.25–1.16 (m, 4H), 0.83–0.80 (m, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 211.4, 50.3, 42.1, 37.1, 25.9, 20.0, 19.4,14.1, 13.8, 13.7 ppm. MS (EI) (m/z) (relative intensity) 156 (M+, 19), 85 (55), 57 (100), 43 (80).

7-Methyl-undecan-5-one[1] (Table 4.2, entry 6 and Table 4.3, entry 2)



^{1}H NMR (600 MHz, $CDCl_3$) δ 2.32–2.29 (m, 3H), 2.18 (dd, *J* = 15.8, 8.2 Hz, 1H), 1.95–1.90 (m, 1H), 1.51–1.47 (m, 2H), 1.25–1.16 (m, 8H), 0.83–0.80 (m, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 211.4, 50.1, 42.8, 36.7, 29.9, 29.7, 25.6, 22.8, 22.1, 19.6, 13.8, 13.7 ppm. MS (EI) (m/z) (relative intensity) 184 (M+, 20), 101 (65), 85 (70), 57 (100), 43 (75).

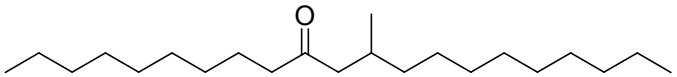
8-Methyl-tridecan-6-one[1] (Table 4.2, entry 7 and Table 4.3, entry 3)



^{1}H NMR (600 MHz, $CDCl_3$) δ 2.32–2.28 (m, 3H), 2.10 (dd, *J* = 15.8, 8.2 Hz, 1H), 1.93–1.90 (m, 1H), 1.52–1.48 (m, 2H), 1.25–1.16 (m, 12H), 0.83–0.80 (m, 9H) ppm; ^{13}C

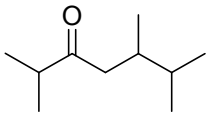
NMR (150 MHz, $CDCl_3$) δ 211.3, 50.1, 43.3, 36.6, 31.7, 31.2, 29.0, 26.4, 23.2, 22.4, 22.2, 19.6, 13.8, 13.7 ppm. MS (EI) (m/z) (relative intensity) 212 (M+, 15), 141 (60), 85 (50), 57 (75), 43 (80).

12-Methyl-henicosan-10-one[1] **(Table 4.2, entry 8 & Table 4.3, entry 5)**



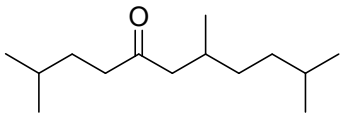
^{1}H NMR (600 MHz, $CDCl_3$) δ 2.31–2.27 (m, 3H), 2.09 (dd, J = 15.8, 8.2 Hz, 1H), 1.93–1.90 (m, 1H), 1.51–1.47 (m, 2H), 1.18 (br s, 28H), 0.82–0.79 (m, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 211.6, 50.5, 43.5, 37.1, 32.0, 32.0, 29.9, 29.8, 29.8, 29.6, 29.5, 29.4, 29.4, 29.4, 27.1, 23.9, 22.8, 22.8, 20.0, 14.2, 14.2 ppm. MS (EI) (m/z) (relative intensity) 212 (M+, 25), 141 (50), 85 (90), 57 (100), 43 (100).

2,5,6-Trimethyl-heptan-3-one (Table 4.2, entry 9 and Table 4.3, entry 6)



^{1}H NMR (600 MHz, $CDCl_3$) δ 2.40–2.36 (m, 3H), 2.10 (dd, J = 15.8, 8.2 Hz, 1H), 1.94–1.87 (m, 1H), 0.85–0.80 (m, 15H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 211.7, 50.5, 43.3, 36.8, 29.3, 26.1, 22.4, 19.9, 14.2, 14.0 ppm. MS (EI) (m/z) (relative intensity) 156 (M+, 18), 127 (25), 85 (60), 57 (100).

2,7,10-Trimethyl-undecan-5-one (Table 4.2, entry 10 and Table 4.3, entry 7)



^{1}H NMR (600 MHz, $CDCl_3$) δ 2.40–2.36 (m, 3H), 2.10 (dd, J = 15.8, 8.2 Hz, 1H), 1.98–1.94 (m, 1H), 1.55–1.43 (m, 4H), 1.28–1.12 (m, 4H), 0.83–0.80 (m, 15H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 211.6, 50.3, 41.3, 36.1, 34.6, 32.5, 29.4, 28.1, 27.6, 22.7, 22.4, 22.3, 22.3, 19.9 ppm. MS (EI) (m/z) (relative intensity) 212 (M+, 37), 141 (50), 85 (90), 57 (100), 43 (100).

References for NMR assignment in Chapter 4

1. I. S. Makarov and R. Madsen, *J. Org. Chem.*, 2013, **78**, 6593−6598.

Chapter 5. Acceptorless dehydrogenative synthesis of 2-substituted quinazolines from 2-aminobenzylamine with primary alcohols or aldehydes by heterogeneous Pt catalysts

5.1 Introduction

Quinazolines are important compounds in organic synthesis and industrial production of pharmaceutical compounds which show various biological activities such as antibacterial,[1] antiviral,[2] antitubercular[3] and anticancer[4] activities. Various methods have been reported for the synthesis of 2-substituted quinazolines. One of the representative methods is the oxidative condensation of 2-aminobenzylamines with aldehydes via aminal intermediates using stoichiometric amount of toxic oxidants such as DDQ,[7] MnO_2[8] and NaClO.[9] Yu et al.[10] reported more atom-efficient synthesis of 2-substituted quinazolines: an aerobic oxidative process by 5 mol% CuCl/DABCO/TEMPO catalyst. Kobayashi et al. reported that Pt/Ir bimetallic nanoclusters cooperated with dimeric catechol derivative effectively catalyzed the aerobic oxidative synthesis of quinazolines from 2-aminobenzylamines and aldehydes at 35 °C under basic conditions.[11] Recently, Fang et al.[12] showed an anaerobic method using [Cp*$IrCl_2$] complex in presence of excess amount (4 equiv) of acceptor (styrene) under basic conditions. The most attractive methodology is an anaerobic method in the absence of any oxidant (acceptor), so called dehydrogenative acceptorless coupling reactions.[13] Considering that alcohols are more stable and readily available than aldehydes, use of primary alcohols instead of aldehydes is also an important alternative, but acceptorless methods are not reported. The only one example using the Ir-catalyst[12] with the acceptor was applicable only to an activated alcohol, benzylalcohol. As a part of our continuing interest in heterogeneous Pt catalysts for the acceptorless dehydrogenation of alcohols[14] and acceptorless dehydrogenative coupling reactions,[15,16] we report herein the first acceptorless method for the synthesis of 2-substituted quinazolines from 2-aminomethyl-phenyl amine and alcohols or aldehydes using a CeO_2-supported Pt catalyst (Pt/CeO_2).

5.2 Experimental

General

Commercially available organic and inorganic compounds (from Tokyo Chemical Industry, Wako Pure Chemical Industries, Kishida Chemical, or Mitsuwa Chemicals) 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. The X-ray photoelectron spectroscopy (XPS) measurements were carried out using a JEOL JPS-900MC with Al*Kα* anode operated at 20 mA and 10 kV. The oxygen 1s core electron levels in support oxides were recorded. Binding energies were calibrated with respect to C_{1s} at 285.0 eV. Prior to the XPS measurement, metal oxide samples were preheated in air at 600 °C for 0.5 h (except for TiO_2 at 500 °C).

Catalyst preparation

CeO_2 (JRC-CEO-1, 157 m^2 g^{-1}), MgO (JRC-MGO-1), TiO_2 (JRC-TIO-4), $SiO_2Al_2O_3$ (JRC-SAL2, Al_2O_3 = 13.75 wt%) and H^+-type BEA zeolite (HBEA, SiO_2/Al_2O_3 = 25±5, JRC-Z-HB25) were supplied from Catalysis Society of Japan. SiO_2 (Q-10, 300 m^2 g^{-1}) was supplied from Fuji Silysia Chemical Ltd. Hydroxides of Zr and La were prepared by hydrolysis of zirconium oxynitrate 2-hydrate and $La(NO_3)_3{\cdot}6H_2O$ in distilled water by gradually adding an aqueous NH_4OH solution (1.0 mol dm^{-3}), followed by filtration of precipitate, washing with distilled water three times, drying at 100 °C for 12 h. $Nb_2O_5{\cdot}nH_2O$ was supplied from CBMM. La_2O_3, ZrO_2, and Nb_2O_5 were prepared by calcination of these hydroxides at 500 °C for 3 h. 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 1 wt% Pt/CeO_2 catalyst was prepared by an impregnation method; a mixture of CeO_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. A pre-reduced catalyst (named Pt/CeO_2) was prepared by pre-reduction of the precursor in a pyrex tube under a flow of H_2 (20 cm^3 min^{-1}) at 500 °C for 0.5 h. Platinum oxides-loaded CeO_2 (PtO_x/CeO_2), as a comparative catalyst, was prepared by calcination of the precursor at 300 °C for 3 h. By using various supports, several pre-reduced Pt catalysts were prepared by the same method as Pt/CeO_2. CeO_2-supported metal catalysts, M/CeO_2 (M = Co, Ni, Cu, Ru, Rh, Pd, Ag and Ir) with metal loading of 1 wt% were prepared by impregnation method in a similar manner as Pt/CeO_2 using an aqueous solution of metal nitrates (for Co, Ni, Cu and Ag), $RuCl_3$, $IrCl_3$, or an aqueous HNO_3 solution of $Rh(NO_3)_3$ or $Pd(NO_3)_2$

Catalytic test

1wt% Pt/CeO_2 (195 mg, 0.01 mmol of Pt) was used as a standard catalyst. After the pre-reduction at 500 °C, we carried out catalytic tests using a batch-type reactor without

exposing the catalyst to air as follows. Typically, the mixture of 2-aminobenzylamine (1.0 mmol) and 1-octanol or 1-octanal (1.2 mmol) in mesitylene (1.2 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 30-48 h under reflux condition; the bath temperature was 170 °C and reaction temperature was *ca.* 165 °C. For the scope and limitation study in Tables 2 and 4, isolated yields of products were determined as follows. After the reaction, the catalyst was removed by filtration and then the reaction mixture was concentrated under vacuum evaporator to remove the volatile compounds. Then, 2-substituted quinazolines were isolated by column chromatography using silica gel 60 (spherical, 63-210 μm, Kanto Chemical Co. Ltd.) with ethylacetate/hexane (5/95 to 15/85) as the eluting solvent, followed by analyses by ^{1}H NMR, ^{13}C NMR and GCMS. For the kinetic, catalyst screening, and catalyst recycle studies, the yields of the un-reacted 2-aminobenzylamine **1a**, 2-substituted quinazoline **3a** and 2-heptyl-1,2,3,4-tetrahydro-quinazoline **2a** were 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).

NMR and GCMS analysis

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

5.3 Results and discussion

First, we studied the acceptorless dehydrogenative synthesis of 2-substituted quinazolines from 2-aminobenzylamine 1a and primary alcohols, which was unprecedented in the literature. We carried out catalyst screening tests adopting the model reaction of 1a (1 mmol) with 1-octanol (1.2 mmol) under the same conditions: reflux in mesitylene under N_2 for 48 h using 1 mol% of metal catalysts. Table 5.1 lists the yields of 2-substituted quinazoline 3a (the main product) and an intermediate,

2-heptyl-1,2,3,4-tetrahydro-quinazoline 2a (a byproduct). Among various transition metal nanoparticles loaded on CeO_2 (entries 1-8), Pt/CeO_2 (entry 1) showed the highest yield (90%) of 3a without forming the byproduct 2a. CeO_2 itself was inert (entry 9). The effect of support materials of Pt catalysts (entries 1, 11-17) showed that CeO_2 was the most effective support of Pt. Other supports such as TiO_2, MgO and Nb_2O_5 gave moderate yields. Consequently, Pt/CeO_2 was found to be the most effective catalyst for the dehydrogenative synthesis of 3a from 1a and 1-octanol.

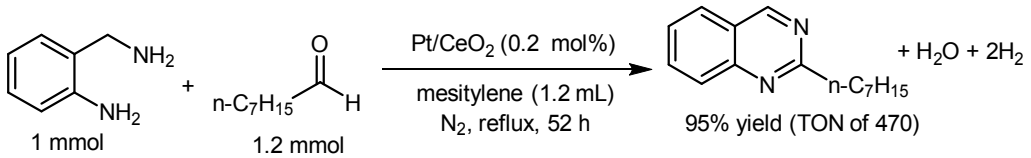
It is established that the O_{1s} binding energy of metal oxides decreases with increase in the electron density of oxygen in the metal oxide, or in other words, basicity of the metal oxide surface.[17-19] In our previous report,[19] we measured the binding energy of the O_{1s} electron in the support oxide by XPS analysis. XPS spectra of Nb_2O_5, TiO_2 and MgO were added to the previous results as shown in Fig. 5.3. The O_{1s} binding energy of the peak maxima decreased in the order of $SiO_2Al_2O_3$ > SiO_2 > γ -Al_2O_3 > Nb_2O_5 > ZrO_2 > TiO_2 > MgO > CeO_2. Fig. 5.4 shows the yield of 3a from 1a and 1-octanol (Table 1) as a function of the O1s binding energy of the support oxides. There is a general tendency that the support with higher O_{1s} binding energy gives higher yield, which indicates that the activity increase with basicity of the support.

With the optimized catalyst in hand, we examined the substrate scope of the dehydrogenative quinazolines syntheses. Table 5.2 shows the isolated yields of the 2-substituted quinazolines from the reaction of 1a with different primary alcohols using 1 mol% of Pt/CeO_2. Linear and branched aliphatic alcohols (entries 1-3) were converted to the corresponding 2-substituted quinazolines in good yields (75-89%). Benzylalcohol and 4-flourobenzylalcohol resulted in moderate yields (52 and 51%) respectively. This is the first example of the acceptorless dehydrogenative synthesis of 2-substituted quinazolines from 1a and various primary alcohols.

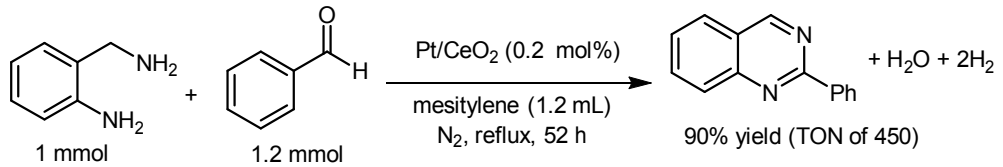
Next, we studied the dehydrogenative synthesis of 2-substituted quinazolines from 1a and aldehydes. Table 5.3 summarizes the result of catalyst screening for the model reaction of 1a and n-octanal. Among various metal-loaded CeO_2 (entries 1-8) and Pt-loaded metal oxides (entries 10-16), Pt/CeO_2, Pt/TiO_2 and Pt/La_2O_3 were found to be effective exhibiting high yields (95-99%) of 1a. On the basis of the results of preliminary studies on the aldehyde scope for this reaction, we selected Pt/CeO_2 as the standard

catalyst. The reaction with CeO_2 gave 20% yield of the non-dehydrogenated intermediate 2a but no yield of the dehydrogenated product 3a (entry 9).

Table 5.4 shows the general applicability of the dehydrogenative synthesis of 2-substituted quinazolines from 1a and aldehydes using 1 mol% of Pt/CeO_2. Various aliphatic aldehydes including linear, branched and cyclic aldehydes (entries 1-7) were converted to the 2-substituted quinazolines in moderate to high isolated yields (50-93%). The reactions of 1a and benzaldehydes with electron-donating and electron-withdrawing substituents proceeded to give moderate to high isolated yield (entries 8-11). For the reactions with n-octanal (eq. 1) and benzaldehyde (eq. 2), we carried out synthesis of 2-substituted quinazolines using small amount (0.2 mol%) of the Pt/CeO_2 catalyst for 52 h, and the results showed 95 and 90% yield, corresponding to the turnover number (TON) of 470 and 450. The TON of 450 for the reaction of 1a and benzaldehyde was higher than those of the previous catalytic systems in the presence of oxidants: TONs of 19 (CuCl/TEMPO/DABCO)[10], 26 ($[IrCp^*Cl_2]_2$/KOH)[12] and 190 (PI/CB-Pt/Ir/ TTSBI/ K_2CO_3)[11].



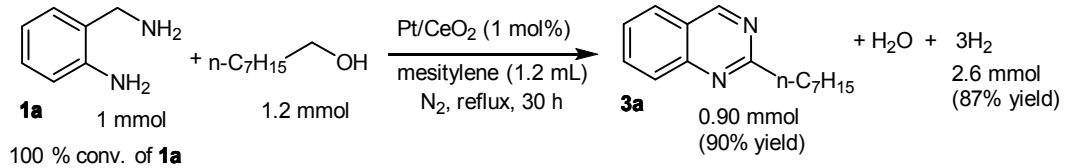
(1)

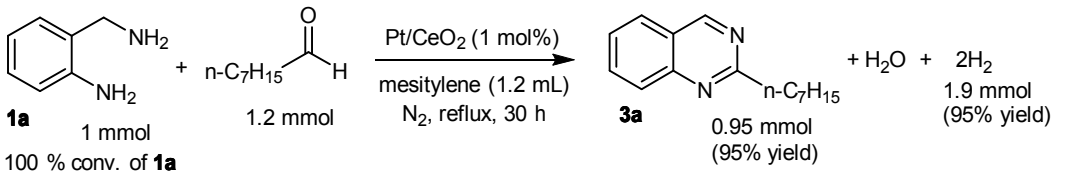


(2)

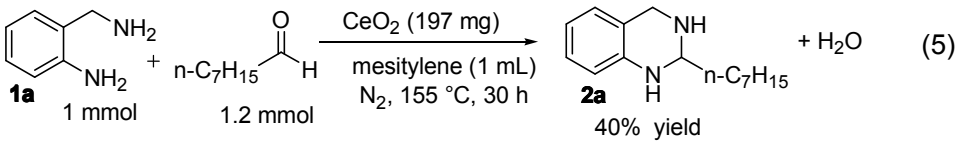
We studied leaching test and reusability of Pt/CeO_2 for the synthesis of 3a from 1a and n-octanal. The reaction was completely terminated by removal of the catalyst from the reaction mixture after 1 h (29% yield of 3a); further heating of the filtrate for 48 h under the reflux conditions did not increased the yield. ICP-AES analysis of the filtrate confirmed that the content of Pt in the solution was below the detection limit (10 ppb). Table 5.1 (entry 1) includes the result of catalyst recycles. After the first cycle, the catalyst was separated from the reaction mixture by centrifugation and was dried at 90 ºC for 3 h and then reduced in H_2 at 300 ºC for 0.5 h. The recovered catalyst showed high yield (90%) in the second and third cycles.

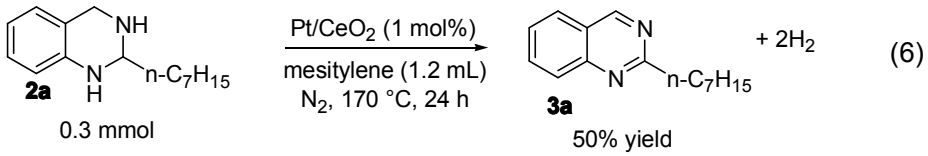
Finally, we carried out mechanistic studies to discuss a possible reaction pathway. We carried out mass spectrometry analysis of gas phase products for the reaction of **1a** with 1-octanol (eq. 3) and *n*-octanal (eq. 4). For the reaction of **1a** with 1-octanol (eq. 3), the yields of gas phase H_2 (87%) and **3a** (90%) were close to each other. For the reaction of **1a** with *n*-octanal (eq. 4), the yields of gas phase H_2 (95%) was identical to that of **3a** (95%). These results indicate that H_2 was generated quantitatively during the dehydrogenative coupling reactions.





The time-yield profiles for the reactions of **1a** with 1-octanol (Fig. 5.1) and **1a** with *n*-octanal (Fig. 5.2) showed typical features of consecutive reaction mechanism via intermediate **2a**; the yield of **2a** initially increased with time and then decreased accompanying increase in the yield of the final product **3a**. The reaction of **1a** and *n*-octanal at 155 °C in the presence of CeO_2 gave 40% yield of the cyclized intermediate **2a** which was isolated and identified by NMR and GCMS (eq. 5). The intermediate **2a** underwent dehydrogenation by Pt/CeO_2 under N_2 atmosphere to give the 2-substituted quinazoline **3a** in 50% yield (eq. 6).





From these results, we propose a plausible catalytic pathway of the synthesis of 2-substituted quinazolines from **1a** with alcohols or aldehydes in Scheme 1. The reaction begins with Pt-catalyzed dehydrogenation of alcohols to aldehydes with liberation of H_2.

Then, CeO_2-promoted condensation of aldehydes and 2-aminobenzylamine **1a** gives cyclized intermediates **2** which undergo Pt-catalyzed dehydrogenation to give 2-substituted quinazolines **3**. The mechanistic role of the basic site of the support is not clear. We speculate that the basic sites promote the dehydrogenation of alcohol (step 1) and **2** (step **3**) via deprotonation of these acidic molecules.

5.4 Conclusion

In summary we have developed the first acceptorless dehydrogenative synthesis of 2-substituted quinazolines from 2-aminobenzylamine and alcohols or aldehydes using Pt/CeO_2 as a reusable heterogeneous catalyst.

References

1. P. M. S. Bedi, V. Kumar and M. P. Mahajan, *Bioorg. Med. Chem. Lett*, 2004, **14**, 5211-5213.
2. T.-C. Chien, C.-S. Chen, F.-H. Yu and J.-W. Chern, *Chem. Pharm. Bull.*, 2004, **52**, 1422-1426.
3. P. Desai, B. Naik, C. M. Desai and D. Patel, *Asian J. Chem.*, 1998, **10**, 615-617.
4. E. A. Henderson, V. Bavetsias, D. S. Theti, S. C. Wilson, R. Clauss and A. L. Jackman, *Bioorg. Med. Chem.*, 2006, **14**, 5020-5042.
5. J. F. Mendes da Silva, M. Walters, S. Al-Damluji and C. R. Ganellin, *Bioorg. Med. Chem.*, 2008, **16**, 7254-7263.
6. H. A. III. Buris, *Oncologist*, 2004, **9**, 10-17.
7. J. J Vandeneynde, J. Godin, A. Mayence, A. Maquestiau and E. Anders, *Synthesis*, **1993** 867-869.
8. Y. Y. Peng, Y. Y. Zeng, G. Y. S. Qiu, L. S. Cai and V. W. Pike, *J. Heterocycl. Chem.*, 2010, **47**, 1240-1245.
9. C. U. Maheshwari, G. S. Kumar, M. Venkateshwar, R. A. Kumar, M. L. Kantam and K. R. Reddy, *Adv. Synth. Catal.*, 2010, **352**, 341-346.
10. B. Han, X. L. Yang, C. Wang, Y. W. Bai, T. C. Pan, X. Chen and W. Yu, *J. Org. Chem.*, 2012, **77**, 1136-1142.
11. H. Yuan, W. J. Yoo, H. Miyamura and S. Kobayashi, *Adv. Synth. Catal.*, 2012, **354**, 2899-2904.
12. J. Fang, J. Zhou and Z. Fang, *RSC. Adv.*, 2013, **3**, 334-336.
13. 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.
14. K. Kon, S. M. A. H. Siddiki and K. Shimizu, *J. Catal.*, 2013, **304** , 63-71.
15. S. M. A. H. Siddiki, K. Kon, A. S. Touchy, and K. Shimizu, *Catal. Sci. Technol.*, 2014, **4**, 1716-17198.
16. C. Chaudhari, S. M. A. H. Siddiki K. Kon, A. Tomita, Y. Tai, and K. Shimizu, *Catal. Sci. Technol.*, 2014, **4**, 1064-1069.

17. Y. Nagai, T. Hirabayashi, K. Dohmae, N. Takagi, T. Minami, H. Shinjoh and S. Matsumoto, *J. Catal.*, 2006, **242**, 103-109.
18. A. Y. Stakheev, Y. Zhang, A. V. Ivanov, G. N. Baeva, D. E. Ramaker and D. C. Koningsberger, *J. Phys. Chem. C*, 2007, **111**, 3938-3948.
19. K. Shimizu, K. Ohshima, Y. Tai, M. Tamura and A. Satsuma, *Catal. Sci. Technol.*, 2012, **2**, 730-738.

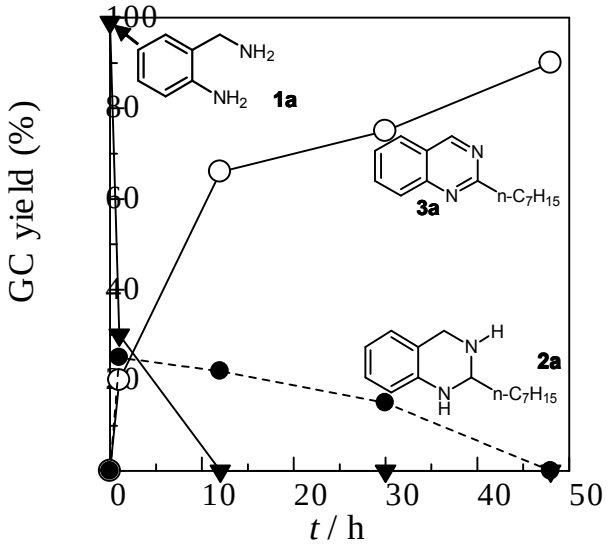


Figure 5.1 Time course of the reaction of **1a** with 1-octanol by Pt/CeO_2. Conditions are shown in Table 5.1.

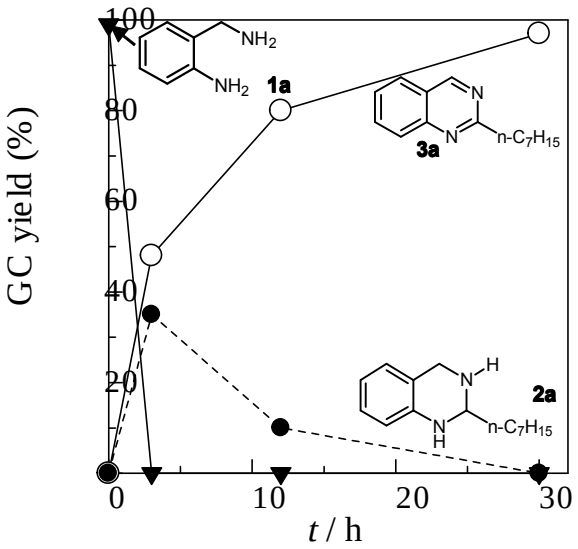


Figure 5.2 Time course of the reaction of **1a** with *n*-octanal by Pt/CeO_2. Conditions are shown in Table 5.3.

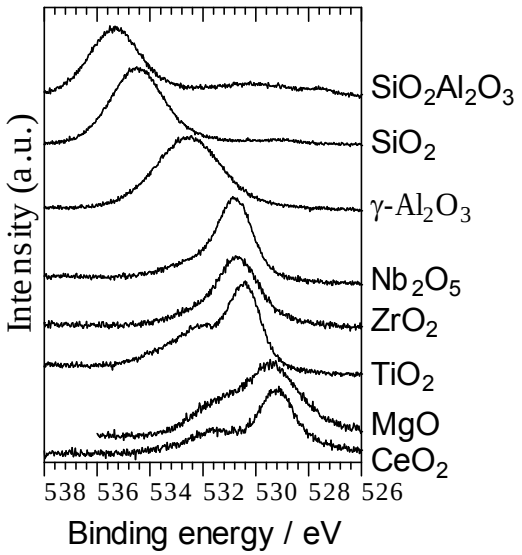


Figure 5.3 XPS spectra of the O(1s) core level region of the support materials.

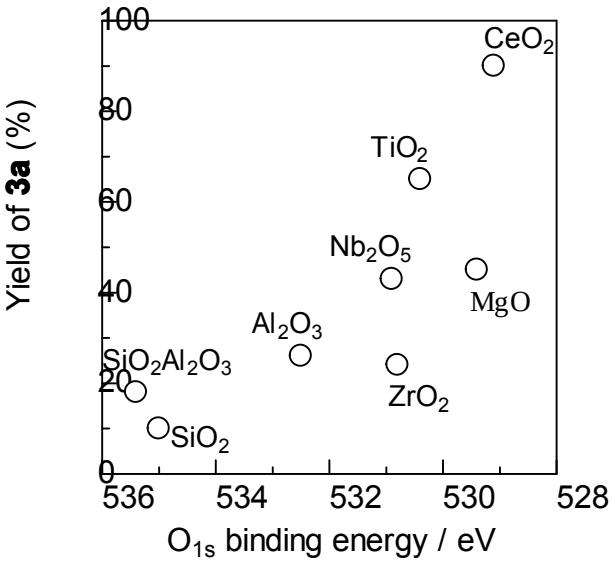
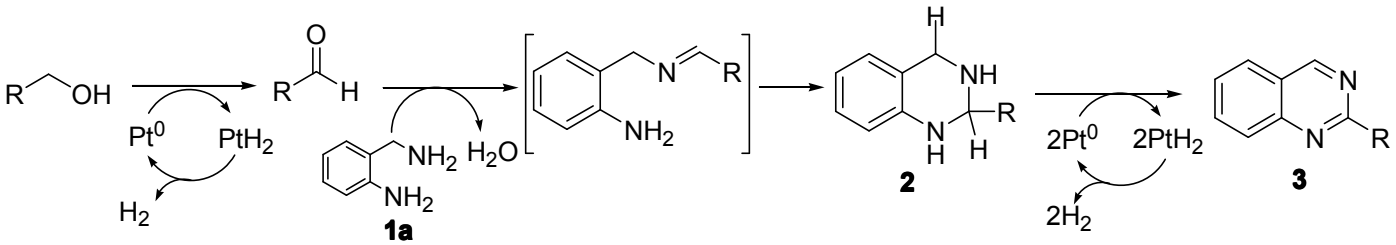
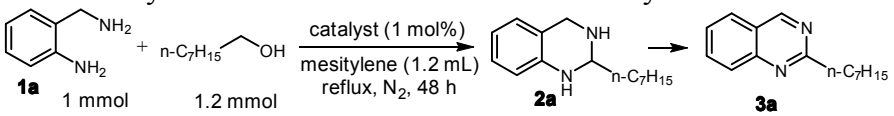


Figure 5.4 Yield of **3a** for the reaction of **1a** with *n*-octanal by Pt-loaded metal oxides as a function of O_{1s} binding energy of support oxides.



Scheme 5.1 A possible pathway of Pt/CeO_2-catalyzed dehydrogenative synthesis of quinazolines **3** from **1a** with alcohols or aldehydes.

Table 5.1 Synthesis of **3a** from **1a** and 1-octanol by 1wt% metal-loaded catalysts.



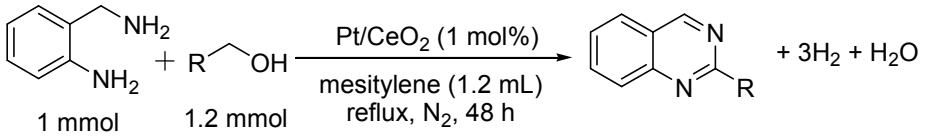
Entry	Catalysts	**2a** yield (%)	**3a** yield (%)[a]
1	Pt/CeO_2	0	90
2	Pd/CeO_2	0	17
3	Ir/CeO_2	20	16
4	Re/CeO_2	10	12
5	Rh/CeO_2	18	10
6	Ru/CeO_2	0	7
7	Cu/CeO_2	0	0
8	Ni/CeO_2	0	0
9[b]	PtO_x/CeO_2	0	0
10[c]	CeO_2	0	0
11	Pt/TiO_2	0	65
12	Pt/MgO	0	45
13	Pt/Nb_2O_5	30	43
14	Pt/Al_2O_3	20	26
15	Pt/ZrO_2	0	24
16	Pt/$SiO_2Al_2O_3$	0	18
17	Pt/SiO_2	0	10
18	Pt/HBEA	0	10
19	Pt/La_2O_3	0	10

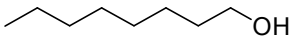
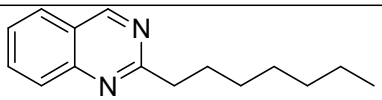
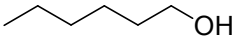
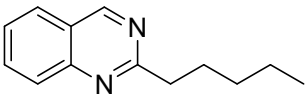
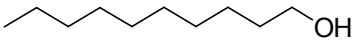
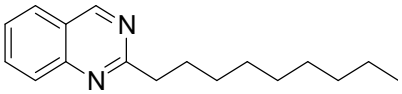
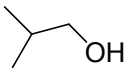
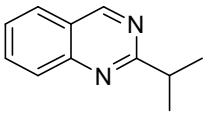
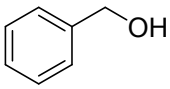
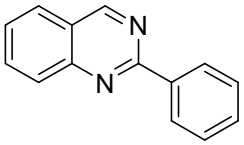
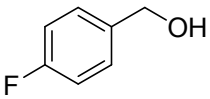
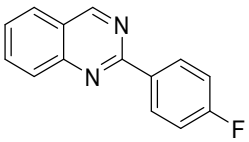
[a] Yield based on **1a** determined by GC.

[b] Tested without pre-reduction.

[c] Catalyst amount was 197 mg.

Table 5.2 Synthesis of 2-substituted quinazolines from **1a** and alcohols by Pt/CeO_2[a]

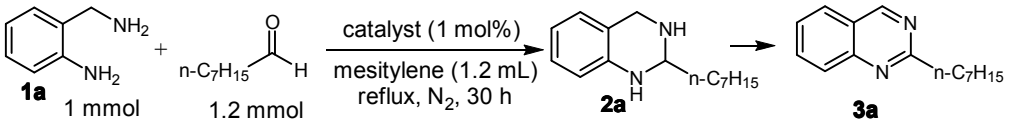


Entry	Alcohol	Product	Isolated yield (%)[a]
1			89
2			75
3			89
4[b]			76
5			52
6			51

[a] Yield based on **1a** determined by weight of the isolated products.

[b] 1.5 mmol alcohol.

Table 5.3 Synthesis of **3a** from **1a** and *n*-octanal with 1wt% metal loaded catalysts.

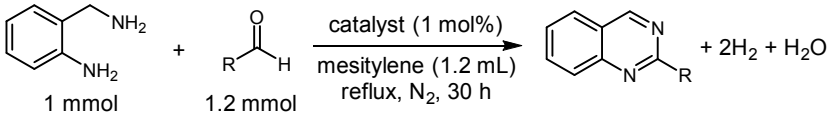


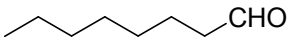
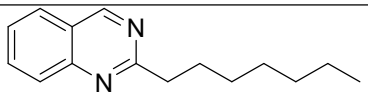
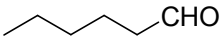
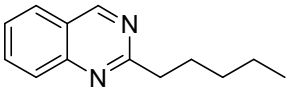
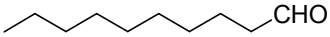
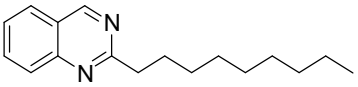
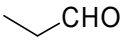
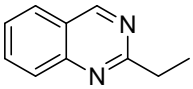
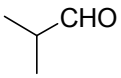
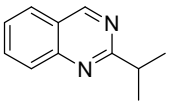
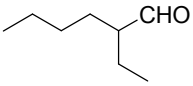
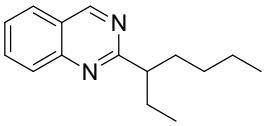
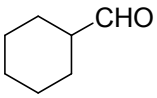
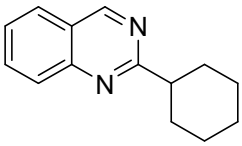
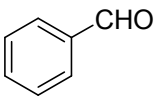
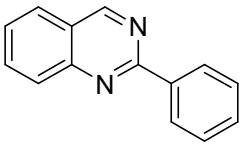
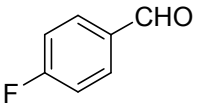
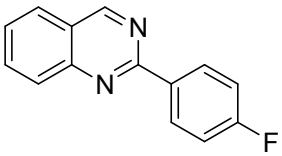
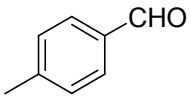
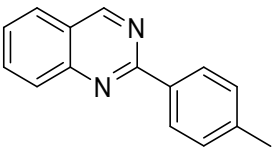
Entry	Catalysts	**2a** yield (%)	**3a** yield (%)[a]
1	Pt/CeO_2	0	98
2	Pd/CeO_2	0	60
3	Rh/CeO_2	17	55
4	Re/CeO_2	7	42
5	Ni/CeO_2	22	18
6	Ir/CeO_2	75	12
7	Ru/CeO_2	60	12
8	Cu/CeO_2	40	10
9[a]	CeO_2	20	0
10	Pt/TiO_2	0	99
11	Pt/MgO	29	56
12	Pt/Nb_2O_5	0	90
13	Pt/Al_2O_3	0	89
14	Pt/ZrO_2	0	70
15	Pt/HBEA	0	69
16	Pt/La_2O_3	0	95

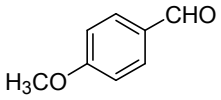
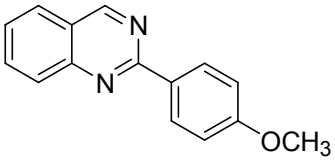
[a] Yield based on **1a** determined by GC.

[b] Catalyst amount was 197 mg.

Table 5.4 Synthesis of 2-substituted quinazolines from **1a** and aldehydes by Pt/CeO_2.



Entry	Aldehyde	Product	Isolated yield (%)[a]
1			93 (95), (90),[c] (90)[d]
2			70
3			92
4[b]			84
5[b]			88
6			50
7			72
8			85
9			77
10			90

11			57

[a] Yield based on **1a** determined by weight of the isolated products. GC yields are in the parentheses.

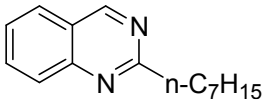
[b] 1.5 mmol aldehyde.

[c] Reuse 1

[d] Reuse 2

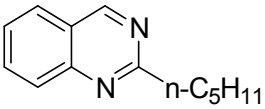
NMR and GCMS analysis

2-Heptyl-quinazoline (Table 5.2, entry 1 and Table 5.4, entry 1)



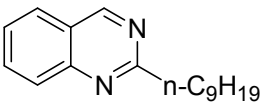
^{1}H NMR (600 MHz, $CDCl_3$) δ 9.31 (s, 1H), 7.94 (d, *J* = 8.22 Hz, 1H), 7.86-7.84 (m, 2H), 7.55 (d, *J* = 8.22 Hz, 1H), 3.08 (t, *J* = 7.56 Hz, 2H), 1.89-1.88 (m, 2H), 1.46-1.40 (m, 2H), 1.39-1.33 (m, 2H), 1.30-1.27 (m, 4H), 0.83 (t, *J* = 6.84 Hz, 3H) ppm; ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 167.9, 160.3, 150.3, 133.9, 127.8, 127.0, 126.9, 123.0, 40.0, 31.7, 29.5, 29.1, 29.0, 22.6, 14.0 ppm. GC-MS m/e 228.16.

2-Pentyl-quinazoline (Table 5.2, entry 2 and Table 5.4, entry 2)



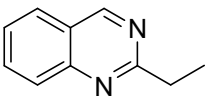
^{1}H NMR (600 MHz, $CDCl_3$) δ 9.33 (s, 1H), 7.95 (d, *J* = 7.56 Hz, 1H), 7.87-7.84 (m, 2H), 7.56 (t, *J* = 7.56 Hz, 1H), 3.09 (t, *J* = 7.68 Hz, 2H), 1.92-1.88 (m, 2H), 1.42-1.34 (m,4H), 0.88 (t, *J* = 6.84 Hz, 3H) ppm; ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 167.9, 160.3, 150.3, 134.0, 127.8, 127.0, 126.9, 123.0, 40.0, 31.7, 28.7, 22.5, 14.0 ppm. GC-MS m/e 200.13.

2-Nonyl-quinazoline (Table 5.2, entry 3 and Table 5.4, entry 3)



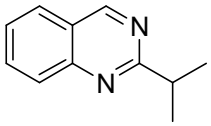
^{1}H NMR (600 MHz, $CDCl_3$) δ 9.27 (s, 1H), 7.91 (d, *J* = 8.22 Hz, 1H), 7.81-7.79 (m, 2H), 7.50 (t, *J* = 8.22 Hz, 1H), 3.06 (t, *J* = 7.56 Hz, 2H), 1.88-1.84 (m, 2H), 1.40-1.35 (m,2H), 1.32-1.27 (m, 2H), 1.22-1.18 (m, 8H), 0.81 (t, *J* = 7.56 Hz, 3H) ppm; ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 167.9, 160.3, 150.3, 133.9, 127.9, 127.0, 126.8, 123.0, 40.0, 31.9, 29.6, 29.6, 29.5, 29.5, 29.3, 22.6, 14.1 ppm. GC-MS m/e 256.19.

2-Ethyl-quinazoline (Table 5.4, entry 4)



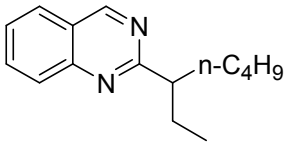
^{1}H NMR (600 MHz, $CDCl_3$) δ 9.34 (s, 1H), 7.96 (d, *J* = 8.22 Hz, 1H), 7.89-7.87 (m, 2H), 7.58 (t, *J* = 8.22, 1H), 3.06 (t, *J* = 7.56 Hz, 2H), 1.46 (t, *J* = 7.56 Hz, 3H) ppm; ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 168.5, 160.4, 150.3, 133.9, 127.8, 127.0, 126.8, 123.0, 33.0, 12.9 ppm. GC-MS m/e 158.08.

2-Isopropyl-quinazoline (Table 5.2, entry 4 and Table 5.4, entry 5)



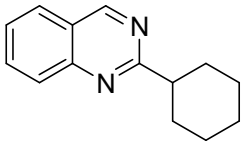
^{1}H NMR (600.17 MHz, $CDCl_3$) δ 9.29 (s, 1H), 7.91 (d, *J* = 8.28 Hz, 1H), 7.80-7.78 (m, 2H), 7.49 (t, *J* = 8.28 Hz, 1H), 3.36-3.32 (m, 1H), 1.39 (d, *J* = 6.90Hz, 6H) ppm; ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 171.7, 160.4, 150.3, 133.8, 128.0, 127.0, 126.8, 123.2, 37.9, 21.8 ppm. GC-MS m/e 172.10.

2-(1-Ethyl-pentyl)-quinazoline (Table 5.4, entry 6)



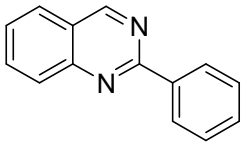
^{1}H NMR (600.17 MHz, $CDCl_3$) δ 9.38 (s, 1H), 8.00 (d, *J* = 8.28 Hz, 1H), 7.9-7.89 (m, 2H), 7.61 (t, *J* = 8.28 Hz, 1H), 3.01-2.99 (m, 1H), 1.93-1.90 (m 2H), 1.82-1.78 (m, 2H), 1.30-1.26 (m, 4H), 0.84-0.80 (m, 6H) ppm; ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 170.5, 160.4, 150.2, 133.8, 128.0, 127.0, 126.8, 123.2, 51.1, 34.5, 29.9, 28.0, 22.8, 14.0, 12.2 ppm. GC-MS m/e 228.16.

2-Cyclohexyl-quinazoline[1] (Table 5.4, entry 7)



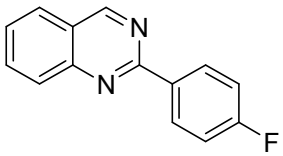
^{1}H NMR (600.17 MHz, $CDCl_3$) δ 9.35 (s, 1H), 7.97 (d, *J* = 8.28 Hz, 1H), 7.82-7.79 (m, 2H), 7.57 (t, *J* = 8.28 Hz, 1H), 3.07-3.03 (m, 1H), 2.03 (d, *J* = 11.08 Hz, 2H), 1.91-1.88 (m, 2H), 1.80-1.76 (m, 3H), 1.50-1.43 (m, 2H), 1.39-1.34 (m, 1H) ppm; ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 170.8, 160.3, 150.3, 133.8, 127.9, 127.0, 126.8, 123.2, 47.9, 31.9, 26.2, 26.0 ppm. GC-MS m/e 212.13.

2-Phenyl-quinazoline[1] (Table 5.2, entry 5 and Table 5.4, entry 8)



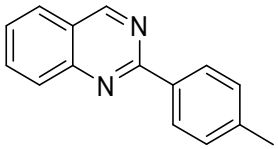
^{1}H NMR (600.17 MHz, $CDCl_3$) δ 9.45 (s, 1H), 8.64 (dd, *J* = 1.38 Hz, *J* = 1.38 Hz, 2H), 8.08 (d, *J* = 8.94 Hz, 1H), 7.88 (m, 2H), 7.60-7.51 (m, 4H) ppm; ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 169.9, 160.4, 150.6, 138.0, 134.0, 130.5, 128.6, 128.5, 127.2, 127.0, 123.5 ppm. GC-MS m/e 206.08.

2-(4-Fluoro-phenyl)-quinazoline[2] (Table 5.2, entry 6 and Table 5.4, entry 9)



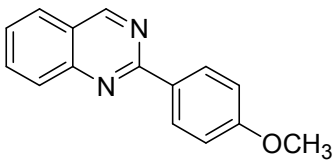
^{1}H NMR (600.17 MHz, $CDCl_3$) δ 9.42 (s, 1H), 8.64-8.61 (m, 2H), 8.05 (d, *J* = 8.94 Hz, 1H), 7.89 (t, *J* = 7.56 Hz, 2H), 7.51 (t, *J* = 7.44 Hz, 1H), 7.22-7.19 (m, 2H) ppm; ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 165.4 (d, *J* = 249.98 Hz, 4-F-C), 163.8, 160.4, 160.0, 150.6, 134.1, 130.6 (d, *J* = 8.66 Hz, meta to 4-F, C×2), 128.5 , 127.2, 127.1, 123.4, 115.6 (d, *J* = 21.67 Hz, ortho to 4-F, C×2) ppm. GC-MS m/e 224.07.

2-(p-Tolyl)-quinazoline[1] (Table 5.4, entry 10)



^{1}H NMR (600.17MHz, $CDCl_3$) δ 9.43 (s, 1H), 8.53 (d, *J* = 8.28 Hz, 2H), 8.06 (d, *J* = 8.28 Hz, 1H), 7.87 (m, 2H), 7.56 (t, *J* = 8.28 Hz, 1H), 7.35 (d, *J* = 8.28 Hz, 2H), 2.45 (s, 3H) ppm; ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 161.0, 160.3, 150.7, 140.8, 135.3, 133.9, 129.3, 128.5, 128.4, 127.0, 126.9, 123.4, 21.4 ppm. GC-MS m/e 220.10.

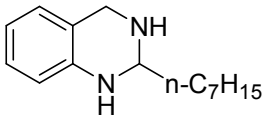
2-(4-Methoxy-phenyl)-quinazoline[1] (Table 5.4, entry 11)



^{1}H NMR (600.17 MHz, $CDCl_3$) δ 9.42 (s, 1H), 8.58 (d, *J* = 6.84 Hz, 2H), 8.04 (d, *J* = 8.28 Hz, 1H), 7.90-7.88 (m, 2H), 7.57 (t, *J* = 8.28 Hz, 1H), 7.05 (d, *J* = 6.84 Hz, 2H) 3.90 (s,

3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 161.8, 160.8, 160.3, 150.8, 134.0, 130.7, 130.1, 128.3, 127.1 126.7, 123.2, 113.9, 55.3. GC-MS m/e 236.09.

2-Heptyl-1,2,3,4-tetrahydro-quinazoline



^{1}H NMR (600.17 MHz, $CDCl_3$) δ 7.01 (t, *J* = 7.56 Hz, 1H), 6.89 (d, *J* = 7.56 Hz, 1H), 6.69-6.66 (m, 1H), 6.51 (d, *J* = 7.56 Hz, 1H), 4.14-4.12 (m, 2H), 3.94 (d, *J* =16.50 Hz, 1H), 1.64-1.58 (m, 2H), 1.53-1.48 (m, 1H), 1.47-1.42 (m, 1H), 1.35-1.27 (m, 10H), 0.91-0.88 (m, 3H); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 143.6, 127.1, 126.1, 121.6, 117.8, 114.8, 66.8, 46.5, 36.6, 31.7, 29.5, 29.1, 24.9, 22.6, 14.0. GC-MS m/e 232.19.

References for NMR assignment in Chapter 5

1 H. Yuan, W. J. Yoo, H. Miyamura and S. Kobayashi, *Adv. Synth. Catal.*, 2012, **354**, 2899.

2 B. Han, X. L. Yang, C. Wang, Y. W. Bai, T. C. Pan, X. Chen and W. Yu, *J. Org. Chem.*, 2012, **77**, 1136.

Chapter 6. Acceptorless dehydrogenative synthesis of benzothiazoles and benzimidazoles from alcohols or aldehydes by heterogeneous Pt catalysts under neutral conditions

6.1 Introduction

Benzazoles such as benzothiazoles and benzimidazoles are considered as important class of chemicals in medicinal chemistry. In particular, 2-substituted benzothiazoles and benzimidazoles are of importance due to their pharmacological and biological activities.[1] The conventional synthetic method of 2-substituted benzothiazoles or 2-substituted benzimidazoles involves condensation of 2-aminothiophenols or 1,2-phenylenediamines with carboxylic acids or their derivatives under acidic conditions or in the presence of dehydrating reagent. Although continuous efforts[2] have been focused on this method, it has serious drawbacks of low atom-efficiency and production of toxic salt wastes. The other important method is the condensation of aldehydes with 2-aminothiophenols or 1,2-phenylenediamines, followed by oxidation by oxidants (H_2-acceptor) such as crotononitrile,[3a] $(NH_4)_2S_2O_8$,[3b] I_2/KI,[3c] H_2O_2/CAN,[3d] polymer supported hypervalent iodine,[3e] or air.[4] However, most of the methods suffer from the use of stoichiometric amount of expensive oxidants,[3] which results in low atom-efficiency. Use of alcohols as starting materials is also attractive because of wide availability and stability of alcohols. The synthesis of 2-substituted benzothiazoles or 2-substituted benzimidazoles have been reported from 2-aminothiophenols or 1,2-phenylenediamines with alcohols using stoichiometric amount of oxidants (MnO_2,[5a] ®T3P/DMSO,[5b] IBX[5c]), H_2-acceptor,[3a] or air.[6] Use of 2-nitroanilines[7a] as a substrate and primary amines[7b] as alkylating reagents are also reported. The most attractive method is the direct synthesis of benzazoles using alcohols (or aldehydes) in the absence of oxidants via acceptorless dehydrogenative coupling.[8] Recently, homogeneous Ru,[8a-c] Ir[8d] and Fe[8e] catalysts and a heterogeneous Ru catalyst[8f] have been reported to be effective for the synthesis of benzazoles from alcohols under acceptor-free conditions. However, the homogeneous systems[8a-e] require more than stoichiometric amount of basic additives or excess amount of alcohols, which results in low atom-efficiency. As a part of our continuing interest in heterogeneous Pt catalysts for the acceptorless dehydrogenative coupling reactions using alcohols under acceptor-free and additive-free conditions,[9] we report herein the Pt catalyzed dehydrogenative synthesis of 2-substituted benzothiazoles and benzimidazoles directly from alcohols or aldehydes

under acceptor-free and additive-free conditions.

6.2 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

γ-Al_2O_3 was prepared by calcination of γ-AlOOH (Catapal B Alumina purchased from Sasol) at 900 °C for 3 h. TiO_2 (JRC-TIO-4), CeO_2 (JRC-CEO-3), MgO (JRC-MGO-3), H^+-type BEA zeolite (HBEA, SiO_2/Al_2O_3 = 25±5, JRC-Z-HB25) and SiO_2-Al_2O_3 (JRC-SAL-2, Al_2O_3 = 13.75 wt%) were supplied from Catalysis Society of Japan. ZrO_2 and La_2O_3 were prepared by calcination (500 °C, 3 h) of hydroxide of Zr and La, which were prepared by hydrolysis of $ZrO(NO_3)_2 \cdot 2H_2O$ and $La(NO_3)_3 \cdot 6H_2O$ with aqueous NH_4OH solution (1.0 mol dm^{-3}), followed by filtration of precipitate, washing with distilled water and drying at 100 °C for 12 h. Nb_2O_5 was prepared by calcination of niobic acid (CBMM) at 500 °C for 3 h. Precursor of 1 wt% Pt/Al_2O_3 or 1 wt% Pt/TiO_2 was prepared by impregnation method; a mixture of the support oxide 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. Pre-reduced catalyst, named Pt/Al_2O_3 and Pt/TiO_2, were prepared by reduction of the precursors in a pyrex tube under a flow of H_2 (20 cm^3 min^{-1}) at 500 °C for 0.5 h. By using various supports, several pre-reduced Pt catalysts (Pt = 1 wt%) were also prepared by the same method. Al_2O_3 or TiO_2-supported metal catalysts, M/Al_2O_3 or M/TiO_2 (M = Ni, Cu, Ru, Pd, Ag, Re and Ir) with metal loading of 1 wt% were prepared by impregnation method in a similar manner as Pt/Al_2O_3 or Pt/TiO_2 using aqueous solution of metal nitrates (Ni, Cu and Ag), $RuCl_3$, $IrCl_3$, NH_4ReO_4 or an aqueous HNO_3 solution of $Pd(NH_3)_2(NO_3)_2$ (Kojima Chemicals Co, Ltd.).

Catalyst test for 2-substituted benzothiazole

For the synthesis of 2-substituted benzothiazoles, Pt/Al_2O_3 (196 mg, 0.01 mmol of Pt) was used as the standard catalyst. After the pre-reduction at 500 °C, we carried out

catalytic tests using a batch-type reactor without exposing the catalyst to air as follows. A mixture of 2-aminothiophenol (1 mmol) and aldehydes or alcohols (1.2 mmol) with *n*-tetradodecane (0.2 mmol) in mesitylene (1.2 mL) was injected to the pre-reduced catalyst inside the reactor (cylindrical pyrex tube) through a septum inlet, followed by filling N_2. Then, the resulting mixture was magnetically stirred for 24 h for alcohols under reflux condition. The products were analyzed and confirmed by GC and GC-MS. The crude product was isolated by column chromatography using silica gel 60 (spherical, 63-210 μm, Kanto Chemical Co. Ltd.) with *n*-hexane/ethyl acetate as the eluting solvent, followed by analyses by GCMS and ^{1}H and ^{13}C NMR.

Catalyst test for 2-substituted benzimidazole

For the synthesis of 2-substituted benzimidazoles, Pt/TiO_2 (196 mg, 0.01 mmol of Pt) was used as the standard catalyst. The reaction procedure is the same as that for the synthesis of 2-substituted benzothiazoles.

NMR and GCMS analysis

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

6.3 Results and discussion

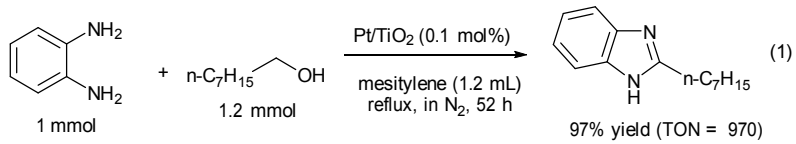
Initially, we investigated acceptorless synthesis of 2-substituted benzothiazole from 2-aminothiophenol and 1-octanol as a model reaction for optimization of catalysts and conditions. Note that previous successful catalytic systems[8b,e] for this reaction were not effective for the reaction with aliphatic alcohols probably because of low reactivity of them. Table 6.1 summarizes the results of the catalyst screening test under the same reaction conditions (reflux in mesitylene under N_2 for 24 h) using 1 mol% of transition metal (Pt, Pd, Ir, Cu, Re, Rh, Ru, Ag and Ni)-loaded Al_2O_3 pre-reduced under H_2 at 500 °C for 0.5 h. The Pt-loaded Al_2O_3 (Pt/Al_2O_3, entry 1) showed the highest yield (97%) of

2-substituted benzothiazole. Pd/Al_2O_3 (entry 2) gave good yield (89%), and the Ir, Cu, Re, Rh, Ru and Ag catalysts (entries 3-7) showed low to moderate yields (13%-57%) of the benzothiazole. Al_2O_3 (entry 10) and Ni/Al_2O_3 (entry 9) did not give the product. Then, we studied the support effect on the activity of Pt-loaded catalysts (entries 1, 10-17). Clearly, Al_2O_3 was the most effective support for this reaction, and Nb_2O_5, CeO_2, SiO_2-Al_2O_3, HBEA zeolite and La_2O_3 gave low to moderate yields (5-64%). The Pt catalysts loaded on MgO, ZrO_2, TiO_2 and SiO_2 did not give the benzothiazole. Consequently, we found that Pt/Al_2O_3 was the best catalyst for the synthesis of the benzothiazole from 2-aminothiophenol and 1-octanol. This is the first successful example of acceptorless dehydrogenative synthesis of 2-substituted benzothiazole from 2-aminothiophenol and less reactive aliphatic alcohol.

Table 6.2 shows general applicability of the dehydrogenative synthesis of 2-substituted benzothiazoles from 2-aminothiophenol and 1.2 equiv. of alcohols or aldehydes using Pt/Al_2O_3 containing 1 mol% of Pt with respect to 2-aminothiophenol. After 24 h of the reaction, the linear aliphatic alcohols (entries 1 and 2), benzyl alcohol (entry 3) were converted to the corresponding 2-substituted benzimidazoles with moderate to high yields. The method was also effective for the reaction with various aldehydes. After 3 h of the reaction, aliphatic aldehydes (entries 4 and 5), an aldehyde with C=C group (entry 6) and benzaldehydes (entries 7 and 8) reacted with 2-aminothiophenol to give the corresponding 2-substituted benzimidazoles with moderate to high yields.

Next, we studied the direct synthesis of 2-substituted benzimidazoles from 1,2-phenylenediamine and alcohols or aldehydes. We adopted the reaction of 1,2-phenylenediamine (1 mmol) with 1-octanol (1.2 mmol) as a model reaction, because only one catalytic method was reported to be effective for the reaction with aliphatic alcohols.[8d] Table 6.3 summarizes the results of the catalyst screening under the same conditions (reflux in mesitylene under N_2 for 24 h). The support screening tests for Pt catalysts showed that Pt/TiO_2 (entry 1) showed higher yield of the 2-substituted benzimidazole than the other Pt-loaded catalysts (entries 11-19). Then, we tested various transition metal-loaded TiO_2 catalysts.. Ir/TiO_2 gave good yield of 80%, and other catalysts gave moderate to low yields (entries 3-9). TiO_2 itself was inert (entry 10). From

these results, Pt/TiO_2 was found to be the most effective catalyst for the dehydrogenative synthesis of the 2-substituted benzimidazole from 1,2-phenylenediamine and 1-octanol. As shown in the eqn. (1), the reaction with 0.1 mol% of the Pt/TiO_2 catalyst for 52 h resulted in 97% yield, corresponding to the turnover number (TON) of 970. The TON of 970 is more than 2 times higher than the state-of-the-art system using a homogeneous Ir catalyst with KO^{t}Bu reported by Kempe and co-workers.[8d]



(1)

With the most effective catalyst, Pt/TiO_2, we investigated substrate scope of the dehydrogenative benzimidazoles synthesis. Table 4 shows the yields of the 2-substituted benzimidazoles from the reaction of 1,2-phenylenediamine with 1.2 equiv. of alcohols or aldehydes using 1 mol% of Pt/TiO_2. Aliphatic alcohols (entries 1-3), an aliphatic aldehyde (entry 4), benzaldehydes (entries 4 and 5) and pyridine-3-carbaldehyde were converted to the desired 2-substituted benzimidazoles in good to high yields.

Considering to the previous reports on acceptorless dehydrogenative synthesis of benzazole derivatives from alcohols [8] and our reports on acceptorless dehydrogenative coupling reactions by heterogeneous Pt catalysts,[9] the present system can proceed via a pathway shown in Scheme 1. The reaction begins with Pt-catalyzed dehydrogenation of alcohols to aldehydes, which undergoes condensation with 2-aminothiophenol or 1,2-phenylenediamine to afford saturated intermediates **2** via imine **1**. Finally, Pt-catalyzed dehydrogenation of **2** gives the unsaturated product **3**. A kinetic study under the conditions in Table 6.4 (entries 1 and 4) showed that the initial formation rate of the benzothiazole by the Pt/TiO_2–catalyzed reaction of 1,2-phenylenediamine with *n*-octanal was 1.7 times higher than that with 1-octanol. This result is consistent with the proposed pathway assuming that the dehydrogenation of alcohols is a relatively slow step.

6.4 Conclusion

In summary, we have developed two heterogeneous catalytic systems for the acceptorless dehydrogenative synthesis of 2-substituted benzazoles under additive-free (neutral) conditions. Pt/Al_2O_3 is effective for synthesis of 2-substituted benzothiazoles

from 2-aminothiophenol and alcohols/aldehydes, and Pt/TiO_2 is effective for synthesis of 2-substituted benzimidazoles from 2-phenylenediamine and alcohols/aldehydes.

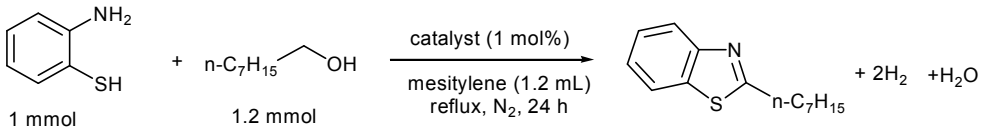
References

1. (a) A. A. Weekes and A. D. Westwell, *Curr. Med. Chem.*, 2009, **16**, 2430–2440; (b) D. A. Horton, G. T. Bourne and M. L. Smythe, *Chem. Rev.*, 2003, **103**, 893–930; (c) T. C. Kuhler, M. Swanson, V. Shcherbuchin, H. Larsson, B. Mellgard and J. E. Sjostrom, *J. Med. Chem.*, 1998, **41**, 1777–1788; (d) M. J. Catob, A. Jovanovskab, M. O. Urbanb, M. Leitlb, R. H. Spencerb, S. A. Kaneb, G. D. Hartmana and M. T. Bilodeaua, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 4059–4063.
2. (a) V. K. Tandon and M. Kumar, *Tetrahedron Lett.*, 2004, **45**, 4185–4187; (b) G. M. Raghavendra, A. B. Ramesha, C. N. Revanna, K. N. Nandeesh, K. Mantelingu and K.S. Rangappa, *Tetrahedron Lett.*, 2011, **52**, 5571–5574; (c) Y. K. Bommegowda, G. S. Lingaraju, S. Thamas, K. S. V. Kumar, C. S. P. Kumara, K. S. Rangappa, M. P. Sadashiva, *Tetrahedron Lett.*, 2013, **54**, 2693–2695; (d) T. B. Nguyen, L. Ermolenko, W. A. Dean, A. Al-Mourabit, *Org. Lett.*, 2012, **14**, 5948–5951; (e) J. A. Seijas, M. P. V. Tato, M. R. C. Reboredo, J. C. Campo and L. R. López, *Synlett.*, 2007, 313–317; (f) T. Hisano, M. Ichikawa, K. Tsumoto and M. Tasaki, *Chem. Pharm. Bull.,* 1982, **30**, 2996–3004; (g) R. N. Nadaf, S. A. Siddiqui, T. Daniel, R. J. Lahoti and K.V. Srinivasan, *J. Mol. Catal. A*, 2004, **214**, 155–160; (h) H. Hikawa, M. Imani, H. Suzuki, Y. Yokoyama and I. Azumaya, *RSC Adv.*, 2014, **4**, 3768–3773.
3. (a) A. J. Blacker, M. M. Farah, M. I . Hall, S. P. Marsden, O. Saidi and J. M. J. Williams, *Org. Lett.*, 2009, **9**, 2039-2042; (b) K. Bahrami, M. M. Khodaei and A. Nejati, *Green Chem*,. 2010, **12**, 1237–1241; (c) P. Gogoi and D. Konwar *Tetrahedron Lett.,* 2006, **47**, 79-82; (d) K. Bahrami, M. M. Khodaei and F. Naali, *J. Org. Chem*. 2008, **17**, 6835–6837; (e) A. Kumar, R. A. Maurya and Pervez Ahmad, *J. Comb. Chem.*, 2009, **11**, 198–201; (f) B. Das, H. Holla and Y. Srinivas, *Tetrahedron Lett.*, 2007, **48**, 61–64.
4. (a) M. A. Chari, D. Shobha, and T. Sasaki, *Tetrahedron Lett.*, 2011, **52**, 5575–5580; (b) G. F. Chen, H. M. Jia, L.Y. Zhang, B. H. Chen and J. T. Li, *Ultrason. Sonochem.,* 2013, **20**, 627–632; (c) R. Shelkar, S. Sarode and J. Nagarkar, *Tetrahedron Lett.*, 2013, **54**, 6986–6990.
5. (a) C. D. Wilfred and R. J. K. Taylor, *Synlett.,* 2004, 1628–1630; (b) G. M. Raghavendra, A. B. Ramesha, C. N. Revanna, K. N. Nandeesh, K. Mantelingu and

K.S. Rangappa, *Tetrahedron Lett.*, 2011, **52**, 5571–5574; (c) Y. P. Zhu, F. C. Jia, M. C. Liu and A. X. Wu, *Org. Lett.*, 2012, **14**, 4414–4417.

6. (a) J. W. Kim, J. He, K. Yamaguchi and N. Mizuno, *Chem. Lett.*, 2009, **38**, 920–921; (b) V. R. Ruiz, A. Corma and M. J. Sabater, *Tetrahedron*, 2010, **66**, 730–735; (c) J. Yu, J. Xu and M. Lu, *Appl. Organometal. Chem.*, 2013, **27**, 606–610.
7. (a) L. De Luca and A. Porcheddu, *Eur. J. Org. Chem.*, 2011, 5791–5795; (b) G. Li, J. Wang, B. Yuan, D. Zhang, Z. Lin, P. Li, H. Huang, *Tetrahedron Lett.*, 2013, **54**, 6934–6936; (c) M. Pizzetti, E. De Luca, E. Petricci, A. Porcheddu and M. Taddei, *Adv. Synth. Catal.* 2012, **354**, 2453–2464.
8. (a) T. Kondo, S. Yang, K. T. Huh, M. Kobayashi, S. Kotachi and Y. Watanabe, *Chem. Lett.*, 1991, 1275–1278; (b) R. Ramachandran, G. Prakash, S. Selvamurugan, P. Viswanathamurthi, J. G. Malecki and V. Ramkumar, *Dalton Trans.,* 2014, **43**, 7889–7902; (c) A. Khalafi-Nezhad and F. Panahi, *ACS Catal.*, 2014, **4**, 1686−1692; (d) T. Hille, T. Irrgang and R. Kempe, *Chem. Eur. J.*, 2014, **20**, 5569–5572; (e) M. Bala, P. K. Verma, U. Sharma, N. Kumar and B. Singh, *Green Chem.*, 2013, **15**, 1687–1693; (f) K. Wada, Abstract in the 16th International Symposium on Relations between Homogeneous and Heterogeneous Catalysis, 2013.
9. (a) S. M. A. H. Siddiki, K. Kon, A. S. Touchy and K. Shimizu, *Catal. Sci. Technol.*, 2014, **4**, 1716–1719; (b) S. K. Moromi, S. M. A. H. Siddiki, M. A. Ali, K. Kon and K. Shimizu, *Catal. Sci. Technol.*, 2014, **4**, 3631–3635.

Table 6.1 Synthesis of benzothiazole from 2-aminothiophenol and 1-octanol with various catalysts.

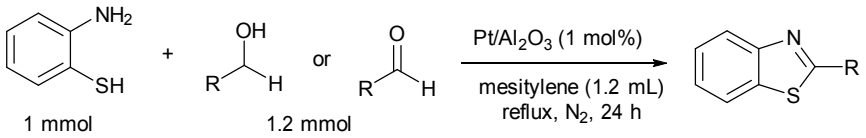


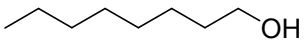
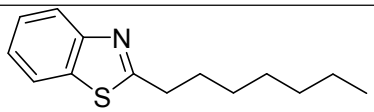
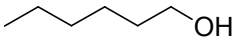
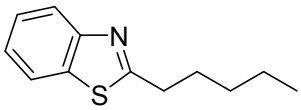
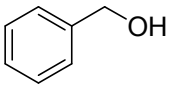
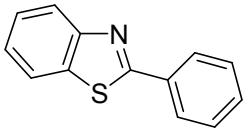
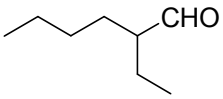
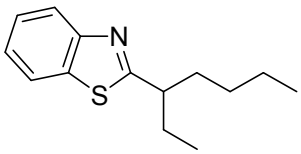
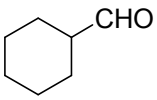
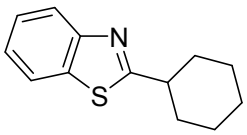
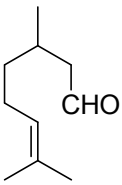
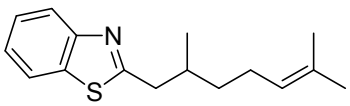
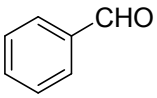
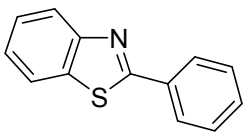
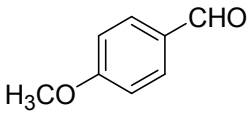
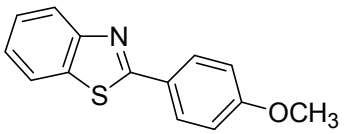
Entry	Catalysts	Yield (%)[a]
1	Pt/Al_2O_3	97
2	Pd/Al_2O_3	89
3	Ir/Al_2O_3	57
4	Cu/Al_2O_3	48
5	Re/Al_2O_3	46
6	Rh/Al_2O_3	44
7	Ru/Al_2O_3	34
8	Ag/Al_2O_3	13
9	Ni/Al_2O_3	0
10[b]	Al_2O_3	0
11	Pt/Nb_2O_5	64
12	Pt/CeO_2	19
13	Pt/SiO_2-Al_2O_3	12
14	Pt/HBEA	10
15	Pt/La_2O_3	5
16	Pt/MgO	0
17	Pt/ZrO_2	0
18	Pt/TiO_2	0
19	Pt/SiO_2	0

[a] Yield based on 2-aminothiophenol determined by GC.

[b] Catalyst amount was 197 mg.

Table 6.2 Synthesis of 2-substituted benzothiazole from 2-aminothiophenol with alcohols or aldehydes by Pt/Al_2O_3.

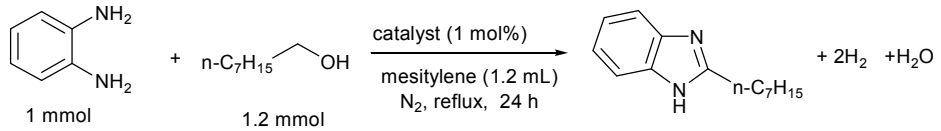


Entry	Alcohol/Aldehyde	Product	Yield (%)[a]
1			97 (90)
2			73 (68)
3			60 (55)
4[b]			65 (61)
5[b]			82 (71)
6[b]			85 (76)
7[b]			93 (89)
8[b]			50 (55)

[a] GC yield based on 2-aminothiophenol. Isolated yield is in the parentheses.

[b] 3 h.

Table 6.3 Synthesis of benzimidazole from 1,2-phenylenediamine and 1-octanol with various catalysts.

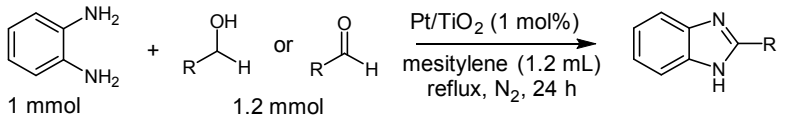


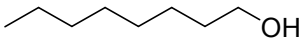
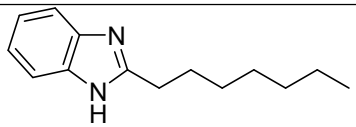
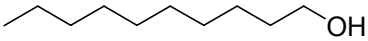
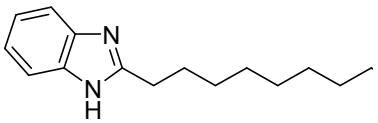
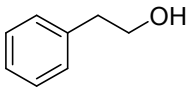
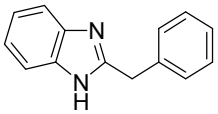
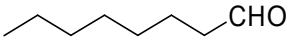
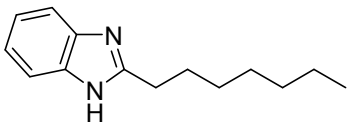
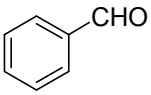
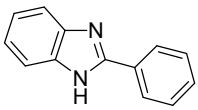
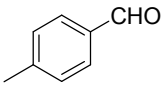
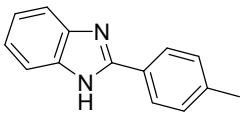
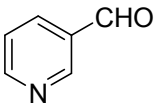
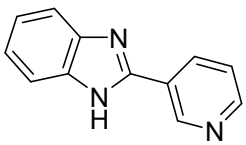
Entry	Catalysts	Yield (%)[a]
1	Pt/TiO_2	94
2	Ir/TiO_2	80
3	Pd/TiO_2	45
4	Rh/TiO_2	34
5	Ru/TiO_2	7
6	Re/TiO_2	0
7	Ag/TiO_2	0
8	Cu/TiO_2	0
9	Ni/TiO_2	0
10[b]	TiO_2	0
11	Pt/ZrO_2	60
12	Pt/La_2O_3	46
13	Pt/Al_2O_3	30
14	$Pt/SiO_2\text{-}Al_2O_3$	20
15	Pt/MgO	0
16	Pt/HBEA	0
17	Pt/Nb_2O_5	0
18	Pt/CeO_2	0
19	Pt/SiO_2	0

[a] Yield based on 1,2-phenylenediamine determined by GC.

[b] Catalyst amount was 197 mg.

Table 6.4 Synthesis of 2-substituted benzimidazole from 1,2-phenylenediamine and alcohols/aldehydes by Pt/TiO_2.

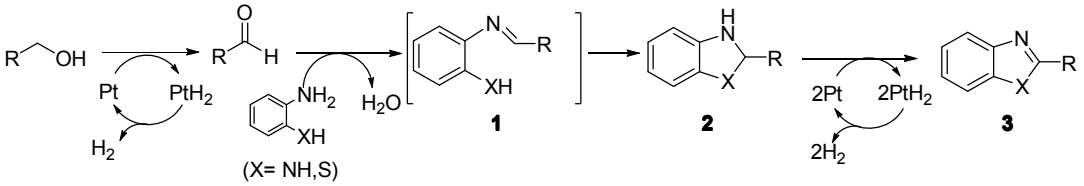


Entry	Alcohol/Aldehyde	Product	Yield (%)[a]
1			94 (87)
2			90 (82)
3			70 (60)
4[b]			95 (90)
5[c]			85(78)
6[c]			80 (75)
7[c]			60 (54)

[a] GC yield based on1,2-phenylenediamine. Isolated yield is in the parentheses.

[b] 14 h.

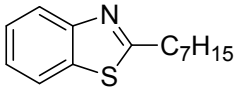
[c] 1 h.



Scheme 6.1 A plausible mechanism for the synthesis of benzimidazoles and benzothiazoles.

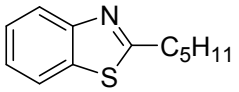
NMR and GCMS analysis

2-Heptyl-benzothiazole[1] (Table 6.2, entry 1)



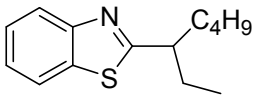
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.28 Hz, 1H), 7.95 (d, *J* = 8.28 Hz, 1H), 7.49 (t, *J* = 8.28 Hz, 1H), 7.41 (t, *J* = 8.28 Hz, 1H), 3.10 (t, *J* = 7.56 Hz, 2H), 1.83-1.79 (m, 2H), 1.39-1.25 (m, 8H), 0.86 (t, *J* = 6.84 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.5, 152.8, 134.6, 125.8, 124.6, 122.0, 121.8, 33.3, 31.1, 28.9, 28.3, 28.3, 22.0, 13.8 ppm. GC-MS m/e 233.

2-Pentyl-benzothiazole[2] (Table 6.2, entry 2)



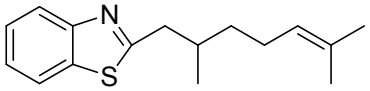
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.28 Hz, 1H), 7.36 (d, *J* = 8.28 Hz, 1H), 6.91 (t, *J* = 8.28 Hz, 1H), 6.83 (t, *J* = 8.28 Hz, 1H), 2.52 (t, *J* = 7.56 Hz, 2H), 1.26-1.23 (m, 2H), 0.80-0.79 (m, 4H), 0.31 (t, *J* = 6.90 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.7, 152.8, 134.6, 125.9, 124.7, 122.1, 122.0, 33.3, 30.6, 28.6, 21.7, 13.8 ppm. GC-MS m/e 205.

2-(1-Ethyl-pentyl)-benzothiazole[3] (Table 6.2, entry 4)



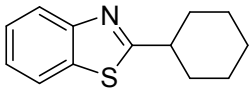
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.22 Hz, 1H), 7.97 (d, *J* = 8.22 Hz, 1H), 7.49 (t, *J* = 8.22 Hz, 1H), 7.41 (t, *J* = 8.22 Hz, 1H), 3.09-3.06 (m, 1H), 1.81-1.74 (m, 4H), 1.32-1.25 (m, 4H), 0.90-0.82 (m, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.8, 152.6, 134.1, 125.8, 124.8, 122.0, 122.1, 45.8, 34.9, 28.7, 28.6, 22.1, 13.7, 11.6 ppm. GC-MS m/e 233.

2-(2,6-Dimethyl-hept-5-enyl)-benzothiazole (Table 6.2, entry 5)



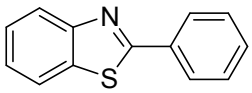
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.22 Hz, 1H), 7.96 (d, *J* = 8.22 Hz, 1H), 7.50 (t, *J* = 8.22 Hz, 1H), 7.42 (t, *J* = 8.22 Hz, 1H), 5.09 (t, *J* = 7.50 Hz, 1H), 3.14-3.11 (m, 1H), 2.97-2.93 (m, 1H), 2.10-1.99 (m, 3H), 1.67 (s, 3H), 1.59 (s, 3H), 1.46-1.41 (m, 1H), 1.31-1.25 (m, 1H), 0.97 (d, *J* = 6.84 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.4, 152.8, 134.7, 130.7, 125.8, 124.6, 124.1, 122.1, 121.8, 40.4, 36.0, 33.2, 25.4, 24.8, 19.1, 17.4 ppm. GC-MS m/e 273.

2-Cyclohexyl-benzothiazole[1] (Table 6.2, entry 6)



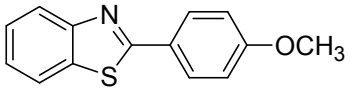
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.28 Hz, 1H), 7.38 (d, *J* = 8.28 Hz, 1H), 6.91 (t, *J* = 8.28 Hz, 1H), 6.83 (t, *J* = 8.28 Hz, 1H), 1.54 (d, *J* = 11.7 Hz, 2H), 1.22 (d, *J* = 12.36 Hz, 2H), 1.11 (d, *J* = 12.36 Hz, 1H), 1.04-0.96 (m, 3H), 0.88-0.72 (m, 2H), 0.73-0.69 (m, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.5, 152.6, 134.0, 125.9, 124.6, 122.2, 122.0, 42.3, 32.7, 25.3,25.3 ppm. GC-MS m/e 217.

2-Phenyl-benzothiazole[1] (Table 6.2, entries 3 and 7)



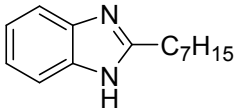
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.22 Hz, 1H), 8.11-8.06 (m, 3H), 7.59-7.54 (m, 5H), 7.46 (t, *J* = 8.22 Hz, 1H) ppm;^{13}C NMR (150 MHz, $CDCl_3$) δ 167.2, 153.5, 134.4, 132.8, 131.4, 129.4, 127.2, 126.6, 125.5, 122.8, 122.3 ppm. GC-MS m/e 211.

2-(4-Methoxy-phenyl)-benzothiazole[1] **(Table 6.2, entry 8)**



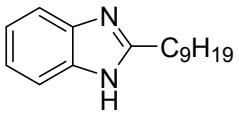
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.22 Hz, 1H), 8.11-8.06 (dd, *J* = 8.22 Hz, 3H), 6.70 (t, *J* = 8.22 Hz, 1H), 6.61 (t, *J* = 8.22 Hz, 1H),6.31 (d, *J* = 8.88 Hz, 2H), 3.09 (s, 3H) ppm;^{13}C NMR (150 MHz, $CDCl_3$) δ 167.0, 161.7, 153.6, 134.2, 128.8, 126.5, 125.5, 125.0, 122.4, 122.1, 114.7, 55.4 ppm. GC-MS m/e 241.

2-Heptyl-1*H*-benzoimidazole[3] **(Table 6.4, entry 1)**



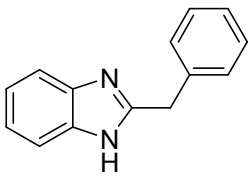
^{1}H NMR (600 MHz, $CDCl_3$) δ 12.2 (bs, 1H), 7.43 (brs, 2H), 7.12 (d, *J* = 4.80 Hz, 2H), 2.81 (t, *J* = 8.22 Hz, 2H), 1.80-1.76 (m, 2H), 1.34-1.28 (m, 8H), 0.87 (t, *J* = 7.50 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.6, 143.8, 134.7, 121.7, 121.3, 118.5, 111.1, 31.7, 29.1, 29.0, 28.9, 28.1, 22.6, 14.4 ppm. GC-MS m/e 216.

2-Nonyl-1*H*-benzoimidazole[3] **(Table 6.4, entry 2)**



^{1}H NMR (600 MHz, $CDCl_3$) δ 12.91 (bs, 1H), 7.53 (d, *J* = 6.84 Hz, 1H), 7.42 (d, *J* = 6.90 Hz, 1H), 7.14-7.11 (m, 2H), 2.80 (t, *J* = 7.56 Hz, 2H), 1.80-1.78 (m, 2H), 1.33-1.26 (m, l2H), 0.86 (t, *J* = 6.84 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.6, 143.3, 134.7, 121.8, 121.2, 118.5, 111.1, 31.8, 29.4, 29.2, 29.2(2C), 29.0, 28.1, 22.6, 14.4 ppm. GC-MS m/e 259.

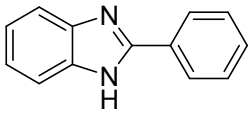
2-Benzyl-1*H*-benzoimidazole[5]**(Table 6.4, entry 3)**



^{1}H NMR (600 MHz, $CDCl_3$) δ 12.36 (bs, 1H), 8.21 (d, *J* = 7.38 Hz, 2H), 7.71-7.70 (m, 1H), 7.60-7.56 (m, 3H), 7.54-7.52 (m, 1H), 7.26-7.23 (m, 2H), 4.18 (s, 2H) ppm; ^{13}C

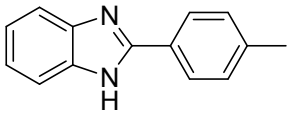
NMR (150 MHz, $CDCl_3$) δ 154.1, 138.2, 129.4 (2C), 129.2, 129.0, 127.1, 121.5, 35.4 ppm. GC-MS m/e 208.

2-Phenyl-1*H*-benzoimidazole[5] (Table 6.4, entry 4)



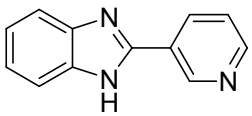
^{1}H NMR (600 MHz, $CDCl_3$) δ 12.96 (bs, 1H), 8.21 (d, *J* = 7.38 Hz, 2H), 7.71-7.70 (m, 1H), 7.60-7.56 (m, 3H), 7.54-7.52 (m, 1H), 7.26-7.23 (m, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 151.8, 144.4, 135.6, 130.7, 130.5, 130.4, 130.1, 129.5, 127.0, 123.1, 122.2, 119.4, 111.9 ppm. GC-MS m/e 194.

2-p-Tolyl-1*H*-benzoimidazole[5] (Table 6.4, entry 5)



^{1}H NMR (600 MHz, $CDCl_3$) δ 12.88 (bs, 1H), 8.10 (d, *J* = 8.28 Hz, 2H), 7.67-7.54 (bs, 2H), 7.38 (d, *J* = 7.44 Hz, 2H), 7.24-7.21 (m, 2H), 3.39 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 151.9, 140.0, 130.0 129.8 (2C), 127.9, 126.8 (3C), 122.8, 122.0, 119.1, 111.6, 21.5 ppm. GC-MS m/e 208.

2-Pyridin-3-yl-1*H*-benzoimidazole[6] (Table 6.4, entry 6)



^{1}H NMR (600 MHz, $CDCl_3$) δ 13.16 (bs, 1H), 8.21 (d, *J* = 1.62 Hz, 1H), 8.72-8.70 (m, 1H), 8.55-8.53 (m, 1H), 7.74 (d, *J* = 8.28 Hz, 1H), 7.64-7.59 (m, 2H), 7.34-7.26 (m, 2H) ppm ; ^{13}C NMR (150 MHz, $CDCl_3$) δ 151.8, 149.3, 148.0, 144.2, 135.4, 134.2, 126.6, 124.5, 123.5, 122.5, 119.6, 112.0 ppm. GC-MS m/e 185.

References for NMR assignment in Chapter 6

1. C. Yu, K. Lee, Y. You and E. J. Cho, *Adv. Synth. Catal.*, 2013, **355**, 1471-1476.
2. M. Zhang, W. T. Lu, W. Ruan, H.J. Zhang, T. B. Wen, *Tetrahedron Lett.*, 2014, **55**, 1806-1809.

3. A. Ghaderi, T. Iwasaki, A. Fukuoka, J. Terao and N. Kambe, *Chem. Eur. J.*, 2013, **19**, 2951-2955.
4. J. Shea, Z. Jianga, and Y. Wang, *Synlett.,* 2009, **12**, 2023-2027.
5. R. G. Xing, Y. N. Li, Q. Liu, Q. Y. Meng, J. Li, X. X. Shen, Z. Liu, B. Zhou, X. Yao and Z. Li. Liu, *Eur. J. Org. Chem.,* 2010, **34**, 6627–6632.
6. G. Naresh, R. Kant and T. Narender, *J. Org. Chem.*, 2014, **79**, 3821–3829.

Chapter 7. General conclusion

Heterogeneously Pt catalyzed direct C-C and C-N bond formation reaction by borrowing hydrogen and acceptorless dehydrogenation methodology give atom efficient routes to valuable chemicals from alcohols under neutral conditions. Chapter 2-6 show the first examples of heterogeneous catalysis for the synthesis of chemicals from alcohols via alkylation of nucleophiles under additive-free conditions. Contrary to organometallic catalysis, heterogeneous Pt catalysts do not requires additives (ligand, acid or base) which increases atom economy. The borrowing hydrogen methodology includes dehydrogenation-condensation-hydrogenation sequence and acceptorless dehydrogenation is combination of dehydrogenation-condensation and cyclization-dehydrogenation steps. The multifunctionality of the metal-loaded basic metal oxide is a key concept in the catalyst design in which the acid and/or base sites on support help selective catalyzes condensation reaction and metal site catalyzes transfer dehydrogenation of alcohol and transfer hydrogenation of condensed intermediate product in borrowing hydrogen methodology. In acceptorless dehydrogenation methodology, metal oxide support catalyzes selective condensation and cyclization reaction and metal sites catalyzes dehydrogenation of alcohol to carbonyl compound as well as dehydrogenation of cyclized intermediate to aromatic product. Both methodologies does not require oxidant or reductants.

The multistep and cascade reactions have been widely performed by homogeneous catalysts using additives. 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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