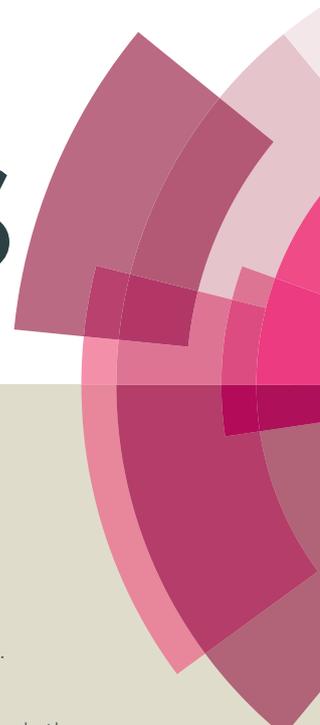


RSC Advances



This article can be cited before page numbers have been issued, to do this please use: K. Shimizu, S. K. Moromi, S. S. M. A. Hakim, Md. A. Ali and A. S. Touchy, *RSC Adv.*, 2014, DOI: 10.1039/C4RA11893F.



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

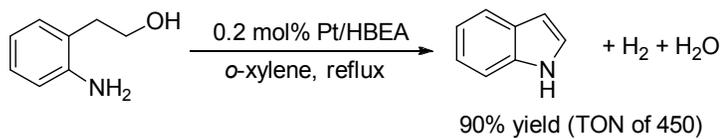
Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. This *Accepted Manuscript* will be replaced by the edited, formatted and paginated article as soon as this is available.

You can find more information about *Accepted Manuscripts* in the [Information for Authors](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the [Ethical guidelines](#) still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

Table of Contents

Heterogeneous Pt catalysts (Pt/Nb₂O₅ and Pt/HBEA) show higher turnover number (TON) than previously reported catalysts for the synthesis of indole via acceptorless dehydrogenative cyclization of 2-(2-aminophenyl)ethanol.



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

Sandomoyee Konika Moromi,^a Abeda Sultana Touchy,^a S. M. A. Hakim Siddiki,^b Md. Ayub Ali,^a Ken-ichi Shimizu^{*a,b}

^a Catalysis Research Center, Hokkaido University, N-21, W-10, Sapporo 001-0021, Japan

^b Elements Strategy Initiative for Catalysts and Batteries, Kyoto University, Katsura, Kyoto 615-8520, Japan

*Corresponding author

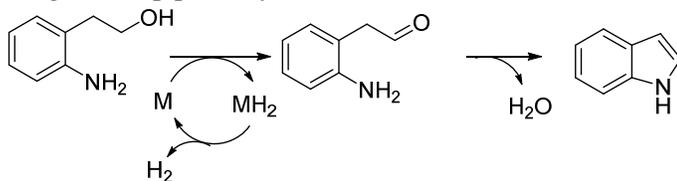
Ken-ichi Shimizu

Catalysis Research Center, Hokkaido University, N-21, W-10, Sapporo 001-0021, Japan

E-mail: kshimizu@cat.hokudai.ac.jp, Fax: +81-11-706-9163

Abstract: We found the first heterogeneous Pt catalysts (Pt/Nb₂O₅ 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 ruthenium⁸⁻¹⁰ and iridium¹¹⁻¹⁴ complexes and a copper/TEMPO system¹⁵ 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 NaOtBu) and oxidant (O₂).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-workers¹⁷ developed a new heterogeneous catalyst, Ru/CeO₂, 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 proceed via the following two step pathway:

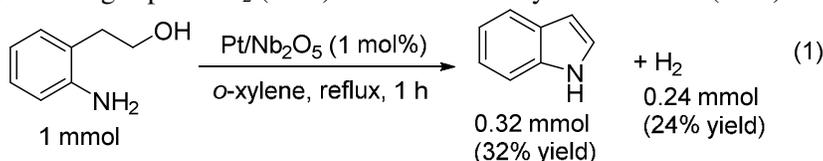


, where dehydrogenation of 2-(2-aminophenyl)ethanol by a metal (M) catalyst is followed by condensation of the amino aldehyde intermediate to give indole. As a part of our continuing interest in heterogeneous Pt catalysts for acceptorless dehydrogenation of alcohols²¹ and acceptorless dehydrogenative coupling reactions of alcohols,^{22,23} we report herein the synthesis of indoles via acceptorless dehydrogenative *N*-heterocyclization 2-(2-aminophenyl)ethanol under additive-free conditions by heterogeneous Pt catalysts, which show higher TON than previous catalytic systems.

We started the *N*-heterocyclization of 2-(2-aminophenyl)ethanol under *o*-xylene reflux conditions in N₂ 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

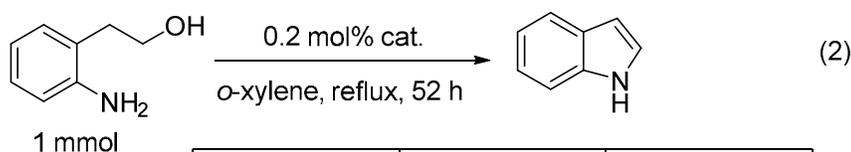
using various transition metal (Pt, Ir, Ru, Re, Pd, Co, Cu, Ag) catalysts supported on Nb₂O₅ pre-reduced in H₂ at 300 °C. Cu and Ag catalysts (entries 7,8) showed no activity and Ru, Re, Pd and Co catalysts (entries 3–6) showed low yields. Ir/Nb₂O₅ (entry 2) gave a good yield of 68%. Among the catalysts tested, Pt/Nb₂O₅ (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, CeO₂, MgO, TiO₂, ZrO₂, Al₂O₃, SnO₂, carbon, SiO₂). Pt/Nb₂O₅ (entry 1) and Pt/HBEA (entry 10) showed higher yields (82–83%) than the other supported Pt catalysts. Pt/CeO₂, Pt/MgO, Pt/TiO₂, Pt/ZrO₂, Pt/Al₂O₃, Pt/SiO₂-Al₂O₃, Pt/C and Pt/SiO₂ (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/Nb₂O₅, that is, a platinum oxides-loaded Nb₂O₅ catalyst. PtO_x/Nb₂O₅ (entry 20) showed a lower yield (10%) than with the pre-reduced catalyst, Pt/Nb₂O₅ (entry 1). Taking into account the result that the activity of the metal-unloaded Nb₂O₅ was negligible (entry 9) and the result that the activity depends strongly on the support, it is suggested that the co-presence of metallic Pt species and specific support materials (Nb₂O₅ 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/Nb₂O₅ under reflux conditions for 7 h. The reactions in toluene and hexane gave low yield (entries 3,4), and the reaction in mesitylene gave 78% yield (entry 2). The reaction in reflux of *o*-xylene gave the highest yield of 93% (entry 1). After the reaction, the catalyst was removed from the mixture and indole was isolated by column chromatography, resulting in high isolated yield of indoles (88%). The reaction in *o*-xylene at lower temperature (130 °C) gave low yield (29%) of indole (entry 5). The reaction under 1atm O₂ in the gas phase (entry 6) gave lower yield (82%) than that under N₂ (93%), indicating that O₂ as a hydrogen acceptor does not accelerate the catalytic reaction. For the reaction under N₂ with Pt/Nb₂O₅, we carried out mass spectrometry analysis of the gas phase products after 1 h. As shown in eqn. (1), the yields of gas phase H₂ (24%) was close to the yield of indole (32%).

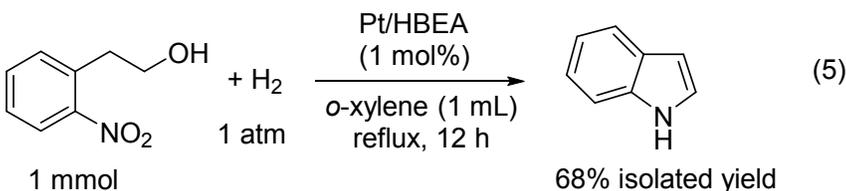
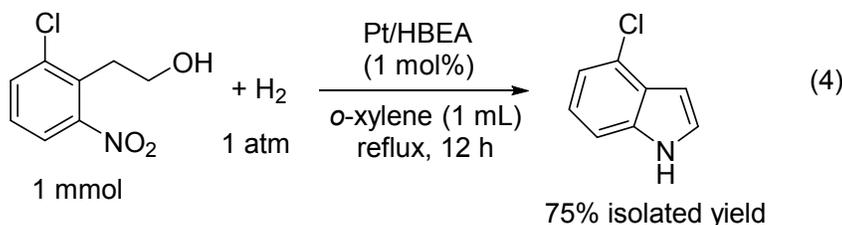
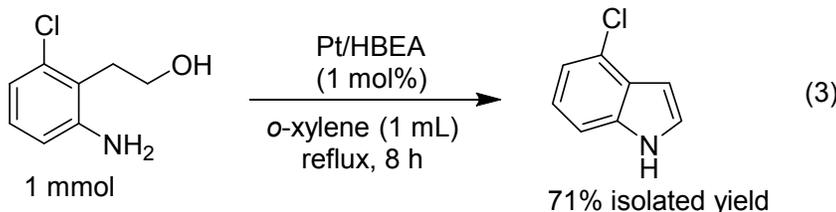


Using Pt/Nb₂O₅ and Pt/HBEA as two of the effective catalysts for this reaction, we carried out detailed catalytic studies. We checked the time course of the reaction under the standard conditions (Fig. 1). For Pt/Nb₂O₅, the yield of indole increased with time and reached 93% after 7 h. For Pt/HBEA, the yield of indole reached 95% after 12 h. Fig. 2 shows the results of catalyst reusability of Pt/Nb₂O₅ 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 H₂ reduction at 300 °C for 0.5 h. The recovered Pt/Nb₂O₅ 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/Nb₂O₅ 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/Nb₂O₅ 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 heterogeneous¹⁷ catalysts in the literature for the same reaction. ICP-AES analysis of the filtrate after the reaction with Pt/HBEA showed that the content of Pt in the solution was quite low (3.4 ppm).



cat.	GC yield	TON
Pt/Nb ₂ O ₅	76%	380
Pt/HBEA	90%	450



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

Since supported Pt catalysts can exhibit a catalytic activity for the reduction of the nitro group to an amino group with H₂, we examined the synthesis of indoles from 2-nitrophenethyl alcohols. As shown in equations (4) and (5), Cl-functionalized 2-nitrophenethyl alcohol and 2-nitrophenethyl alcohol were selectively converted to the corresponding indole derivatives in moderate isolated yields under balloon H₂ pressure for 12 h in the presence of 1 mol% of Pt/HBEA.

In summary, we reported that Pt/Nb₂O₅ and Pt/HBEA acted as effective heterogeneous catalysts for the synthesis of indoles via acceptorless dehydrogenative cyclization of 2-(2-aminophenyl)ethanol. These catalysts showed higher TON than previously reported catalysts, and the Pt/Nb₂O₅ 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, SiO₂/Al₂O₃ = 25±5, JRC-Z-HB25), CeO₂ (JRC-CEO-3), MgO (JRC-MGO-3), TiO₂ (JRC-TIO-4) and SiO₂-Al₂O₃ (JRC-SAL-2, Al₂O₃ = 13.75 wt%) were supplied from Catalysis Society of Japan. Nb₂O₅ was prepared by calcination of niobic acid (CBMMI) at 500 °C for 3 h. SnO₂ was prepared by calcination of H₂SnO₃ (Kojundo Chemical Laboratory Co., Ltd.) at 500 °C for 3 h. ZrO₂ was prepared by calcination of a hydroxide of Zr at 500 °C for 3 h.²³ γ-Al₂O₃ was prepared by calcination of γ-AlOOH (Catapal B Alumina purchased from Sasol) at 900 °C for 3 h. Precursor of 5 wt% Pt/Nb₂O₅ was prepared by an impregnation method; a mixture of Nb₂O₅ and an aqueous HNO₃ solution of Pt(NH₃)₂(NO₃)₂ was evaporated at 50 °C, followed by drying at 90 °C for 12 h. A pre-reduced catalyst, named Pt/Nb₂O₅, was prepared by pre-reduction of the precursor in a pyrex tube under a flow of H₂ (20 cm³ min⁻¹) at 300 °C for 0.5 h. Platinum oxides-loaded Nb₂O₅ (PtO_x/Nb₂O₅), 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/Nb₂O₅. Nb₂O₅-supported metal catalysts, M/Nb₂O₅ (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/Nb₂O₅ using an aqueous solution of metal nitrates (for Co, Cu, Ag), RuCl₃, IrCl₃, NH₄ReO₄ or an aqueous HNO₃ solution of Pd(NO₃)₂.

Typically, 5 wt% Pt/Nb₂O₅ (39 mg, 0.01 mmol of Pt) was used as a standard catalyst. After the pre-reduction at 300 °C, we carried out catalytic tests using a batch-type reactor without exposing the catalyst to air as follows. A mixture of 2-(2-aminophenyl)ethanol (1.0 mmol) and *n*-dodecane (0.2 mmol) in *o*-xylene (1 mL) was injected to the pre-reduced catalyst inside the reactor (cylindrical glass tube) through a septum inlet, followed by filling N₂. 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 (H₂) 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 ¹H and ¹³C NMR (JEOL-ECX 600 operating at 600.17 and 150.92 MHz, respectively) with tetramethylsilane as an internal standard.

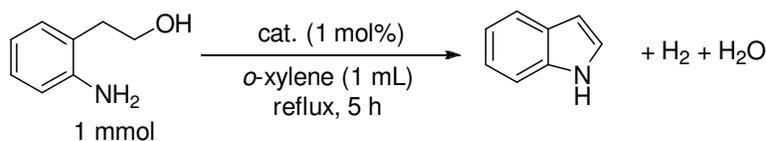
Acknowledgment

This work was supported by Grant-in-Aids for Scientific Research B (26289299) from MEXT (Japan), a MEXT program "Elements Strategy Initiative to Form Core Research Center" and a Grant-in-Aid for Scientific Research on Innovative Areas "Nano Informatics" (25106010) from JSPS.

Notes and references

1. a) R. J. Sundberg, *The Chemistry of Indoles*; Academic Press: New York, 1970; b) L. S. Hegedus, *Angew. Chem., Int. Ed.*, 1988, **27**, 1113–1226; c) T. L. Gilchrist, *J. Chem. Soc., Perkin Trans. 1*, **1999**, 2849–2866.
2. G. W. Gribble, *J. Chem. Soc., Perkin Trans. 1*, **2000**, 1045–1075
3. S. Cacchi and G. Fabrizi, *Chem. Rev.*, 2005, **105**, 2873–2920.
4. J. Barluenga, F. Rodríguez and F. T. Fañanás, *Chem.–Asian J.*, 2009, **4**, 1036–1048.
5. M. Zhang, F. Xie, X. T. Wang, F. Yan, T. Wang, M. Chen and Y. Ding, *RSC Adv.*, 2013, **3**, 6022–6029.
6. M. Tursky, L. L. R. Lorentz-Petersen, L. B. Olsen and R. Madsen, *Org. Biomol. Chem.*, 2010, **8**, 5576–5582.

7. W. Hammerschmidt, A. Baiker, A. Wokaun and W. Fluhr, *Appl. Catal.*, 1986, **20**, 305–312.
8. Y. Tsuji, S. Kotachi, K.-T. Huh and Y. Watanabe, *J. Org. Chem.*, 1990, **55**, 580–584.
9. T. Kondo, T. Kanda, Daisuke Takagi, Kenji Wada, Yu Kimura and Akio Toshimitsu, *J. Heterocycl. Chem.*, 2012, **86**, 1015–1022.
10. S. C. Ghosh and S. H. Hong, *Eur. J. Org. Chem.*, **2010**, 4266–4270.
11. K. Fujita, K. Yamamoto and R. Yamaguchi, *Org. Lett.*, 2002, **4**, 2691–2694.
12. S. Whitney, R. Grigg, A. Derrick and A. Keep, *Org. Lett.*, 2007, **9**, 3299–3302.
13. C.-F. Fu, Y.-H. Chang, Y.-H. Liu, S.-M. Peng, C. J. Elsevier, J.-T. Chen and S.-T. Liu, *Dalton Trans.*, **2009**, 6991–6998.
14. G. Guisado-Barríos, J. Hiller and E. Peris, *Chem.–Eur. J.*, 2013, **19**, 10405–10411.
15. J. C. A Flanagan, L. M. Dornan, M. G. McLaughlin, N. G. McCreanor, M. J. Cook and M. J. Muldoon, *Green Chem.*, 2012, **14**, 1281–1283.
16. R. Bernini, S. Cacchi, G. Fabrizi, S. Niembro, A. Prastaro, A. Shafir and A. Vallribera, *ChemSusChem*, 2009, **2**, 1036–1040.
17. S. Shimura, H. Miura, K. Wada, S. Hosokawa, S. Yamazoe and M. Inoue, *Catal. Sci. Technol.*, 2011, **1**, 1340–1346.
18. a) C. Gunanathan and D. Milstein, *Science*, 2013, **341**, 249–260; b) G. E. Döbereiner and R. H. Crabtree, *Chem. Rev.*, 2010, **110**, 681–703; c) C. Chen and S. Hyeok Hong, *Org. Biomol. Chem.*, 2011, **9**, 20–26; d) T. Hille, T. Irrgang, and R. Kempe, *Chem. Eur. J.*, 2014, **20**, 5569–5572; e) S. Michlik and R. Kempe, *Nat. Chem.* 2013, **5**, 140–144; f) F. Xie, M. Chen, X. Wang, H. Jiang and M. Zhang, *Org. Biomol. Chem.*, 2014, **12**, 2761–2768.
19. H. Wang, J. Zhang, Y.-M. Cui, K.-F. Yang, Z.-J. Zheng and L.-W. Xu, *RSC Adv.*, 2014, **4**, 34681–34686.
20. X. Wang, M. Chen, F. Xie and M. Zhang, *RSC Adv.*, 2014, **4**, 14744–14751.
21. K. Kon, S. M. A. H. Siddiki and K. Shimizu, *J. Catal.*, 2013, **304**, 63–71.
22. S. M. A. H. Siddiki, K. Kon, A. S. Touchy and K. Shimizu, *Catal. Sci. Technol.*, 2014, **4**, 1716–1719.
23. S. K. Moromi, S. M. A. H. Siddiki, Md. A. Ali, K. Kon and K. Shimizu, *Catal. Sci. Technol.*, 2014, **4**, 3631–3635.

Table 1. Catalyst screening for indole synthesis from 2-(2-amino-phenyl)-ethanol.^a

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.**Table 2.** Indole synthesis from 2-(2-amino-phenyl)-ethanol by Pt/Nb₂O₅.^a

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

^a Conditions: 1 mol% Pt/Nb₂O₅, 1.0 mmol 2-(2-amino-phenyl)-ethanol, 1 mL solvent, reflux, in N₂, 7 h. Yield was determined by GC.^b *T* = 130 °C.^c in 1 atm O₂.

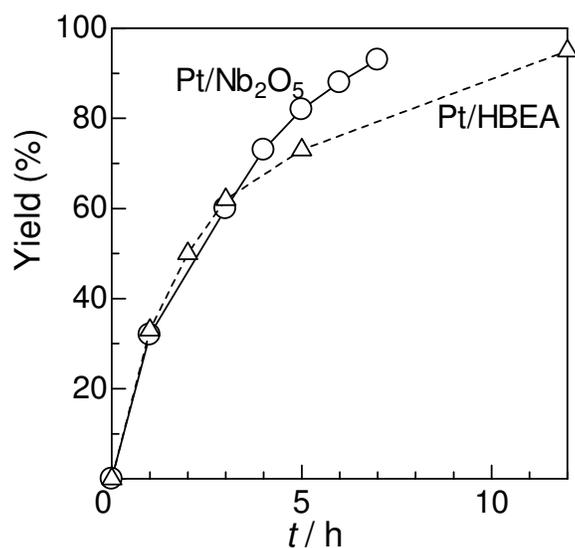


Fig. 1 Yields of indole vs time for *N*-heterocyclization of 2-(2-aminophenyl)ethanol under *o*-xylene reflux conditions in N₂ by Pt/Nb₂O₅ (○) or Pt/HBEA (△).

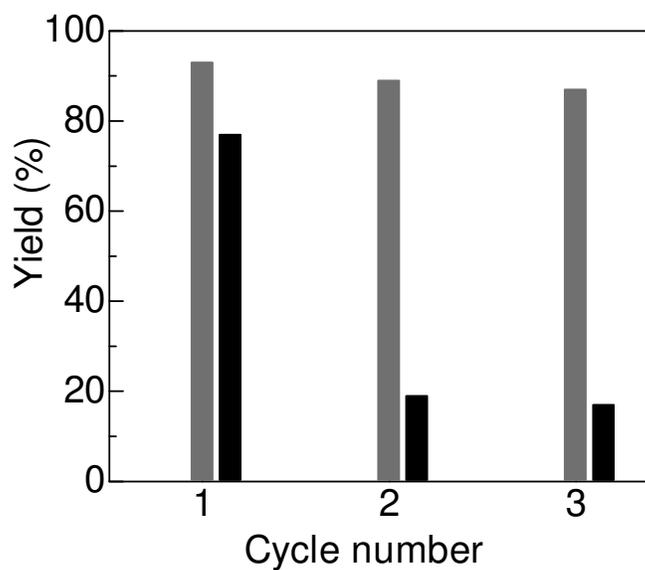


Fig. 2. Reuse of Pt/Nb₂O₅ (gray bars) or Pt/HBEA (black bars) for *N*-heterocyclization of 2-(2-aminophenyl)ethanol under *o*-xylene reflux conditions in N₂ for 7 h.