Direct synthesis of lactams from keto acids, nitriles, and H_2 by heterogeneous Pt catalysts

S. M. A. H. Siddiki,[a] Abeda S. Touchy,[a] Ashvini Bhosale,[a] Takashi Toyao,[a,b] Yuji Mahara,[b] Junya Ohyama,[b,c] Atsush Satsuma,[b,c] Ken-ichi Shimizu*[a,b]

Abstract: We report herein the first general catalytic system for direct synthesis of *N*-substituted γ- and δ-lactams by reductive amination/cyclization of keto acids (including levulinic acid) with nitriles and H_2 under mild conditions (7 bar H_2, 110 °C, solvent-free). The most effective catalyst, Pt and MoOx co-loaded TiO_2 (Pt-MoOx/TiO_2), shows a wide substrate scope, high turnover number (TON), and good reusability.

Introduction

Sustainable use of biomass is a major challenge in chemistry. Selective reductive transformation of biomass to chemicals via platform compounds plays a key role in this research area.[1] Levulinic acid (LA) is a key platform compound, because it can be obtained by acid-catalyzed dehydration of lignocellulosic biomass and can be converted to various chemicals.[1] Among the chemicals, *N*-alkyl-5-methyl-2-pyrrolidones (in other word, *N*-substituted γ-lactams), which can be produced by reductive amination of LA, are industrially used as solvents, surfactants, complexing agents, and intermediates for fine chemicals.[2,3] Previous non-catalytic[4] and catalytic[5-10] methods for this reaction used formic acid[4-11] or a hydrosilane[9] as a reductant. Most of the methods used homogeneous catalysis which suffer from difficulties in catalyst/product separation and catalyst reuse and needs of additives, expensive reductants, or a toxic solvent (dichloromethane).[4] Uses of a reusable heterogeneous catalyst and molecular H_2 as a reductant[11] can make this reaction more practical. Recently, we have reported a reusable heterogeneous catalyst, Pt and MoOx co-loaded TiO_2 (Pt-MoO_X/TiO_2), for the synthesis of *N*-substituted γ-lactams from LA, primary amines and H_2.[12] Later, several heterogeneous catalytic systems (Pt/TiO_2,[13] FeNi nanoparticles[14]) were reported to be effective for this type of transformation.

Considering that some of the nitriles[15-17] and nitro compounds are the intermediates of primary amines, one-pot reactions of them with LA and H_2 can provide a sustainable and practical route to the γ-lactams. Very recently, Corma, Iborra and co-workers[18] have reported the first general method for one-pot synthesis of the *N*-substituted γ-lactams via reductive amination of ethyl levulinate with nitro compounds under 10 bar H_2 using a heterogeneous Pt catalyst, though the method requires large amount of ethyl levulinate (3 equiv. with respect to the nitro compounds).[18] As for the use of nitriles alternative to primary amines, to our knowledge, only one patent by Manzer[19] reported the synthesis of the *N*-substituted γ-lactams from LA and nitriles (3-penteneitrile and benzonitrile) under H_2 using Pd, Rh, Ru, or Pt loaded on carbon or Al_2O_3 catalysts. However, the method has several disadvantages such as low yields (< 43.4%), limited scope, no example of catalyst reuse, low turnover number (TON), and necessities of high H_2 pressure (55-69 bar), high temperature (150 °C), and dioxane as solvent.

During our efforts on catalytic hydrogenation reactions by Pt-MoO_X/TiO_2,[12,20,21] inspired by previous efforts on the utilization of nitriles as primary amine surrogate,[19,22] we have found that Pt-MoO_X/TiO_2 selectively catalyzes the synthesis of *N*-substituted γ- and δ-lactams from 1:1 mixture of keto acids (including LA) and nitriles under 7 bar H_2 at 110 °C in the absence of solvent. To our knowledge, this is the first example of general catalytic system for direct synthesis of *N*-substituted lactams from keto acids, nitriles, and H_2. It should be noted that the selective reaction of nitriles with equimolar amount of keto acids under H_2 is a challenging reaction, because hydrogenation of nitriles to primary amines (intermediates of the lactam synthesis) is accompanied by the formation of secondary and tertiary amines.[15-17]

Results and Discussion

Table 1 summarizes the results for catalyst screening using 5 wt% metal-loaded metal oxides containing 0.01 mmol (1 mol%) of the active metals with respect to LA. Reaction of neat LA (**1a**, 1 mmol) with *n*-octanenitrile (**2a**, 1 mmol) under 7 bar H_2 at 110 °C for 24 h was used as a model reaction. No reaction occurred in the catalyst-free conditions (entry 1). The metal-free MoO_X/TiO_2 support showed only 2% yield of the desired product, 5-methyl-1-octyl-pyrrolidin-2-one (**3a**). Among the MoOx/TiO_2-supported metal catalysts (entries 3-10), Pt-MoO_X/TiO_2 (entry 3) showed the highest yield (85%) of **3a**. For Pt-MoO_X/TiO_2, increasing the Mo content from 7 wt% (entry 3) to 15 wt% (entry 11) resulted in higher yield (92%) of **3a**. The most effective catalyst, Pt-MoO_X/TiO_2 with 15 wt% loading of Mo (entry 11), is hereafter used as the standard catalyst. Note that the yields of byproducts, di-*n*-octylamine (**4a**) and tri-*n*-octylamine (**5a**), for this catalyst are relatively low compared to

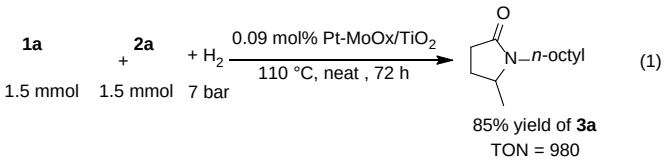
[a] Dr. S. M. A. H. Siddiki, Dr. A. S. Touchy, Dr. K. Kon, Dr. T. Toyao, Prof. Dr. K. Shimizu
Institute for Catalysis, Hokkaido University, N-21, W-10, Sapporo, Japan
E-mail: kshimizu@cat.hokudai.ac.jp
[b] Y. Mahara, Dr. Ohyama, Prof. Dr. Satsuma
Graduate School of Engineering, Nagoya University, Nagoya 464-8603, Japan
[c] Dr. T. Toyao, Dr. Ohyama, Prof. Dr. Satsuma, Prof. Dr. K. Shimizu
Elements Strategy Initiative for Catalysis and Batteries, Kyoto University, Katsura, Kyoto 615-8520, Japan

the other catalysts. Figure 1 shows the time course of the reaction by the standard catalyst. The profile shows selective conversion of **2a** to the desired product **3a** while the yields of byproducts (**4a** and **5a**) leveled-off at the initial period of the reaction.

Pt/TiO_2 (entry 12) showed lower yield of **3a** than Pt-MoO_X/TiO_2 (entry 11). In our previous report, this tendency was observed for the **3a** synthesis from LA (**1a**), *n*-octylamine (instead of *n*-octanenitrile) under H_2.[12] Based on the fact that **3a** yield increased with increase in the negative shift of the C=O stretching band in the IR spectra of adsorbed acetone on these catalysts, we proposed that activation of C=O group of **1a** by Lewis acid sites of MoO_X/TiO_2 is responsible for the high activity of Pt-MoO_X/TiO_2.[12] As described later, the reaction of **1a** with amine is a key step of the present system. Hence, the high activity of Pt-MoO_X/TiO_2 in Table 1 can be due to cooperation of Mo^{n+} (Lewis acid) sites with Pt sites (H_2 dissociation sites).

Next, we studied the effect of various reaction conditions on the catalytic properties of Pt-MoO_X/TiO_2 for the reaction of LA (**1a**) with *n*-octanenitrile (**2a**) for 24 h (Table 2). The reactions of 1 mmol **2a** with various amount of **1a** at 100 °C under the solvent-free conditions (entries 1-3) showed that the **2a** conversion and the **3a** yield (based on **2a**) did not increase with increase in the amount of **1a**. The reactions of 1 mmol **1a** with various amount (1-1.5 mmol) of **2a** showed that the excess amount of **2a** gave lower amount of **3a** and higher amount of byproducts (**4a**, **5a**) than the stoichiometric condition (results not shown). Thus, we adopted the reaction of 1 mmol **1a** with 1 mmol **2a** as the standard conditions. With increase in the H_2 pressure from 3 bar (entry 1) to 5 and 7 bar (entries 4,5), the conversion of **2a** and the yield of **3a** increased. Under 7 bar H_2, the yield of **3a** increased with the temperature upto 110 °C (entry 6), but further increase in the temperature (entries 7,8) decreased the yield of **3a** and increased in the yields of byproducts (**4a**, **5a**). At the optimal temperature (110 °C) and H_2 pressure (7 bar), the reaction in various solvent showed that the solvent-free conditions (entry 6) gave higher yield of **3a** than the reactions in the solvent, such as toluene, *o*-xylene, *n*-decane, and dioxane (entries 9-12). Summarizing these results, we determined the standard conditions: **1a** / **2a** = 1/1, 110 °C, 7 bar H_2, without solvent.

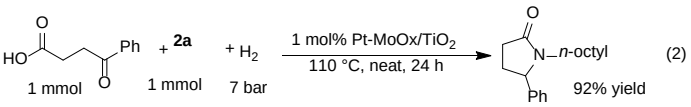
ICP-AES analysis of the filtrate showed that the Pt content in the solution was below the detection limit. These results confirm that the reaction is attributed to the heterogeneous catalysis of Pt-MoO_X/TiO_2. Figure 2 shows the result of catalyst recycle test. After the standard reaction, followed by adding 3 mL 2-propanol to the mixture, the catalyst separation from the mixture by filtration, washing the catalyst with 6 mL acetone, drying the catalyst at 90 °C (12 h), and by reduction of it at 300 °C (0.5 h), the recovered catalyst showed high yields of **3a** (90-84%) during the following 4 cycles. As shown eqn. (1), the standard reaction with 0.09 mol% of Pt-MoO_X/TiO_2 (5.3 mg) gave 85% yield of **3a**. This value corresponds to TON of 980.



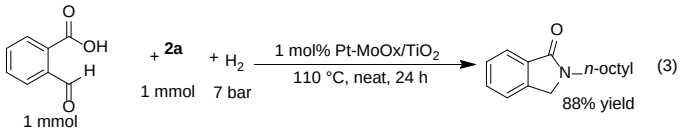
(1)

Then, we studied the scope of nitriles for the catalytic reaction. Table 3 shows the yields of *N*-substituted γ-lactams (*N*-substituted-5-methyl-2-pyrrolidones) from LA and various nitriles under 7 bar H_2 by 1 mol% Pt-MoO_X/TiO_2. Aliphatic nitriles (entries 1,2), dimethylaminopropionitrile (entry 3), ethyl cyanoacetate (entry 4), methoxypropionitrile (entry 5), benzonitrile (entry 6), benzonitrile derivatives with electron-donating (entries 7,8) and electron-withdrawing (entry 9) substituents, 2-naphthonitrile (entry 10), 3-cyanopyridine (entry 11), 3-cyanothiophene (entry 12), 3-cyanofurane (entry 13), phenylacetonitrile (entry 14), phenylacetonitrile derivatives with electron-donating (entries 15,16) and electron-withdrawing (entry 17) substituents, and 2-naphthylacetonitrile (entry 18) were selectively converted to the corresponding γ-lactams in good to high yields (upto 92%). The results show that nitriles with a wide range of functional groups were well-tolerated under our reaction conditions. The catalytic properties of our method are superior to those in an earlier patent,[19] where low yields (<43.4%) of lactams have been obtained only for two nitriles under high H_2 pressure (55-69 bar) at high temperature (150 °C).

As shown in equations (2) and (3), the method was applicable to direct synthesis of *N*-substituted γ-lactams from keto acid or 2-carboxybenzaldehyde and *n*-octanenitrile (**2a**) under H_2.



(2)

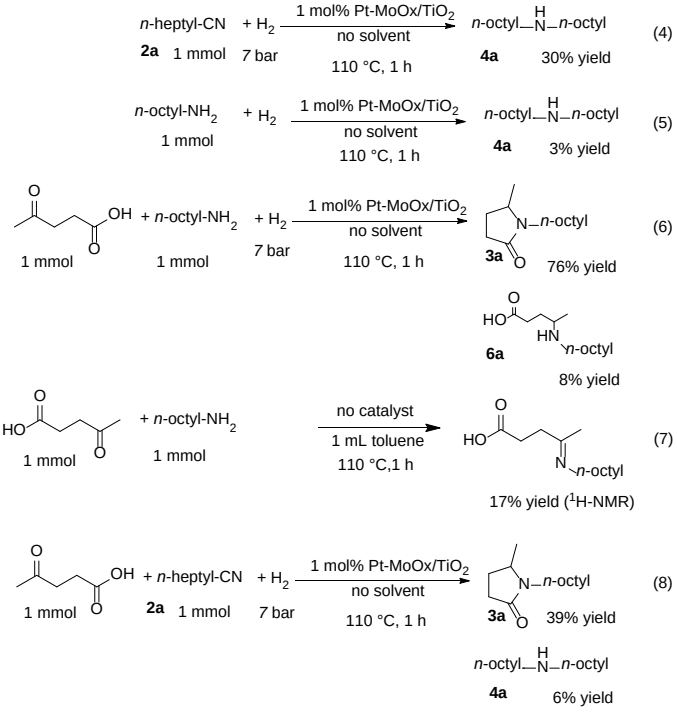


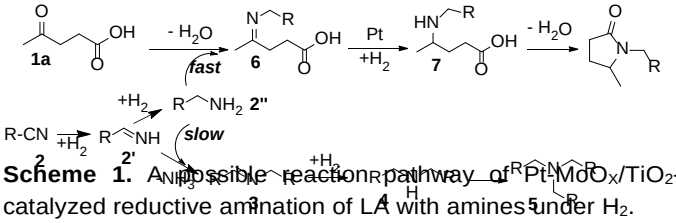
(3)

The same method was applicable to the synthesis of *N*-substituted δ-lactams from 4-acetylbutyric acid with various nitriles (Table 4). The reactions of aliphatic nitrile (entry 1), benzonitrile (entry 2), its derivatives with electron-donating (entry 3,4) and electron-withdrawing (entry 5) substituents, 3-cyanopyridine (entry 6), 3-cyanofurane (entry 7), and phenylacetonitrile (entry 8) afforded the *N*-aryl δ-lactams in 76-92% yields. To our knowledge, this method is the first general catalytic system for direct synthesis of *N*-substituted γ- and δ-lactams from keto acids and nitriles with H_2.

Next, we discuss a reaction pathway (Scheme 1) which is supported by the results of the control reactions in equations (4)-(8) at 110 °C for 1 h. First, we studied the side reaction pathways from nitriles (**2**) to secondary amine (**4**). Under 7 bar H_2, *n*-octanenitrile **2a** was hydrogenated to give di-*n*-octylamine **4a** in 30% yield. Self-coupling of *n*-octylamine

under 7 bar H_2, eqn. (5), resulted in lower yield of **4a** (3%) than the hydrogenation of *n*-octanenitrile in eqn. (4). Considering the literature,[17] the most probable route from nitriles to secondary amines is shown in Scheme 1. The nitrile **2** is hydrogenated to give imine **2'** and primary amine **2''**. The imine **2'** reacts with the primary amine **2''** to give the secondary imine **3** which is hydrogenated to secondary amine **4**.[17] Our results in eqn. (4) and (5) are consistent with this scheme; the secondary amine (**4a**) is not produced by self-coupling of the primary amine but by the hydrogenation of the nitrile via the imine intermediate **2'**. If the reaction of the primary amine **2''** with **1a** under H_2 (target reaction) is faster than the reaction of the primary amine **2''** with the imine intermediate **2'** (side reaction), the lactam **8** could be selectively obtained. This assumption is verified by the higher yield of the lactam (76%) by the reaction of **1a** and *n*-octylamine under H_2, eqn. (6), than the yield of secondary amine **4a** (30%) in eqn. (4). Thermal condensation of the primary amine with **1a** under N_2, eqn. (7), was also fast; it gave the imine intermediate **6** in 17% yield (by ^{1}H-NMR) even under the catalyst-free conditions. The C=N bond in the intermediate **6** can be hydrogenated to give the final intermediate **7**, which undergoes intramolecular amidation to give the lactam and H_2O. We observed the intermediate **7** as a byproduct of the reaction of LA, *n*-octylamine and H_2 in eqn. (6). The yield of the lactam from *n*-octanenitrile **2a** (39%) in eqn. (8) is lower than that from *n*-octylamine (76%) in eqn. (6), which is consistent with the pathway in Scheme 1. From the above mechanistic discussion, the reason of the selective conversion of nitriles to the lactams (with low formation of secondary and tertiary amines) is due to the faster reaction of the primary amine **2''** with keto acid than with the imine intermediate **2'**.





Scheme 1. A possible reaction pathway of Pt-MoO_x/TiO_2-catalyzed reductive amination of LA with amines under H_2.

Finally, we discuss the structure of the standard Pt-MoOx/TiO_2 catalyst. Previously,[12,20] we reported detailed characterization of Pt-MoOx/TiO_2 (with Mo loading of 7 wt%) by temperature programmed reduction in H_2, X-ray absorption spectroscopy, CO adsorption, and TEM and the structural model was proposed as follows. Thin layer (or small clusters) of MoOx species covers the surface of TiO_2, and Pt metal nanoparticles with mean diameter of 4.7 nm are supported on the Mo oxides-covered TiO_2. Exposed Mo^{n+} cations on the surface MoOx species act as Lewis acid sites, while Pt sites act as H_2 dissociation sites. The MoOx-covering model was based on the indirect evidences. Hence, we carried out the microscope studies to obtain the direct evidence on the model. Figure 3 shows TEM images of Pt-MoOx/TiO_2 (Pt = 5 wt%, Mo = 15 wt%). Pt metal particles with size in a range of 3-5 nm are observed on the support surface, while MoOx particles are not observed.

To achieve elemental mapping over a catalyst particle, we carried out high-angle annular dark-field scanning transmission electron microscopy (HAADF-STEM),[23] in conjunction with EDX analysis in Figure 4. Yellow pixels (Pt) are observed on the 2-5 nm sized white particles. Cyan pixels (Mo) are not aggregated but highly dispersed over the TiO_2 particle (red pixels) and on the Pt particles. The absence of aggregated Mo species are consistent with the structural model of Pt-MoOx/TiO_2 proposed in our previous study;[20] thin layer (or small clusters) of MoOx species covers the surface of TiO_2, and Pt metal nanoparticles are supported on the MoOx-covered TiO_2. Additionally, the presence of Mo on the Pt particles shown in Figure 4 suggests that some of the MoOx species are present on the Pt particles. The interface between Pt particle and MoOx thin layer and perimeter between Pt particle and MoOx on it can act as Pt/ Mo^{n+} (Lewis acid) cooperative sites which effectively catalyze the present catalytic reaction.

Conclusions

We have found the first general and reusable catalytic system for one-pot synthesis of *N*-substituted lactams by reductive conversion of keto acids (including levulinic acid) with nitriles and H_2 under mild conditions (7 bar H_2, 110 °C, solvent-free) using the Pt-MoOx/TiO_2 catalyst. This method may be a sustainable route to *N*-substituted lactams from biomass.

Experimental Section

General

Commercially available organic compounds (from Tokyo Chemical Industry, Sigma-Aldrich, or Kanto Chemical Co. Ltd.) were used without further purification. The GC (Shimadzu GC-2014) and GCMS (Shimadzu GCMS-QP2010) analyses were carried out with Ultra ALLOY capillary column UA$^+$-1 (Frontier Laboratories Ltd.) using nitrogen and He as the carrier gas.

Catalyst preparation

TiO_2 (JRC-TIO-4, 50 m^2 g^{-1}) was supplied from Catalysis Society of Japan. The M-MoO_X/TiO_2 catalysts (M = 5 wt% Pt, Ir, Ru, Rh, Pd, Re, Ni, Co, Cu; 7 or 15 wt% Mo) were prepared by a sequential impregnation method as follows. Metal sources were aqueous HNO_3 solutions of $Pt(NH_3)_2(NO_3)_2$, $Rh(NO_3)_3$, and $Pd(NH_3)_2(NO_3)_2$ and aqueous solution of $RuCl_3$, NH_4ReO_4, nitrates (Ni, Co, Cu), and $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$. MoO_3-loaded TiO_2 (MoO_3/TiO_2) was prepared by mixing TiO_2 powder with aqueous solution of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (50 mL), followed by evaporation of the mixture at 50 °C, drying the solid at 90 °C for 12 h, and by calcination in air at 500 °C for 3 h. Then, MoO_3/TiO_2 and aqueous HNO_3 solution of $Pt(NH_3)_2(NO_3)_2$ were mixed, evaporated, dried at 90 °C to yield a Pt(II)-loaded precursor. Before the catalytic experiment, the catalysts were prepared by reduction of the precursor in a Pyrex tube under flowing H_2 (20 cm^3 min^{-1}) at 300 °C for 0.5 h.

Catalytic reactions

The catalytic reactions were carried out as follows. After the reduction, the as-prepared catalyst in the closed Pyrex tube sealed with a septum inlet was cooled to room temperature under H_2, followed injection of mixture of 1 mmol levulinic acid (LA), 1 mmol nitriles, and 0.2 mmol *n*-dodecane. Then, the septum was removed under air, a magnetic stirrer bar was put in the tube, followed by inserting the tube inside stainless autoclave (28 cm^3). After being sealed, the reactor was charged with 7 bar H_2 and heated at 110 ˚C under stirring (500 rpm). After 24 h, the reactor was cooled followed by adding 2-propanol (6 cm^3) to the mixture, followed by removal of the catalyst by filtration, conversions and yields of products were determined by GC using *n*-dodecane as an internal standard using the GC-sensitivity estimated by the commercial compounds (nitriles) or isolated products. For the reactions in Table 3 and 4, the mixture after the reaction was concentrated under vacuum evaporator to remove the volatile compounds, and then lactams were isolated by column chromatography using silica gel 60 (spherical, 63-210 μm, Kanto Chemical Co. Ltd.) with hexane/ethylacetate (7/3) as the eluting solvent, followed by analyses by ^{1}H NMR, ^{13}C NMR and GCMS.

Characterization

Transmission electron microscopy (TEM) and high-angle annular dark-field scanning transmission electron microscopy (HAADF-STEM), in conjunction with energy dispersive X-ray spectroscopy (EDS) mapping images were taken on a JEM-2100F (JEOL) operated at 200 kV accelerating voltage. The samples for TEM, STEM and EDS analyses were prepared by putting drops of a methanol solution onto a carbon-coated copper grid.

Acknowledgements

This work was supported by the ENEOS Hydrogen Trust Fund, KAKENHI grants JP16H06595 and JP17H01341 from JSPS, and a MEXT program "Elements Strategy Initiative to Form Core Research Center". The authors are indebted to the technical division of the Institute for Catalysis (Hokkaido University) for the manufacturing of experimental equipment.

Keywords: amination • hydrogenation • keto acids • nitriles

[1] a) A. Corma, S. Iborra, A. Velty, *Chem. Rev*. **2007**, *107*, 2411–2502; b) P. Mäki-Arvela, I. L. Simakova, T. Salmi, D. Y. Murzin, *Chem. Rev*. **2013**, *114*, 1909–1971; c) J. Pritchard, G. A. Filonenko, R. Van Putten, E. J. M. Hensen, E. A. Pidko, Chem. Soc. Rev. **2015**, *44*, 3808– 3833; d) K. Tomishige, Y. Nakagawa, M. Tamura, *Green Chem.* **2017**, *19*, 2876–2924.

[2] L. E. Manzer, *US Patent* 6743819 B1, **2004**.

[3] L. E. Manzer, *US Patent* 2006/247443A1, **2006**.

[4] Y. Wei, C. Wang, X. Jiang, D. Xue, Z. T. Liu, J. Xiao, *Green Chem.* **2014**, *16*, 1093–1096.

[5] Y. B. Huang, J. J. Dai, X. J. Deng, Y. C. Qu, Q. X. Guo, Y. Fu, *ChemSusChem* **2011**, *4*, 1578–1581.

[6] Y. Wei, C. Wang, X. Jiang, D. Xue, J. Li, J. Xiao, *Chem. Commun.* **2013**, *49*, 5408–5410.

[7] C. Ortiz-Cervantes, M. Flores-Alamo, J. J. García, *Tetrahedron Lett*. **2016**, *57*, 766–771.

[8] A. Ledoux, L. S. Kuigwa, E. Framery, B. Andrioletti, *Green Chem*. **2015**, *17*, 3251–3254.

[9] Y. Ogiwara, T. Uchiyama, N. Sakai, *Angew. Chem. Int. Ed*. **2016**, *55*, 1864–1867.

[10] X. L. Du, L. He, S. Zhao, Y. M. Liu, Y. Cao, H. He, K. N. Fan, *Angew. Chem. Int. Ed*. **2011**, *50*, 7815–7819.

[11] L. E. Manzer, F. E. Herkes, *US Patent* 0192933, **2004**.

[12] A. S. Touchy, S. M. A. H. Siddiki, K. Kon, K. Shimizu, *ACS Catal*. **2014**, *4*, 3045–3050.

[13] J. D. Vidal, M. J. Climent, P. Concepcion, A. Corma, S. Iborra, M. J. Sabater, *ACS Catal*. **2015**, *5*, 5812–5821.

[14] G. Chieffi, M. Braun, D. Esposito, *ChemSusChem* **2015**, *8*, 3590–3594.

[15] C. de Bellefon, P. Fouilloux, *Catal. Rev. Sci. Eng*. **1994**, *36*, 459–506.

[16] S. Werkmeister, K. Junge, M. Beller, *Org. Process Res. Dev*. **2014**, *18*, 289–302.

[17] D. B. Bagal, B. M. Bhanage, *Adv. Synth. Catal*. **2015**, *357*, 883–900.

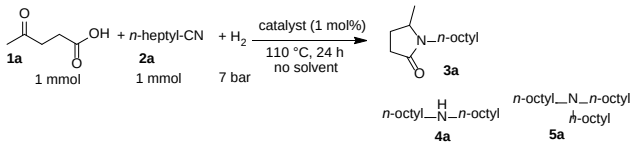
[18] J. D. Vidal, M. J. Climent, A. Corma, D. P. Concepcion, S. Iborra, *ChemSusChem* **2017**, *10*, 119 – 128

[19] L. E. Manzer, *US Patent* 0204592, 2004.

[20] A. S. Touchy, S. M. A. Siddiki, W. Onodera, K. Kon, K. Shimizu, *Green Chem.* **2016**, *18*, 2554–2560.

[21] T. Toyao, S. M. A. H. Siddiki, K. Ishihara, K. Kon, W. Onodera, K. Shimizu, *Chem. Lett.* **2017**, *46*, 68–70.
[22] a) B. Kang, Z. Fu, S. H. Hong, *J. Am. Chem. Soc*. **2013**, *135*, 11704–11707; b) J. Kim, S. H. Hong, *Org. Lett*. **2014**, *16*, 4404–4407; c) H. Sajiki, T. Ikawa, K. Hirota, *Org. Lett*. **2004**, *6*, 4977–4980; d) T. Ikawa, Y. Fujita, T. Mizusaki, S. Betsuin, H. Takamatsu, T. Maegawa, Y. Monguchi, H. Sajiki, *Org. Biomol. Chem*. 2012, *10*, 293–394.
[23] J. Ohyama, H. Ishikawa, Y. Mahara, T. Nishiyama, A. Satsuma, *Bull. Chem. Soc. Jpn*. **2016**, *89*, 914–921.

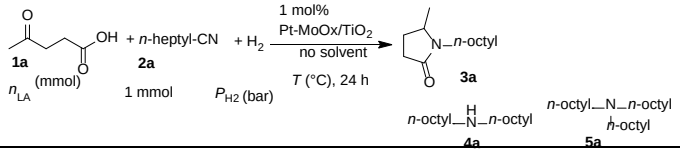
Table 1. Catalytic synthesis of **3a** from **1a**, **2a** and H_2.[a]



Entry	Catalysts	Conv. (%)	Yield (%) 3a	4a	5a
1	blank	0	0	0	0
2	MoO_X/TiO_2	4	2	0	0
3	Pt-MoOx/TiO_2	100	85	6	9
4	Ir-MoOx/TiO_2	10	6	1	1
5	Ru-MoOx/TiO_2	6	3	0	0
6	Rh-MoOx/TiO_2	68	28	17	21
7	Pd-MoOx/TiO_2	85	51	9	23
7	Re-MoOx/TiO_2	9	7	0	0
8	Ni-MoOx/TiO_2	8	6	0	0
9	Co-MoOx/TiO_2	6	2	0	0
10	Cu-MoOx/TiO_2	5	2	0	0
11[b]	**Pt-MoOx/TiO_2**	**100**	**92**	**3**	**5**
12	Pt/TiO_2	61	34	11	15

[a] Conversion of **2a** and yields were determined by GC. Mo loading is 7 wt% for entries 2-10. [b] Mo =15 wt%

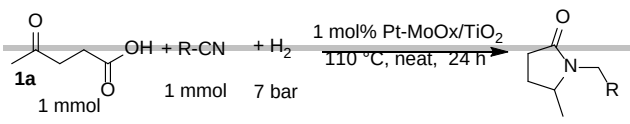
Table 2. Reaction of **1a** with **2a** and H_2 by Pt-MoO_X/TiO_2 under various conditions.[a]

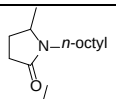
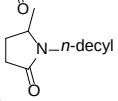
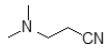
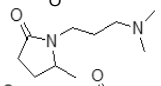
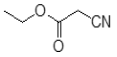
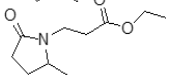
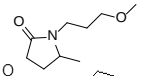
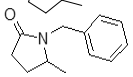
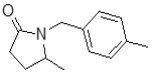
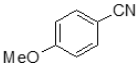
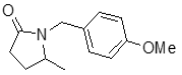
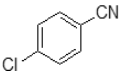
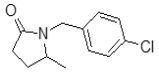
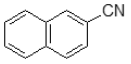
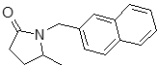
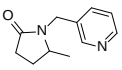
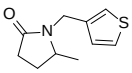
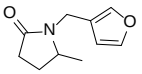
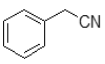
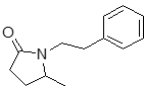
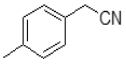
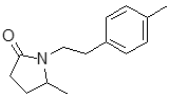
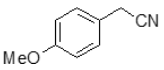
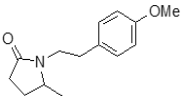
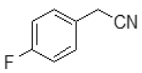
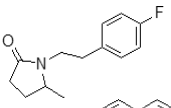
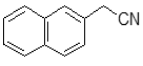
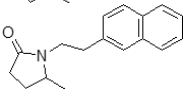


Entry	n_{LA} [mmol]	P_{H2} [bar]	T [°C]	Solvent	Conv. [%]	Yield [%] 3a	4a	5a
1	1	3	100	no	78	6	3	6
2	1.2	3	100	no	78	7	3	5
3	1.5	3	100	no	76	6	3	5
4	1	5	100	no	88	8	3	5
5	1	7	100	no	96	8	4	6
6	**1**	**7**	**110**	**no**	**100**	**9**	**3**	**5**
7	1	7	120	no	100	8	5	10
8	1	7	140	no	100	7	7	15
9	1	7	110	toluene	65	4	9	11
10	1	7	110	*o*-xylene	53	3	6	9
11	1	7	110	*n*-decane	26	1	4	6
12	1	7	110	dioxane	17	8	4	5

[a] Conversion of **2a** and yields were determined by GC.

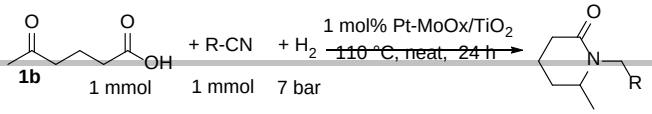
Table 3. Synthesis of γ-lactams from **1a** and nitriles under H_2.

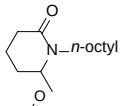
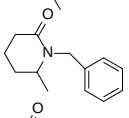
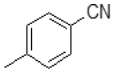
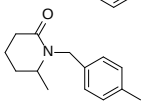
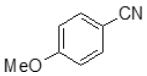
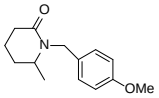
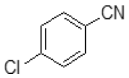
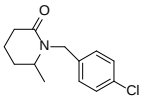
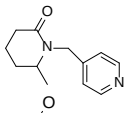
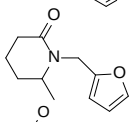
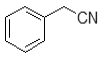
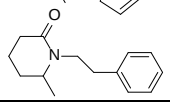


Entry	Nitriles	Products	Yield (%)[a]
1	**2a**		92
2	*n*-decanenitrile		90
3			(88)
4			(85)
5			(73)
6			82
7			88
8			87
9			72
10			91
11			(76)
12			83
13			81
14			84
15			76
16			75
17			72
18			88

[a] Isolated yields. GC yields are in parentheses.

Table 4. Synthesis of δ-lactams from 4-acetylbutyric acid (**1b**) and nitriles under H_2.



Entry	Nitriles	Products	Yield (%)[a]
1	**2a**		96
2			94
3			92
4			95
5			78
6			86
7			88
8			92

[a] Isolated yields.

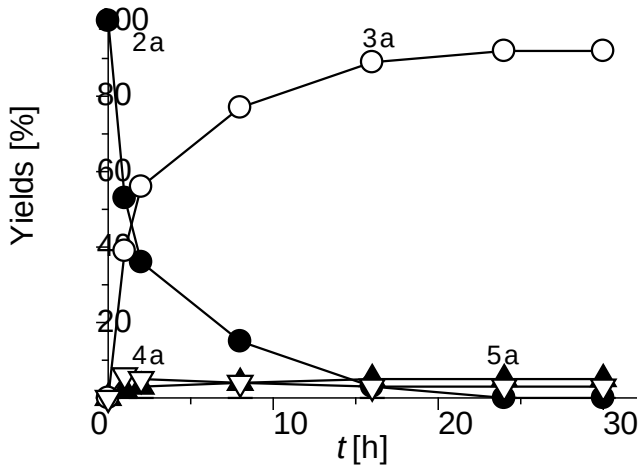


Figure 1. Time-yields profile; conditions are in Table 1 (entry 11).

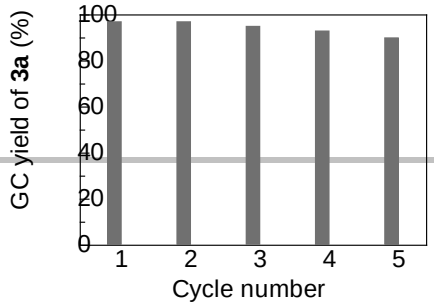


Figure 2. Reuse of Pt-MoO_X/TiO_2 for **3a** synthesis under conditions in entry 6 of Table 2.

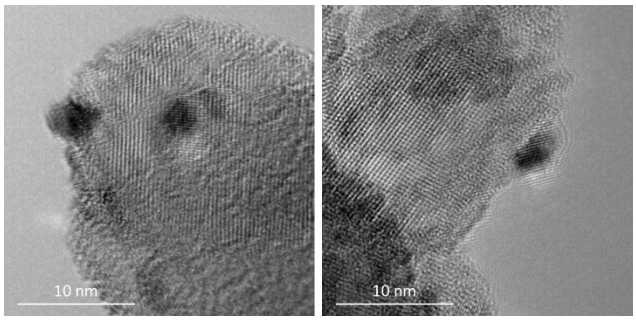


Figure 3. Representative TEM images of Pt-MoOx/TiO_2.

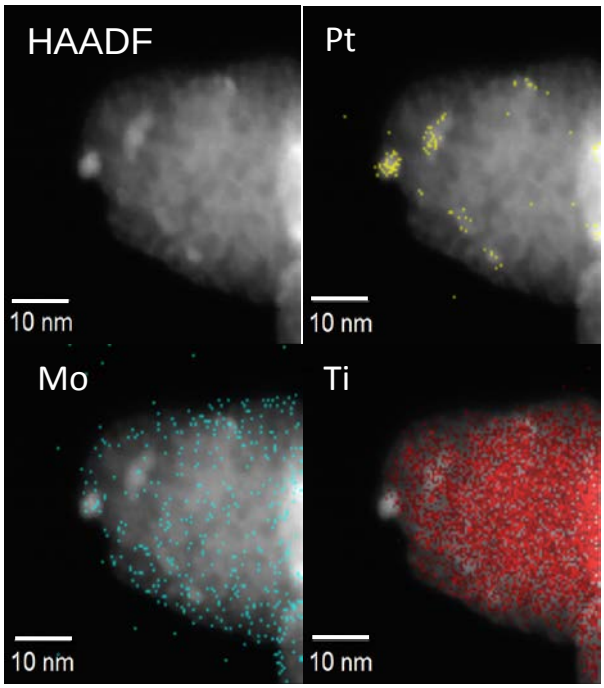
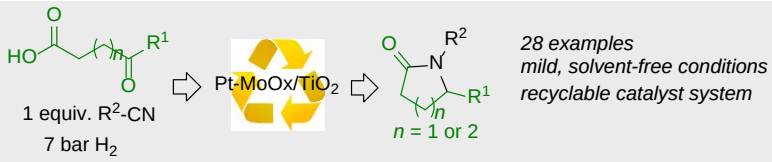


Figure 4. HAADF-STEM images superimposed with EDX elements mapping of Pt-MoOx/TiO_2. The yellow, cyan, and red pixels in the mapping correspond to Pt, Mo, and Ti, respectively.

Entry for the Table of Contents (Please choose one layout)

Layout 2:

FULL PAPER



S. M. A. H. Siddiki, A. S. Touchy, A. Bhosale, T. Toyao, Y. Mahara, J. Ohyama, A. Satsuma, K. Shimizu

Page No. – Page No.

Direct synthesis of lactams from keto acids, nitriles, and H_2 by heterogeneous Pt catalysts

We report the first general and reusable catalytic system for one-pot synthesis of *N*-substituted lactams by reductive conversion of keto acids (including levulinic acid) with nitriles and H_2 under mild conditions.