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Catalytic transformation of functionalized carboxylic acids using multifunctional rhenium complexes

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Carboxylic acids (CAs) are one of the most ubiquitous and important chemical feedstocks available from biorenewable resources, CO_2, and the petrochemical industry. Unfortunately, chemoselective catalytic transformations of CH_nCO_2H ($n = 1–3$) groups into other functionalities remain a significant challenge. Herein, we report rhenium^V complexes as extremely effective precatalysts for this purpose. Compared to previously reported heterogeneous and homogeneous catalysts derived from high- or low-valent metals, the present method involves a α-C–H bond functionalization, a hydrogenation, and a hydrogenolysis, which affords functionalized alcohols with a wide substrate scope and high chemoselectivity under relatively mild reaction conditions. The results represent an important step toward a paradigm shift from 'low-valent' to 'high-valent' metal complexes by exploring a new portfolio of selective functional group transformations of highly oxygenated organic substrates, as well as toward the exploitation of CAs as a valuable biorenewable feedstock.

Carboxylic acids (CAs) are abundantly available from a variety of natural resources and the petrochemical industry, while several emerging technologies aim to produce CAs via thermal[1–4] or photo-induced[5–7] immobilization of CO_2 in organic frameworks. The functional group transformation (FGT) and subsequent reduction of CAs hence represent an important research subject to furnish alcohols for platform/fine chemicals[1–11], biofuels[11–13], and electric power-storage materials[14]. Among those FGTs, the catalytic C–H bond functionalization of CAs[15–17], followed by hydrogenation[18–23], could potentially widen the diversity of alcohols thus available. Unfortunately, this route remains unattainable, given that a general method for the selective catalytic activation of different functional groups (FGs) in CAs presents many challenges. Generally, CAs contain thermodynamically stable and kinetically inert α-C–H hydrogen atoms (carboxylates: $pK_a = 34–40$ in DMSO), which are less acidic than those of the CO_2H group ($pK_a = 10–13$ in DMSO), while the carbonyl carbon atoms of CAs are less electrophilic than those of other carbonyl groups. The development of new catalytic strategies to chemoselectively activate the CH_nCO_2H ($n = 1–3$) groups of aliphatic CAs should expand the synthetic utility of functionalized CAs as important platform/fine chemicals.

Previously reported attempts to selectively transform CAs are predominantly based on specifically developed molecular catalysts. For example, the selective α-C–H bond functionalization of CAs is accomplished by catalytic BH_3 in the presence of stoichiometric amounts of amines[15]. Moreover, CO_2H moieties have been used as directing groups for the Pd-catalyzed C–H bond functionalization of spatially distal sp^2 or sp^3 carbon atoms[16,17], and as traceless activating groups for decarboxylative carbon–carbon bond formations[24–27]. The latter two methods are based on redox catalysis, involving low-valent (d_3–d_{10}) metals such as $Ni^{0–III}$, $Pd^{0,II}$, $Ru^{0,II,IV}$, $Ir^{I,III}$, or $Rh^{I,III}$. Despite the numerous beneficial features of low-valent metal species, the catalytic FGT of CAs (including hydrogenation) frequently suffers from several drawbacks, i.e., side reactions including the oxidative addition of the substrate at high temperatures, decarboxylation, and over-reduction (Fig. 1a)[23], as well as catalyst deactivation by ligation/chelation of one or more heteroatom-containing FGs to the metal center. For example, in hydrodesulfurization reactions in biorefinery and mature oil refinery processes, hydrogenation catalysts are frequently deactivated by thiophenes[28,29]. Recently developed molecular Ru^{II} complexes[18] are able to catalytically hydrogenate CAs, but are not compatible with several FGs (e.g. bromoaryls, thienyls, and amides). To avoid such catalyst deactivation, the

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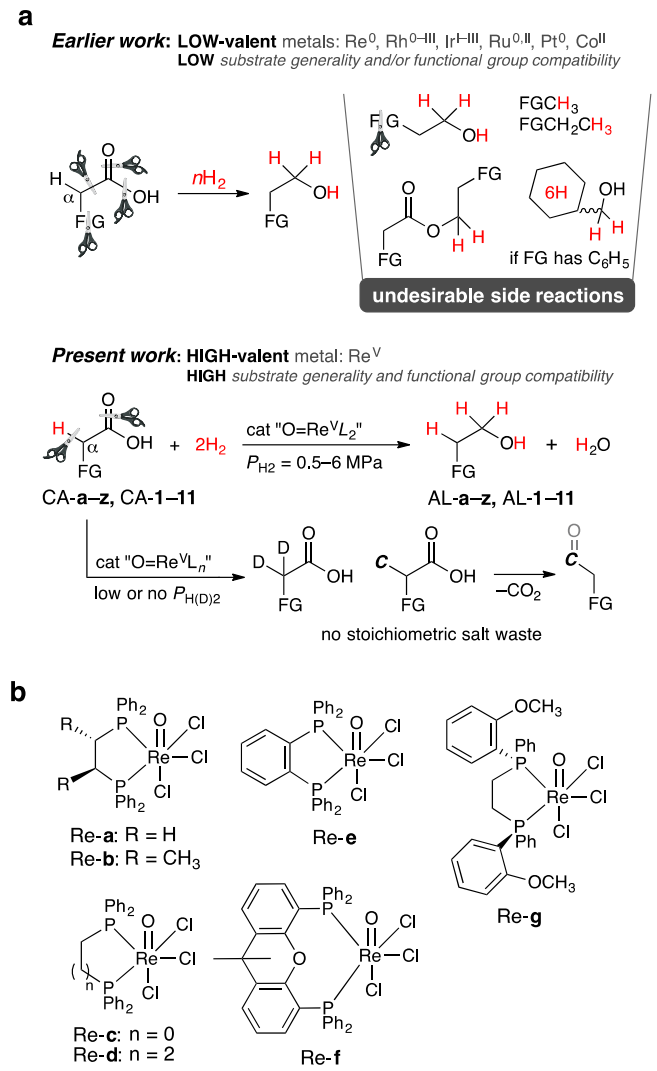


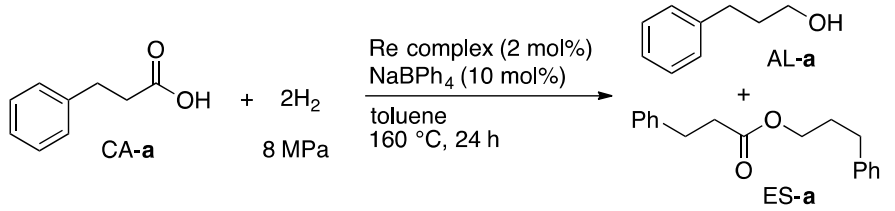
Figure 1. Overview of the present work (**a**). Overcoming the drawbacks of previously reported catalytic systems for the chemoselective hydrogenation of CAs. FG = functional group, L = ligand, ***C*** = carbon fragment. (**b**) Some Re^{V} = O complexes tested thus far for CA hydrogenation.

robustness and inertness of the catalyst toward many different FGs is of crucial importance, while new concepts for the selective activation of CH_nCO_2H groups (n = 1–3) in CAs must be developed. High-valent (d_0–d_2)[30] transition metals may represent more promising prospectives than their low-valent analogues, considering that the former are less susceptible to oxidative addition and π-back donation than the latter. Therefore, we have developed molecular single-active-site rhenium^{V} complexes (Fig. 1b) that selectively hydrogenate and/or functionalize a wide range of functionalized CAs. The majority of high-valent Re complexes have thus far been used for oxidation[31] and deoxydehydration[31,32], rather than for FGT of CA (α-C–H functionalization[15] and hydrogenation[23,33]).

Results

Catalytic hydrogenation of functionalized CAs. We recently reported a systematic study on the nature of cationic mononuclear Ru^{II} carboxylates as catalyst precursors for the self-induced hydrogenation of CAs[18]. Simultaneously, a similar hydrogenation mechanism involving cobalt(II)-triphos catalysts (triphos: $CH_3C[CH_2PPh_2]_3$) was proposed by Elsevier and Bruin[19]. Subsequently, we extended the putative hydrogenation mechanism to high-valent metal catalysts[34], as the originally proposed mechanism seemed to involve acid–base cooperative catalysis rather than a redox-based catalytic cycle.

Initially, we evaluated a series of commercially available high-valent Re catalyst precursors. Treatment of a toluene solution of 3-phenylpropanoic acid (CA-**a**) with catalytic amounts of $(CH_3)Re^{VII}O_3$, $IRe^{V}O_2(PPh_3)_2$, $Cl_3Re^{V}O(O=PPh_3)[(CH_3)_2S]$, $Cl_3Re^{V}O(PPh_3)_2$, or $Cl_3Re^{V}O(Ph_2PCH_2PPh_2)$ (Re-**c**, Fig. 1b; Ph = C_6H_5) under an H_2 atmosphere (P_{H2} = 8 MPa) at 160 °C for 24 h induced virtually no reaction (*cf.* Table 1, entry 1 and Supplementary Table 1). In contrast, the cationic Re species from each of the latter four complexes (2 mol% each), formed upon treatment with $Na[B(C_6H_5)_4]$ (10 mol%) ($[Re]_0$ = 2.5 mM), afforded 3-phenylpropan-1-ol (AL-**a**) in 14–62% and 3-phenylpropyl 3-phenylpropanoate (ES-**a**) in 5–11% (entry 2 and Supplementary Table 1). The highest yield of AL-**a** (72%) was obtained using Re-**c** (entry 3). Encouraged by these results, we used several



Entry	Re complex	Na[BPh_4]	Yield % of AL-a	Yield % of ES-a
1	$Cl_3Re^{V}O[P(C_6H_5)_3]_2$	—	~1	~1
2	$Cl_3Re^{V}O[P(C_6H_5)_3]_2$	+	62	9
3	Re-**c**	+	72	5
4	Re-**a**	+	>98	~1
5	Re-**d**	+	46	6
6	Re-**e**	+	89	5
7	Re-**f**	+	34	5
8	$Cl_3Re^{III}[CH_3C(CH_2P(C_6H_5)_2)_3]$	+	9	4
9	$Cl_3Re^{III}[P(C_6H_5)_3]_2(CH_3CN)$	+	37	5

Table 1. Re complexes for the catalytic hydrogenation of CA-**a**. Unless otherwise specified: CA-**a**:Re:Na[$B(C_6H_5)_4$] = 100:2:10 (mol%); $[Re]_0 = 2.5$ mM; $P_{H2} = 8$ MPa, 160 °C, 24 h. Ph = C_6H_5. Yields % are determined by ^{1}H NMR using the internal standard anisole.

Re^{V} precatalysts (Re-**a**,**d**–**f**) obtained from $Cl_3Re^{V}O(O=PPh_3)[(CH_3)_2S]$[35] and bidentate diphosphine ligands (entries 4–7). The best results were observed for $Cl_3Re^{V}O[Ph_2P(CH_2)_2PPh_2]$[35] (Re-**a**), which furnished AL-**a** in >98% yield (entry 4) together with negligible amounts of ES-**a** (~1%). This result stands in sharp contrast to many homogeneous and heterogeneous catalysts, which induce undesirable CA esterification and deoxygenation with the generated alcohols[36–38]. The exclusive formation of AL-**a** suggests that undesirable over-reductions (e.g. dearomatic hydrogenation and hydrogenolysis) of AL-**a**, and/or decarboxylation of CA-**a**, are prevented. This high FG tolerance surpasses that of $Mo(CO)_6$-Rh/Al_2O_3 ($P_{H2} = \sim 10$ MPa, 150 °C), in which benzene rings of the CAs are hydrogenated[39]. Moreover, the low-valent Re^0 carbonyl cluster $Re_2(CO)_{10}$ is unable to catalyze the hydrogenation of *n*-$C_{14}H_{29}CO_2H$ in dimethoxyethane at 170 °C, even at $P_{H2} = \sim 10$ MPa[39]. Similarly, non-oxo complexes of Re^{III} exhibited low to negligible catalytic activity (entries 8 and 9).

Although both low- and high-valent Re species in hetero-multimetallic catalysts such as $Re_2(CO)_{10}$-$Ru_3(CO)_{12}$[39], $Re_2(CO)_{10}$-Rh/Al_2O_3[39], Re_2O_7-OsO_4[40], ReO_x-Pd/SiO_2[41], ReO_x/TiO_2[42], and Re/TiO_2[43] have been investigated for CA hydrogenation[23,33], the specific 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 rather limited substrate scope, with diverse Re entities (Re^0, Re^{III}, Re^{IV}, Re^{VI}, and Re^{VII}, calcined and reduced at 400–500 °C with H_2) on TiO_2 determined by XPS analysis[42,43]. Even though heterogeneous ReO_3 promotes CA hydrogenation under high H_2 pressure (P_{H2} = ca. 20.5 MPa, ~165 °C), the *in situ* esterification is non-negligible and benzoic acid is partially hydrogenated[44].

Using K[$B(C_6H_5)_4$] instead of Na[$B(C_6H_5)_4$] with Re-**a** under milder conditions ($P_{H2} = 4$ MPa, 150 °C, 24 h) increased the yield of AL-**a** from 55% to 80% (Supplementary Table 2). After further optimization of the reaction conditions (Supplementary Table 3) ($[Re\text{-}\mathbf{a}]_0 = 2.5$ mM in toluene or THF, Re-**a**:K[$B(C_6H_5)_4$] = 0.02:0.1, P_{H2} = 2–4 MPa, 140–160 °C), a variety of CAs were tested (Fig. 2a–c and Supplementary Table 4). The hydrogenation of brominated CA-**b** with Re-**a** afforded AL-**b** with an intact bromobenzene fragment (Fig. 2a). Low-valent metal species such as previously developed Ru^{II} complexes[18] lose their catalytic activity almost immediately upon reaction with CA-**b**, affording only negligible amounts of AL-**b** (<1%), presumably due to the oxidative addition of the C–Br bond to the Ru center. The new hydrogenation reaction is applicable to a wide range of functionalized and simple CAs (Fig. 2b). The hydrogenation of CA-**a** with Re-**a** proceeded under even milder conditions ($P_{H2} = 2$ MPa, 160 °C, 72 h), affording AL-**a** in 85% yield. Simple aliphatic CAs (CA-**c**–**f**), 17-hydroxyheptadecanoic acid (CA-**g**), and alkoxy-substituted CAs (CA-**h**–**j**) were also hydrogenated under these conditions. The double bonds of the α,β-unsaturated CAs (*E*)-3-(4-chlorophenyl)acrylic acid (CA-**l**), (*E*)-2-methyl-3-phenylacrylic acid (CA-**m**), and (*E*)-3-(4-(methoxycarbonyl)phenyl)acrylic acid (CA-**n**) were hydrogenated uniformly, affording saturated alcohols AL-**l**–**n**. Nevertheless, numerous FGs, including chlorobenzenes, ethers, alcohols, esters (CA-**n**), indole (CA-**p**), amide (CA-**q**), thiophene (CA-**u**), and pyrroles (CA-**r**–**t**) were tolerated well and barely inhibited the hydrogenation. *N*-Protected natural α-amino acids (CA-**r**–**t**) were hydrogenated under racemization of the stereogenic carbon centers. Alcohols AL-**b**–**t** 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-**a** (2 mol%) and K[$B(C_6H_5)_4$] (10 mol%) afforded 1-nonanol in ~10% yield under harsh conditions ($P_{H2} = 4$ MPa, 180 °C, 24 h; $[Re]_0 = 2.5$ mM) (Supplementary Table 5), which suggests that ester and amide groups are tolerated under mild hydrogenation conditions. In contrast, $LiAlH_4$ or $LiBH_4$ reduce the CA moieties and bromoaryl, ester, or amide functionalities.

While aliphatic CAs generally represent excellent substrates for the present hydrogenation strategy, the hydrogenation of benzoic acid (CA-**w**) has rarely been examined[18–21,43]. Indeed, hydrogenation of CA-**w** with Re-**a**

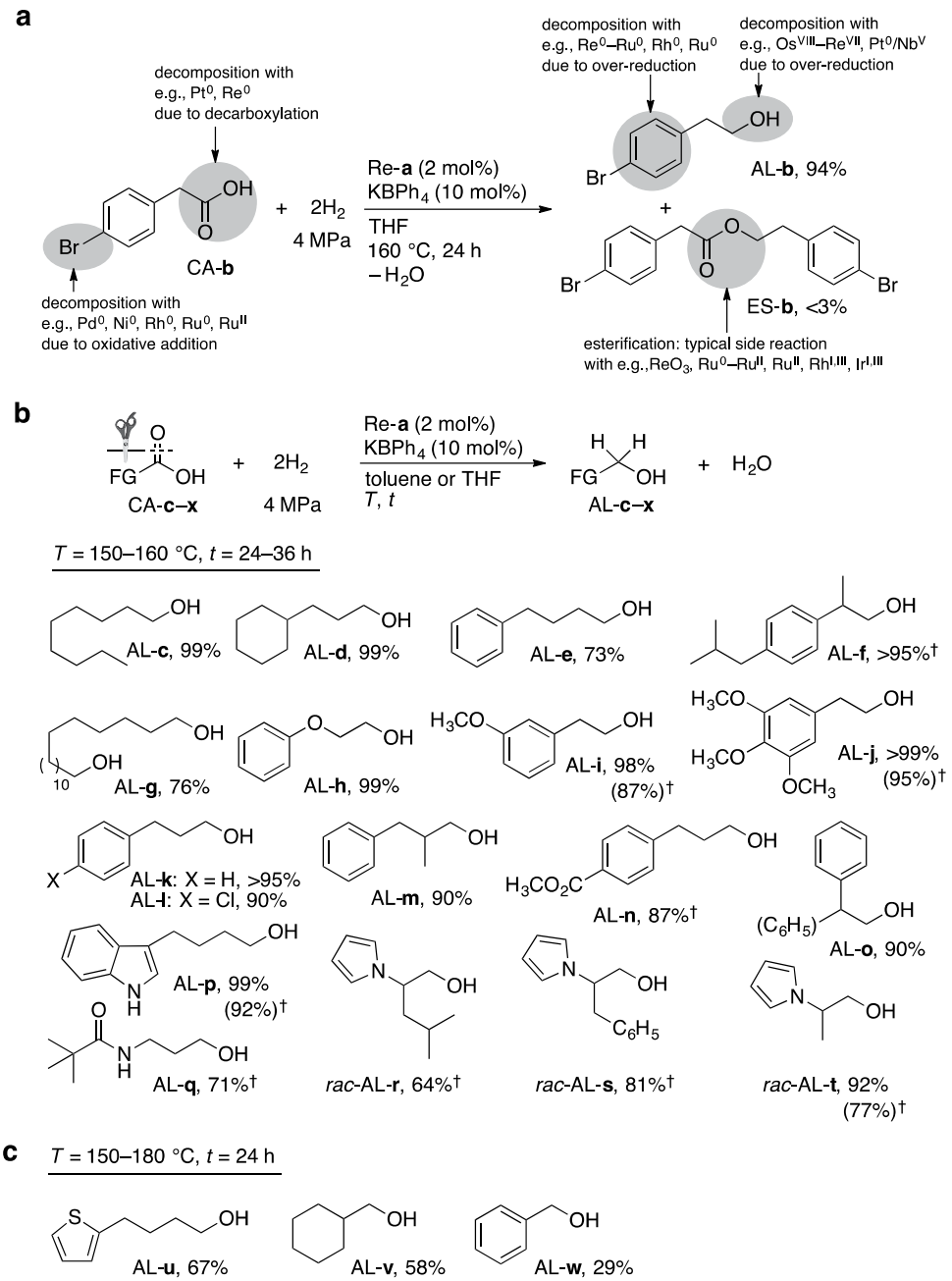


Figure 2. Catalytic hydrogenation of various CAs using Re-a. See Supplementary Tables 1–5 for experimental details. (**a**) In contrast to the low selectivity potentially obtainable with previously reported methods, hydrogenation of CA-**b** with Re-**a** afforded AL-**b** selectively. (**b**) CAs hydrogenated in relatively high yields. CA-**g** is a monocarboxylic acid, while CA-**l**–**n** are 2-enyl-1-CAs (for the exact structures, see main text. †Isolated yield. (**c**) CAs hydrogenated in lower yields.

proceeded sluggishly even under slightly harsher conditions (P_{H2} = 4 MPa, 180 °C, 24 h), affording benzyl alcohol (AL-**w**) in 29% yield (Fig. 2c). To improve this result, a new $Re^{V}OCl_3$ complex (Re-**b**) with a more robust five-membered Re–ligand metallacycle (due to the Thorpe-Ingold effect) was synthesized. The hydrogenation of CA-**w** with Re-**b** (2 mol%) and $K[B(C_6H_5)_4]$ (10 mol%) proceeded more effectively (P_{H2} = 4 MPa, 160 °C, 40 h) with full conversion of CA-**w** to furnish AL-**w** in high yield (95%) (Fig. 3a). For comparison, AL-**w** is generated in 93% (95% selectivity) and 62% yield under harsher conditions using a Ru-triphos (2 mol%, P_{H2} = ca. 5 MPa, 220 °C, 24 h)[21] and Co-triphos complex (2.5 mol%, P_{H2} = ca. 8 MPa, 100 °C, 22 h)[19], respectively.

The hydrogenation of aliphatic CAs was reinvestigated using Re-**b** (2 mol%), furnishing a higher yield of AL-**a** (93%) under milder conditions (P_{H2} = 2 MPa, 160 °C, 24 h) compared to Re-**a** (35%) and Re-**g** (32%) (Supplementary Table 1). Even at lower P_{H2} (P_{H2} = 0.5 MPa, 180 °C, 48 h), CA-**a** was hydrogenated effectively with Re-**b** to afford AL-**a** (84%) and ES-**a** (7%) (Supplementary Tables 6 and 7). The furan (FR) and pyridine moieties of CA-**y**,**z**, and CA-**4** were well tolerated. Other CAs such as benzoic acid derivatives (CA-**x**–**z** and CA-**5**–**10**) were

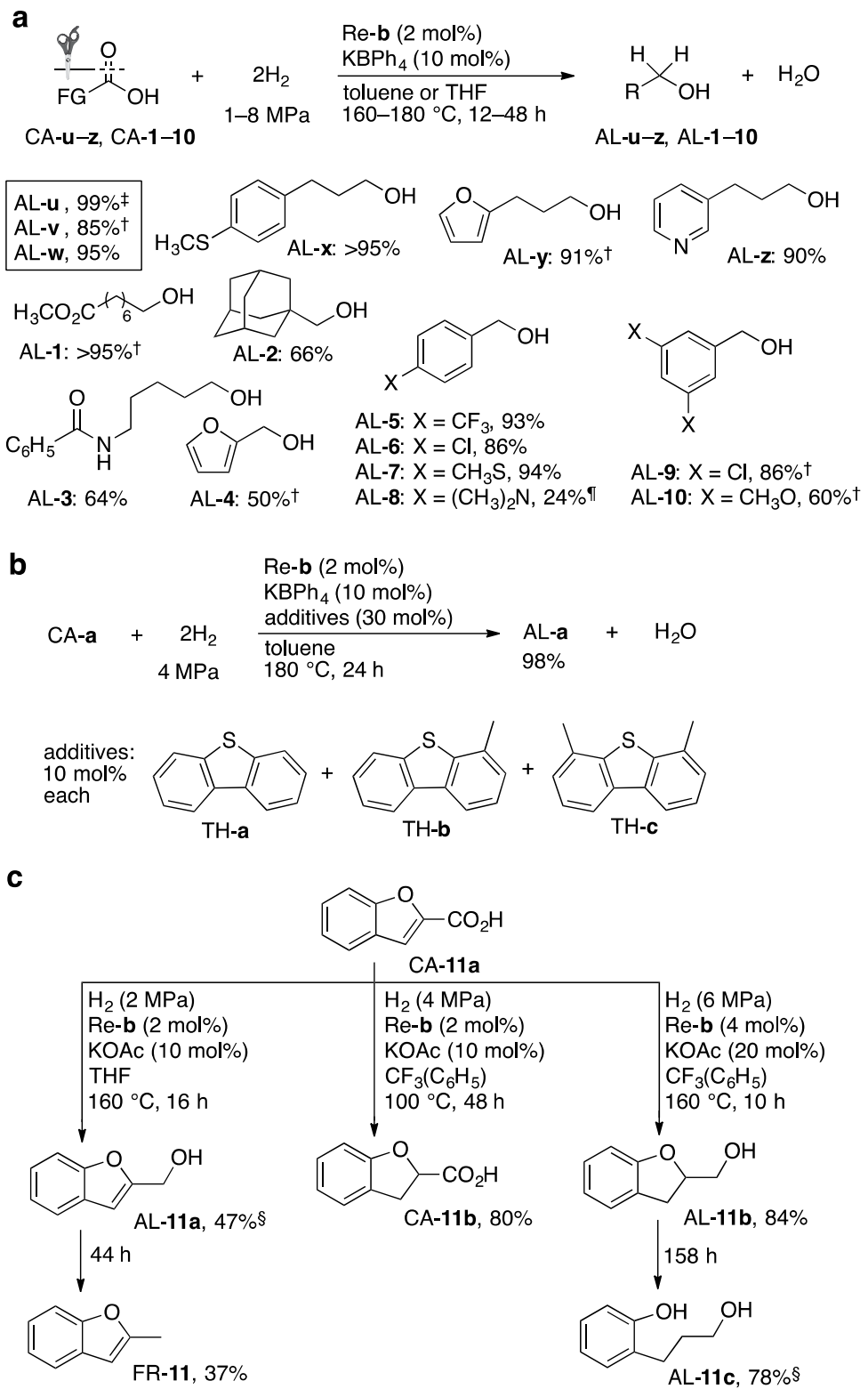


Figure 3. Improved chemoselective hydrogenation of CAs and hydrogenolysis of the resulting α-alkoxy alcohols using Re-b. See Supplementary Tables 6–10 for experimental details. (**a**) Substrate scope for the catalytic hydrogenation of CAs using Re-**b**. Unless otherwise noted, the corresponding esters were obtained in ≤5%. †THF was used instead of toluene. ‡Isolated yield: 83%. ¶Ester ES-**8** (~11%) was also obtained. (**b**) Re^{V}-catalyzed CA hydrogenation in the presence of typical sulfur-containing substances generated by hydrodesulfurization during the refinement process of mature oil. **c**. Selective hydrogenation of CA-**11a** and further hydrogenolysis. Yields (%) are based on CA-**11a**. §AL-**11b** (16–20%) was also obtained.

poorly hydrogenated by Re-**a**, but underwent smooth hydrogenation with Re-**b**, affording the corresponding alcohols in high yield and selectivity (Supplementary Table 8).

Molecular Re^{VII} and Re^{V} species are able to catalyze the hydrogenation of sulfoxides, which affords dialkyl sulfides as the major product[33]. Surprisingly, the hydrogenation of CA with Re-**b** was barely inhibited by sulfur-containing CAs or thiophene (TH) derivatives such as CA-**u**,**x** and CA-**7** (Supplementary Table 8). For example, 4-(thien-2-yl)-substituted CA-**u** was hydrogenated with Re-**b** to give AL-**u** in 99% yield; hydrogenation of CA-**x** proceeded almost quantitatively even at milder P_{H2} (P_{H2} = 1 MPa, 180 °C, 12 h). In many cases, sulfur-containing substances poison precious metal hydrogenation catalysts. However, Re-**b** was not deactivated by benzothiophene or dibutylsufide (30 mol%), affording AL-**a** in 99% in both cases (P_{H2} = 4 MPa, 160 °C, 24 h). Even in the presence of a mixture of dibenzothiophene derivatives (TH-**a–c**), which are detrimental to conventional hydro-desulfurization catalysts[28,29], no negative effects were observed at P_{H2} = 4 MPa (Fig. 3b; Supplementary Table 9). In contrast, TH slightly decreases the hydrogenation rate of the bimetallic catalyst OsO_4-Re_2O_7, although over-reduction of the hydrocarbon was diminished[40].

Compared to the selective formation of AL-**4** from furan-2-carboxylic acid (CA-**4**), the π-extended derivative CA-**11a** showed intriguing reactivity upon reaction with Re-**b** and H_2 (Fig. 3c; Supplementary Table 10). CA-**11a** underwent either full hydrogenation of all non-aryl unsaturated bonds to afford AL-**11b**, or chemoselective reduction, i.e., a carbonyl hydrogenation to afford AL-**11a** or an α,β-ene hydrogenation to furnish CA-**11b**. Even hydrodeoxygenation (HDO), which is uncommon for Re complex catalysts, was achieved by varying the reaction parameters: hydrogenolysis of the different C–O bonds of the reaction intermediates AL-**11a** and AL-**11b** afforded FR-**11** and alcoholic phenol AL-**11c**, 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.

Catalytic α-C–H bond functionalization of CAs. So far, Re-**a** and Re-**b** have provided the best catalytic results for the hydrogenation of a broad variety of CAs under relatively mild conditions. However, as previously discussed, Re-**a** induces the epimerization of *N*-protected amino acids such as CA-**r–t** (P_{H2} = 4 MPa, 160 °C). This result suggests that a catalyst derived from Re-**a** easily deprotonates the α-C–H moiety of these CAs, while the racemization may occur before or during the hydrogenation. Indeed, decreasing P_{H2} (1 → 0.1 MPa) under otherwise identical conditions resulted in the apparent full recovery of CA-**a**, i.e., a recovery most likely due to a very fast α-C–H deprotonation–protonation sequence. Likewise, replacing H_2 with D_2 [Re-**b** (2 mol%), $K[B(C_6H_5)_4]$ (10 mol%), P_{D2} = 0.1 MPa, 180 °C] did not introduce deuterium on the carbonyl carbons; instead, in the absence of a solvent, the α-CH_2 group of CA-**a** underwent fast H/D exchange to generate CA-**a**-d_n (n = 1, 2), whereby 98% of the α-CH_2 moieties of CA-**a** were deuterated (Fig. 4a, top). Using 0.4 mol% of Re-**b** and 2 mol% of $K[B(C_6H_5)_4]$ afforded a deuteration of 80%, while Re-**b** (2 mol%), $K[B(C_6H_5)_4]$ (10 mol%), or KOAc (10 mol%) on their own resulted in negligible deuteration (≤5%) of the C2 position of CA-**a** under otherwise identical conditions (Supplementary Table 11). Increasing the catalyst loading and D_2 pressure (P_{D2} = 1 MPa, 180 °C, 36 h, [Re-**b**]$_0$ = 5.0 mM in toluene) furnished AL-**a**-d_n (n = 3 and 4) in 99% yield (deuteration: C1 = 93%, C2 >93%) (Fig. 4a, middle). In comparison, a combination of $Ru^{II}_2Cl_2(\mu\text{-}Cl)_2(\mu\text{-}OH_2)(Ph_2P(CH_2)_4PPh_2)_2$ (2 mol%) and Na(acetylacetonate) (10 mol%), which is an effective catalyst system for CA hydrogenation (P_{H2} = 2–6 MPa, 160 °C)[18], resulted in 0% deuteration of CA-**a** under milder conditions (P_{D2} = 0.1 MPa, 180 °C). The hydrogenation of aldehyde AD-**a** (P_{D2} = 0.9 MPa) afforded AL-**a**-d_1 in quantitative yield, while C2 was not deuterated (Fig. 4a, bottom). Even with the much higher acidity of the α-C–H of aldehydes (pK_a = ~16 in H_2O) than that of carboxylates (pK_a 34–40 in DMSO), enolization of the aldehyde was prevented. Methyl 3-phenylpropionate underwent neither C2 deuteration nor hydrogenation (α-C–H of esters: pK_a = ~30 in DMSO), and full recovery of the ester was achieved under similar reaction conditions (P_{D2} = 0.9 MPa, 180 °C, 12 h).

Treating CA-**a** with acid anhydrides (AAs) in the presence of catalytic Re-**b** and KOAc, and in the absence of H_2 and a solvent, afforded unsymmetrical ketones (KEs) KE-**a–c** in acceptable yields (Fig. 4b; Supplementary Table 12). In the absence of Re-**b** under otherwise identical conditions, KE-**a** was obtained in substoichiometric amounts (24%) relative to KOAc (30 mol%). This result highlights an important advantage of the method presented herein over previously reported strategies to synthesize methyl or phenyl ketones based on MeLi or PhLi, followed by aqueous workup[45], or on $ArB(OH)_2$/AAs and Pd catalysts[26], which produce stoichiometric amounts of salts. The Dakin–West conditions (stoichiometric base in AA)[46] are useful mainly for the synthesis of methyl ketones from amino acids and α-arylacetic acids, but catalytic base only promote the catalytic formation of KE-**a** from CA-**a**[47]. In contrast, the present method opens a new route to the catalytic synthesis of KEs from two different CAs without generating any salt waste, albeit that one of the CAs must be converted to the AAs via dehydration before the reaction. Most likely, α-C–H deprotonation of CA-**a** and subsequent addition of the resulting enolate to the AA generates an intermediate β-ketoacid, which could undergo rapid decarboxylation to afford KE-**a–c**.

The deprotonation of the α-C–H moiety of CA-**a** with Re-**b** proceeds hence even in the absence of H_2. However, decarboxylation frequently occurs before the deprotonative functionalization of the α-C–H groups of CAs when using low-valent transition metal catalysts[24–27] or slightly basic reagents in buffered solutions[48]. For example, the intramolecular aldol cyclization of CA-**12** in AcOH using an excess of NaOAc (4.4 equiv relative to CA-**12**) exclusively promoted the decarboxylative dehydration (path *a*, Fig. 4c)[48]. The latter involves β-hydroxycarboxylic acid intermediate **I**, which generates FR-**12** upon elimination of the CO_2H group. In contrast, Re complexes induce a double α-C–H deprotonation via the following fast reaction sequence: 1) α-C–H deprotonation of CA-**12**, 2) enolate addition, and 3) α-C–H deprotonation of **I** (path *b*). Using multifunctional Re^{V} complexes, the formation of CA-**11a** prevails over that of FR-**12** (Fig. 4c). When catalytic Re-**b** or $Cl_3Re^{V}O(O=PPh_3)[(CH_3)_2S]$ was used individually with a catalytic amount of KOAc, CA-**11a**/FR-**12** were obtained in 33%/24% and 70%/18% yield, respectively. In this particular case, CA-**11a** was obtained in higher

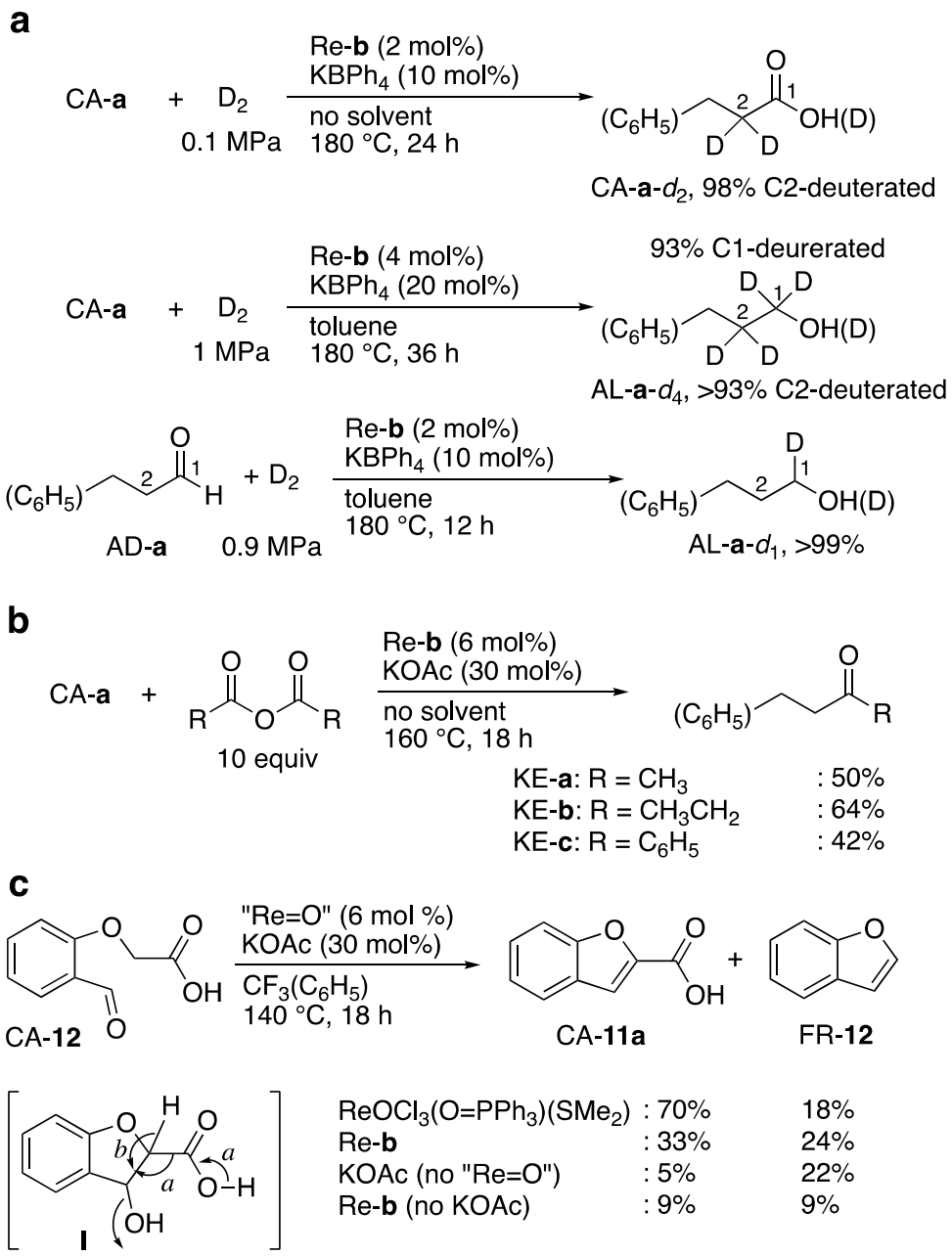


Figure 4. α-C–H functionalization of CAs. (**a**) C1- and/or C2-deuteration. (**b**) Intermolecular C–C bond formation in acid anhydrides to afford ketones. (**c**) Intramolecular aldol condensation. *a*: Decarboxylative dehydration; *b*: Second deprotonation followed by dehydration.

selectivity in the absence of a bidentate phosphine. $Cl_3Re^{V}O(O=PPh_3)[(CH_3)_2S]$ alone afforded CA-**11a**/FR-**12** in 2%/4% yield (Supplementary Table 13).

Discussion

To verify the potential involvement of high-valent Re species in the catalytic cycle, several control experiments were carried out using CA-**a** and CA-**11a**. Initially, solutions of the resting state of the catalysts, generated by the treatment of Re-**a** or Re-**b** with K[BPh_4] during the hydrogenation of CA-**a** (P_{H2} = 1.5 MPa, 180 °C), were prepared separately, and the samples were analyzed directly by electrospray ionization-mass spectrometry (ESI-MS) (Supplementary Figs. 1–3). In both cases, $[(PP)_2Re^{V}H_4]^+$, which does not contain the oxygen atom of the original Re = O group anymore (Fig. 5a), was detected as the major species [*m/z* Calcd: 987.2571, Found: 987.2578 for *PP* = dppe[49]; *m/z* Calcd: 1043.3198, Found: 1043.3170 for *PP* = (2*S*,3*S*)-bis(diphenylphosphino)butane (chiraphos)]. The ^{1}H NMR spectra in toluene-d_8 revealed signals for the four hydrides of $[(PP)_2Re^{V}H_4]^+$ derived from Re-**b** as a quintet (J_{P-H} = 19.8 Hz) at −4.98 ppm[49]. This result suggests that these four hydrides are magnetically equivalent, and that they are coupled to four magnetically equivalent phosphorus atoms. This conclusion

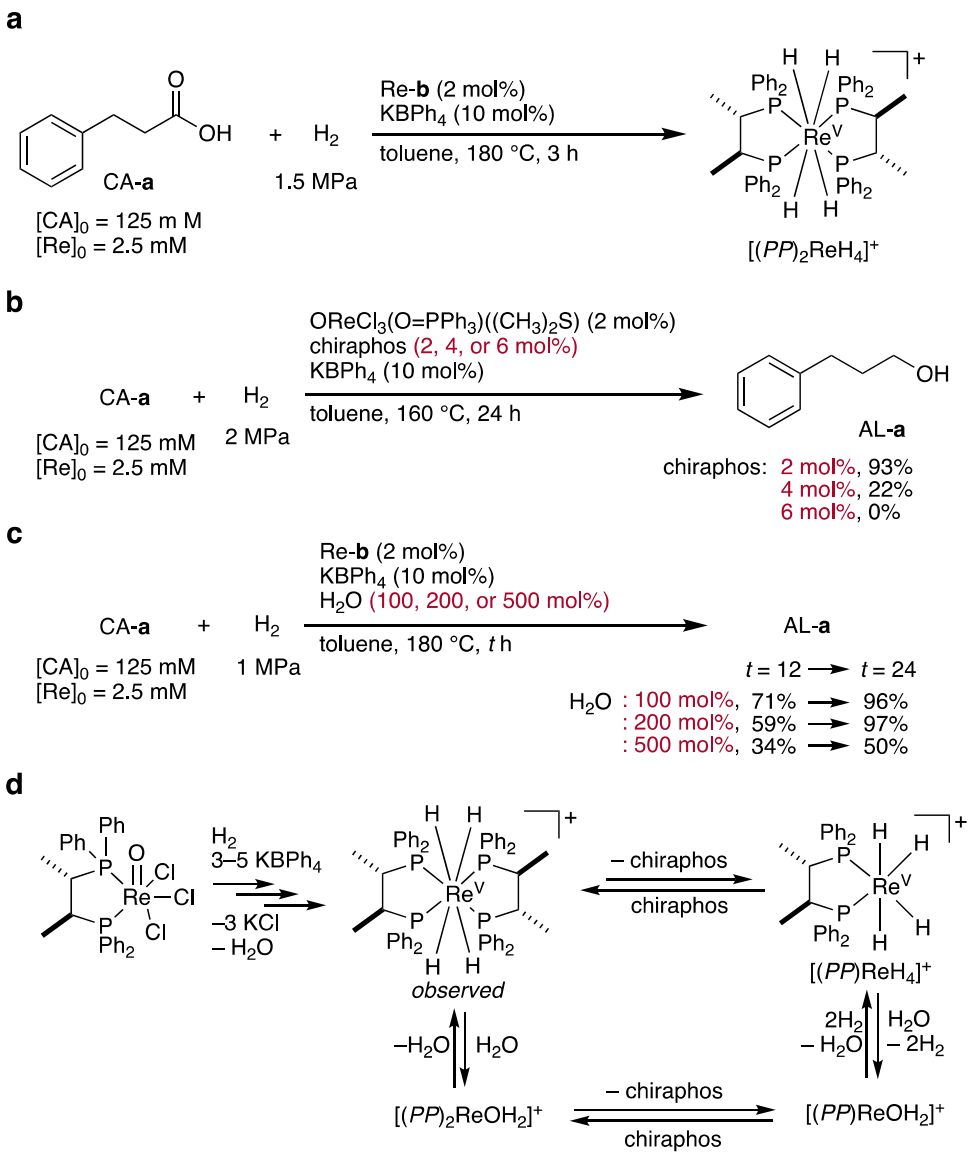


Figure 5. Control experiments to elucidate the structural change of Re-b in the presence of CA-a, H_2, and K[BPh]$_4$. (**a**) Predominant complex detected by ESI-MS: Re/(chiraphos)$_2$. (**b**) Effect of the quantity of chiraphos on the reaction rate. (**c**) Effect of the quantity of water on the reaction rate. (**d**) Proposed structural changes in the equilibria involving the catalytically most important species, [(*PP*)ReH$_4$]$^+$, upon reaction with H_2O, chiraphos, and H_2.

is supported by the presence of only one intensive, sharp $^{31}P\{^1H\}$ NMR singlet at 47.9 ppm. The structure should thus adopt C_2-symmetry, wherein the four hydrides should be located in more apical than equatorial positions on the Re center, as the latter should be occupied by the four phosphorus atoms[49]. In contrast, the ESI-MS spectrum obtained from the solution of Re-**a** exhibited a set of unknown signals. One of these signals could represent [(*PP*)$_2$Re^{II}(OCO(CH$_2$)$_2$Ph)]$^+$ (*m*/*z* Calcd: 1132.2872, Found: 1132.2894), which was not observed for the sample prepared from Re-**b**. This clearly suggests that Re-**b** is structurally more robust than Re-**a**, and consequently affords [(*PP*)$_2$Re^{V}H$_4$]$^+$ more efficiently.

K[BF$_4$] was ineffective in the hydrogenation of CA-**a** when combined with Re-**a** (Supplementary Table 2; entry 7: P_{H2} = 4 MPa, 150 °C, 24 h). Likewise, only a marginal amount of AL-**a** (2%) was obtained when Re-**b** and K[BF$_4$] were subjected to similar conditions ([Re-**b**]$_0$ = 2.5 mM; P_{H2} = 4 MPa, 150 °C, 24 h). Even at higher temperature (180 °C, 12 h, P_{H2} = 1.5 MPa), AL-**a** was produced in only 10% yield, which is substantially less effective than using K[BPh$_4$] (AL-**a**: 92%; ES-**a**: 3%; under otherwise identical conditions). The reaction mixture obtained at 180 °C showed non-negligible intensities of MS signals that are consistent with [(*PP*)$_2$Re^{IV}H$_2$Cl]$^+$ and [(*PP*)$_2$Re^{V}H$_3$Cl]$^+$ (*PP* = chiraphos; Supplementary Fig. 4), in addition to signals that were tentatively assigned to the resting state of the catalyst [(*PP*)$_2$Re^{V}H$_4$]$^+$. The former two structures should be of little relevance to the catalyst, considering that they are only produced in the presence of K[BF$_4$]. Similarly, [(*PP*)$_2$Re^{V}H$_4$]$^+$ should not be considered as a catalytically active species, but rather as a resting state of the catalyst or precatalyst. When the hydrogenation of

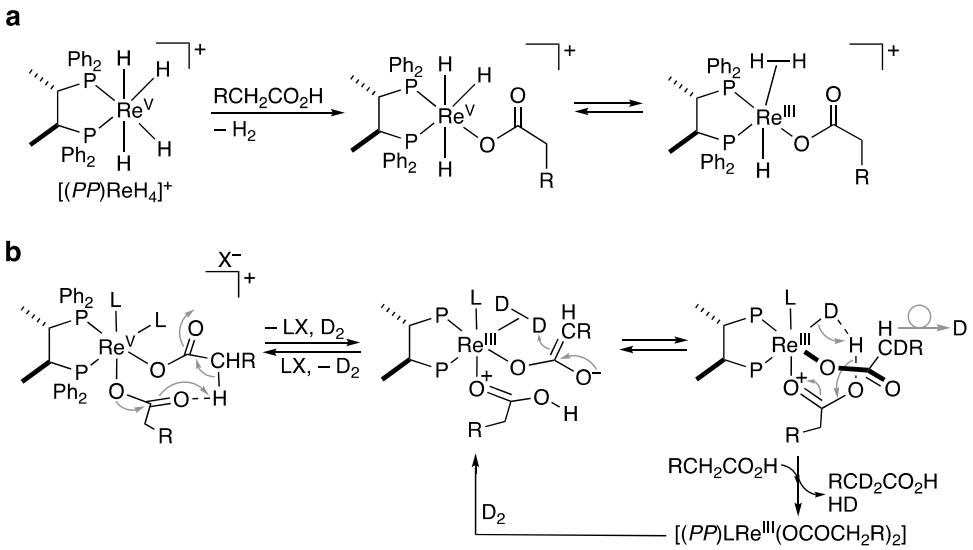


Figure 6. Proposed mechanism for the catalytic hydrogenation, and the deprotonation of α-C–H (R = $PhCH_2$ or alkyl). (**a**) Formation of $[(PP)ReH_3(OCOCH_2R)]^+$ for the "CA-self-induced hydrogenation of CA". (**b**) Initial deprotonation and subsequent iterative H–D exchange reactions of CA, which form the catalytic cycle (L and X = D, Cl, or RCH_2CO_2). The CA ($R'CO_2H$) and carboxylate ($R'CO_2^-$) (irrespective of how many deuterium atoms are incorporated at the α-position, i.e., α-*C*-d_0, α-*C*-d_1, or α-*C*-d_2) attached to a Re center could mutually interchange by intramolecular proton transfer $[(R'CO_2H)Re(OCOR') \leftrightarrows (R'CO_2)Re(HOCOR')]$ or intermolecularly exchange with free CA [e.g. $Re(OCOR') + RCH_2CO_2H \leftrightarrows Re(OCOCH_2R) + R'CO_2H$].

CA-**a** (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), chiraphos (4 or 6 mol%), and $K[BPh_4]$ (10 mol%), the yield of AL-**a** significantly decreased (22% and 0%, respectively) compared to that obtained from using 2 mol% of chiraphos (AL-**a**: 93%) (Fig. 5b; *cf*. Supplementary Tables 14 and 15). These results suggest that the most likely catalytically active species retains a 1:1 Re–chiraphos complexation, which could be readily generated by detachment of one chiraphos ligand from $[(PP)_2Re^VH_4]^+$.

Accordingly, Re-**b** should decompose slightly during the hydrogenation to form $[(PP)_2Re^VH_4]^+$ under concomitant release of chiraphos and the generation of phosphine-free Re species. Re black and/or Re nanoparticle are easily obtained from dehydrative reduction/decomposition of heterogeneous, high-valent Re-oxo species in the hydrogenation of CAs at 150–250 °C (P_{H2} = ~20 MPa)[50]. Therefore, a mercury test[51,52] was carried out, in which Hg(0) (338 mol%) was added during the hydrogenation of CA-**11a** with Re-**b** and KOAc (20 mol%) ($[Re\text{-}\mathbf{b}]_0$ = 5.0 mM in $PhCF_3$, P_{H2} = 6 MPa, 160 °C, 168 h) to examine a potential catalysis by Re nanoparticles. However, the addition of Hg did not affect the catalytic activity of the hydrogenation or the hydrogenolysis (AL-**11b**: 33%; AL-**11c**: 63%; *cf*. Fig. 3c).

When H_2O (100, 200, or 500 mol% with respect to CA-**a**) was added prior to starting the hydrogenation of CA-**a** with Re-**b**, the reaction rate for the formation of AL-**a** (99% after 12 h) observed in the absence of such a pre-addition of H_2O was considerably retarded (AL-**a**: 71%, 59%, and 34%, respectively). However, the integrity of the catalysis was sustained, and extending the reaction time to 24 h increased the yield of AL-**a** significantly (96%, 97%, and 50%, respectively) (Fig. 5c). 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 (Fig. 5d)[50,53]. All control experiments suggest that the mononuclear Re species $[(PP)Re^V(\eta^1\text{-}H)_4]^+$ represents an important precursor (albeit presumably outside the catalytic cycle) that subsequently affords the cationic mononuclear Re-carboxylate $[(PP)Re^V(\eta^1\text{-}H)_3(OCO(CH_2)_2Ph)]^+$ upon reaction with CA-**a** (Fig. 6a) in an initial critical point of the catalytic cycle. This interpretation is consistent with our previous observations, which identified the related cationic metal carboxylate $[(PP)Ru^{II}(OCO(CH_2)_2Ph)]^+$ as the key intermediate in a catalytic cycle involving the "CA-self-induced hydrogenation of CA"[18]. However, at this point, a catalytic involvement of $[(PP)Re^{III}(\eta^1\text{-}H)(\eta^2\text{-}H_2)(OCO(CH_2)_2Ph)]^+$ (Fig. 6a), which could also be derived from $[(PP)Re^{III}(\eta^1\text{-}H)_2]^+$ in the presence or absence of η^2-H_2 coordination, cannot be ruled out with certainty.

In contrast, a treatment of catalytic Re-**b** (6 mol%) with KOAc (30 mol%) and CA-**a** in the absence of H_2 in excess Ac_2O (160 °C, 4 h), which promotes the Dakin–West reaction, afforded a sample solution that showed ESI-MS signals consistent with $[(PP)Re^VCl(OCO(CH_2)_2Ph)_3]^+$ (*m*/*z* Calcd: 1095.2714, Found: 1095.2756), i.e., a dehydrated form of the corresponding Re = O species (Supplementary Fig. 5). A similar set of MS signals was observed by sampling a reaction mixture obtained from treating Re-**b** (0.4 mol%) with $K[BPh_4]$ (2 mol%), CA-**a**, and D_2 (0.1 MPa) at 180 °C for 18 h in the absence of solvent (Supplementary Fig. 6). Therein, the detected $[(PP)Re^VCl(OCO(CH_2)_2Ph)_3]^+$ should not be a catalytically active species for the H–D exchange, considering that deuterium was not incorporated in the three carboxylates. In sharp contrast, when Re-**a** was used instead of Re-**b** under otherwise identical conditions (P_{D2} = 0.1 MPa), $[(PP)Re^VCl(OCO(CH_2)_2Ph)_3]^+$ was not detected (*PP* = dppe), and the typical separation pattern of the MS signals corresponding to Re complexes was barely observed, which suggests ready decomposition of the Re complexes at 180 °C to Re black or

nanoparticles (Supplementary Fig. 7). In a similar fashion, the use of Re-**a** under comparable conditions (in the absence of H_2) in the Dakin–West reaction resulted only in a significant detachment of dppe from the Re center (Supplementary Fig. 8). Indeed, deuteration at the α-position of CA-**a** hardly proceeded (deuteration: ~3%) using Re-**a** at $P_{D2} = 0.1$ MPa, whereas at $P_{D2} = 1.0$ MPa ($[\text{Re-}\mathbf{a}]_0 = 5$ mM in toluene, 180 °C, 36 h), AL-**a**-d_{3-4} (>95%) was obtained as the major product (deuteration: C1 = 85%, C2 = ~92%). To summarize the behavior of Re-**a**: in the absence of H_2 or at low H_2 pressure (P_{H2} ~0.1 MPa), a 1:1 Re–dppe complexation in Re-**a** is rather unstable at 160–180 °C, while a good yield of $[(\text{dppe})_2\text{Re}^{\text{V}}\text{H}_4]^+$ is obtained at higher H_2 pressure (e.g. $P_{H2} = 1.0$ MPa). These experiments lead to the provisional conclusion that an H–D exchange reaction of CA-**a** should – at least partially – involve a "CA-self-induced deprotonation of CA" promoted by an intramolecular hydrogen transfer in $[(PP)\text{Re}^{\text{III}}\text{L}(\text{OCO}(\text{CH}_2)_2\text{Ph})_2]$ (Fig. 6b). However, a definite conclusion, excluding e.g. hitherto unobserved catalytically active species, should require further detailed experiments and analyses.

In conclusion, the use of $\text{Re}^{\text{V}}(=\text{O})$-diphosphine complexes provides a novel operationally simple concept for the selective activation and functionalization of $\text{CH}_n\text{CO}_2\text{H}$ groups ($n = 1$–3). This method combines an unprecedented substrate scope with outstanding functional group compatibility. Furthermore, sulfur components, i.e., poisons for conventional low-valent transition metal hydrogenation catalysts, do not affect the catalytic performance. High-valent transition metal complexes have traditionally been underestimated in the context of the hydrogenation of CAs, hydrogenolysis of alcohols, C–H bond functionalization, and hydrogenation of compounds with more reactive unsaturated bonds (e.g. C=C and C=O)[33]. Our results represent an important step toward the development of new catalyst systems for carbon[54] and hydrogen management[55], that allow the formation of asymmetric carbon–carbon bonds and hydrogenations using biomass-derived renewable feedstocks. Rhenium is one of the rarest elements in the Earth's crust, and a commercial price of Re source we used to synthesize different Re complexes is more expensive than, or comparable to, that of a Ru source, from which our previous Ru complexes were prepared[18], and is ca. one forth that of rhodium- and iridium sources used for CA hydrogenation[36]. Since $\text{Co}(\text{BF}_4)_2$ used by Elsevier/Bruin[19] is much economical, an effort to lower a Re load in hydrogenation is ongoing research in our laboratory.

Methods

Representative hydrogenation of CA-a with Re-b. 3-Phenylpropanoic acid (CA-**a**) (0.5 mmol, 75.0 mg), $KBPh_4$ (0.05 mmol, 17.9 mg), $ReOCl_3$[(*S*,*S*)-Chiraphos] (Re-**b**) (0.01 mmol, 7.3 mg) and a magnetic stirring bar, were placed in a dried glass tube that was inserted in an autoclave, which was purged with Ar gas several times. Anhydrous THF (4.0 mL) was added under a continuous flow of Ar, and the autoclave was purged five times with H_2 (1 MPa). The autoclave was pressurized with H_2 ($P_{H2} = 2$ MPa) at 25 °C and heated to 160 °C, where the mixture was stirred (500 rpm) for 24 h. Then, the autoclave was cooled to 0 °C, before the reaction mixture was transferred to a 100 mL round bottom flask containing $CHCl_3$. The mixture was concentrated (~30 mmHg, 40 °C), and the residue was dissolved in $CDCl_3$ and analyzed by ^{1}H NMR spectroscopy. Yields of 3-phenyl-1-propanol (AL-**a**) (93%) and 1-(3-phenylpropyl)-3-phenylpropanoate (ES-**a**) (~1%) were calculated based on the integration ratio of their signals relative to the internal standard mesitylene and by GC-MS analysis, respectively.

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Author Contributions

M.N. majorly led and conducted the experiments and compound characterization for CA hydrogenation, and α-C–H bond functionalization of CAs using Re complexes; S.A. and M.N. equally contributed except that S.A. made the initial discovery of CA hydrogenation using Re complexes and conducted the initial parts of CA hydrogenation experiments; and K.T. improved the CA hydrogenation experiments using Re-**b**. S.S. directed the project and wrote the manuscript.

Additional Information

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