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Catalytic Reductive Transformations of Carboxylic and Carbonic Acid Derivatives Using Molecular Hydrogen

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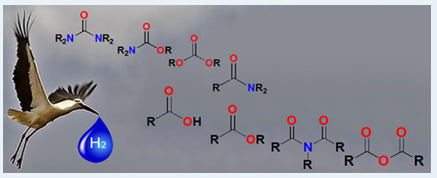
ABSTRACT: A comprehensive overview on homogeneous catalytic hydrogenation of carboxylic acids and its derivatives as well as carbonic acid derivatives with transition metal-based molecular catalysts is described. Despite the tremendous potential in the hydrogenation of these less electrophilic carbonyl compounds using molecular hydrogen in synthetic organic chemistry, their reduction still relies mostly on the stoichiometric use of metal hydride reagents, such as $LiAlH_4$, $NaBH_4$, and their derivatives. For the past decade, a significant and rapid progress in particularly ester hydrogenation has been achieved by utilization of conceptually new bifunctional molecular catalysts originating from the metal−ligand cooperation effects. The bifunctional-catalyst-promoted hydrogenation using molecular hydrogen is now realized to be a practical tool in synthetic organic chemistry in both academia and industry. The industrial outlook for the present hydrogenation is bright because of its operational simplicity, scope, economic viability, and growing awareness of the need for green chemistry.



KEYWORDS: *ester hydrogenation, carboxylic acid derivatives hydrogenation, carbonic acid derivatives hydrogenation, bifunctional catalysis, homogeneous hydrogenation*

1. INTRODUCTION

Molecular hydrogen (H_2), the most atom-efficient reducing chemical agent, is a component of the largest-volume human-made chemical reactions, hydrogenation of organic compounds.[1−3] Reduction of functional groups with molecular hydrogen is one of the fundamental reactions in organic chemistry.[4] In particular, enantioselective reduction of prochiral compounds using chiral molecular catalysts,[5−7] is now realized to be a powerful and practical tool for the development of successful processes in the field of fine chemicals, chiral drugs, and perfumes as well as optical materials.[8,9]

Significant progress in the field of selective hydrogenation of C═O double bonds of ketones and aldehydes with both chiral and achiral catalysts has been made in the branch of homogeneous transition metal-based molecular catalysis.[6,10−20] Until now, however, there has been little progress in the hydrogenation of polar organic functionalities bearing less electrophilic carbonyl groups, such as carboxylic acids and their derivatives as well as carbonic acid derivatives (Scheme 1), despite its tremendous potential for synthetic organic chemistry. The homogeneous reduction of carboxylic acid derivatives still relies mostly on the stoichiometric use of metal hydride reagents, such as $LiAlH_4$, $NaBH_4$, and their derivatives.[21,22] Therefore, much effort should be directed to explore effective catalytic hydrogenations, which may positively contribute to the concept of green chemistry through the development of environmentally benign processes.

The present Review represents a comprehensive overview on homogeneous transition metal-based catalytic reductive transformations with molecular hydrogen of carboxylic acids and its derivatives as well as carbonic acid derivatives (carbonates, carbamates, ureas), in which the carbon−heteroatom bonds are converted into carbon−hydrogen single bonds. The overall process could be viewed as hydrogenation, hydrogenolysis, or both, the former being the transformation of C═O double bonds into the C(H)−O(H) single bonds and the latter being the breaking of the C−X (X = N, O, S) single bonds with molecular hydrogen. Catalytic hydrogenation of some carboxylic acid derivatives based on Ru-mediated heterolytic dihydrogen cleavage was reviewed by us in 2007[23] or by others for different transition metals in a book chapter,[24] and selective reduction of carboxylic acid derivatives by catalytic hydrosilylation was recently reviewed.[25] In the present Review, the hydrogenation of carboxylic acid derivatives containing C═O double bonds will be viewed in the order[26] of the approximately expected decrease of the C═O bond electrophilicity as presented in Scheme 1, although this parameter does not necessary correlate with a reactivity.

Although reduction of alkenes, alkynes, aldehydes, or ketones over the heterogeneous catalysts is known to be usually facile, the heterogeneous hydrogenation of esters or carboxamides still demands more drastic reaction conditions.[4] Addressing the reaction chemistry of heterogeneous catalytic hydrogenation of polar functionalities is beyond our scope. Catalytic hydrogenolysis of esters to alcohols focusing mostly on heterogeneous systems was partially reviewed over 18 years ago.[27]

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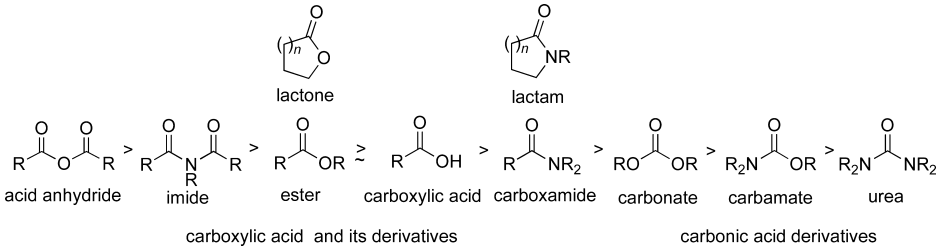
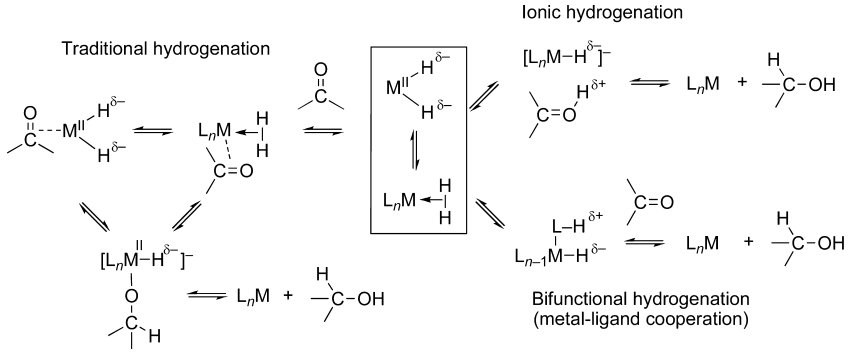
Scheme 1. Carboxylic Acids and Their Derivatives As Well As Carbonic Acid Derivatives Containing C═O Double Bonds, Objects of the Catalytic Hydrogenation Using Molecular Hydrogen, Placed with Approximately Expected Decrease of C═O Electrophilicity



Scheme 2. Types of Cleavage of Molecular Hydrogen on Transition Metal Complexes and Types of Hydrogen Transfer from the Hydride Complexes to C═O Bonds



2. MOLECULAR HYDROGEN ACTIVATION ON TRANSITION METAL COMPLEXES

In the catalytic cycles of the hydrogenation, molecular hydrogen usually primarily interacts with a metal center of the transition metal complexes by coordination at a vacant coordination site or by a substitution of a weak ligand including a solvent molecule to generate a η^2-dihydrogen complex.[1,28−31] A near continuum of H−H bond distance (d_{HH}) exists for the dihydrogen complexes ranging from 0.8 to 1.6 Å determined by X-ray crystallography and NMR analyses. Along this continuum, three categories of complexes, each with distinct properties, are classified: the true dihydrogen complexes (0.8−1.0 Å), elongated H_2 complexes (1.0−1.3 Å), and compressed dihydrides (1.3−1.6 Å).[1] These are relative terms, since the H−H bond is always stretched on binding to the central metal. In addition, two small hydrogen atoms form the smallest molecule, which is highly fluxional in solution.

The coordination of molecular hydrogen to transition metals is known to increase its acidity.[32−38] Free H_2 is an extremely weak acid with a pK_a estimated to be 49 in THF,[1] but when H_2 is bound to a highly electrophilic cationic metal, the acidity of the H_2 molecule in the resulting dihydrogen complex increases at least up to 41 orders of magnitude, reaching a pK_a value as low as 7.8[34] in THF (cf. 7.8 for triflic acid[39]). In addition, the dihydrogen complexes are substantially more acidic (kinetic acidity) than most of the "classical" hydrido complexes of transition metals.[37]

The fundamentally important activation of H_2 toward splitting to give the dihydride complex via oxidative addition is sensitive to the electron density on the metal, nature of the ligands, and solvent used for the reaction.[1,40] Dihydrogen-, monohydride, and di(poly)hydride complexes obtained by the coordination, by homo- or heterolytic cleavage of molecular hydrogen on transition metal complexes (or both) have been recognized as active catalysts or intermediates in catalytic cycles, as shown in Scheme 2. Homolytic dihydrogen cleavage changes the oxidation state of a metal by 2 via the oxidative addition to generate the classical di(poly)hydride complex or the monohydride alkyloxy complex. The hydrogenation with traditional catalysts always proceeds via this pathway, and thus, the catalyst requires at least one vacant site for binding of a reacting substrate (for example, a ketone), followed by insertion into a M−H bond and subsequent reductive elimination step.[28,41]

Contrary to traditional hydrogenation, the ionic hydrogenation of ketones occurs by a proton transfer to a ketone without its preliminary coordination (i.e., in the outer coordination sphere) from a typically cationic dihydrogen complex or a metal dihydride followed by a hydride transfer from a neutral metal hydride.[41] It will not necessarily make a big difference whether a dihydride or a dihydrogen complex or an equilibrium mixture of these two complexes is the proton donor, as long as this species is sufficiently acidic.[41] On the other hand, heterolytic dihydrogen cleavage with the transition metal complexes that does not change the coordination number or the oxidation state of the central metal produces formally a "hydride" on the metal center and a "proton" on the ligand attached to the metal, which is the case of bifunctional (metal−ligand cooperation) hydrogenation.[42,43] The heterolytic H_2 cleavage is a key step in the catalytic hydrogenation of ketones and aldehydes as well as C═C double bonds.

In the mid 1960s, Wilkinson and co-workers clearly demonstrated heterolytic H_2 cleavage by a reaction of $RuCl_2(PPh_3)_3$ with H_2 in the presence of ethanol, leading to a hydride complex, $RuHCl(PPh_3)_3$ and HCl, in which ethanol[44] or triethylamine[45] in benzene solution act as a base. In 1987 and 1991, Fryzuk and co-workers found that a 16-electron amido Ir and Rh complexes bearing PNP tridentate ligand (κ^3-

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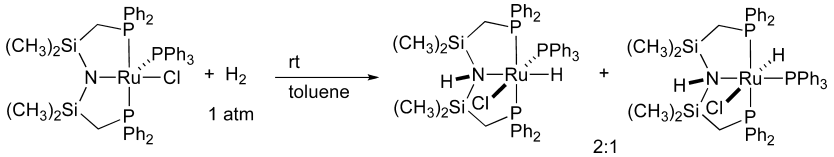
Scheme 3. Heterolytic H_2 Cleavage by a Fryzuk's Ru Amide Complex[47]



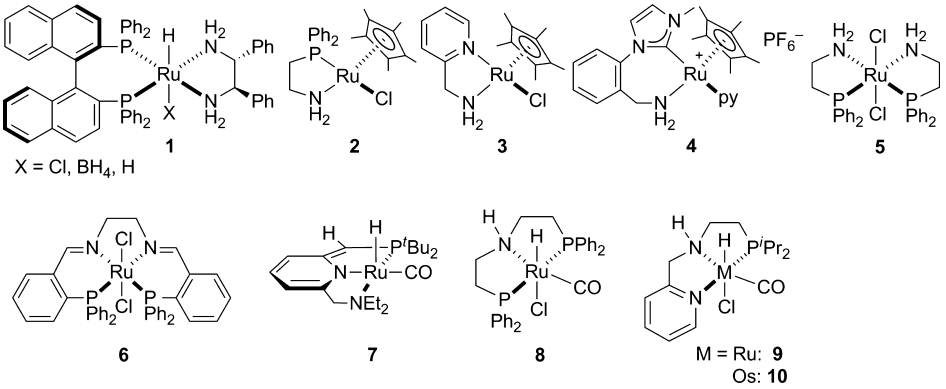


Figure 1. Examples of selected bifunctional molecular catalysts or precatalysts for homogeneous hydrogenation of esters, lactones, carboxamides and lactams.

P,N,P-N(Si(CH$_3$)$_2$CH$_2$PPh$_2$)$_2$[46] and an analogous Ru complex[47] promote the heterolytic cleavage of H_2 at room temperature to give an 18-electron hydride amine complex in aprotic media under atmospheric H_2, in which the amido ligand acts as a base for a H^+ acceptor, as shown in Scheme 3.

This Fryzuk's finding of the activation of hydrogen with metal amide complexes inspired intensive efforts to develop conceptually new bifunctional molecular catalysts based on the metal−ligand cooperation effects for hydrogenation of polar functionalities, including ketones, aldehydes, and imines. In fact, many powerful bifunctional catalysts have been developed for practical hydrogenation of polar functionalities in which the bifunctional nature based on the metal−ligand cooperation effect is crucial to activate both molecular hydrogen and polarized functionalities, C═O and C═N double bonds in the hydrogenation processes.

In particular, recent rapid progrees in the hydrogenation of esters and lactones has highly relied on conceptually new bifunctional molecular catalysts originating from the metal/NH acid−base synergy effect (Noyori, Ikariya, Morris, and others)[42] or aromatization−dearomatization concept (Shvo, Bäckvall, Casey, Milstein, and others).[42] Under relatively mild conditions, the hydrogen molecule can be readily activated and transferred to polarized functionalities, including C═O and C═N double bonds via a hydride intermediate complex. Chiral bifunctional catalyst-promoted stereoselective hydrogenation of C═O and C═N double bonds of ketones and imines is now realized to be a powerful tool to access chiral alcohols and amines in organic synthetic procedures in both academia and industry.[6]

Figure 1 shows conceptually new bifunctional molecular catalysts originally developed for hydrogenation of simple ketones, aldehydes, and imines, which are now applicable to hydrogenation of esters, lactones, carboxamides, and lactams. For example, bifunctional Ru-BINAP catalyst RuHX(binap)(diamine) (X: Cl, BH_4, H) **1** and Cp*Ru precatalysts Cp*RuCl[(κ^2-L,*N*-L(CH$_2$)$_2$NH$_2$] (*L* = P(C$_6$H$_5$)$_2$, NR$_2$, 2-py) **2** and **3** as well as [Cp*Ru(C−N)py]PF$_6$ (C−N: 1-(2-aminomethylphenyl)-3-methylimidazol-2-ylidene) **4** in the presence of a base effect the hydrogenation of imides, esters, and some carboxamides. Complex **5** bearing two 2-diphenylphosphinoethylamine (P−N) ligands (P−N: (C$_6$H$_5$)$_2$P(CH$_2$)$_2$NH$_2$) or complex **6** bearing PNNP ligand in combination with the base serve as efficient catalysts for ester hydrogenation (vide infra). A particular note is the pincer-type catalyst **7** operative based on the Milstein's aromatization−dearomatization bifunctional concept as well as pincer precatalysts **8**−**10** operative based on the Noyori−Ikariya M/NH bifunctional effect exhibit excellent catalytic performance in the hydrogenation of esters and carboxamides as well as organic carbonates and carbamates to methanol in reasonably good yields.

Catalytic performance of the bifunctional catalysts in the hydrogenation of polar functionalities is the consequence of the compromise between the steric and electronic effects of the chelating amine ligands, pincer-type tridentate ligands, and others. For example, Ikariya's group demonstrated the importance of ligand modification for the hydrogenation of polar functionalities. The newly developed half-sandwich-type bifunctional precatalysts, Cp*RuCl(P−N), **2**, combined with a base efficiently promote hydrogenation of imides and epoxides in addition to ketones, whereas Cp*RuCl(N−N) precatalyst (N−N: (CH$_3$)$_2$N(CH$_2$)$_2$NH$_2$], **3**, is effective for ketone reductions but not for imide reactions. The difference in their reactivity may be attributed to the delicate balance of the electronic factors of the tertiary amino and phosphino groups in the possible active amine hydride species, Cp*RuH[κ^2−L,*N*−L(CH$_2$)$_2$NH$_2$] (L = P(C$_6$H$_5$)$_2$ and N(CH$_3$)$_2$). In the hydrogen transfer from the amine hydrido Ru complex to ketones, the acidic amine proton and the metal hydride cooperatively activate the reactant and are transferred to C═O double bonds via a bifunctional mechanism (outer sphere mechanism). The electron-withdrawing nature of the phosphorus atom increases the Lewis acidity of the NH$_2$ proton to facilitate hydrogen transfer to polar functionalities. Similarly, the ligand modification of the pincer-type tridentate Ru bifunctional catalysts

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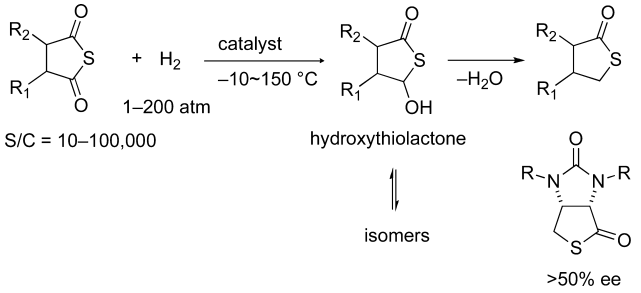
7−9 is also crucially important to determine the catalytic performance in terms of reactivity and selectivity in the hydrogenation of esters and carboxamides (vide infra).

2.1. Hydrogenation of Cyclic Thioanhydrides. Thioesters and thiolactones are useful synthetic intermediates that have been used, for example, as acylating reagents, building blocks for heterocyclic compounds, and precursors of acyl radicals and anions in asymmetric aldol reactions.[48,49] Among the reported synthetic procedures,[49] organic thioesters could be potentially obtained via catalytic hydrogenation of thioanhydrides that are easily available from commercial anhydrides and sodium sulfide.[50] In particular, the practical interest could be viewed for selective hydrogenation of cyclic thioanhydrides to produce thiolactones. Despite the potential advantages, however, relatively limited data are available for the hydrogenation of these compounds, even using stoichiometric reagents.[51,52]

In a 2006 patent,[53] Bonrath and co-workers from DSM Nutritional Products disclosed the catalytic hydrogenation together with transfer hydrogenation of cyclic thioanhydrides, 2,5-thiophenedione derivatives, which produced chemoselectively thiolactones or hydroxythiolactones, their isomeric products, or both, as shown in Scheme 4. For the homogeneously catalyzed reactions, the active catalysts based on Ru, Rh, and Ir complexes generated in situ by mixing suitable commercially available precursors with the 2 equiv of monodentate phosphine or 1 equiv of diphosphine ligand(s) can be used. Asymmetric hydrogenation with chiral catalysts bearing chiral atropisomeric diphosphine ligands gave chiral thiolactones in limited yields and with moderate enantiomeric excess, up to 50% ee, as shown in Scheme 4.[54] Further reductions of the obtained thiolactones with the employed catalytic systems[53] did not proceed at all.

Scheme 4. Chemo- and Stereoselective Catalytic Hydrogenation of the Cyclic Thioanhydrides[53]

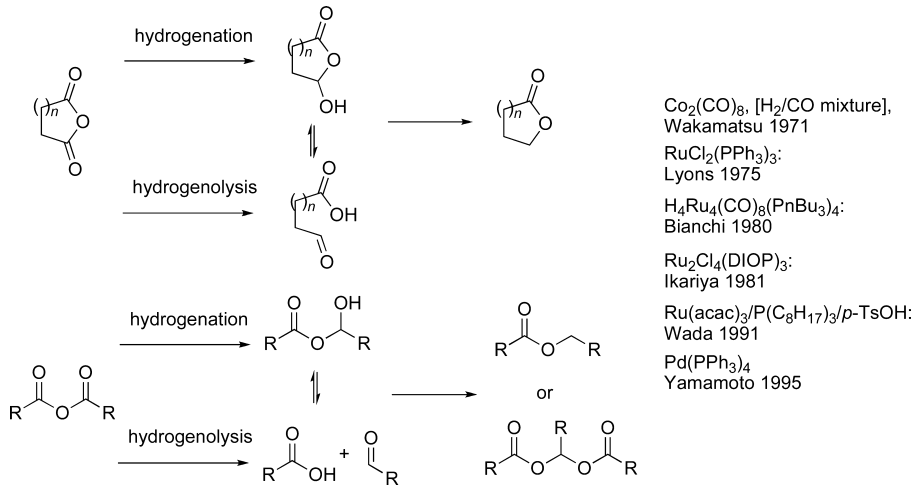


2.2. Hydrogenation of Cyclic and Acyclic Carboxylic Acid Anhydrides. Selective reduction of cyclic anhydrides to lactones represents considerable potential for synthetic applications. In particular, catalytic enantioselective hydrogenation via desymmetrization of cyclic *meso*-anhydrides can be a powerful synthetic tool to produce chiral products as an alternative to stoichiometric reductions.[55] In view of their chemical nature, the hydrogenation reactions of anhydrides should be performed directly in neat anhydrides or in dry aprotic solvents (THF, dioxane, toluene). Reductions of several cyclic anhydrides by sodium borohydride[56] or lithium borohydride[57] have been reported usually to produce lactones.

Catalytic homogeneous hydrogenation of carboxylic acid anhydrides could follow two general pathways, depending on the metal and, notably, its oxidation state: formation of aldehydic acids from cyclic substrates or a mixture of aldehydes and acids from acyclic substrates by typically using Co^0 or Pd^0 catalysts and formation of lactones or esters, typically with Ru^{II} catalysts from cyclic and acyclic substrates, respectively, as shown in Scheme 5.

The details of the reduction could be viewed through pathways including hydrogenation or hydrogenolysis steps (or both), as outlined in Scheme 5. For example, in the reduction of cyclic acid anhydrides, formation of aldehydic acid could be viewed via hydrogenolysis of the C−O single bond or alternatively, via hydrogenation of the C═O double bond to produce the hydroxylactone, which is in tautomeric equilibrium with the corresponding aldehydic acid.[58] A mixture of the aldehydes and acids could be obtained via the formal hydrogenolysis of the C−O single bond of acyclic acid anhydrides or, alternatively, via unstable hydroxyester intermediates generated from the hydrogenation of the starting compound. Drent disclosed in a patent that the hydrogenation of a carboxylic acid anhydride in the presence of a homogeneous catalyst gave a 1:1 mixture of an acid and an alkylidene dicarboxylate, which is possibly derived from the

Scheme 5. Typical Examples of Chemoselectivity in the Hydrogenation of Cyclic and Acyclic Anhydrides with the Catalytic Systems



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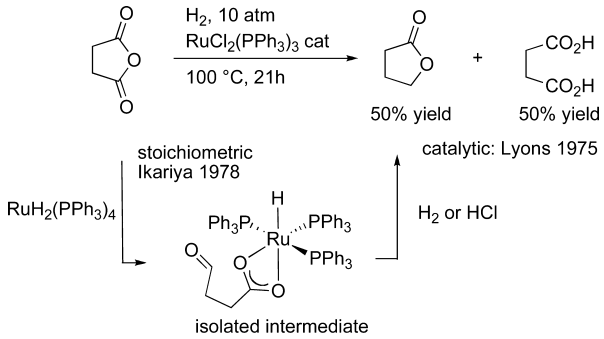
reaction of hydroxyester intermediate with the corresponding aldehyde.[59] The subsequent formal dehydration provides lactone or ester. Notably, the resulting water hydrolyzes the starting acid anhydride into the corresponding acid. Thus, depending on the rates of the hydrolysis and the hydrogenation/hydrogenolysis, the composition of products is varriable (vide infra).

It has been known since 1960s that when CO/H_2 mixtures are used, cobalt octacarbonyl catalyzes the reduction of phthalic[60] and succinic anhydrides[61] or some acyclic anhydrides[61] to produce aldehydic acids or a mixture of aldehydes and acids, respectively. Later, Yamamoto and co-workers reported that the hydrogenation of acyclic carboxylic acid anhydrides with S/C = 100 in the presence of $Pd(PPh_3)_4$ as the catalyst under 30 atm of H_2 pressure at 80 °C produced aldehydes and acids in 24−99% yield, depending on the reaction conditions,[62,63] in which oxidative addition of cyclic and acyclic anhydrides to the Pd^0 is a key step of the catalytic reaction.

Ikariya demonstrated in 1978 that a stoichiometric reaction of $Ru(H)_2(PPh_3)_4$ with succinic anhydride gave an octahedral complex, $RuH(PPh_3)_3[CH(O)(CH_2)_2CO_2]$,[64] which is a possible intermediate in the $RuCl_2(PPh_3)_3$-catalyzed chemoselective hydrogenation of cyclic anhydrides into lactones originally reported by Lyons in 1975,[65,66] as shown in Scheme 6. After treatment of the intermediate with H_2 or HCl, γ-butyrolactone and water are liberated.

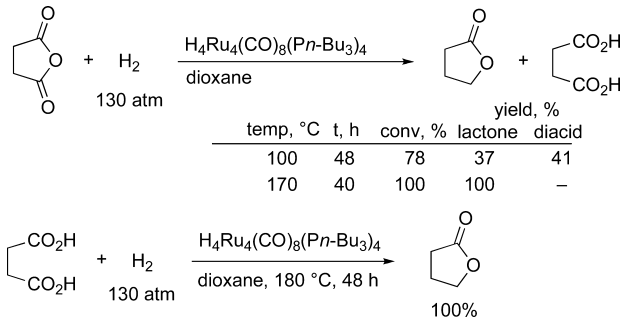
Scheme 6. Isolation of the Intermediate in the $RuCl_2(PPh_3)_3$-Catalyzed Hydrogenation of Succinic Anhydride



Marked improvement in the hydrogenation of carboxylic acid anhydrides with $RuCl_2(PPh_3)_3$ catalyst by the addition of $SnCl_2$ was observed in a patent application.[67] The catalytic activity of Lyons's system,[66] as well as related catalyst systems, $Ru_2Cl_4(diop)_3$,[68] $Ru_2Cl_4(PPh_2(CH_2)_4PPh_2)_3$,[69] $RuCl_2(ttp)$,[69] and ternary $Ru(acac)_3/P(n\text{-}C_8H_{17})_3/p\text{-}TsOH$,[70] was not high enough, even at over 100 °C, probably because of hydrolysis of the product lactones to free acid with water liberated during the reaction. In fact, free carboxylic acids were directly observed among the products of the catalytic reactions.[66] Wada and co-workers from Mitsubishi Kasei Corp. demonstrated that the catalytic activity of the catalyst, $Ru(acac)_3/P(n\text{-}C_8H_{17})_3$ outlined in Scheme 5 could be greatly improved (S/C = 800) by the addition of a catalytic amount of external acids such as *p*-TsOH.[70]

Piacenti and co-workers demonstrated[71] that succinic anhydride was effectively hydrogenated to the lactone in almost quantitative yield under high temperature and pressure conditions using cluster carbonyl hydride catalyst $H_4Ru_4(CO)_8(Pn\text{-}Bu_3)_4$, as shown in Scheme 7. Separate experiments showed that the byproduct acid was also effectively

Scheme 7. Hydrogenation of Succinic Anhydride and Succinic Acid in the Presence of $H_4Ru_4(CO)_8(Pn\text{-}Bu_3)_4$[71]



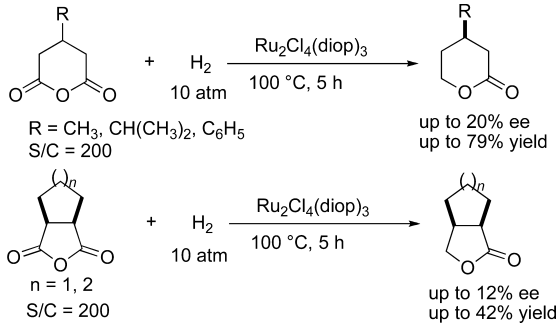
hydrogenated into lactone or ester (vide infra, section Hydrogenation of Carboxylic Acids), albeit under forced conditions (Scheme 7). Thus, acid anhydrides could be converted into corresponding lactones or esters at higher temperatures or using different catalytic systems. Note that direct hydrogenation of mixtures of acids and aldehydes into esters is described using heterogeneous catalytic systems.[72] Such processes were formulated as important in stabilizing the corrosive and reactive components in the bio-oil.[73]

When unsymmetrically substituted cyclic anhydrides are used, regioselectivity in the hydrogenation is different from those typically observed in the stoichiometric metal hydride reagents. For example, the stoichiometric reduction of unsymmetrical cyclic anhydride using $NaBH_4$ or $LiAlH_4$ usually occurs at the more hindered carbonyl group to give the corresponding γ-lactones.[74,75] However, hydrogenation catalysts $RuCl_2(PPh_3)_3$[76] or $Ru_2Cl_4(dppb)_3$[69] or $RuCl_2(ttp)$[69] reduced regioselectively the less hindered carbonyl group of the anhydrides to produce the corresponding lactones.

Ikariya and Yoshikawa reported in early 1980s the first example of catalytic asymmetric hydrogenation of prochiral or cyclic *meso*-anhydrides to chiral lactones using chiral Ru catalyst, $Ru_2Cl_4(diop)_3$, in which the chiral catalyst can discriminate one of the enantiotopic groups in these substrates.[68] As shown in in Scheme 8, chiral lactones with up to 20% ee were obtained.

Twenty-five years later, an appealing example of enantioselective hydrogenation of cyclic *meso*-anhydrides to chiral

Scheme 8. First Examples of Enantioselective Hydrogenation of Prochiral and Cyclic *meso*-Anhydrides, DIOP = 2,3-O-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane[68]



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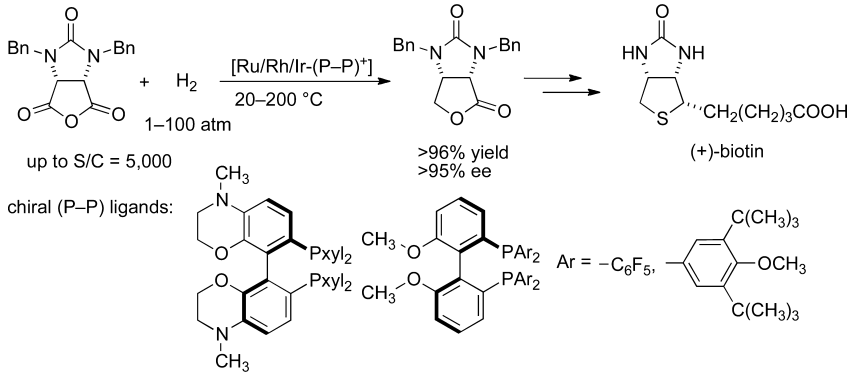
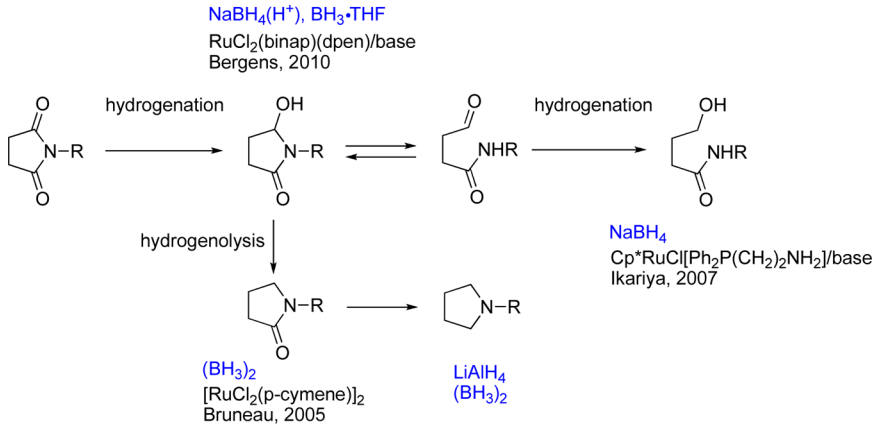
Scheme 9. Asymmetric Hydrogenation of the Cyclic *meso*-Anhydride into D-Lactone Catalyzed by Chiral Ru, Rh, or Ir Complexes[54,77,78]



Scheme 10. Chemoselectivity in the Reduction of Cyclic Imides with Alumo- or Borohydride Reagents or the Transition Metal-Based Catalytic Systems



lactones was demonstrated by DSM Nutritional Products' group.[54,77,78] As shown in Scheme 9, chiral Ru, Rh, or Ir complexes bearing atropisomeric diphosphine ligands effected the asymmetric hydrogenation to give the chiral lactone in almost quantitative yields and with excellent enantiomeric excess. The resulting *N*-benzyl-protected chiral lactone can be used as a key building block in the industrial synthesis of (+)-biotin.[54]

Thus, homogeneous catalytic enantioselective hydrogenation of the *meso*-anhydrides catalyzed by chiral molecular catalysts is now applicable to the synthesis of a variety of lactones that are suitable intermediates in the fine chemicals area.[79] On the other hand, no successful results have yet been obtained in the enantioselective hydrogenation of prochiral cyclic anhydrides. The chiral product with up to 51% ee is reported in a patent.[79] Recently, using chiral Ru catalysts bearing chiral bidentate ligands under conditions described in Lyons's report (vide supra),[66] Kitamura reported highly chemoselective formation of the D-lactone relevant for biotin production (S/C = 2000), however, with a moderate enantiomeric excess, although in almost quantitative yield.[80]

2.3. Hydrogenation of Imides and Related Compounds. Imides derived from carboxylic acids are structurally related to acid anhydrides, although in general, they are less reactive.[26] Among the imides, prochiral cyclic imides such as 4-substitued glutarimides and cyclic *meso*-imides, such as 3,4-disubstituted succinimides, represent an interesting and useful class of starting compounds in asymmetric synthesis. Hydrogenation of cyclic imides with achiral catalysts is also a useful method for the preparation of lactams or carboxamide alcohols.

Carbonyl-selective reductions of *N*-substituted cyclic imides mostly rely on the stoichiometric amount of metal hydride reagents in organic synthesis. In particular, the reaction pathways are mainly dependent on the kind of metal hydride compounds. For example, in the reduction of cyclic imides with $NaBH_4$, hydroxylactam or carboxamide alcohol or its mixture could be obtained, as shown in Scheme 10.[81−86] Chiral hydroxylactone was obtainable using BH_3·THF in the presence of 0.5 equiv of chiral oxazaborolidines.[87,88] B_2H_6 reduction of 3,3-substitued succinimides gives regiospecifically a mixture of the corresponding lactams and cyclic amines.[89] $LiAlH_4$ reduction[90,91] provides cyclic amine as a major product. In contrast to the stoichiometric reduction, catalytic hydrogenation of an imide produces a lactam or a hydroxylactam under relatively mild conditions, as shown in Scheme 10. Under forced conditions, an aldehydic carboxamide that exsits in a tautomeric equilibrium mixture with the preferred hydroxylactam[84] presumably undergoes hydrogenation to the carboxamide alcohol.

N-Methylsuccinimide was converted into 2-pyrrolidinone in moderate yield, 28%, at 100 °C under 8 atm of H_2 in water containing water-soluble Ru catalysts, $RuCl_3·3H_2O$, $[RuCl_2(dmso)_4]$, or $[Ru(dmp)(H_2O)_2](PF_6)_2$ (dmp = 2,9-dimethylphenanthroline).[92] Later, Bruneau, Dixneuf, and co-workers demonstrated in 2005 that $[Ru_4H_6(p\text{-cymene})_4]Cl_2$ or $[RuCl_2(p\text{-cymene})]_2$ are efficient catalyst precursors for the

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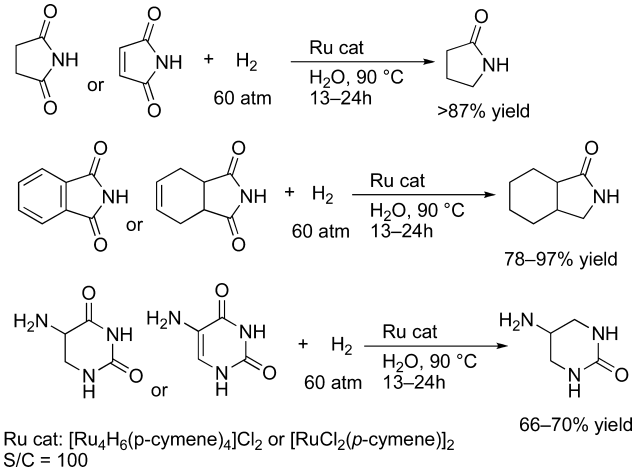
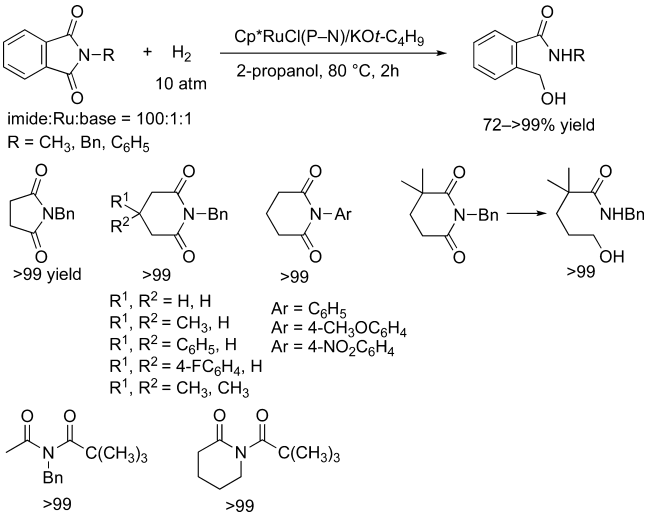
selective transformation of cyclic imides into saturated lactams in water. The product lactams were isolated in up to 97% yields, as shown in Scheme 11;[93] however, these catalysts also hydrogenate the C═C double bonds in the same molecules.

Scheme 11. Chemoselective Hydrogenation of Imides Catalyzed by Ru Complexes[93]



Ikariya and co-workers found that a variety of imides are chemoselectively reducible to the corresponding alcohols and carboxamides in 2-propanol containing bifunctional Ru precatalyst, Cp*RuCl(P−N) **2**, and the base KO*t*-C_4H_9 as the catalytic system under mild conditions, as shown in Scheme 12.[94] The structural modification of chelating amine ligands is

Scheme 12. Chemoselective Hydrogenation of Imides Catalyzed by Bifunctional Cp*RuCl(P−N) 2/Base Catalyst[94]

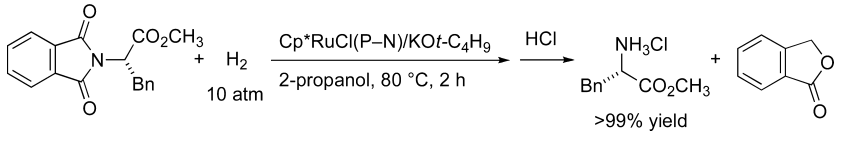


crucial to determine the catalytic performance, as discussed previously. In contrast to the P−N ligand, analogous Cp*RuCl-[κ^2-*N*,*N*-$(CH_3)_2N(CH_2)_2NH_2$)] catalyst **3** exhibits no catalytic activity toward the imide hydrogenation. The difference in their reactivity can be explained by the electronic factor of tertiary amino and phosphino group in the ligands. The Brønsted acidity of the NH_2 group in the possibly active species, Cp*RuH[κ^2-L,*N*-$L(CH_2)_2NH_2$] (L = NMe_2 or PPh_2) is responsible for the range of reducible polar bonds (vide supra). Another notable feature is that the tertiary amine variant $(C_6H_5)_2P(CH_2)_2N(CH_3)_2$ as the ligand is completely ineffective, presenting strongly the crucial importance of the NH group in the ligand for the M/NH bifunctional activation of the carbonyl compounds. The present hydrogenation method is characterized by its excellent chemoselectivity and a wide substrate scope as well as controllable steroselectivity with chiral catalysts under neutral conditions. In particular, the product distribution in a case of unsymmetrically substituted imides was delicately influenced by steric and electronic factors of the substrates. For example, the sterically congested pivaloyl group in the cyclic and acyclic imides was selectively hydrogenated to give the corresponding amide alcohol or amide and alcohol mixture, respectively, although the less substituted acyl group in the 3,3-dimethyl substituted glutarimide was exclusively hydrogenated to give the corresponding amide alcohol, as shown in Scheme 12. The orientation of the two carbonyl groups possibly plays a key role in the selectivity.

Its unique chemoselective hydrogenation is applicable to the deprotection of primary amines from *N*-phthaloyl-protected amino acid ester derivatives in Gabriel amino acid synthesis. *N*-phthaloyl-L-Phe methyl ester undergoes hydrogenation under neutral conditions to generate *N*-(*o*-hydroxymethylbenzoyl)-L-Phe methyl ester without any loss of the ee value after acid hydrolysis, as shown in Scheme 13.[94]

The chiral version of the Cp*RuCl(P−N) catalyst bearing the chiral P−N ligand derived from L-proline promoted the enantioselective hydrogenation of prochiral 4-arylglutarimides via desymmetrization to provide the corresponding hydroxyamides with excellent enantiomeric excesses and in high yields, as shown in Scheme 14.[94] The resulting chiral hydroxyamides are readily converted by a ring-closing, followed by deprotection, to give chiral piperidinone derivatives, which serve as important synthetic intermediates for a number of physiologically active chiral compounds, including the antidepressant paroxetine. Synthetic advantages were also demonstrated by enantioselective hydrogenation of readily accessible bicyclic imides with the *N*-3,4-$(OCH_2O)C_6H_3$ group derived from cyclic dicarboxylic acids, as shown in Scheme 14. The desymmetrization of these imides with chiral catalyst gave the corresponding hydroxyamides with excellent enantiomeric excesses.[95] Thus, the cyclic dicarboxylic acids can be transformed to chiral cyclic compounds bearing two different functional groups on two chiral centers, which would otherwise require tedious multistep synthesis. The present imide hydrogenation with bifunctional catalysts provides a versatile synthetic method in organic synthesis.

Scheme 13. Deprotection of *N*-Phthaloyl Amino Acid Derivative Promoted by Cp*RuCl(P−N) 2/Base Catalyst[94]



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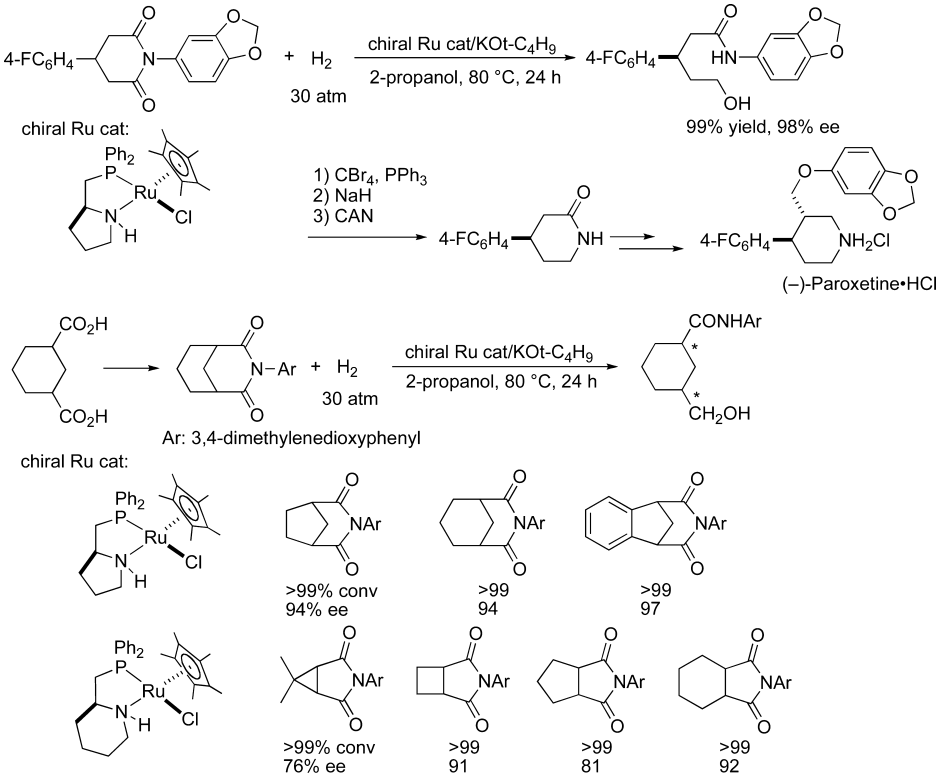
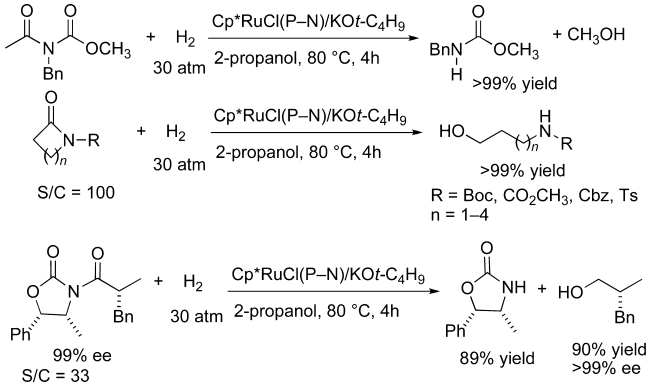
Scheme 14. Enantioselective Hydrogenation of Prochiral Cyclic and Bicyclic Imides with Bifunctional Chiral Cp*RuCl(P−N)/Base Catalysts[94,95]



Similarly to the hydrogenation of imides with the catalyst **2**, *N*-acylcarbamates and *N*-acyloxazolidinone can be hydrogenated to give preferentially the deacylation products, as shown in Scheme 15.[96] *tert*-Butyl alcohol is the preferable solvent for the hydrogenation of substrates because sterically small alcoholic solvents sometimes cause undesired alcoholysis of the substrates, although the reaction of *N*-alkoxycarbonyl protected cyclic carboxamides (lactams) gave preferentially *N*-protected aminoalcohols in almost quantitative yield. The rates of the reaction strongly rely on the electron-withdrawing nature of substituents on nitrogen in the substrates, the rate increasing in the order of Cbz < Boc < CO_2CH_3 < SO_2CH_3 ≈ Ts.

Scheme 15. Hydrogenation of *N*-Acylcarbamates and Related Compounds with Cp*RuCl(P−N)/Base Catalyst.[96]



Beller and co-workers recently reported chemoselective reduction of N-substituted phthalimides with polymethylhydrosiloxane as the hydrogen source in the presence of fluoride ions, giving the corresponding N-substituted isoindolinone in good to excellent yields.[100]

2.4. Hydrogenation of Esters and Lactones. Hydrogenation of esters or lactones to corresponding alcohols is also an industrially important process. Fatty alcohols, for example, have been commercially produced by hydrogenation of fatty acid esters for more than 70 years.[27,101,102] These reactions are traditionally carried out over Adkins−Lazier copper chromite

reductive treatment of chiral *N*-acyloxazolidinones, which are useful synthetic intermediates in the asymmetric synthesis developed by Evans,[97] as shown in Scheme 15. For example, *N*-acyloxazolidinone undergoes selective hydrogenation in the presence of Cp*RuCl(P−N) and KO*t*-C_4H_9 to furnish the corresponding chiral alcohol, without any damage to the stereochemistry, along with the original chiral auxiliary in high yields. This method may be an environmentally benign catalytic alternative to the method using $LiAlH_4$, which sometimes causes difficulty in the recovery of the chiral auxiliaries.

Recently, Bergens and co-workers demonstrated that chiral RuH_2(*R*-binap)[(*R*,*R*)-diamine] (**1**) combined with the base KO*t*-C_4H_9 effects monohydrogenation of N-substituted phthalimides with S/C = 200 under 30 °C to give the desired hydroxy lactams in moderate to good yields. Increasing the reaction temperature to 60 °C caused further reduction to give the corresponding carboxamide alcohols. Notably, at the lower temperature of 0 °C, cyclic *meso*-imides can be hydrogenated enantioselectively via desymmetrization, leading to chiral hydroxy lactams with excellent enantiomeric excesses, as shown in Scheme 16.[98,99] The chiral products can be directly converted to useful chiral compounds.

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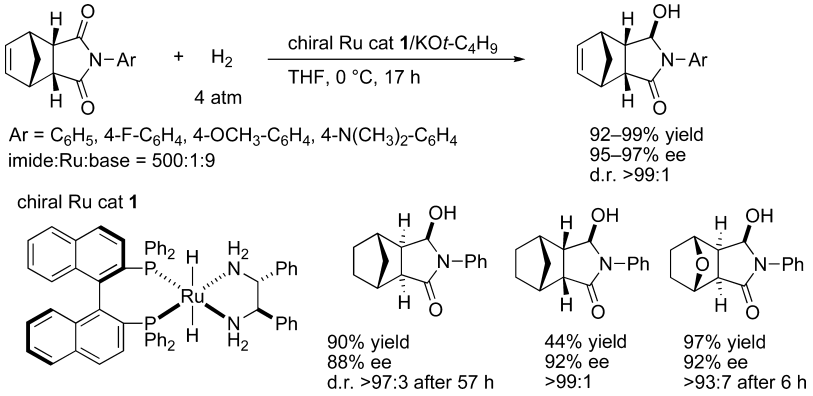
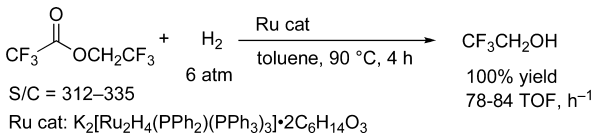
Scheme 16. Chemo- and Enantioselective Hydrogenation of Cyclic Imides into Hydroxyl Actams Catalyzed by RuH_2(*R*-binap)[(*R*,*R*)-diamine]/Base Catalyst[98,99]



heterogeneous catalyst[103] or its related systems under 20−60 atm hydrogen pressure conditions at 200−300 °C.[27,104,105] Recently, novel catalytic processes for the selective transformation of biogenic substrates such as triglycerides, carbohydrates, or their derivatives was extensively investigated for the utilization of biomass resources.[106−108] Suitable tuning of the catalytic systems would not only allow converison of the biomass-derived platform chemicals to esters or lactones,[72] but also perform further transformations.[107] For example, γ-valerolactone has been proposed as one of the key components in biomass utilization,[109] and its reduction product, 1,4-pentanediol, could undergo dehydration to yield 2-methyltetrahydrofuran (2-Me-THF) under hydrogenation conditions.[107,110] The homogeneous catalyst is well appreciated in its reduction for serious safety reasons, since 2-Me-THF is readily convertible to peroxides under air oxidation conditions.[110] 2-Me-THF is advocated as an alternative solvent in the pharmaceutical industry and is also considered as a fuel component.[106,111−113]

In 1980, Grey and co-workers reported the first homogeneous hydrogenation of activated esters, such as trifluoroacetate esters and dimethyl oxalate, to their corresponding fluorinated alcohols and methyl glucolate, respectively, catalyzed by the anionic potassium hydrido(phosphine)ruthenate complex, $K_2[Ru_2H_4(PPh_2)(PPh_3)_3]\cdot 2C_6H_{14}O_3$ in toluene, as shown in Scheme 17.[114−118] Later, the actual catalyst in this system was

Scheme 17. First Homogeneous Hydrogenation of Activated Esters[114−118]

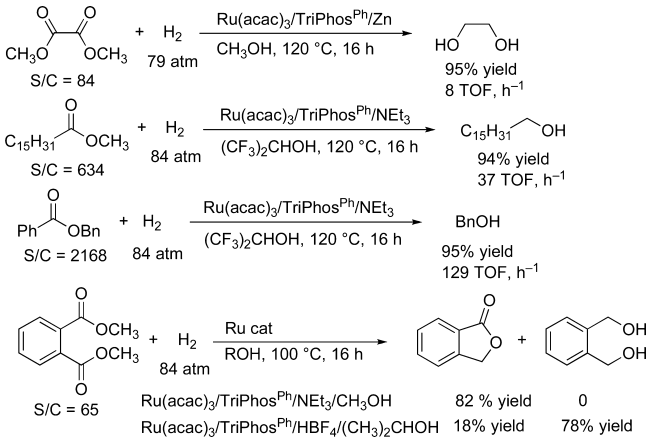


proposed to be $RuH_4(PPh_3)_3$.[38] However, simple unactivated esters were hardly hydrogenated under the same conditions to give the products in less than 22% yield.

In 1985, Piacenti reported that ruthenium carbonyls, $Ru_4H_4(CO)_8(PR_3)_4$ or $Ru_2(OAc)_2(CO)_4(PR_3)_2$ exhibited catalytic activity to hydrogenation of dimethyl oxalate under forced conditions (130−200 atm of H_2, 120−180 °C) to give methyl glucolate in almost quantitative yield.[119−125] Further reduction of methyl glucolate hardly proceeded to provide ethylene glycol under the same conditions because the resulting glucolate is a less activated ester than dimethyl oxalate. The diol formation from dimethyl oxalate, however, is possible via a two-step process.[123,124] Sterically congested and less activated dimethyl *o*-phthalate hardly underwent hydrogenation, giving the product in only 21% conversion and with low selectivity. Some byproduct stemmed from esterification, transesterification, and decarboxylation, and others were formed.[119] Wada and co-workers from Mitsubishi Kasei Corp. demonstrated in 1992 that a combined catalyst system of $Ru(acac)_3/P(n\text{-}C_8H_{17})_3$ with acid promoters such as NH_4PF_6 or H_3PO_4 causes a significant improvement in the catalytic activity in the hydrogenation of γ-butyrolactone to 1,4-butanediol at 200 °C under 50 atm of H_2 pressure,[126] which is higher than that required for the reduction of succinic anhydride into γ-butyrolactone (vide supra).[70,127]

In 1997−1998, homogeneous hydrogenation of dimethyl oxalate into ethylene glycol under substantially milder conditions[128] as well as the first successful example of hydrogenation of unactivated esters[129] was reported by Elsevier and Teunissen. As shown in Scheme 18, after the optimization

Scheme 18. Hydrogenation of Dimethyl Oxalate and Unactivated Esters Using Traditional Homogeneous Catalyst System, $Ru(acac)_3$/TriPhos^{Ph}[128−130]



of the reaction conditions and tuning of the catalyst systems, almost complete and selective conversion of dimethyl oxalate to ethylene glycol was achieved using the catalyst system $Ru(acac)_3$/TriPhos^{Ph}/Zn (TriPhos^{Ph} = $CH_3C(CH_2PPh_2)_3$) in dry methanol,[130] in which the Zn additive possibly activates the ester carbonyl function to facilitate the reaction. The same

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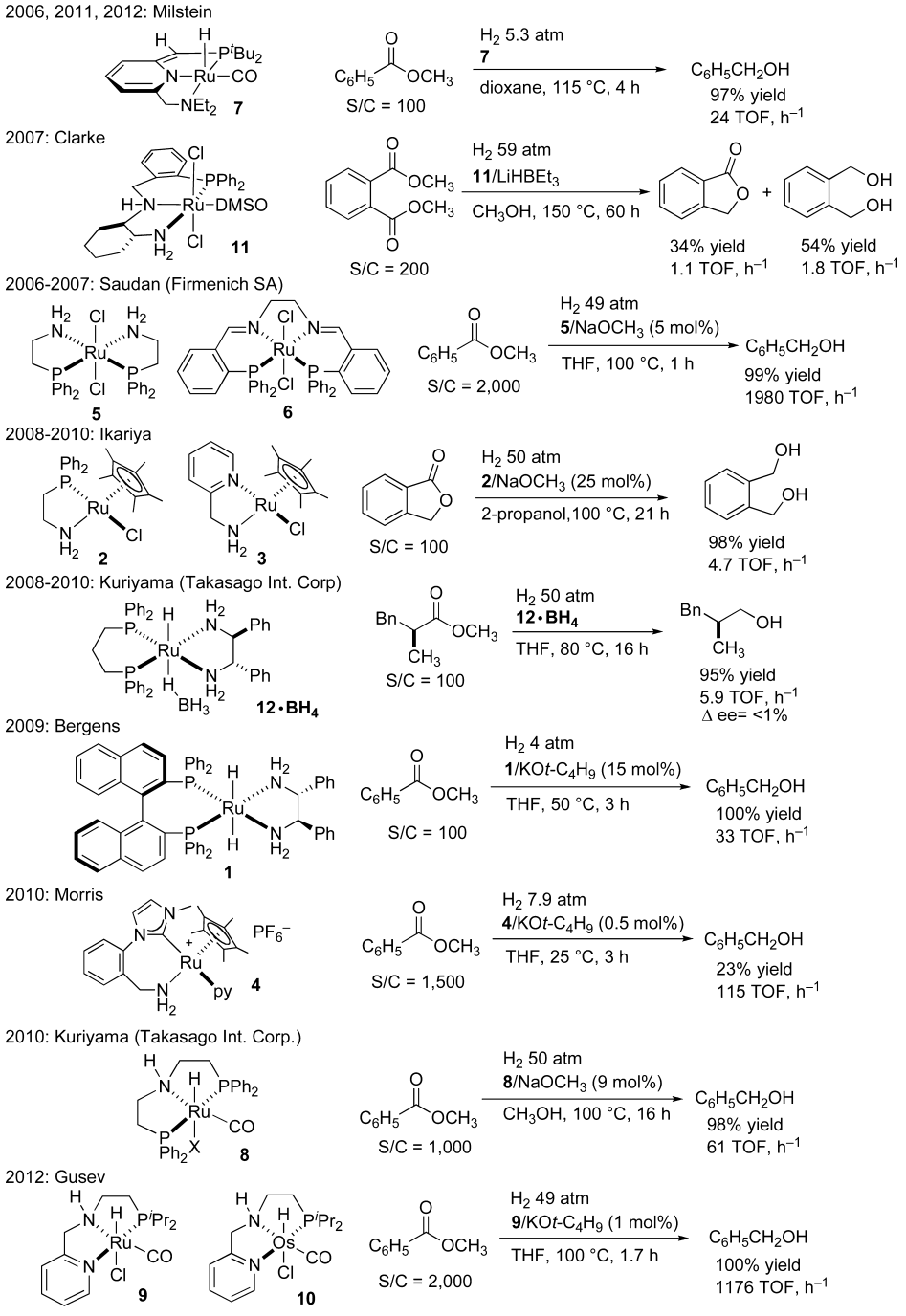
Scheme 19. Homogeneous Hydrogenation of Esters Based on Bifunctional Catalytic Systems (Placed in Chronological Order)



catalyst system, except Zn was replaced with triethylamine, promoted the hydrogenation of methyl palmitate to give the corresponding alcohol in 94% yield. The temperature and hydrogen pressure are still elevated compared with those for simpler ketones reduction. Slight modification of the ligand by replacing the phosphorus atom with a sulfur atom allowed selective hydrogenation of dimethyl oxalate to methyl glycolate for the same catalytic system,[131] whereas introduction of a nitrogen atom caused slower reaction rates.[132] When the combined system based on $Ru(acac)_3/P(n\text{-}C_8H_{17})_3/Zn$ was used for the hydrogenation of $C_6H_5CH_2CO_2CH_3$ ($C_6H_5CH_2$: Bn) under low hydrogen pressure conditions (<10 atm),mainly transesterification processes took place.[133,134]

Recently, the catalytic system $Ru(acac)_3$/ligand/additive (ligand = $P(n\text{-}C_8H_{17})_3$ or $TriPhos^{Ph}$ ($TriPhos^{Ph}$ = $CH_3C(CH_2PPh_2)_3$), or TPPTS (TPPTS = 3,3′,3″-phosphinidynetris(benzenesulfonic acid) trisodium salt), additive = NH_4PF_6) was successfully applied to homogeneous catalytic hydrogenation for a multistep conversion of sucrose or levulinic acid into γ-valerolactone or further into 1,4-pentanediol or 2-Me-THF (vide infra).[107,110] Some mechanistic studies are also available for this process.[135]

In 2002, Behr and co-workers reported catalytic system having two transition metal complexes, $Rh(acac)(CO)_2$ and $Mo(CO)_6$, for hydrogenation of lactones and carboxylic acids.[136] The mixed catalyst system exhibited reasonably good catalytic activity, whereas biphasic hydrogenation with the

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water-soluble Rh/TPPTS catalyst[137] gave an isomeric mixture of unsaturated carboxylic acids. The bimetallic catalytic system was recently shown to be, in fact, heterogeneous.[138,139]

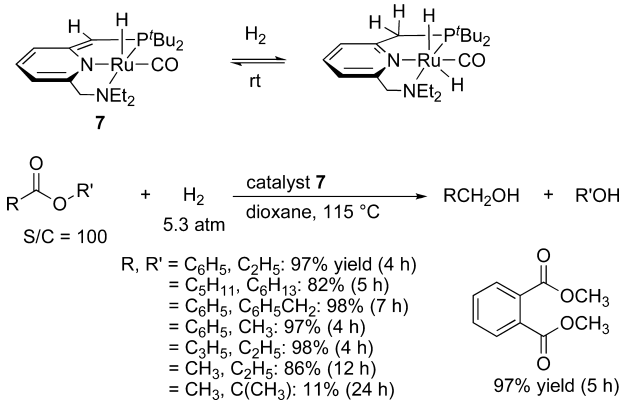
Prior to the recent significant progress in ester hydrogenation with newly developed bifunctional molecular catalysts that have been achieved by several groups since 2006, homogeneous catalytic hydrogenation using traditional[140−147] and bifunctional[148] catalysts had been under development at several companies. Results of these works recently appeared in patent applications.[149−151] Scheme 19 lists representative examples of hydrogenation of relatively simple and less-activated esters with the bifunctional catalysts in chronological order.

In 2006, Milstein and co-workers found that their originally developed 16e pincer-type complex RuH(NNP^{tBu})(CO), **7**[152] (NNP^{tBu} = 2-(di-*tert*-butyl-phosphinomethyl)-6-*N*,*N*-diethylaminomethylpyridine), can facilitate activation and reversible room temperature heterolytic H_2 cleavage to give the corresponding 18-electron *trans*-dihydride complex, based on the metal/ligand cooperation via aromatization-dearomatization of pyridine-based pincer-type ligands,[153] as shown in Scheme 20. In fact, complex **7** can efficiently facilitate hydrogenation of nonactivated aliphatic and medium-activated aromatic esters to alcohols under relatively mild and neutral conditions, as shown in Scheme 20.[152] Notably, the analogous pincer Ru complex RuH(P^{tBu}NP^{tBu})(CO) (PNP = 2,6-bis-(di-*tert*-butyl-phosphinomethyl)pyridine) is almost inactive in these reactions.

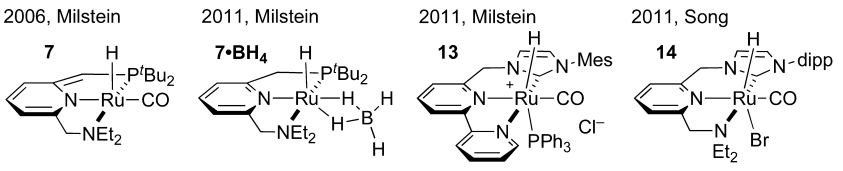
In 2007, Clarke and co-workers demonstrated that the structurally defined chiral pincer-type complex $RuCl_2$(NNP)(DMSO) (**11**) (NNP = *N*-(2-diphenylphosphanylbenzyl)-cyclohexane-1,2-diamine) bearing an NH unit effects the hydrogenation of dimethyl *o*-phthalate into *o*-xylylene glycol upon treatment with $LiBHEt_3$ or KO*t*-C_4H_9 as the base in methanol under relatively forced conditions, as shown in Scheme 19.[24,154] The catalyst **11** was less active than Elsevier's catalytic system based on a traditional catalyst (vide supra) and Milstein bifunctional catalysts (vide supra), possibly because of a difference in the structure of these pincer ligands, the former being the 5,6-membered chelating structure, the later one being the 5,5-chelating structure.

Since the discovery of Milstein's pincer catalyst **7** for the hydrogenation of esters, modified pincer-type systems have been developed in the same group; namely, catalysts **7**•BH_4,[155] **13**,[156] and **15**[157] (Scheme 21). This modification includes the modification of the NNP tridentate ligand with the NNC bipyridine−NHC carbene chelating ligand. Since the NHC ligands are generally more electron-rich and strongly bound to the metal, their corresponding complexes could exhibit different catalytic activity in comparison with the analogous phosphine versions. Song and co-workers reported independently the carbene complex, Ru−NNC catalyst **14**,[158] which is structurally similar to Milstein's catalyst **13**. Both complexes **13** and **14** exhibited almost identical activity in the hydrogenation of aromatic esters as well as aliphatic simple esters. In the presence of a base, the corresponding mixture of alcohols was obtained in excellent yields, as shown in Scheme 21. The catalytic reactions in the presence of modified catalysts **13** and **14** are 2 times faster in the hydrogenation of aromatic esters relative to Milstein's original Ru−NNP catalyst **7**. For example, ethyl benzoate was hydrogenated in a quantitative yield within 2 h

Scheme 20. Reversible Hydrogen Cleavage by Milstein-Complex 7 and Corresponding Catalytic Ester Hydrogenation[152]



Scheme 21. Milstein-Type Bifunctional Pincer Catalysts for Ester Hydrogenation[a]



cat	R	R'	P_{H_2}, atm	S/C	time, h	temp, °C	solvent	yield	TOF, h^{-1}
7	C_6H_5	CH_3	5.3	100	4	115	dioxane	97	24
7•BH$_4$	C_6H_5	CH_3	10	200	12	110	THF	96	16
13/KO*t*-C_4H_9	C_6H_5	C_2H_5	50	4000	12	110	toluene	71	237
13/KO*t*-C_4H_9	C_6H_5	C_2H_5	5.4	100	2	135	toluene	97	49
14/KO*t*-C_4H_9	C_6H_5	C_2H_5	5.2	100	2	105	toluene	98	49
7	C_5H_{11}	C_6H_{13}	5.3	100	5	115	dioxane	82	16
7•BH$_4$	C_5H_{11}	C_6H_{13}	10	200	12	110	THF	94	16
13/KO*t*-C_4H_9	C_4H_9	C_5H_{11}	5.4	100	2	135	toluene	96	48
14/KO*t*-C_4H_9	CH_3	CH_3	5.2	100	2	105	toluene	96	48
14/KO*t*-C_4H_9	CH_3	Bn	5.2	100	3	105	toluene	90	30
14/KO*t*-C_4H_9	CH_3	$C(CH_3)_3$	5.2	100	2	105	toluene	93	47

[a]Mes = 2,4,6-trimethylphenyl; dipp = 2,6-diisopropylphenyl.

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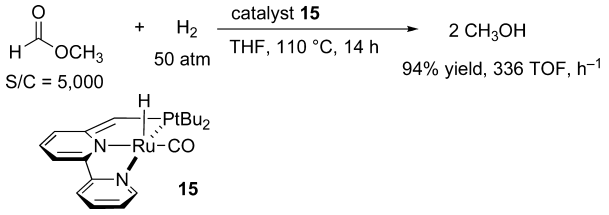
using catalyst **13**/base or **14**/base, whereas catalyst **7** needed a 4 h-reaction time for completion of the reaction under almost identical conditions. Notably, under 50 atm H_2, catalyst **13** hydrogenated ethyl benzoate with S/C = 4000 to produce benzyl alcohol in 71% yield after 12 h (TOF = 237 h^{-1}). Simple ethyl acetate was hydrogenated in a quantitative yield within 2 h using catalyst **14**/base, and NNP catalyst **7** gave the product in 86% yield after 12 h. In the absence of H_2 in the system, catalysts **7** and **7·BH$_4$** promoted the reverse process, dehydrogenation of alcohols to form esters or lactones.[153,155]

Recently, catalysts **13**/base and **15** were found to effect the hydrogenation of cyclic diesters derived from biomass (S/C = 100) at 110−135 °C under 6−50 atm of H_2 to produce the corresponding 1,2-diols in up to 93% yield after 12−48 h.[159] No racemization took place when a chiral diester (L-lactide) was used.

Notably, the modified NNP^{tBu} pincer Ru catalyst **15** bearing the bipyridine unit in the ligand can hydrogenate methyl formate and even dimethyl carbonate (vide infra) at 110 °C under 50 atm of H_2 to give methanol as the sole product, as shown in Scheme 22.[157]

Scheme 22. Hydrogenation of Methyl Formate with Milstein's Catalyst 15[157]

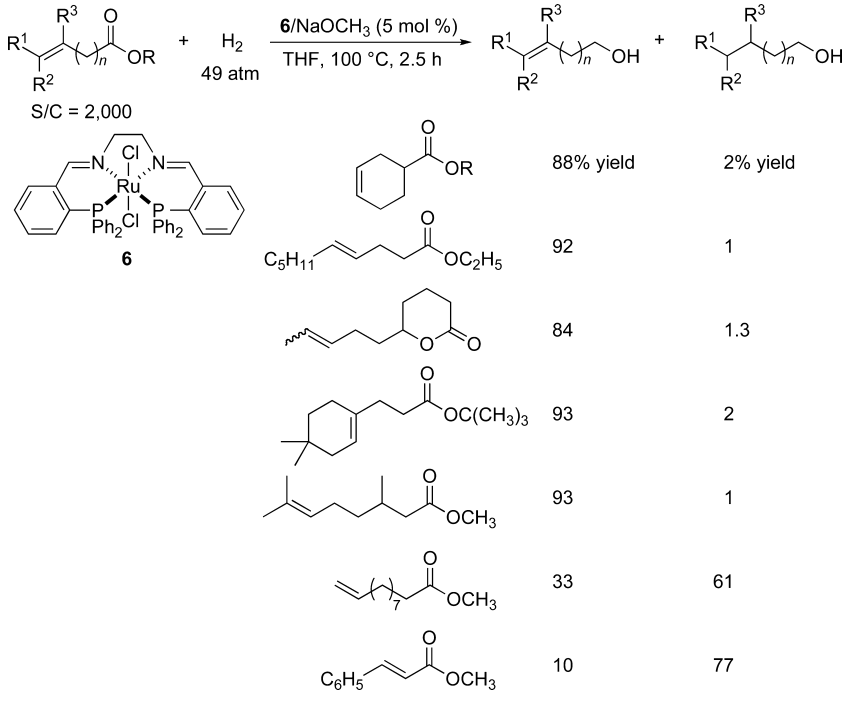


In 2006−2007, Saudan and co-workers (Firmenich SA) reported that Morris-type[160,161] $RuCl_2(P{-}N)_2$ (**5**) and Gao−Noyori−Ikariya's PNNP-tetradentate Ru precatalyst **6**[162−165] in the presence of a base efficiently catalyzed hydrogenations of aliphatic and aromatic esters, as shown in Scheme 19.[166−172] The activity of catalyst **5** can be compared with Elsevier's classical system Ru(acac)$_3$/TriPhos^{Ph}/Zn and Milstein's catalyst **7** under the reported conditions: for example, the reduction of benzyl benzoate with **5** (TON = 1980, TOF = 1980 h^{-1}) is 1 order faster than the Elsevier system (TON = 2060, TOF = 129 h^{-1}) and 2 orders faster than Milstein catalyst **7** (TON = 98, TOF = 14 h^{-1}). Under 50 atm of H_2, however, the TOF increased up to 237 h^{-1} (TON = 2840) for the hydrogenation of ethyl benzoate using Milstein catalyst **13**/base. Complex **5** can be used as an efficient catalyst for the hydrogenation of long-chain diesters to produce nonadecane-1,19-diol as well as tricosane-1,23-diol in high yields;[173] however, it is not active for hydrogenation of chiral esters.[174]

Notably, THF is the best solvent for the reaction with precatalysts **5** and **6**, and the reaction in methanol did not proceed at all, possibly because of the catalyst deactivation. In the tested hydrogenation of unsaturated esters in the presence of **6**, the C=C double bond in the same molecules was mostly unaffected, except for terminal and conjugated olefinic C=C double bond, as shown in Scheme 23.

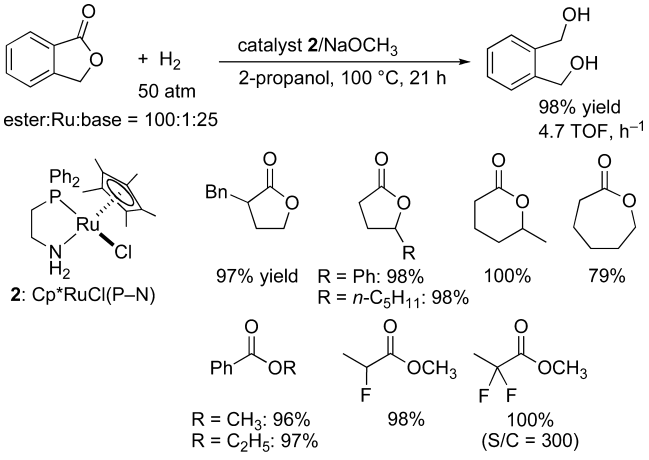
In 2008, Ikariya and co-workers found that bifunctional catalyst **2**, Cp*RuCl(P−N), and a large amount of the base promotes the hydrogenation of lactones and simple esters, leading to the corresponding diols and alcohols, respectively.[175,176] For example, phthalide was cleanly reduced to *o*-xylyleneglycol under 50 atm of H_2 at 100 °C in the presence of catalyst **2**, as shown in Scheme 24. A variety of aprotic solvents, including THF, dioxane, and toluene, can be equally used as alcoholic solvents under similar conditions. The amount of base has a significant influence on the reaction rate, and the addition of more than 25 equiv of $NaOCH_3$ as the base to the Cp*RuCl(P−N) complex resulted in an improvement of its catalytic performance, although the reason for this is still unclear. As shown in Scheme 24, a variety of esters and lactones

Scheme 23. Chemoselectivity in Esters or Lactones Reduction Using Bifunctional PNNP-Tetradentate Ru Precatalyst 6[168]



dx.doi.org/10.1021/cs300341g | ACS Catal. 2012, 2, 1718−1741

Scheme 24. Homogeneous Reduction of Esters or Lactones with Bifunctional Cp*RuCl(P−N) 2/Base Catalyst[175,176]

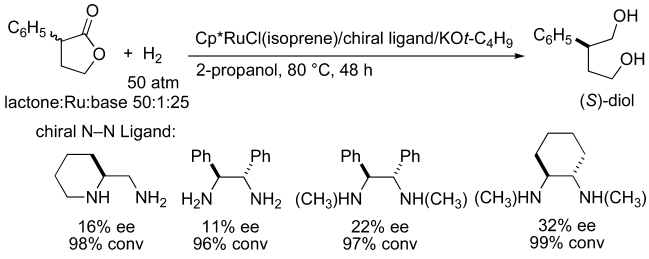


can be hydrogenated to give the corresponding alcohols and diols, respectively. In particular, fluorinated substrates, as expected, are rapidly hydrogenated under the same conditions.

Structural modification of the protic chelating amine ligand of the Cp*Ru catalyst system causes marked improvement in the catalytic performance and provides efficient access to diols from lactones, as shown in Scheme 25.[177] The present N−N ligand is more effective for hydrogenation of lactones than P−N ligands. For example, precatalyst **3** Cp*RuCl(N−N) (N−N: 2-$C_5H_4NCH_2NH_2$) bearing a pyridyl amine chelating ligand combined with 25 mol % of $NaOCH_3$ as a base efficiently effected hydrogenation of several kinds of lactones at 100 °C under 50 atm of H_2 in 2-propanol to give the corresponding diols in reasonably good to excellent yields. The catalytic activity of Ikariya's catalyst is comparable with Milstein's RuH(NNP)(CO) pincer complex **7**, although the latter works without any base additive under lower H_2 pressure condition.[152]

Both Cp*RuCl(N−N) and Cp*RuCl(P−N) catalyst systems need a large amount of the base for a smooth reaction. The coexistent base causes a reversible deprotonation in the substrates having a relatively acidic C−H bond, leading to racemization of chiral nonracemic substrates with a tertiary stereogenic center at the α-carbon. Thanks to the basic reaction conditions, chiral Cp*RuCl (chiral N−N) catalysts bearing a range of chiral 1,2-diamine ligands did promote asymmetric hydrogenation of α-phenyl-γ-butyrolactone to give chiral (*S*)-diol via dynamic kinetic resolution (DKR) with up to 32% ee, as illustrated in Scheme 26. Among the variety of chiral amines tested for the reaction, chiral 1,2-diaminocyclohexane ligand

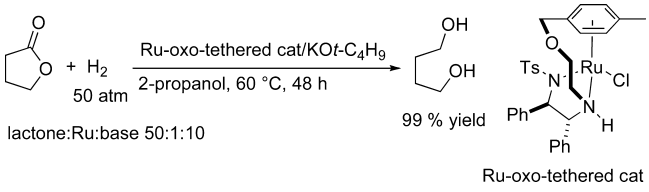
Scheme 26. Hydrogenative DKR of the (±)- of α-Phenyl-γ-butyrolactone[177]



gave the best results. Although the enantioselectivity was still moderate, this result indicates for the first time that a suitable design of chiral catalyst system can provide direct access to chiral diols from racemic esters.[177]

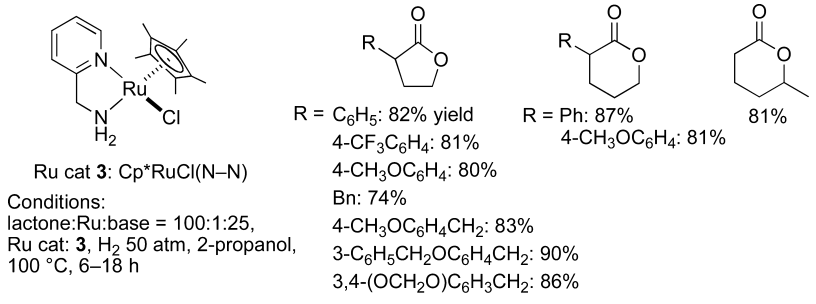
Recently Ikariya and co-workers from Takasago Int. Corp. demonstrated that a newly developed chiral oxo-tethered (N−N) Ru complex, which represents a second generation catalyst for asymmetric hydrogenation and transfer hydrogenation of ketones, could be used in the hydrogenation of γ-butyrolactone, as shown in Scheme 27.[178]

Scheme 27. Hydrogenation of γ-Butyrolactone Catalyzed by Newly Developed Oxo-Tethered Ru/Base Catalyst[178]



In 2008−2010, Kuriyama and co-workers from Takasago Intern. Corp. developed a series of catalytic systems for the hydrogenation of esters and lactones under mild conditions in the presence of the modified Noyori-type chiral catalyst **12**, RuHX(diphosphine)(diamine).[174,179,180] Notably, the well-tuned complex RuH(η^1-BH_4)(dppp)(dpen) (DPPP = diphenylphosphinopropane) (**12·BH_4**) allows hydrogenation of chiral esters to chiral alcohols without serious loss of their optical purities under neutral conditions. In fact, the precatalyst **12·BH_4**, easily available from the reaction of $RuCl_2$(dppp)(dpen) and $NaBH_4$, can be used as a base-free catalyst for hydrogenation of β-substitued protected chiral α-keto esters. The corresponding chiral alcohols were obtained in excellent yields and with <1% loss in their optical purity, as shown in Scheme 28. In the case of unprotected esters, lower yields and a serious loss of entiomeric excess (Δee) were observed.

Scheme 25. Homogeneous Reduction of Lactones with Bifunctional Cp*Ru(N−N)/Base Catalyst[177]



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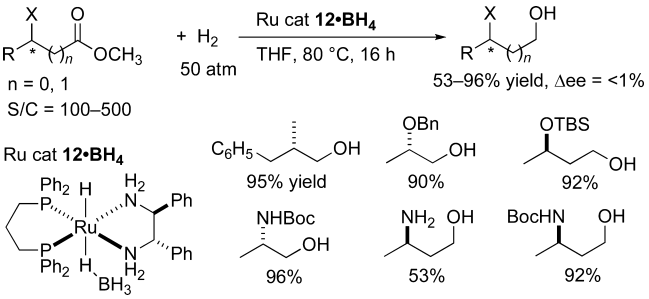
Scheme 28. Hydrogen Reduction of α- and β-Substitued Chiral Esters To Produce Chiral Alcohols without a Serious Loss in the Optical Purity[174,179,180]



In 2009, Bergens evaluated the details of the reaction pathways for hydrogenation of esters or lactones using Noyori-type catalyst **1** in THF.[181] He found that the hydrogenation of ethyl hexanoate with S/C = 60 in THF containing *trans*-RuH_2[(*R*)-binap]][(*R*,*R*)-dpen] catalyst **1** and 4 equiv of $KN[Si(CH_3)_3)_2]$ as the base proceeds even at −20 °C under 4 atm of H_2 to give a mixture of 1-hexanol and ethanol in 23% yield after 4 h. Similarly to the report of Saudan,[168] no catalytic activity was found in protic solvents. Despite product inhibition, several esters or lactones could be hydrogenated in 100% yield using 1−2 mol % of catalyst **1** in THF at 30−50 °C under 4 atm of H_2 for 3−4 h. Notably, a stoichiometric reaction of γ-butyrolactone with complex **1** under ∼2 atm of H_2 in a molar ratio of lactone/Ru/KO*t*-C_4H_9 = 3:1:2 at −80 °C in THF-d_8 gave the hemiacetal oxido Ru complex in 76% yield as a result of a formal carbonyl insertion into the Ru−H bond, as shown in Scheme 29. No intermediates expected from the concerted mechanism via the pericyclic transition state were detected during the reaction of γ-butyrolactone with catalyst **1**. The same alkoxido complex was obtained from the reaction of the amido Ru complex with free hemiacetal at −80 °C in almost quantitative yield. The resulting hemiacetal oxide complex is then transformed into the alkoxido Ru complex under hydrogen atmosphere (Scheme 29). This conversion occurs slowly at −80 °C and is complete when the temperature is raised to −40 °C.[181]

In 2010, Morris and co-workers reported that a newly developed Ru catalyst, **4**, Cp*Ru(C−N)py]PF_6 (C−N: 1-(2-aminomethylphenyl)-3-methylimidazol-2-ylidene) bearing a chelating amine ligand attached to a *N*-heterocyclic carbene unit catalyzes hydrogenation of methyl benzoate to benzyl alcohol and methanol with S/C = 1500 under 7−25 atm of H_2 (Scheme 19). The TOF at 50 °C is reaching up to 585 h^{-1} after 2 h and 25 atm of H_2 with 78% conversion.[182] No other side products were observed in the mixture. The catalytic activity of **4** is comparable with the catalyst *trans*-$RuCl_2(\kappa^2$-*P*,*N*-$PPh_2CH_2CH_2NH_2)_2$ (**5**) at higher temperature 100 °C and under 49 atm H_2 pressure.

Recently, Kuriyama and co-workers from Takasago Int. Corp. found more efficient catalysts RuHCl(CO)(dpa) (**8**) and $RuH(HBH_3)(CO)$(dpa) (**8·BH$_4$**) (dpa = HN-$(CH_2CH_2PPh_2)_2$)[183,184] for hydrogenation of simple and chiral esters, as shown in Scheme 30.[185−187] Methanol can be used as a practical solvent for the hydrogenation of methyl esters. Since methanol is also a byproduct, the complicated separation problems can be minimized, leading to operational simplicity. Notably, the base-free catalyst **8·BH$_4$** as well as **12·BH$_4$** (vide supra) worked efficiently for selective hydrogenation of protected α- or β-hydroxy esters and N-protected α- or β-amino acid esters to produce the chiral alcohols without or with <1% loss in optical purity.

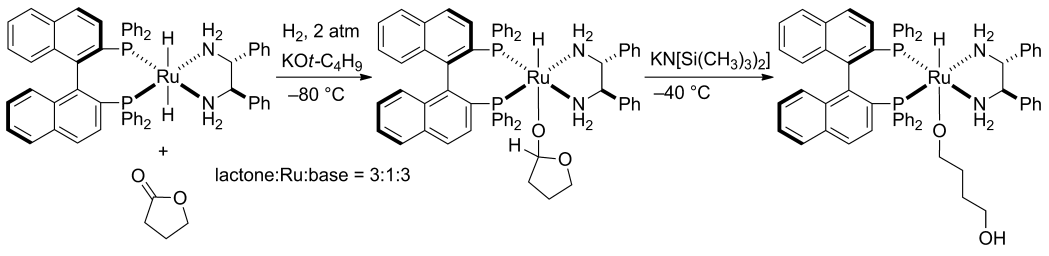
Potential industrial application of RuHCl(CO)(dpa) catalyst **8** was also demonstrated[186] by the hydrogenation of 2200 kg of methyl (*R*)-lactate with 99.6% ee into (*R*)-1,2-propandiol at 30 °C (*S*/*C* = 5000), producing the product in 96% yield with 99.2% ee after 12 h, as summarized in Scheme 30.[187] In another example, hydrogenation of methyl *l*-menthoxyacetate with an S/C ratio of 2000 into 2-(*l*-menthoxy)ethanol, the reaction was completed in 5 h at 80 °C. The final product was obtained in 87% yield after distillation without the exothermic quench reaction of the metal hydride.[186]

Recently, Ikariya and Otsuka from Central Glass Co. LTD demonstrated very rapid hydrogenation of esters bearing fluorine atoms into the α-position using catalyst **8** in methanol at room temperature. As shown in Scheme 31, the hydrogenation of fluorinated esters with S/C = 20 000 proceeded smoothly, even at 35−40 °C, to give the corresponding alcohols almost quantitatively. Notably, highly fluorinated esters, including $CF_3CO_2CH_3$, $CClF_2CO_2CH_3$, $C_2F_5CO_2CH_3$, were selectively hydrogenated to hemiacetal intermediates under the same conditions. Fluoral hemiacetal was obtained in 89% conversion with 98% selectivity.[188,189]

In 2012, Schlaf and Gusev and co-workers reported catalytic hydrogenation of hexyl octanoate to 1-hexanol and 1-octanol at 220 °C and under 54 atm of H_2 using the hydrido Os complex [*trans*-$OsH_2(CO)(P^{iPr}N(H)P^{iPr})_2$)] bearing tridentate amino-diphosphine ligand[190−192] $P^{iPr}N(H)P^{iPr}$ = $HN(CH_2CH_2P^iPr_2)_2$ with N−H functionality.[193] This Os complex was capable of hydrogenating fully saturated triglycerides, giving cetyl and stearyl alcohols.

Recently, Gusev and co-workers extensively modified the original $P^{iPr}N(H)P^{iPr}$ ligand to find much more active pincer-type Ru precatalyst **9** and Os precatalyst **10** (Scheme 32). These complexes contain a new tridentate hemilabile NN(H)-P^{iPr} ligand bearing N−H functionality [NN(H)P^{iPr}: 2-$C_5H_4NCH_2NH(CH_2)_2P(CH(CH_3)_2)_2$], which can be viewed as the tridentate ligand from formally combined Ikariya's P−N

Scheme 29. Intermediates in Lactone Hydrogenation Catalyzed by Noyori-Type Bifunctional Catalyst[181]



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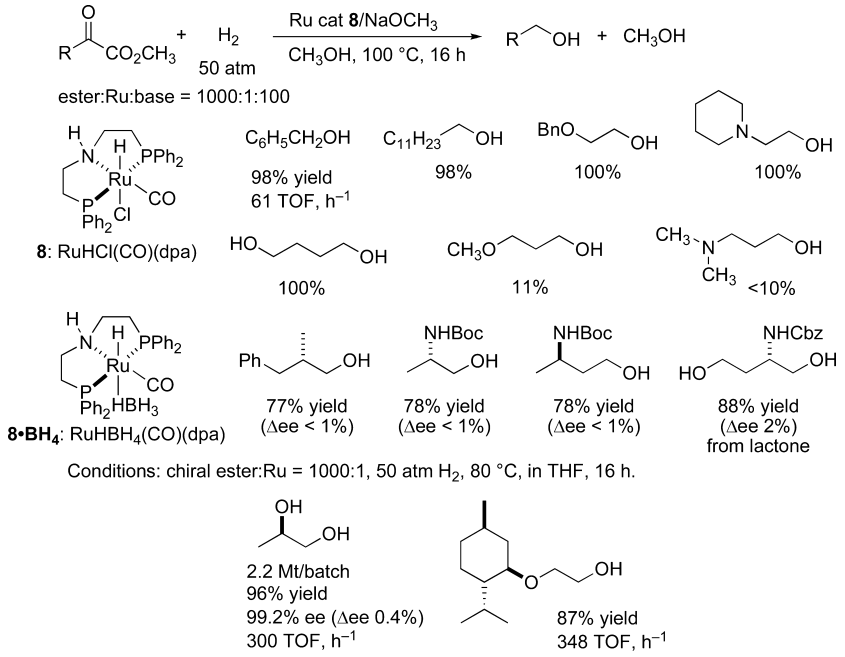
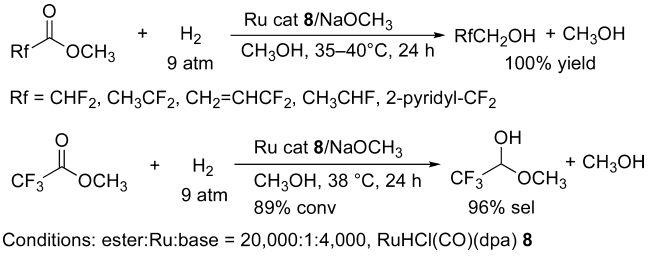
Scheme 30. Hydrogen Reduction of α- and β-Substitued Chiral Methyl Esters and Lactones with Takasago's RuHX(CO)(dpa) Complexes (X = Cl, BH_4)[185−187]



Scheme 31. Rapid Hydrogenation of Fluorinated Esters with RuHCl(CO)(dpa) (8) Catalyst[188,189]



and N−N bidentate ligands (complexes **2** and **3**), in which the phenyl substituent on the phosphorus atom is replaced with an isopropyl group, as shown in Scheme 32. These NNP^{iPr} complexes are also regarded as modified pincer catalysts by replacement of the one phosphine part of the tridentate $P^{iPr}N(H)P^{iPr}$ aminodiphosphine ligand[190−192] in $[MH_2(CO)(\kappa^3\text{-}P,N,P\text{-}HN(CH_2CH_2P^iPr_2)_2)]$ (M = Ru, Os) complexes[194,195] with a 2-pyridyl group, by analogy with Milstein pincer complex $RuH(NNP^{tBu})(CO)$ **7**, which is more active than $RuH(P^{tBu}NP^{tBu})(CO)$ (vide supra).

The newly developed pincer-type precatalysts **9** and **10** as well as their derivatives, **16** and **17** prepared from **9** or **10** and KO*t*-C_4H_9, exhibit excellent catalytic performance in the hydrogenation of esters to alcohols.[196−198] For example, catalysts **9** and **10** and dimeric complexes **16** and **17** are versatile and highly practical catalysts for ester hydrogenation, as shown in Scheme 32. In fact, hydrogenation of methyl benzoate with S/C = 2000 in the presence of complexes **9**/base, **10**/base, **16**, or **17** under 49 atm of H_2 at 100 °C in THF proceeded rapidly to the corresponding alcohol in almost quantitative yield after 1−1.7 h. In particular, the dimeric ruthenium catalyst **16** in the absence of additional base gave the product, benzyl alcohol, in 90% yield with 18 000 TON (TOF = 1059 h^{-1}) in 17 h, which is 30 times faster than the hydrogenation rate reported in methanol after 16 h for RuHCl(CO)(dpa) (**8**) combined with 5 mol % $NaOCH_3$ as the additional base, under the identical conditions.[185] The catalytic activity of **16** in this reaction is 1 order of magnitude higher than those of the Ru−PNP catalyst, $[RuH_2(CO)(P^{iPr}N(H)P^{iPr})]$,[196] but is comparable to that of catalyst **5** under almost identical conditions.[168]

Even at 40 °C, the reaction with S/C = 2000 using catalyst **16** gave the product in reasonably good yield, 82%. Increasing the reaction temperature to 100 °C caused a significant increase in the conversion, as shown in Scheme 32. The osmium dimer **17** is also an efficient catalyst for hydrogenation of methyl benzoate, however, at a slower rate compared with **16**. A wide range of esters, including less-activated esters, could be effectively hydrogenated into the corresponding alcohols in the presence of dimers **16** and **17** under neutral conditions (vide infra), except for dimethyl oxalate and *o*-bromo-substituted benzoate (Scheme 32). In the reduction of ε-caprolactone or methyl hexanoate, osmium catalyst **17** exhibited better activity than ruthenium catalyst **16**. Catalyst **17** was used in the successful reduction with an S/C = 1000−3000 of glyceryl trioleate and a sample of domestic olive oil, which is a natural mixture of triglycerides of oleic (∼85%), linoleic (∼2−3%), and palmitic acids (main components), leading to the corresponding unsaturated alcohols, in which the olefinic part is intact during the reaction (Scheme 32).

Catalytic activity can be compared with other catalyst systems. The hydrogenation of methyl hexanoate with catalysts **16** and **17** gave 93−100% yield in 1.5−2 h, which is comparable with the reduction of methyl octanoate with catalyst **5** in the presence of $NaOCH_3$ (10 mol %) under the same conditions, giving the product in 94% yield after 2.5 h.[168] The reduction of ethyl acetate with osmium dimer **17** was completed in 3 h (Scheme 32), although **14**/base[158] requires a 20 times higher catalyst loading to reach 99% conversion in 2 h under 5.3 atm of H_2 at 105 °C. Catalyst **17** is ∼3 times less active and slower in the reduction of chiral α-hydroxy acid ester than Takasago's

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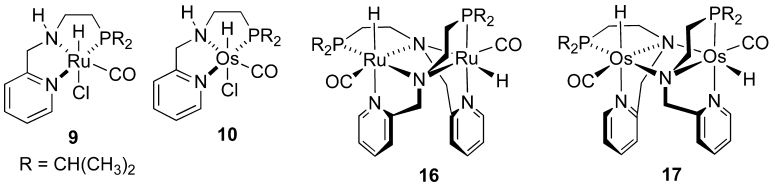
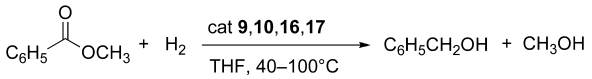
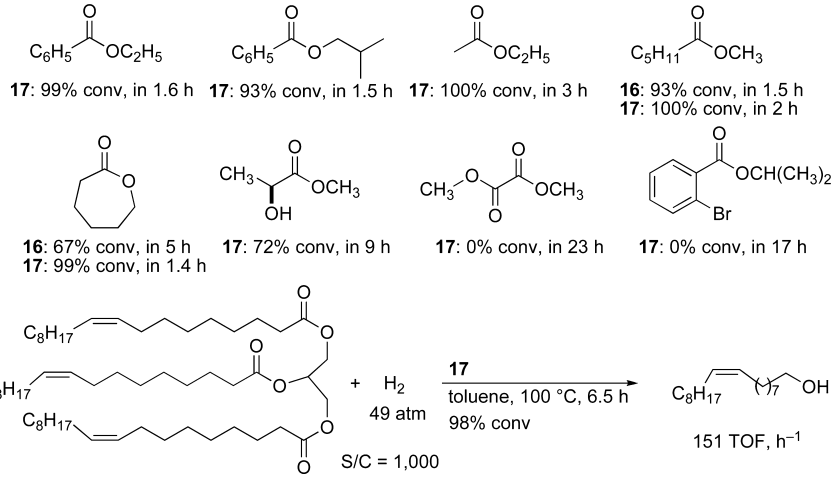
Scheme 32. Catalytic hydrogenation of esters with Gusev's Ru and Os complexes 9, 10, 16, and 17.[196−198]





cat	S/C	temp, °C	t, h	conv, %
9/KOt-C_4H_9 (1 mol %)	2,000	100	1.7	100
10/KOt-C_4H_9 (1 mol %)	2,000	100	1.5	100
16	2,000	100	1.0	100
17	2,000	100	1.5	99
16	2,000	40	17	82
17	2,000	40	22	28
16	2,000	80	1.2	88
17	2,000	80	2.2	76
16	10,000	100	14	100
16	20,000	100	17	90

Scope and limitations: (Conditions: ester:cat = 2,000:1, 49 atm H_2, 100 °C, in THF)

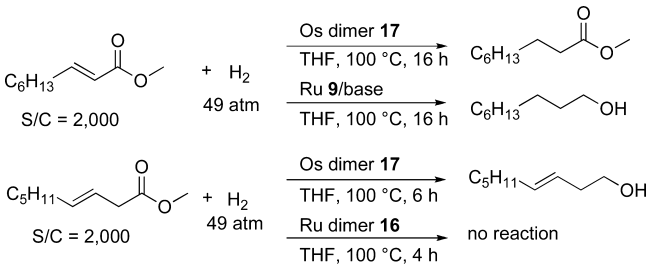


RuHCl(CO)(dpa) catalyst **8**/base.[187] No information about Δee is provided.

The catalytic performance in terms of activity and chemoselectivity of the catalysts **9**, **16**, and **17** was also tested using unsaturated esters having C═C double bonds.[196] The outcome of the reaction is highly influenced by the employed catalyst and nature of the substrate. For example, hydrogenation of *α,β*-unsaturated methyl 2-nonenoate almost quantitatively afforded methyl 2-noneoate with the osmium dimer **17**, whereas deeper reduction to saturated alcohol was observed with **9**/base. Osmium dimer **17** selectively catalyzed reduction of methyl 3-nonenoate to 3-nonenol, whereas the ruthenium dimer **16** is totally inactive, as shown in Scheme 33. The detailed experimental data suggest two possible mechanisms for the ester hydrogenation: the bifunctional outer sphere proposed by Noyori−Ikariya and the classical inner-sphere mechanism proposed by Milstein. More works should be required to draw the conclusive pathways for this productive hydrogenation.

2.5. Hydrogenation of Carboxylic Acids. Hydrogenation of free carboxylic acid is also an attractive molecular transformation. In particular, the hydrogenation of fatty carboxylic acids to the corresponding alcohols is an industrially important process. Usually, the catalysts that are active for the

Scheme 33. Catalytic hydrogenation of alkenoates with Gusev's Ru and Os complexes 9, 16, and 17



hydrogenation of esters or lactones are also effective for the reduction of carboxylic acids. In general, however, the hydrogenation of carboxylic acids could be less effective than related esters and less selective because the reduction of a carboxylic acid proceeds normally through an aldehyde and then a primary alcohol, leading to side reactions, including esterification and over-reduction, depending on the catalyst activity, as depicted in Scheme 34. When the catalytic activity is high enough, alcohols are obtainable as the final products. Over-reduction into hydrocarbons could usually be a problem when a heterogeneous catalyst is used under forced conditions.

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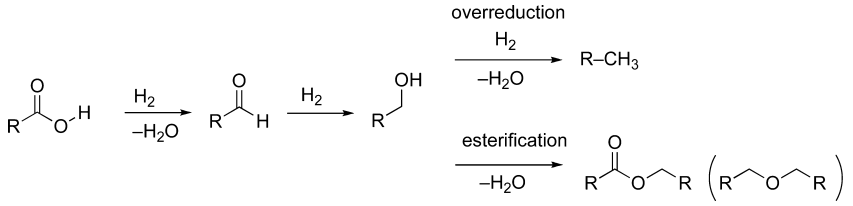
Scheme 34. Chemoselectivity in the Hydrogenation of Carboxylic Acids



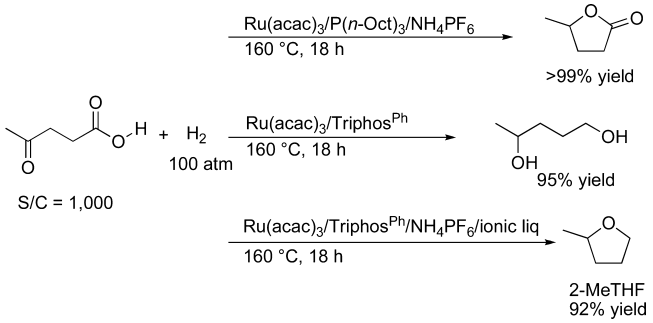
In 1977, Piacenti reported that asymmetric C═C double bond hydrogenation of α,β-unsaturated bicarboxylic citraconic and mesaconic acids in the presence of the soluble cluster ruthenium carbonyl hydride, $H_4Ru_4(CO)_8((-)\text{-diop})_2$ at 120−170 °C and under 130 atm of H_2 gave the corresponding saturated dicarboxylic acids in 83−89% yield and with 1−8% ee. Notably, the unsaturated and saturated lactones were obtained as byproducts in 11−17% total yield. This hydrogenation represents the first example of the catalytic reduction of a free carboxylic acid in the homogeneous phase, although it has low efficiency in reductive transformation of free COOH group.[199,200] The same group then reported the hydrogenation of saturated monocarboxylic acids at 100−200 °C under a H_2 pressure of 100−200 atm, producing the corresponding esters as major products in 2−74% yields and the hydrogenation of several bicarboxylic acids with $H_4Ru_4(CO)_8(PBu_3)_4$ as a precatalyst to give the corresponding lactones as major or sole products.[71] The isolable ruthenium carbonyl carboxylates, which were detected in the crude of the hydrogenation of acetic acid in the presence of $H_4Ru_4(CO)_8(PBu_3)_4$ as catalytic precursor,[71] are catalytically active in the hydrogenation of acetic acid into ethyl acetate (up to 40% yield after 48 h) under forced conditions (T = 180 °C, 130 atm of H_2).[121,201]

Hydrogenation of decanoic acid with a soluble rhenium/osmium bimetallic catalyst was reported by Yoshino and co-workers.[202] Under a hydrogen pressure from 25 to 100 atm and a temperature ranging from 100−120 °C, decanol was formed in 85% yield and with up to 90% selectivity. Esters and hydrocarbons were detected as byproducts.

Hydrogenation of monocarboxylic acids into alcohols in up to 98% yield using bimetallic catalysts consisting of group 8−10 late transition complexes, such as $M(acac)_3$ (M = Rh, Ru) or $Ru_3(CO)_{12}$ and group 6 or 7 early transition metal carbonyls, such as $M(CO)_6$ (M = Mo, W) or $Re_2(CO)_{10}$ was reported by Fuchikami and co-workers.[203] These systems reduced the aromatic ring as well as the C═C double bonds in the reactions at 140−170 °C under 100 atm of H_2. Similarly, Behr reported the hydrogenation of 2-ethylheptanoic acid into 2-ethylheptanol using a mixture of $Ru(acac)(CO)_2$ and $Mo(CO)_6$ at high temperature and pressure.[136] Recently, Whyman demonstrated that catalysis using these bimetallic catalyst systems proceeded, in fact, in the heterogeneous phase.[138,139]

Chemoselective hydrogenation of levulinic acid, which is easily available from lignocellulosic biomass through carbohydrates, into γ-valerolactone, 1,4-pentadiol, or 2-methyltetrahydrofuran (2-MeTHF) in the presence of the traditional catalyst systems, $Ru(acac)_3$/TriPhos^{Ph}[107,110] or $RuCl_3\cdot 3H_2O/PPh_3$[204] was recently reported. For example, the hydrogenation with the combined catalyst system, $Ru(acac)_3/P(n\text{-Oct})_3/NH_4PF_6$ under 100 atm of H_2 at 160 °C preferentially gave γ-valerolactone in >99% yield after 18 h, and the catalyst system $Ru(acac)_3$/TriPhos^{Ph} afforded 1,4-pentadiol in 95% yield, whereas 2-MeTHF was obtainable using the catalyst system $Ru(acac)_3$/TriPhos$^{Ph}/NH_4PF_6$/ionic liquid in 92% yield, as summarized in Scheme 35.[107] In this process, valuable products γ-valerolactone or 2-MeTHF are obtained through esterification steps. Mechanistic studies are available for this process.[135]

Scheme 35. Selective Conversion of Levulinic Acid[107]



In 2007, Cole-Hamilton reported that hydrogenation of a nonanoic acid in the presence of ammonia using the $Ru(acac)_3$/TriPhos^{Ph} catalyst system at 164 °C under 39 atm of H_2 for 14 h gave a mixture of the corresponding primary amine, secondary amine, alcohol, and secondary amide.[205,206] The combined catalyst system $Ru(acac)_3$/TriPhos^{Ph}/Zn was also effective for hydrogenation of succinic or fumaric acid to 1,4-butandiol under 79 atm of H_2 at 120 °C for 48 h.[207] Selective homogeneous hydrogenation of carboxylic acids into alcohols is under development at several companies.[140,142,208−211]

Notably, no bifunctional catalyst yet has been disclosed for the hydrogenation of carboxylic acids, possibly because the basic bifunctional catalyst strongly interacts with free acids, leading to a deactivated species. Most of the reported homogeneous catalyst systems for carboxylic acid hydrogenation are focused on bimetallic or Ru-TriPhos^{Ph} systems under typically more forced conditions than conditions reported for ester hydrogenations (vide supra).

2.6. Hydrogenation of Carboxamides. Carboxamides or simply amides with a less electrophilic carbonyl group are still one of the challenging targets in the hydrogenation of carboxylic acid derivatives.[212] Possible reaction pathways in the hydrogenation of carboxamides or lactames are presented in Scheme 36. Path A, which represents reductive cleavage of the C═O bond along with production of water, is a typical pathway for heterogeneous systems[213] or traditional homogeneous catalysts, whereas path B, which represents CO reduction followed by C−N bond cleavage, is a typical pathway for Ikariya's bifunctional catalysts or Milstein's bifunctional catalysts.

Fuchikami and co-workers reported that the combined catalyst systems of group 8−10 late transition metal carbonyls and group 6 or 7 early transition metal carbonyls are active in

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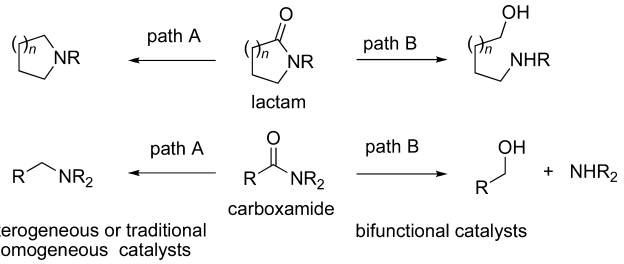
Scheme 36. Chemoselectivity in the Hydrogenation of Carboxamides or Lactames



the hydrogenation of carboxamides or lactams in DME containing 1−3 mol % catalyst under forced conditions, 100 atm of H_2, at 160−180 °C. Various amines were obtainable via dehydration (path A, Scheme 36) in good to excellent yields after 8−36 h.[214] These catalyst systems are also effective for hydrogenation of carboxylic acids to afford alcohols selectively (vide supra).[203] However, these bimetallic catalysts[136,203] were recently shown to be, in fact, heterogeneous catalysts generated from the homogeneous catalysts during the reaction.[138,139,215]

Homogeneous hydrogenation of propanamide with Ru(acac)$_3$/TriPhos^{Ph} was reported in the patent applications, in which a complicated mixture of amines and alcohols was obtained with low selectivity, as shown in Scheme 37.[142] Cole-Hamilton later reported that secondary and tertiary amines were identified as main products in the hydrogenation of butanamide using the same catalytic system under similar conditions.[205] An addition of aqueous ammonia to the catalyst [Ru_2(TriPhos^{Ph})$_2Cl_3$] in THF caused a significant improvement in the product yield to up to 85% (Scheme 37).[205] Notably, the hydrogenation of *N*-phenylnonamide with catalyst Ru(acac)$_3$/TriPhos^{Ph} proceeded smoothly to give the corresponding secondary amine in up to 99% yield.[205,206]

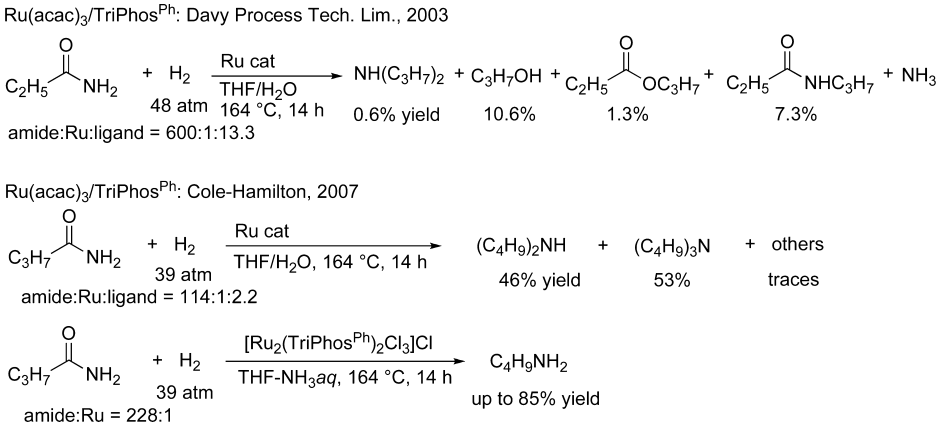
In 2008, Ikariya's group disclosed selective and direct hydrogenation of lactams and carboxamides to form carboxiamido alcohols and a mixture of amines and alcohols, respectively, using the catalyst **3** Cp*RuCl(N−N) (N−N: 2-$C_5H_4NCH_2NH_2$) combined with the base (path B in Scheme 36).[216] The substrate scope of the carboxamides was delicately influenced by the electronic nature of the substituent on the nitrogen, as shown in Scheme 38. For example, *N*-phenylpyrrolidinone was smoothly hydrogenated in 2-propanol containing 10 mol % **3** to give 4-(phenylamino)butan-1-ol in 73% isolated yield, although *N*-benzylpyrrolidinone was reluctant under similar conditions. Nevertheless, a wide variety of carboxamides were susceptible to the present hydrogenation as long as they had an aryl group on their nitrogen, as listed in Scheme 38. The inertness of carboxamides lacking any aryl group on the nitrogen allowed a chemoselective hydrogenation of a certain type of amide esters bearing an ester unit in the same molecule, which cleanly gave the hydroxyalkyl-substituted lactams under similar conditions. Notably, in the hydrogenation of lactams bearing no substituent on the nitrogen, the corresponding cyclic amines can be obtained via selective dehydration (path A in Scheme 36).[217]

Milstein's group also reported that bifunctional pincer-type catalyst **15** effected the hydrogenation of carboxamides under mild pressure and neutral conditions to give amines and alcohols in good to excellent yields, as shown in Scheme 39.[218] The TOF of the catalysts is 1 order magnitude smaller than described for ester hydrogenations using the same or similar catalysts (vide supra).

Recently, Bergens and co-workers demonstrated that Noyori-type chiral dihydride complex RuH_2(binap)(diamine) **1**, which is the active catalyst for ester or lactone hydrogenation (vide supra), is applicable to the hydrogenation of some carboxamides to the corresponding amino alcohols via path B in Scheme 36. The reaction with S/C = 10−50 under 50 atm of H_2 at 100 °C gave the products in moderate yields.[219] The same group found that newly prepared cationic precatalyst **18** (see Scheme 41)[219,220] or $RuCl_2$(P−N)$_2$ **5** (see Figure 1) are very active for the hydrogenation of *N*-phenylpyrrolidin-2-one with the highest TON (up to 7100 after 24 h) and TOF (up to 296 h^{-1} after 24 h) reported to date in the carboxamide hydrogenation under homogeneous condition, as shown in Scheme 40.[219] Precatalyst **18** combined with the base KN[$SiMe_3$]$_2$, promoted the hydrogenation of variety of lactams or esters with *S*/*C* = 1,000 to give the desired products in moderate to excellent yields as shown in Scheme 41. Begnens' system based on the precatalyst **18** is more active than Milstein's bifunctional catalyst **15** and than Ikariya's bifunctional precatalyst **3**. For example, in the reduction of *N*-phenylbenzamide, the TON = 500 (TOF = 20.8 h^{-1}) after 24 h was achieved for **18**, TON = 92 (TOF = 1.9 h^{-1}) for **5** after 48 h, TON = 8 (TOF = 0.3 h^{-1}) for **3** after 24 h.

Under the hydrogenation conditions in the presence of the base, both complexes **5** and **18**, because of the structural similarity, could generate the same active species. In fact,

Scheme 37. Hydrogenation of Carboxamides with the Ru-TriPhos^{Ph} Catalyst



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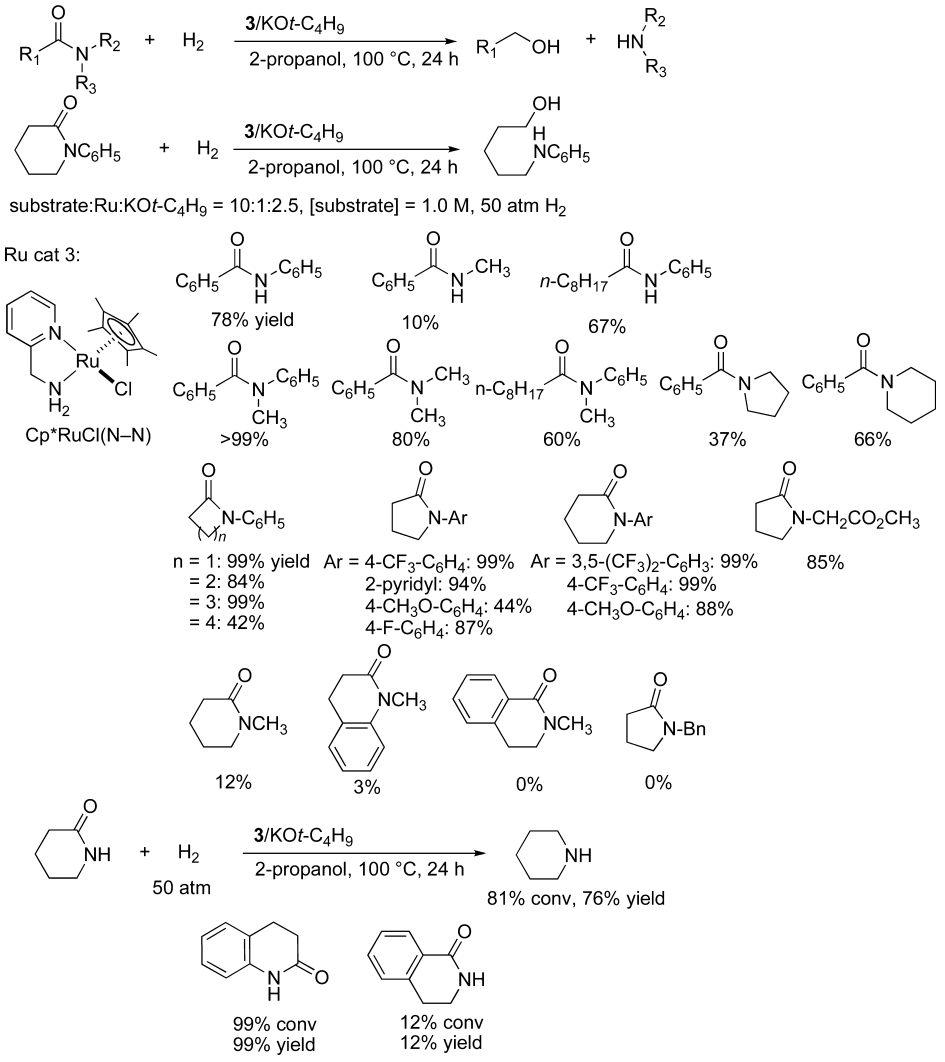
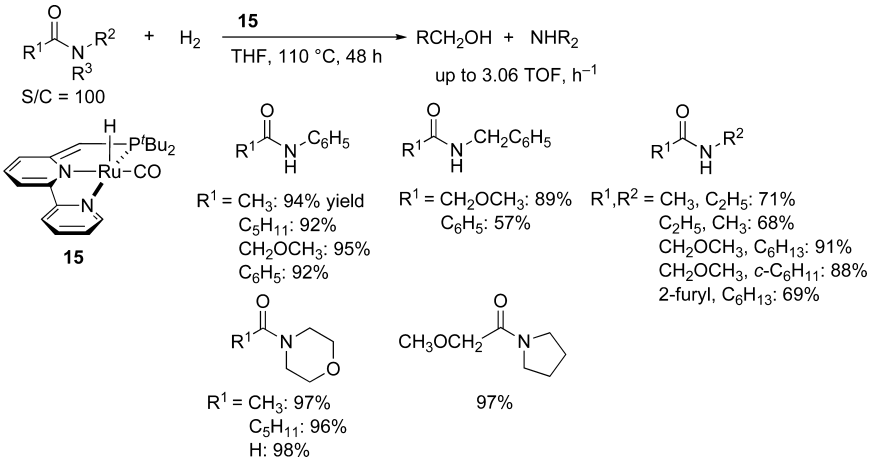
Scheme 38. Lactames or Carboxamides Hydrogenation Using Ikariya's Bifunctional Catalyst 3[216,217]



Scheme 39. Hydrogenation of Carboxamides with Milstein-Type Bifunctional Catalyst 15[218]



complex **18** or **5** readily reacts with atmospheric H_2 and 3 equiv of $KN[SiMe_3]_2$ in THF to form a similar mixture composed of three ruthenium monohydrides, which transforms further under 4 atm of H_2 in the presence of 10 equiv of the same base at room temperature to generate a symmetrical dihydride as the major product, which was tentatively assigned to *trans*-$[Ru(H)_2(Ph_2P(CH_2)_2NH_2)_2]$.[219]

2.7. Hydrogenation of Organic Carbonates, Carbamates, and Ureas. Mild catalytic hydrogenation of organic carbonates, carbamates, and urea derivatives to methanol, which is a fuel and a key chemical intermediate for industry, is of

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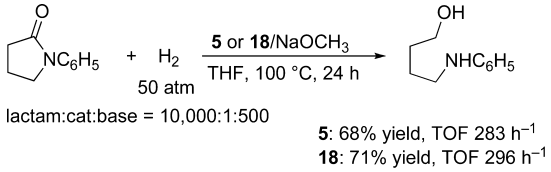
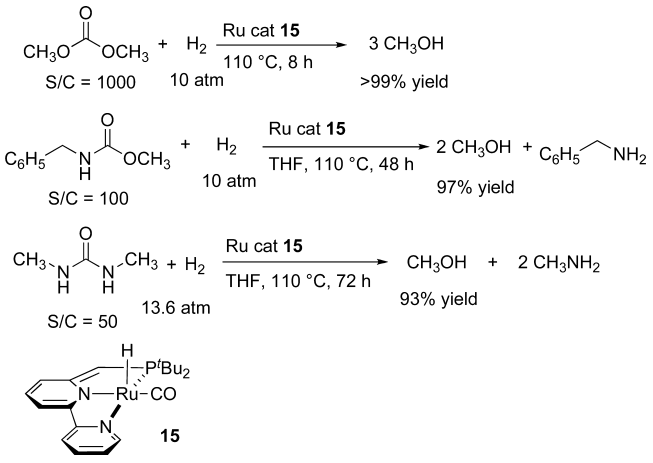
Scheme 40. Hydrogenation of *N*-Phenylpyrrolidin-2-one Using 5 or 18 and NaOMe[219,220]



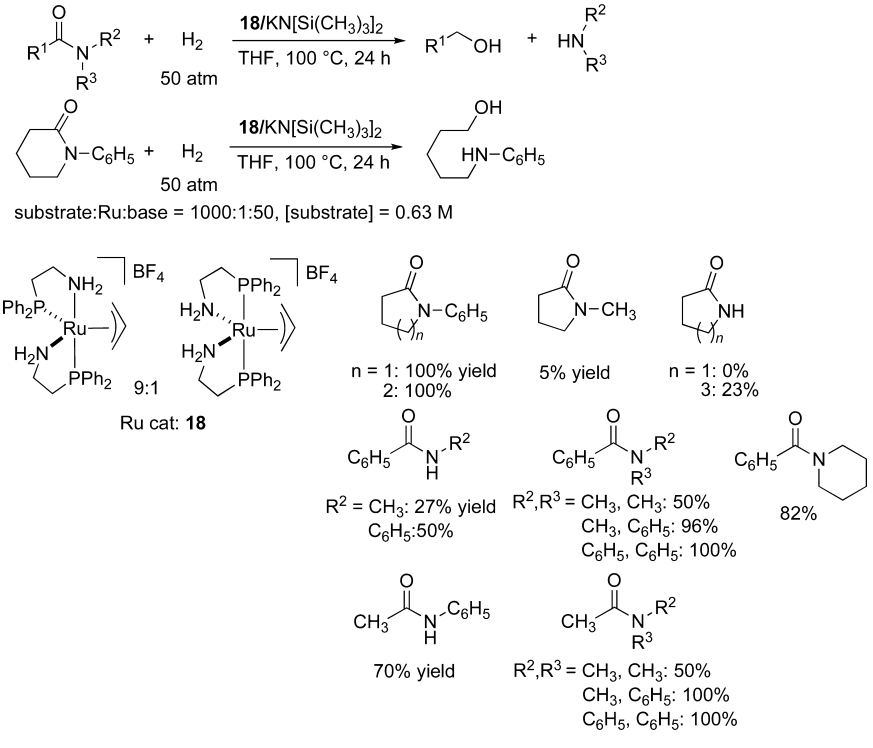
significant interest because these compounds can be produced from CO_2. Although hydrogenation of these compounds is the indirect access to methanol from CO_2,[221,222] the transformation of the carbon dioxide into methanol under mild conditions is an attractive process to a chemist. Methanol has already been industrially produced by hydrogenation of CO and CO_2 for more than 80 years,[223] but this is only possible at high temperatures (250−300 °C) and pressures with heterogeneous catalysts. Catalytic hydrogenation of these compounds was reported recently, and for the first time by Milstein group.[157,224] Due to very low electrophilicity of the carbonyl group (Scheme 1), as a result of resonance effects involving alkoxy or amido groups, development of efficient hydrogenation of carbonic acid derivatives is the most challenging. The hydrogenations were efficiently catalyzed by Milstein's bifunctional PNN Ru pincer catalysts bearing the pyridine- and bipyridine-based tridentate ligands. The reactions proceeded smoothly under neutral and mild temperatures and under mild hydrogen pressures in the absence of solvent, representing a minimum waste process and the ultimate "green" reactions. Some representative examples are presented in Scheme 42. Dimethyl carbonate can be quantitatively transformed into methanol after 1−8 h, depending on the reaction conditions used. The TON > 990 (TOF = 124 h^{-1} after 8 h) for this reaction obtained in the absence of the solvent was improved up to TON = 4400 (TOF = 314 h^{-1} after 14 h) when the reaction was carried out under higher hydrogen pressure (50 atm) in THF. Gusev's catalyst **17** also effected the hydrogenation of dimethyl carbonate to methanol with S/C = 2000 in THF with 85% conversion after 5.7 h at 100 °C (49 atm of H_2).[196] Recently density functional theory studies describing the hydrogenation of dimethyl carbonate catalyzed by complex 7 appeared.[225]

Scheme 42. Hydrogenation of Organic Carbonates, Carbamates and Urea Derivatives Using Milstein's Bifunctional Catalyst 15[157,224]



Methyl *N*-benzyl carbamate can be hydrogenated into the corresponding products (97% yield based on MeOH) using **15**, although at a lower S/C (100) and longer reaction time (TON = 97, TOF = 2 h^{-1} after 48 h).[157] Hydrogenation of various urea derivatives with S/C = 50 proceeds slowly to give the corresponding amines and methanol in good to excellent yields after 72 h.[224]

Scheme 41. Lactams or Carboxamides Hydrogenation Using Bergens' Bifunctional Precatalyst 18[219,220]



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3. SUMMARY AND OUTLOOK

This Review has described a comprehensive overview on homogeneous catalytic hydrogenation of carboxylic acids and its derivatives as well as carbonic acid derivatives with transition metal-based molecular catalysts. Despite the tremendous potential in the hydrogenation of these less electrophilic carbonyl compounds using molecular hydrogen in synthetic organic chemistry, their reduction has relied mostly on the stoichiometric use of metal hydride reagents, such as $LiAlH_4$, $NaBH_4$, and their derivatives. Significant and rapid progress, particularly ester hydrogenation, has been achieved for the past decade by utilization of conceptually new bifunctional molecular catalysts originating from the metal−ligand cooperation effects based on Noyori−Ikariya's metal−ligand NH synergy effect or Milstein's aromatization−dearomatization concept. However, most molecular catalysts still need relatively forced reaction conditions in terms of the temperature and pressure. Only a limited number of catalyst systems for the hydrogenation at room temperature and under lower hydrogen pressure conditions have been developed. The development of base-free catalysts for hydrogenation is also highly desirable from a practical point of view, since the base could promote undesired catalysis including hydrogenation itself.[226,227]

Of particular note are the base-free catalysts that promoted hydrogenation of chiral esters bearing protected α- or β-hydroxy groups to give the corresponding chiral alcohols without serious loss in the enantiomeric excess values and the chiral catalysts that allowed enantioselective hydrogenation of α-substituted γ-butyrolactones, giving chiral diols via dynamic kinetic resolution. Therefore, the rational design of new molecular catalyst systems is crucially important to explore unprecedented catalytic performance for hydrogenation of polar functionalities. The industrial outlook for the present hydrogenation with the sophisticated catalyst is also bright because of its excellent catalytic performance, operational simplicity, and economic viability as well as the growing awareness of the need for green chemistry. We believe the next generation catalysts would offer a great opportunity to open up new reduction chemistry using the H_2 molecule and industrial processes.

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Notes

The authors declare no competing financial interest.

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