ChemPubSoc Europe

DOI: 10.1002/cssc.201501461

CHEMSUSCHEM Communications

Direct Hydrogenation of Biobased Carboxylic Acids Mediated by a Nitrogen-centered Tridentate Phosphine Ligand

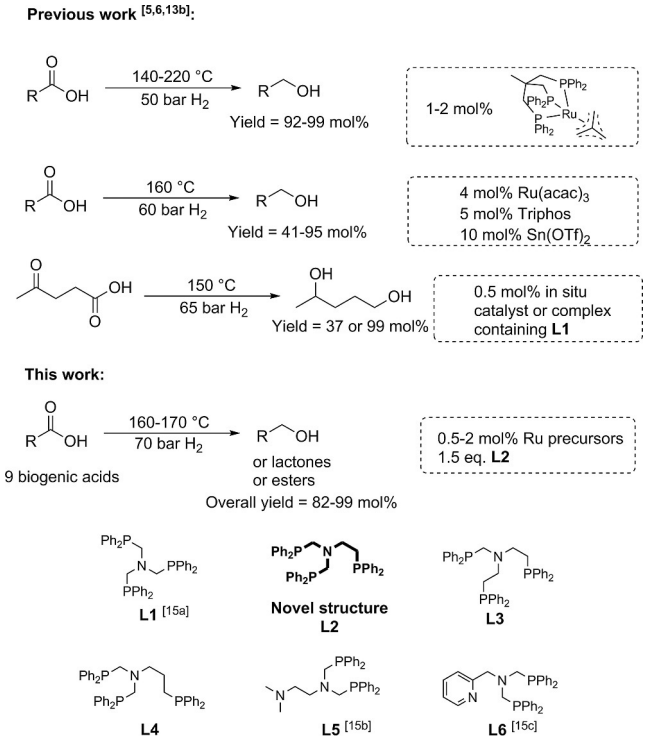
Li Deng,*[a] Bin Kang,[a] Ulli Englert,[b] Jürgen Klankermayer,[a] and Regina Palkovits*[a]

A novel nitrogen-centered tridentate ligand was identified from a series of multidentate ligands and applied for the direct hydrogenation of 9 biogenic acids into alcohols, lactones and esters with high yields. Comparison of substrates and ruthenium precursors suggested that the Ru^{II} hydride cationic species was more active to transform acids than the corresponding lactone or esters.

Carboxylic acids including lactic acid, levulinic acid, and itaconic acid are an important class of building blocks produced in biorefineries.[1–3] Catalytic hydrogenation is an ideal way to convert oxygen-rich carboxylic acids into alcohols or lactones.[4–7] However, the direct hydrogenation of carboxylic acids remains a challenging task in homogeneous catalysis. Although the green reductant H_2 has been successfully applied to hydrogenate esters and amides using various noble or non-noble metal catalysts under mild conditions,[8–11] there are only few excellent examples for carboxylic acid hydrogenation.[4–6] A very efficient homogeneous catalyst system was introduced by Klankermayer and Leitner, using $Ru(acac)_3$ and the tridentate ligand triphos in combination with acidic additives.[5a] Based on mechanistic investigations the molecularly defined complex Ru(triphos)(TMM) (TMM = trimethylene methane) could be established, demonstrating unprecedented performance in the hydrogenation of carboxylic and carbonic acid derivatives.[5] Very recently, the triphos-based catalytic system could be further improved and established as a general method for carboxylic acid and amide hydrogenation.[6]

Despite the success of the discussed catalytic systems and the deep understanding of the role of metal complexes and acid additives in reaction mechanisms, only a limited number of ruthenium catalysts or ligands are effective for this reaction. To the best of our knowledge, only ruthenium catalysts based on three types of ligands, that is, trialkylphosphines,[7] triphos,[12] and the nitrogen-centered triphos analogue **L1**,[13] have been reported. Moreover, the efficient hydrogenation of several biogenic acids using complexes with trialkylphosphines or triphos ligands required high reaction temperatures (ca. 200 °C) or strong acid additive.[5–7,14] Using a **L1** based complex, only the efficient hydrogenation of levulinic acid to 1,4-pentandiol (PDO) and 2-methyltetrahydrofuran has been reported.[13b]

Considering the limited number of suitable catalysts and the importance of a direct hydrogenation of carboxylic acids, the investigation of more catalyst structures and ligands for this challenging reaction becomes imperative. Therefore, we synthesized a class of nitrogen-centered multidentate phosphine ligands and applied them with ruthenium precursors to catalyze the hydrogenation of biogenic acids (Scheme 1 and Supporting Information, Scheme S1). Compared to the synthesis of the reported tripodal ligands **L1** with C_3 symmetry, using amines instead of ammonia as starting material facilitates access to more candidates for hydrogenation due to the diversity of available amine building blocks. Herein, **L2** was identified as a new ligand for the direct hydrogenation of various



Scheme 1. Direct hydrogenation of carboxylic acids using homogeneous Ru-catalysts containing triphos-type ligands.

[a] Dr. L. Deng, B. Kang, Prof. Dr. J. Klankermayer, Prof. Dr. R. Palkovits
Institut für Technische und Makromolekulare Chemie
RWTH Aachen University
Worringerweg 2, 52074 Aachen (Germany)
E-mail: deng.li@itmc.rwth-aachen.de
palkovits@itmc.rwth-aachen.de

[b] Prof. Dr. U. Englert
Institute of Inorganic Chemistry
RWTH Aachen University
Aachen (Germany)

Supporting Information for this article is available on the WWW under http://dx.doi.org/10.1002/cssc.201501461.

biogenic acids into alcohols, lactones, and esters in the absence of acid additive, with overall yields from 82 to 99 mol%.

We began our investigation with synthesis of the ligands listed in Scheme 1. Substitution with diphenylphosphino lithium and Mannich-like reaction was employed to functionalize ammonia, primary, and secondary amines to afford nitrogen-centered multidentate phosphine ligands **L1**–**L6**. Among them, **L1** was reported as an analogue of triphos to form various ruthenium complexes and applied to the hydrogenation of levulinic acid.[13] Herein, we chose **L1** as benchmark ligand to examine the catalytic activities of the combination of $Ru(acac)_3$ and these ligands in the hydrogenation of levulinic acid. As shown in Table 1, only gamma-valerolactone (GVL) and trace amount of PDO were generated, and no 2-mehyltetrahydrofuran was detected when solely using 0.2 mol% $Ru(acac)_3$ as catalyst. As reported previously, the benchmark ligand **L1** dramatically improved this reaction, giving 22 mol% of PDO and 75 mol% GVL. To our delight, the novel ligand **L2**, which has one ethylene linker between the central nitrogen atom and a terminal diphenyl phosphino moiety, exhibited comparable performance (entry 3). Further modification of the linkers gave another two novel structures, **L3** containing two ethylene linkers and **L4** containing a diphenyl phosphino propyl group. However, they were inferior to **L2**. The replacement of the remote diphenyl phosphino group with amines or pyridine afforded ligands **L5** and **L6**, which were also less effective in this reaction. Based on the **L2**/$Ru(acac)_3$ catalyst, we examined the reaction conditions for the hydrogenation of levulinic acid (Supporting Information, Table S1). Under optimized conditions, 66 mol% PDO and 33 mol% GVL could be obtained in the presence of 0.5 mol% of the in situ-generated catalyst at 160 °C.

Further optimization of the **L2**-based catalytic system was carried out on the basis of the ruthenium precursors screening.

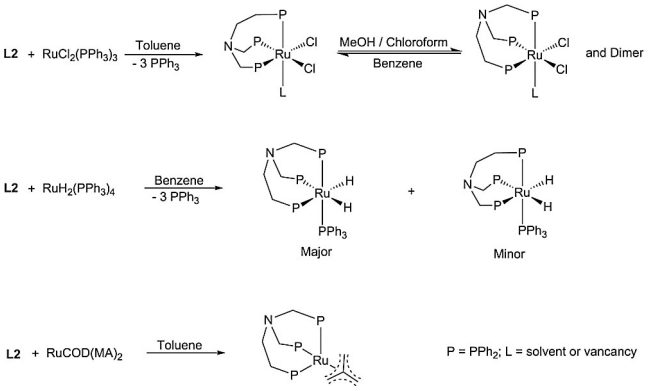
Table 1. Catalytic hydrogenation of levulinic acid using ruthenium precursors and various ligands.[a]

Entry	Ligands	Ruthenium precursor	Amount of precursor [mol%]	Yield of GVL [mol%]	Yield of PDO [mol%]
1	–	$Ru(acac)_3$	0.2	99	<1
2	**L1**	$Ru(acac)_3$	0.2	75	22
3	**L2**	$Ru(acac)_3$	0.2	70	24
4	**L3**	$Ru(acac)_3$	0.2	88	11
5	**L4**	$Ru(acac)_3$	0.2	95	4
6	**L5**	$Ru(acac)_3$	0.2	88	10
7	**L6**	$Ru(acac)_3$	0.2	91	6
8	**L2**	$Ru(acac)_3$	0.5	33	66
9	**L2**	$RuCl_2(PPh_3)_3$	0.2	95	3
10	**L2**	$RuHCl(PPh_3)_3$	0.2	78	19
11	**L2**	$RuH_2(CO)(PPh_3)_3$	0.2	97	<1
12	**L2**	$RuCOD(methylallyl)_2$	0.2	97	2
13	**L2**	$RuH_2(PPh_3)_4$	0.2	32	61
14	**L2**	$RuH_2(PPh_3)_4$	0.5	2	98
15	–	$RuH_2(PPh_3)_4$	0.2	95	3

[a] Reaction conditions: 10 mmol substrate, 5 mL THF, 1.5 equiv ligand, 70 bar H_2, 160 °C, 18 h.

As shown in Table 1, entries 9~14, chloride-containing precursors $RuCl_2(PPh_3)_3$ afforded mainly GVL and low yields of PDO. $RuH_2(CO)(PPh_3)_3$ also catalyzed the conversion of levulinic acid to GVL. The results indicate that the chloride and carbonyl coordinating groups were detrimental for this catalytic hydrogenation, though hydrides were presented. The PPh_3-free precursor $RuCOD(methylallyl)_2$ which was used to generate active Ru(trimethylenemethane)triphos complex for catalytic hydrogenation, was also tested. However, it did not exhibit activity in the presence of **L2**. Using 0.2 mol% of the dihydride complex $RuH_2(PPh_3)_4$, the yield of PDO could be improved to 61 mol%. To our delight, close to full conversion could be achieved in the presence of 0.5 mol% $RuH_2(PPh_3)_4$ and **L2**, which is comparable to the performance of the ruthenium dihydride complex generated from the benchmark **L1**.[13b] Note that $RuH_2(PPh_3)_4$ was not able to catalyze the reaction efficiently without **L2**. In addition, the combination of the other ligands and $RuH_2(PPh_3)_4$ were also examined and presented in Table S1.

To further understand the above results at a molecular level, the coordination of **L2** with ruthenium complexes $RuCl_2(PPh_3)_3$, $RuH_2(PPh_3)_4$, and $Ru(methylallyl)_2(COD)$ was investigated by $^{31}P\{^1H\}$ NMR and single-crystal X-ray diffraction (XRD) techniques. Owing to the presence of two phosphorus species in **L2** (Supporting Information, Figure S3), after treatment with $RuCl_2(PPh_3)_3$ in toluene, a doublet peak at 40 ppm and a triplet peak at 59 ppm appeared with a peak area ratio of 2:1 (Supporting Information, (Figure S11), indicating that all three diphenylphosphine groups were coordinated to the ruthenium center. The remote phosphine group took *trans* position and the two identical phosphine groups attached to two *cis*-positions based on the position of the possibly coordinated solvent or vacancy (Scheme 2). However, after column separation using a methanol/chloroform mixture as mobile phase, the complex changed into a structure in which the two near phosphine groups occupied a *cis*- and a *trans*-site of ruthenium, respectively. Correspondingly, a ^{31}P NMR spectrum exhibited three triplet peaks with equal peak areas from 22 to 30 ppm. Interestingly, the two isomers have a reversible transformation according to the ^{31}P NMR



Scheme 2. Isomers of the complex obtained from **L2** with $RuCl_2(PPh_3)_3$, $RuH_2(PPh_3)_4$ and $RuCOD(methylallyl)_2$.

spectra. In the reaction solvent THF, signals of both isomers could be observed in ^{31}P NMR (Figure S11). According to ESI–MS analysis, both cations of dimers and monomers were detected (*m/z* calculated for $[Ru_2(\mu\text{-}Cl)_3(\mathbf{L2})_2]^+$ 1559.1581, found 1559.1499; *m/z* calculated for $[RuCl(\mathbf{L2})]^+$ 762.0944, found 762.0906). Single-crystal XRD analysis revealed that the Ru^{II} complex contains a dinuclear $[Ru_2(\mu\text{-}Cl)_3(\mathbf{L2})_2]$ cation (Supporting Information, Figure S8) and a chloride counteranion. The compound crystallizes as a chloroform solvate; further details are given in the Supporting Information. In agreement with the performance of **L2**/$RuCl_2(PPh_3)_3$, 0.2 mol% $[Ru_2(\mu\text{-}Cl)_3(\mathbf{L2})_2]Cl$ was only able to convert 11 mol% levulinic acid to PDO.

Owing to the flexible coordination structures, **L2** and $RuH_2(PPh_3)_4$ in THF also generated two isomers by readily replacing three PPh_3 moieties according to the ^{31}P NMR spectra in which two groups of peaks were found (Supporting Information, Figures S12 and S13). The major group contains four peaks with equal areas while the other group has three peaks with an area ratio of 2:1:1. This suggest that the Ru^{II} center of the major isomer was coordinated by the remote phosphine group at *cis* position. The other two phosphine groups occupied a *cis*-site and a *trans*-site related to the position of the PPh_3 moiety while the minor isomer contained two identical phosphine groups at *cis*-sites and a remote phosphine at a *trans*-site. Moreover, ^{1}H NMR also shows two unequal hydride peaks at 8.1 and 8.7 ppm. Unlike complexes from **L2**/$RuCl_2(PPh_3)_3$, no dimeric product was found by ESI–MS. A peak at *m/z* of 990.2236 indicates the formation of a monomeric cation $[RuH(PPh_3)\mathbf{L2}]^+$ (calculated *m/z*: 990.2245), which is a possible active species regarding the mechanism of the hydrogenation of acids with Ru(acac)$_3$/triphos.[6a] Therefore, the complex $RuH_2(PPh_3)$**L2** should be identified as two monomeric dihydride structures (Scheme 2). Unlike the reported complex $RuH_2(PPh_3)$**L1**,[13b] $RuH_2(PPh_3)$**L2** did not give single crystals due to the coexistence of the two isomers. To prepare a PPh_3-free complex, Ru(methylallyl)$_2$(COD) with one equivalent of **L2** was heated in toluene for 6 days. The resulting complex shows a triple peak at 33 ppm and a double peak at 37 ppm in ^{31}P NMR spectra with an area ratio of 1:2. According to ^{1}H and ^{13}C NMR spectra, the trimethylenemethane acts as the counter anion ligand (Supporting Information, Figure S14), indicating the formation of Ru(trimethylenemethane)**L2**. The molecular structure of the complex was also identified by single-crystal XRD analysis (Supporting Information, Figure S15); it crystallizes as a THF solvate. In the presence of 0.2 mol% $RuH_2(PPh_3)$**L2** complex, 15 mol% PDO was generated. Adding three equivalents of PPh_3 improved the yield to 27 mol%, respectively. Similarly, Ru(trimethylenemethane)**L2** delivered 14 mol% PDO. The promoting effect of PPh_3 was also observed in the presence of one or four equivalent of PPh_3 (Table S2). These results suggest that PPh_3 released from the in situ-generated catalyst $RuH_2(PPh_3)_4$/**L2** is beneficial for the hydrogenation reaction.

The transformation of levulinic acid to PDO in dry THF did not proceed via GVL as intermediate in the presence of **L2** and ruthenium precursors, because GVL as substrate decreased the PDO yield (Supporting Information, Table S3). Water formation presents the major difference between the reduction of levulinic acid and GVL or alkyl levulinates, respectively. Therefore, we added one equivalent of water with GVL into the reaction system, improving the PDO yield significantly to above 90 mol%. In the presence of water, GVL is likely to be hydrolyzed to 4-hydroxyl pentanoic acid, which may act as real intermediate of PDO. More evidence could be found by comparing lactic acid, succinic acid, and butyric acid with their corresponding esters. These results suggested that the **L2**/Ru catalysts are more reactive towards the hydrogenation of carboxylic acids rather than esters or lactones as substrates. A plausible reason for the discrimination between acids and esters is that the Ru^{II}-hydride cation generated in the presence of a proton source is responsible for the catalytic hydrogenation of carboxylic acid in anion form.

To expand the substrate scope, several biogenic acids were hydrogenated using **L2** and ruthenium precursors (Table 2). Like the hydrogenation of levulinic acid, lactic acid could be fully converted to 1,2-propanediol under the same conditions. For dicarboxylic acid substrates (entries 2–5), 1 mol% of ruthenium precursors, higher temperature, and longer reaction time were required to achieve high yields of lactones. Although no diols were generated from these dicarboxylic acids, butyrolac-

Table 2. Hydrogenation of biogenic acids using **L2**/Ru precursors.[a]

Entry	Ruthenium precursor	Amount of precursor [mol%]	Substrate	*T* [°C]	*t* [h]	Products	Yield [mol%]
1	$RuH_2(PPh_3)_4$	0.5	lactic acid	160	18	1,2-propanediol	99
2[b]	$RuH_2(PPh_3)_4$	1	itaconic acid	160	48	methyl-γ-butyrolactone	95
3[c]	Ru(acac)$_3$	1	succinic acid	170	48	butyrolactone	93
4[c]	Ru(acac)$_3$	1	fumaric acid	170	48	butyrolactone	95
5[c]	Ru(acac)$_3$	1	maleic acid	170	48	butyrolactone	88
6	$RuH_2(PPh_3)_4$	2	octanoic acid	170	48	octyloctanoate	78
						octanol	5
7	$RuH_2(PPh_3)_4$	2	butyric acid	170	48	butylbutanoate	47
						butanol	35
8	$RuH_2(PPh_3)_4$	2	acetic acid	170	48	ethylacetate	45
						ethanol	39

[a] Reaction conditions: 5 mmol substrates, 5 mL THF, 1.5 equivalent of **L2** based on Ru precursors, 70 bar H_2. [b] The products are α-methyl-γ-butyrolactone and β-methyl-γ-butyrolactone with a ratio of 9:5. [c] 5 mL 2-methyltetrahydrofuran was used as solvent.

tone could be hydrogenated to 1,4-butanediol under similar conditions (Table S3). To hydrogenate alkyl carboxylic acids (entries 6~8), 2 mol% $RuH_2(PPh_3)_4$ and 3 mol% **L2** were used. As a result, the major product from octanoic acid was octyl octanoate (78 mol%). For butyric and acetic acid, alcohol yields were higher.

In summary, a class of nitrogen-centered multidentate phosphine ligands is tested for the hydrogenation of carboxylic acids. Among them, catalysts based on the novel compound **L2** exhibit good activity for this challenging reaction. Comparison of various ruthenium precursors and different substrates suggests the **L2**-based Ru^{II}-hydride cation as active species. The coordination structure of **L2** with $RuCl_2(PPh_3)_3$ and $RuH_2(PPh_3)_4$ reveals that **L2** chelates with the Ru^{II} centre in two manners: two equal phosphines at *cis* sites, or at both *cis* and *trans* sites. With **L2**-based catalysts, 9 biogenic acids are hydrogenated to alcohols, lactones, and esters with yields of 82~99 mol% in the absence of acidic additives. Considering the efficiency and benign conditions, more efforts are necessary to develop catalytic systems for these challenging transformations. We believe that exploring nitrogen-centered multidentate ligands will provide more robust catalysts suitable to gradually achieve the efficient and benign hydrogenation of carboxylic acids.

Acknowledgements

The authors thank Heike Boltz, Elke Biener, and Hannelore Eschemann for GC measurements and Ines Bachmann for NMR analysis. L.D. thanks the Alexander von Humboldt foundation for financial support. This work was performed as part of the Cluster of Excellence "Tailor-Made Fuels from Biomass" funded by the Excellence Initiative by the German federal and state governments to promote science and research at German universities.

Keywords: carboxylic acids · homogeneous catalysis · hydrogenation · ruthenium · tridentate ligands

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Received: October 28, 2015
Published online on January 8, 2016