ChemComm

COMMUNICATION

Highly efficient transformation of levulinic acid into pyrrolidinones by iridium catalysed transfer hydrogenation†

Yawen Wei,[a] Chao Wang,*[a] Xue Jiang,[a] Dong Xue,[a] Jia Li[a] and Jianliang Xiao*[ab]

Levulinic acid (LA) is transformed into pyrrolidinones *via* iridium-catalysed reductive amination using formic acid as the hydrogen source under aqueous conditions. The catalytic system is the most active and performs under the mildest conditions ever reported for the reductive amination of LA.

Over 90% of chemicals are derived from fossil resources, which are limited and non-renewable. Renewable biomass could be an ideal replacement for fossil resources to provide fuels and particularly, chemicals.[1] Indeed, selective transformation of biomass into value-added products has attracted much attention, but it is still a challenge for chemists. LA, which can be obtained by simple acidic dehydration of carbohydrates,[2] has been identified as a platform chemical from biomass-derived products.[1o] For example, it has been transformed into γ-valerolactone (GVL)[3] and pyrrolidinones,[4] which can serve as platform molecules for various applications in fuel and fine chemical industries.[1h,x,y,4a,b] However, successful catalytic systems for converting LA to pyrrolidinones by reductive amination (RA) are few.[4] The first examples were reported by Shilling,[4f] Crook[4e] and their co-workers, and later by Manzer,[4a,b,g,h] Cao and co-workers, in which heterogeneous hydrogenation was used.[4c] The first homogeneous RA of LA was reported only recently by Fu and co-workers.[4d]

During the transformation of carbohydrates into LA, an equal molar amount of formic acid is produced under aqueous conditions.[1e] Formic acid is a green reducing reagent and is frequently used in transfer hydrogenation reactions as the hydrogen source.[5] Thus, it would be ideal to use formic acid as a hydrogen source in the reductive transformation of LA in water (Scheme 1). Successful demonstration of this idea has been reported.[1w,3a,d,h,j,4c,d,6] However, in these systems, either harsh conditions are required[3j] or the real reducing reagent is actually hydrogen gas, which comes from *in situ* decomposition of formic acid.[3d,h,4c,d] Thus, true transfer hydrogenation of LA with formic
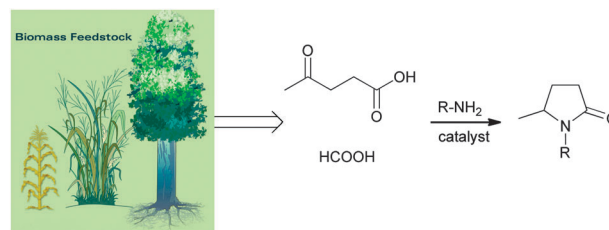
Scheme 1 Transformation of biomass-derived LA into fine chemicals.

acid remains an unrealised challenge. Herein, we disclose the first transfer hydrogenation system for RA of LA to produce pyrrolidinones using formic acid as the hydrogen source and structurally well-defined homogeneous catalysts under mild conditions.

Recently, we discovered that cyclometalated iridium complexes are highly efficient catalysts for reductive amination of carbonyl groups with formic acid as the hydrogen source.[7] These iridicycle catalysts are also effective for transfer hydrogenation and RA of carbonyls in water.[8] As aliphatic ketones were suitable substrates and carboxylic groups could be tolerated under the conditions, we reasoned that LA might also be a viable substrate. Hence, we set out to investigate whether or not the iridicycle complexes could be exploited for the RA of LA. Water was chosen as solvent not only because of its considerable environmental and economical benefits but also due to the fact that biomass-derived LA and formic acid are generated in water.[9]

The RA of LA with *p*-anisidine using pure formic acid as the hydrogen source was initially carried out in neat water at 80 °C for 12 h with **1a** as catalyst, which was shown to be the best RA catalyst in our previous work (Scheme 2).[7] However, no reaction took place under these conditions.

As solution pH is crucial for RA and aqueous transfer hydrogenation reactions,[10] we turned our attention to the effect of solution pH on the RA by addition of HCOONa to adjust the solution pH. As is shown in Scheme S1 (ESI†), the pH indeed affects the reaction dramatically. The reaction only took place at a narrow acidic pH window (around 2–5). The best activity was observed at *ca.* pH 3.5, with a 75% conversion in 1 h at 80 °C at an impressive substrate to catalyst ratio (S/C) of 3000. To the best of our knowledge, this is the highest S/C ever reported for homogeneous reduction of LA.

a Key Laboratory of Applied Surface and Colloid Chemistry, Ministry of Education, Department of Chemistry & Chemical Engineering, Shaanxi Normal University, Xi'an, 710062, China. E-mail: c.wang@snnu.edu.cn

b Department of Chemistry, University of Liverpool, Liverpool, L69 7ZD, UK. E-mail: j.xiao@liv.ac.uk; Fax: +44 (0)151-7943588

Communication
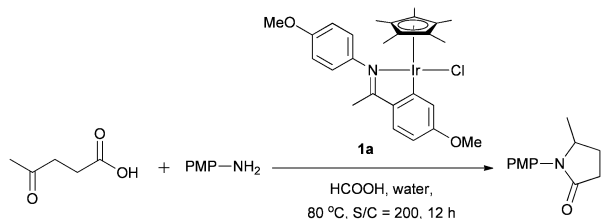
Scheme 2 Attempted RA of LA with *p*-anisidine catalysed by **1a**. Reaction conditions: LA (0.5 mmol), *p*-anisidine (0.6 mmol), **1a** (0.0025 mmol), HCOOH (2.5 mmol), water 3 mL, 80 °C, 12 h. PMP = *para*-methoxylphenyl.

Aiming to find a more active catalyst, we next examined the effect of different substituents *para* to the imino group on the coordinating phenyl ring of the iridicycle catalysts at pH 3.5, as well as the activities of some other metal catalysts. The results are summarised in Table S1 (ESI†). For iridicycle catalysts, the electron-donating methoxyl group benefits the reaction, while methyl or hydrogen atoms afforded a relatively low conversion (Table S1, entries 1–3, ESI†). All the electron-withdrawing groups gave similarly lower conversions compared with catalyst **1a** (Table S1, entries 4–7, ESI†). The other catalysts showed low or almost no activities even at higher catalyst loadings (Table S1, entries 8–12, ESI†).

Further optimisation of the reaction conditions for **1a**, including increasing the amount of amine, catalyst loading and concentration, led to a satisfactory isolated yield of 94% at a 3.2 mmol scale of LA (Table 1, entry 1). The substrate scope of reacting LA with different amines was then examined with catalyst **1a** at S/C = 2000 and pH 3.5. As can be seen from Table 1, the RA afforded good yields for a range of aromatic amines. In particular, those with relatively electron-donating substituents gave higher yields than ones with electron-withdrawing substituents. Thus, over 90% of isolated yields were obtained in 2 h for 4-OMe, 4-Me and 4-H substituted substrates (Table 1, entries 1–3). However, for the halide and 4-OCF$_3$ substituents, a longer time of 4 h was required to reach reasonably good yields (Table 1, entries 4–7). Installing a substituent at the 3-position of aniline decreases the reaction rate, possibly due to steric hindrance (Table 1, entries 8 and 9). This is further evidenced by the poor reactivity of 2,5-dimethoxyl aniline (<10% conversion).

Table 1 RA of LA with aromatic amines[a]

Entry	R	Product	Time (h)	Yield[b] (%)
1	4-OMe	**2a**	2	94
2	4-CH$_3$	**2b**	2	93
3	4-H	**2c**	2	91
4	4-F	**2d**	4	88
5	4-Cl	**2e**	4	73
6	4-Br	**2f**	4	86
7	4-OCF$_3$	**2g**	4	72
8[c]	3-OMe	**2h**	12	76
9	3,4-Me	**2i**	12	82

[a] Reaction conditions: LA (3.2 mmol), *p*-anisidine (8.6 mmol), catalyst (0.0016 mmol), aqueous HCOOH–HCOONa solution (14.5 M, 3 mL), 80 °C, 1 h. [b] Isolated yield. [c] S/C of 1000 was used.

Table 2 RA of LA with aliphatic amines[a]

Entry	R	Product	Time (h)	Yield[b] (%)
1	Benzyl	**2j**	4	86
2	4-OMe-benzyl	**2k**	4	94
3	3-OMe-benzyl	**2l**	12	94
4[c]	2-OMe-benzyl	**2m**	24	96
5	3,4-OMe-benzyl	**2n**	24	94
6	4-F-benzyl	**2o**	12	91
7[d]	*n*-Octyl	**2p**	12	88
8[e]	*n*-Undecyl	**2q**	12	73

[a] The reaction conditions were the same as in Table 1. [b] Isolated yield. [c] S/C of 200 was used. [d] pH = 4.5, S/C of 500 was used. [e] MeOH as solvent, HCOOH–Et$_3$N azeotrope as a hydrogen source, and S/C = 500.

The catalytic system also worked well for aliphatic amines (Table 2). Thus, 86% yield was achieved for benzylamine in 4 h at an S/C of 2000. Varying the position of the methoxyl substituent on the phenyl ring of the benzyl group affects the reaction rate, with increasing steric hindrance requiring longer reaction time or a lower S/C ratio (Table 2, entries 2–4). For instance, whilst (4-methoxyphenyl)methanamine afforded 94% yield in 4 h under the standard conditions, the 2-methoxy-substituted analogue gave a similar yield but at a much reduced S/C ratio and a much longer time (Table 2, entry 2 *vs.* 4). Long chain aliphatic amines are more difficult substrates. Thus, 1-octylamine needed an S/C of 500 and pH 4.5 to reach a good yield in 12 h (Table 2, entry 7), presumably due to the poor miscibility of the amine with water and catalyst. Not surprisingly, for 1-undecylamine, it was necessary not only to increase the catalyst loading but also to use a more powerful solvent MeOH and the HCOOH–Et$_3$N azeotrope as the hydrogen source (Table 2, entry 8), presumably due to the insolubility of 1-undecylamine in water.

The generality of this catalytic system was further tested in the reaction of 5-oxohexanoic acid with various amines to produce six membered heterocycles, which are another class of important heterocycle compounds (Table 3). Interestingly, the highest yield was obtained with the slightly electron-withdrawing 4-F substituted aniline (Table 3, entries 1–4), in contrast to the RA of LA (Table 1). Again, 1-octylamine requires an S/C of 500 (Table 3, entry 5).

A proposed mechanism for the transformation of LA into pyrrolidinones is presented in Scheme 3. The formation of iridium hydride from iridicycle catalysts is now well established.[11] Based on

Table 3 RA of 5-oxohexanoic acid[a]

Entry	R	Product	Time (h)	Yield[b] (%)
1	4-OMe-phenyl	**2r**	12	84
2	4-F-phenyl	**2s**	12	97
3	4-OMe-benzyl	**2t**	24	82
4	4-F-benzyl	**2u**	12	81
5[c]	*n*-Octyl	**2v**	12	86

[a] The reaction conditions were the same as in Table 1. [b] Isolated yield. [c] S/C = 500.
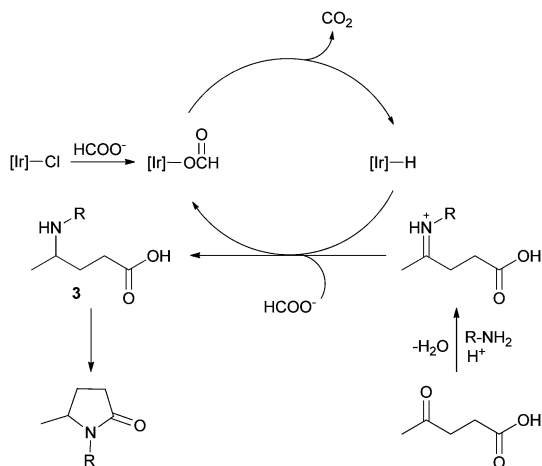
Scheme 3 Proposed mechanism for iridium-catalysed RA of LA.

our previous studies on RA,[10e,11] we believe that an iminium intermediate, generated *in situ* under the acidic conditions, is reduced by an iridium hydride. To gain insight into the cyclisation step, we isolated and characterised the RA product **3** (R = PMP). Full conversion of **3** to **2a** was observed under the standard conditions in 1 h, but without the iridium catalyst. In fact, when running the NMR of **3** in $CDCl_3$, spontaneous cyclisation happened (Scheme S2, ESI†), indicating that the iridicycle catalyst is not required for this step.

In conclusion, the first and a highly efficient transfer hydrogenation system for RA of LA has been developed, which uses formic acid as the hydrogen source under aqueous conditions, allowing transformation of LA into valuable pyrrolidinones under mild conditions. The system is also applicable to 5-oxohexanoic acid to produce six membered heterocycles. This mild and green system provides a practical means for converting biomass-derived chemicals into value-added products.

References

1 (a) J. R. Rostrup-Nielsen, *Science*, 2005, **308**, 1421–1422; (b) G. W. Huber, S. Iborra and A. Corma, *Chem. Rev.*, 2006, **106**, 4044–4098; (c) M. Schlaf, *Dalton Trans.*, 2006, 4645–4653; (d) J. N. Chheda, G. W. Huber and J. A. Dumesic, *Angew. Chem., Int. Ed.*, 2007, **46**, 7164–7183; (e) A. Corma, S. Iborra and A. Velty, *Chem. Rev.*, 2007, **107**, 2411–2502; (f) L. D. Schmidt and P. J. Dauenhauer, *Nature*, 2007, **447**, 914–915; (g) P. Gallezot, *ChemSusChem*, 2008, **1**, 734–737; (h) J. J. Bozell, *Science*, 2010, **329**, 522–523; (i) J. J. Bozell and G. R. Petersen, *Green Chem.*, 2010, **12**, 539–554; (j) U. Biermann, U. Bornscheuer, M. A. R. Meier, J. O. Metzger and H. J. Schäfer, *Angew. Chem., Int. Ed.*, 2011, **50**, 3854–3871; (k) D. J. Braden, C. A. Henao, J. Heltzel, C. C. Maravelias and J. A. Dumesic, *Green Chem.*, 2011, **13**, 1755–1765; (l) A. A. Rosatella, S. P. Simeonov, R. F. M. Frade and C. A. M. Afonso, *Green Chem.*, 2011, **13**, 754–793; (m) S. Van de Vyver, J. Geboers, P. A. Jacobs and B. F. Sels, *ChemCatChem*, 2011, **3**, 82–94; (n) S. Chikkali and S. Mecking,

Angew. Chem., Int. Ed., 2012, **51**, 5802–5808; (o) P. Gallezot, *Chem. Soc. Rev.*, 2012, **41**, 1538–1558; (p) J. C. Serrano-Ruiz, A. Pineda, A. M. Balu, R. Luque, J. M. Campelo, A. A. Romero and J. M. Ramos-Fernández, *Catal. Today*, 2012, **195**, 162–168; (q) F. W. Lichtenthaler and S. Mondel, *Pure Appl. Chem.*, 1997, **69**, 1853–1866; (r) G. W. Huber, J. N. Chheda, C. J. Barrett and J. A. Dumesic, *Science*, 2005, **308**, 1446–1450; (s) P. Gallezot, *Catal. Today*, 2007, **121**, 76–91; (t) H. Zhao, J. E. Holladay, H. Brown and Z. C. Zhang, *Science*, 2007, **316**, 1597–1600; (u) G. Yong, Y. Zhang and J. Y. Ying, *Angew. Chem., Int. Ed.*, 2008, **47**, 9345–9348; (v) J. B. Binder and R. T. Raines, *J. Am. Chem. Soc.*, 2009, **131**, 1979–1985; (w) T. Thananatthanachon and T. B. Rauchfuss, *Angew. Chem., Int. Ed.*, 2010, **49**, 6616–6618; (x) J. Q. Bond, D. M. Alonso, D. Wang, R. M. West and J. A. Dumesic, *Science*, 2010, **327**, 1110–1114; (y) J. P. Lange, R. Price, P. M. Ayoub, J. Louis, L. Petrus, L. Clarke and H. Gosselink, *Angew. Chem., Int. Ed.*, 2010, **49**, 4479–4483.

2 (a) W. F. Stephen, *US Pat.*, 5608105, 1997; (b) M. G. Viswas and A. H. Milford, *US Pat.*, 5859263, 1999; (c) A. F. William and E. C. John, *US Pat.*, 6054611, 2000.

3 (a) H. Heeres, R. Handana, D. Chunai, C. Borromeus Rasrendra, B. Girisuta and H. Jan Heeres, *Green Chem.*, 2009, **11**, 1247–1255; (b) L. Deng, Y. Zhao, J. Li, Y. Fu, B. Liao and Q. X. Guo, *ChemSusChem*, 2010, **3**, 1172–1175; (c) J. C. Serrano-Ruiz, D. Wang and J. A. Dumesic, *Green Chem.*, 2010, **12**, 574–577; (d) X. L. Du, Q. Y. Bi, Y. M. Liu, Y. Cao and K. N. Fan, *ChemSusChem*, 2011, **4**, 1838–1843; (e) A. M. Hengne, N. S. Biradar and C. V. Rode, *Catal. Lett.*, 2012, **142**, 779–787; (f) S. G. Wettstein, J. Q. Bond, D. M. Alonso, H. N. Pham, A. K. Datye and J. A. Dumesic, *Appl. Catal., B*, 2012, **117–118**, 321–329; (g) H. Mehdi, V. Fábos, R. Tuba, A. Bodor, L. T. Mika and I. T. Horváth, *Top. Catal.*, 2008, **48**, 49–54; (h) L. Deng, J. Li, D. M. Lai, Y. Fu and Q. X. Guo, *Angew. Chem., Int. Ed.*, 2009, **48**, 6529–6532; (i) F. M. A. Geilen, B. Engendahl, A. Harwardt, W. Marquardt, J. Klankermayer and W. Leitner, *Angew. Chem., Int. Ed.*, 2010, **49**, 5510–5514; (j) D. Kopetzki and M. Antonietti, *Green Chem.*, 2010, **12**, 656–660; (k) F. M. A. Geilen, B. Engendahl, M. Hölscher, J. Klankermayer and W. Leitner, *J. Am. Chem. Soc.*, 2011, **133**, 14349–14358.

4 (a) L. E. Manzer, *US Pat.*, 6743819, 2004; (b) L. E. Manzer, *US Pat.*, 6841520, 2005; (c) X. L. Du, L. He, S. Zhao, Y. M. Liu, Y. Cao, H. Y. He and K. N. Fan, *Angew. Chem., Int. Ed.*, 2011, **50**, 7815–7819; (d) Y. B. Huang, J. J. Dai, X. J. Deng, Y. C. Qu, Q. X. Guo and Y. Fu, *ChemSusChem*, 2011, **4**, 1578–1581; (e) L. R. Crook, B. A. Jansen, K. E. Spencer and D. H. Watson, *GB Pat.*, 1036694, 1996; (f) W. L. Shilling, *US Pat.*, 3235562, 1996; (g) L. E. Manzer and F. E. Herkes, *US Pat.*, 2004192933, 2003; (h) L. E. Manzer, *WO Pat.*, 2004084633, 2004.

5 (a) M. Wills, M. Palmer, A. Smith, J. Kenny and T. Walsgrove, *Molecules*, 2000, **5**, 4–18; (b) S. Gladiali and E. Alberico, *Chem. Soc. Rev.*, 2006, **35**, 226–236; (c) T. Ikariya and A. J. Blacker, *Acc. Chem. Res.*, 2007, **40**, 1300–1308; (d) X. F. Wu and J. L. Xiao, *Chem. Commun.*, 2007, 2449–2466; (e) C. Wang, X. F. Wu and J. L. Xiao, *Chem.–Asian J.*, 2008, **3**, 1750–1770.

6 T. Thananatthanachon and T. B. Rauchfuss, *ChemSusChem*, 2010, **3**, 1139–1141.

7 C. Wang, A. Pettman, J. Bacsa and J. L. Xiao, *Angew. Chem., Int. Ed.*, 2010, **49**, 7548–7552.

8 (a) Q. Lei, Y. W. Wei, D. Talwar, C. Wang, D. Xue and J. L. Xiao, *Chem.–Eur. J.*, 2013, **19**, 4021–4029; (b) Y. W. Wei, D. Xue, Q. Lei, C. Wang and J. L. Xiao, *Green Chem.*, 2013, **15**, 629–634.

9 (a) T. Dwars, E. Paetzold and G. Oehme, *Angew. Chem., Int. Ed.*, 2005, **44**, 7174–7199; (b) C. J. Li, *Chem. Rev.*, 2005, **105**, 3095–3166; (c) A. Chanda and V. V. Fokin, *Chem. Rev.*, 2009, **109**, 725–748.

10 (a) S. Ogo, T. Abura and Y. Watanabe, *Organometallics*, 2002, **21**, 2964–2969; (b) S. Ogo, K. Uehara, T. Abura and S. Fukuzumi, *J. Am. Chem. Soc.*, 2004, **126**, 3020–3021; (c) X. F. Wu, X. G. Li, F. King and J. L. Xiao, *Angew. Chem., Int. Ed.*, 2005, **44**, 3407–3411; (d) Y. Himeda, N. Onozawa-Komatsuzaki, S. Miyazawa, H. Sugihara, T. Hirose and K. Kasuga, *Chem.–Eur. J.*, 2008, **14**, 11076–11081; (e) C. Wang, C. Q. Li, X. F. Wu, A. Pettman and J. L. Xiao, *Angew. Chem., Int. Ed.*, 2009, **48**, 6524–6528.

11 C. Wang, H. Y. T. Chen, J. Bacsa, C. R. A. Catlow and J. L. Xiao, *Dalton Trans.*, 2013, **42**, 935–940.