NJC

One-pot synthesis of cyclohexylamine and *N*-aryl pyrroles via hydrogenation of nitroarenes over $Pd_{0.5}Ru_{0.5}$-PVP catalyst

Journal:	*New Journal of Chemistry*
Manuscript ID	NJ-COM-02-2021-000922.R2
Article Type:	Communication
Date Submitted by the Author:	20-Apr-2021
Complete List of Authors:	Nagaoka, Katsutoshi; Nagoya University, Department of Chemical Systems Engineering, Graduate school of Engineering; Chaudhari, Chandan; Nagoya University Graduate School of Engineering School of Engineering, Ikeda, Yasuyuki; Furuya Metal Co.,Ltd., Sato, Katsutoshi; Kyoto University, Elements Strategy Initiative for Catalysts and Batteries Terada, Kenji ; Furuya Metal Co.,Ltd. Abe, Naoya; Furuya Metal Co.,Ltd.

COMMUNICATION

One-pot synthesis of cyclohexylamine and *N*-aryl pyrroles via hydrogenation of nitroarenes over $Pd_{0.5}Ru_{0.5}$-PVP catalyst

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Chandan Chaudhari,*[a] Katsutoshi Sato,[a,b] Yasuyuki Ikeda,[c] Kenji Terada,[c] Naoya Abe,[c] and Katsutoshi Nagaoka*[a]

Direct synthesis of cyclohexylamine via hydrogenation of nitrobenzene over monometallic (Pd, Ru or Rh) and bimetalllic (Pd_xRu_{1-x}) catalysts was studied. $Pd_{0.5}Ru_{0.5}$-PVP catalyst was the most effective catalyst for this reaction. The catalyst was reused and applied for the synthesis of *N*-aryl pyrroles and quinoxalines from nitrobenzenes.

Development of effective and environmental-friendly synthetic methods is a great challenge. In that context, synthetic methods that accomplish multi-step reactions in single reaction vessel are highly desirable to reduce energy consumption and chemical waste. Cyclohexylamine is an important intermediate for the synthesis of artificial sweeteners, metal corrosion, inhibitors, rubber vulcanizing additives, dyestuffs and plasticizers.[1-3] Several catalytic methods have been reported for the synthesis of cyclohexylamine such as hydrogenation of aniline[4-9] or flammable and hazardous nitrocyclohexane,[10] amination of cyclohexanone or cyclohexanol,[11] amination of chlorocyclohexane.[12] Among them, hydrogenation of aniline is a simple and atom-efficient route for the synthesis of cyclohexylamine. However, aniline is produced by the hydrogenation of nitrobenzene. Therefore, direct synthesis of cyclohexylamine via hydrogenation of nitrobenzene is more practical.

In 1972, direct synthesis of cyclohexylamine from nitrobenzene cyclohexylamine was reported by using supported Rh catalyst.[20] This was the first example of direct synthesis of cyclohexyl amine with high pressure (6.8 MPa) of H_2. Decades later, carbon-supported Ni- and Pd-based catalysts were reported to be effective for similar transformation using low pressure (3.5 MPa)[21] and/or additive (LiOH).[21,22] The basic additive (LiOH) was used to neutralize the surface acidic sites on carbon support and consequently, the selectivity for cyclohexylamine was enhanced. Additive-free conditions were also investigated by using supported Ru catalysts.[23,24] However, these catalytic methods suffer from use of high temperature (> 150 °C) and high pressure (> 3 MPa).

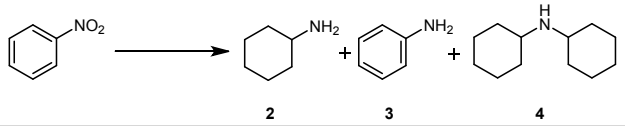
Recently, we have synthesized $Pd_{0.5}Ru_{0.5}$-PVP solid solution alloy and applied as a cheap alternative and pseudo-Rh catalyst for CO oxidation and automobile exhaust purification.[25,26] Furthermore, $Pd_{0.5}Ru_{0.5}$-PVP showed excellent activity for the chemoselective hydrogenation of heteroarenes and arenes.[27] In continuation of exploration of new applications of $Pd_{0.5}Ru_{0.5}$ catalyst, we report herein one-pot synthesis of cyclohexylamine and *N*-aryl pyrroles via hydrogenation of nitrobenzene under mild reaction conditions (Table S2).

Initially, we studied the effect of pressure on the hydrogenation of nitrobenzene using $Pd_{0.5}Ru_{0.5}$-PVP. As shown in Table 1, it was clearly indicated that the hydrogen pressure affected the selectivity of products, while no change in conversion of nitrobenzene was observed (entries 1-5). Using the low pressure (0.5-1 MPa) of H_2, aniline was a major product but it was not sufficient for the hydrogenation of benzene ring. When the hydrogen pressure was increased to 2 MPa, the high yield (95%) of cyclohexylamine was obtained. Increasing the pressure further (> 2 MPa) decreased the yield of cyclohexylamine. Next, we explored the composition of Pd_1Ru_{1-x}-PVP catalyst influenced the catalytic activity (entries 6 and 7). $Pd_{0.7}Ru_{0.3}$ catalyst was less active for the ring hydrogenation step, and 41 % yield of aniline was obtained, along with 43% yield of cyclohexylamine. In contrast, $Pd_{0.3}Ru_{0.7}$ catalyst gave higher yield (83%) of cyclohexylamine but the yield was lower than that for $Pd_{0.5}Ru_{0.5}$-PVP. The Pd-Ru site might be responsible for high selectivity. Finally, monometallic Pd and Ru catalyst delivered aniline as the major product (entries 8-9), and monometallic Rh catalyst produced 64% yield of cyclohexylamine (entry 10).

[a] *Department of Chemical Systems Engineering, Graduate School of Engineering, Nagoya university, Furo-cho, Chikusa-ku, Nagoya, 464-8603, Japan.*
Email: nagaoka.katsutoshi@material.nagoya-u.ac.jp
Email: chaudhari.chandan.subhash@d.mbox.nagoya-u.ac.jp
[b] *Elements Strategy Initiative for Catalysts and Batteries (ESCIB), Kyoto University, Katsura, Kyoto 615-8520, Japan.*
[c] *Furuya Metal Co., Ltd., Higashitsukuba Niihari Kogyodanchi,57-4, Sawabe, Tsuchiura City, Ibaraki 300-4104, Japan.*
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

COMMUNICATION

Table 1 one-pot synthesis of cyclohexylamine by metal catalysts[a]



2 3 4

Entry	Catalyst	Particle size(nm)[b]	H_2 (MPa)	Conv. (%)	Yield[2] (%)[b]	Yield[3] (%)[b]	Yield[4] (%)[b]
1	$Pd_{0.5}Ru_{0.5}$-PVP	5.6 ± 1.6	0.5	99	3	92	0
2	$Pd_{0.5}Ru_{0.5}$-PVP	5.6 ± 1.6	1	99	44	37	6
3	**$Pd_{0.5}Ru_{0.5}$-PVP**	**5.6 ± 1.6**	2	**99**	**95**	**2**	**1**
4	$Pd_{0.5}Ru_{0.5}$-PVP	5.6 ± 1.6	3	99	90	0	1
5	$Pd_{0.5}Ru_{0.5}$-PVP	5.6 ± 1.6	4	99	87	0	1
6	$Pd_{0.3}Ru_{0.7}$-PVP	2.4 ± 0.8	2	99	83	0	2
7	$Pd_{0.7}Ru_{0.3}$-PVP	4.2 ± 2.8	2	99	43	41	10
8	Ru-PVP	8.4 ± 2.4	2	99	30	60	2
9	Pd-PVP	4.8 ± 0.8	2	99	10	88	1
10	Rh-PVP	5.4 ± 1.0[b]	2	95	64	4	5

[a]Reaction conditions: nitrobenzene (1 mmol), catalyst (1.4 mol%), cyclohexane (1 mL), 2 MPa H_2, 100 °C, 6 h. [b]GC yield. [c]Ref. 37.

It is well-known that the solvent always plays a crucial role in hydrogenation reactions by enhancing the activity and controlling byproducts formation. Therefore, we tested four alternative solvents for the nitrobenzene hydrogenation reaction: THF, 1,4-dioxane, toluene, and water (Figure 1). In all these solvents, full conversion of nitrobenzene was achieved, but the yield of cyclohexylamine was highest in cyclohexane. The reaction in water delivered substantial amounts of *N*-dicyclohexylamine and cyclohexanol as byproducts.

To study versatility of $Pd_{0.5}Ru_{0.5}$-PVP catalyst, we carried out hydrogenation reaction of substituted nitrobenzene (Table 2). Hydrogenation of nitrobenzene bearing electron donating group (-CH_3) showed high yield of 4-methylcyclohexylamine (entry 2). Nitrobenzene with electron withdrawing group (-Cl) proceeded to dechlorination reaction, and 92% cyclohexylamine was obtained (entry 3). The chemo-selectivity of $Pd_{0.5}Ru_{0.5}$-PVP was investigated using 4-nitroacetophenone substrate. The acetyl group was completely hydrogenated to hydroxyl and 1-(4-aminocyclohexyl)-ethanol was observed (60 %). Furthermore, the hydrodeoxygenation of 1-(4-aminocyclohexyl)-ethanol gave 40% yield of 4-ethylcyclohexylamine. Next, we applied our protocol for the synthesis of industrially important chemical 4,4'-diaminodicyclohexylmethane (H12MDA) which is an important intermediate for the synthesis of polyurethanes via 4,4'-diisocyanatodicyclohexylmethane routes.[28] H12MDA is generally produced through the following two step procedure, i) synthesis of 4,4'-diaminodiphenylmethane (MDA) from aniline and formaldehyde,[29-31] ii) hydrogenation of MDA to H12MDA.[7,32,33] $Pd_{0.5}Ru_{0.5}$-PVP catalyst showed the moderate yield (76%) of H12MDA by hydrogenation of MDA. This result demonstrated the first successful example of the direct synthesis of H12MDA from 4, 4'-dinitrodiphenylmethane (entry 5). Furthermore, we hydrogenated 3-nitropyridine to 3-aminopiperidine which is an essential ingredient for the synthesis of alogliptin, a dipeptidyl peptidase-4 inhibitor (entry 6).[34]

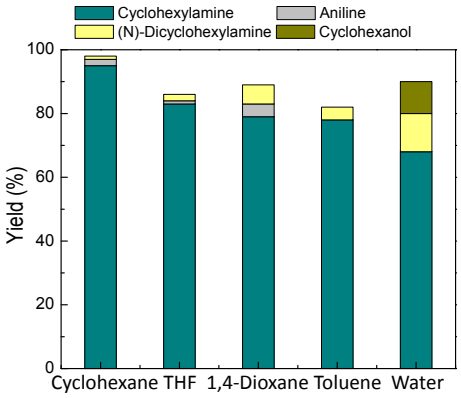
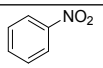
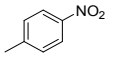
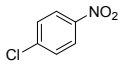
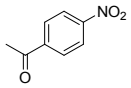
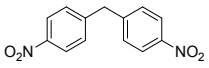


Figure 1. The effect of solvent on the hydrogenation of nitrobenzene to cyclohexylamine.

The recyclability of $Pd_{0.5}Ru_{0.5}$-PVP catalyst was examined for the hydrogenation of nitrobenzene to cyclohexylamine under optimized reaction conditions. After finishing the reaction, the catalyst was washed with acetone multiple times, separated by centrifugation, and dried at 80 °C under vacuum for 12 h.

Table 2 Hydrogenation of substituted nitrobenzene by $Pd_{0.5}Ru_{0.5}$-PVP[a]

Entry	Nitroarenes	Time (h)	Conv. (%)	GC Yield (%)
1		6	99	92
2		12	99	89
3		12	99	92[b]
4		24	99	60[c]
5[d]		48	99	76[e]
6[f]		48	99	95

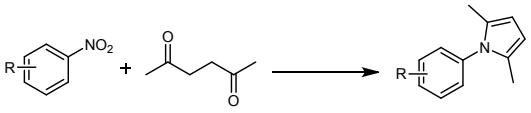
[a]Reaction conditions: nitroarene (1 mmol), $Pd_{0.5}Ru_{0.5}$-PVP (1.4 mol% metal), cyclohexane (1 mL), 100 °C. [b]Cyclohexylamine. [c]4-ethylcyclohexylamine [d]5 MPa H_2 [e]MDA was obtained. [e]3 MPa.

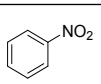
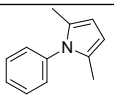
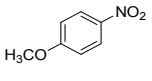
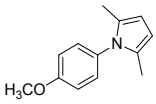
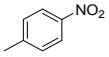
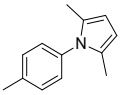
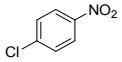
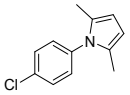
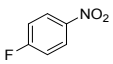
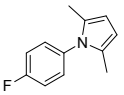
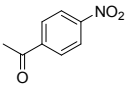
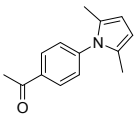
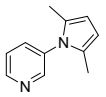
$Pd_{0.5}Ru_{0.5}$-PVP catalyst was reused three times without any loss in catalytic activity (Fig S1).

In recent years, one-pot synthesis of heterocycles such as pyrroles from nitroarenes has attracted the attention of researchers due to high atom-economy of this strategy. Pyrroles are important motifs in various natural products and synthetic medicinal agents. Pyrrole derivatives show a wide range of biological activities such as antibacterial, antiviral, anti-inflammatory, antitumor, and anti-oxidants.[35-38] Heterogeneous (Pd, Pt, Rh, and Co) catalysts based and Indium- mediated methods have been developed for the synthesis of pyrrole from nitrobenzene and 2,5-hexanedione.[39-45] However, these methods require additives,[43-45] toxic gas (CO)[40,42,43] and have limited scope.[39]

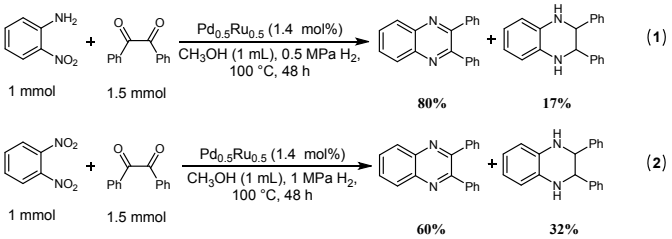
Encouraged by the results of hydrogenation of nitrobenzene, we carried out one-pot syntheses of pyrroles from substituted nitrobenzene and 2,5-hexanedione using low pressure (0.5 MPa) of H_2. As shown in Table 3, the effect of substituent of nitrobenzene on heterocyclization of pyrrole was not observed and excellent yields were obtained when nitrobenzene bearing electron-donating group and electron-withdrawing group was used (entries 1-5). In the presence of other reducible functional group (-$COCH_3$), $Pd_{0.5}Ru_{0.5}$-PVP catalyst showed the chemo-selectivity for the hydrogenation of nitro group and formed corresponding pyrrole (entry 6). 3-Nitropyridine was converted to corresponding pyrroles but heterocyclization step was partially retarded in this reaction (entry 7). Considering the activity for pyrrole synthesis, the scope of $Pd_{0.5}Ru_{0.5}$-PVP was expanded for the synthesis of *N*-containing heterocycle such as quinoxalines from 1,2-dinitrobenzene or 2-nitroaniline and benzil. When 2-nitroaniline was used, high yield of quinoxalines was obtained in 48 h (eq. 1) and dinitrobenzene gave moderate yield (eq. 2).

Table 3 One-pot synthesis of *N*-aryl pyrroles from nitroarenes and 2,5-hexanedione by $Pd_{0.5}Ru_{0.5}$-PVP[a]



Entry	Nitroarenes	Product	Conv. (%)	GC Yield (%)
1			99	97
2			99	99
3			99	99
4			99	82
5			99	91
6			82	70
7			99	61[b]

[a]Reaction conditions: nitroarene (1 mmol), 2,5-hexanodione (1 mmol), $Pd_{0.5}Ru_{0.5}$-PVP (1.4 mol% metal), methanol (1 mL), 0.5 MPa H_2, 100 °C, 24h. [b]3-aminopyridine was obtained as byproduct.



Conclusions

We have developed an effective method using $Pd_{0.5}Ru_{0.5}$-PVP for direct synthesis of cyclohexylamine via hydrogenation of nitrobenzene under mild reaction conditions. By using this catalyst, one-pot synthesis of *N*-aryl pyrroles and quinoxalines was achieved from nitrobenzene. The catalyst was reused and tolerant to different functional groups of nitrobenzene.

Conflicts of interest

There are no conflicts to declare.

Acknowledgments

This research was supported by the ACCEL program, Japan Science and Technology Agency (JST, JPMJAC1501).

Notes and references

1. S. Narayanan, R. Unnikrishnan and V. Vishwanathan, *Appl. Catal., A*, 1995, **129**, 9.
2. M. Chatterjee, M. Sato, H. Kawanami, T. Ishizaka, T. Yokoyama and T. Suzuki, *Appl. Catal., A,* 2011, **396**, 186.
3. G. Mink and L. Horvath, *React. Kinet. Catal. Lett.*, 1998, **65**, 59.
4. M. Chatterjee, M. Sato, H. Kawanami, T. Ishizaka, T. Yokoyama and T. Suzuki, *Appl. Catal., A*, 2011, **396**, 186.
5. G. Mink and L. Horváth, *React. Kinet. Catal. Lett.*, 1998, **65**, 59.
6. H. S. Kim, S. H. Seo, H. Lee, S. D. Lee, Y. S. Kwon and I. M. Lee, *J. Mol. Catal. A: Chem.*, 1998, **132**, 267.
7. S. G. Oh, V. Mishra, J. K. Cho, B. J. Kim, H. S. Kim, Y. W. Suh and Y. J. Kim, *Catal. Commun.*, 2014, **43**, 79.
8. H. Greenfield, *J. Org. Chem.*, 1964, **29**, 3082.
9. C. F. Winans, *Ind. Eng. Chem.*, 1940, **32**, 1215.
10. X. Wang, N. Perret, M.A. Keane, *Appl. Catal., A,* 2013, **467**, 575.
11. J. Becker, J.P.M. Niederer, M. Keller, W.F. Ho¨lderich, *Appl. Catal., A*, 2000,**197**, 229.
12. L. Hong-bin*, Fine Chem. Intermed*., 2012, **1**, 7.
13. X. Cui, F. Shi and Y. Deng, *ChemCatChem*, 2012, **4**, 333.
14. X. Meng, H. Cheng, Y. Akiyama, Y. Hao, W. Qiao, Y. Yu, F. Zhao, S. I. Fujita and M. Arai, *J. Catal.*, 2009, **264**, 1.
15. Y. Motoyama, Y. Lee, K. Tsuji, S. H. Yoon, I. Mochida and H. Nagashima, *ChemCatChem*, 2011, **3**, 1578.
16. N. Sakai, K. Fujii, S. Nabeshima, R. Ikeda and T. Konakahara, *Chem. Commun.*, 2010, **46**, 3173.
17. J. Skupińska and G. Smółka, *React. Kinet. Catal. Lett.*, 1998, **63**, 313.
18. J. Wisniak and M. Klein, *Ind. Eng. Chem. Prod. Res. Dev.*, 1984, **23**, 44.
19. F. Zhao, R. Zhang, M. Chatterjee, Y. Ikushima and M. Arai, *Adv. Synth. Catal.*, 2004, **346**, 661.
20. T. A. Joseph, N. Y. Westbury and J. C. Nils, *Us Pat.*, 3,678,108N 1972.
21. X. Lu, Y. Chen, Z. Zhao, H. Deng, D. Zhou, C. Wei, R. Nie and Q. Xia, *RSC Adv.*, 2016, **6**, 15354.
22. X. Lu, J. He, R. Jing, P. Tao, R. Nie, D. Zhou and Q. Xia, *Sci. Rep.*, 2017, **7**, 2676.
23. F. Leng, I. C. Gerber, P. Lecante, S. Moldovan, M. Girleanu, M. R. Axet and P. Serp, *ACS Catal.*, 2016, **6**, 6018.
24. H. Li, Z. Li, D. Ji and G. Li, *Catal. Commun*., 2018, **104**, 91.
25. K. Kusada, H. Kobayashi, R. Ikeda, Y. Kubota, M. Takata, S. Toh, T. Yamamoto, S. Matsumura, N. Sumi, K. Sato, K. Nagaoka and H. Kitagawa, *J. Am. Chem. Soc.*, 2014, **136**, 1864.
26. K. Sato, H. Tomonaga, T. Yamamoto, S. Matsumura, N. D. B. Zulkifli, T. Ishimoto, M. Koyama, K. Kusada, H. Kobayashi, H. Kitagawa and K. Nagaoka, *Sci. Rep*., 2016, **6**, 28265.
27. C. Chaudhari, K. Sato, Y. Nishida, T. Yamamoto, T. Toriyama, S. Matsumura, Y. Ikeda, K. Terada, N. Abe, K. Kusuda, H. Kitagawa and K. Nagaoka, *RSC Advance,* 2020, **10**, 44191.
28. H.-W. Michalczak, S. Kohlstruk, M. Kreczinski, G. Grund and R. Lomoelde, *US Pat*., 0,036,154 A1, 2010.
29. R. J. Rahaim and R. E. Maleczka, *Org. Lett.*, 2005, **7**, 5087.
30. S. M. Baghbaniana, M. Farhang, S. M. Vahdat and M. Tajbakhsh, *J. Mol. Catal. A-Chem*., 2015, **407**, 128.
31. R. J. Rahaim Jr. and R. E. Maleczka Jr., *Synthesis*, 2006, **19**, 3316.
32. H. S. Kim, S. H. Seo, H. Lee, S. D. Lee, Y. S. Kwon and I. -M. Lee, *J. Mol. Catal. A-Chem*., 1998, **132**, 167.
33. J. Cao, F. Han, L. Wang, X. Huang, Y. Cao, P. He, H. Yang, J. Chen and H. Li, *RSC Adv.*, 2020, **10**, 16515.
34. Y. Sheng, T. Rongsheng, L. Tao, Y. Hanrong, *CN Pat.*, 103,865,964 A, 2014.
35. P. A. Jacobi, L. D. Coults, J. S. Guo and S. I. Leung, *J. Org. Chem*., 2000, **65**, 205.
36. A. Furstner, *Angew. Chem.*, 2000, **39**, 3013.
37. A. Furstner, H. szillat, B. Gobor and R. Mynott, *J. Am. Chem. Soc.*, 1998, **120**, 8305.
38. D. L. Boger, C. W. Boyce, M. A. Labrili, C. A. Sehon and Q. Jin, *J. Am. Chem. Soc.*, 1999, **121**, 54.
39. F. G. Cirujano, A. Leyva-Pérez, A. Corma and F. X. L. I Xamena, *ChemCatChem*, 2013, **5**, 538.
40. J. W. Park and Y. K. Chung, *ACS Catal.*, 2015, **5**, 4846.
41. Z. Gong, Y, Lei, P. Zhou and Z. Zhang, *New J. Chem.*, 2017, **41**, 10613.
42. A. Serrano-Maldonado, E. Martin and I. Guerrero-Ríos, *Eur. J. Inorg. Chem.*, 2019, 2863.
43. P. Ryabchuk, T. Leischner, C. Kreyenschulte, A. Spannenberg, K. Junge and M. Beller, *Angew. Chem.*, 2020, **132**, 18838.
44. H. Lee and B. H. Kim, *Tetrahedron*, 2013, **69**, 6698.
45. B. H. Kim, S. Bae, A. Go, H. Lee, C. Gong and B. M. Lee, *Org. Biomol. Chem.*, 2016, **14**, 265.

Authorship contribution

Chandan Chaudhari: designing of research, data collection-analysis and writing-editing. **Katsutoshi Sato:** data curation and validation. **Katsutoshi Nagaoka**: designing of research, data collection-analysis and writing-editing. **Yasuyuki Ikeda, Kenji Terada and Naoya Abe:** catalyst preparation.