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

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CeO_2-supported Pt nanoparticle catalysts enabled the acceptorless dehydrogenative synthesis of 2-substituted quinazolines from 2-aminobenzylamine with aliphatic and benzyl primary alcohols or aldehydes with low catalyst loading, wide substrate scope and good catalyst reusability, demonstrating the first acceptor-free and additive-free catalytic system for this reaction.

Quinazolines are important compounds in organic synthesis and the industrial production of pharmaceutical compounds which show various biological activities[1–6] such as antibacterial,[1] antiviral,[2] antitubercular[3] and anticancer[4,6] 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 amounts of toxic oxidants such as DDQ,[7] MnO_2 (ref. 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).

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 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. 3. The O_{1s} binding energy of the peak maxima decreased in the order of $SiO_2Al_2O_3 > SiO_2 > \gamma\text{-}Al_2O_3 > Nb_2O_5 > ZrO_2 > TiO_2 > MgO > CeO_2$. Fig. 4 shows the yield of **3a**

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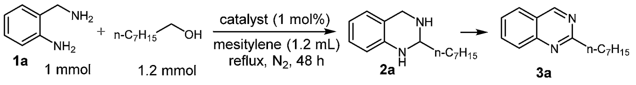
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c4ra09205h

Table 1 Synthesis of **3a** from **1a** and 1-octanol by 1 wt% 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.

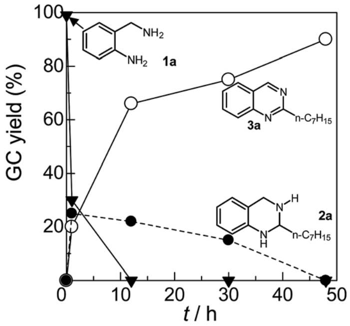


Fig. 1 Time course of the reaction of **1a** with 1-octanol by Pt/CeO_2. Conditions are shown in Table 1.

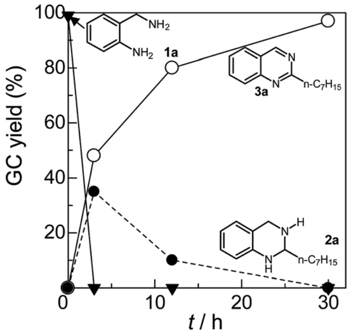


Fig. 2 Time course of the reaction of **1a** with *n*-octanal by Pt/CeO_2. Conditions are shown in Table 3.

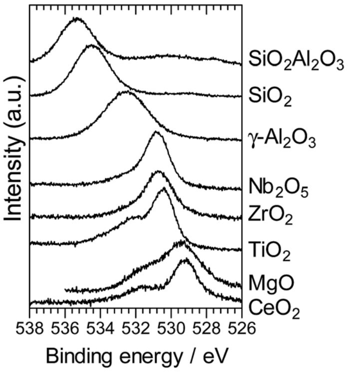


Fig. 3 XPS spectra of the O(1s) core level region of the support materials.

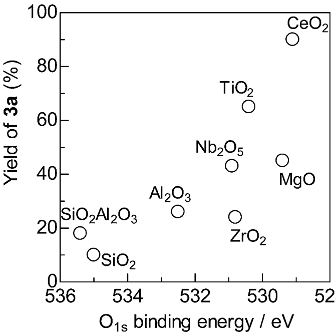
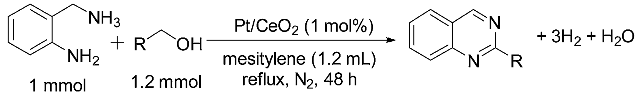


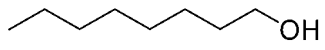
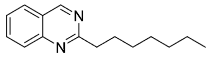
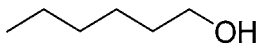
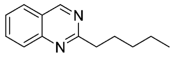
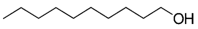
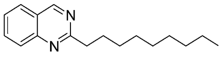
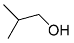
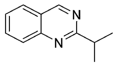
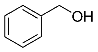
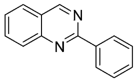
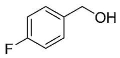
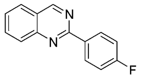
Fig. 4 Yield of **3a** for the reaction of **1a** with *n*-octanal by Pt-loaded metal oxides as a function of O_{1s} binding energy of support oxides.

from **1a** and 1-octanol (Table 1) as a function of the O_{1s} 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 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

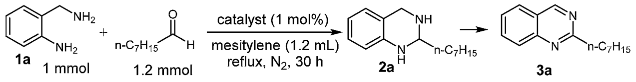
Table 2 Synthesis of 2-substituted quinazolines from **1a** and alcohols by Pt/CeO_2[a]



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

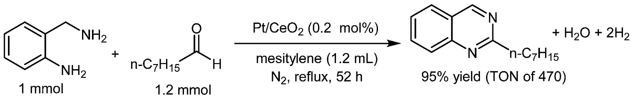
[a] Yield based on **1a** determined by weight of the isolated products. [b] 1.5 mmol alcohol.

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

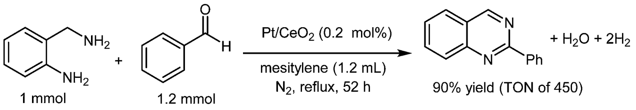


Entry	Catalysts	**2a** yield (%)	**3a** yield[a] (%)
1	Pt/CeO_2	0	98
2	Pd/CeO_2	0	60
3	Rh/CeO_2	17	55
4	Re/CeO_2	7	42
5	Ni/CeO_2	22	18
6	Ir/CeO_2	75	12
7	Ru/CeO_2	60	12
8	Cu/CeO_2	40	10
9[b]	CeO_2	20	0
10	Pt/TiO_2	0	99
11	Pt/MgO	29	56
12	Pt/Nb_2O_5	0	90
13	Pt/Al_2O_3	0	89
14	Pt/ZrO_2	0	70
15	Pt/HBEA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

[a] Yield based on **1a** determined by GC. [b] Catalyst amount was 197 mg.

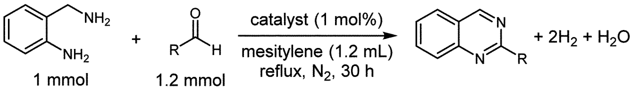


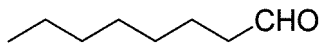
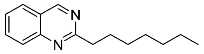
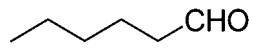
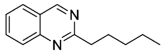
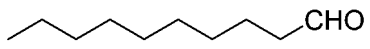
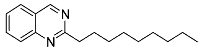
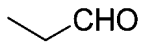
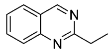
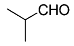
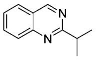
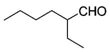
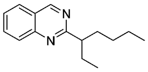
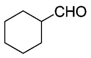
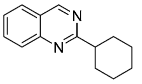
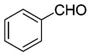
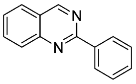
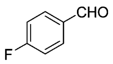
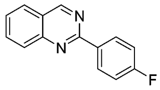
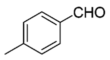
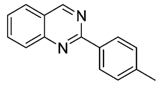
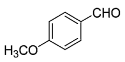
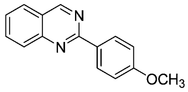
(1)



(2)

Table 4 Synthesis of 2-substituted quinazolines from **1a** and aldehydes by Pt/CeO$_2$



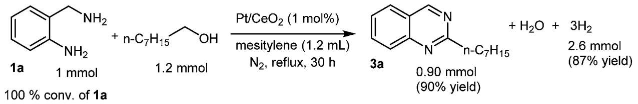
Entry	Aldehyde	Product	Isolated yield[a] (%)
1			93 (95), (90),[c] (90)[d]
2			70
3			92
4[b]			84
5[b]			88
6			50
7			72
8			85
9			77
10			90
11			57

[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.

alcohols (entries 1–3) were converted to the corresponding 2-substituted quinazolines in good yields (75–89%). Benzylalcohol and 4-fluoro benzylalcohol resulted in moderate yields (52, 51%). 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 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 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 (eqn (1)) and



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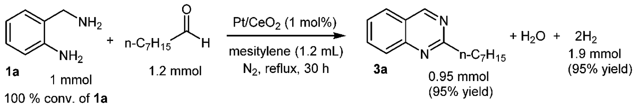
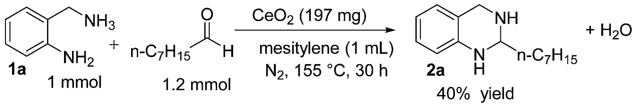


(4)



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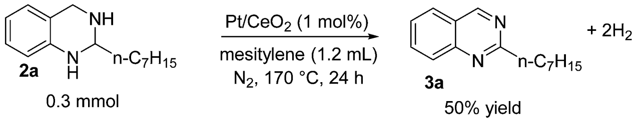
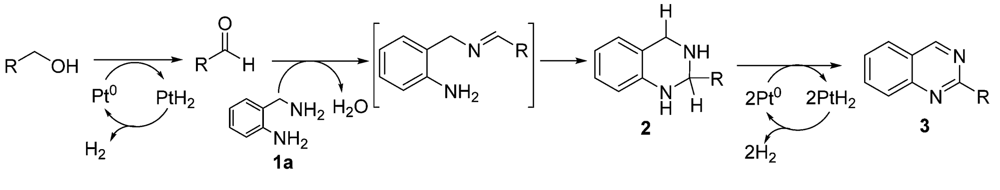


(6)



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

benzaldehyde (eqn (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]

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 4 (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 °C for 3 h and then reduced in H_2 at 300 °C 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 (eqn (3)) and *n*-octanal (eqn (4)). For the reaction of **1a** with 1-octanol (eqn (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 (eqn (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. 1) and **1a** with *n*-octanal (Fig. 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 (eqn (5)). The intermediate **2a** underwent dehydrogenation by Pt/CeO_2 under N_2 atmosphere to give the 2-substituted quinazoline **3a** in 50% yield (eqn (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.

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.

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