

# Article

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ACS Catal., Just Accepted Manuscript • DOI: 10.1021/acscatal.8b02814 • Publication Date (Web): 10 Oct 2018 Downloaded from http://pubs.acs.org on October 10, 2018

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# Acceptorless Dehydrogenative Synthesis of Pyrimidines from Alcohols and Amidines Catalyzed by Supported Pt Nanoparticles

Sharmin Sultana Poly,<sup>†</sup> S. M. A. Hakim Siddiki,<sup>\*†</sup> Abeda S. Touchy,<sup>†</sup> Kah Wei Ting,<sup>†</sup> Takashi Toyao,<sup>†,‡</sup> Zen Maeno,<sup>†</sup> Yasuharu Kanda,<sup>§</sup> Ken-ichi Shimizu<sup>\*†,‡</sup>

<sup>†</sup> Institute for Catalysis, Hokkaido University, N-21, W-10, Sapporo 001-0021, Japan
<sup>‡</sup> Elements Strategy Initiative for Catalysts and Batteries, Kyoto University, Katsura, Kyoto
615-8520, Japan

<sup>§</sup> Applied Chemistry Research Unit, College of Environmental Technology, Graduate School of Engineering, Muroran Institute of Technology, 27-1 Mizumoto, Muroran 050-8585, Japan

\*Corresponding authors

S. M. A. Hakim Siddiki, Ken-ichi Shimizu

E-mail: hakim@cat.hokudai.ac.jp, kshimizu@cat.hokudai.ac.jp

# ABSTRACT

A one-pot, acceptorless dehydrogenative method, using a carbon-supported Pt catalyst (Pt/C) along with KO*t*Bu, has been developed for the synthesis of 2,4,6-trisubstitutedpyrimidines from secondary and primary alcohols, and amidines. The reaction takes place efficiently using a wide range of substrate scopes (32 examples with isolated yields up to 92%). The Pt/C catalyst that promotes this process is reusable and has a higher turnover number (TON) than those employed in previously reported methods. The results of mechanistic studies suggest that the process takes place through a pathway that begins with Pt-catalyzed acceptorless dehydrogenation of the alcohol substrate, which is followed by sequential condensation, cyclization and dehydrogenation. Measurements of the turnover frequency combined with the results of density functional theory calculations on different metal surfaces suggest that the adsorption energy of H on the Pt surface is optimal for the acceptorless dehydrogenation process, which causes the higher catalytic activity of Pt over those of other metals.

# **KEYWORDS:** pyrimidines, acceptorless dehydrogenative coupling, multi-component reaction, heterogeneous platinum catalysts, density functional theory

#### **1. INTRODUCTION**

Heterogeneous catalysts that promote one-pot reactions leading to value-added chemicals have attracted much attention.<sup>1,2</sup> Among various types of organic transformations that fall in this category, H<sub>2</sub> evolving, acceptorless dehydrogenation (AD) reactions have been developed to synthesize various types of organic compounds.<sup>3</sup> AD reactions have advantages not shared by traditional reactions employing stoichiometric amounts of inorganic substances or  $O_2$  as oxidants, because they do not require the use of oxidants or sacrificial hydrogen acceptors.<sup>4–6</sup> As a result, AD reactions do not generate stoichiometric amounts of waste.<sup>7</sup> Gaseous H<sub>2</sub> generated in these processes is also valuable and can potentially be utilized as an energy source. Because homogeneous catalysts normally suffer from product separation and catalysts recycling issues, their heterogeneous counterparts are typically better suited for AD reactions.<sup>3,8</sup> However, the development of heterogeneous catalysts for reactions that produce value-added chemicals is challenging because of the empirical approaches that are used in their development.<sup>9</sup> Also, the complexity of surface reactions makes predicting catalyst performance a formidable task.<sup>10</sup> Consequently, an important target in the development of environmentally friendly, atom-efficient AD reactions is the design of heterogeneous catalysts showing high activities, stabilities and recyclabilities in the absence of hydrogen acceptors.

Selective catalytic transformation of alcohols, which are readily available and sustainable substrates, to fine chemicals is a growing area of interest in catalysis, organic synthesis and green sustainable chemistry.<sup>5,11–18</sup> One representative example of the transformation of alcohols to fine chemicals is the catalytic one-pot synthesis of nitrogen-containing heterocycles (indoles,<sup>19–21</sup> quinolines,<sup>22,23</sup> pyrroles,<sup>24–32</sup> pyridines,<sup>33–36</sup> pyrimidines,<sup>37–39</sup> and quinazolines<sup>40</sup>), which have broad applications as pharmaceutical and flavoring agents, agrochemicals and other functional chemicals.<sup>41,42</sup> The methods are based on AD reactions of alcohols that initially form carbonyl compounds, which are then transformed to products through multiple condensation/dehydrogenation reactions occurring in the same vessel. A recent advance made in this area is the synthesis of 2,4,6-trisubstituted-pyrimidines from primary and secondary alcohols, along with amidines using

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homogeneous transition metal catalysts with a basic additive (KOtBu). Following the first report by Kempe et al. describing the use of a homogenous Ir catalyst to promote this process,<sup>37</sup> Kirchner et and Kempe et al.<sup>39</sup> individually developed new methods using less expensive Mn complexes al.<sup>38</sup> as homogeneous catalysts. These catalytic methods for the preparation of 2,4,6-trisubstituted-pyrimidines are more atom-efficient and sustainable than their conventional counterparts, exemplified by reactions of amidines with  $\alpha$ ,  $\beta$ -unsaturated ketones, <sup>43</sup>  $\alpha$ ,  $\alpha$ -dibromo oxime ethers with Grignard reagents,<sup>44</sup> alkynes and nitriles using TfOH,<sup>45</sup> and the cascade synthesis of pyrimidines from propargylic alcohols and amidines using the transition metal catalysts BaMnO<sub>4</sub>.<sup>46</sup> Although the catalytic method for synthesis of pyrimidines from alcohols and amidines is attractive, it suffers from low turnover number (TON) and difficulties with catalyst/product separation and catalyst recycling.<sup>37–39</sup> Consequently, the development of a highly efficient heterogeneous catalyst for this reaction, which have a wide scope, could overcome these problems. To date, however, only homogeneous catalysts have been used to promote this process. Our group recently reported a series of studies of AD reactions and acceptorless dehydrogenative coupling (ADC) reactions of alcohols that are promoted by heterogeneous carbon-supported Pt catalysts (Pt/C).<sup>21,32,40,47-49</sup> This approach has advantages associated with the use of a recyclable heterogeneous catalyst and the facility of catalyst preparation. It is anticipated that this catalytic system would find applications to other challenging reactions that produce value-added chemicals in one-pot manner.

In studies described below, targeted at uncovering these applications, we developed a new heterogeneous catalytic system to promote AD reactions that form 2,4,6-trisubstituted-pyrimidines from diverse combinations of primary and secondary alcohols, along with amidines. The Pt/C catalyst developed for these processes has reusability and displays a higher turnover number (TON) than previously used homogeneous catalysts.<sup>37–39</sup> In addition, the results of fundamental studies have led to elucidate a plausible mechanism for the process and to an understanding of factors that affect the catalytic activities of various metal nanoparticle catalysts.



Wide substrate scope

Scheme 1. Pyrimidine synthesis using AD reactions.

#### 2. EXPERIMENTAL SECTION

#### General

Commercially available organic and inorganic compounds, except for the amidine-hydrochlorides, (from Tokyo Chemical Industry, Wako Pure Chemical Industries, and Sigma Aldrich, Kishida Chemical, or Mitsuwa Chemicals) were used without purification. Amidines were extracted twice from commercially available amidine-hydrochlorides (0.1 mol) using 0.33 mol KOH, 70 mL H<sub>2</sub>O and 50 mL CH<sub>2</sub>Cl<sub>2</sub>, and dried using a rotary evaporator before use in reactions. Benzyl- $\alpha$ , $\alpha$ -d<sub>2</sub> alcohol (BzCD<sub>2</sub>OH, 99.5 atom %D) and 1-phenylethan-1-d<sub>1</sub>-ol (C<sub>6</sub>H<sub>5</sub>CD(OH)CH<sub>3</sub>, 98 atom %D) were obtained from Sigma Aldrich. GC (Shimadzu GC-14B and GC-2014) and GCMS (Shimadzu GCMS-QP2010) analyses were performed with an Ultra ALLOY capillary column UA<sup>+</sup>-1 (Frontier Laboratories Ltd.) using He or N<sub>2</sub> as the carrier gas. <sup>1</sup>H and <sup>13</sup>C NMR measurements were performed with JEOL-ECX 600 operating at 600.17 and 150.92 MHz, respectively. Tetramethylsilane was used as the internal standard.

#### **Catalyst Preparation**

Carbon was obtained commercially from Kishida Chemical. SiO<sub>2</sub> (Q-10) was supplied by Fuji Silysia Chemical Ltd. CeO<sub>2</sub> (JRC-CEO3), TiO<sub>2</sub> (JRC-TIO-4), MgO (JRC-MGO-3), and H\*-exchanged  $\beta$ zeolite (H $\beta$ , SiO<sub>2</sub>/Al<sub>2</sub>O<sub>3</sub> = 25±5, JRC-Z-HB25) were obtained from the Catalysis Society of Japan. ZrO<sub>2</sub> was synthesized by hydrolysis of zirconium oxynitrate 2-hydrate in an aqueous solution of NH<sub>4</sub>OH, followed by filtration, washing with distilled water, drying at 100 °C for 12 h and finally calcination at 500 °C for 3 h.  $\gamma$ -Al<sub>2</sub>O<sub>3</sub> was prepared by calcining  $\gamma$ -AlOOH (Catapal B Alumina, Sasol) at 900 °C for 3 h. Nb<sub>2</sub>O<sub>5</sub> was prepared by calcining Nb<sub>2</sub>O<sub>5</sub>·*n*H<sub>2</sub>O (Companhia Brasileira de Metalurgia e Mineração (CBMM)) at 500 °C for 3 h. The Pt/C precursor was prepared by the impregnation method as follows. A mixture of carbon (10 g) and an aqueous HNO<sub>3</sub> solution of Pt(NH<sub>3</sub>)<sub>2</sub>(NO<sub>3</sub>)<sub>2</sub> containing 4.96 wt% of Pt (10.62 g) and 50 mL of ion-exchanged water was added to a round-bottom flask (500 mL). The mixture was stirred for 15 min at room temperature (200 rpm). The mixture was evaporated to dryness at 50 °C. This was followed by drying at 90 °C under ambient pressure for 12 h. Prior to each experiment, a Pt/C catalyst (5 wt% Pt loading) was prepared by

 reducing the precursor in a Pyrex tube under a H<sub>2</sub> flow (20 cm<sup>3</sup> min<sup>-1</sup>) at 300 °C for 0.5 h. Other supported Pt catalysts (5 wt% Pt loadings) were prepared in the same manner. In addition, M/C (M = Rh, Ir, Ru, Pd, Re, Cu, Ni) catalysts were prepared in a similar method using aqueous HNO<sub>3</sub> solutions of Rh(NO<sub>3</sub>)<sub>3</sub> or Pd(NH<sub>3</sub>)<sub>2</sub>(NO<sub>3</sub>)<sub>2</sub>, or aqueous solutions of metal nitrates (for Ni, Cu), IrCl<sub>3</sub>·*n*H<sub>2</sub>O, RuCl<sub>3</sub>, or NH<sub>4</sub>ReO<sub>4</sub>. Metal loadings were adjusted to 5 wt%. Platinum oxides-loaded carbon (PtOx/C) was prepared by calcining the Pt(NH<sub>3</sub>)<sub>2</sub>(NO<sub>3</sub>)<sub>2</sub>-loaded carbon at 300 °C for 0.5 h in air.

#### **Catalyst Characterization**

X-ray diffraction (XRD; Rigaku Miniflex) measurements were conducted using Cu K- $\alpha$  radiation. N<sub>2</sub> adsorption measurements were carried out by using AUTOSORB 6AG (Yuasa Ionics Co.). The sizes of supported metal particles were estimated by using transmission electron microscopy (TEM) using a JEOL JEM-2100F TEM operated at 200 kV. CO adsorption experiments were carried out at room temperature by using BELCAT (MicrotracBEL). Prior to each CO adsorption experiment, a sample (0.1 g) was heated in a flow of 5% H<sub>2</sub>/Ar (20 mL min<sup>-1</sup>) at 300 °C for 10 min. Pt L<sub>3</sub>-edge X-ray absorption near-edge structures (XANES) and extended X-ray absorption fine structures (EXAFS) were determined in a transmittance mode at the BL01B1 with a Si(111) double crystal monochromator in SPring-8 operated at 8 GeV (Proposal No. 2017B1279). The Pt/C catalyst following the recycle study in Fig. 1 was sealed in cells made of polyethylene under N<sub>2</sub>, and then the spectrum was measured at room temperature. The EXAFS analysis was carried out using the REX ver. 2.5 program (RIGAKU). The parameters for Pt–O and Pt–Pt shells were provided by the FEFF6.

#### Typical Procedure for the Catalytic Reactions

Pt/C (39 mg; 1 mol% Pt with respect to benzamidine **3a**) was used as the standard catalyst. After reduction, the catalyst was placed in a closed glass tube sealed with a septum inlet and cooled to room temperature under H<sub>2</sub>. Toluene (2 mL) was injected through the septum inlet into the glass tube containing the pre-reduced catalyst. Next, the septum was removed, and secondary alcohol **1** (1.25 mmol), primary alcohol **2** (1.5 mmol), amidine **3** (1.0 mmol), KO*t*Bu (1.5 mmol), *n*-dodecane (0.25 mmol) and a magnetic stirrer bar were added to the tube followed by filling N<sub>2</sub> through the septum

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inlet. Then, the resulting mixture was magnetically stirred (400 rpm) under reflux conditions. For the standard catalyst screening reactions of 1-phenylethanol, benzyl alcohol and benzamidine (Table 1), reaction optimizations (Table 2), kinetic studies and control reactions, the conversions and yields of products were determined by using GC with *n*-dodecane as the internal standard. GC-sensitivities were estimated using isolated products or commercial compounds. In substrate scope studies (**Schemes 1-4**), products were isolated by using column chromatography on silica gel 60 (spherical, 40–100 µm, Kanto Chemical Co. Ltd.) using hexane/ethyl acetate (9:1, v/v) as the eluent, and yields of the isolated products were determined. Products were identified by using <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy in combination with GCMS, in which the mass spectrometer was equipped with the same column as that used for GC analyses. Analysis of the gaseous product (H<sub>2</sub>) was carried out by using mass spectrometry (BELMASS).

Recycling experiments were performed with the following procedure. After each catalytic run, 2-propanol (3 mL) was added to the mixture. The catalyst was separated by using centrifugation and washed with water (3 mL) and acetone (6 mL). Subsequently, the catalyst was dried at 110 °C for 3 h and reduced at 300 °C for 0.5 h under an atmosphere of H<sub>2</sub>. Subsequently, the recovered Pt/C catalyst was placed in the reactor with a mixture of the substrate and KO*t*Bu. Note that the initial rates were obtained on the basis of product yields after a reaction time of 1 h where the product yields are below 30%.

#### **3. RESULTS AND DISCUSSION**

#### **Optimization of the Catalyst and Reaction Conditions**

In the initial phase of studies aimed at developing a heterogeneous catalytic system to promote 2,4,6-trisubstituted-pyrimidine forming AD reactions, catalyst screening was performed using the reaction of 1-phenylethanol (1a, 1.25 mmol), benzyl alcohol (2a, 1.5 mmol) and benzamidine (3a, 1.0 mmol) and KOtBu (1.5 mmol) in refluxing toluene for 24 h. Table 1 shows the yields of 2,4,6-triphenylpyrimidine (4a), based on benzamidine, for various AD reactions promoted by Pt nanoparticles on different support materials and various metal nanoparticles on carbon containing 0.01 mmol (1 mol%) of the active metal. Under these conditions, reactions do not take place in the absence of the catalyst (entry 1). The results show that platinum oxides-loaded carbon ( $PtO_x/C$ , entry 2) does not promote the reaction. In contrast, metallic Pt-loaded carbon (Pt/C), reduced with H<sub>2</sub> at 300 °C, catalyzes a reaction that occurs in 95% yield (entry 3), while use of pre-reduced, air-exposed Pt/C (Pt/C-air in entry 4) leads to a lower yield (57%). The yields of AD reactions promoted by Pt/C are higher than those catalyzed by Pt-loaded metal oxides (ZrO<sub>2</sub>, Al<sub>2</sub>O<sub>3</sub>, CeO<sub>2</sub>, TiO<sub>2</sub>, SiO<sub>2</sub>, MgO, H<sub>β</sub> zeolite, Nb<sub>2</sub>O<sub>5</sub>, entries 5-12). The Pt-loaded metal oxides catalysts were characterized by XRD (Figure S1), N<sub>2</sub> adsorption (Figure S2), and CO adsorption measurements as well as TEM and XAFS measurements as previously reported.<sup>50</sup> Moreover, the Pt/C catalyst promotes a higher yielding reaction than do other transition metal nanoparticles supported on carbon (Ir/C, Ni/C, Pd/C, Rh/C, Ru/C, Re/C, Cu/C, and Ag/C) shown in entries 13-20.

Using the most effective catalyst, Pt/C, we conducted a study targeted at finding optimal conditions for the reaction of **1a**, **2a**, and **3a** (**Table 2**). Inspection of the results arising from reactions promoted by Pt/C and KOtBu in various solvents at reflux (entries 1-5) showed that reaction in toluene (entry 1) forms **4a** in the highest yield. A survey of reactions in refluxing toluene with different basic additives (entries 1, 6-8) showed that KOtBu (entry 1) leads to a higher yield than with the other basic additives (NaOtBu, NaOH, KOH). It was also demonstrated that the reaction hardly proceeds in the absence of a base (entry 9). Consequently, we adopted refluxing toluene using Pt/C and KOtBu as the standard conditions for reaction of **1a**, **2a**, and **3a**.

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Table 1. Ca 2a and ber	atalyst scree nzamidine <b>3a</b>	ning for syı ı.	nthesis of pyrimid	ine <b>4a</b> from 1	1-phenylethanol <b>1a</b>	, benzyl alcohol
I	<u>^</u>	$NH_2$	1 mal% catalyst	Ph ↓		

+	Ph OH + 1 mol% catalyst	
Ph´ `OH 1a	2a Ph NH 1.5 mmol KOtBu	
1.25 mmol	1.5 mmol 1 mmol 24 h	4a
Entry	Catalyst	Yield (%) <sup>a</sup>
1	None	0
2	PtO <sub>x</sub> /C	0
3	Pt/C	95
4	Pt/C-air	57
5	Pt/ZrO <sub>2</sub>	70
6	Pt/Al <sub>2</sub> O <sub>3</sub>	67
7	Pt/CeO <sub>2</sub>	65
8	Pt/TiO <sub>2</sub>	63
9	Pt/SiO <sub>2</sub>	61
10	Pt/MgO	53
11	Pt/Hβ	43
12	Pt/Nb <sub>2</sub> O <sub>5</sub>	38
13	Ir/C	45
14	Ni/C	36
15	Pd/C	34
16	Rh/C	31
17	Ru/C	26
18	Re/C	19
19	Cu/C	15
20	Ag/C	11

<sup>a</sup> GC yield.

# Table 2. Optimization of the conditions for pyrimidine forming reaction of 1a, 2a and 3a. Ph

Ph OH + 1a	Ph OH + $Ph$ NH <sub>2</sub> 2a $Ph$ NH 3a	1 mol% Pt/C 1.5 mmol base reflux, 24 h Ph	`Ph
1.25 mmol	1.5 mmol 1 mmol	4a	
Entry	Base	Solvent	Yield (%) <sup>a</sup>
1	KO <i>t</i> Bu	toluene	95
2	KO <i>t</i> Bu	<i>n</i> -octane	66
3	KO <i>t</i> Bu	o-xylene	69
4	KO <i>t</i> Bu	mesitylene	71
5	KO <i>t</i> Bu	tert-amyl alcohol	78
6	NaO <i>t</i> Bu	toluene	65
7	NaOH	toluene	70
8	КОН	toluene	61
9	none	toluene	0
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<sup>a</sup> GC yield.

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#### Catalytic Properties and Scope of the Reaction

The heterogeneous nature and reusability of the catalytic system developed for the AD reactions were confirmed by the results of the recycling test shown in **Figure 1**. After carrying out the standard AD reaction for 24 h, the catalyst was separated from the mixture by using filtration, dried at 110 °C for 3 h and then reduced in a H<sub>2</sub> atmosphere at 300 °C for 0.5 h. The recovered catalyst was found to promote an AD reaction to form **4a** in high yields (88-95%) that gradually decrease over five cycles. In a separate series of experiments, the initial rates of **4a** formation were determined for each cycle. The results (gray bars in **Figure 1**) show that the initial rates also gradually decrease with increasing number of cycles. It should also be noted that a 2nd run without the H<sub>2</sub> reduction step afforded **4a** in 71% yield, which is lower than the yield obtained with an H<sub>2</sub> reduction, indicating that the H<sub>2</sub> reduction is necessary for optimal recycling.

To assess possible reasons for the gradual catalyst deactivation in the recycling processes described above, structural characterization was carried out on the recovered Pt/C catalyst following the 5th cycle of reactions by using X-ray absorption near-edge structural (XANES) and extended X-ray absorption fine structure (EXAFS) analysis (Figure 2), and TEM analysis (Figure 3). The results of EXAFS curve fitting analysis are shown in Table 3. Note, characterization of freshly prepared Pt/C was reported in our previous study.<sup>49</sup> The XANES feature of the fresh Pt/C catalyst is similar to that of Pt foil, indicating that the Pt species are metallic. It was also found that the intensity of white-line is slightly increased after 5th cycles of the reaction and decreased by the subsequent  $H_2$ reduction. This result indicates that the Pt species is oxidized during the reaction. Subsequent  $H_2$ reduction is necessary to obtain metallic Pt and thus effective for the optimal recycling. The EXAFS of Pt/C after the 5th catalytic cycle followed by H<sub>2</sub> reduction consists of Pt-Pt bonds at 2.74 Å, a distance that is close to that of Pt foil (2.76 Å) with the coordination numbers of 10.1. This observation shows that Pt in the catalyst after the 5th cycle followed by H<sub>2</sub> reduction exist in the metallic state, which is consistent with the XANES result. However, the particle size distribution, estimated by using TEM analysis (Figure 3), shows that the fraction of Pt metal particles with diameters above 7 nm increases during recycling. The volume-area mean diameter  $(D)^{51}$  of Pt

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particles in the recycled Pt/C ( $6.5 \pm 1.6 \text{ nm}$ ) is larger than that in fresh Pt/C ( $5.2 \pm 1.1 \text{ nm}$ ), an increase that is likely responsible for the slight decrease in the catalytic activity seen after the 5th cycle. The coordination number for the catalyst after recycling and subsequent H<sub>2</sub> reduction was found to be 10.1, and this result is in accordance with these observations.

This catalytic system is applicable to gram scale synthesis of pyrimidines. This capability was demonstrated by reaction of 12.5 mmol of **1a**, 15 mmol of **2a**, 10 mmol of **3a** and 15 mmol of KO*t*Bu using 0.05 mol% of Pt/C catalyst for 120 h, which produces **4a** in 89% yield corresponding to a TON of 1780. As the data in **Table 4** demonstrate, the new method has two advantages over those previously developed including a more than 10 times higher TON and reusability of the catalyst.



**Figure 1.** Catalyst reuse for the synthesis of **4a** from **1a**, **2a**, and **3a** promoted by Pt/C and KO*t*Bu under the standard conditions shown in Table 2 (entry 1): (navy bars) **4a** yields after 24 h and (gray bars) initial rates of **4a** formation.



**Figure 2.** Pt L<sub>3</sub>-edge (A) XANES spectra and (B) EXAFS Fourier transforms of Pt/C before and after the catalyst recycling.



Figure 3 Typical TEM images and Pt particle size distributions of Pt/C before and after recycling.

Ph OH + 1a	Ph <sup>^</sup> OH 2a	+ Ph NH <sub>2</sub> + And NH 3a	0.05 mol% Pt/C 15 mmol KOtBu reflux, 120 h Ph N N Ph N Ph A	
12.5 mmol	15 mmol	10 mmol	89% Yield	
Catalyst		TON	Catalyst reuse	Ref.
Ir complex		158	no	37
Mn complex	K	172	no	39
Mn complex	ĸ	48	no	38
Pt/C		1780	5th cycles	This study

Table 4. TON and catalyst reusability for synthesis of 4a from 1a, 2a and 3a.

The substrate scope of the Pt/C-catalyzed process was explored next. The results show that the catalytic system is effective in promoting AD reactions of various primary alcohols (benzylic and heterocyclic), secondary alcohols (aliphatic, 1-phenylethanol) and amidines. In these processes, pyrimidines are generated in high yields (78-92%) (Scheme 2-5). The scope of secondary alcohols 1 in this process is seen by viewing the results in **Scheme 2**, which show that high yields of isolated pyrimidines attend AD reactions of various secondary alcohols 1 with benzylalcohol 2a and benzamidine 3a. Reactions of 1-phenylethanol and its derivatives with electron-withdrawing and

-donating groups at *para*-positions produce the corresponding pyrimidines (**4a** to **4e**) with good to excellent yields (82-92%). AD reaction of 1-(naphthalen-2-yl)ethan-1-ol with **2a** and **3a** also generates the corresponding pyrimidine **4f** in 81% yield. Finally, AD reaction with 3-methyl butan-2-ol gave the pyrimidine **4g** occurring in 84% yield, demonstrates the applicability of the method to aliphatic secondary alcohols.



Scheme 2. Synthesis of pyrimidines from, 2a and 3a, and secondary alcohols. Isolated yields are shown.

The results in **Scheme 3** show the scope of primary alcohols **2**, including aromatic, heterocyclic and aliphatic alcohols, in the new AD reaction. Benzyl alcohols with different substituents at *para*-positions react with 1-phenylethanol **1a** and benzamidine **3a** to produce the corresponding pyrimidines (**4h-4m**) in good to high isolated yields (82-92%). 2-Naphthylmethanol also forms pyrimidine analogue **4n** in an acceptable 89% yield. Primary alcohols containing heterocycles groups, such as piperonyl, pyridyl, furyl and thiophenyl, are converted to the corresponding pyrimidines (**4o-4r**) in high isolated yields (78-89 %). Also, AD reactions of aliphatic primary alcohols, cyclohexylmethanol and iso-butyl alcohol with **2a** and **3a** yield the corresponding pyrimidines (**4s**, **4t**) in high isolated yields. Significantly, (4-(trifluoromethyl)phenyl)methanol, 2-naphthylmethanol and 2-furylmethanol are the first examples of primary alcohols that undergo reactions with 1-phenylethanol and benzamidine to form trisubstituted-pyrimidines.

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Scheme 3. Synthesis of pyrimidines from 1a, primary alcohols and 3a. Isolated yields are shown.

The results of pyrimidine forming AD reaction of different benzamidines with 1-phenylethanol and benzyl alcohol are displayed in **Scheme 4**. Benzamidines possessing strongly (*p*-methoxyphenyl), weakly (*p*-methylphenyl) electron donating groups, and a weakly electron withdrawing (*p*-chlorophenyl, *p*-fluorophenyl) groups react with **1a** and **2a** to produce the corresponding pyrimidines (**4u-4x**) in excellent yields (85-91%). Guanidine and methylguanidine also react with **1a** and **2a** to form the corresponding pyrimidines (**4y** and **4z**) in excellent respective 91% and 88% yields.



**Scheme 4**. Synthesis of pyrimidines from **1a**, **2a** and different amidines. Isolated yields are shown, <sup>a</sup> GC yield.

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**Scheme 5** shows the results of AD reactions of *para*-substituted 1-phenylethanols, various primary alcohols, including *p*-substituted benzylalcohols (**4aa-4cc**) and 2-butanol (**4dd-4ff**), with various amidines (benzamidine and guanidine). The observations demonstrate that the new process is applicable to various combinations of substrates, and it generates the corresponding pyrimidines (**4aa-4ff**) in excellent isolated yields (87-93%). It should be noted that products **4ee** and **4ff** are important intermediates in the total synthesis of rosuvastatin, which is used as a pharmaceutical drug for treatment of patients with high levels of cholesterol.<sup>52</sup> Compared to those previously devised, the new heterogeneous catalytic system is characterized by the higher isolated yields of pyrimidine forming reactions.



**Scheme 5**. Synthesis of pyrimidines from various secondary alcohols, primary alcohols and amidines. Isolated yields are shown.

# **Mechanistic Study**

The mechanism of the AD reaction was not discussed in reports of pioneering studies probing the use of homogeneous catalysts owing to the lack of experimental information.<sup>37–39</sup> In the current effort, we carried out kinetic studies and control reactions, summarized in equations (1)-(6), which provide observations that enable us to propose a possible mechanistic pathway for the reaction (**Scheme 6**). First, the time course of AD reaction of **3a** over Pt/C under the standard conditions was monitored (**Figure 4A**). The results show that initially (t = 0.5 h), the amount of acetophenone **1a**' and benzaldehyde **2a**' increases and then decreases as the reaction time is increased. Simultaneously, the amount of benzylideneacetophenone (**5a**) increases with time until 2 h, after which it decreases along with a corresponding increase in the amount of product, triphenylpyrimidine **4a**. A measurement of the evolution of H<sub>2</sub> (eqn. 1) shows that an almost theoretical amount of this gas is formed at t = 0.5 h, demonstrating the occurrence of acceptorless dehydrogenation.

PhOH	* Ph OH *	Ph NH2	1 mol% Pt/C 1.5 mmol KOtBu 2 mL toluene	Ph N N + Ph Ph	Ph Ph	
1 mmol	1 mmol	1 mmol	reflux, 0.5 h	0.08 mmol	0.15 mmol	
33% conv.	35% conv.	10% conv.		8% yield	15% yield	
	Theoretical	amount of evo	lved H <sub>2</sub> + 0.08 mmol	+ CH <sub>3</sub> + Ph O	$Ph \sim 0 + H_2$	(1)
	= 0.76 mmo	1	. 0.00 mmor	0.09 mmol	0.10 mmol 0.74 mmol	
				9% yield	10% yield 74% yield	

The above results suggest that the mechanistic pathway for the process, shown in **Scheme 6**, begins with a step in which acceptorless dehydrogenations of primary and secondary alcohols take place to form the corresponding aldehydes and ketones. The second step of the process involves base-catalyzed Claisen-Schmidt condensation of acetophenone with benzaldehyde to form chalcones. The roles played by Pt and KOtBu (base) is evidenced by the results of the control reaction of acetophenone **1a**' and benzaldehyde **2a**' with KOtBu, which produces chalcone **5a** in 95% yield (eqn. 2), and by the observation that this reaction is not catalyzed by Pt/C in the absence of KOtBu (result not shown) nor does reaction of 1-phenylethanol **1a** and benzyl alcohol **2a** with KOtBu in refluxing toluene for 4 h yield chalcone **5a** (eqn. 3). Moreover, in the presence of Pt/C and KOtBu,

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reaction of 1-phenylethanol **1a** and benzyl alcohol **2a** generates chalcone **5a** in 95% yield (eqn. 4), while Pt/C does not catalyze the dehydrogenation reaction when base is absent (eqn. 5). These results indicate that the dehydrogenation step catalyzed by Pt is assisted by KO*t*Bu, which likely promotes deprotonation of alcohols, and that the second condensation step is catalyzed by KO*t*Bu. The third step, involving condensation of **5a** with benzamidine **3a**, is followed by dehydrogenation of the formed intermediate 2,4,6-triphenyl-1,6-dihydropyrimidine **6a** that produces the final product **4a**. In the presence of Pt/C, reaction of **5a** with **3a** forms triphenylpyrimidine **4a** in 90% yield (eqn. 6).



**Scheme 6**. Plausible mechanism for AD reaction of 1-phenylethanol, benzyl alcohol and benzamidine that generates 2,4,6-triphenylpyrimidine.



**Figure 4.** Plots of the amounts of benzamidine **3a**, acetophenone **1a'**, benzaldehyde **2a'**, chalcone **5a** and triphenylpyrimidine **4a** versus reaction time over (A) Pt/C, (B) Pt/Al<sub>2</sub>O<sub>3</sub>, (C) Pt/ZrO<sub>2</sub>, and (D) Pt/MgO catalysts.

In order to gain additional insight into the mechanism of the AD reaction, kinetic isotope effect (KIE) studies were conducted using **1a** (PhCH(OH)CH<sub>3</sub> or PhCD(OH)CH<sub>3</sub>), **2a** (PhCH<sub>2</sub>OH or PhCD<sub>2</sub>OH) and **3a** (**Figure 5**). The results show that the rate constant for reaction of PhCH(OH)CH<sub>3</sub>, PhCH<sub>2</sub>OH, and **3a** ( $k_{HH}$ ) is larger than that for the reaction of PhCD(OH)CH<sub>3</sub>, PhCD<sub>2</sub>OH, and **3a** ( $k_{HH}$ ) is larger than that for the reaction of PhCD(OH)CH<sub>3</sub>, PhCD<sub>2</sub>OH, and **3a** ( $k_{DD}$ ). The difference corresponds to a KIE ( $k_{HH}/k_{DD}$ ) of 2.8 (**Figure 5B**). Also, the KIE for the reaction of **1a** and **2a** to **5a** was found to be 1.5 (**Figure 5A**), which is smaller than that for reaction of **1a**, **2a**, and **3a** to form **4a**. Based on these results, we suggest that step involving dehydrogenation of **6a** to form **4a** is kinetically more important than dehydrogenation of **1a** and **2a**. This proposal is supported by a comparison that show that the initial rate of the reaction in the 4th step is about 6-times smaller than that of the 1st and 2nd steps (**Scheme 7**).



Scheme 7. Comparison of the initial rates of reactions corresponding to the 1st and 2nd steps (1a and 2a to 5a) with that of the 4th step (5a and 3a to 4a).



**Figure 5.** Kinetic isotopic effect analysis (A) for chalcone (**5a**) formation and (B) for triphenylpyrimidine (**4a**) formation under the conditions shown in Table 2 (entry 1).

#### Origin of the High Catalytic Activity of Pt/C

Summary of characterization and catalytic results for supported Pt catalysts tested in this study is given in **Table 5** in order to discuss the effect of supports. We employed the standard reaction of **1a**, 2a and 3a for this discussion. Specific surface areas (S<sub>BET</sub>) were determined by using the Brunauer-Emmett-Teller (BET) method. Volume-area mean diameter (D) of metal particles were obtained from our previous reports describing particle size distributions using results of TEM analysis of the same catalysts.<sup>50</sup> To evaluate catalytic activity, initial rates of the product (**4a**) formation per total metal atoms in the catalyst ( $N_T$ ) were measured under the conditions where conversion of **1a**, 2a and 3a are below 50%. Finally, the multiple of initial rates and dispersion yields gives the turnover frequency (TOF) per surface metal atoms given. Investigations on the initial reaction rates show that Pt/ZrO<sub>2</sub>, Pt/Al<sub>2</sub>O<sub>3</sub>, and Pt/MgO catalysts also exhibit relatively high initial rates in addition to the Pt/C catalyst. However, inspection of time course plots shows that the 4a yields for Pt/ZrO<sub>2</sub>, Pt/Al<sub>2</sub>O<sub>3</sub>, and Pt/MgO leveled off after certain reaction time, resulting in the low 4a yields (Figure 4B-D), while the 4a yield for Pt/C monotonically increased over time (Figure 4A). In order to get insights of this catalyst deactivation, CO adsorption experiments for the catalysts before and after the reaction were performed. The obtained results are listed in Table 5. The number of CO adsorbed on Pt/C remained almost unchanged even after the reaction. On the contrary, the number of CO adsorbed on the other supported Pt catalysts markedly decreased after the reaction. These observations indicate that a reason of the high performance of the Pt/C catalyst can be attributed to high tolerance of Pt on the carbon support toward the reaction condition.

Origin of the high catalytic performance of Pt/C compared to other transition metals loaded carbon catalysts is discussed next. The results of the kinetic studies described in the previous section show that dehydrogenation of **6a** to **4a** is a kinetically important step in the AD reaction. In addition, the KIE value of 1.5 for reaction of **1a** with **2a** to form **5a** suggests that the first step involving dehydrogenation of alcohols also contributes to the rate of the overall process. Generally, dehydrogenation activities of metal surfaces depend on metal-hydrogen (M–H) bond energies or adsorption energies of a H atom on the surface, which can be assessed theoretically by using density functional theory (DFT).<sup>53,54</sup> The

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first elementary step for the dehydrogenation processes on a metal surface forms a surface adsorbed H atom. Metals with low H adsorption energy are not efficient promoters of this step, while metals with very large H adsorption energies are not effective for the promoting the subsequent step, namely removal of H<sub>2</sub> from the surface via M–H bond dissociation. Considering the Brønsted–Evans–Polanyi (BEP) relation and the Sabatier principle,<sup>55–57</sup> it is reasonable to suggest that the new one-pot reaction described above is most effectively catalyzed by a metal that has a moderate H adsorption energy. In an attempt to verify this hypothesis, we conducted a quantitative analysis of the activity trends for the standard reaction of **1a**, **2a** and **3a** catalyzed by various transition metals loaded carbon catalysts.

**Table 6** lists the initial rates per  $N_{\rm T}$  as well as TOF per surface metal atoms. D of metal particles were estimated using particle size distributions using results of TEM analysis of the catalysts (See Fig. S3-S12 in the Supporting Information for more details). The D values of the catalysts were found to have similar sizes in the range of 3.8-7.0 nm except for Ag/C (31.7 nm). It is known that dispersion (fraction of the exposed metal atoms) of metal nanoparticles correlates with the D value owing to the fact that *D* values estimated by TEM agrees with mean particle diameters estimated from the number of surface atoms on the spherical particles.<sup>51</sup> Considering the fact that the fraction of low coordination surface atoms is relatively low for the metal particles above 3.8 nm,<sup>58</sup> we employed the most stable and common planes for each metal to obtain volume-area mean diameters in order to estimate the dispersion from D and density of metal. Namely, the (111) surface was used for metals having a face-centered-cubic (fcc) structure, while the (0001) surface was used for metals having a hexagonal-close-packed (hcp) structure. In our recent study, we theoretically estimated the adsorption energies of a H atom on Pt(111), Ir(111), Pd(111), Rh(111), Cu(111), Ni(111), Ru(0001), and Re(0001) surfaces by using DFT calculations.<sup>59</sup> Figure 6 shows the TOF per surface metal atoms for various metal catalysts as a function of the adsorption energy of a H atom as well as the d-band center, which is a well-known descriptor of catalytic activities.<sup>60-62</sup> The plot shows the existence of a volcano-type dependence of the catalytic activity on both the H adsorption energy and the d-band center, and that Pt catalyst display the highest catalytic activities. The result suggests that Pt catalysts that have an optimum strength of the Pt–H bond and the d-band center are suitable for

promoting AD reactions, resulting in higher catalytic activity of Pt than the other metals. This conceptional finding might be useful for the rational design of new catalytic systems for similar types of metal nanoparticle catalyzed organic reactions without the need to conduct extensive trial-and-error studies.

Catalyst	$S_{BET}^{a}(m^{2} g^{-1})$	CO <sub>ads</sub> <sup>b</sup> (µmol g <sup>-1</sup> )	CO <sub>ads after</sub> <sup>c</sup> (µmol g⁻¹)	<i>D</i> <sup>d</sup> (nm)	$V_0 = (\text{mol mol}_{Pt}^{-1} \text{ h}^{-1})$	TOF <sup>f</sup> (h <sup>-1</sup> )
Pt/C	924	62.3	64.3	4.6	21	86.4
Pt/ZrO <sub>2</sub>	91	46.3	<0.1	6.2	14.4	79.8
Pt/Al <sub>2</sub> O <sub>3</sub>	149	126.1	2.8	2.3	10.8	21.9
Pt/CeO <sub>2</sub>	104	98.5	<0.1	2.9	9.7	25.2
Pt/TiO <sub>2</sub>	52	139.5	0.1	2.1	8.9	16.4
Pt/SiO <sub>2</sub>	318	58.5	0.5	4.9	7.8	34.2
Pt/MgO	24	38.6	18.3	7.5	16.5	109.4
Pt/Hβ	511	148.4	10.7	1.9	7.7	13.3
Pt/Nb <sub>2</sub> O <sub>5</sub>	74	44.8	1.3	6.5	5.8	33.2

 Table 5. Summary of characterization and catalytic results for supported Pt catalysts.

<sup>a</sup> Determined form  $N_2$  adsorption isotherm.

<sup>b</sup> Number of CO adsorbed on the catalysts.<sup>50</sup>

° Number of CO adsorbed on the catalysts after reaction.

<sup>d</sup> Average particle size of the supported Pt before catalytic reactions estimated by CO adsorption experiments.<sup>50</sup>

<sup>e</sup> Initial rate of **4a** formation (mol h<sup>-1</sup>) divided by total metal atoms in the catalyst,  $N_T$  (mol).

<sup>f</sup> TOF per surface metal atom defined as TOF =  $V_0$  (mol mol<sub>Pt</sub><sup>-1</sup> h<sup>-1</sup>) ×  $N_s/N_T$ .  $N_s$  is the number of surface metal atoms derived from CO adsorption experiments for fresh catalysts.

**Table 6.** Summary of characterization, catalytic results and details of analysis for various carbon

 supported metal catalysts.

Supported metal	D <sup>a</sup> (nm)	Phase <sup>b</sup>	Crystal plane <sup>b</sup>	<i>N</i> <sup>°</sup> (nm <sup>-2</sup> )	) <i>N</i> s/ <i>N</i> T <sup>d</sup>	V <sub>0</sub> <sup>e</sup> (mol mol <sub>metal</sub> <sup>-1</sup> h <sup>-1</sup> )	) TOF <sup>f</sup> (h <sup>-1</sup> )	E <sub>Had</sub> <sup>g</sup> (eV)
Pt	4.4	fcc	111	14.6	0.31	21.0	66.9	-2.81
lr	4.9	fcc	111	14.6	0.26	8.0	30.9	-2.74
Re	3.9	hcp	0001	15.1	0.35	2.4	6.8	-3.17
Pd	8.3	fcc	111	14.8	0.17	6.5	39.6	-2.99
Rh	3.8	fcc	111	15.6	0.35	12.7	36.2	-2.91
Ru	6.4	hcp	0001	16.3	0.21	4.5	21.2	-2.99
Ag	31.7	fcc	111	13.3	0.045	0.5	10.1	-2.21
Cu	9.3	fcc	111	17.7	0.14	2.0	15.3	-2.6
Ni	7.0	fcc	111	18.8	0.17	7.3	41.9	-2.92

<sup>a</sup> Volume mean diameter of supported metal particles estimated by TEM analysis.

<sup>b</sup> Crystal plane of the metal surface for calculation of dispersion and DFT study.

<sup>c</sup> Number of metal atoms per unit area (nm<sup>2</sup>) on the assumed surface.

<sup>d</sup> Dispersion of supported metals,  $N_S/N_T$ , where  $N_S$  is the number of surface metal atoms and  $N_T$  is the total number of metal atoms in the supported metals.

<sup>e</sup> Initial rate of **4a** formation (mol h<sup>-1</sup>) divided by total metal atoms in the catalyst,  $N_T$  (mol).

<sup>f</sup> TOF per surface metal atom defined as TOF =  $V_0$  (mol mol<sub>metal</sub> <sup>-1</sup> h<sup>-1</sup>)×  $N_S/N_T$ .

<sup>g</sup> Adsorption energy of a H atom on the assumed metal surface.<sup>59</sup>





**Figure 6**. TOF (per surface metal atoms) for the standard reaction promoted by various metal-loaded carbon catalysts (M/C) as a function of (A) the adsorption energy of H on the metal surface and (B) the d-band center.

# CONCLUSIONS

In the effort described above, we developed a new catalytic system for the one-pot synthesis of 2,4,6-trisubstitutedpyrimidines by AD reaction of secondary and primary alcohols with amidines, promoted by a Pt/C catalyst and KOtBu. The catalyst used in this process is heterogeneous and, thus, recyclable. Compared with previously devised catalytic AD reactions, the new process has the following advantages: (1) easy catalyst/product separation, (2) catalyst recyclability, (3) higher TON and (4) higher isolated yields of pyrimidines even in reactions of challenging substrates such as guanidine. The results of kinetic studies and DFT calculations on various metal surfaces suggest that the higher activity of the Pt catalyst as compared to those of other metal catalysts is a consequence of the optimum strength of Pt-hydrogen bond, which is required for efficient operation of the acceptorless dehydrogenation steps. The results should be a useful guide to rationalizing the properties of catalytic systems, and the design of new catalysts.

# **AUTHOR INFORMATION**

Corresponding author

- S. M. A. Hakim Siddiki, Ken-ichi Shimizu
- E-mail: hakim@cat.hokudai.ac.jp, kshimizu@cat.hokudai.ac.jp

# ASSOCIATED CONTENT

# Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at http://pubs.acs.org. TEM images and NMR data.

# ACKNOWLEDGEMENT

This study was supported financially by a JSPS KAKENHI grant 17H01341, 18K14051 and 18K14057 from the Japan Society for the Promotion of Science (JSPS) and by the Japanese Ministry of Education, Culture, Sports, Science, and Technology (MEXT) within the projects "Integrated Research Consortium on Chemical Sciences (IRCCS)" and "Elements Strategy Initiative to Form Core Research Center", as well as by the JST-CREST project JPMJCR17J3. The authors are indebted to the technical division of the Institute for Catalysis (Hokkaido University) for manufacturing experimental equipment. X-ray absorption measurements were performed at the BL-01B1 facility of SPring-8 at the Japan Synchrotron Radiation Research Institute (JASRI) (No. 2017B1279)

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