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FEATURE ARTICLE

Catalytic hydrogenation of carboxylic acids using low-valent and high-valent metal complexes

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Carboxylic acids are ubiquitous in bio-renewable and petrochemical sources of carbon. The hydrogenation of carboxylic acids to alcohols generates water as the only by-product, and thus represents a sustainable method for the production of these alternative energy carriers/platform chemicals on a large scale. Herein, we offer a brief account on the development of this new concept and molecular insights into cationic mononuclear low- and high-valent transition-metal complexes for the hydrogenation of carboxylic acids.

1. Introduction

A rich variety of carboxylic acids (CAs) is abundantly available from fossil and other natural sources. The hydrogenation of CAs to alcohols, which can be used as alternative organic energy (H_2) carriers or as platform chemicals, remains as attractive as it is challenging.[1] According to a 2004 report from the US Department of Energy (DOE), the vast majority of high-value-added chemicals from biomass at that time were CAs,[2] although the order, nature, and number of the CAs should have changed since, given the technological advancements in that period.[3] However, there should be hardly any doubt that CAs will remain on such lists, given that they represent a highly attractive biomass feedstock, and they are most likely also on other confidential lists that are usually not disclosed by industry.

Alternatively, CAs can be produced artificially, e.g. from CO_2, H_2, and olefins.[4] More recently, it has been demonstrated that light-derived energy may offer great potential for the synthesis of CAs: for example, using a photosensitizer in a micro-channel allows to transform CO_2 and amines into α-amino CAs.[5] Treating CO_2 with *ortho*-carbonyl-substituted toluene derivatives under exposure to LED light (365 nm)[6] results in the formation of different CAs even though this reaction is thermodynamically unfavorable ($\Delta G > 0$). Furthermore, formic acid is obtained from the hydrogenation of CO_2[7] or from the photo-reduction of CO_2 with H_2O using solar energy.[8] Further improvements on the reduction methods for CO_2 may be beneficial for the "methanol economy", i.e., the anthropogenic chemical carbon cycle.[9] The identification of carbon-neutral alternatives to fossil fuels represents a major milestone on the way to sustainable development goals (SDGs). When CAs are sourced from biomass and/or produced from CO_2, they represent indeed a potential renewable resource.

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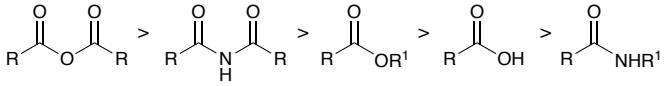
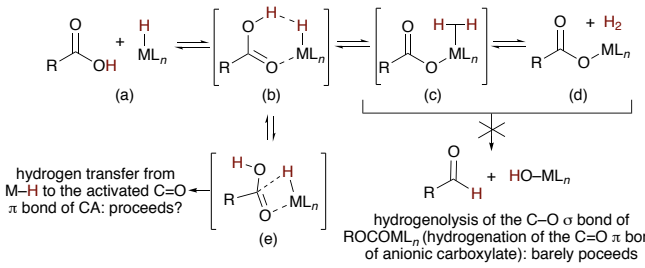


Fig. 1 CA derivatives, ordered according to their expected decreasing electrophilicity of the C=O group in their catalytic hydrogenation using molecular hydrogen (H_2).

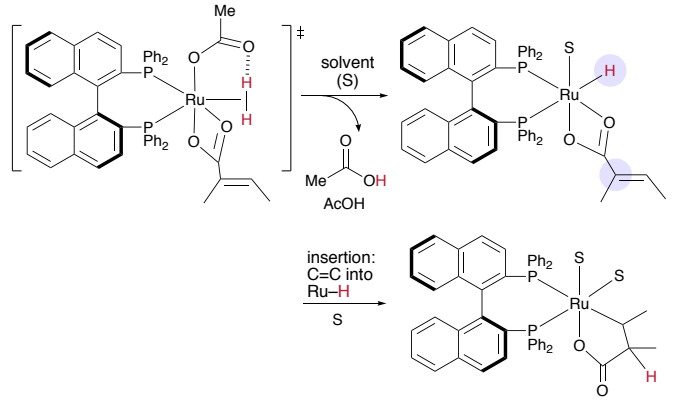
Moreover, the hydrogenation of CAs is an ideal method for the bulk production of alcohols, given that water is the only byproduct of this reaction. Hydrogenation methods that are widely applicable to a broad spectrum of CAs and that selectively produce alcohols should therefore be highly desirable. Even though simple molecular hydrogenation catalysts that enable such conversions remain scarce, our systematic studies have disclosed a prototypical catalyst structure for the hydrogenation of CAs.[10]

Similar to amides, CAs exhibit relatively unreactive electrophilic carbonyl carbon atoms (Fig. 1) and α-C–H hydrogen atoms with very low acidity.[11] So far, these features have significantly hampered the development of new approaches to the catalytic hydrogenation and carbon–carbon bond formation reaction at CH_nCOOH moieties of $R_{3-n}CH_nCOOH$ (n = 1–3).

The catalytic hydrogenation of CA derivatives such as esters[12] and amides[13] proceeds well under basic to neutral conditions, while investigations into similar hydrogenations using a CA as the acidic reaction medium are scarce, as they should not operate efficiently.[12] Considering the *ex vi termini* acidity of CAs, it is understandable that the rational design of single-active-site catalysts that effectively hydrogenate the thermodynamically stable and kinetically inert COOH group is no mundane task. Compared to the hydrogenation of CAs, i.e., the addition of H_2 followed by elimination of H_2O, which has so far not been explored in detail, the dehydrative amidation and esterification



Scheme 1. Major equilibria (a)→(b)→(c)→(d) and vice versa (d)→(c)→(b)→(a) involving CA, metal hydride, H_2 and metal carboxylate. (a) CA and metal hydride (H–ML$_n$) afford (b) a CA–metal coordination complex under subsequent formation of (c) a η^2-H_2–metal complex that undergoes H–H bond cleavage, which generates (d) a metal carboxylate (ROCO–ML$_n$) and free H_2. A deviated process from (b) to (e) would facilitate the hydrogenation of CA via a hydride transfer to the CA.



Scheme 2. The insertion of C=O bonds of tiglic acid (CA-**1**) or AcOH into Ru–H bonds in asymmetric hydrogenations is not observed. Purple parts reacted.

of CAs with amines[14] and alcohols,[15] respectively, share a richer history of advanced research. Such stepwise reactions, which involve the addition of O–H or N–H bonds to the double bond of HOC=O, followed by the elimination of H_2O to form new C–O or C–N bonds, are frequently catalyzed by Brønsted or Lewis acids; this feature could offer an advantage for the inherently acidic CAs, and these reactions should thus be much more accessible than the hydrogenation of CAs. Conversely, in the CA hydrogenation, metal hydride intermediates (H–ML$_n$; L = ligand; n = 0–4) that are commonly generated in the presence of H_2 would be rapidly neutralized by the excess of CA under concomitant formation of H_2 and the corresponding metal carboxylates (ROCO–ML$_n$), which are not easily hydrogenated (Scheme 1).[16]

Metal carboxylates could also recapture H_2 and regenerate H–ML$_n$, which would result in the major equilibrium [ROCO–ML$_n$ + H_2 ↔ H–ML$_n$ + RCO_2H] [(a) ↔ (b) ↔ (c) ↔ (d)]. It had indeed been proposed much earlier that the neutral Ru-acetate species [$Ru^{II}(OAc)_2P_2$] and [$Ru^{II}(OAc)(OC(O)R)P_2$] (OAc = $CH_3CO_2^-$) could trap and activate H_2 to generate the H–Ru(OC(O)R)P_2 species in the asymmetric hydrogenation of internal olefins of α,β-unsaturated CAs such as tiglic acid (MeCH=C(Me)COOH: CA-**1**)[17] (Scheme 2). During this reaction, acetic acid (AcOH) is expelled from the metal center;[18] however, at the time, AcOH was considered merely an undesirable by-product and removed from the catalytic cycle. In addition, the COOH group of CA-**1** remained un-hydrogenated, acting merely as an innocent directing group for the hydrogenation of the olefin.

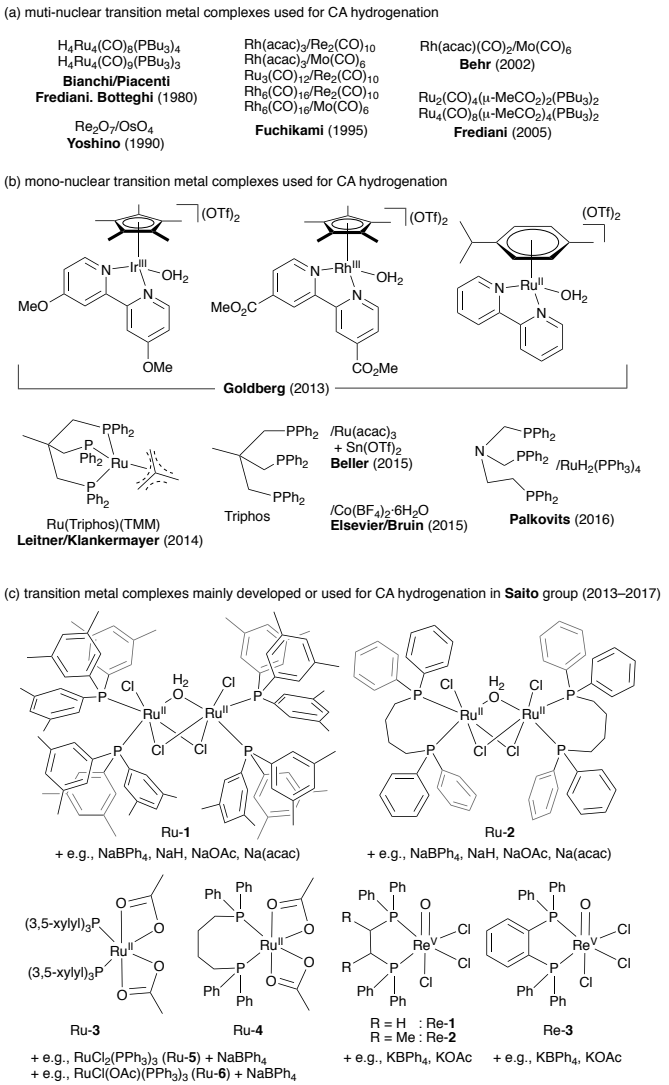


Fig. 2 Transition-metal complexes for the catalytic hydrogenation of CAs using H_2. (a) Multi-nuclear transition metal complexes; (b) mono-nuclear transition metal complexes; (c) transition metal complexes in Saito group (2013–2017) mainly developed or used for CA hydrogenation.

Nevertheless, we speculated that the hydrogenation of CA may potentially occur, given the possible process (b) → (e), which deviates from the major equilibria (a) ↔ (d).

Apart from the meticulous efforts dedicated to tackle the inherent obstacles of the "carboxylate-formation mechanism", which is operative during the hydrogenation of the CAs, multinuclear metal (cluster) complexes were tested in earlier studies (Fig. 2a). Heterobimetallic catalysts,[19] which seem more intuitive or pragmatic, successfully reduce CAs to the corresponding alcohols, albeit at the expense of concomitant side reactions, which include dearomatic hydrogenations or overreductions under harsh conditions. A higher catalytic activity of binuclear Ru-carboxylato complexes[20] relative to that of mononuclear derivatives and the importance of intermediary Ru(acyl)(alkoxy) complexes that are different from ours, were briefly noted, albeit that little evidence was provided.

In contrast, mononuclear metal complexes have very rarely been examined (Fig. 2b). One of the earliest attempts, using the

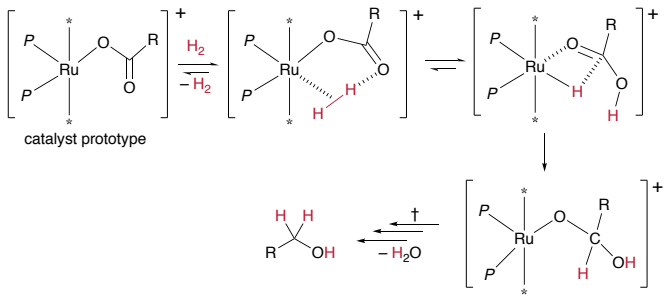
Ru-acetato complex $Ru(CO)_2(OCOCH_3)_2(PBu_3)_2$ (Bu = $CH_3(CH_2)_3$), did not lead to the hydrogenation of the COOH groups of CA-**1** and its olefin-hydrogenated form, 2-methylbutanoic acid (P_{H2} = ca. 13 MPa, T = 100 °C).[21] In contrast, the hydrogenation of acetic acid (AcOH) proceeded, but merely afforded the ester ethyl acetate (AcOEt), which was ascribed to "unknown catalytic species". More recent studies by Goldberg *et al.* on functionalized bipyridine-coordinated Ru, Ir, and Rh catalysts[22] showed that small aliphatic CAs such as AcOH can be hydrogenated under milder reaction conditions (P_{H2} = 0.3–5 MPa, T = 120 °C) with a rather high turnover number (TON = ~800; for comparison, an Ir complex with $Sc(OTf)_3$ gives TON ≈ 1700); however, the generated alcohol, e.g., ethanol (EtOH), likewise undergoes an *in situ* esterification with AcOH, which affords AcOEt as the major product. Moreover, the corresponding Ir catalyst, which is derived from its precatalyst (Fig. 2b), decomposes into Ir black at temperatures >120 °C. Furthermore, it has been demonstrated experimentally[22] that CAs with shorter aliphatic carbon chains such as AcOH react much more rapidly, which is consistent with previous investigations.[20,21] With increasing size of the CA from C_1 to C_4, the corresponding carboxylate carbon atom becomes more electron-rich and thus less susceptible to nucleophilic attacks from metal hydrides (H–ML_n).

In the development of CA hydrogenation methods based on molecular catalysts, the most critical issues to be addressed in order to ensure high reactivity and selectivity for the generation of alcohols should therefore be the discovery of rational ways: (i) to hydrogenate the carboxylic acid (COOH) before the metal carboxylate (COO^-) is formed; (ii) to prevent the *in situ* generation of esters; (iii) to subsequently convert the esters thus generated *in situ* to the parent CA in the presence of H_2O, i.e., to develop water-stable catalysts; and (iv) to hydrogenate not only CAs but also esters in a one-pot fashion using the same catalyst system. Meanwhile, (iii) and (iv) have partially but reasonably solved by Beller *et al.*[23] and Leitner/Klankermayer *et al.*,[24] respectively, using Ru-Triphos (Triphos = 1,1,1-tris(diphenylphosphinomethyl)ethane) complexes (Fig. 2b). The complexes were used with cooperative Lewis acids such as $Sn(OTf)_2$ under relatively strenuous hydrogenation conditions (typically: P_{H2} = 5–6 MPa, T = 160–220 °C). In the context of (iv), more germinal studies by Elsevier *et al*. have demonstrated great potential for a Ru-Triphos system to effectively hydrogenate esters (typically: P_{H2} = 7.0–8.5 MPa, T = 100 °C).[25] Thorough subsequent studies by Leitner/Klankermayer *et al.* resulted in improved Ru-Triphos catalyst systems for the hydrogenation of esters,[24] in which methyl benzoate and alkyl formates, formed *in situ* from the esterification of formic acid that is generated by the hydrogenation of CO_2 with the alcohol solvent, were hydrogenated under conditions that are simpler than those reported by Elsevier, and milder (typically: P_{H2} = 3–5 MPa, T = 140 °C)[24] than those for the hydrogenation of CAs (typically: P_{H2} = 5 MPa, T = 220 °C).[24] Thus, in many cases, the CA hydrogenation should in effect be the result of an *in situ*-generated ester (lactone), which serve as an intermediate and undergo hydrogenation more effectively.[24a,24b,26] Cole-Hamilton *et al.* have used another Ru-Triphos system for the hydrogenation of relatively activated amides such as anilides, which engage in selective C=O bond cleavage in preference to C–N bond cleavage.[27] Leitner/Klankermayer *et al.*[24,26a,26b] and Frediani *et al.*[26c] have used similar systems for hydrogenation of 4-keto-CAs and 1,4-dicarboxylic acids (C_4 constituting the main chain), which are essentially the hydrogenation of the ketone or the corresponding anhydrides of a five-membered ring system *in situ* formed from the 1,4-diCAs, respectively, followed by hydrogenation of the resulting γ-lactones in both cases. A nitrogen-centered Triphos variant has been introduced by Palkovits *et al*. for the hydrogenation of a similar series of bio-based dicarboxylic acids and small/medium size CAs including octanoic acid, even though the major products are frequently linear and cyclic esters, which the catalyst cannot hydrogenate further into the corresponding alcohols (P_{H2} = 7 MPa, T = 160–170 °C).[28] The Ru-Triphos system represents the current state-of-the-art and marked a milestone in the history of hydrogenation; however, the reason why Triphos is among the best ligands for the hydrogenation of many CA derivatives upon minor changes to the reaction conditions remains unclear. Moreover, since experimental proof for the underlying different catalytic mechanisms that underpin these hydrogenation systems remain elusive, some *ab initio* calculations on various mechanisms have been carried out.[24a,26e,29]

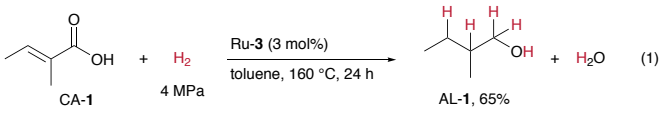
Until 2015, our seminal studies had been the only ones that reported a molecular prototype obtained from the rational design of a single-active-site Ru catalyst for the hydrogenation of CAs (Fig. 2c).[10a] Four different precatalyst complexes (Ru-**1**–Ru-**4**) were mainly developed and used for the generation of single-active-site cationic Ru carboxylates. The CA-derived carboxylate coordinated to the Ru center initially functions as a proton acceptor for the heterolytic cleavage of a H–H bond, and subsequently also as a acceptor for a hydride from $[Ru–H]^+$, which was generated in the first step (Scheme 3).

This catalytic cycle thus represents a "CA self-induced CA hydrogenation". In the meantime, similar catalytic mechanisms involving "cationic metal mono-carboxylates" were proposed theoretically by *ab initio* calculations of catalytic cycles that involve a hydrogenation of CAs with a Co-Triphos complex[29] and one for the hydrogenation of HCO_2H, *in situ* formed from the reduction of CO_2 using a Ru-Triphos complex.[26e]

The catalysts developed in our group afford the corresponding alcohols selectively from a variety of CAs with



Scheme 3. Carboxylic acid (CA) self-induced hydrogenation of CA; *P*: coordinating phosphine; †multiple steps for the regeneration of the catalyst: (i) capture of a second molecule of H_2; (ii) hydrogenation of the aldehyde; (iii) exchange of the alkoxide on Ru with CA, which generates the cationic Ru-carboxylate "catalyst prototype".



(1)

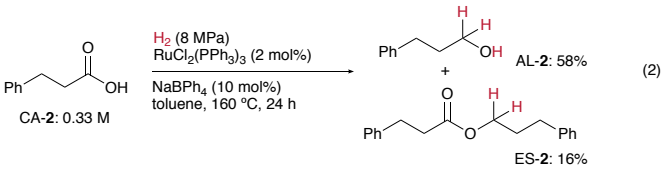
longer and bulkier carbon chains, relative to smaller CAs mainly tested by other research groups so far. Our systems exhibit a higher functional-group tolerance than other state-of-the-art catalysts for CA hydrogenation, even though ours suffer from a selectivity that still remains unsatisfactory. For example, both the COOH and olefinic groups of CA-**1** were hydrogenated using a catalytic amount of Ru-**3** (eq 1). The corresponding esters were generated in 5±3% (average of three runs). Quite unlike the Ru-Triphos systems, the hydrogenation of esters is not promoted, clearly indicating that the CAs are more reactive than the esters under the applied conditions in the "CA self-induced CA hydrogenation" mechanism, which is quite different from the catalytic cycle for the hydrogenation of esters. This catalyst system may thus constitute a milestone toward the development of catalytic hydrogenation methods for carbon feedstock derived from biomass or CO_2.

In this feature article, our long-standing concerns and challenges to tackle CA hydrogenation using catalytic Ru^{II} and Re^{V} complexes[10] would be presented. The germinal Ru systems disclosed the simplest structure of catalyst (prototypical catalyst or catalyst prototype) among those we ever had that would significantly benefit future development and molecular design of more elaborated catalysts. Even though many metal-based heterogeneous catalysts[30] and bioorganisms[31] have also been developed for the hydrogenation of CAs, their discussion is beyond the scope of this article.

2. Low-valent ruthenium complexes for CA hydrogenation[10a]

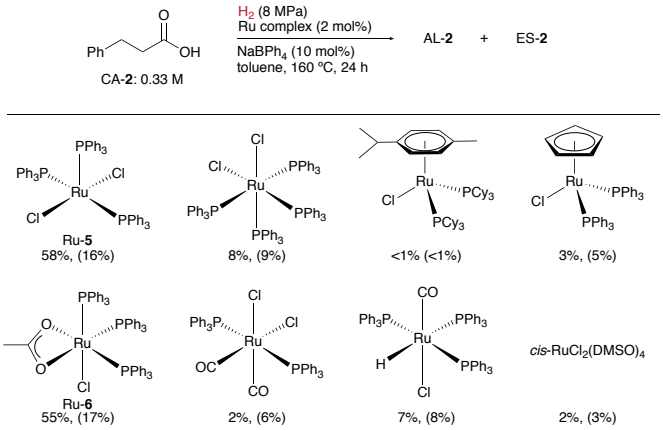
The discovery of the importance of $[Ru(OC(O)R)P_2]^+$

Since the milestone discovery of the Wilkinson-type ruthenium complex $RuCl_2(PPh_3)_3$ (Ru-**5**) for the hydrogenation of olefins in the 1960s,[32] molecular single-active-site catalysts that hydrogenate CAs effectively have scarcely been investigated systematically[22] as mentioned above. We had also been examining a more custom-tailored ligand–ruthenium systems, $(PN)_2Ru$[33]- and (PNNP)Ru complexes[34] that are effective for hydrogenation of unactivated amides, but the efforts exerted could not give any solutions or even a clue to achieve CA hydrogenation. All what was left behind us at the time was stepping back to reexamine the Wilkinson's milestone complex Ru-**5**. However, Ru-**5** of its own was unable to hydrogenate 3-phenylpropionic acid (CA-**2**) even under harsh reaction conditions (P_{H2} = 8 MPa, T = 160 °C, t = 24 h). In sharp contrast, using a combination of Ru-**5** (2 mol%: $[Ru]_0$ = 6.7 mM) and $NaBPh_4$ (10 mol%), under otherwise identical conditions resulted in the formation of alcohol AL-**2** and the ester



(2)

Table 1. Initial screening of Ru complexes for hydrogenation of CA. Yields in parentheses are of ES-**2**.



$Ph(CH_2)_2CO_2(CH_2)_3Ph$ (ES-**2**) in 58% and 16% yield, respectively (overall conversion of CA-**2**: 92%) (eq 2)!

Those two reactions merely suggest that a cationic Ru species $[L_nRu^{II}]^+$ should be of critical importance for a successful hydrogenation. Other sodium salt additives were also tested: $NaB[3,5\text{-}(CF_3)_2C_6H_3]_4$, $NaBF_4$, $NaPF_6$, NaOTs, NaOTf and $NaNTf_2$, were totally disappointing (AL-**2**: 0–17%); NaH and NaOAc instead of $NaBPh_4$ gave similar successful results. Ruthenium source was also changed from Ru-**5** (Table 1): in the presence of $NaBPh_4$, $RuCl_2(PPh_3)_4$, $RuHCl(CO)(PPh_3)_3$, $RuCl_2(CO)_2(PPh_3)_2$, Ru(*p*-cymene)$Cl_2[P(C_6H_{11})_3]$, $Ru(C_5H_5)Cl(PPh_3)_2$, *cis*-$RuCl_2(DMSO)_4$, and $Ru(C_5H_5)Cl$(dppm) (DMSO = dimethylsulfoxide; dppm = 1,1-bis(diphenylphosphino)methane) were screened, consistently giving AL-**2** and ES-**2** as low as 10%. Among Ru sources screened, the acetato complex $RuCl(OAc)(PPh_3)_3$ (Ru-**6**) only afforded AL-**2** (55 %) and ES-**2** (17 %) in yields similar to those achieved by Ru-**5**.

Since a catalytic amount of the Ru-acetato complex Ru-**6** can readily undergo ligand exchange with excess CA-**2** in the reaction mixture, the general formula "$[Ru(OC(O)R)]^+$" (R = aliphatic group) is first assigned to the critical structure of the catalyst. However, how many phosphines at least should be coordinated to a Ru center for mean acceleration of hydrogenation rate?

The best molar amount of PPh_3 relative to Ru sufficient to catalyse the hydrogenation of CA-**2** was thus examined. Ru-Triphos catalysts have three phosphines coordinated to a Ru center, and our long-standing concern at the time was whether this "three" is a critical number for CA hydrogenation. The precatalyst was switched from Ru-**5** to $RuCl_2(DMSO)_4$ (2 mol%, $[Ru]_0$ = 6.7 mM) and varying molar amounts of the phosphine ligand PPh_3 were used in the presence of 10 mol% $NaBPh_4$. The best results, which provided similar hydrogenation rates, were observed for a 2:1 and 3:1 ratio of PPh_3 and $RuCl_2(DMSO)_4$ (AL-**2**: 32±1%, ES-**2**: 15±1%), while a 1:1 ratio was disappointing (AL-**2**: 3%; ES-**2**: 6%).

Thus, from a number of combinations of monodentate phosphine and $RuCl_2(DMSO)_4$ in a 2:1 molar ratio tested, P(3,5-$(CH_3)_2(C_6H_3))_3$ (P(3,5-xylyl)$_3$) afforded the best yield (AL-**2** (ES-**2**): 49 % (14 %)). Since "two" phosphines, not "three", seem to be

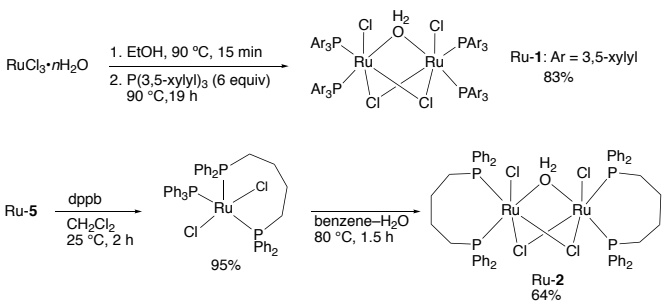
enough, combinations of bidentate diphosphine and $RuCl_2(DMSO)_4$ in a 1:1 ratio were also examined. Among no more than twenty diphosphines tested, 1,4-(diphenylphosphino)butane (dppb) proved to be the best (AL-**2**: 52 %, ES-**2**: 14 %; P_{H2} = 8 MPa, T = 160 °C, t = 24 h).

To make a brief remark here on the critical factors revealed at this stage of catalyst development, we can conclude that $[Ru(OC(O)R)P_2]^+$ species as the prototypical structure, wherein two phosphines and (at least) one carboxylate (or acetate) are bound to a cationic Ru center, would be critical to ensure a CA hydrogenation.

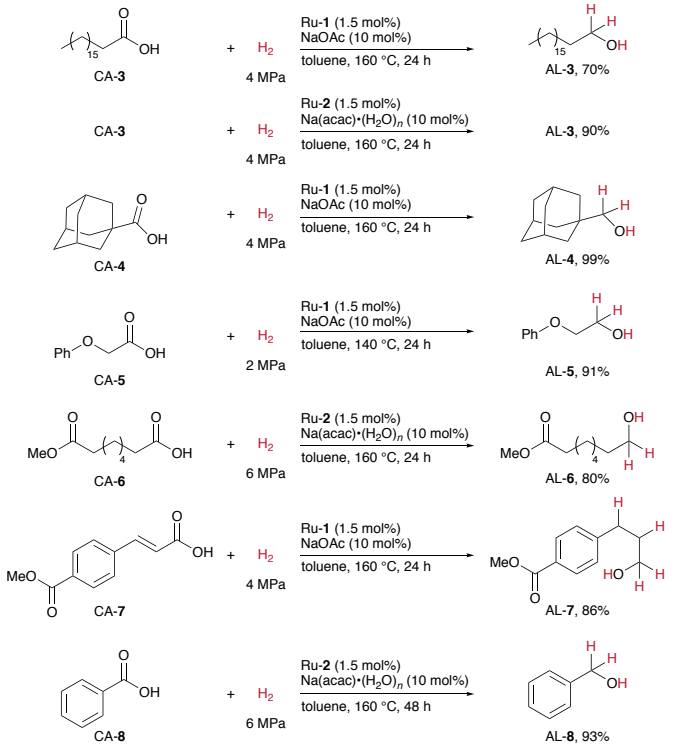
Synthesis of $RuCl_2P_2$-type precatalysts for CA hydrogenation

In order to gain further insight into the importance of the "two" phosphines for more effective CA hydrogenation, the corresponding Ru complex was synthesized, following the experimental procedure reported for the synthesis of Ru-**5**.[32a] In practice, Wilkinson-type 16e⁻ complex $Ru^{II}Cl_2(P(3,5\text{-xylyl})_3)_3$ was not obtained. Instead, the binuclear 18e⁻ Ru complex $Ru^{II}_2Cl_2(\mu\text{-}Cl)_2(\mu\text{-}OH_2)(P(3,5\text{-xylyl})_3)_4$ (Ru-**1**) was isolated in 83% yield as a reddish brown precipitate (Scheme 4). As a solid, Ru-**1** can be easily stored and handled under atmospheric conditions. Coordination of a third phosphine ligand to the Ru center, analogous to the formation of Ru-**5**, proved to be less favourable, presumably due to the steric hinderance of Ru-**1**. This structural preference is consistent with the observation that a 2:1 ratio between the monodentate phosphine (PPh_3 or $P(3,5\text{-xylyl})_3$) and Ru promised efficient catalysis. When using Ru-**1** (1 mol%) with $NaBPh_4$ (10 mol%), hydrogenation of CA-**2** proceeded more effectively, even under a lower hydrogen pressure (P_{H2} = 4 MPa), affording AL-**2** and ES-**2** in 65% and 12% yield, respectively (T =160 °C, t = 24 h; conversion of CA-**2**: 92%). Replacing $NaBPh_4$ with NaOAc and Na(acac) (acac = acetylacetonate) resulted in comparable effectiveness, furnishing AL-**2** (ES-**2**) in 62% (15%) and 64% (14%) yield, respectively. The hydrogenation rate was virtually independent of $[CA\text{-}2]_0$ when using Ru-**1**/NaOAc. In the meantime, it became clear that the structure of diruthenium complex Ru-**2** bearing $\mu\text{-}H_2O$, similar to Ru-**1**, was easily derived by simply heating $RuCl_2(PPh_3)(dppb)$ in benzene–H_2O.[35]

The reaction conditions for CA hydrogenation were further optimized by slightly increasing the load of Ru-**1** or Ru-**2** to 1.5 mol% so that the hydrogenation was accelerated relative to the simultaneously occurring *in situ* esterification. Furthermore, the more atom-economical NaOAc than $NaBPh_4$ was also used as additive for the hydrogenation of various CAs (P_{H2} = 2–6 MPa, T = 140–160 °C) (Scheme 5). Aliphatic linear acid CA-**3** was hydrogenated, exclusively producing alcohol AL-**3**. Use of Ru-**2** showed better catalytic activity for the hydrogenation of rather small carboxylic acids. For the hydrogenation of the sterically most demanding (kinetically the most inert) CA-**4**, a slower reaction rate was observed with Ru-**2**, whereas AL-**4** was generated faster using Ru-**1** with no esterification. CA-**5** (α-phenoxyacetic acid) was one of the most reactive CAs tested, and hydrogenation proceeded smoothly even under relatively mild conditions (P_{H2} = 2 MPa, T = 140 °C). When the hydrogenation of CA-**5** with Ru-**1** (1.5 mol%) and NaOAc (10 mol%) was stopped after 6 h (AL-**5**: 50%), more than 90% of free AcOH (based on added NaOAc) were detected by ^{1}H NMR. This result suggests the exclusive formation of a $[Ru(OCOCH_2OPh)]^+$ species, which does not promote the hydrogenation of AcOH, but should be responsible for hydrogenation of CA-**5** (i.e. a CA-**5** self-induced CA-**5** hydrogenation). This is in agreement with the previous arguments, in which $[Ru(OC(O)R)]^+$ complex derived from Ru-**6** gave an active catalyst. The CO_2H groups of CA-**6** and CA-**7** were hydrogenated more rapidly than the interior aliphatic and aromatic esters under preservation of the methyl ester moieties. In addition, when a 1:1 molar mixture of CA-**4** and ethyl stearate ($CH_3(CH_2)_{16}CO_2CH_2CH_3$) was subjected to hydrogenation conditions (Ru-**1** (1.5 mol%), NaOAc (10 mol%); P_{H2} = 4 MPa, T = 160 °C, t = 24 h), AL-**4** was obtained in 99% yield, while the ester was recovered unchanged. An external ester also did not inhibit the catalysis and catalytically active species should be accessible only by a CA covalently attached to the Ru center. Esters that cannot covalently bind to the Ru complex may have little chance to be a part of an integral



Scheme 4. Synthesis of Ru-**1** and Ru-**2**. $RuCl_2(PPh_3)(dppb)$ was synthesized by simply modifying the literature procedure.[35]



Scheme 5. Representative examples of catalytic hydrogenation of CAs using Ru-**1** or Ru-**2**.

structure of the catalyst. Unfortunately, the olefin of CA-**7** was easily hydrogenated. In general, Na(acac)·$(H_2O)_n$ is a better additive than NaOAc, when Ru-**2** was used to induce catalytic species more rapidly.

Benzoic acid (CA-**8**) was one of the least reactive substrates. In order to reconfirm that indeed the suspected "CA self-induced CA hydrogenation" could also be observed with this rather inert CA, the hydrogenation of CA-**8** was carried out with Ru-**1** and NaOAc using three different initial concentrations [CA-**8**]$_0$ (t = 6 h). As a result, a 0th order rate with respect to [CA-**8**]$_0$ corroborates a CA-**8** self-induced CA-**8** hydrogenation, as in the case of CA-**2**. These preliminary kinetic studies indicated that the apparent reaction rate of CA hydrogenation at the same parameters for [H_2] and T is independent of [CA]$_t$ and almost constant, assuming a constant [[Ru(OC(O)R)]$^+$]$_t$. In other words, the velocity of the rate-determining step should change only upon varying the concentration of [Ru(OC(O)R)]$^+$. It is therefore suggested that CA-**2** and CA-**8** should be involved not only as integral "carboxylates" of the catalysts for cleaving the H–H bond, but also as "protonated carboxylates" that are spontaneously activated by cationic Ru center and reduced by the resulting [Ru–H]$^+$, which is generated in the first step of the CA self-induced CA hydrogenation.

Ru-1 and Ru-2 vs. Ru-Triphos systems

It should be noted again that an elegant approach that differs from ours was reported by Leitner and Klankermayer *et al.*, who proposed [Ru(Triphos)(OCOH)]$^+$ and Ru(Triphos)(TMM) (TMM = trimethylenemethane) species as the catalytically active species for the hydrogenation of CO_2 (P_{H2} = 5 MPa, T = 140 °C) and CA-**8** (P_{H2} = 5 MPa, T = 220 °C),[24a] giving CH_3OH[26e] and AL-**8**, respectively. Nevertheless, $RuCl_2(DMSO)_4$/Triphos (2 mol% each) proved to be a less effective catalyst than Ru-**1** and Ru-**2** for hydrogenation of CA-**2** (AL-**2**: 22%, ES-**2**: 13%) under otherwise identical reaction conditions. The catalyst systems $Ru(acac)_3$/Triphos (2 mol% each)[26a,26d] and [Ru(Triphos)(TMM)][24b,26e] (2 mol%) were also tested (P_{H2} = 8 MPa, T = 160 °C, t = 24 h) independently by us, but the observed reactivity was consistently low (AL-**2**: 22% and 10% and ES-**2**: 10% and 8%, respectively). In contrast, Ru-**2** (1 mol%) with Na(acac) (10 mol%) was tested under milder hydrogenation conditions (P_{H2} = 4 MPa, T = 160 °C, t = 24 h), which furnished an improved yield of AL-**2** (78%) and ES-**2** (10%) with almost quantitative conversion of CA-**2**.

Ru-1 vs. Ru-2

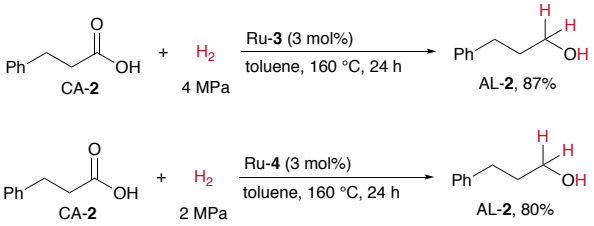
Using Ru-**2**, it was also possible to hydrogenate the relatively unreactive substrate CA-**8** under reasonably milder conditions than those reported,[24a] affording AL-**8** in 93% yield (Scheme 5). The increased catalytic activity of Ru-**2** relative to that of Ru-**1** for hydrogenation of CAs could also be demonstrated by the following experiment: Ru-**1** and Ru-**2** (1.5 mol% each) were used separately with Na(acac) (10 mol%) for the hydrogenation of CA-**8** under conditions (P_{H2} = 4 MPa, T = 160 °C, t = 48 h) milder than optimized ones, giving AL-**8** in 26% and 56%, respectively (benzyl benzoate: 2% and 1%, respectively). Moreover, the hydrogenation of other substrates that were relatively inert to the Ru-**1**/NaOAc system also proceeded more readily when using Ru-**2**/Na(acac). Another advantage of Ru-**2** over Ru-**1** is the structural robustness of the catalyst derived from Ru-**2** under aqueous conditions. However, Ru-**2** is not necessarily a better precatalyst. For example, Ru-**1** shows a higher catalytic activity than Ru-**2**, given a steric bulkiness of carboxylic acids such as CA-**4**. Drawbacks of the present hydrogenation with both Ru-**1** and Ru-**2** thus far observed are that: (1) the amide and thiophene functionalities retarded the catalysis; and (2) the olefins were hydrogenated, although the high chemoselectivity and concurrent compatibility of aromatic rings and ester moieties were maintained.

Advanced Ru complexes used for CA hydrogenation under lower P_{H2}: Ru-3 and Ru-4

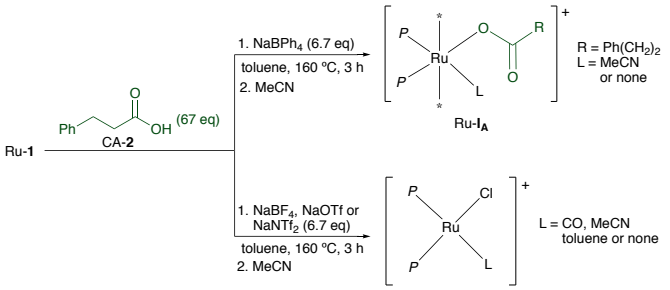
Isolation of mono-nuclear Ru precatalyst was also attempted, since preliminary kinetic studies showed that the reaction rate is almost 1st order with respect to [Ru]$_0$ (*vide supra*). When a 1:20 mixture of Ru-**1** and NaOAc was heated to 90 °C, Ru-**3** was isolated in 49% yield. The hydrogenation of CA-**2** with Ru-**3** (3 mol%, [CA-**2**]$_0$ = 333 mM) (P_{H2} = 4 MPa, T = 160 °C, t = 24 h) *in the absence of NaOAc* gave AL-**2** (ES-**2**) in 87% (6%) yield (Scheme 6), which slightly exceeded or is comparable to the result previously obtained with Ru-**1**/NaOAc. A similar Ru-diacetato complex Ru-**4** was readily synthesized from Ru-**2** and was found to be one of the most active Ru catalysts for the hydrogenation of CA-**2** (but not necessarily the most active catalyst for other CAs) giving AL-**2** (ES-**2**) in 80% (5%) yield even under relatively mild conditions (P_{H2} = 2 MPa, T = 160 °C, t = 24 h) using a lower [CA-**2**]$_0$ of 167 mM, while a slightly decreased yield of AL-**2** resulted by further lowering P_{H2} to 1 MPa (AL-**2**: 53%). Hydrogenation using Ru-**3** proceeded comparably under similarly a lower [CA-**2**]$_0$, but with more selective production of the alcohol (vs. ester), which could, at least partially, be ascribed to retardation of bimolecular esterification concurrently occurring between CA-**2** and AL-**2**.

More insights into the importance of [Ru(OC(O)R)P_2]$^+$

The prospective resting state of these catalysts, a [Ru(OC(O)R)P_2]$^+$ species, was also elucidated by a number of electrospray ionization-high resolution mass spectroscopy (ESI-HRMS) studies. Treatment of Ru-**1** with $NaBPh_4$ in toluene for 3 h at 160 °C resulted in the formation of the catalytically



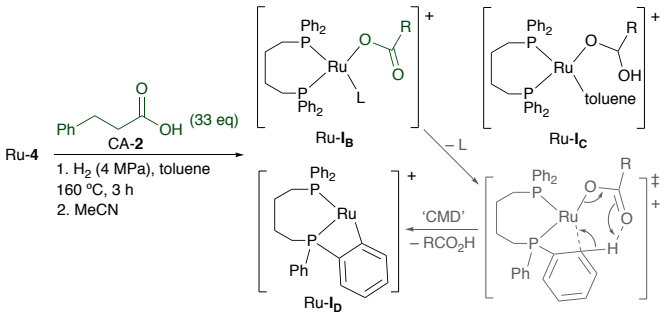
Scheme 6. The simplest methods for CA hydrogenation using Ru-**3** or Ru-**4**. [Ru]$_0$ = 10 mM.



Scheme 7. The structures obtained by ESI-MS analyses. [Ru-**1**]$_0$ = 10 mM, [CA-**2**]$_0$ = 333 mM. Good additive ($NaBPh_4$) that generates the prototypical catalyst Ru-$\mathbf{I_A}$ and bad additives ($NaBF_4$, NaOTf and $NaNTf_2$) that cannot abstract all the Cl groups.

important structure '[Ru(OC(O)R)P_2]$^+$', consistent with Ru-$\mathbf{I_A}$, showing the corresponding primary HRMS signals (Scheme 7). In sharp contrast, the signals of Ru-$\mathbf{I_A}$ were barely or not obtained when $NaBF_4$, NaOTf or $NaNTf_2$ were used as additives instead of $NaBPh_4$. One of the original Cl groups of Ru-**1** remained unaffected, or was replaced by CO. The structure '[Ru(CO)(OC(O)R)P_2]$^+$' was only determined when using NaB[3,5-$(CF_3)_2(C_6H_3)$]$_4$, another ineffective additive for CA hydrogenation. When a toluene solution of a 1:6.7:67 mixture of Ru-**1**, NaOAc and CA-**2** was heated to 160 °C for 3 h, Ru-$\mathbf{I_A}$ (L = MeCN and none) were detected as the primary HRMS signals. After a toluene solution of Ru-**4** (3 mol%) and CA-**2** was heated at 160 °C for 3 h under H_2 (4 MPa), reasonable signals corresponding to Ru-$\mathbf{I_B}$ and Ru-$\mathbf{I_C}$, in addition to Ru-$\mathbf{I_D}$, were detected (Scheme 8). The formation of Ru-$\mathbf{I_D}$ also suggests that intramolecular C–H bond activation through Ru-$\mathbf{I_B}$ by a concerted metalation–deprotonation (CMD) mechanism (Scheme 8), giving Ru–Ar species,[36] would be detrimental to maintaining a higher concentration of effective catalyst(s) for CA hydrogenation. This corresponds to a catalyst deactivation pathway.

The results obtained from this systematic study on cationic, mononuclear Ru mono-carboxylate catalyst prototypes enabled a rational approach to the design of CA hydrogenation catalysts. The results demonstrate that CAs should act not only as integral "carboxylates" for the catalysts to cleave the H–H bond, but also as "protonated carboxylates" that are simultaneously activated and reduced by the resulting [Ru–H]$^+$, which is generated during the initial CA self-induced CA hydrogenation. It should be noted that a proposition, by Elsevier and Bruin *et al.*, of a similar hydrogenation mechanism involving cationic Co^{II}-Triphos



Scheme 8. The structures Ru-$\mathbf{I_B}$, Ru-$\mathbf{I_C}$ and Ru-$\mathbf{I_D}$ obtained by ESI-MS analyses and speculated transition state that promotes CMD giving Ru-$\mathbf{I_D}$. R = $Ph(CH_2)_2$, L = MeCN. [Ru-**4**]$_0$ = 10 mM, [CA-**2**]$_0$ = 333 mM.

carboxylates[29] was almost simultaneous with our publication (2015).[10a] Li *et al*. have very recently coined our "CA self-induced CA hydrogenation" catalyst "Saito catalyst" and proposed, based on *ab initio* calculations, that a possible mechanistic scenario for the catalytic cycle could involve *neutral Ru dicarboxylate* complexes,[37] which stands in contrast to the *cationic Ru monocarboxylate* that we have proposed.

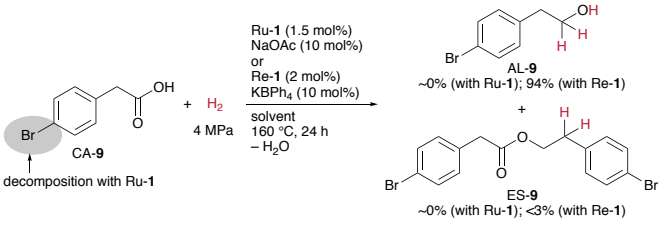
As the permutations of monodentate and bidentate phosphines as well as transition metals are virtually infinite, many options are available for the optimization of the ligand and metal center in terms of catalytic performance (e.g. reactivity and functional-group tolerance/compatibility) under milder conditions.

3. High-valent rhenium complexes for CA hydrogenation[10b]

Ru-1 vs. Re-1

One notable disadvantage of our germinal Ru^{II}-based catalysts (Ru-**1**–Ru-**4**) shown above is their low functional-group (FG) tolerance and compatibility. For instance, a Ru^{II} catalyst[10a] derived from Ru-**1** is deactivated almost immediately upon reaction with CA-**9**, affording only negligible amounts of AL-**9** (<1%) (Scheme 9), presumably due to the oxidative addition of the C–Br bond of the bromoarene to the low-valent Ru^{II} (d^6) center. If we were able to achieve more chemoselective hydrogenation of CAs in the absence of undesirable side reactions involving the COOH or other potentially present functional groups, such methods may potentially be useful for organic synthesis. However, studies on functional-group tolerance, which may provide useful information for organic synthesis, had been elusive prior to the report of our second-generation hydrogenation precatalysts that include Re-**1**–Re-**3**.

To avoid such catalyst deactivation, the robustness and inertness of the catalyst toward many different FGs is of critical importance, and new concepts for the selective activation and hydrogenation of COOH groups in CAs must be developed. High-valent (d^0–d^4)[38] transition metals may represent more promising perspectives than their low-valent (d^5–d^{10}) analogues, considering that the former are less susceptible to oxidative addition and π-back donation compared to the latter. Therefore, we have developed molecular single-active-site rhenium^V (Re^V) complexes including Re-**1**–Re-**3** that selectively hydrogenate a wide range of functionalized CAs.[10b] Treatment of CA-**9** with Re-**1** (2 mol%) and $KBPh_4$ (10 mol%) in THF for 24 h at 160 °C under P_{H2} = 4 MPa resulted in the formation of AL-**9** in 94% yield and



Scheme 9. Comparison experiments between hydrogenations with Ru-**1** in toluene and Re-**1** in THF. [Ru-**1**]$_0$ = 10 mM, [Re-**1**]$_0$ = 2.5 mM.

negligible formation of ES-**9** (Scheme 9), whereby the bromobenzene fragment remained intact.

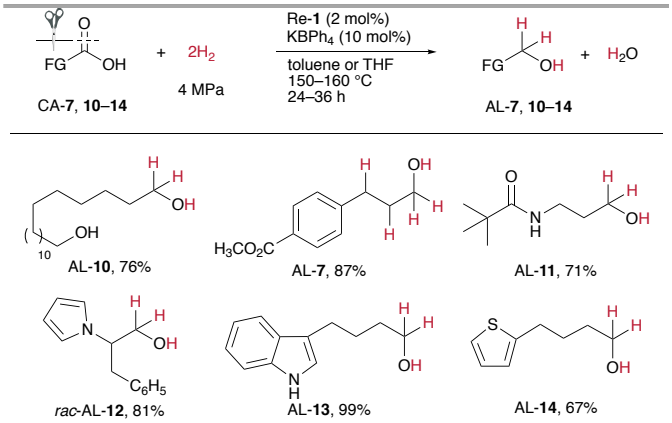
The potential of homogeneous and heterogeneous high-valent Re species for CA hydrogenation

It should be noted that the majority of high-valent Re complexes have thus far been used for oxidations[39] and deoxydehydrations,[40] rather than for the FG transformation/hydrogenation of CH_nCOOH (n = 1–3) moieties of CAs (α-C–H functionalization[41] and hydrogenation[30,42]). Initially, we expected that the putative hydrogenation mechanism "CA self-induced CA hydrogenation" should be easily extended from low-valent Ru^{II} (d^6) to high-valent Re^{V} (d^2),[43] given that the mechanism seems to be strengthened when an acid–base (high valent Re^+ and $^-OC(O)R$) cooperative catalysis rather than a redox-based catalysis is operational. To put it simply, the former acid–base catalysis is more compatible with high-valent metal species, in which a stronger σ_{H-H}–d(e_g) orbital interaction (σ-bond) corresponding to an acid–base interaction is followed by intramolecular deprotonation by a weak base ($^-OC(O)R$), whereas the redox system needs well-balanced σ_{H-H}–d(e_g) and σ^*_{H-H}–d(t_{2g}) interactions (total contributions for bonding: σ-bond + π-back donation), which are commonly accepted conventional mechanism that triggers H–H bond activation and cleavage, more compatibly promoted by low-valent metal catalysts.

Identification of the most effective Re^{V} complex catalyst for CA hydrogenation

On the outset, we examined a series of high-valent Re precatalysts using CA-**2** as model substrate. Treatment of a toluene solution of CA-**2** with catalytic $(CH_3)Re^{VII}O_3$, $IRe^{V}O_2(PPh_3)_2$, $Cl_3Re^{V}O(O{=}PPh_3)[(CH_3)_2S]$, $Cl_3Re^{V}O(PPh_3)_2$, or $Cl_3Re^{V}O(Ph_2PCH_2PPh_2)$ with P_{H2} = 8 MPa at 160 °C for 24 h induced virtually no reaction. In contrast, the cationic Re species from each of the latter four complexes (2 mol% each), formed upon treatment with $NaBPh_4$ (10 mol%) ($[Re]_0$ = 2.5 mM), afforded AL-**2** in 14–62% and ES-**2** in 5–11%. The highest yield of AL-**2** (72%) was obtained using Re-**1**. Subsequently, we tested several Re^{V} precatalysts, synthesized from $Cl_3Re^{V}O(O{=}PPh_3)[(CH_3)_2S]$,[44] with different bidentate diphosphine ligands. Under otherwise identical reaction conditions, $Cl_3Re^{V}O[Ph_2P(CH_2)_2PPh_2]$[45] (Re-**1**) and $Cl_3Re^{V}O[Ph_2PC_6H_4PPh_2]$ (Re-**3**) afforded the best result among those tested, furnishing AL-**2** (ES-**2**) in >98% (~1%) and 89% (5%) yield, respectively. This result stands in sharp contrast to many homogeneous and heterogeneous catalysts, which induce undesirable over-reductions (e.g. dearomatic hydrogenation and hydrogenolysis), CA esterification and deoxygenation of the generated alcohols.[22,45,46] The low-valent Re^0 carbonyl cluster $Re_2(CO)_{10}$ is unable to catalyse the hydrogenation of n-$C_{14}H_{29}CO_2H$ at 170 °C, even at P_{H2} = ~10 MPa.[19b] Similarly, non-oxo complexes of Re^{III} ($Cl_3Re^{III}[CH_3C(CH_2PPh_2)_3]$ or $Cl_3Re^{III}(PPh_3)_2(CH_3CN)$) (2 mol%) with $NaBPh_4$ (10 mol%) exhibited low catalytic activity (AL-**2**: 9% and 37%, respectively). Although both low- and high-valent Re species in hetero-multimetallic catalysts such as $Re_2(CO)_{10}$-$Ru_3(CO)_{12}$,[19b] $Re_2(CO)_{10}$-Rh/Al_2O_3,[19b] Re_2O_7-OsO_4,[19a] ReO_x-Pd/SiO_2,[47] ReO_x/TiO_2,[48] and Re/TiO_2[30b] have been investigated for CA hydrogenation,[30,42] the role of Re in these catalysts remains unclear. Recent examples of ReO_x/TiO_2 and Re/TiO_2 catalysis have shown high alcohol selectivity with a limited substrate scope, with diverse Re entities (Re^0, Re^{III}, Re^{IV}, Re^{VI}, and Re^{VII}, obtained by calcination and reduction at 400–500 °C with H_2) on TiO_2 determined by XPS analysis.[30b,48] Heterogeneous ReO_3 promotes CA hydrogenation under high H_2 pressure (P_{H2} = ca. 20.5 MPa, ~165 °C); nevertheless, the *in situ* esterification is non-negligible and CA-**8** is only partially hydrogenated.[49]

Table 2. Functionalized CA hydrogenation using Re-**1**.



$Re^{V}P_2$ complexes for chemoselective CA hydrogenation

Using $KBPh_4$ in place of $NaBPh_4$ under milder conditions (Re-**1** (2 mol%), P_{H2} = 4 MPa, 150 °C, 24 h) increased the yield of AL-**2** from 55% to 80%. After further optimization of the reaction conditions ($[Re\text{-}1]_0$ = 2.5 mM in toluene or THF, Re-**1**:$KBPh_4$ = 0.02:0.1, P_{H2} = 2–4 MPa, 140–160 °C), a variety of CAs were hydrogenated (Table 2).

The new hydrogenation reaction is applicable to a wide range of functionalized and simple CAs (Table 2). The hydrogenation of CA-**2** with Re-**1** proceeded under even milder conditions (P_{H2} = 2 MPa, 160 °C, 72 h), affording AL-**2** in 85% yield. 17-hydroxyheptadecanoic acid (CA-**10**) were also hydrogenated effectively, in addition to simple aliphatic CAs, under these conditions giving AL-**10**. The double bonds of the α,β-unsaturated (*E*)-3-(4-(methoxycarbonyl)phenyl)acrylic acid (CA-**7**), (*E*)-3-(4-chlorophenyl)acrylic acid, and (*E*)-2-methyl-3-phenylacrylic acid were hydrogenated uniformly, affording the corresponding saturated alcohols in high yields (87– >95%). Numerous FGs, including chlorobenzenes, ethers, alcohols of CA-**10** and AL-**10**, the esters of CA-**7** and AL-**7**, the amides of CA-**11** and AL-**11**, the pyrroles of CA-**12** and AL-**12**, the indole of CA-**13** and AL-**13**, and thiophene of CA-**14** and AL-**14** were all tolerated well and barely inhibited the hydrogenation. *N*-Protected natural α-amino acid ((*S*)-phenylalanine) CA-**12** was hydrogenated under epimerization of the stereogenic carbon center, giving *rac*-AL-**12**. Alcohols AL-**7** and AL-**10**–**14** were produced uniformly and almost exclusively, while esterification was consistently negligible (<5%). A control experiment revealed that CAs are hydrogenated faster than the esters

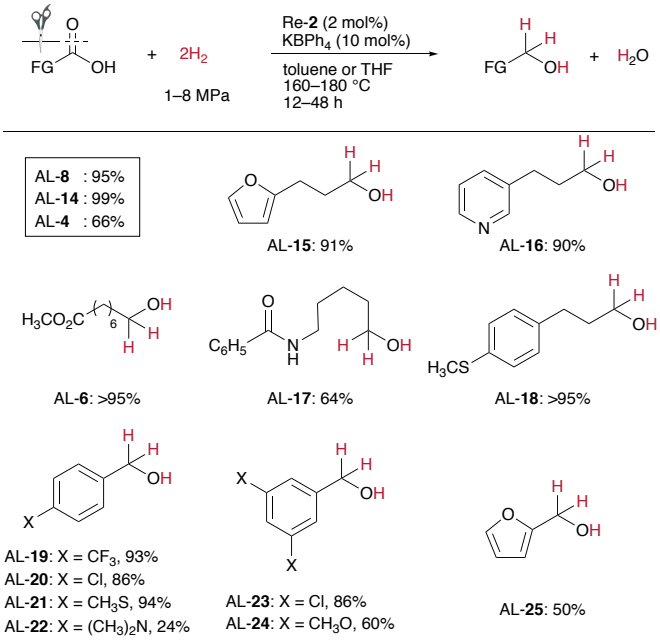
under the applied conditions. For example, hydrogenation of methyl nonanoate with a mixture of Re-**1** (2 mol%) and $KBPh_4$ (10 mol%) afforded 1-nonanol in ~10% yield even under harsh conditions (P_{H2} = 4 MPa, 180 °C, 24 h; $[Re]_0$ = 2.5 mM), which clearly suggests that ester groups could more effectively tolerate milder hydrogenation conditions. In contrast, $LiAlH_4$ or $LiBH_4$ reduce the CA moieties and bromoaryl, ester, and amide functionalities.

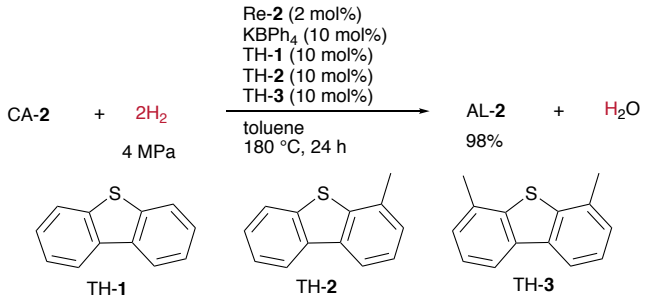
Re-1 vs. Re-2

While aliphatic CAs generally represent excellent substrates for the present hydrogenation strategy, the hydrogenation of CA-**8**[10,23,24a,29,30b] with Re-**1** indeed proceeded sluggishly even under harsher conditions (P_{H2} = 4 MPa, 180 °C, 24 h), affording AL-**8** in 29% yield. To improve this result, a new $Re^{V}OCl_3P_2$ complex (Re-**2**, Fig. 2), with a more robust five-membered framework imposed by Re-Chiraphos (Chiraphos: [(*S*)-$(Ph_2P)(CH_3)CH]_2$) complexation, was introduced and used for hydrogenation of CA-**8** (Re-**2** (2 mol%), $KBPh_4$ (10 mol%); P_{H2} = 4 MPa, 160 °C, 40 h), affording full conversion of CA-**8** to furnish AL-**8** in 95% yield (Table 3). For comparison, AL-**8** was generated in moderate yield (62%) under harsher P_{H2} with a larger amount of a Co-Triphos complex (2.5 mol%, P_{H2} = ca. 8 MPa, 100 °C, 22 h).[29]

Based on the primary positive results with Re-**2**, hydrogenation of aliphatic CAs was reinvestigated using Re-**2** (2 mol%) (Table 3), furnishing a higher yield of AL-**2** (93%) under milder conditions (P_{H2} = 2 MPa, 160 °C, 24 h) compared to Re-**1** (35%). Even at a lower P_{H2} (P_{H2} = 0.5 MPa, 180 °C, 48 h), CA-**2** was hydrogenated effectively with Re-**2** to afford AL-**2** (84%) and ES-**2** (7%). The furan (FR), pyridine, ester, amide, and sulfide moieties of CA-**6** and CA-**15**–**18** were well tolerated. Other CAs such as aromatic CA derivatives CA-**19**–**25** were also poorly hydrogenated by Re-**1**, but underwent smoother hydrogenation

Table 3. Functionalized CA hydrogenation using Re-**2**.



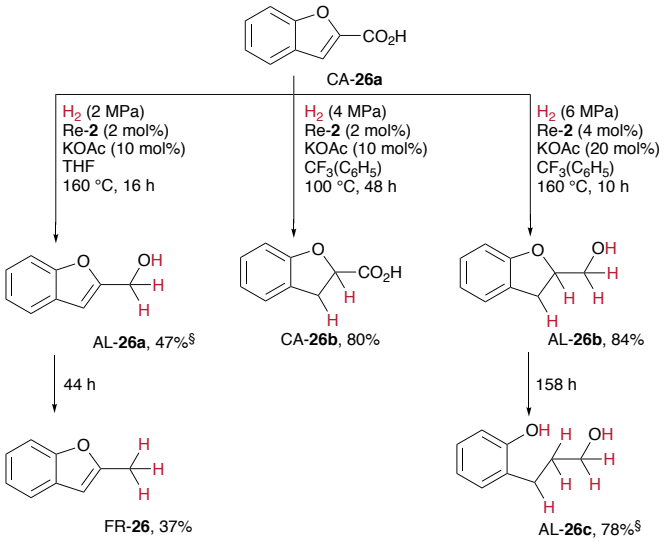


Scheme 10. Re^{V}-catalysed CA hydrogenation in the presence of typical sulfur-containing substances generated by the hydrodesulfurization during the refinement process of mature oil.

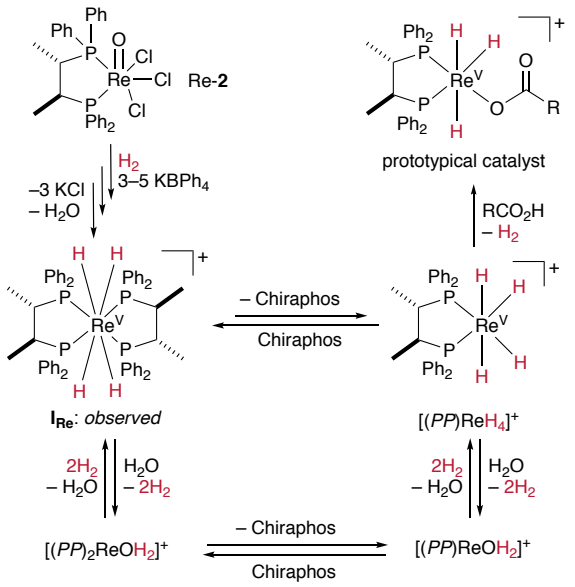
with Re-**2**, affording the corresponding alcohols in high yield and selectivity, except that CA-**22** and CA-**25** remained as rather unreactive substrates. Similarly, sterically bulky CA-**4** underwent moderate hydrogenation, giving AL-**4** in 66% yield.

Molecular Re^{VII} and Re^{V} species are able to catalyse the hydrogenation of sulfoxides, which affords dialkyl sulfides as the major product.[42] Likewise, the hydrogenation of CA with Re-**2** was barely inhibited by sulfur-containing CAs or thiophene (TH) derivatives (Scheme 10). For example, 4-(thien-2-yl)-substituted CA-**14** was hydrogenated to give AL-**14** in 99% yield (Table 3); hydrogenation of CA-**18** proceeded almost quantitatively even at a milder P_{H2} (P_{H2} = 1 MPa, 180 °C, 12 h). In many cases, sulfur-containing substances poison precious metal hydrogenation catalysts. However, Re-**2** (2 mol%) was not deactivated by benzothiophene or dibutyl sulfide (30 mol% each), affording AL-**2** in 99% in both cases (P_{H2} = 4 MPa, 160 °C, 24 h). Even in the presence of a mixture of dibenzothiophene derivatives (TH-**1**–**3**), which are detrimental to conventional hydro-desulfurization catalysts,[50] no negative effects were observed at P_{H2} = 4 MPa. In contrast, TH slightly decreases the hydrogenation rate of the bimetallic catalysis promoted by OsO_4-Re_2O_7, although over-reduction to the hydrocarbon was diminished.[19a]

Compared to the selective formation of AL-**25** from furan-2-carboxylic acid, the π-extended derivative of CA-**25**, CA-**26a**, should be more reactive than CA-**25**, since various anionic or



Scheme 11. Selective hydrogenation of CA-**26a** and further hydrogenolysis. Yields (%) are based on CA-**26a**. §AL-**26b** (16–20%) was also obtained.



Scheme 12. Plausible formation of $[ReH_3(OC(O)CH_2R)(PP)]^+$ as a prototypical catalyst for the "CA self-induced hydrogenation of CA", derived from Re-**2**.

cationic reaction intermediates and/or transition states derived from CA-**26a**, if any, could be stabilized by π-conjugation effects. In fact, CA-**26a** showed intriguing reactivity upon reaction with Re-**2** and H_2 (Scheme 11). CA-**26a** underwent either full hydrogenation of all non-aryl unsaturated bonds to afford AL-**26b**, chemoselective reduction, i.e., a carbonyl hydrogenation to afford AL-**26a**, or selective α,β-ene hydrogenation to furnish CA-**26b**. Even hydrodeoxygenation (HDO), which is uncommon for Re complex-based catalysis, was achieved by varying the reaction parameters: hydrogenolysis of the different C–O bonds of the reaction intermediates AL-**26a** and AL-**26b** afforded FR-**26** and alcoholic phenol AL-**26c**, respectively. To the best of our knowledge, this represents the first example of a directed, catalytic CA hydrogenation and subsequent hydrogenolysis in one pot using molecular catalysts.

Insights into catalytic Re species

Re^0 nanoparticle was proven to be catalytically innocent by a mercury (Hg^0) test. Other control experiments based on ^1H and $^{31}P\{^1H\}$ NMR, in addition to ESI-HRMS analyses, clarified that $[Re^VH_4(PP)_2]^+$ (*P* = one phosphine coordination to a metal center) was generated[51] as an observable species during a promising CA hydrogenation (Scheme 12). However, $[Re^VH_4(PP)_2]^+$ should not be considered as catalytically active, but rather as a resting state of the catalyst or precatalyst. In fact, when the hydrogenation of CA-**2** (P_{H2} = 2 MPa, 160 °C, 24 h) was carried out using $ORe^VCl_3(O{=}PPh_3)((CH_3)_2S)$ (2 mol%: $[Re]_0$ = 2.5 mM), bidentate diphosphine ligand *PP* (Chiraphos: 4 or 6 mol%) and $KBPh_4$ (10 mol%), the yield of AL-**2** significantly decreased (22% and 0%, respectively) compared to that obtained from using 2 mol% of Chiraphos (AL-**2**: 93%). These results suggest that the most likely catalytically active species retains a 1:1 Re–*PP* complexation, which could be readily generated by detachment of one *PP* ligand from $[Re^VH_4(PP)_2]^+$.

To clarify whether H_2O affects catalyst deactivation or activation, a 200 mol% of H_2O relative to CA-**2** was added before starting the hydrogenation. The hydrogenation rate for the formation of AL-**2** was considerably retarded over the reaction time of 12 h (AL-**2**: 59%); however, the integrity of the catalysis was sustained, and further extending the time to 24 h increased the yield of AL-**2** to 97%. This result implies that Re=O species should only play a peripheral role in the catalysis, considering that H_2O should shift the reaction equilibrium from a ReH_2 species to a Re=O structure.[34,52] All the control experiments suggest that the mononuclear Re species $[Re^V(\eta^1\text{-}H)_4(PP)]^+$ represents an important precatalyst (albeit presumably outside the catalytic cycle) that subsequently affords, upon reaction with CA-**2**, the cationic mononuclear Re-carboxylate $[Re^V(\eta^1\text{-}H)_3(O(C{=}O)(CH_2)_2Ph)(PP)]^+$ (Scheme 12), which serves as an initial critical point of the catalytic cycle. This interpretation is consistent with our previous observations, which identified the related $[Ru^{II}(O(C{=}O)(CH_2)_2Ph)(PP)]^+$ as the key intermediate in a catalytic cycle involving the "CA self-induced CA hydrogenation".[10a] However, at this point, a catalytic involvement of $[Re^{III}(\eta^1\text{-}H)(\eta^2\text{-}H_2)(O(C{=}O)(CH_2)_2Ph)(PP)]^+$, which could also be derived from $[Re^{III}(\eta^1\text{-}H)_2(PP)]^+$ in the presence or absence of $\eta^2\text{-}H_2$ coordination, cannot be ruled out with certainty.

Conclusions

The "CA self-induced CA hydrogenation" promoted by the prototypical Ru catalyst (Scheme 3) should be further applicable to other homogeneous hydrogenation catalysts based on both base- and precious metals, as well as both on low- and high-valent metal species. However, detailed *in silico* analyses of the mechanistic intricacies of the catalytic cycle involving the "CA self-induced CA hydrogenation" have only just begun. The rational molecular design of the catalysts is required in order to close some of the apparent deactivation pathways in order to improve the catalyst TON significantly. Catalytic CA hydrogenations that proceed under mild and relatively neutral conditions could be expanded to include the transformation of optically active CAs (e.g. α-amino acids) into fine chemicals with promising scalability and without racemization. Such advanced catalyst systems will be realized by modifying structural and electronic features of monodentate and bidentate phosphines successfully used for Ru catalysts and Re catalysts shown here. The identification of metal carboxylates that are potentially able to hydrogenate CO_2 and bio-renewable resources in high oxidation states will contribute significantly to the future development of chemical processes directed toward sustainable development goals (SDGs).

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Notes and references

1 D. Teichmann, W. Arlt, P. Wasserscheid and R. Freymann, *Energy Environ. Sci.*, 2011, **4**, 2767–2773.
2 T. Werpy and G. Petersen, Top value added chemicals from biomass volume I–results of screening for potential candidates from sugars and synthesis gas, https://www.nrel.gov/docs/fy04osti/35523.pdf, (accessed May 2018).
3 J. J. Bozell and G. R. Petersen, *Green Chem.*, 2010, **12**, 539–554.
4 T. G. Ostapowicz, M. Schmitz, M. Krystof, J. Klankermayer and W. Leitner, *Angew. Chem. Int. Ed.*, **2013**, *52*, 12119–12123.
5 H. Seo, M. H. Katcher and T. F. Jamison, *Nat. Chem*., 2016, **9**, 453–456.
6 Y. Masuda, N. Ishida and M. Murakami, *J. Am. Chem. Soc.*, 2015, **137**, 14063–14066.
7 (a) R. Tanaka, M. Yamashita and K. Nozaki, *J. Am. Chem. Soc.*, 2009, **131**, 14168–14169; (b) W.-H. Wang, Y. Himeda, J. T. Muckerman, G. F. Manbeck and E. Fujita, *Chem. Rev.*, 2015, **115**, 12936–12973; (c) Q. Liu, L. Wu, R. Jackstell and M. Beller, *Nat. Commun.*, 2015, **6**, 5933; (d) P. G. Jessop, T. Ikariya and R. Noyori, *Nature*, 1994, **368**, 231–233; (e) P. G. Jessop, T. Ikariya and R. Noyori, *Chem. Rev.*, 1995, **95**, 259–272.
8 (a) S. Sato, T. Arai, T. Morikawa, K. Uemura, T. M. Suzuki, H. Tanaka and T. Kajino, *J. Am. Chem. Soc.*, 2011, **133**, 15240–15243; (b) T. Arai, S. Sato and T. Morikawa, *Energy Environ. Sci.*, 2015, **8**, 1998–2002.
9 (a) G. A. Olah, G. K. S. Prakash and A. Goeppert, *J. Am. Chem. Soc.*, 2011, **133**, 12881–12898; (b) G. A. Olah, *Angew. Chem. Int. Ed.*, 2013, **52**, 104–107.
10 (a) M. Naruto and S. Saito, *Nat. Commun.*, 2015, **6**, 8140; (b) M. Naruto, S. Agrawal, K. Toda and S. Saito, *Sci. Rep*., 2017, **7**, 3425.
11 P. A. Dub and T. Ikariya, *ACS Catal.*, 2012, **2**, 1718–1741.
12 (a) M. L. Clarke, *Catal. Sci. Technol.*, 2012, **2**, 2418–2423; (b) S. Werkmeister, K. Junge and M. Beller, *Org. Process Res. Dev.*, 2014, **18**, 289–302.
13 A. M. Smith and R. Whyman, *Chem. Rev.*, 2014, **114**, 5477–5510. Recent results from our group, see refs. 33 and 34.
14 (a) V. R. Pattabiraman and J. W. Bode, *Nature*, 2011, **480**, 471–479; (b) R. M. de Figueiredo, J.-S. Suppo and J.-M. Campagne, *Chem. Rev.*, 2016, **116**, 12029–12122; Very recent results: (c) K. Wang, Y. Lu and K. Ishihara, *Chem. Commun*., 2018, **54**, 5410–5413; from our group: (d) D. N. Sawant, D. B. Bagal, S. Ogawa, K. Selvam and S. Saito, *Org. Lett*., 2018, **20**, 4397–4400.
15 For reviews, see: (a) J. Otera, in *Esterification; Methods, Reactions, and Applications*, Wiley-VCH, Weinheim, 2003, ch. 1, pp. 5–145; (b) K. Ishihara, *Tetrahedron*, 2009, **65**, 1085–1109.
16 R. H. Morris, in *The Handbook of Homogeneous Hydrogenation*, ed. J. G. de Fries and C. J. Elsevier, Wiley-VCH, Weinheim, 2007, vol. 1, ch. 3, pp. 45–70.
17 M. T. Ashby and J. Halpern, *J. Am. Chem. Soc.*, 1991, **113**, 589–594.
18 (a) A. B. Chaplin and P. J. Dyson, *Inorg. Chem.*, 2008, **47**, 381–390; (b) M. Kitamura, M. Tsukamoto, Y. Bessho, M. Yoshimura, U. Kobs, M. Widhalm and R. Noyori, *J. Am. Chem. Soc.*, 2002, **124**, 6649–6667.
19 (a) K. Yoshino, Y. Kajiwara, N. Takaishi, Y. Inamoto and J. Tsuji, *J. Am. Oil Chem. Soc.*, 1990, **67**, 21–24; (b) D.-H. He, N. Wakasa and T. Fuchikami, *Tetrahedron Lett.*, 1995, **36**, 1059–1062.
20 (a) M. Bianchi, G. Menchi, F. Francalanci, F. Piacenti, U. Matteoli, P. Frediani and C. Botteghi, *J. Organomet. Chem.*, 1980, **188**, 109–119; (b) A. Salvini, P. Frediani, M. Bianchi, F. Piacenti, L. Pistolesi and L. Rosi, *J. Organomet. Chem.*, 1999, **582**, 218–228.
21 A. Salvini, P. Frediani, C. Giannelli and L. Rosi, *J. Organomet. Chem.*, 2005, **690**, 371–382.
22 T. P. Brewster, A. J. M. Miller, D. M. Heinekey and K. I. Goldberg, *J. Am. Chem. Soc.*, 2013, **135**, 16022–16025.
23 X. Cui, Y. Li, C. Topf, K. Junge and M. Beller, *Angew. Chem. Int. Ed.*, 2015, **54**, 10596–10599.
24 (a) T. Stein, M. Meuresch, D. Limper, M. Schmitz, M. Ho, J. Coetzee, D. J. Cole-Hamilton, J. Klankermayer and W. Leitner, *J. Am. Chem. Soc.*, 2014, **136**, 13217–13225; (b) S. Wesselbaum, T. V. Stein, J. Klankermayer and W. Leitner, *Angew. Chem. Int. Ed.*, 2012, **51**, 7499–7502.
25 (a) H. T. Teunissen and C. J. Elsevier, *Chem. Commun.*, 1997, 667–668; (b) H. T. Teunissen and C. J. Elsevier, *Chem. Commun.*, 1998, 1367–1368.
26 (a) F. M. A. Geilen, B. Engendahl, A. Harwardt, W. Marquardt, J. Klankermayer and W. Leitner, *Angew. Chem. Int. Ed.*, 2010, **49**, 5510–5514; (b) F. M. A. Geilen, B. Engendahl, M. Hölscher, J. Klankermayer and W. Leitner, *J. Am. Chem. Soc.*, 2011, **133**, 14349–14358; (c) L. Rosi, M. Frediani and P. Frediani, *J. Organomet. Chem.*, 2010, **695**, 1314–1322; (d) H. Mehdi, V. Fábos, R. Tuba, A. Bodor, L. T. Mika and I. T. Horváth, *Top. Catal.*, 2008, **48**, 49–54; (e) S. Wesselbaum, V. Moha, M. Meuresch, S. Brosinski, K. M. Thenert, J. Kothe, T. vom Stein, U. Englert, M. Hölscher, J. Klankermayer and W. Leitner, *Chem. Sci.*, 2015, **6**, 693–704; (f) C. A. Huff and M. S. Sanford, *J. Am. Chem. Soc.*, 2011, **133**, 18122–18125; (g) C. Delhomme, D. Weuster-Botz and F. E. Kühn, *Green Chem*., 2009, **11**, 13–26.
27 (a) A. A. Núñez Magro, G. R. Eastham and D. J. Cole-Hamilton, *Chem. Commun.*, 2007, 3154–3156; (b) J. Coetzee, D. L. Dodds, J. Klankermayer, S. Brosinski, W. Leitner, A. M. Z. Slawin and D. J. Cole-Hamilton, *Chem. Eur. J.*, 2013, **19**, 11039–11050.
28 L. Deng, B. Kang, U. Englert, J. Klankermayers and R. Palkovits, *ChemSusChem*, 2016, **9**, 177–180.
29 T. J. Korstanje, J. I. van der Vlugt, C. J. Elsevier and B. de Bruin, *Science*, 2015, **350**, 298–302.
30 For review, see: J. Pritchard, G. A. Filonenko, R. van Putten, E. J. M. Hensen and E. A. Pidko, *Chem. Soc. Rev.*, 2015, **44**, 3808–3833. For selected examples, see: (a) H. G. Manyar, C. Paun, R. Pilus, D. W. Rooney, J. M. Thompson and C. Hardacre, *Chem. Commun.*, 2010, **46**, 6279–6281; (b) T. Toyao, S. M. A. H. Siddiki, A. S. Touchy, W. Onodera, K. Kon, Y. Morita, T. Kamachi, K. Yoshizawa and K. Shimizu, *Chem. Eur. J.*, 2017, **23**, 1001–1006; (c) J. Ullrich and B. Breit, *ACS Catal.*, 2018, **8**, 785–789.
31 For review, see: K. Napora-Wijata, G. A. Strohmeier and M. Winkler, *Biotechnol. J.*, 2014, **9**, 822–843.
32 (a) T. A. Stephenson and G. Wilkinson, *J. Inorg. Nucl. Chem.*, 1966, **28**, 945–956; (b) J. M. Brown, *Angew. Chem. Int. Ed.*, 1987, **26**, 190–203.
33 T. Miura, I. E. Held, S. Oishi, M. Naruto and S. Saito, *Tetrahedron Lett.*, 2013, **54**, 2674–2678.
34 T. Miura, M. Naruto, K. Toda, T. Shimomura and S. Saito, *Sci. Rep.*, 2017, **7**, 1586.
35 K. S. Macfarlane, I. S. Thorburn, P. W. Cyr, D. E. K. Chau, S. J. Rettig and B. R. James, *Inorg. Chim. Acta*, 1998, **270**, 130–144.
36 (a) L. Ackermann, *Chem. Rev*., 2011, **111,** 1315–1345; (b) P. B. Arockiam, C. Bruneau and P. H. Dixneuf, *Chem. Rev*., 2012, **112,** 5879–5918.

37 Q. Lu, J. Song, M. Zhang, J. Wei and C. Li, *Dalton Trans.*, 2018, **47**, 2460–2469.
38 B. E. Bursten and R. H. Cayton, *Organometallics*, 1987, **6**, 2004–2005.
39 G. S. Owens, J. Arias and M. M. Abu-Omar, *Catal. Today*, 2000, **55**, 317–363.
40 T. J. Korstanje and R. J. M. K. Gebbink, *Top. Organomet. Chem.*, 2012, **39**, 129–174.
41 (a) Y. Morita, T. Yamamoto, H. Nagai, Y. Shimizu and M. Kanai, *J. Am. Chem. Soc.*, 2015, **137**, 7075–7078; (b) H. Nagai, Y. Morita, Y. Shimizu and M. Kanai, *Org. Lett.*, 2016, **18**, 2276–2279; (c) K. Ishizawa, H. Nagai, Y. Shimizu and M. Kanai, *Chem. Pharm. Bull.*, 2018, **66**, 231–234.
42 (a) S. C. A. Sousa, I. Cabrita and A. C. Fernandes, *Chem. Soc. Rev.*, 2012, **41**, 5641–5653; (b) P. M. Reis, P. J. Costa, C. C. Romão, J. A. Fernandes, M. J. Calhorda and B. Royo, *Dalton Trans.*, 2008, 1727–1733; (c) J. B. Arterburn and M. C. Perry, *Tetrahedron Lett.*, 1996, **37**, 7941–7944.
43 Preliminary results of this report were used in a patent application, see: S. Saito, R. Noyori, S. Agrawal and M. Naruto, JP Appl. #2013-268047, Filed: Dec 25, 2013.
44 O. Sigouin and A. L. Beauchamp, *Inorg. Chim. Acta*, 2005, **358**, 4489–4496.
45 K. Kon, W. Onodera, S. Takakusagi and K. Shimizu, *Catal. Sci. Technol.*, 2014, **4**, 3705–3712.
46 A. S. Touchy, K. Kon, W. Onodera and K. Shimizu, *Adv. Synth. Catal.*, 2015, **357**, 1499–1506.
47 Y. Takeda, Y. Nakagawa and K. Tomishige, *Catal. Sci. Technol.*, 2013, **2**, 2221–2223.
48 B. Rozmysłowicz, A. Kirilin, A. Aho, H. Manyar, C. Hardacre, J. Wärnå, T. Salmi and D. Y. Murzin, *J. Catal.*, 2015, **328**, 197–207.
49 H. S. Broadbent and W. J. Bartley, *J. Org. Chem.*, 1963, **28**, 2345–2347.
50 (a) I. V. Babich and J. A. Moulijn, *Fuel*, 2003, **82**, 607–631; (b) P. S. Kulkarni and C. A. M. Afonso, *Green Chem.*, 2010, **12**, 1139–1149.
51 M. Freni, R. Demichelis and D. Giusto, *J. Inorg. Chem*. 1967, **29**, 1433–1439.
52 H. S. Broadbent, G. C. Campbell, W. J. Bartley and J. H. Johnson, *J. Org. Chem.*, 1959, **24**, 1847–1854.