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COMMUNICATION

One-pot Synthesis of Pyrrolidones from Levulinic Acid and Amines/ Nitroarenes/Nitriles over Ir-PVP Catalyst

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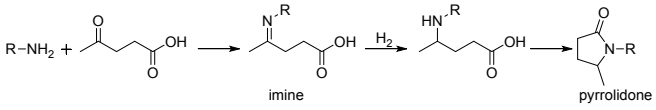
Synthesis of pyrrolidones via reductive amination of levulinic acid with aniline was examined over polypyrrolidone-stabilized metal nanoparticles catalysts. Among them, Ir metal was the most effective and applicable for reductive amination of levulinic acid with nitroarenes/nitriles. Importantly, this catalyst was used to one-pot synthesis of the anti-inflammatory drug indoprofen from 2-formylbenzoic acid and 2-(4-nitrophenyl)propanoic acid.

Due to limited stock of fossil fuel, the catalytic transformation of renewable biomass into useful chemicals have gained much attention both in academia and industry.[1] For example, biomass-derived levulinic acid (LA), which can be produced by acidic hydrolysis of carbohydrates, is used for the synthesis of a wide range of chemicals, including *N*-substituted-5-methyl-pyrrolidones, γ-valerolactone, 2-methyl tetrahydrofuran, 1,4-pentanediol, β-acetylacrylic acid, and δ-amino levulinic acid.[2] In particular, *N*-substituted-5-methyl-pyrrolidones, which are produced by reductive amination of LA, are used as surfactants, solvents, and pharmaceutical intermediates.[3] The reductive amination of LA involves three steps: (i) formation of an imine,(ii) hydrogenation of the imine, and (iii) cyclization of the resulting amine (Scheme 1).



Scheme 1. Synthesis of N-substituted-5-methyl-pyrrolidones

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† Footnotes relating to the title and/or authors should appear here.
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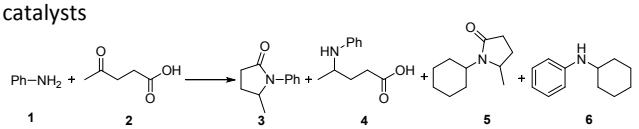
The production of LA by acidic hydrolysis of carbohydrates is accompanied by the generation of formic acid, which is therefore an attractive hydrogen source for the reductive amination of LA. In 2011, Fu *et al.* developed the first homogeneous $[Ru(p\text{-cymene})Cl_2]_2$ catalyst for reductive amination of LA with amine using formic acid and expensive phosphine ligand.[4] Later, Ir complex was reported for reductive amination using mixture of formic acid/sodium formate under acidic reaction conditions.[5] Garcia *et al*. examined ligand-free reductive amination of LA in presence of $[Ru_3(CO)_{12}]$ catalyst under neutral conditions.[6] Heterogeneous NHC-based Ru, Au/ZrO_2, Raney nickel catalysts have also been reported using formic acid as hydrogen source but these catalysts require high temperature (120-180 °C).[7] In addition, Fe complexes, InI_3, and $AlCl_3$ have been investigated as catalysts for reductive amination of LA with hydrosilane as the hydrogen source. However, the high cost of hydrosilane and waste issues make it unfavorable for reductive amination.[8] Some non-catalytic methods showed excellent activity but some of them require high temperature (100–200 °C), require critical purification process.[9] Compared with hydrosilane and formic acid, H_2 gas is an atom-economical hydrogen source for direct reductive amination of LA. In 1947, Frank reported Raney nickel catalyzed synthesize of pyrrilidone via reductive amination of LA with methyl amine using harsh conditions (140 °C, 70-140 bar H_2).[10] Homogeneous Ir catalysts were reported for reductive amination for LA and amines using hydrogen gas, but these catalysts have difficulties such as catalysts-product separation and necessity of special handling of catalysts.[11] Several heterogeneous Pt, Pd, Ru, Ni, FeNi catalysts have been reported.[12] However, these catalytic system suffer from use of additive, high temperature (>100 °C), high pressure (>10 bar H_2). Furthermore, the reported catalysts were designed for reductive amination of LA with amines only (Table S2).

Amines are generally produced by hydrogenation of nitroarenes or nitriles, reductive amination of LA with nitroarenes or nitriles is a direct and atom-ecomical way to the synthesis of pyrrolidones. In 2017, Supported Pt catalysts were examined for reductive amination of ethyl levulinate with nitro compounds at 120 °C.[13] Next, Shimizu *et al.* developed a Pt-

MoO_x/TiO_2 catalyst for reductive amination of LA by amines or nitriles at 100–110 °C.[14] Herein, we report one-pot synthesis pyrrolines via reductive amination of LA with amines, nitroarene, and nitriles by Ir-PVP catalyst under mild conditions. To our knowledge, we have demonstrated the first example of one-pot synthesis of anti-inflammatory drug indoprofen via reductive amination of 2-formylbenzoic acid with 2-(4-nitrophenyl)propanoic acid.

Initially, we examined the reductive amination of LA (**2**) with aniline (**1**) over polyvinylpyrrolidone (PVP) stabilized various metal nanoparticles under mild reaction conditions (5 bar H_2, 30 °C and neat). As summarized in Table 1, Ir-PVP catalyst demonstrated the superiority for full conversion (99%) and high yield of pyrrolidone (95%). Although Pt-PVP and Ru-PVP also showed high conversions, the moderate yield of pyrrolidone was obtained with aromatic ring hydrogenated product (1-cyclohexyl-5-methyl-pyrrolidone). Diphenylamine (**5**) and *N*-cyclohexylaniline (**6**) were observed as byproducts in presence of Pd-PVP. Rh-PVP catalyst was essentially inactive under the tested conditions.

Table 1. Reduction of amination of levulinic acid over various catalysts



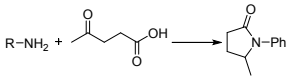
Entry	Catalyst	Conv. (%)	Yield[b] (%) **3**	Yield[b] (%) **4**	Yield[b] (%) **5**	Yield[b] (%) **6**
1	Ir-PVP	99	95	3	0	0
2	Pt-PVP	99	75	0	15	0
3	Pd-PVP	94	61	0	0	14
4	Ru-PVP	99	68	0	14	0
5[c]	Rh-PVP	80	5	0	0	0

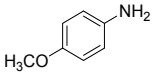
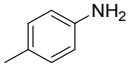
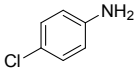
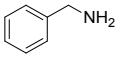
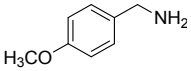
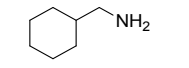
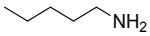
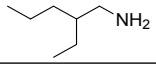
[a]Reaction conditions: **1** (1 mmol), **2** (2 mmol), catalyst (1.4 mol %), H_2 (5 bar), neat, 30 °C, 24 h. [b]GC yield. [c]Unknown byproducts were obtained.

To study general applicability of Ir-PVP catalysts, we carried out the reactions of LA with various amines under aforementioned reaction conditions (Table 2). Note that 4-Methoxyaniline, 4-methylaniline, and 4-chloroaniline are solid amines, we used methanol as solvent to facilitate better dispersion. Aniline with electron-donating group or electron-withdrawing group gave high to moderate yield of corresponding pyrrolidone (entries 2-4). Benzylamine and 4-methoxybenzylamine were efficiently transformed to corresponding pyrrolidone (entries 5 and 6). The reduction amination of linear and branched amines proceeded to high yield of desired products (entries 7-10).

Furtheremore, the general applicabilty of Ir-PVP was expanded for one-pot synthesis pyrrolidone via reductive amination of of LA with nitroarenes (Table 3). These reactions were performed in methanol because all the nitro compounds except nitrobenzene were solids. Reaction of LA and nitrobenzene for 72 h afforded a 95% yield of the desired pyrrolidone (entry 1). The catalyst was tolerent to different functional group of nitronbenzene and effieciently converted to corresponding pyrrolidone (entries 2-5).

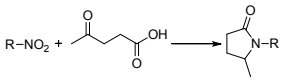
Table 2. Reductive amination of LA with various amines

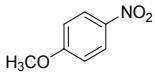
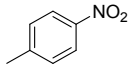
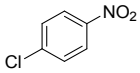
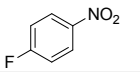


Entry	substrate	Conv.(%)	Yield[b] (%)
1		99	95
2[c]		99	98
3[c]		99	62
4[c]		99	50
5		99	80
6		99	93
7		85	74
8		99	90
9		99	87
10		96	65

[a]Reaction conditions: amine (1 mmol), LA (2 mmol), catalyst (1.4 mol %), H_2 (5 bar), neat, 30 °C, 24 h. [b]GC yield. [c]Methanol used as solvent in case of solid amine (1 mL).

Table 3. One-pot synthesis of pyrrolidone from LA and nitroarenes



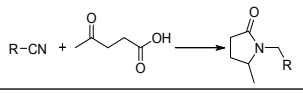
Entry	substrate	Conv.(%)	Yield[b] (%)
1		99	95
2		99	88
3		99	84
4		99	64
5		99	74

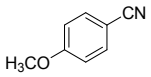
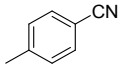
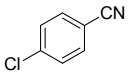
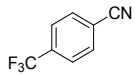
[a]Reaction conditions: nitroarene (1 mmol), LA (2 mmol), catalyst (1.4 mol %), H_2 (10 bar), methanol (1 mL), 30 °C, 72 h. [b]GC yield.

We also carried out one-pot syntheses of pyrrolidones from LA and nitriles under the same conditions (10 bar H_2 and methanol). Benzonitrile with an electron-donating or electron-

withdrawing group on the phenyl ring afforded good yields of pyrrolidones. (Table 4, entries 2-5).

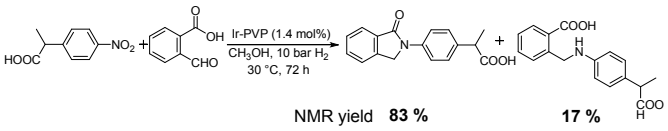
Table 4. One-pot synthesis of pyrrolidone from LA and nitriles



Entry	substrate	Conv.(%)	Yield[b] (%)
1		99	95
2		99	88
3		87	78
4		99	89
5		99	88

[a]Reaction conditions: nitrile (1 mmol), LA (2 mmol), catalyst (1.4 mol %), H_2 (10 bar), methanol (1 mL), 30 °C, 72 h. [b]GC yield.

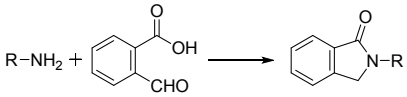
N-Substituted isoindolinones are important scaffolds for medicinal chemistry owing to their wide range of biological activities. For instance, indoprofen is a nonsteroidal anti-inflammatory drug with isoindolinone skeleton.[15] Several catalysts have reported for the synthesis of isoindoline using high temperature and/or high pressure.[8a, 8c, 11, 12e, 12g] Reductive amination of 2-formylbenzoic acid with various amines was carried out using methanol and 10 bar H_2 (Table 5). An electron-donating group containing aniline gave higher yield than electron-withdrawing group containing aniline (entries 2-4). The catalyst was able to transform various amine such as linear, branched and amino alcohol to corresponding to isoindolinones (entries 6-10). Furthermore, Ir-PVP catalyst was highly active for the synthesis of indoprofen (Scheme 2). Previously, indoprofen was synthesized in two-step method via reductive amination of 2-formylbenzoic acid using $InCl_3$ and hydrosilane.[16] Notably, this is the first example of one-step synthesis of indoprofen using reductive amination approach.

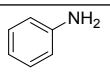
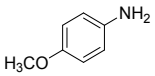
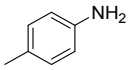
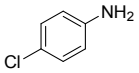
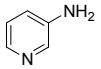
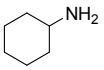
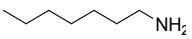
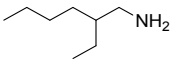
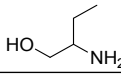


Scheme 2. One-pot synthesis of indoprofen from 2-formyl benzoic acid and 2-(4-nitrophenyl)propionic acid

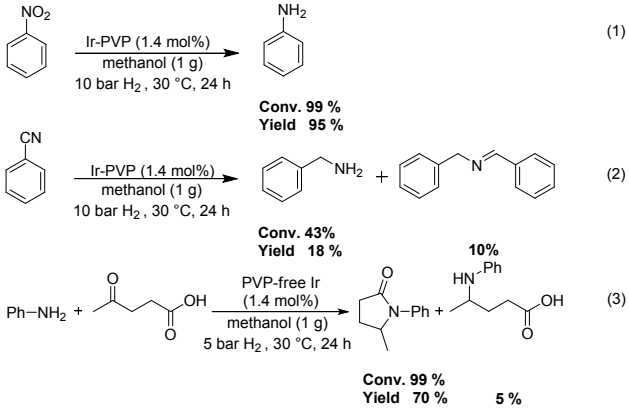
Next, the reusability of Ir-PVP was studied for reductive amination of LA with aniline under optimized reaction condition. After 1st cycle, the catalyst was separated by centrifugation from reaction mixture, washed by acetone, and dried at 40 °C for 12 h under vacuum**.** The dried catalyst was used for the next cycle. Ir-PVP catalyst was reused three times without any loss in activity (Fig. S4). Additionally, we analysed the recovered catalyst by scanning transmission electron microscopy (STEM) and XRD to detect the aggregation of Ir nanoparticles. No aggregation was observed in the recovered catalyst (Fig. S5 & S6). Furthermore, XRD analysis showed that the crystallite size (1.22 nm) did not change in reused catalyst (Fig. S7). Time-yield profile for reductive amination of LA by aniline was examined (Fig. S7). It showed a consecutive reaction mechanism via uncyclized intermediate (4-anilinopentanoic acid). The yield of uncyclized intermediate was increased initially, then underwent cyclization and transformed to final desire product.

Table 5. Reductive amination of 2-formylbenzoic acid with amines



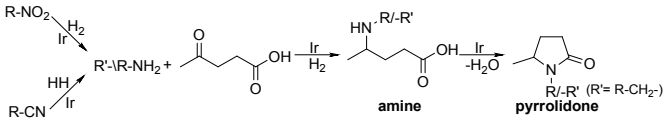
Entry	substrate	Conv.(%)	Yield[b] (%)
1		99	95
2		99	73
3		99	85
4		99	50
5		99	57
6		99	83
7		99	96
8		99	99
9		99	77
10		99	97

[a]Reaction conditions: amine (1 mmol), 2-formylbenzoic acid (2 mmol), catalyst (1.4 mol %), H_2 (10 bar), methanol (1 mL), 30 °C, 24 h. [b]GC yield.



To study reaction mechanism, we performed the reactions eqn. (1)-(3). Nitrobenzene was effectively hydrogenated to aniline by using Ir catalyst. Hydrogenation of nitrile was proceed to primary amine with secondary imine as byproduct. Probably, primary amine was produced selectively in presence

of carbonyl group of LA due to quick trapping of generated primary amine as imine simultaneously. Next, the role of PVP in catalytic cycle was also investiagated. Lower yield of pyrrolidone was obtained over PVP-free Ir catalyst due to aggregation of Ir nanoparticles. On other hand, PVP-stabilized Ir nanoparticles with small size contains higher surface site which may be reponsible for carbobyl functionality of LA which lead to the high yield of pyrrolidone.[17] The low selectivity of Pt, Pd, Ru or Rh catalysts can be explain by Sabatier principle. Too weak or too strong interaction between catalyst surface and adsorbed species may be proceed to poor selectivity.[18] However, the effect of large partcile size of catalysts (Pd, Ru or Rh) on selectivity can not be ruled out. Additional work is necessary to fully elucidate the reason for high reactivity of Ir nanoparticles. From these results, we proposed a plaussible mechanism in which the reaction began with Ir-PVP catalyzed hydrogenation of nitroarene/nitriles to corresponding primary amine (Scheme 3). The condensation reaction between the primary amine and LA generates imine, which is hydrogenated to a secondary amine in the presence of the Ir nanoparticles. Finally, cyclization of the secondary amine gives the pyrrolidone product.



Scheme 3. Reaction route for reductivce amination of LA

Conclusions

In summary, Ir-PVP catalyst was effective for reductive amination of levunilic acid under mild conditions (5 bar H_2, 30 °C). This is the first direct method for reductive amination of levunilic acid with amines/nitroarenes/nitriles. Moreover, the catalyst was reused and showed excellent activity for reductive amination of 2-formylbezoic acid as well. Using this approach, the anti-inflammatory drug, indoprofen was synthesized for the first time. Reductive amination by Ir-PVP catalyst could offer an atom-economical route for synthesis of isoindoline-based other drugs and this possibility will be explored in future work.

Conflicts of interest

There are no conflicts to declare.

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