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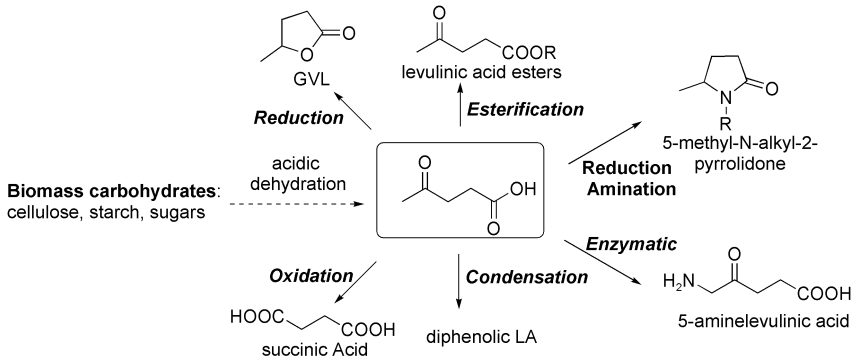
Ruthenium-Catalyzed Conversion of Levulinic Acid to Pyrrolidines by Reductive Amination

Yao-Bing Huang, Jian-Jun Dai, Xiao-Jian Deng, Yan-Chao Qu, Qing-Xiang Guo, and Yao Fu*[a]

The current global mass consumption of non-renewable fossil fuels is forcing academic and industrial scientists to find alternative sustainable resources.[1] The transformation of biomass into fuels and value-added chemicals[2] could be crucial to this endeavour and has been a strong research focus in recent years. Carbohydrates, the main component of biomass, could be converted into many chemicals such as ethanol, hydroxymethylfurfural (HMF),[3] levulinic acid (LA),[4] and furfural.[5]

Levulinic acid, an important platform chemical,[6] can also be produced by large-scale hydrolysis of furfurylalcohol or biobased cellulosic feedstocks.[7] Moreover, LA is a promising starting material for many different useful intermediates and fine chemicals by oxidation,[8] reduction,[9] condensation,[10] and esterification[11] (Scheme 1). For example, γ-valerolactone may be used as a liquid fuel, food additive and solvent;[12] 5-aminolevulinic acid is a highly active, biodegradable, and nontoxic herbicide and insecticide.[13]



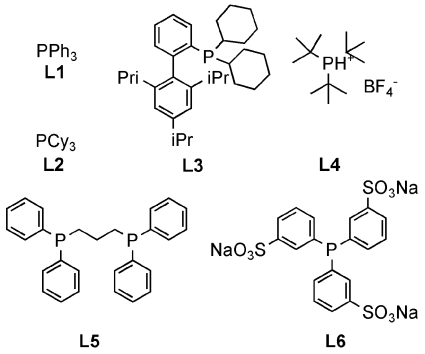
Scheme 1. Conversion of LA to useful compounds.

Additionally, pyrrolidines, such as 5-methyl-*N*-(methyl, aryl, alkyl, cycloalkyl)-2-pyrrolidone, are used as industrial solvents, surfactants, and complexing agents.[14] They are also employed in pharmaceutical formulations, transdermal patch formulation, grease removal formulation, agrochemical composition and stripping formulation.[14]

To produce pyrrolidines from LA, Shilling[15] and Crook[16] reported that silica gel-supported nickel or the Raney nickel catalyst could be used to transform LA to 5-methyl-2-pyrrolidone by gas-phase reductive amination. Recently, Manzer et al.[17,14a] reported that LA and its ester can be transformed into *N*-alkyl-5-methyprrolidones with a variety of metals. Furthermore, they developed a one-step process for converting LA and nitro compounds into aryl-, alkyl-, and cycloalkylpyrrolidones.[18] Under the same reaction conditions, aryl and alkyl nitriles could also react with LA in the presence of Ir/SiO_2, Ru/Al_2O_3, and Pd/C.[14b] However, these procedures usually require either high pressure/temperature or have a low to moderate yield. Thus, a more novel and efficient system is required.

According to the research of Beller,[19] Laurenczy,[20] and others,[21] formic acid (FA) will decompose under mild conditions to yield hydrogen. Furthermore, Horváth et al. have developed a pioneering route using LA/FA mixtures obtained by glucose dehydration for the synthesis of γ-valerolactone.[12b] Herein we report a new route to convert LA derived from biomass-based carbohydrates to pyrrolidines without need of an external H_2 supply.[22] The hydrogenation step was accomplished with formic acid produced from acidic dehydration of biomass-based carbohydrates. The advantages of the new route are its good atom economy and that it avoids the energy-intense extraction of LA from its aqueous solution with formic acid. (Scheme 2).

We began our research with LA, formic acid, and primary amines with various catalysts in the absence of solvent. On trying different ruthenium catalysts, we found that combining dichloro(*p*-cymene)ruthenium(II) dimer **1** with different phosphine ligands **L1**–**L6** afforded good results (Table 1, entries 1–6). When the ligand was changed to



[a] *Y.-B. Huang, J.-J. Dai, X.-J. Deng, Y.-C. Qu, Prof. Q.-X. Guo, Prof. Y. Fu*
Anhui Province Key Laboratory of Biomass Clean Energy
Department of Chemistry
University of Science and Technology of China
Hefei 230026 (PR China)
Fax. (+86) 551-360-6689
E-mail: fuyao@ustc.edu.cn

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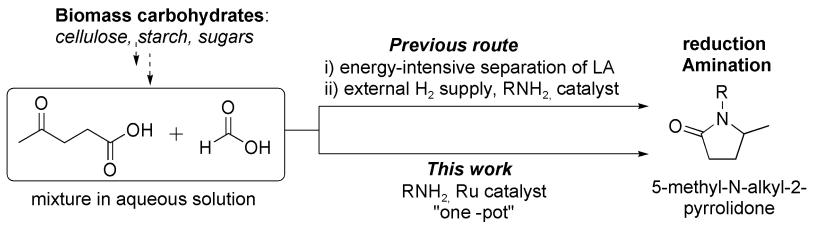
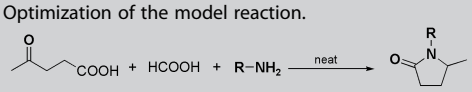


Scheme 2. Previous route vs. new transformation.

Table 1. Optimization of the model reaction.



Entry	R	Catalyst[a]	Ligand[b]	T [°C]	t [h]	Yield[c] [%]
1	Bn	$RuCl_3 \cdot H_2O$	**L1**	120	12	3
2	Bn	$Ru(PPh_3)_3Cl_2$	–	120	12	5
3	Bn	Ru/C	–	120	12	34
4	Bn	**1**	**L1**	120	12	7
5	Bn	**1**	**L2**	120	12	83
6	Bn	**1**	**L3**	120	12	76
7	Bn	**1**	**L4**	120	12	95
8	Bn	**1**	**L5**	120	12	21
9	Bn	**1**	**L6**	120	12	22
10[d]	Bn	**1**	**L4**	120	12	94
11[e]	Bn	**1**	**L4**	120	12	70
12	Bn	**1**	**L4**	100	12	94
13[d]	Bn	**1**	**L4**	80	12	93
14[d]	Bn	**1**	**L4**	60	12	80
15[d]	Bn	**1**	**L4**	80	6	85
16	Bn	–	–	80	12	8
17[d]	Ph	**1**	**L4**	80	12	20
18	Ph	**1**	**L4**	120	12	50
19	Ph	**1**	**L4**	140	12	38
20	Ph	**1**	**L5**	120	12	28
21	Ph	**1**	**L6**	120	12	43
22	Ph	$RuCl_3 \cdot H_2O$	**L1**	120	12	8
23[f]	Ph	**1**	**L4**	120	12	72
24[f]	Ph	–	–	120	12	5

Reaction conditions: LA/FA/amine = 1:1:1, **1**. [a] 1 mol%. [b] 3 mol%. [c] GC-MS yield. [d] Catalyst 0.5 mol%. [e] Catalyst 0.2 mol%. [f] LA/FA/amine = 2:2:1.

PtBu$_3$, the reaction reached full conversion and gave a 95% yield according to GC. Other ligands, dppp and tppts showed low activity (entries 8–9). On lowering the catalyst loading to 0.5 mol% and 0.2 mol%, the yields were 94% and 70% respectively (entries 10–11). When the reaction temperature was lowered to 80 °C, the catalyst still showed high efficiency (entries 12–15). The reaction gave poor results in the absence of the catalyst (entry 16). When a phenylamine ligand was employed under the optimal conditions, the yield was only 20% and some side product (*N*-phenylformamide) was detected (entry 17). However, by changing the ratio of LA/FA/amine to 2:2:1, the yield of the target product increased and the side product was suppressed (entries 17–24).[23]

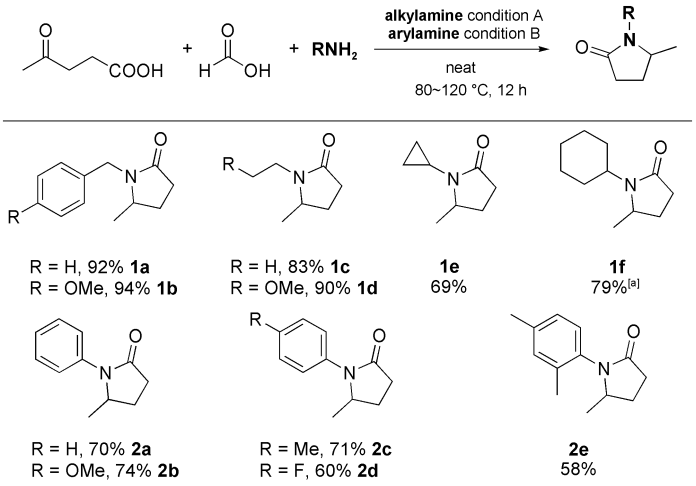
These experiments produced a small library of pyrrolidines. The isolated yield of 5-methyl-*N*-benzyl-2-pyrrolidines from benzyl-amine is 92% (Scheme 3, **1a**). An electron donating substituent on the phenyl ring gave a higher yield of 94% (Scheme 3, **1b**). *n*-Butylamine and 2-methoxyethanamine, representative of straight-chain alkyl-amines, gave the corresponding pyrrolidines in good to excellent yields (Scheme 3, **1c**, **1d**). However, the reaction using a secondary amine gave a moderate yield (69%), most likely due to sterics (Scheme 3, **1e**). By using excess LA and FA, cyclohexylmethanamine gave **1f** in 79% yield (Scheme 3, **1f**). Several arylamines were also selected to synthesize 5-methyl-*N*-arylpyrrolidines. An obvious electric effect was determined: the activity of arylamines decreased when the substituent became more electron-withdrawing (Scheme 3, **2a**–**2d**) and showed the arylamine to react more easily with FA. An *ortho*-substituent on the phenyl ring further decreased the reactivity (Scheme 3, **2e**).

These results demonstrate that pyrrolidines can be prepared easily from LA, which is in turn obtained via acidic dehydration of biomass-derived carbohydrates without an external H_2 supply. We looked next into making the transformation practical for the acidic dehydration process in water. As illustrated in our previous work,[12c] LA could be produced simply from several types of biomass-based carbohydrates in yields between 35%–58% (Table 2). The yield of FA is higher than that of LA and H_2 sourced from FA decomposed would be enough for further use in hydrogenations.

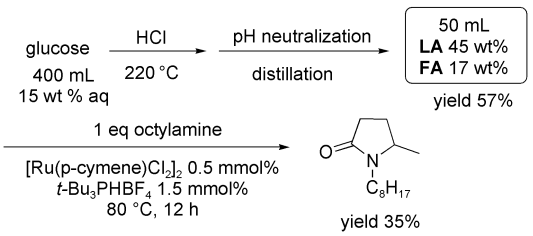
A 50 wt% aqueous solution of LA/formic acid (1:1) was prepared to simulate an acidic dehydration system. Strikingly, we found that the transformation of LA to pyrrolidines could be achieved in the simulated system with only a slightly lower yield (Scheme 4). Notably, a 25 wt% ammonia or methylamine solution could be used instead of their gaseous forms as the amine sources to produce the corresponding pyrrolidines (Scheme 4, **1g**, **1f**). Compared to their amine gas equivalents, these raw materials are much cheaper and they can be more conveniently handled.

Finally, we applied the catalytic system to the transformation of glucose into pyrrolidines and enlarged the process to a laboratory-scale (Scheme 5). Acidic dehydration with additional treatment gave an aqueous mixture (50 mL, 42 wt% LA, 17 wt% formic acid) from glucose (400 mL, 15 wt% aqueous solution),[12c] to which the catalyst and amines were added. Reductive amination at 80 °C produced the 5-methyl-*N*-octyl-2-pyrrolidone, an industrial surfactant, in 62% yield. The overall yield of the pyrrolidone from glucose is 34%. Supported phosphine ligands containing ruthenium enable the recycling of the expensive catalytic from the reaction mixture. Our future work would focus on preparing the supported heterogeneous catalyst.

In summary, we have developed a convenient and effective procedure that converts LA derived from biomass-based carbohydrates into pyrrolidines with [Ru(*p*-cymene)Cl$_2$]$_2$/*t*-Bu$_3$PHBF$_4$ catalysis without need for intermediate purification or an exter-



Scheme 3. Transformation of LA/FA to pyrrolidines with different amines in neat conditions. Conditions A: LA (1 mmol), FA (1 mmol), amine (1 mmol), **1** (0.5 mol%), *t*-Bu_3PHBF_4 (1.5 mol%), 80 °C, 12 h. Isolated yields. Conditions B: LA (2 mmol), FA (2 mmol), amine (1 mmol), **1** (1 mol%) *t*-Bu_3PHBF_4 (3 mol%) 120 °C, 12 h. Isolated yields. [a] LA/FA/amine = 2:2:1 (mmol).



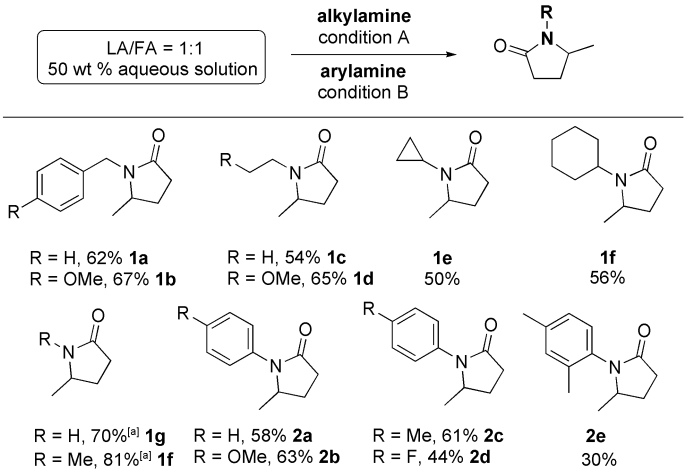
Scheme 5. Transformation of glucose to pyrrolidines.

nal H_2 supply.[24] This procedure can be utilized to produce a family of building blocks that may find important application as intermediates or final chemicals in industry. In a laboratory-scale experiment, glucose was transformed into pyrrolidine in 34% yield by an operationally simple sequence (acidic dehydration and Ru-catalyzed reductive amination). Further research would focus on the effective catalytic conversion of LA to different value-added chemicals and biofuels.

Table 2. LA and FA prepared from acid-catalyzed biomass carbohydrates at 220 °C, as detailed in our previous work.[12c]

Entry	Carbohydrate	LA yield [mol%]	FA yield [mol%]
1[a]	microcrystalline cellulose	35.4	45
2[a]	α-cellulose	45.2	49
3[a]	starch	53.7	58
4[b]	glucose	57.7	76

[a] Conditions: 20 g of carbohydrate in 400 mL of aqueous HCl (0.8 M). [b] Conditions: 15 wt% glucose in 400 mL of aqueous HCl (0.8 M).



Scheme 4. Transformation of LA/FA solution to pyrrolidines with different amines. Conditions A: LA (1 mmol), FA (1 mmol), H_2O (150 mg), amine (1 mmol), **1** (0.5 mol%) *t*-Bu_3PHBF_4 (1.5 mol%), 80 °C, 12 h. Isolated yield (based on amine), 80 °C, 12 h. Isolated yields. Conditions B: LA (2 mmol), FA (2 mmol), H_2O (250 mg), amine (1 mmol), **1** (1 mol%) *t*-Bu_3PHBF_4 (3 mol%) 120 °C, 12 h. Isolated yields (determined by amine). [a] LA/FA/amine = 1:1:3. Isolated yields (based on LA).

Experimental Section

Levulinic acid (LA, 99%), formic acid (FA, 98%), Ru catalyst and α-cellulose were supplied by Aladdin Reagent Co. Ltd. The ligands used in the literature were all purchased from Alfa Aesar. Glucose and amines were purchased from Sinopharm Chemical Reagent Co. Ltd. All reactions were carried out in an oven-dried flask under an atmosphere of nitrogen. Flash column chromatography was performed with silica gel (200–300 mesh). NMR spectra were recorded using a Bruker Avance 300 and 400 instruments. Gas chromatographic (GC) analyses were performed on a Shimadzu GC-2014 Series GC System. GC-MS analysis was performed on Thermo Scientific AS 3000 Series GC-MS System. MS analyses were performed on Finnigan LCQ advantage Max Series MS System.

Experimental Procedures for reaction without solvent or in water: A disposable tube with a plastic screwcap top, Teflon septum, and stir bar was charged with the desired amount of catalyst (0.2~1 mol%) and ligand (3 eq to metal). If the amine was a solid, it was added simultaneously. The tube was evacuated and refilled with nitrogen three times. LA (1~2 mmol), FA (1~2 mmol), and amine were added by syringe under a flow of nitrogen. (If the reaction was in water, solutions of LA and FA were added). The reaction was allowed to run for 6~12 h, whereupon it was cooled to room temperature, then diluted with aqueous Na_2CO_3 solution. The resulting mixture was extracted with diethyl ether. The separated organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel.

Experimental Procedures for converting glucose to pyrrolidines: 400 mL, 15 wt% glucose and 0.8 M HCl solution was loaded to a 500 mL stainless steel autoclave, which was then heated to 220 °C under vigorous stirring for 1 h. The mixture was transferred to a 200 mL flask and then, after partial neutralization (pH 2) and filtration, to a pressure-equalizing dropping funnel. The filtrate was distilled under vacuum and concentrated to 50 mL using a

cullet-packed column. Finally, the concentrated mixture of FA and LA was added to the catalyst and amine. The autoclave was flushed with nitrogen and stirred at 1000 rpm. The autoclave temperature was elevated to the target temperature in 30 min and cooled in water to room temperature after the reaction. The reaction mixture was sampled, diluted 100 times in acetone and analyzed by GC-MS.

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Keywords: amination · amines · homogeneous catalysis · renewable resources · ruthenium

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