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

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We found the first heterogeneous Pt catalysts (Pt/Nb$_2$O$_5$ and Pt/HBEA) for the synthesis of indoles *via* acceptorless dehydrogenative cyclization of 2-(2-aminophenyl)ethanol, showing higher turnover number (TON) than previously reported catalysts.

Indoles are important organic compounds, which are widely used for the syntheses of pharmaceuticals and agrochemicals.[1–4] Various methods to prepare indoles were reported.[1–6] Oxidative or dehydrogenative N-heterocyclization of 2-(2-aminophenyl)ethanol alcohols is one of the most promising protocols,[7–17] since the starting alcohol is easily prepared by the condensation of 2-nitrotoluene with formaldehyde in the presence of bases, followed by the reduction of a nitro functionality to an amino one.[8] Heterogeneous copper catalysts were reported to catalyze the reaction at high temperatures (>200 °C).[7] Homogeneous transition metal catalysts, such as ruthenium[8–10] and iridium[11–14] complexes and a copper/TEMPO system[15] catalyzed the reaction at lower temperatures but have problems such as difficulties in catalyst/product separation and catalyst reuse and needs of additives such as base or acceptor. A supported Au catalyst also required basic additives (200 mol% of NaO*t*Bu) and oxidant (O$_2$).[16] From a viewpoint of sustainable chemistry, acceptorless dehydrogenative coupling methodology[5,6,18–20] under neutral conditions using a reusable catalyst is most attractive. Recently, Wada and co-workers[17] developed a new heterogeneous catalyst, Ru/CeO$_2$, that was effective for acceptorless dehydrogenative synthesis of indole from 2-(2-aminophenyl)ethanol in the absence of any additives. As discussed in the previous studies on this reaction, the reaction can proceeds *via* the following two step pathway:
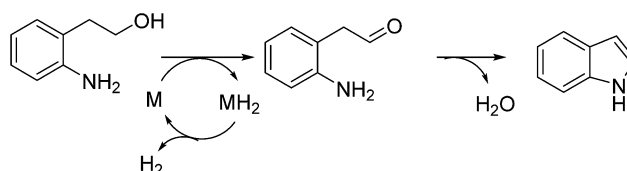
where dehydrogenation of 2-(2-aminophenyl)ethanol by a metal (**M**) catalyst is followed by condensation of the amino aldehyde intermediate to give indole. As a part of our continuing interest in heterogeneous Pt catalysts for acceptorless dehydrogenation of alcohols[21] and acceptorless dehydrogenative coupling reactions of alcohols,[22,23] we report herein the synthesis of indoles *via* acceptorless dehydrogenative N-heterocyclization of 2-(2-aminophenyl)ethanol under additive-free conditions by heterogeneous Pt catalysts, which show higher TON than previous catalytic systems.

We started the N-heterocyclization of 2-(2-aminophenyl) ethanol under *o*-xylene reflux conditions in N$_2$ as a model system in order to optimize catalytic conditions. Table 1 (entries 1–8) summarizes the results of the initial catalyst screening test under the same reaction conditions using various transition metal (Pt, Ir, Ru, Re, Pd, Co, Cu, Ag) catalysts supported on Nb$_2$O$_5$ pre-reduced in H$_2$ at 300 °C. Cu and Ag catalysts (entries 7 and 8) showed no activity and Ru, Re, Pd and Co catalysts (entries 3–6) showed low yields. Ir/Nb$_2$O$_5$ (entry 2) gave a good yield of 68%. Among the catalysts tested, Pt/Nb$_2$O$_5$ (entry 1) showed the highest yield (82%) of indole. Entries 10–19 show the results of Pt catalysts loaded on the other supports (HBEA zeolite, CeO$_2$, MgO, TiO$_2$, ZrO$_2$, Al$_2$O$_3$, SnO$_2$, carbon, SiO$_2$). Pt/Nb$_2$O$_5$ (entry 1) and Pt/HBEA (entry 10) showed higher yields (82–83%) than the other supported Pt catalysts. Pt/CeO$_2$, Pt/MgO, Pt/TiO$_2$, Pt/ZrO$_2$, Pt/Al$_2$O$_3$, Pt/SiO$_2$–Al$_2$O$_3$, Pt/C and Pt/SiO$_2$ (entries 11–19) gave low to moderate yields (9–69%). To study the effect of the oxidation state of Pt species on the activity, we tested the activity of a pre-oxidized catalyst named PtO$_x$/Nb$_2$O$_5$, that is, a platinum oxides-loaded Nb$_2$O$_5$ catalyst. PtO$_x$/Nb$_2$O$_5$ (entry 20) showed a lower yield (10%) than the pre-reduced catalyst, Pt/Nb$_2$O$_5$ (entry 1). Taking into account the result that the activity of the metal-unloaded Nb$_2$O$_5$ is negligible

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**Table 1** Catalyst screening for indole synthesis from 2-(2-amino-phenyl)-ethanol

Entry	Catalyst	Yield[a] (%)
1	Pt/Nb$_2$O$_5$	82
2	Ir/Nb$_2$O$_5$	68
3	Ru/Nb$_2$O$_5$	9
4	Re/Nb$_2$O$_5$	2
5	Pd/Nb$_2$O$_5$	1
6	Co/Nb$_2$O$_5$	1
7	Cu/Nb$_2$O$_5$	0
8	Ag/Nb$_2$O$_5$	0
9[b]	Nb$_2$O$_5$	1
10	Pt/HBEA	77
11	Pt/CeO$_2$	69
12	Pt/MgO	69
13	Pt/TiO$_2$	47
14	Pt/ZrO$_2$	42
15	Pt/Al$_2$O$_3$	22
16	Pt/SiO$_2$–Al$_2$O$_3$	15
17	Pt/SnO$_2$	9
18	Pt/C	15
19	Pt/SiO$_2$	10
20	PtO$_x$/Nb$_2$O$_5$	10
21	Blank	0

[a] Yield was determined by GC. [b] Catalyst amount was 39 mg.

(entry 9) and the result that the activity depends strongly on the support, it is suggested that the co-presence of metallic Pt species and specific support materials (Nb$_2$O$_5$ or HBEA) is important factor of highly active catalysts. Note that indole was not produced in the absence of a catalyst (entry 21).

Table 2 shows the effect of reaction conditions on the yield of indole for the reaction of 2-(2-aminophenyl)ethanol by Pt/Nb$_2$O$_5$ under reflux conditions for 7 h. The reactions in toluene and hexane gave low yield (entries 3 and 4), and the reaction in mesitylene gave 78% yield (entry 2). The reaction in reflux of o-xylene gave the highest yield of 93% (entry 1). After the reaction, the catalyst was removed from the mixture and indole was

isolated by column chromatography, resulting in high isolated yield of indoles (88%). The reaction in o-xylene at lower temperature (130 °C) gave low yield (29%) of indole (entry 5). The reaction under 1 atm O$_2$ in the gas phase (entry 6) gave lower yield (82%) than that under N$_2$ (93%), indicating that O$_2$ as a hydrogen acceptor did not accelerate the catalytic reaction. For the reaction under N$_2$ with Pt/Nb$_2$O$_5$, we carried out mass spectrometry analysis of the gas phase products after 1 h. As shown in eqn (1), the yields of gas phase H$_2$ (24%) was close to the yield of indole (32%).
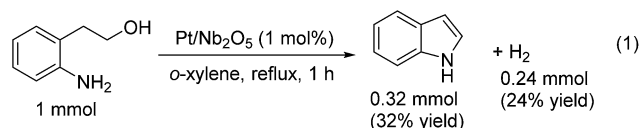
Using Pt/Nb$_2$O$_5$ and Pt/HBEA as two of the effective catalysts for this reaction, we carried out detailed catalytic studies. We checked the time course of the reaction under the standard conditions (Fig. 1). For Pt/Nb$_2$O$_5$, the yield of indole increased with time and reached 93% after 7 h. For Pt/HBEA, the yield of indole reached 95% after 12 h. Fig. 2 shows the results of catalyst reusability of Pt/Nb$_2$O$_5$ and Pt/HBEA. After completion of the reaction, 2-propanol (1 mL) was added to the reaction mixture and the catalyst was separated by centrifugation. The recovered catalyst was washed with acetone three times, followed by centrifugation and drying in an oven (under air) at 90 °C for 12 h and then H$_2$ reduction at 300 °C for 0.5 h. The recovered Pt/Nb$_2$O$_5$ catalyst showed high yield for the second and the third cycle. In contrast, the recovered Pt/HBEA catalyst showed low yields in the second and third cycles. Thus, Pt/Nb$_2$O$_5$ was found to be a better catalyst in terms of reusability.

In order to evaluate TON of the catalytic system, next we carried out the reaction with small amount of the catalysts. As shown in eqn (2), the reactions with 0.2 mol% of Pt/Nb$_2$O$_5$ and Pt/HBEA for 52 h resulted in 76% and 90% yields, corresponding to TONs of 380 and 450, respectively. The TON by Pt/HBEA is 3–25 times larger than those by homogeneous[8–15] and heterogeneous[17] catalysts in the literature for the same reaction. ICP-AES analysis of the filtrate after the reaction with Pt/HBEA

Table 2 Indole synthesis from 2-(2-amino-phenyl)-ethanol by Pt/Nb$_2$O$_5$[a]

Entry	Solvent	Conv.(%)	Yield (%)
1	o-Xylene	100	93
2	Mesitylene	100	78
3	Hexane	74	5
4	Toluene	65	23
5[b]	o-Xylene	44	29
6[c]	o-Xylene	99	82

[a] Conditions: 1 mol% Pt/Nb$_2$O$_5$, 1.0 mmol 2-(2-amino-phenyl)-ethanol, 1 mL solvent, reflux, in N$_2$, 7 h. Yield was determined by GC. [b] $T = $ 130 °C. [c] In 1 atm O$_2$.

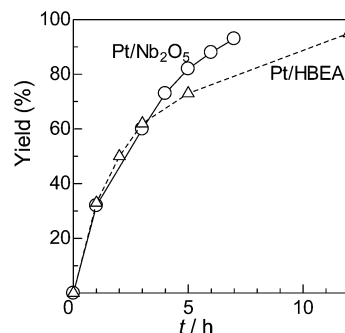**Fig. 1** Yields of indole $vs.$ time for N-heterocyclization of 2-(2-amino-phenyl)ethanol under o-xylene reflux conditions in N$_2$ by Pt/Nb$_2$O$_5$ (○) or Pt/HBEA (△).
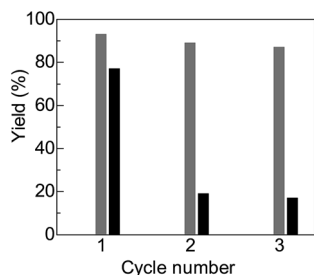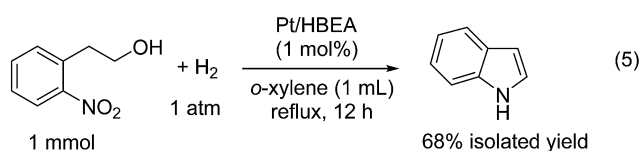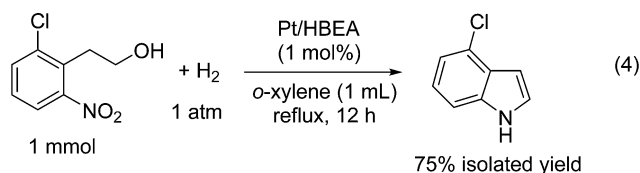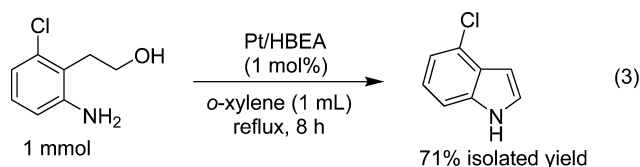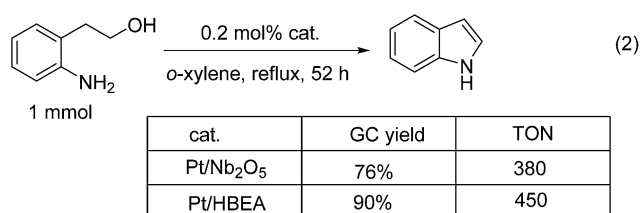
Fig. 2 Reuse of Pt/Nb$_2$O$_5$ (gray bars) or Pt/HBEA (black bars) for N-heterocyclization of 2-(2-aminophenyl)ethanol under o-xylene reflux conditions in N$_2$ for 7 h.

showed that the content of Pt in the solution was quite low (3.4 ppm).

$$(2)$$

cat.	GC yield	TON
Pt/Nb$_2$O$_5$	76%	380
Pt/HBEA	90%	450

$$(3)$$

71% isolated yield

$$(4)$$

75% isolated yield

$$(5)$$

68% isolated yield

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

Since supported Pt catalysts can exhibit a catalytic activity for the reduction of the nitro group to an amino group with H$_2$, we examined the synthesis of indoles from 2-nitrophenthyl alcohols. As shown in eqn (4) and (5), Cl-functionalized 2-nitro-phenthyl alcohol and 2-nitrophenthyl alcohol were selectively

converted to the corresponding indole derivatives in moderate isolated yields under balloon H$_2$ pressure for 12 h in the presence of 1 mol% of Pt/HBEA.

In summary, we reported that Pt/Nb$_2$O$_5$ and Pt/HBEA acted as effective heterogeneous catalysts for the synthesis of indoles via acceptorless dehydrogenative cyclization of 2-(2-amino-phenyl)ethanol. These catalysts showed higher TON than previously reported catalysts, and the Pt/Nb$_2$O$_5$ catalyst was reusable.

Experimental section

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.

H$^+$-type BEA zeolite (HBEA, SiO$_2$/Al$_2$O$_3$ = 25 ± 5, JRC-Z-HB25), CeO$_2$ (JRC-CEO-3), MgO (JRC-MGO-3), TiO$_2$ (JRC-TIO-4) and SiO$_2$–Al$_2$O$_3$ (JRC-SAL-2, Al$_2$O$_3$ = 13.75 wt%) were supplied from Catalysis Society of Japan. Nb$_2$O$_5$ was prepared by calcination of niobic acid (CBMMI) at 500 °C for 3 h. SnO$_2$ was prepared by calcination of H$_2$SnO$_3$ (Kojundo Chemical Laboratory Co., Ltd.) at 500 °C for 3 h. ZrO$_2$ was prepared by calcination of a hydroxide of Zr at 500 °C for 3 h.[23] γ-Al$_2$O$_3$ was prepared by calcination of γ-AlOOH (Catapal B Alumina purchased from Sasol) at 900 °C for 3 h. Precursor of 5 wt% Pt/Nb$_2$O$_5$ was prepared by an impregnation method; a mixture of Nb$_2$O$_5$ and an aqueous HNO$_3$ solution of Pt(NH$_3$)$_2$(NO$_3$)$_2$ was evaporated at 50 °C, followed by drying at 90 °C for 12 h. A pre-reduced catalyst, named Pt/Nb$_2$O$_5$, was prepared by pre-reduction of the precursor in a Pyrex tube under a flow of H$_2$ (20 cm^3 min^{-1}) at 300 °C for 0.5 h. Platinum oxides-loaded Nb$_2$O$_5$ (PtO$_x$/Nb$_2$O$_5$), as a comparative catalyst, was prepared by calcination of the precursor in air at 300 °C for 3 h. By using various supports, several pre-reduced Pt catalysts were prepared by the same method as Pt/Nb$_2$O$_5$. Nb$_2$O$_5$-supported metal catalysts, M/Nb$_2$O$_5$ (M = Co, Cu, Ru, Pd, Ag, Re, Ir) with metal loading of 5 wt% were prepared by impregnation method in a similar manner as Pt/Nb$_2$O$_5$ using an aqueous solution of metal nitrates (for Co, Cu, Ag), RuCl$_3$, IrCl$_3$, NH$_4$ReO$_4$ or an aqueous HNO$_3$ solution of Pd(NO$_3$)$_2$.

Typically, 5 wt% Pt/Nb$_2$O$_5$ (39 mg, 0.01 mmol of Pt) was used as a standard catalyst. After the pre-reduction at 300 °C, we carried out catalytic tests using a batch-type reactor without exposing the catalyst to air as follows. A mixture of 2-(2-amino-phenyl)ethanol (1.0 mmol) and n-dodecane (0.2 mmol) in o-xylene (1 mL) was injected to the pre-reduced catalyst inside the reactor (cylindrical glass tube) through a septum inlet, followed by filling N$_2$. Then, the resulting mixture was magnetically stirred for 5 h under reflux condition; the bath temperature was 155 °C and reaction temperature was $ca.$ 144 °C. The yield of indole was determined by GC using n-dodecane as an internal standard. The analysis of the gas phase product (H$_2$) was carried out by the mass spectrometer (BELMASS). To determine the isolated yield of indole, indole was isolated by column chromatography using

silica gel 60 (spherical, 63–210 μm, Kanto Chemical Co. Ltd.) with hexane/ethylacetate (95/5) as the eluting solvent, followed by analyses by GCMS and ^{1}H and ^{13}C NMR (JEOL-ECX 600 operating at 600.17 and 150.92 MHz, respectively) with tetramethylsilane as an internal standard.

Acknowledgements

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