Organometallic Catalysis

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The N–H Functional Group in Organometallic Catalysis

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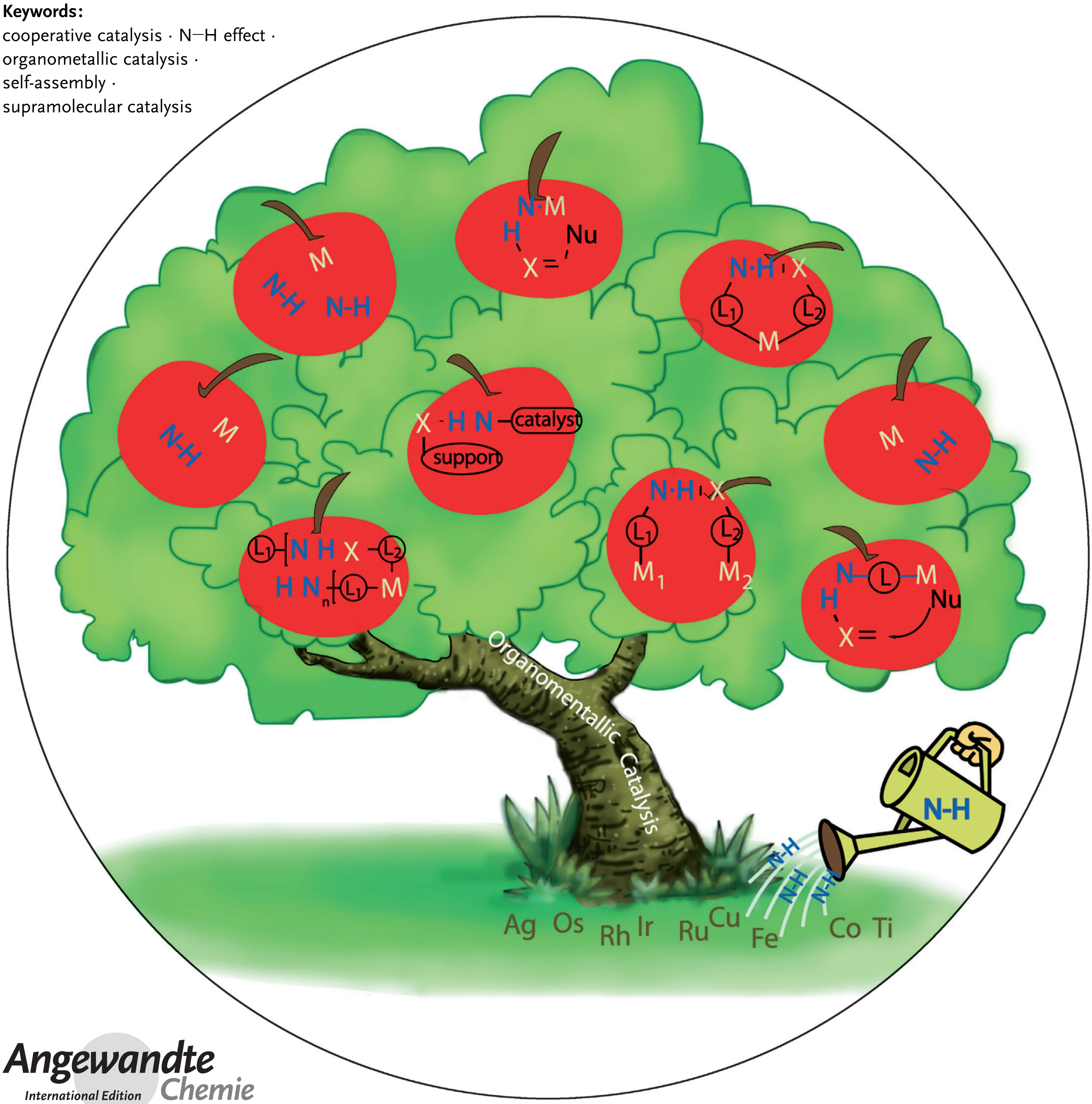

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The organometallic approach is one of the most active topics in catalysis. The application of NH functionality in organometallic catalysis has become an important and attractive concept in catalyst design. NH moieties in the modifiers of organometallic catalysts have been shown to have various beneficial functions in catalysis by molecular recognition through hydrogen bonding to give catalyst–substrate, ligand–ligand, ligand–catalyst, and catalyst–catalyst interactions. This Review summarizes recent progress in the development of the organometallic catalysts based on the concept of cooperative catalysis by focusing on the NH moiety.

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1. Introduction

Organometallic catalysis is a powerful method for molecular transformations in organic synthesis and chemical industry.[1] Organometallic catalysts, which are generally composed of central metals and coordinating ligands, play one of the central roles in homogenous catalysis. The metal is usually the catalytic center where the reaction proceeds, and the ligand plays a significant role by changing the electronic properties of the metal and adjusting the steric circumstances around the metal center. Although many breakthroughs have been achieved in the field of organometallic catalysis over the past decades,[1] the development of new efficient catalysts, especially with high activities and selectivities, is still highly desirable to meet the increasing demands of organic transformations under very mild reaction conditions. To promote further development of organometallic catalysis, various new concepts and strategies have been actively introduced to this area. For example, recently multifunctionalization and self-assembly have been widely employed for the development of new ligands and catalysts.[2] In contrast to traditional organometallic catalysis, multifunctional catalysis employs metal–metal and/or metal–ligand cooperations to realize chemical transformations as a natural enzyme does.[2] The self-assembly strategy utilizes noncovalent interactions instead of covalent bonds to connect different units to generate supramolecular ligands and/or catalysts in situ, thus simplifying catalyst synthesis and expanding ligand and catalyst diversities.[2o,q,a-b,af,aj,al–an]

The ligand is the key for the implementation of self-assembly and multifunctional strategies in organometallic catalysis. Along with the chelating atoms, additional functional groups are usually required to implement these catalytic strategies. NH moieties in organometallic catalysts can serve as coordination groups, hydrogen bonding donors, hydrogen bonding acceptors, and/or proton sources. These functions can be utilized to achieve metal–ligand multifunctional catalysis and/or to form self-assembled ligands and catalysts. Moreover, NH moieties are readily available, chemically stable, and easily introduced to the ligands. Therefore, the NH moiety is the ideal functional group for the formation of multifunctional and self-assembled catalysts. Many breakthroughs have been achieved in this area during the last two decades. The NH functions, that is the additional and beneficial effects of the NH groups on catalytic transformation, ligand assembly, and/or catalyst formation in organometallic catalysis will be focused on in this Review.

NH functions in organometallic catalysis can be classified into five categories according to the types of interaction with substrates, ligands, or catalysts (Figure 1):

(1) M−NH catalysis: The NH moieties directly coordinate to the central metal, and the NH protons take part in the catalytic event by cooperation with the metal-bonded species (Nu) (Figure 1 a).

(2) M⋯NH catalysis: The NH moieties usually do not directly bind to central metal by a coordinating interaction, but cooperate with the metal-bounded species (Nu) in the catalytic process by activation and/or recognition of substrates. The position of the NH moieties relative to the metal center is crucial to the efficiency of the cooperative catalysis (Figure 1 b).

(3) Assembly of ligands: The NH moieties do not participate in catalytic process, but promote in situ formation of self-assembled ligands through hydrogen bonding (Figure 1 c).

(4) Assembly of catalysts: The NH moieties initiate the formation of self-assembled catalysts through hydrogen bonding (Figure 1 d).

(5) Immobilization of homogeneous catalysts: The NH moieties anchor homogeneous catalysts to an inorganic or organic support, polymerize homogeneous monomers to form self-supported catalysts, or heterogenize homo-

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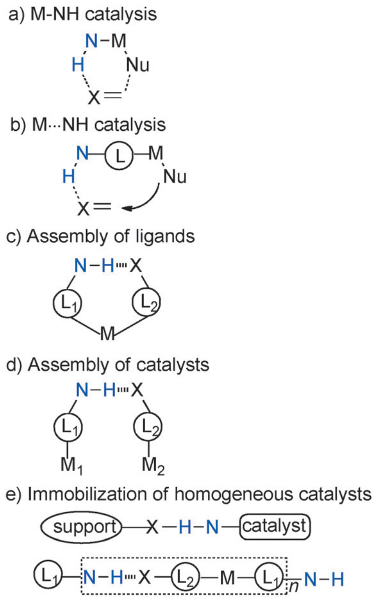


Figure 1. NH functions in organometallic catalysis. X represents a hydrogen-bonding acceptor atom, such as N, O, and S; L, L_1, and L_2 represent coordinating moieties of ligands.

geneous catalysts at the end of a reaction through hydrogen bonding interactions (Figure 1 e).

Although many successful applications of NH functions in organometallic catalysis have been achieved, reviews on this chemistry are still very limited. Noyori,[2d,f–h,l,m,r] Ikariya,[2t–v,z,aa,ag,ai] Andersson and Bäckvall,[2s] and others[2p,y,ae] have contributed several excellent reviews on M–NH bifunctional catalysis recently; however, a thorough review including diverse aspects of NH functions in organometallic catalysis have not been reported to date. Based on this situation, we try to include, classify, and summarize the main aspects of N-H functions in organometallic catalysis in this Review, and we try to provide an overview of this chemistry and provide useful perspectives for future development of this exciting area.

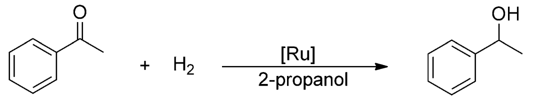
2. M–NH Catalysis

2.1. M–NH-Catalyzed Hydrogenation of C=O and C=N Bonds

Hydrogenation of C=O and C=N bonds to alcohols and amines, respectively, is among the most important organic transformations. The M–NH system has shown high catalytic activity and excellent chemo-, diastereo-, and enantioselectivities in the hydrogenation. The metal in the catalyst system can be Ru, Rh, Ir, Fe, or Os.

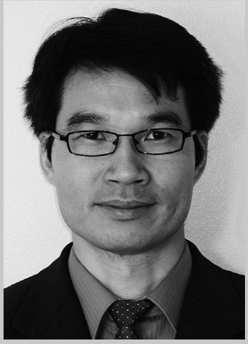
2.1.1. Ru–NH-Catalyzed Hydrogenation of C=O and C=N Bonds

One of the most successful examples of M–NH catalysis is the Ru(phosphine)$_2$–diamine system developed by Noyori and co-workers in 1995.[3] The system showed exceptionally high catalytic activity for hydrogenation of ketones. In the studies of Ru-catalyzed hydrogenation of acetophenone, a dramatic acceleration effect of ethylenediamine on the reaction was observed (Scheme 1).[2f,3] For example, when $[RuCl_2(PPh_3)_3]$ alone was used, the turnover frequency (TOF) was less than 5 h^{-1} (Scheme 1, entry 1). However, when $[RuCl_2(PPh_3)_3]$ was combined with 1 equiv of ethylenediamine and 20 equiv of KOH, the hydrogenation rate was enhanced remarkably, with a TOF of 6700 h^{-1} under otherwise identical conditions (Scheme 1, entry 2). Further screening of diamine additives showed that the NH moiety of the chelating amine was the key for this superhigh catalytic efficiency, as chelating amines without NH moieties, such as *N*,*N*,*N*′,*N*′-tetramethylethylendiamine (TMEDA) did not



entry	[Ru]	TOF [h^{-1}]
1	$[RuCl_2(PPh_3)_3]$	< 5
2	$[RuCl_2(PPh_3)_3]/\mathbf{NH_2}(CH_2)_2\mathbf{NH_2}/KOH$ (1:1:20)	6700
3	$[RuCl_2(PPh_3)_3]/\mathbf{N(CH_3)_2}(CH_2)_2\mathbf{N(CH_3)_2}/KOH$	very low

Scheme 1. NH effect on the Ru-catalyzed hydrogenation of acetophenone.

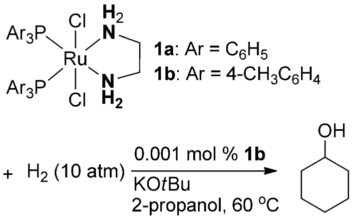


Baoguo Zhao received his Ph.D. degree from the Shanghai Institute of Organic Chemistry, Chinese Academy of Science, under the supervision of Professor Kuiling Ding in 2006. He then worked with Professor Yian Shi for five years as a postdoctoral fellow at the Department of Chemistry of Colorado State University. In 2011 he joined the Shanghai Normal University as a full professor. His current research interests include the development of new methods and novel chiral catalysts for asymmetric reactions.

Zhaobin Han received a B.S. degree in chemistry from Nanjing University in 2003 and a Ph.D. degree from the Shanghai Institute of Organic Chemistry under the supervision of Prof. Kuiling Ding and Prof. Xumu Zhang in 2009 working on development of novel chiral spiro ligands for Ir-catalyzed asymmetric hydrogenation. He continued his research in Prof. Kuiling Ding's group as a research associate until 2012, and is currently a postdoctoral research associate in Prof. Michael J. Krische's group at the University of Texas at Austin.

show any acceleration effect for the hydrogenation (Scheme 1, entry 3).

Further research confirmed that the active catalyst for the highly active catalytic system was *trans*-[$RuCl_2$(phosphine)$_2$(1,2-diamine)] complex **1a** (Scheme 2).[4]

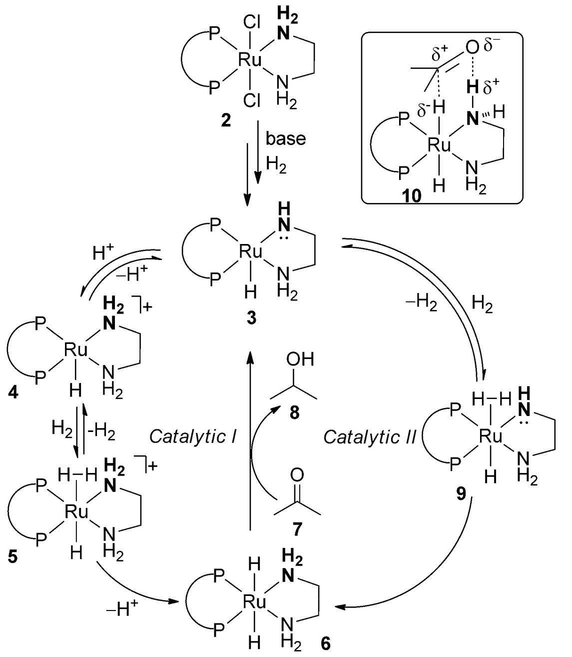


Scheme 2. Highly active *trans*-[$RuCl_2$(phosphine)$_2$(1,2-diamine)] complexes for ketone hydrogenation.

The pre-prepared complex exhibited even higher activity and productivity in the hydrogenation of ketones than the catalyst formed in situ from Ru^{II} precursor, ethylenediamine, and base. For example, cyclohexanone was smoothly hydrogenated in 2-propanol by using 0.001 mol% of **1b** as catalyst, giving cyclohexanol in 96% yield with an initial TOF of 563000 h^{-1} (Scheme 2). Besides the unprecedented catalytic activity, the [$RuCl_2$(phosphine)$_2$(1,2-diamine)] system also exhibited excellent chemo- and stereoselectivities in the hydrogenation of ketones.[4,5]

Mechanistic studies provided an explanation for the high catalytic efficiency and the profound NH effect of the chelating amines.[6] A metal–ligand bifunctional mechanism was proposed for the ketone hydrogenation (Scheme 3). The reaction starts with the generation of the active species, 16e amido Ru complex **3**, from [$RuCl_2$(phosphine)$_2$(1,2-diamine)] (**2**) under basic conditions and a H_2 atmosphere. The following reaction likely involves two different pathways, catalytic cycle I and catalytic cycle II, which are dependent on reaction conditions. When the hydrogenation is carried out in protic solvent, such as alcohols, the amido nitrogen of complex **3** is easily protonated to form cationic 16e complex **4**, which then combines H_2 to form intermediate **5**. Deprotonation from the η^2-H_2 ligand of **5** gives the reducing 18e Ru dihydride **6**, which reacts with ketone **7** to give alcohol product **8** and regenerate 16e amido Ru complex **3**, completing the catalytic cycle I. On the other hand, if the hydrogenation proceeds in aprotic solvents or with high concentration of base, catalytic cycle II may predominate in the following reaction of the 16e Ru complex **3**. Coordination of a H_2 molecule to the Ru center of **3** reversibly generates complex **9**, followed by heterolytic cleavage of the H_2 in **9** to form the dihydride **6**. Ru dihydride **6** reduces ketone **7** to give alcohol product **8** and regenerate the 16e amido Ru complex **3**, completing the catalytic cycle II.

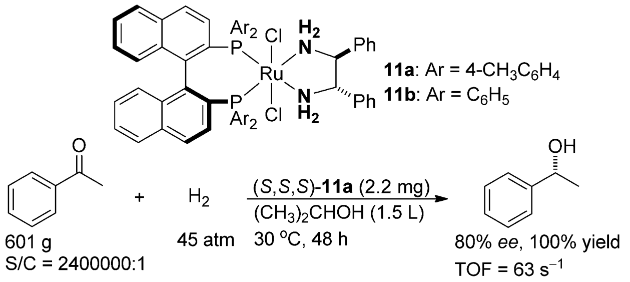
Kuiling Ding received his Ph.D. degree from Nanjing University under the supervision of Prof. Yangjie Wu in 1990. Then he joined Zhengzhou University as an assistant professor and was promoted as a full professor in 1995. He spent two years in Japan as a postdoctoral fellow and a UNESCO research fellow with Prof. Teruo Matsuura at Ryukoku University (1993–1994) and Prof. Koichi Mikami at Tokyo Institute of Technology (1997–1998) before he moved to the Shanghai Institute of Organic Chemistry in 1999. His research interests include the development of new methods and novel chiral catalysts for asymmetric catalysis.



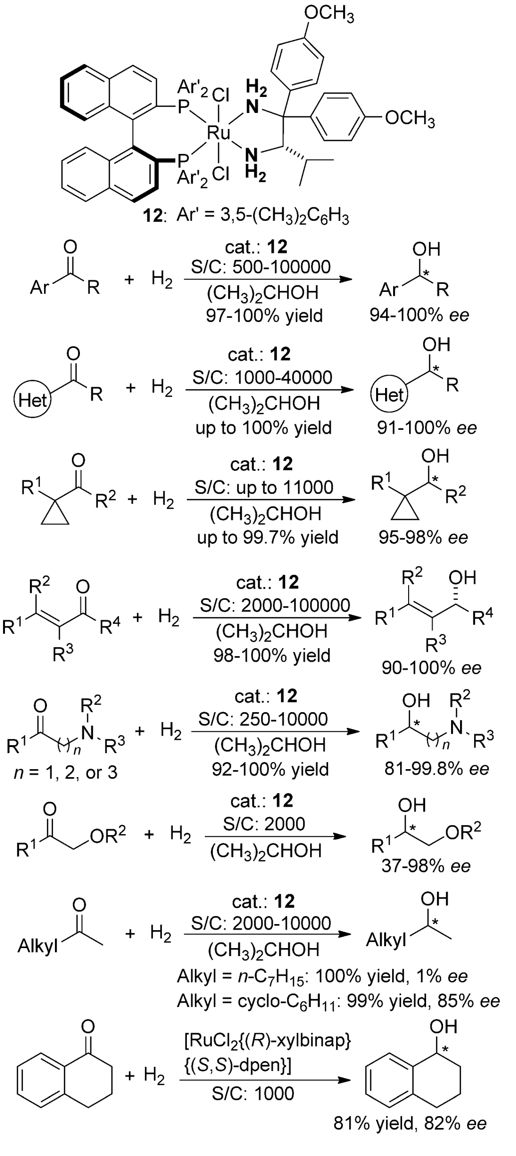
Scheme 3. Proposed metal–ligand bifunctional mechanism for Ru–NH catalyzed hydrogenation of ketones.

The reaction of the 18e Ru dihydride **6** and ketone **7** is proposed to proceed via a concerted outer-sphere mechanism (Scheme 3). The ketone substrate does not directly interact with the Ru center. A hydride from the Ru center and a proton from the NH_2 ligand are simultaneously delivered onto the carbonyl group of ketone **7** via a six-membered pericyclic transition state **10**. To form transition state **10**, at least one NH end of the chelating amine is needed. This concerted hydrogenation mechanism most likely accounts for the high catalytic efficiency and the dramatic NH effect.

The corresponding chiral Ru–NH catalyst system composed of chiral phosphines and diamines developed by Noyori exhibited unprecedentedly high activities in asymmetric hydrogenation of ketones (Scheme 4).[3,4] For example, 601 g of acetophenone was smoothly hydrogenated by using 2.2 mg of ruthenium complex (*S*,*S*,*S*)-**11a** as catalyst, giving the corresponding chiral alcohol in quantitative yield and 80% *ee* (Scheme 4).[4] The TON of the reaction was up to 2400000. The enantioselectivity of the reaction was moderate, but it can be significantly improved by introducing more bulky phosphine ligands, such as 2,2′-bis(di-3,5-xylylphosphino)-1,1′-binaphthyl (XylBINAP) and/or more bulky diamine ligands, such as 1,1-di(4-anisyl)-2-isopropyl-1,2-ethylenediamine (DAIPEN) (Scheme 5).[2f,3–5,7,8] For example, ruthenium com-



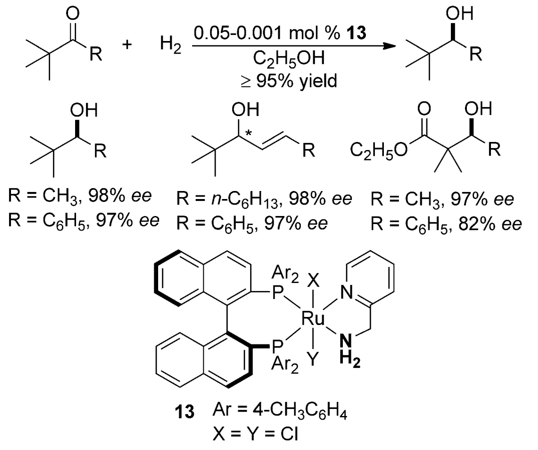
Scheme 4. Highly efficient hydrogenation of acetophenone.



Scheme 5. Asymmetric hydrogenation of various ketones in the presence of [RuCl$_2$(phosphine)$_2$(1,2-diamine)] catalyst.

plex **12**, generated from XylBINAP and DAIPEN, is a highly efficient catalyst for asymmetric hydrogenation of various aromatic ketones,[7a] heteroaromatic ketones,[7b] cyclopropyl ketones,[2f,7a] olefinic ketones,[7a] amino ketones,[8] and α-alkoxy ketones,[2f] giving the corresponding alcohols in high yields and excellent enantioselectivities (Scheme 5). The catalyst system tolerates various functional groups, such as F, Cl, Br, I, CF_3, OCH_3, $OCH_2C_6H_5$, COOR, NO_2, NH_2, NR_2, and NRCOR (R = H, alkyl, or aryl) in the substrates. However, the [RuCl$_2$(phosphine)$_2$(1,2-diamine)] system has not yet been efficient enough for the asymmetric hydrogenation of α-tetralones and simple dialkyl ketones, such as nonan-2-one (Scheme 5).[2f]

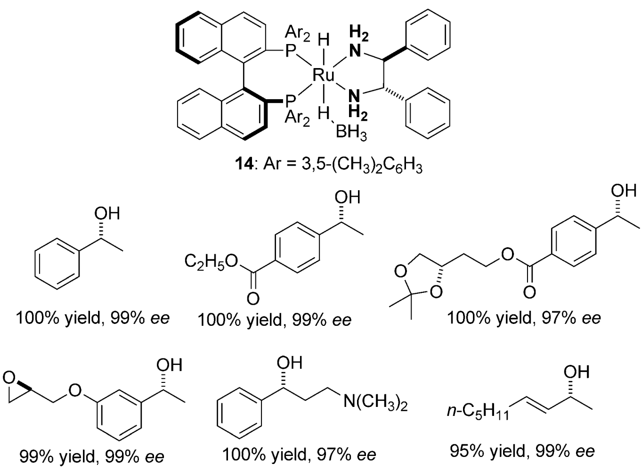
For an obvious steric reason, highly bulky ketones, such as *tert*-alkyl ketones, were extremely difficult substrates for asymmetric hydrogenation. For example, only 20 % yield and 14 % *ee* were obtained in the asymmetric hydrogenation of pinacolone by using *trans*-[RuCl$_2${(*S*)-tolbinap}{(*S*,*S*)-dpen}] (**11a**) as catalyst.[9a] In 2005, Noyori developed Ru complex **13**, which is very efficient for enantioselective hydrogenation of *tert*-alkyl ketones (Scheme 6).[9a] The high activity of complex **13** most likely lies in the fact that the small size of the NH_2/pyridine hybrid ligand allows the approach of the sterically bulky substrate to the Ru catalyst. As shown in Scheme 6, a wide range of *tert*-alkyl ketones were efficiently hydrogenated in ethanol by using complex **13** as catalyst, giving various chiral *tert*-alkyl carbinols with high enantiomeric purities. This catalyst is also effective for acyl silanes, affording various chiral α-hydroxysilanes in high yields and excellent *ee* values.[9b]



Scheme 6. Asymmetric hydrogenation of *tert*-alkyl ketones with Ru catalyst **13**.

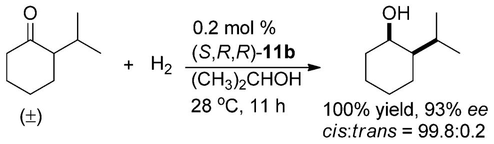
Usually the base, such as KOH or *t*-C_4H_9OK, is critically important for the in situ generation of an active amido species **3** from a [RuCl$_2$(diphosphine)(diamine)] complex in the hydrogenation (Scheme 3). For base-sensitive substrates, a hydrogenation procedure under neutral conditions would be highly desirable. To meet this demand, Noyori developed a new Ru complex **14** in 2001 (Scheme 7).[10] Complex **14** catalyzed asymmetric hydrogenation of ketones under base-free conditions with high activity and good enantioselectivity (Scheme 7). Base-labile groups, such as an epoxy ring, were well tolerated in the hydrogenation.

[RuCl$_2$(diphosphine)(diamine)] complexes have also been used as efficient catalysts for dynamic kinetic resolution of racemic ketones.[5b,11] For configurationally labile α-ketones,

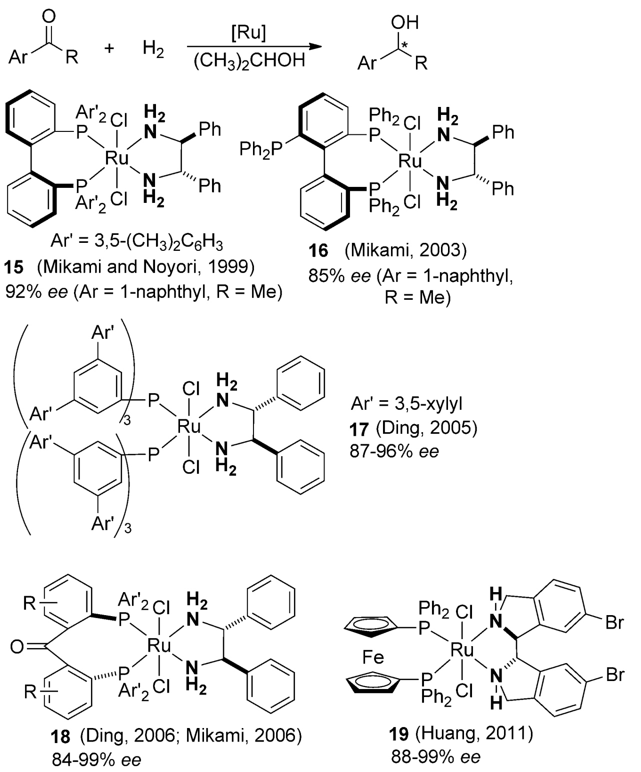


Scheme 7. Asymmetric hydrogenation of ketones under neutral conditions catalyzed by Ru complex **14**.

in situ stereomutation occurred during the asymmetric hydrogenation. Chiral alcohols with contiguous stereogenic centers could thus be obtained in quantitative yields (Scheme 8).[5b]



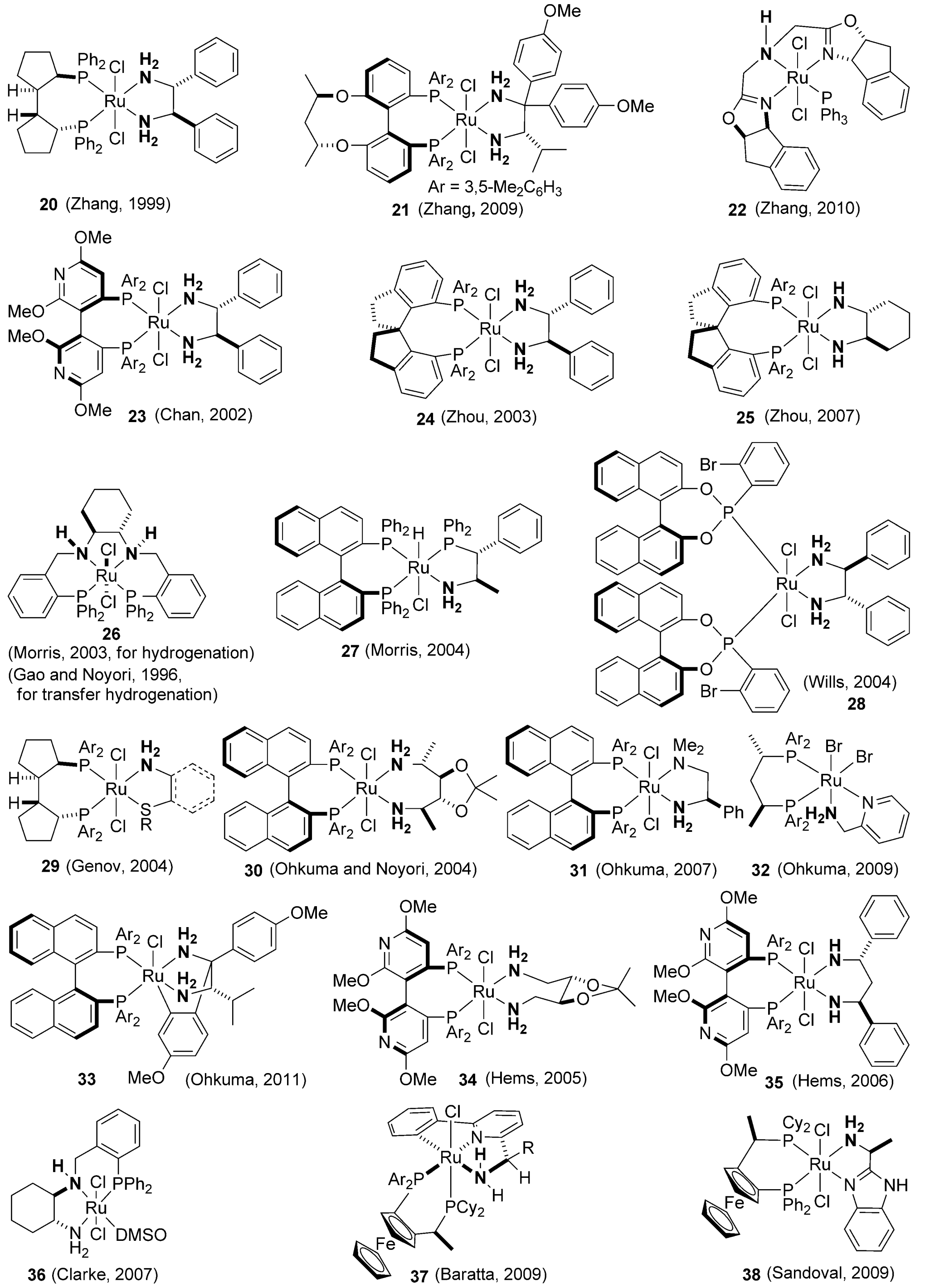
Scheme 8. Asymmetric hydrogenation of a racemic α-substituted ketone.



Scheme 9. Asymmetric hydrogenation of ketones catalyzed by ruthenium complexes with achiral phosphines and chiral diamines.

The asymmetric activation concept can be applied to the [RuCl$_2$(diphosphine)(diamine)] system.[12] When a racemic or achiral diphosphine along with a chiral diamine was used, high enantioselectivity was still obtained in the hydrogenation (Scheme 9).[12–15] For example, Mikami and Noyori used an achiral biphosphine, such as the 2,2′-[(3,5-dimethylphenyl)-phosphanyl]biphenyl ligand (DM-BIPHEP), instead of a chiral ligand to form ruthenium complex **15** for the asymmetric hydrogenation of aryl ketones.[13a] Good enantioselectivity (up to 92% *ee*) was achieved in the hydrogenation of 1′-acetonaphthone catalyzed by **15**. By following similar strategies, Mikami applied chiral ruthenium complex **16** generated from an achiral tridentate phosphine ligand to asymmetric hydrogenation of 1′-acetonaphthone, giving the corresponding alcohol in 85% *ee* and quantative yield.[13b] In 2005, Ding and co-workers developed Ru complex **17** from inexpensive monodentate achiral phosphine ligands and enantiopure diphenylethylenediamine (DPEN).[14a] Complex **17** efficiently catalyzed hydrogenation of various aromatic ketones with excellent enantioselectivities (87–96% *ee*). In 2006, Mikami[13c] and Ding[14b,c] independently reported the same Ru complex **18**, which displayed good enantiocontrol in asymmetric hydrogenation of aromatic ketones. Very recently, Huang and co-workers developed Ru catalyst **19** from a rigid chiral diamine and an achiral diphospine (DPPF), which catalyzed asymmetric hydrogenation of simple aromatic ketones with 88–99% *ee*.[15]

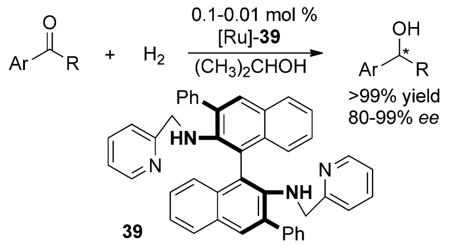
Following the pioneering work of Noyori, various catalysts analogous to [RuCl$_2$(diphosphine)(diamine)] have been developed on the basis of the M—NH catalysis concept (Scheme 10). In 1999, Zhang and co-workers developed a new Ru catalyst **20** from a rigid 1,4-bisphosphine (2*R*,2′*R*)-bis(diphenylphosphino)-(1*R*,1′*R*)-dicyclopentane (BICP) and (*R*,*R*)-diphenylethylenediamine (DPEN).[16] Catalyst **20** exhibited moderate to good enantioselectivities (26–93% *ee*) in the hydrogenation of aromatic ketones. Very recently, the same group reported Ru catalysts **21** and **22** for asymmetric hydrogenation of ketones.[17] High activities (S/C up to 1000000) and excellent enantioselectivities (93–>99% *ee* for **21** and 42–97% *ee* for **22**) were observed in the hydrogenation. In 2002, Chan and co-workers reported Ru complex **23**, which was an efficient catalyst for asymmetric hydrogenation of aromatic ketones (S/C up to 100000 and *ee* up to >99%).[18] Zhou and co-workers developed a series of spiro diphosphine ligands and successfully applied them to Ru^{II}-catalyzed asymmetric hydrogenation of ketones in the presence of chiral diamines.[19] Catalysts **24** and/or **25** demonstrated excellent performances in asymmetric hydrogenation of aromatic ketones,[19a,b] racemic α-arylketones,[19b] α-arylaldehydes,[19c] and α-aminoketones,[19d,e] giving various chiral alcohols with very high enantio- and diastereoselectivities. In 2003, Morris and co-workers clearly demonstrated that some transfer hydrogenation catalysts also catalyzed the hydrogenation of ketones efficiently.[20a,21] The catalyst **26**



Scheme 10. Other representative Ru–phosphine–amine hydrogenation catalysts.

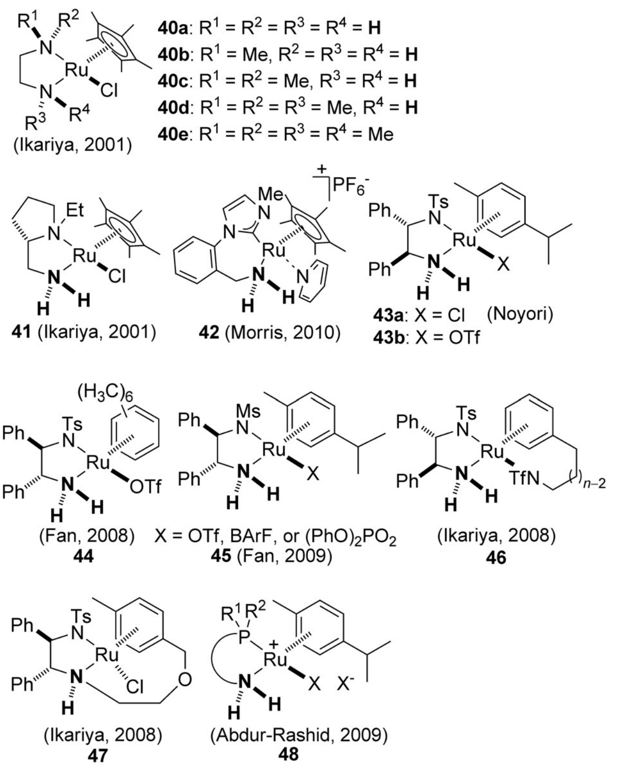
exhibited excellent catalytic activity (S/C up to 10^6) in the hydrogen of acetophenone, albeit in low enantioselectivity (13–25% *ee*).[20a,b] In 2004, the same group reported Ru complex **27** for asymmetric hydrogenation of ketones, affording the corresponding secondary alcohols with moderate enantioselectivities.[20c,d] Wills and co-workers used monodentate phosphorous ligands instead of biphosphines to prepare corresponding Ru complex **28**, which showed good asymmetric induction ability in the asymmetric hydrogenation of ketones.[22] Genov and co-workers developed Ru catalyst **29** from achiral chelating thioamines for asymmetric hydrogenation of aromatic ketones in 2004.[23] A series of aryl alcohols with 76–96% enantiopurities were obtained in the hydrogenation. Ohkuma and co-workers developed Ru complexes **30**–**33** by using different chiral diamines and phosphines.[24] Complex **30** showed 92–99% enantioselectivity in the asymmetric hydrogenation of difficult substrate 1-tetralones.[24a] Complex **31** is an efficient catalyst for the hydrogenation of aromatic ketones,[24b,c] α-heteroatom-substituted ketones,[24b,c] aryl vinyl ketones,[24d] and heterocycloalkyl ketones,[24g] giving the corresponding chiral alcohols with high ee values. Complexes **30** and **32** showed high catalytic activities (S/C up to 50000 for **30** and 100000 for **32**) and excellent enantioselectivities (97–>99% *ee* for **30** and 88% *ee* for **32**) in the asymmetric hydrogenation of bicyclic ketones.[24e,f] Very recently, the same group reported a novel ruthenabicyclic complex **33**, which displayed excellent performances in asymmetric hydrogenation of various ketones.[24h] Exceptionally high catalytic activities (TOF up to 35000 min^{-1}) and excellent enantioselectivities (77–>99% *ee*) were realized in the hydrogenation. Hems investigated the influence of diamine ligands on asymmetric hydrogenation of ketones.[25] Catalysts **34** and **35** were prepared from chiral 1,4-diamine and 1,3-diamine, respectively. Both catalysts displayed good to excellent enantiocontrol abilities in asymmetric hydrogenation of aromatic ketones. Clarke and co-workers developed Ru complex **36** from a chiral tridentate ligand in 2007, which catalyzed asymmetric hydrogenation of bulky ketones with moderate to good enantioselectivities.[26] Baratta[27] and Sandoval[28] developed Ru catalysts **37** and **38**, respectively, from 1-[1-(dicyclohexylphosphano)ethyl]-2-(diarylphosphano)ferrocene) (Josiphos), which are both good catalysts for asymmetric hydrogenation of ketones. As can been from Scheme 10, all of these Ru catalysts for asymmetric hydrogenation of ketones feature NH moieties in the amine ligands, which play a significant role for the activity of the catalysis.

In 2006, Kitamura and co-workers used phosphine-free tetradentate ligand **39** to form a new Ru catalyst, which was also highly efficient for the asymmetric hydrogenation of ketones under base-free conditions (Scheme 11).[29]

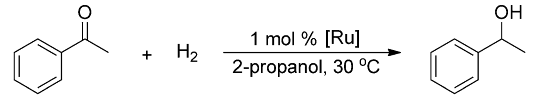


Scheme 11. A Ru–pyridine–amine catalyst in the hydrogenation of ketones.

Apart from the Ru(phosphine)$_2$–amine system discussed above, some Ru–(η^n-arene)–amine complexes are also highly active for the hydrogenation of C=O and C=N bonds. A phosphorus ligand is no longer a necessary constituent for this kind of catalyst. The representative catalysts of this category are listed in Scheme 12, including Ru–(η^5-Cp*)–amine (Cp* = pentamethylcyclopentadienyl, η^5-C_5Me_5) complexes **40**–**42** and Ru–(η^6-C_6R_6)–amine complexes **43**–**48**. Similar to the case of [$RuCl_2$(diphosphine)(diamine)], the NH moieties in these catalysts were also found to play an essential role in their catalytic activity in the hydrogenation of ketones. For example, Ikariya found that phosphine-free Cp*Ru–diamine complexes **40a**–**d** with NH ends could catalyze the hydrogenation of ketones with high efficiency (Scheme 13).[30] However, the catalyst **40e** containing a diamine ligand fully capped with methyl groups was completely ineffective for the reaction. Chiral Ru catalyst **41** derived from L-proline showed moderate to good selectivities (64–95% *ee*) in the asymmetric hydrogenation of aromatic ketones.[30] Morris developed Cp*Ru complex **42** from a chelating N-heterocyclic carbene bearing an NH_2 group, which was found to be an active catalyst for hydrogenation of polar bonds including ketones, an epoxide, ester, and ketimine under mild conditions.[31a] Catalyst **42** displayed much higher catalytic activity in the hydrogenation of acetophenone than a related Ru complex with a phosphine–NH_2 ligand (TOF up to 17600 h^{-1} for **42**). Mechanistic studies supported an outer-sphere bifunctional mechanism for the hydrogenation of ketones catalyzed by **42**.[31b,c]



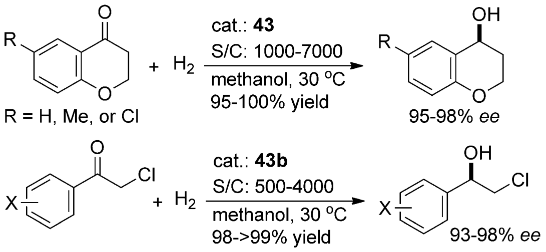
Scheme 12. Representative Ru(η^n-arene)–amine hydrogenation catalysts.



[Ru]	40a	40b	40c	40d	40e
Conv. [%]	41	98	100	57	0

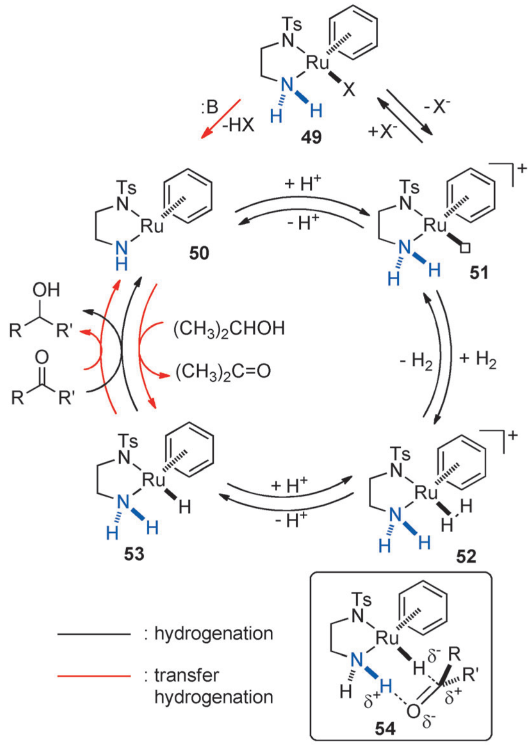
Scheme 13. NH effect in hydrogenation of acetophenone catalyzed by **40**.

In 2006, Noyori and co-workers reported an asymmetric hydrogenation of 4-chromanones, one type of challenging substrates in asymmetric hydrogenation owing to their cyclic structures and the relatively high acidity of the α-H of the carbonyl group, by using η^6-arene–Ru^{II} complexes **43** as catalyst (S/C up to 7000) under nonbasic conditions, affording the corresponding chiral alcohols with 95–98 % *ee* (Scheme 14).[32] The catalyst **43b** also displayed high enantioselectivities in the hydrogenation of α-chloro aromatic ketones (Scheme 14).[33] The chloro groups remained untouched in the reaction.



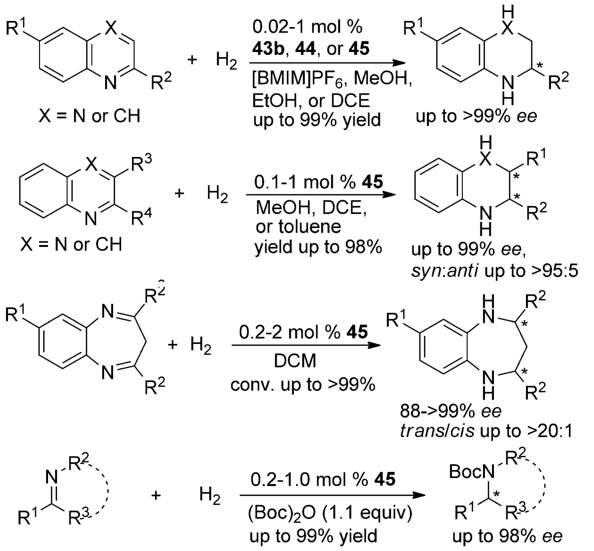
Scheme 14. Asymmetric hydrogenation of ketones catalyzed by Ru complexes **43**.

Complexes **43** are also highly efficient for asymmetric transfer hydrogenation of both C=O and C=N bonds,[34] indicating that hydrogenation[35] and transfer hydrogenation should be mechanistically related to each other. A complex mechanism has been proposed for the η^6-arene/TsDPEN-Ru^{II}-catalyzed hydrogenation and transfer hydrogenation of ketones.[32,35b,c,e] As shown in Scheme 15, ketone hydrogenation may proceed via the pathway indicated by the black arrow. Ionization of complex **49** generates 16e cationic Ru^{II} species **51**, which accommodates a H_2 molecule to form η^2-H_2 complex **52**. Heterolytic cleavage of the H_2 in **52** produces the reducing RuH species **53**, followed by hydrogenation of ketone to give alcohol product and amido Ru species **50**. Protonation of **50** by the solvent or the added acid regenerates the cationic Ru complex **51**, completing the catalytic cycle of the hydrogenation. On the other hand, when a strong base such as KOH and KO*t*Bu is used, the reaction can be switched to transfer hydrogenation catalyzed by **49**, which proceeds via the pathway indicated by the red arrow in Scheme 15. The precatalyst Ru complex **49** is converted into amido ruthenium species **50** by elimination of HX under the basic reaction conditions. Dehydrogenation of 2-propanol by **50** forms the RuH species **53**, which in turn reduces the ketone substrate to give the alcohol product, regenerating **50**. This mechanistic scenario demonstrates that the hydrogenation and the transfer hydrogenation are mechanistically linked by sharing the same intermediates, including amido Ru species **50** and RuH species **53**. Moreover, the reduction of ketones in the two reactions follows the same transition state, that is, six-membered pericyclic transition state **54** (Scheme 15), to form alcohol products. This may explain the reason for the similar NH effects observed in hydrogenation and transfer hydrogenation of ketones.

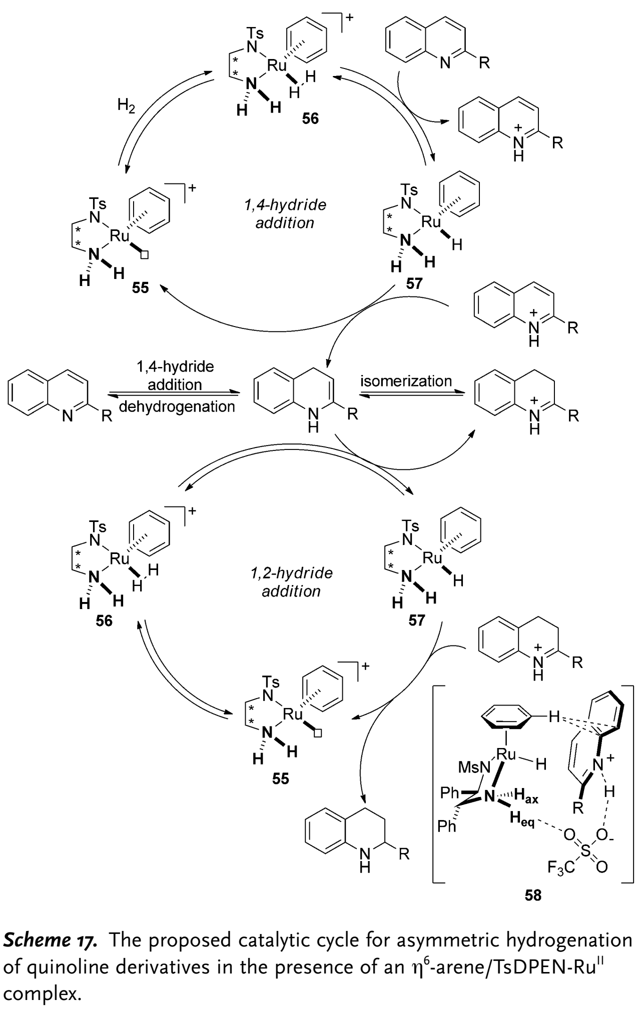


Scheme 15. Mechanism for hydrogenation (black arrows) and transfer hydrogenation (red arrow) of ketones catalyzed by an η^6-arene/TsDPEN-Ru^{II} complex.

Recently, Fan and co-workers demonstrated that η^6-arene/TsDPEN-Ru^{II} complexes, such as **43b**, **44**, and **45**, were outstanding catalysts for asymmetric hydrogenation of 2-substituted and 2,3-disubstituted quinolines,[36a,b,d,e] 2-substituted and 2,3-disubstituted quinoxalines,[36f] 2,4-disubstituted 1,5-benzodiazepines,[36i] *N*-alkyl ketimines,[36g,j] cyclic *N*-alkyl imines,[36h] and cyclic *N*-sulfonylimines,[36c] affording the corresponding biologically and chemically important chiral amines with excellent enantioselectivities in high yields (Scheme 16).[37] Mechanistic studies on the hydrogenations of quinolines revealed that the reduction involves a reaction sequence of 1,4-hydride addition, isomerization, and 1,2-hydride addition (Scheme 17).[36a,d] The ionized ruthenium complex **55** reversibly accommodates a H_2 molecule to form a H_2–Ru intermediate **56**. Deprotonation of the coordinated H_2 in **56** affords a RuH species **57** and a protonated quinoline followed by 1,4-hydride addition of **57** to the activated quinoline to form an enamine intermediate and regenerate the 16e ruthenium complex **55**. The enamine deprotonates another equivalent of **56** to form the RuH species **57** again and an iminium intermediate. Reduction of the iminium by **57** gives the final product 1,2,3,4-tetrahydroquinoline with the regeneration of the 16e ruthenium complex **55**. Computational studies suggested that the 1,2-hydride addition proceeds via a ten-membered cyclic transition state **58** with the involvement of the counteranion TfO$^-$. The enantioselectivity originates from the hydrogen bonding among TfO$^-$, the NH moiety of the ligand, and substrate, as well as the CH/π interaction between the η^6-arene ligand and the fused phenyl ring of the dihydroquinoline. It is obvious that the function of



Scheme 16. Asymmetric hydrogenation of C=N bonds with **43b**, **44**, or **45**. BMIM = 1-butyl-3-methylimidazolium, DCE = 1,2-dichloroethane, DCM = dicloromethane, Boc = *tert*-butoxycarbonyl.



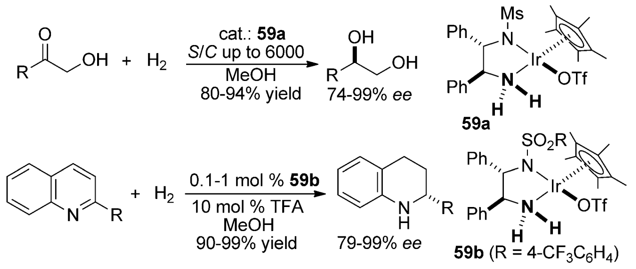
Scheme 17. The proposed catalytic cycle for asymmetric hydrogenation of quinoline derivatives in the presence of an η^6-arene/TsDPEN-Ru^{II} complex.

the NH moiety in the ligand shown in Scheme 17 is different from that observed in the ketone hydrogenation (Scheme 15). The involvement of the interaction between the NH moiety and the counteranion X^- was further shown by **45**-catalyzed asymmetric hydrogenation of 1,5-benzodiazepines.[36i] Ruthenium complexes **45** with weakly coordinating anions, such as BArF$^-$, gave *R*,*R*-products, whereas the catalysts with hydrogen-bond-forming anions, such as OTf$^-$ and $(PhO)_2PO_2^-$ induced *S*,*S*-configuration. The reversal of enantioselectivity observed in the presence of different counteranions X^- (BArF$^-$ versus OTf$^-$ or $(PhO)_2PO_2^-$) in **45** has been rationalized based on their dramatic changes of the corresponding transition states.[36i]

Much attention has also been paid to tethered Ru catalysts for hydrogenation of the C=O bond, which is due to their increased stability. For example, Ikariya reported tethered chiral Ru catalysts **46** and **47** for asymmetric hydrogenation of ketones (Scheme 12), which showed high activities (S/C up to 1000 for **46** and 40000 for **47**) and excellent enantioselectivities (92–98% *ee* for **46** and up to > 99% *ee* for **47**).[38] Abdur-Rashid and co-workers invented a series of Ru catalysts **48** from phosphine ligands bearing NH_2 ends for hydrogenation of ketones and aldehydes with high catalytic activities (S/C up to 5000; Scheme 12).[39]

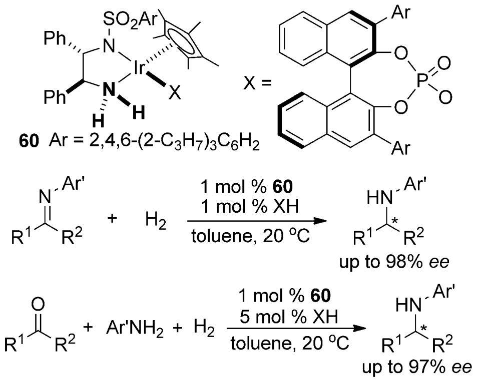
2.1.2. Ir−NH or Rh−NH-Catalyzed Hydrogenation of C=O and C=N Bonds

The concept of NH catalysis has also been extended to the development of iridium and rhodium catalyst systems for the hydrogenation of C=O and C=N bonds besides ruthenium catalysts discussed above. In 2007, Ohkuma and co-workers found that phosphine-free Cp*Ir^{III} complex **59a** is an efficient catalyst for asymmetric hydrogenation of α-hydroxy ketones, giving a series of chiral 1,2-ethanediols with high enantiopurities (74–99% *ee*; Scheme 18).[40] In 2008, Fan and Xu successfully applied the Ir complex **59b** to the asymmetric hydrogenation of quinolines, affording various chiral 1,2,3,4-tetrahydroquinolines in 90–99% yields with 79–99% *ee* (Scheme 18).[41]



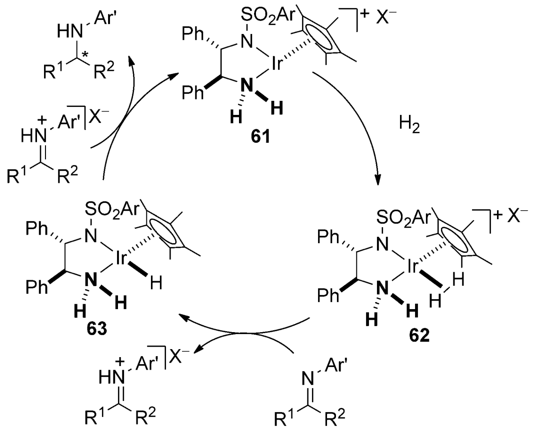
Scheme 18. Asymmetric hydrogenation of α-hydroxy ketones and quinolines in the presence of Ir complexes **59a**,**b**. TFA = trifluoroacetic acid.

Xiao and co-workers developed Ir complex **60** with a BINOL-based phosphoric acid anion in 2008, which catalyzed hydrogenation of acyclic imines and hydrogenative amination of ketones, giving a series of chiral amines with high optical purities (Scheme 19).[42] The reaction begins with the activation of H_2 by ionized Ir cationic complex **61** to give



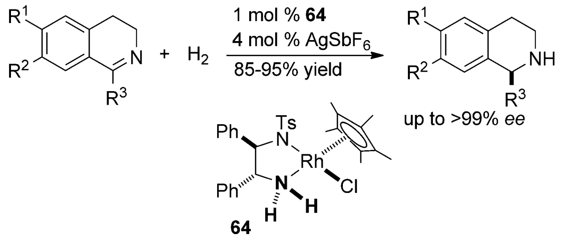
Scheme 19. Asymmetric hydrogenation of acyclic imines and hydrogenative amination of ketones in the presence of Ir complex **60**.

Ir–H_2 species **62** (Scheme 20).[42c] Heterolytic cleavage of H_2 in **62** forms an iminium cation and a reducing IrH species **63**, followed by hydride transfer from **63** to the protonated imine to give the amine product and regenerate the ionized Ir complex **61**, thus completing the catalytic cycle.



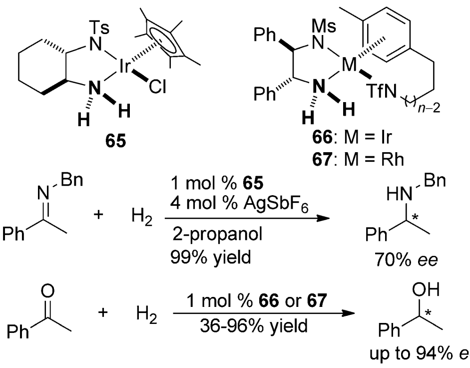
Scheme 20. The proposed catalytic cycle for Ir-catalyzed asymmetric hydrogenation of imines.

Xiao and co-workers also used the chiral Rh complex **64** for asymmetric hydrogenation of cyclic imines, affording various chiral cyclic amines in good yields with high ee values (Scheme 21).[43]



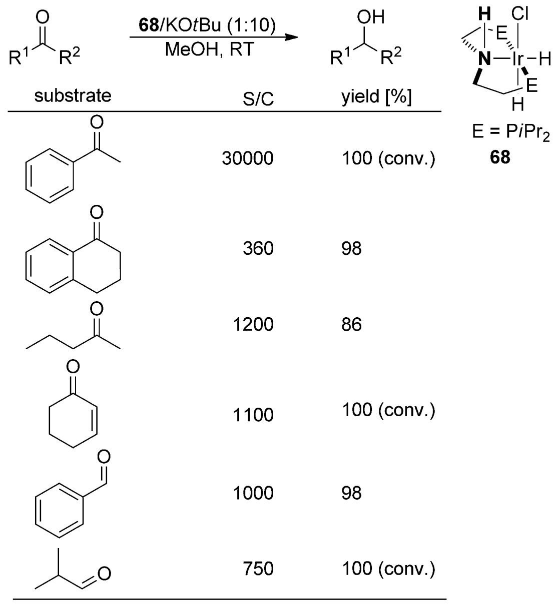
Scheme 21. Asymmetric hydrogenation of cyclic imines in the presence of Rh complex **64**.

In 2009, Ikariya and co-workers reported asymmetric hydrogenation of acyclic imines catalyzed by **65** with moderate enantioselectivities (Scheme 22),[44a] and the same group recently investigated asymmetric hydrogenation of acetophenone using Ir complex **66** and Rh complex **67** as the catalyst (Scheme 22).[44b] A moderate to good level of enantioselective control was observed in the hydrogenations.[45]

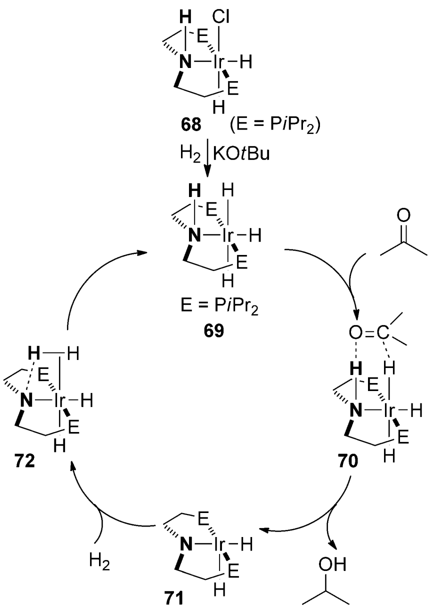


Scheme 22. Asymmetric hydrogenation of acyclic imine and ketones in the presence of Ir or Rh complexes **65**–**67**.

Abdur-Rashid and co-workers used Ir pincer complex **68** to catalyze hydrogenation of ketones and aldehydes to give various secondary and primary alcohols in high yields and under mild conditions (Scheme 23).[46a] A bifunctional mechanism was proposed for the hydrogenation (Scheme 24). Ir pincer complex **68** reacts with base to generate reductive IrH complex **69**. Complex **69** reduces carbonyl group via a concerted six-membered cyclic transition state **70** to give the alcohol product and amido Ir complex **71**. Heterolytic cleavage of H_2 via transition state **72** regenerates the active



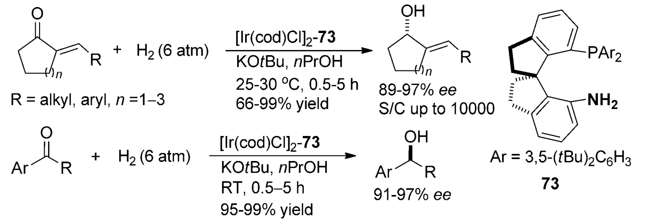
Scheme 23. Hydrogenation of ketones and aldehydes in the presence of complex **68**.



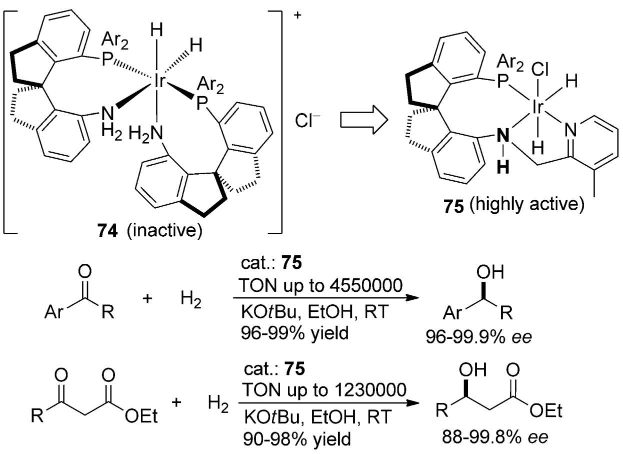
Scheme 24. The proposed mechanism for hydrogenation of ketone catalyzed by **68**.

IrH complex **69**, thus completing the catalytic cycle. The iridium catalyst **68** is also very active for transfer hydrogenation of ketones and imine.[46b] Acetophenones were completely reduced to the corresponding secondary alcohols under transfer hydrogenation conditions with a very high molar ratio of substrate to catalyst (S/C up to 100000).

Recently, Zhou and co-workers reported the asymmetric hydrogenation of α-arylmethylene cycloalkanones and aromatic ketones catalyzed by complex Ir-**73** (Scheme 25).[47a,b]



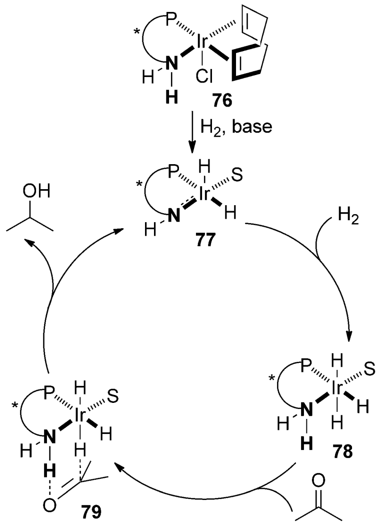
Scheme 25. Asymmetric hydrogenation of ketones catalyzed by Ir-**73**. cod = 1,5-cyclooctadiene.



Scheme 26. Asymmetric hydrogenation of ketones catalyzed by Ir catalyst **75**.

Excellent enantioselectivities and high yields were obtained in the reaction. Introduction of one or two methyl groups onto the nitrogen atom of **73** resulted in dramatic decrease of catalytic activity and enantioselectivity, indicating the crucial role of NH$_2$ group in the aminophosphine ligand **73** for the high catalytic activity.[47b] On the other hand, the formation of Ir^I species **74** with two ligands (**73**) was disclosed to be responsible for catalyst deactivation in a period of time.[47b] Accordingly, a series of Ir complexes **75** with ligands having a pyridine sidearm were developed by the same group to prevent the formation of the inactive species **74** for the asymmetric hydrogenation of ketones (Scheme 26).[47c] Exceptionally high catalytic activities (with TON of up to 4550000) were observed in the hydrogenation of aromatic ketones and β-aryl-β-keto esters catalyzed by **75**.[47c,d]

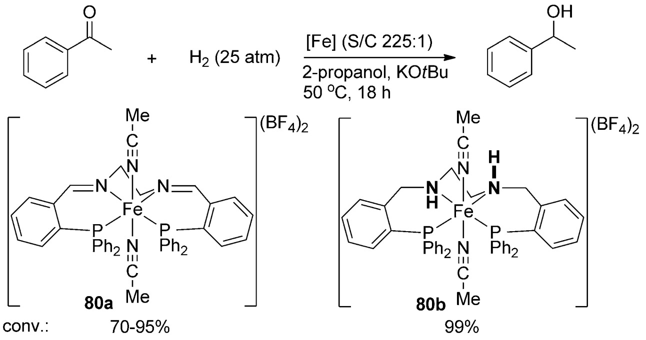
A possible catalytic cycle was proposed by the group based on detailed mechanistic studies (Scheme 27).[47b] Treatment of catalyst precursor **76** with base under H$_2$ atmosphere forms active amido Ir species **77**, which reacts with H$_2$ to give the Ir hydride species **78**. Complex **78** reduces the ketone via a six-membered cyclic transition state **79** to give an alcohol product and regenerate catalyst **77**, thereby completing the catalytic cycle. The NH group of the catalyst acts as a proton shuttle in the catalytic cycle.



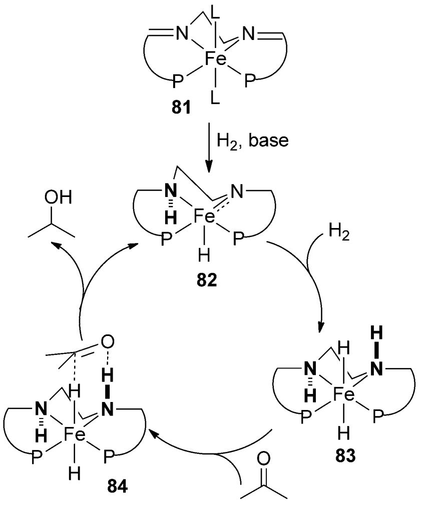
Scheme 27. The proposed mechanism for hydrogenation of ketones catalyzed by Ir-aminophosphine.

2.1.3. Fe—NH or Os—NH-Catalyzed Hydrogenation of C=O

The cooperative effect of the NH group in the ligand has also been observed in Fe- and Os-catalyzed hydrogenation of ketones. In 2008, Morris reported Fe-catalyzed hydrogenation of ketones using complex **80a** or **80b** as catalyst (Scheme 28).[48] It was believed that the imine linkage in complex **80a** was hydrogenated to form amine complex **80b** under the reaction conditions. Complex **80b** likely served as the active catalyst in the hydrogenation. The reaction was assumed to follow an outer-sphere mechanistic pathway (Scheme 29),[48b–d] which is analogous to the [RuCl$_2$(diphosphine)(diamine)]-catalyzed ketone hydrogenation shown in Scheme 3. The NH group was thought to be involved in the hydrogenation via a six-membered ring transition state **84**.

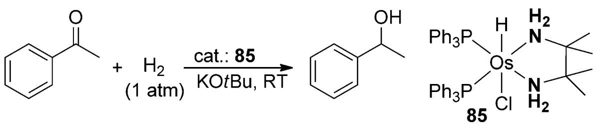


Scheme 28. Fe-catalyzed hydrogenation of ketones.

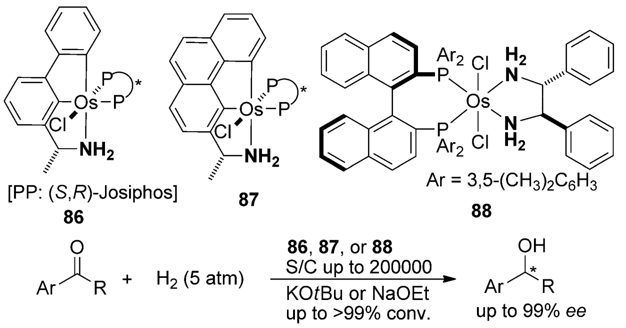


Scheme 29. Proposed mechanism for Fe-catalyzed hydrogenation of ketones.

In 2005, Morris found that Os complex **85** with a diamine ligand was catalytically active for hydrogenation of ketones at room temperature with a high conversion of ketones (Scheme 30).[49] In 2008, Baratta reported chiral Os complexes **86–88** with NH moieties that catalyzed asymmetric transfer hydrogenation and hydrogenation of aryl ketones with high activities (TOF up to $10^6\,h^{-1}$) and excellent enantioselectivities (Scheme 31).[50] The Os–NH$_2$ linkage was thought to be involved in the hydrogenation through hydrogen bonding with ketone and/or alcohol.



Scheme 30. Hydrogenation of a ketone in the presence of Os complex **85**.

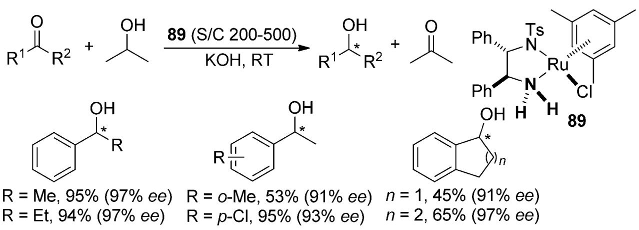


Scheme 31. Asymmetric hydrogenation of ketones catalyzed by Os complexes **86–88**.

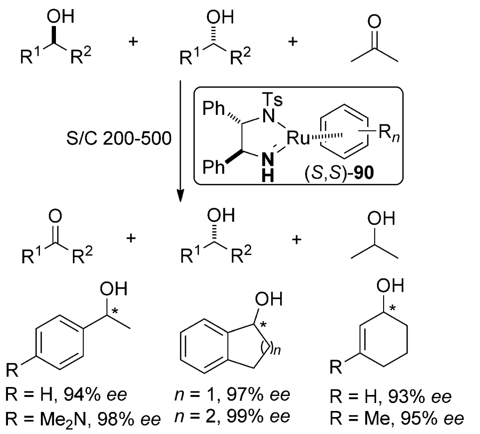
2.2. M–NH-Catalyzed Transfer Hydrogenation of C=O and C=N Bonds

2.2.1. Ru–NH-Catalyzed Transfer Hydrogenation of C=O and C=N Bonds

Similar to the case for hydrogenation reactions, the Ru–NH catalyst system is also very efficient for transfer hydrogenation of ketones, for which the NH moiety is found to be critically important for the reactivity. Noyori and co-workers first applied the Ru–NH catalyst to transfer hydrogenation of ketones in 1995.[34] The phosphine-free TsDPEN-based Ru complex **89** displayed high activity and excellent enantioselectivity in the asymmetric transfer hydrogenation of aromatic ketones (Scheme 32).[34,51a] Further studies indicated that α,β-acetylenic ketones,[51b] deuterated benzaldehydes,[51c] and imines[52] were also smoothly transfer-hydrogenated with 2-propanol or formic acid by using **89** or structurally similar ruthenium complexes, such as **43**, as catalysts, giving the corresponding chiral alcohols or amines with high optical purities in high yields.[53,54] Treatment of the ruthenium complexes with base would generate amido Ru catalysts such as **90** in Scheme 33, which could be applied to kinetic resolution of racemic secondary alcohols.[55] The kinetic



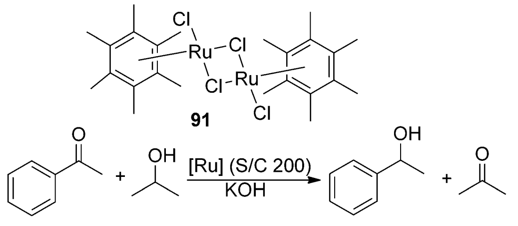
Scheme 32. Asymmetric transfer hydrogenation of ketones catalyzed by **89**.

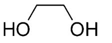
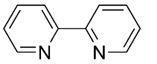
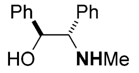


Scheme 33. Kinetic resolution of racemic secondary alcohols catalyzed by **90**.

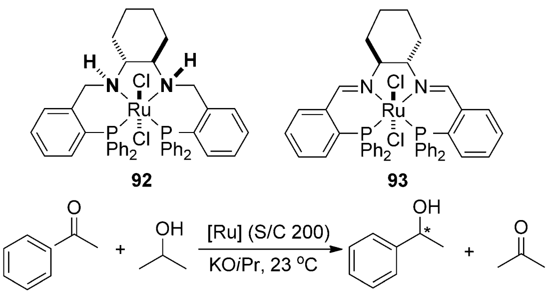
resolution proceeded by oxidative dehydrogenation of the secondary alcohols in acetone, which is a reverse process of transfer hydrogenation, affording various chiral secondary alcohols with high optical purities.

A significant cooperative effect of the NH group was observed in Ru(η^6-arene)–amine catalyzed transfer hydrogenation of ketones (Scheme 34).[56] The catalysts generated from ethanolamines showed high catalytic activities in the transfer hydrogenation of acetophenone (Scheme 34, entries 3 and 5).[56] The ligands without an NH end group, such as ethylene glycol and 2,2′-bipyridyl, did not show any acceleration effect for the reaction (Scheme 34, entries 2 and 4). A similar NH effect was also observed in the transfer hydrogenation of ketones catalyzed by Ru–phosphine–amine complexes (Scheme 35).[21] For example, the complex **92** bearing NH moieties catalyzed transfer hydrogenation of acetophenone in a 91% yield and 97% *ee*.[21,57] However, structurally similar imine Ru complex **93** was almost ineffective for the reaction under otherwise identical conditions. Only a 3% yield of 1-phenylethanol with 18% *ee* was obtained in the reaction.



entry	catalyst	TOF [h^{-1}]
1	**91**	3
2	**91** + 	10
3	**91** + 	227
4	**91** + 	18
5	**91** + 	92% ee 94% yield

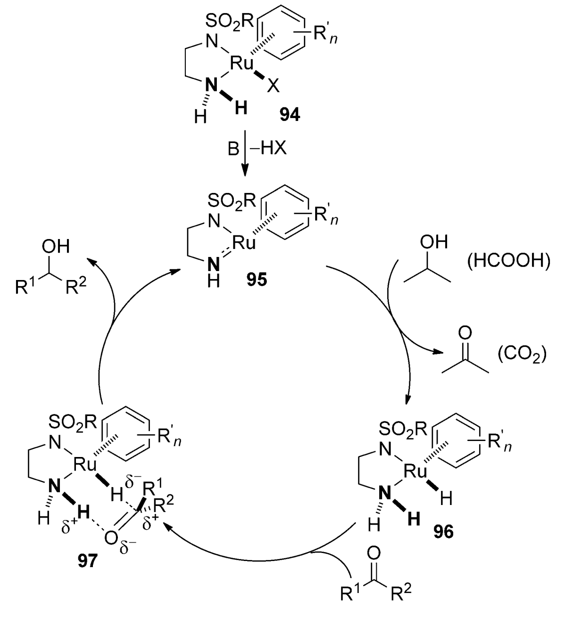
Scheme 34. Transfer hydrogenation of acetophenone catalyzed by Ru(η^6-arene)–amine complexes.



catalyst	yield	ee
92	91%	97%
93	3%	18%

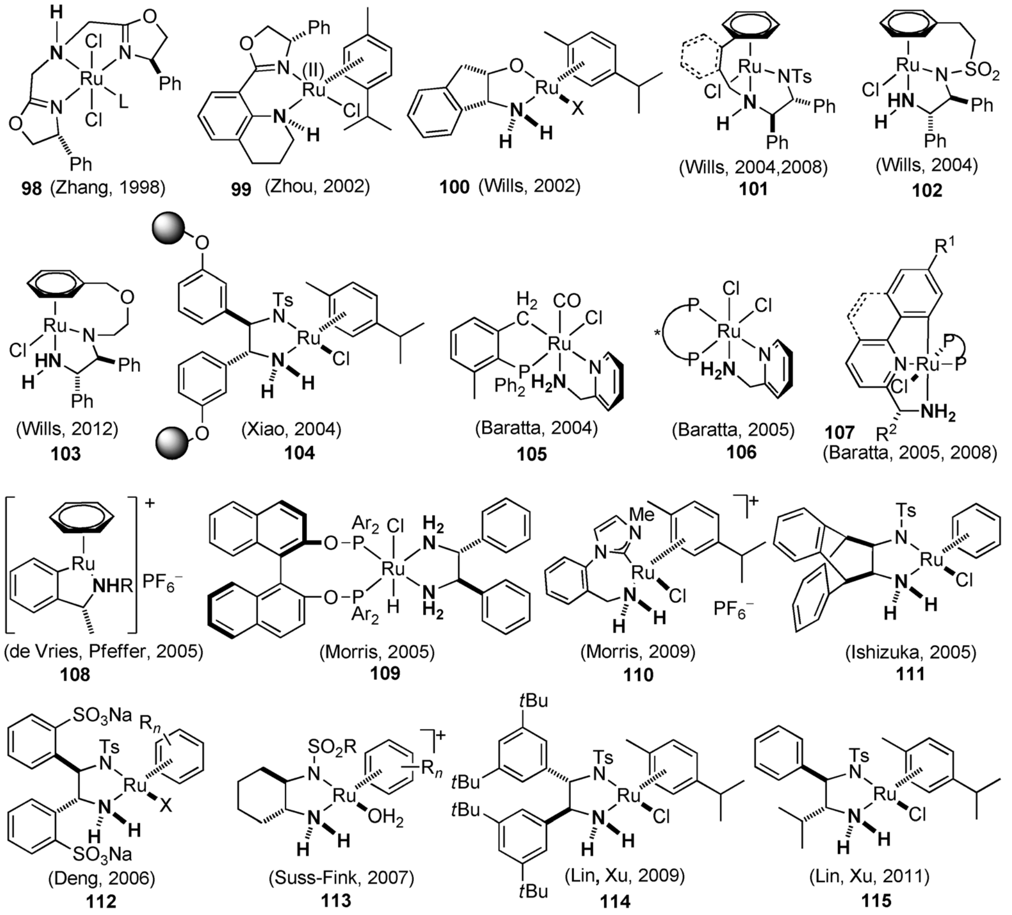
Scheme 35. Asymmetric transfer hydrogenation of acetophenone catalyzed by **92–93**.

The reaction mechanism of the transfer hydrogenation has been extensively studied, and the generally accepted mechanism is shown in Scheme 36.[58] Ru complex **94** is transformed into an active amido Ru species **95** by elimination of HX in the presence of base. Amido Ru **95** reacts with 2-propanol or formic acid to form hydride species **96**, which reduces ketones via a six-membered cyclic transition state **97** to give the alcohol products and regenerate the catalyst amido Ru **95**. The NH moiety acts as proton donor in the transfer hydrogenation, and thus it is crucial for catalytic activity and selectivity.



Scheme 36. The proposed catalytic cycle for Ru-catalyzed transfer hydrogenation of ketones.

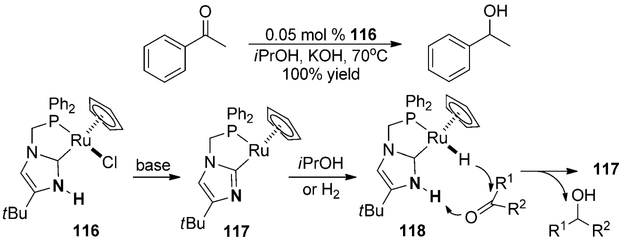
The excellent performances of Ru complex **89** in asymmetric transfer hydrogenation inspired the development of



Scheme 37. More examples of chiral Ru catalysts for transfer hydrogenations.

new catalysts (Scheme 37). In 1998, Zhang and co-workers found that Ru catalyst **98** with a tridentate nitrogen ligand having an NH moiety exhibited moderate to excellent enantioselectivities (19–98 % *ee*) in the asymmetric transfer hydrogenation of aromatic ketones.[59] Zhou and co-workers developed chiral Ru catalyst **99** for asymmetric transfer hydrogenation of aromatic ketones in 2002, and moderate enantioselectivities (50–83 % *ee*) were observed in the reaction.[60] Wills and co-workers developed Ru catalyst **100** containing (1*R*,2*S*)-1-aminoindan-2-ol ligand in 2002, which catalyzed transfer hydrogenation of ketones to give various alcohols with 7–98 % *ee*.[61a] The same group also later developed tethered Ru complexes **101**–**103**.[61b–l] All of these are excellent catalysts for asymmetric transfer hydrogenation of ketones. The NH moiety was crucial for the tethered ruthenium catalyst.[61j] Methylation of the NH group in **101** resulted in almost complete loss of catalytic activity. Xiao discovered that Noyori's Ru(η^6-arene)–amine catalysts, such as **43**, were even more efficient for transfer hyrogenation in water with HCO_2Na than in organic media with HCO_2H–NEt_3 azeotrope.[62,63] A much higher reaction rate and comparable enantioselectivity were observed in the aqueous transfer hydrogenation. It was suggested that the water facilitates the decarboxylation of HCO_2Na to form the reductive RuH species **96** (Scheme 36), accelerates the hydrogen transfer from **96** to ketone by hydrogen bonding with the ketone oxygen, and stabilizes the active catalyst **95** by converting it into a more stable hydroxy species, thus resulting in the amazing water effect in the transfer hydrogenation.[62d,f] Immobilization of the homogenous catalyst gave a poly(ethylene glycol)-supported counterpart **104**, which was also highly effective for transfer hydrogenation of aromatic ketones in water with high activities, excellent enantioselectivities, and good reusability.[62b,c] Baratta and co-workers reported Ru catalysts **37** and **105**–**107**, which demonstrated high catalytic activities and excellent enantioselectivities in transfer hydrogenation of various ketones.[64] Ruthenacycle **108** has also proven to be active and enantioselective for transfer hydrogenation of prochiral ketones.[65] Morris and co-workers developed Ru catalyst **109** from a BINOL-based phosphorous ligand in 2005, which showed good enantioselectivities (80–93 % *ee*) in asymmetric transfer hydrogenation of aromatic ketones.[66] The same group also developed ruthenium(II) complex **110** from a chelating carbene–NH_2 ligand in 2009 for transfer hydrogenation of acetophenone to 1-phenylethanol.[67] Ishizuka and co-workers prepared Ru complex **111** from a conformationally rigid, bulky *cis*-diamine for asymmetric transfer hydrogenation of aromatic ketones.[68] Good to excellent enantioselectivities (up to 99 % *ee*) were observed in the reaction. Deng and co-workers developed a water-soluble Ru catalyst **112** from disulfonated DPEN, which displayed high activities and excellent enantioselectivities in the asymmetric transfer hydrogenation of imines and iminiums in water.[69] Süss-Fink and Canivet investigated the influence of diamine ligands on the asymmetric transfer hydrogenation of ketones.[70] Catalyst **113** generated from chiral cyclohexane-1,2-diamine showed moderate enantioselectivities in the asymmetric transfer hydrogenation of aromatic ketones and imines in water. Lin and Xu developed Ru catalyst **114** from sterically bulky diamine in 2009.[71a] The complex **114** catalyzed transfer hydrogenation of 2-acylarylcarboxylates in aqueous medium with high enantioselectivities. The chiral alcohols formed were transformed in situ into enantiomerically pure phthalides by intramolecular lactonization. Two years later, the same group reported Ru catalyst **115** which was prepared from an unsymmetrical vicinal diamine ligand.[71b] The Ru catalyst **115** exhibited excellent enantioselectivities (up to 98% *ee*) in the asymmetric transfer hydrogenation of aromatic ketones.

Very recently, Grotjahn found that Ru complex **116**, ligated by a protic N-heterocyclic carbene–phosphine ligand, was active for transfer hydrogenation of acetophenone (Scheme 38).[72] Although the NH moiety does not coordinate directly with the ruthenium center as in the Ru(phosphine)$_2$–diamine system, a similar bifunctional mechanism was proposed for the transfer hydrogenation of ketones catalyzed by **116**.

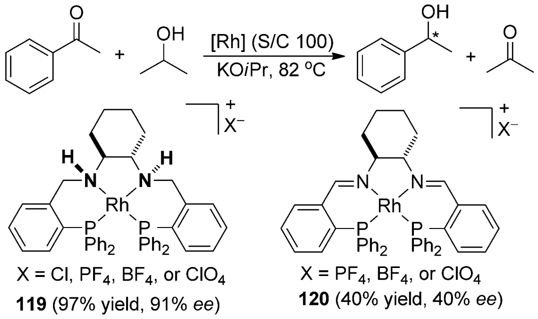


Scheme 38. Transfer hydrogenation of ketones catalyzed by Ru complex **116**.

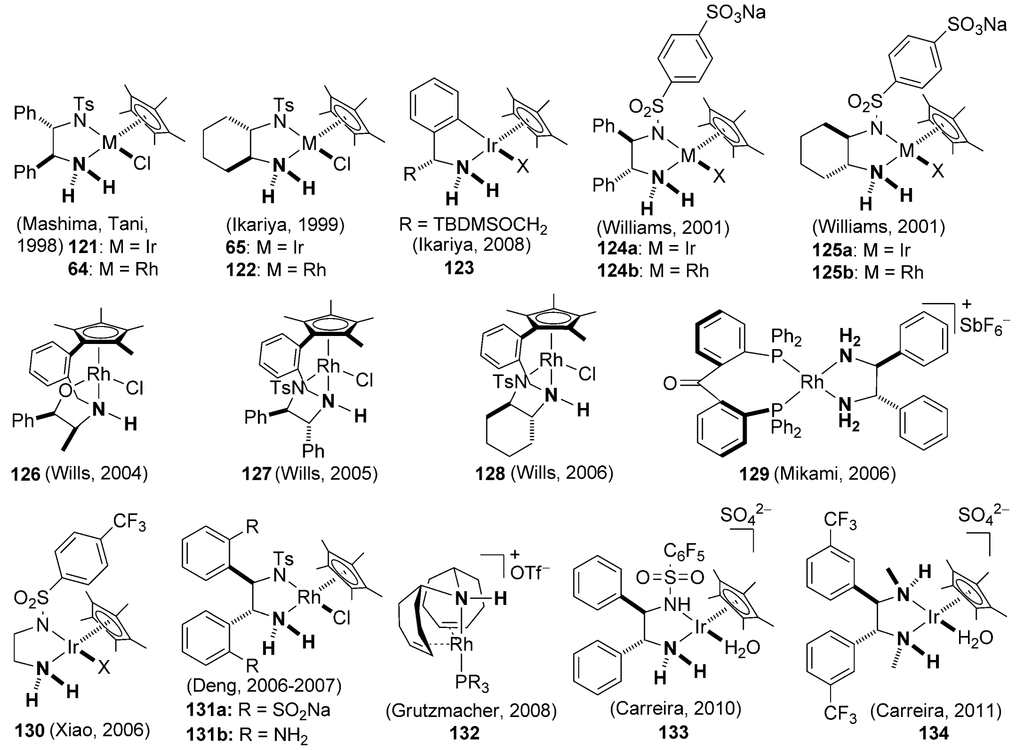
2.2.2. *Rh—NH and Ir—NH-Catalyzed Transfer Hydrogenation of C=O and C=N Bonds*

In analogy with Ru—NH catalysts, Rh—NH and Ir—NH complexes have also been found to be highly active for catalytic transfer hydrogenation of ketones and imines; the NH moieties proved to be critically important for the reactivity of the catalysis. For example, Gao and co-workers showed that NH-containing Rh complex **119** exhibited much higher enantioselectivity and catalytic activity than the structurally similar complex **120** in the asymmetric transfer hydrogenation of acetophenone (Scheme 39), indicating that the NH moieties in catalyst **119** are responsible for the high catalytic efficiency.[73] The observed dramatic NH effect implies that the NH moieties are likely involved in the process of the ketone reduction.[2g,73,74]

Various Rh and Ir catalysts have been developed for transfer hydrogenation of ketones and imines as summarized in Scheme 40. All of the catalysts contain NH moieties, which exhibit an analogous cooperative effect in the catalysis. Mashima and Tani applied DPEN-based Rh and Ir catalysts **64** and **121** to asymmetric transfer hydrogenation of aromatic ketones in 1998, and high enantioselectivities (84–99% *ee*) were obtained in the reaction.[75] Very recently, Xiao and co-workers extended the scope of the Rh and Ir catalysts to transfer hydrogenation of ketones and imines in water.[76] Various chiral alcohols and amines were prepared in excellent enantioselectivities and good yields under aqueous conditions. Lee and co-workers recently reported the asymmetric transfer hydrogenation of cyclic sulfamidate imines catalyzed by **64**, affording various sulfamidates in high yields and *ee*.[77] Ikariya and co-workers reported Ir catalyst **65** and Rh catalyst **122** in 1999, which were generated from enantiomerically pure *trans*-1,2-cyclohexanediamine.[78a] Both Rh catalysts **64** and **122** were highly enantioselective and active in the asymmetric transfer hydrogenation of aromatic ketones, α-aminoalkyl α′-chloromethyl ketones, and α-chlorinated ketones.[78] The same group also reported the asymmetric transfer hydrogenation of acetophenone catalyzed by Ir complex **123** with moderate enantioselectivity (up to 66% *ee*).[79] Williams and co-workers developed Rh and Ir catalysts **124** and **125** from water-soluble diamine ligands, which exhibited good to excellent selectivities (73–97% *ee*) in the asymmetric transfer hydrogenation of acetophenones under aqueous conditions.[80] Wills and co-workers developed tethered Rh catalysts **126**–**128** from chiral aminoalcohol and monotosylated diamines.[81] It was found that the length of the tether in the catalyst was crucial for the activity and the enantioselectivity in the asymmetric transfer hydrogenation of C=O and C=N bonds. Mikami and co-workers prepared enantiopure Rh complex **129** from achiral benzophenone diphosphine and chiral diamine ligand DPEN.[82] Complex **129** displayed excellent enantiocontrol ability (89–99% *ee*) in the asymmetric transfer hydrogenation of acetophenone and derivatives. In 2006, Xiao and co-workers found that an achiral Ir catalyst **130**, which was generated from ethylenediamine derivative, is very active and highly chemoselective in transfer hydrogenation of aldehydes.[83] The catalyst tolerates a wide variety of functional groups, including nitro groups, halogens, ketones, and olefins, in the aldehyde substrates. Deng and co-workers reported the asymmetric transfer hydrogenation of ketones and imines catalyzed by **131a** and



Scheme 39. Asymmetric transfer hydrogenation of acetophenone catalyzed by PNNP/Rh complexes.



Scheme 40. Representative Rh and Ir catalysts for transfer hydrogenation.

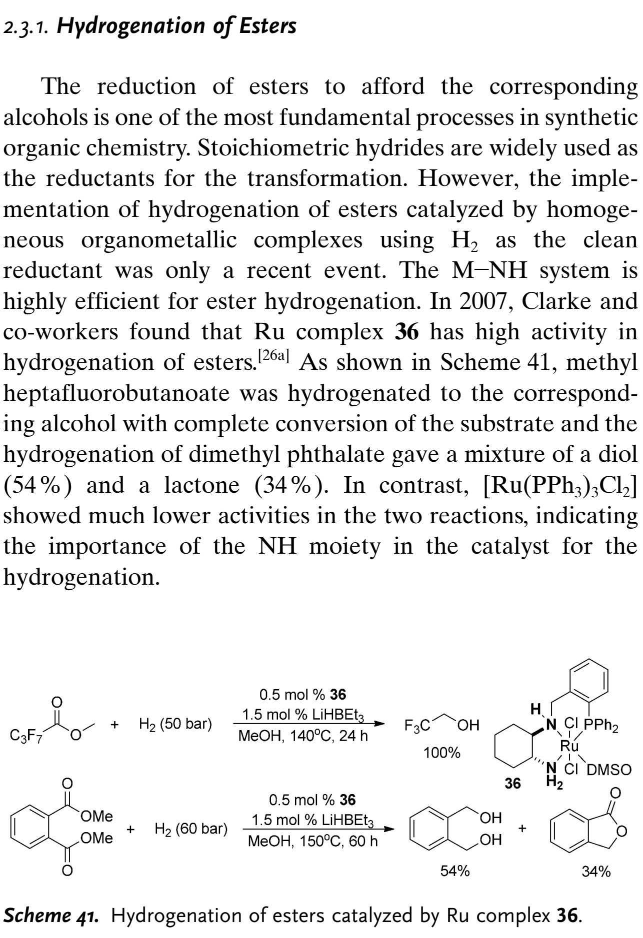
131b in water to give various chiral alcohols and amines with high enantioselectivities.[84] Grützmacher developed Rh–diolefin–amine complex **132** for transfer hydrogenation of ketones and activated olefins using ethanol as hydrogen donor.[85b] High catalytic activity (TOF up to 750000 h^{-1}) was obtained in the transfer hydrogenation of cyclohexanone. This catalyst was also active for hydrogenation of ketones.[85a] Carreira and co-workers reported Ir complexes **133** and **134** recently.[86] Both were shown to be highly active and enantioselective for asymmetric transfer hydrogenation of α-cyano and α-nitro acetophenones in water.

2.3. M–NH-Catalyzed Hydrogenation/Transfer Hydrogenation of Other Polar Bonds

In comparison with hydrogenation and transfer hydrogenation of ketones and imines, the reduction of esters, imides (or amides), nitriles, CO_2, and epoxides remained a more challenging theme in homogeneous catalysis. The M–NH catalyst systems also demonstrated promising activity and selectivity in hydrogenation and transfer hydrogenation of the above-mentioned substrates, where the NH moiety in the catalyst was found to be critically important for the reactivity. The following section of this Review will summarize the advances in the reduction of other polar bonds apart from ketones and imines with M–NH catalyst systems, thus highlighting the NH cooperative effect in the catalysis.

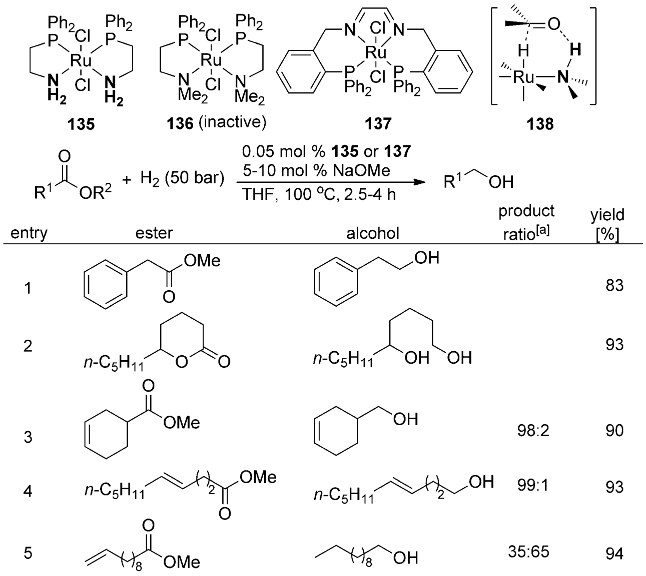
2.3.1. Hydrogenation of Esters

The reduction of esters to afford the corresponding alcohols is one of the most fundamental processes in synthetic organic chemistry. Stoichiometric hydrides are widely used as the reductants for the transformation. However, the implementation of hydrogenation of esters catalyzed by homogeneous organometallic complexes using H_2 as the clean reductant was only a recent event. The M–NH system is highly efficient for ester hydrogenation. In 2007, Clarke and co-workers found that Ru complex **36** has high activity in hydrogenation of esters.[26a] As shown in Scheme 41, methyl heptafluorobutanoate was hydrogenated to the corresponding alcohol with complete conversion of the substrate and the hydrogenation of dimethyl phthalate gave a mixture of a diol (54%) and a lactone (34%). In contrast, $[Ru(PPh_3)_3Cl_2]$ showed much lower activities in the two reactions, indicating the importance of the NH moiety in the catalyst for the hydrogenation.



Scheme 41. Hydrogenation of esters catalyzed by Ru complex **36**.

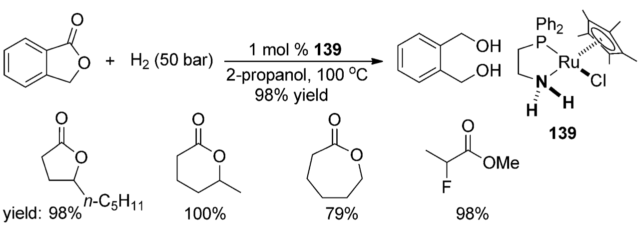
Saudan and co-workers found that ruthenium complexes **135** and **137** are highly active catalysts for hydrogenation of esters, providing various alcohols in high yields (Scheme 42).[87] Excellent chemoselectivity for the ester group over an isolated internal C–C double bond was observed in the hydrogenation. The reduction was proposed to proceed via a six-membered ring transition state **138** with the involvement of the NH moiety. Although catalyst **137** does not have an NH moiety, it is probable that the NH moieties are formed in situ by hydrogenation of the imine linkages under the reaction conditions. The hydrogenation mechanism is supported by the fact that the structurally similar complex **136** with NMe_2 moieties is inactive for the ester hydrogenation.



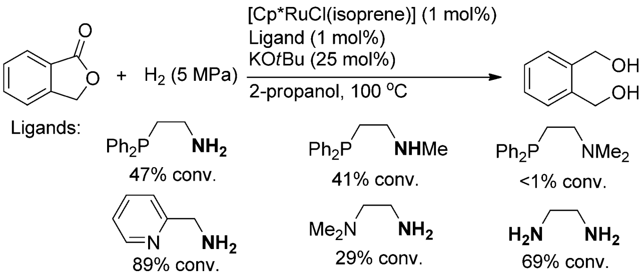
[a] The ratio of unsaturated alcohol to saturated alcohol.

Scheme 42. Hydrogenation of esters catalyzed by Ru complexes **135**–**137**.

In 2008, Ikariya and co-workers reported an efficient hydrogenation of lactones by using Ru complex **139** as catalyst, affording various diols in good yields (Scheme 43).[2ai,88] Ligand effect was investigated for the reaction, and the ligand without NH end was found to be ineffective for the lactone hydrogenolysis (Scheme 44).[88b] It is obvious that the NH moiety in the ligand is indispensable for the high hydrogenation activity.

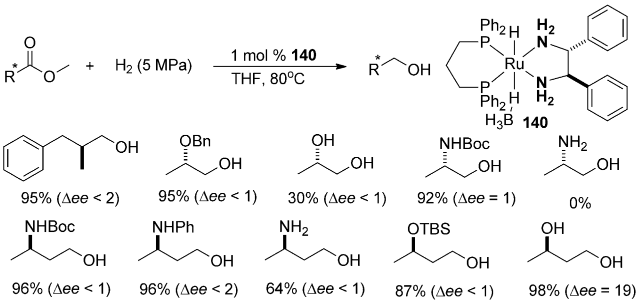


Scheme 43. Hydrogenation of lactones in the presence of Ru complex **139** as catalyst.

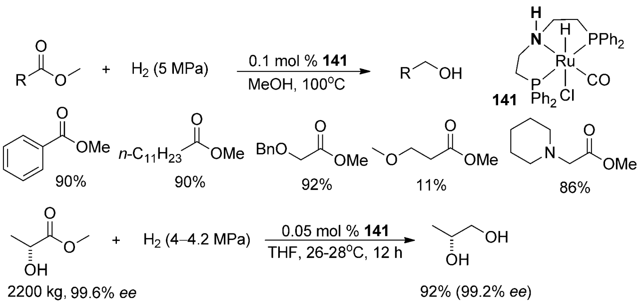


Scheme 44. The effect of amino ligands in the Ru-catalyzed hydrogenation of lactones.

In 2010, Kuriyama reported a hydrogenation of optically active esters by using Ru complex **140** as catalyst (Scheme 45).[89a] Various optically alcohols were prepared in high yields with negligible loss of optical purities. Recently, the same group developed Ru complex **141** which showed very high catalytic activity in the hydrogenation of esters (Scheme 46).[89b] Simple esters and also functionalized esters were efficiently hydrogenated by using 0.1 mol % of **141** as catalyst. The practicality of the catalyst was demonstrated in a large-scale ester hydrogenation. Up to 2200 kg of methyl (*R*)-lactate (99.6 % *ee*) was smoothly hydrogenated to give 1,2-propanediol with 99.2 % *ee* in 92 % yield. Very recently, the hydrogenation of both cyclic carbonates and polycarbonate has been realized by Ding and co-workers under relatively mild conditions in the presence of catalyst **141**, affording



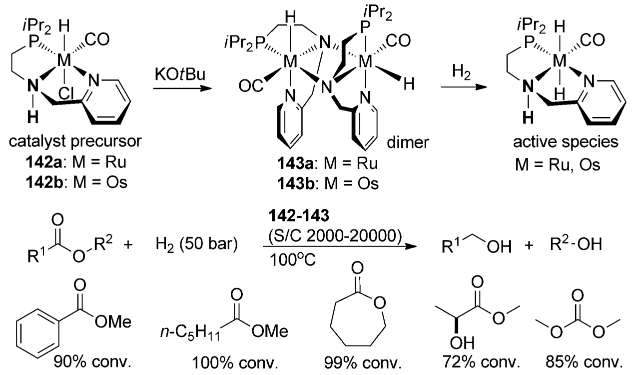
Scheme 45. Hydrogenation of optically active esters catalyzed by Ru complex **140**.



Scheme 46. Hydrogenation of various esters by using Ru complex **141** as catalyst.

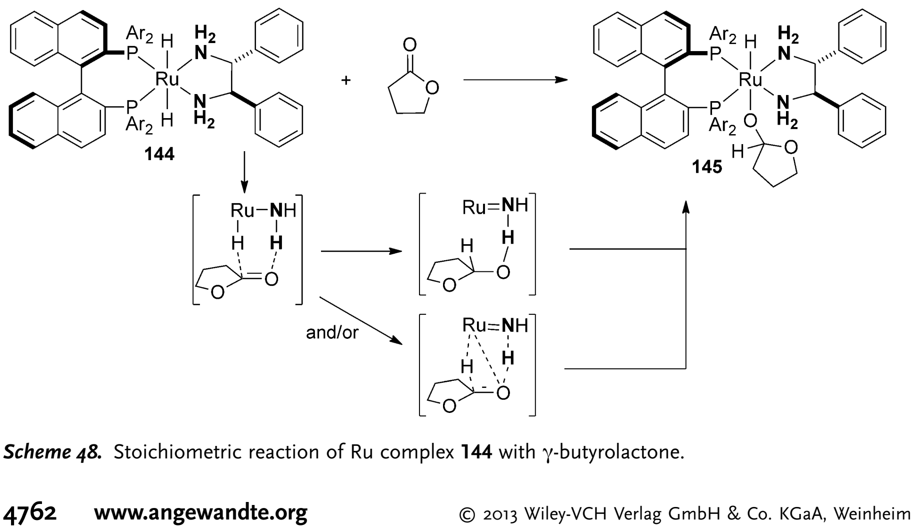
methanol and the corresponding diols with very high efficiency and excellent selectivity.[89c] This process has provided a facile approach for the simultaneous production of two important bulk chemicals, methanol and ethylene glycol (EG), from ethylene carbonate, which is industrially available by reacting ethylene oxide with CO_2. The coupling of the present catalytic system with the process of ethylene carbonate production in the omega process is expected to establish a new bridge from CO_2 and ethylene oxide to methanol and EG. Apart from the clean production of diols, a big bonus of the present procedure is the efficient chemical utilization of CO_2, which is a distinct advantage in terms of sustainability over the omega process, which gives back CO_2. Moreover, this catalytic system has also provided a potential process for the as a resource for the utilization of waste poly(propylene carbonate) to afford 1,2-propylene diol and methanol through hydrogenative depolymerization, and a convenient method for the preparation of deuterated methanol from CO_2 and D_2. The mechanistic study clearly indicated that the NH moiety of the ligand is critically important in facilitating the reduction of the carbonate C=O bond through secondary coordination sphere interactions with substrates.

Gusev found that Ru and Os complexes **142a,b** and the corresponding dimers **143a,b** were highly efficient for hydrogenation of esters to alcohols (Scheme 47).[90] Up to 18000 turnovers in 17 h were obtained in the hydrogenation of methyl benzoate catalyzed by Ru dimer **143a**. The Os dimer **143b** was even highly effective for the hydrogenation of triglycerides to give fatty alcohols directly. The Ru and Os dihydride complexes were assumed to be the active species for the ester hydrogenation.



Scheme 47. Hydrogenation of various esters by using Ru or Os complexes **142** and **143** as catalyst.

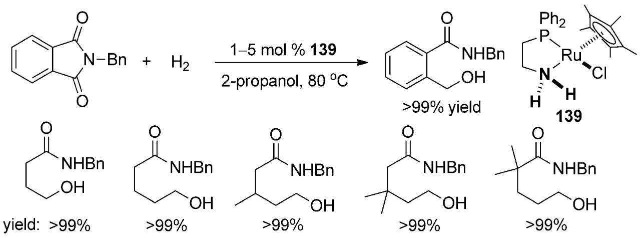
Bergens and co-workers investigated the reaction mechanism of ester hydrogenation by monitoring the reaction between Ru complex **144** and γ-butyrolactone (Scheme 48).[91] A Ru–NH bifunctional mechanism was proposed for the reduction of esters, which is analogous to Ru–NH-catalyzed hydrogenation of ketones. The NH group in the catalyst serves as a proton deliverer in the ester hydrogenation, highlighting the importance of the NH moiety for the ester hydrogenation.



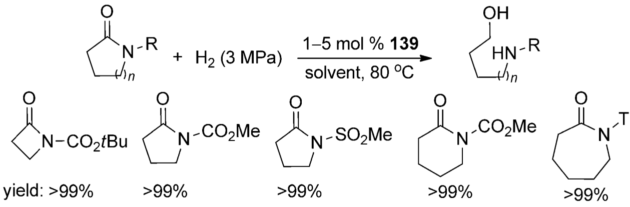
Scheme 48. Stoichiometric reaction of Ru complex **144** with γ-butyrolactone.

2.3.2. *Hydrogenation of Imides and Amides*

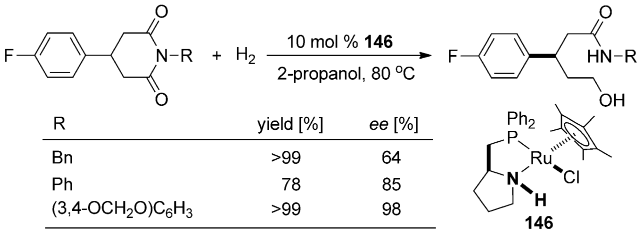
In 2007, Ikariya reported chemoselective hydrogenation of cyclic imides by using Ru complex **139** as catalyst, affording the corresponding hydroxycarboxamides in high yields (Scheme 49).[92a] Complex **139** is also an efficient catalyst for deep hydrogenation of *N*-acylcarbamates and *N*-acylsulfonamides, giving a series of amino alcohols under mild conditions (Scheme 50).[88a,92b] When chiral Ru complex **146** was applied to the hydrogenation of *meso*-cyclic imides (Scheme 51), various optically active monohydrogenated hydroxycarboxamides were obtained in high yields and good enantioselectivities.[92a] Bicyclic imides also undergo hydrogenative desymmetrization in the presence of **146**, affording chiral cyclic hydroxy imides with complete conversions of the imides and excellent *ee* values for the products (Scheme 52).[92c]



Scheme 49. Hydrogenation of cyclic imides by using Ru complex **139** as catalyst.

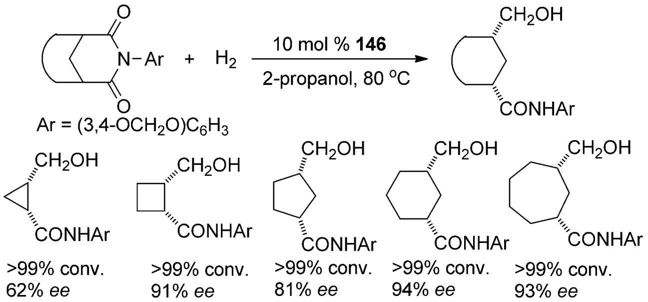


Scheme 50. Hydrogenation of *N*-acylcarbamates and *N*-acylsulfonamides in the presence of **139**.



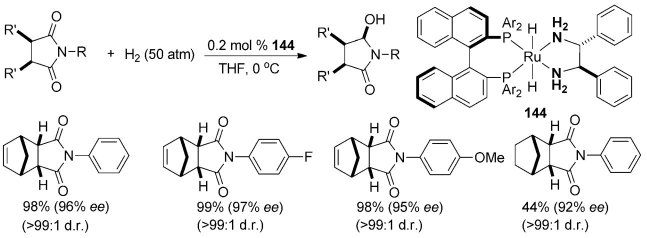
R	yield [%]	*ee* [%]
Bn	>99	64
Ph	78	85
(3,4-OCH$_2$O)C$_6$H$_3$	>99	98

Scheme 51. Enantioselective hydrogenative desymmetrization of *meso*-cyclic imides in the presence of **146**.

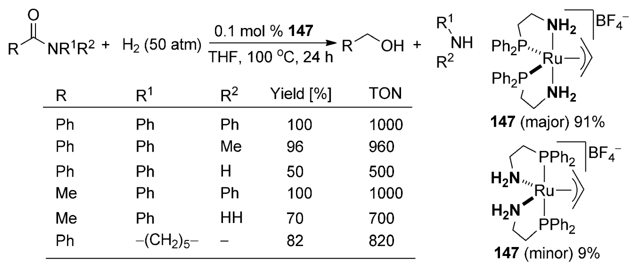


Scheme 52. Enantioselective hydrogenative desymmetrization of bicyclic imides in the presence of **146**.

In 2010, Bergens and co-workers reported an enantioselective desymmetrization of *meso*-cyclic imides through monohydrogenation of imides by using Noyori-type Ru complex **144** as catalyst, giving chiral cyclic hydroxy lactams with multiple stereogenic centers in good yields with high *ee* values (Scheme 53).[93a] The same group also reported Ru complex **147** in 2011, which is an efficient catalyst for hydrogenation of simple amides to alcohols and free amines (Scheme 54).[93b] A plausible mechanism was proposed for the hydrogenation of amide (Scheme 55). Reductive RuH species **148** reacts with amides via six-membered cyclic transition states **149** and/or **150** to form ruthenium hemiaminalkoxide **151**, which is further converted into imide Ru **152** and hemiaminalkoxide **153**. Compound **153** and imide Ru **152** are further hydrogenated to form the products (alcohol and amine) and regenerate RuH species **148**, completing the catalytic cycle. The NH group in the catalyst activates the amide substrate by hydrogen bonding with O atom, as shown in the possible transition states **149** and **150**.

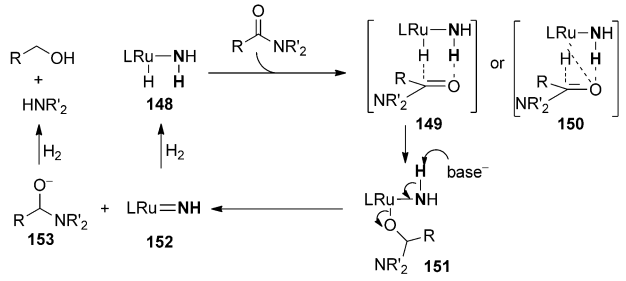


Scheme 53. Enantioselective desymmetrization of *meso*-cyclic imides by monohydrogenation of imides by using Ru complex **144** as catalyst.



R	R^1	R^2	Yield [%]	TON
Ph	Ph	Ph	100	1000
Ph	Ph	Me	96	960
Ph	Ph	H	50	500
Me	Ph	Ph	100	1000
Me	Ph	HH	70	700
Ph	–(CH$_2$)$_5$–	–	82	820

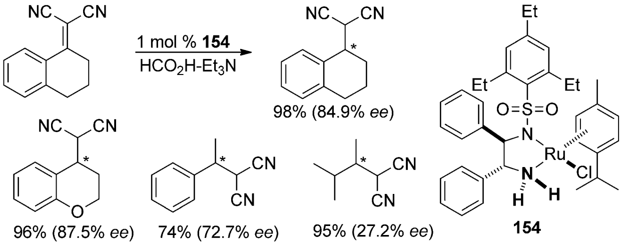
Scheme 54. Hydrogenation of simple amides to alcohols and free amines in the presence of Ru complex **147**.



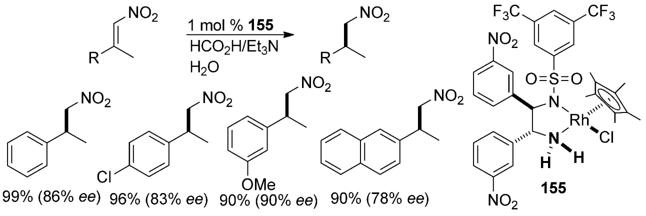
Scheme 55. The proposed mechanism for Ru-catalyzed hydrogenation of amides.

2.3.3. *Hydrogenation of Activated C=C Bonds*

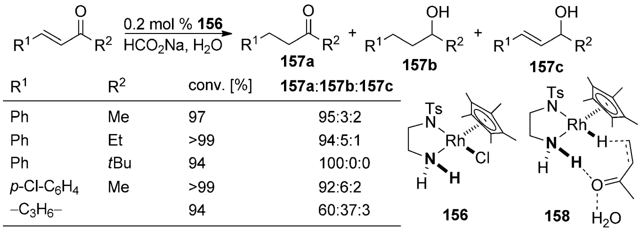
In 2004, Deng and co-workers reported an enantioselective transfer hydrogenation of malononitriles by using Ru complex **154** as catalyst (Scheme 56).[94a,b] Various dinitrile products were obtained in moderate to good enantioselectivities through the reaction. In 2010, the same group developed a Rh catalyst **155** for asymmetric transfer hydrogenation of β,β-disubstituted nitroalkenes in water, affording various optically active nitroalkanes in good yields and high enantioselectivities (Scheme 57).[94c] They also reported transfer hydrogenation of unsaturated ketones in water catalyzed by Rh complex **156** (Scheme 58).[94d] The hydrogenation showed high chemoselectivity at the C–C double bond over carbonyl group. Accordingly, a 1,4-addition mechanism involving



Scheme 56. Asymmetric transfer hydrogenation of malononitriles by using Ru complex **154** as catalyst.



Scheme 57. Rh-catalyzed asymmetric transfer hydrogenation of β,β-disubstituted nitroalkenes in water.

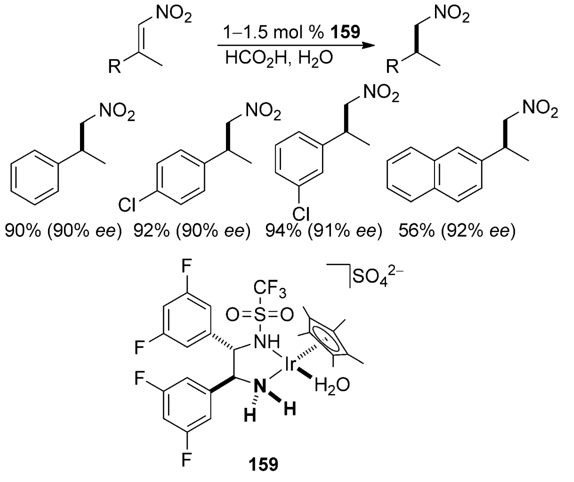


R^1	R^2	conv. [%]	157a:157b:157c
Ph	Me	97	95:3:2
Ph	Et	>99	94:5:1
Ph	*t*Bu	94	100:0:0
p-Cl-C_6H_4	Me	>99	92:6:2
–C_3H_6–		94	60:37:3

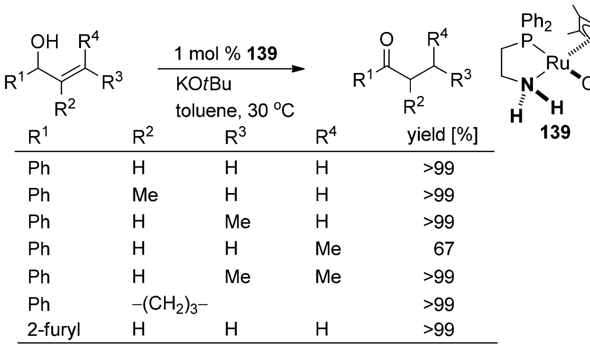
Scheme 58. Rh-catalyzed transfer hydrogenation of unsaturated ketones in water.

transition state **158** was proposed for the reaction, whereby the NH group participates in the reaction by forming hydrogen bond with the carbonyl group of the unsaturated ketone.

In 2009, Carreira and co-workers presented an enantioselective transfer hydrogenation of (*E*)-β,β-disubstituted nitroalkenes in water using Ir complex **159** as catalyst (Scheme 59).[95] A series of nitroalkenes were efficiently hydrogenated under mild and easily handled conditions, giving chiral nitroalkanes with excellent enantioselectivities in high yields.



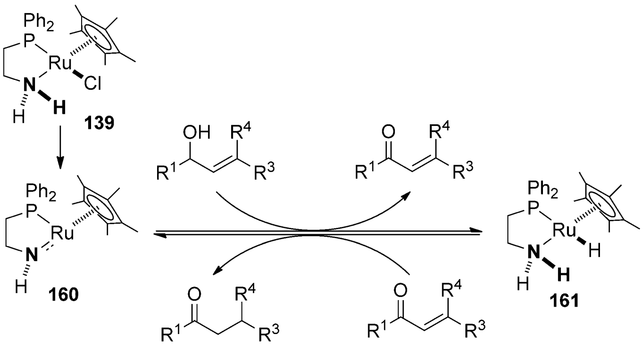
Scheme 59. Ir-catalyzed asymmetric transfer hydrogenation of nitroalkenes.



R^1	R^2	R^3	R^4	yield [%]
Ph	H	H	H	>99
Ph	Me	H	H	>99
Ph	H	Me	H	>99
Ph	H	H	Me	67
Ph	H	Me	Me	>99
Ph	–$(CH_2)_3$–			>99
2-furyl	H	H	H	>99

Scheme 60. Ru-catalyzed isomerization of allylic alcohols to ketones.

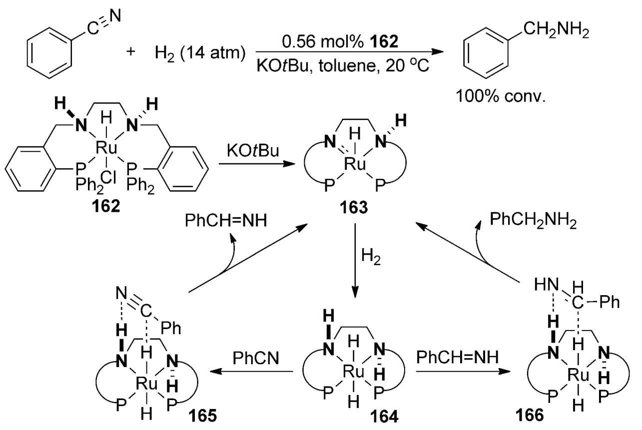
In 2005, Ikariya and co-workers found that Ru complex **139** was an efficient catalyst for isomerization of allylic alcohols to ketones (Scheme 60).[96] Various allylic alcohols were converted into the corresponding ketones in high yields under mild conditions. A plausible mechanism was proposed for the isomerization (Scheme 61). Ru amido complex **160**, which is generated in situ from **139** by treatment with base, dehydrogenates allylic alcohol to form α,β-unsatuated ketone and RuH species **161**. Reductive RuH species **161** in turn transfer the hydride and the NH_2 proton to the C–C double bond of the previously generated α,β-unsatuated ketone to form ketone product and regenerate Ru amido complex **160**, thus completing the catalytic cycle.



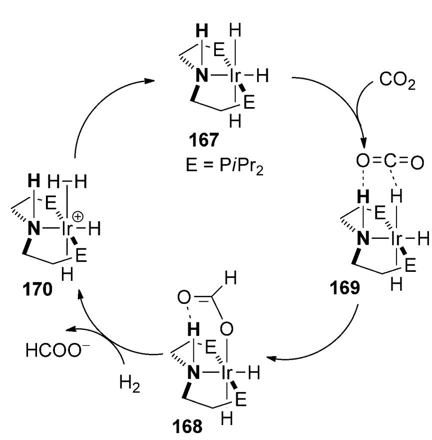
Scheme 61. A plausible mechanism for Ru-catalyzed isomerization of allylic alcohols to ketones.

2.3.4. Hydrogenation of Nitriles

The direct hydrogenation of nitriles to afford the corresponding amines is a facile and clean process in organic synthesis.[97] In 2007, Morris and co-workers found that benzonitrile can be hydrogenated to benzylamine with complete conversion under mild conditions by using Ru complex **162** as catalyst with NH functionality in the ligand (Scheme 62).[98] Mechanistic studies supported outer sphere pathway for the nitrile hydrogenation. Hydridoamido Ru complex **163**, which is generated in situ by reaction of **162** with base, splits dihydrogen heterolytically to form RuH species **164**. Complex **164** delivers a hydride from the ruthenium and a proton from the NH moieties to the nitrile via a six-membered ring transition state **165** as in Ru–NH-catalyzed ketone hydrogenation, forming an imine intermediate. The



Scheme 62. Ru-catalyzed hydrogenation of benzonitrile and the related catalytic mechanism.

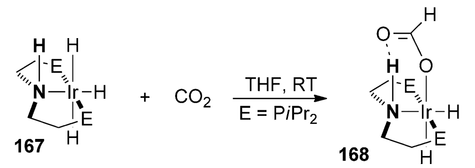


Scheme 64. The proposed mechanism for Ir-catalyzed hydrogenation of CO_2.

imine is further hydrogenated by complex **164** via a similar transition state **166** to give the final product benzylamine and regenerate hydridoamido catalyst **163**.

2.3.5. *Hydrogenation of CO_2*

Reduction of CO_2 has attracted much attention owing to global climate concerns. Recently, Hazari and co-workers found that a pincer-type Ir complex system with an NH moiety in the ligand was very efficient in the catalytic hydrogenation of CO_2 (Scheme 63).[99] Ir complex **167** readily reacted with CO_2 in less than 5 min at room temperature to form air- and moisture-stable Ir complex **168**. Complex **168** showed very high catalytic activity in hydrogenation of CO_2 to give a formate product. A TON of up to 348000 was achieved for the reaction at 185 °C. A mechanism for the CO_2 hydrogenation was proposed based on computational studies (Scheme 64). NH moiety in the catalyst is crucial for the insertion of CO_2 into Ir—H bond. Hydrogen bonding of the NH group with CO_2 lowers the activation energy, thus facilitating the reaction of trihydride complex **167** with CO_2 to form relatively stable Ir complex **168**. Displacement of the formate of **168** by H_2 gives dihydrogen complex **170** and releases the formate product. Deprotonation of **170** regenerates the reductive Ir complex **167**, thus completing the catalytic cycle.



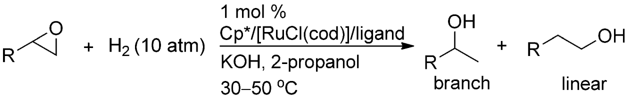
$$\underset{(1:1)}{H_2 + CO_2} \xrightarrow[\text{1 M KOH aq. (10 mL), 24 h}]{\textbf{168}\text{ (20 nmol)},\ 2\times10^{-4}\text{ mol \% relative to KOH}} HCOOK$$

T [°C]	P [psi]	yield [%]	TON	TOF
125	800	1	3820	159
145	800	10	49400	2058
165	800	24	118000	4917
185	800	70	348000	14500

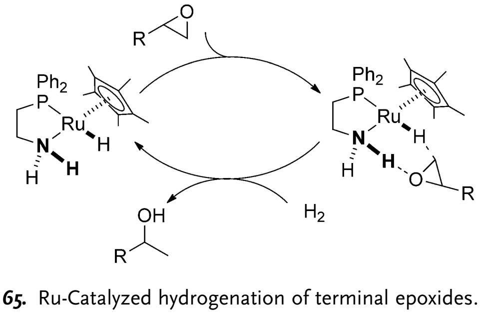
Scheme 63. Ir-Catalyzed hydrogenation of CO_2.

2.3.6. *Hydrogenation of Epoxides*

Hydrogenation of terminal epoxides can provide a useful method for the preparation of secondary alcohol if the reaction occurs chemoselectively at the terminal C—O bond. Ikariya and co-workers employed Ru catalysts with ligands bearing NH functional groups for chemoselective hydrogenation of terminal epoxides (Scheme 65).[100] Various terminal epoxides were hydrogenated under mild conditions to give secondary alcohols in good yields and high regioselec-



ligand	R	yield [%]	b:l
Ph_2P NMe_2	Ph	5	>99:1
Ph_2P **NH**Me	Ph	15	>99:1
Ph_2P **NH_2**	Ph	63	89:11
Ph_2P **NH_2**	n-C_6H_{13}	93	>99:1
Ph_2P **NH_2**	$PhOCH_2$	99	>99:1

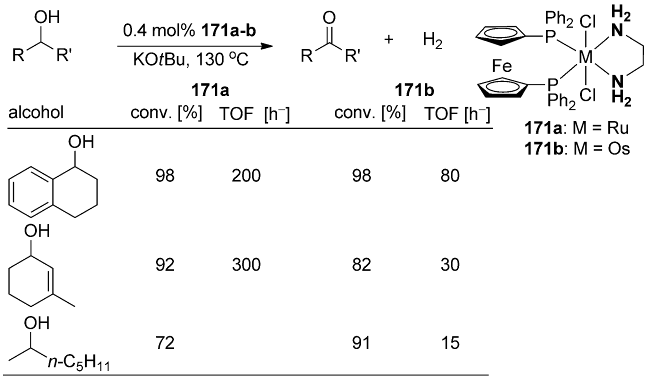


Scheme 65. Ru-Catalyzed hydrogenation of terminal epoxides.

tivities. The NH group in the ligand played an important role for the epoxide hydrogenation. The ligand without a NH end group was not effective for the hydrogenation. The hydrogenation was assumed to proceed via a six-membered ring transition state in which the NH cooperates with RuH to reduce the epoxide.

2.4. M–NH-Catalyzed Dehydrogenation

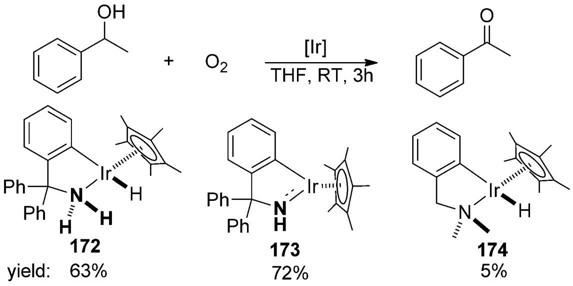
As a reverse process of hydrogenation of carbonyl groups, dehydrogenation of alcohols to ketones can also be catalyzed by a M–NH system. Recently, Baratta and co-workers reported Ru- and Os-catalyzed dehydrogenation of secondary alcohols to ketones (Scheme 66).[101] Ru complex **171a** showed somewhat higher catalytic activity than the corresponding Os complex **171b** in alcohol dehydrogenation.



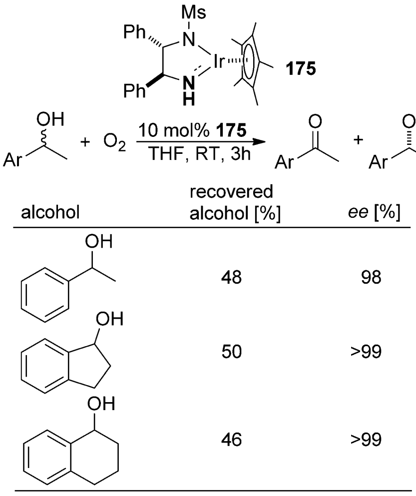
alcohol	171a conv. [%]	171a TOF [h⁻]	171b conv. [%]	171b TOF [h⁻]
	98	200	98	80
	92	300	82	30
	72		91	15

Scheme 66. Dehydrogenation of alcohols to ketones catalyzed by **171a,b**.

Alternatively, Ir-catalyzed dehydrogenative oxidation of alcohols by using O_2 as oxidant has been reported by Ikariya and co-workers (Scheme 67).[102a,b] The NH moiety in the Ir catalyst was found to be crucial for the efficiency of the dehydrogenative oxidation. Iridium complexes **172** and **173** showed similar catalytic activities for the reaction, while the complex **174** with *N*,*N*-dimethylamino group was ineffective in the catalysis. When a chiral iridium complex **175** was applied to the dehydrogenative oxidation, kinetic resolution of secondary alcohols was achieved with high efficiency, affording the corresponding optically active alcohols with excellent enantioselectivities (Scheme 68).



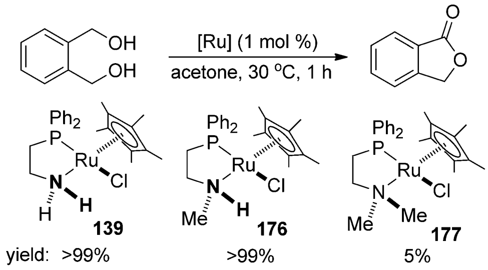
Scheme 67. Ir-Catalyzed dehydrogenative oxidation of alcohols: ligand effect.



alcohol	recovered alcohol [%]	*ee* [%]
	48	98
	50	>99
	46	>99

Scheme 68. Kinetic resolution of secondary alcohols based on Ir-catalyzed dehydrogenative oxidation of alcohols.

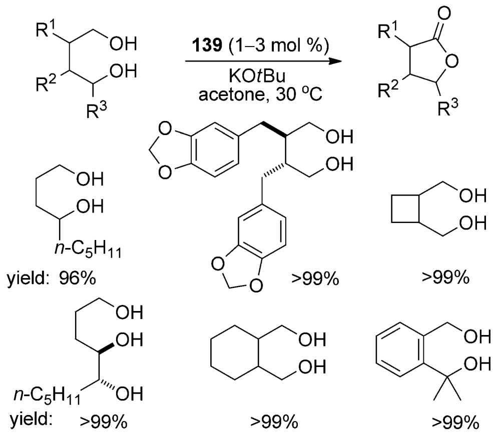
By using acetone as hydrogen acceptor, Ikariya and co-workers developed an efficient Ru-catalyzed oxidative lactonization of 1,4-diols under mild conditions (Scheme 69).[102c]



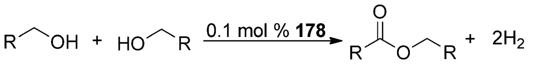
Scheme 69. Ru-catalyzed oxidative lactonization of 1,4-diols: ligand effect.

The obvious activity difference among the structurally similar catalysts **139**, **176**, and **177** suggests that the NH groups played an important role in the catalysis. A wide range of 1,4-diols were highly reactive for the transformation, affording various lactones with excellent chemoselectivies (Scheme 70).

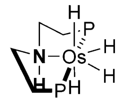
Gusev and co-worker recently developed Os-catalyzed dehydrogenative coupling of primary alcohols to esters (Scheme 71).[103] The reaction showed improved efficiency at high temperature. When one equivalent of primary amine was presented in the reaction, amine alkylation by the primary alcohols was observed, giving the corresponding secondary amines in good yields (Scheme 72). The formation of the amines was believed to proceed by an Os-catalyzed reaction sequence, including dehydrogenation of the alcohol, imine formation, and hydrogenation of the imine. Very recently, this



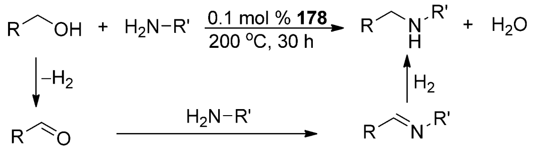
Scheme 70. Ru-catalyzed oxidative lactonization of 1,4-diols.



R	T [°C]	time [h]	yield [%]
Et	97	8	3
*n*Pr	118	24	16
*i*Bu	131	22	79


(P = P*i*Pr$_2$)
178

Scheme 71. Os-catalyzed dehydrogenation of primary alcohols to esters.

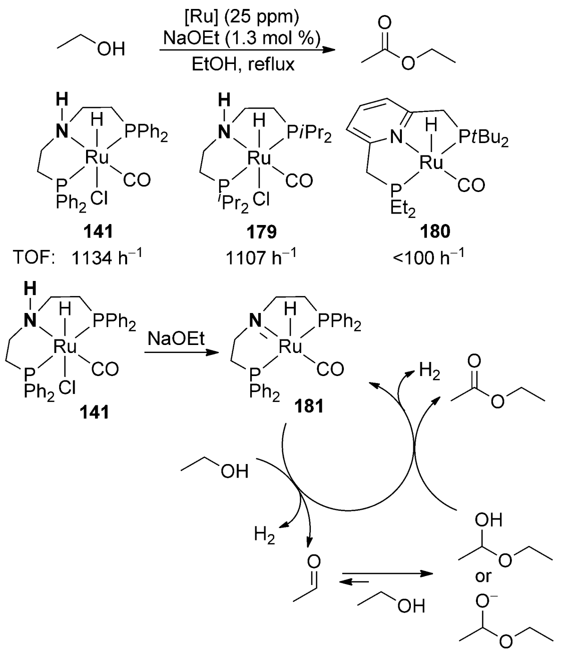


R	R'	yield [%]
Me	*n*-C$_6$H$_{13}$	81
Me	Cy	92
H	Ph	64

Scheme 72. Os-catalyzed alkylation of primary amine with alcohols.

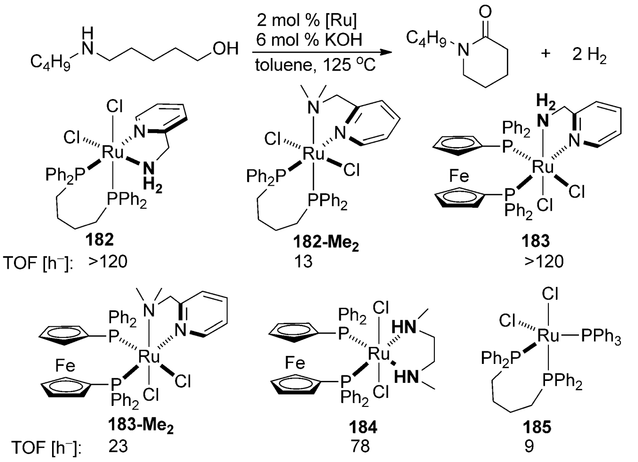
group demonstrated that Os dimer **143b** was also highly active for dehydrogenative oxidation of primary alcohols to esters.[90] The molar ratio of alcohol to metal could be up to 4000 in the reaction.

Very recently, Beller and co-workers contributed a process for the synthesis of ethyl actetate by dehydrogenation of ethanol by using PNP–Ru complex as catalyst (Scheme 73).[104] Complexes with NH moieties, such as **141** and **179**, showed much higher activity than those without NH units, such as **180**, in the dehydrogenation, implying that the NH moiety is crucial for the process. Amido ruthenium complex **181**, which is generated from **141** by NaOEt-promoted elimination of HX, was assumed to be the active dehydrogenation catalyst. Complex **181** catalyzed the dehydrogenation of ethanol and subsequent hemiacetal to form the ethyl acetate, releasing two equivalents of H_2.

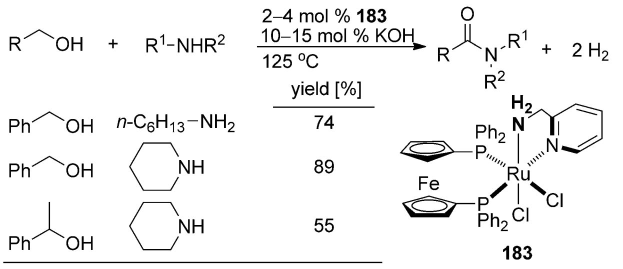


Scheme 73. Ru-catalyzed dehydrogenation of ethanol to synthesis of ethyl actetate.

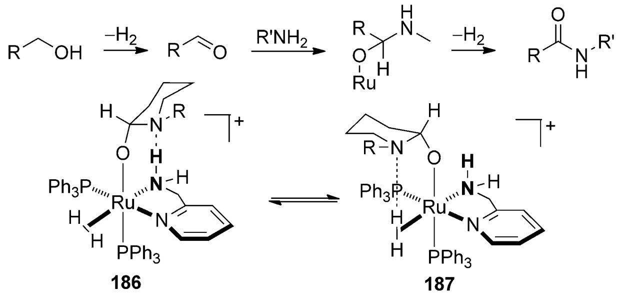
Crabtree and co-workers reported the synthesis of amides from primary alcohols and amines by Ru–NH catalyzed dehydrogenation (Scheme 74).[105] The ligand in the Ru catalyst was disclosed to have significant impact on the efficiency of the dehydrogenation. The ligands with NH ends showed much higher catalytic activity than those without NH ends in the dehydrogenation of amino alcohol to form cyclic amide, indicating that the NH moiety in the catalyst plays an important role in the reaction. When a mixture of primary alcohols and amines were submitted to the reaction, simple amides were formed in good yields (Scheme 75). The reaction was proposed to proceed by a stepwise process (Scheme 76).



Scheme 74. Ru-Catalyzed dehydrogenation of amino alcohols to cyclic amides.



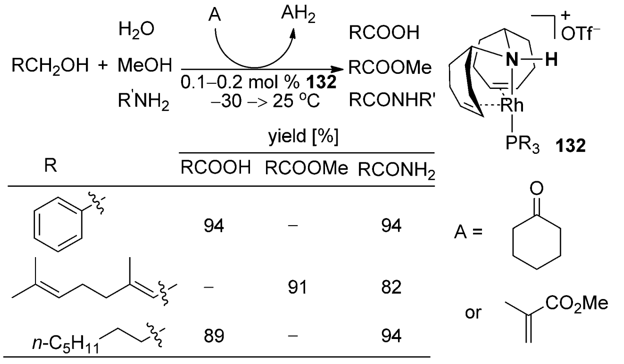
Scheme 75. Ru-Catalyzed dehydrogenation of alcohols and amines to amides.



Scheme 76. Proposed catalytic mechanism for the Ru-catalyzed dehydrogenation of alcohols and amines to amides.

Primary alcohol undergoes dehydrogenation to give aldehyde which is trapped by amine to form Ru-bound hemiaminal intermediate. The Ru-bound hemiaminal is further dehydrogenated to give the amide product. The profound NH effect of the ligand was explained by the authors based on computational studies. Intermediates **186** and **187** are close in energy but have different energy barriers to release H_2 from the Ru centers. In the intermediate **186**, the N atom of the hemiaminal is hydrogen-bonded by the NH group of the ligand, thus H_2 is free from interaction with the hemiaminal N, resulting in easier release of the H_2 from the Ru center. That might explain the reason for why the catalysts with the ligands having NH ends showed much higher activity than those without NH ends in the dehydrogenative amide formation.

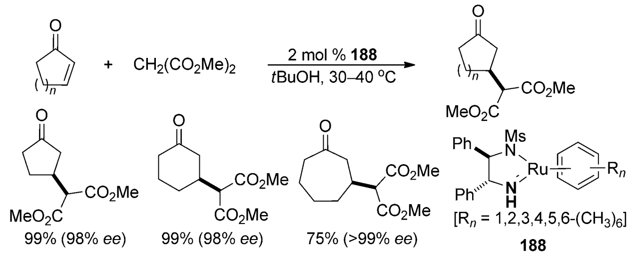
Grützmacher demonstrated that Rh complex **132** was a versatile catalyst for dehydrogenative coupling of primary alcohols with water, methanol, and amines to give the corresponding acids, esters, and amides in high yields under mild conditions (Scheme 77).[106] Low catalyst loading, good tolerance of functional groups, and high chemoselectivities were observed in the reaction, making the process be synthetically attractive.



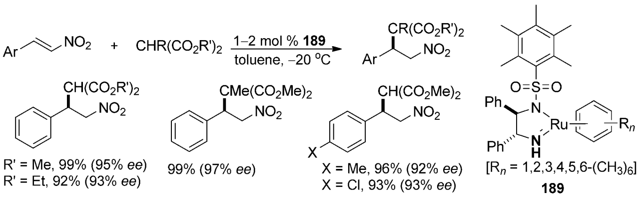
Scheme 77. Rh-catalyzed dehydrogenation coupling of alcohols with H_2O, MeOH, and amines.

2.5. M–NH-Catalyzed Conjugate Addition

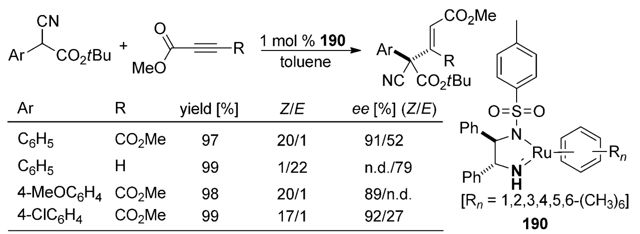
As discussed above, most of the reaction systems using M–NH catalysts are related to the hydrogenation or dehydrogenation processes. Moreover, M–NH complexes have also been used as the bifunctional catalysts in the conjugate addition for C–C bond formation. Ikariya and co-workers successfully applied the M–NH system to conjugate addition of various donors to acceptors. Excellent enantioselectivies and high activities were achieved in the conjugate addition of malonates to cyclic enones (Scheme 78),[107a,c,d] 1,3-dicarbonyl compounds to nitroalkenes (Scheme 79),[107b] α-substituted cyanoacetates to acetylenic esters (Scheme 80),[107e] and α-cyanoacetates to azodicarboxylates (Scheme 81)[107f] by using



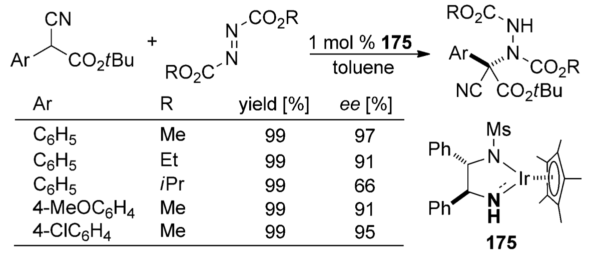
Scheme 78. Ru-catalyzed conjugate addition of malonates to cyclic enones.



Scheme 79. Ru-catalyzed conjugate addition of 1,3-dicarbonyl compounds to nitroalkenes.



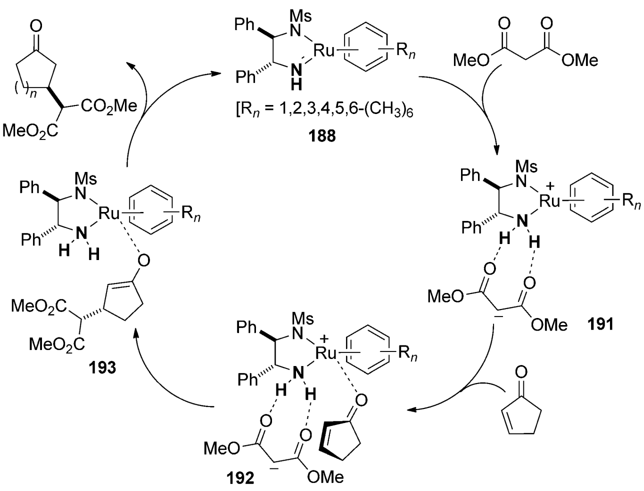
Scheme 80. Ru-catalyzed conjugate addition of α-substituted cyanoacetates to acetylenic esters.



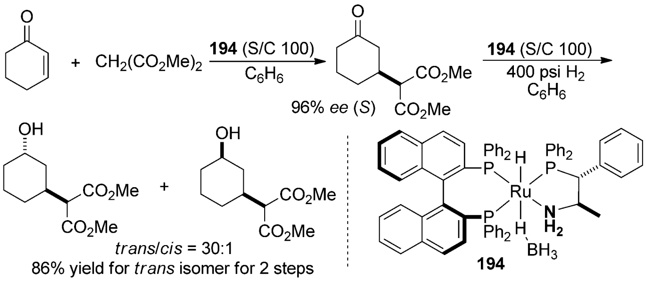
Ar	R	yield [%]	ee [%]
C_6H_5	Me	99	97
C_6H_5	Et	99	91
C_6H_5	*i*Pr	99	66
4-$MeOC_6H_4$	Me	99	91
4-ClC_6H_4	Me	99	95

Scheme 81. Ru-catalyzed conjugate addition of α-cyanoacetates to azodicarboxylates.

amido Ru complexes **188**–**190** and Ir complex **175** as catalysts. According to experimental and computational studies, the authors proposed a plausible mechanism for the additions (Scheme 82).[108] For example, in the addition of malonate to cyclic enone catalyzed by **188** (Scheme 78), the amido Ru complex **188** reacts with malonate first to form an intermediate **191** in which two amino protons chelate with malonate anion by two hydrogen bonds. The positive Ru center of **191** coordinates a molecule of cyclic enone to enhance its electrophilicity, followed by enantioselective C–C bond formation to form Ru enonate species **193**. Intermediate **193** releases Michael addition product to regenerate catalyst amido Ru species **188**, completing the catalytic cycle.



Scheme 82. Proposed mechanism for Ru-catalyzed Michael addition of malonate to cyclic enone.

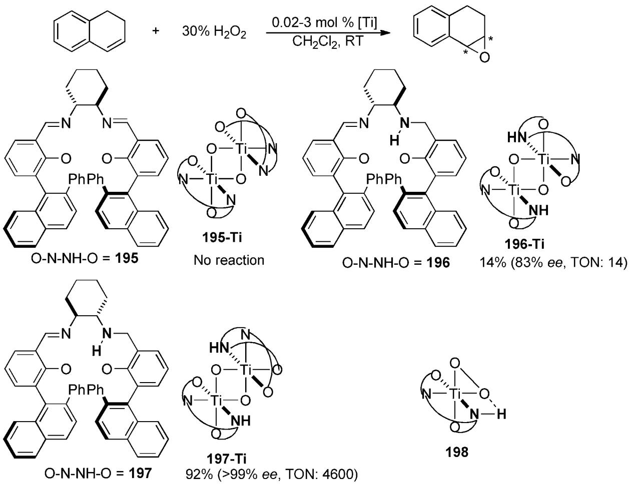


Scheme 83. Ru-catalyzed tandem Michael addition/hydrogenation sequence.

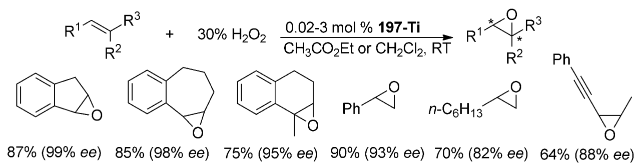
Morris and co-workers reported a tandem Michael addition/hydrogenation sequence by using a single catalyst, chiral Ru complex **194** (Scheme 83).[109] High enantioselectivity for the Michael addition and excellent diastereoselectivity for the following hydrogenation were observed in the reaction sequence, resulting in the formation of a highly enantioenriched alcohol with multiple enantiogenic centers.

2.6. M–NH-Catalyzed Olefin Epoxidation

The dramatic impact of the NH moiety in the catalysis were observed not only in the hydrogenation/dehydrogenation and Michael addition reactions, but also in the oxidations. Katsuki and co-workers discovered that NH groups in Ti catalysts has a significant synergetic effect in the expoxidation of olefin with aqueous H_2O_2 as the oxidant in terms of activity and enantioselectivity.[110] Catalyst **197**-**Ti**, which was generated from half-reduced salen ligand **197**, showed excellent enantioselectivity and high activity in the epoxidation of 1,2-dihydronaphthalene (Scheme 84). However, structurally similar catalyst **195**-**Ti** generated from NH-free salen **195** was totally ineffective for the epoxidation, indicating the critical importance of NH moiety in the Ti catalyst. The authors proposed that peroxotitanium complex **198**, which could be formed in situ from **197**-**Ti** by treatment with hydrogen peroxide, acted as the active oxidation species in the olefin epoxidation. The peroxotitanium species is activated by an intramolecular hydrogen bond with the NH proton for the following oxidation of olefins, which accounts for the dramatic NH effect in the enantioselective epoxidation of olefins. As shown in Scheme 85, catalyst **197**-**Ti** was effective for the epoxidation of cyclic olefins, enyne, styrene, and simple terminal olefin, giving various epoxides in good yields and excellent enantioselectivities.

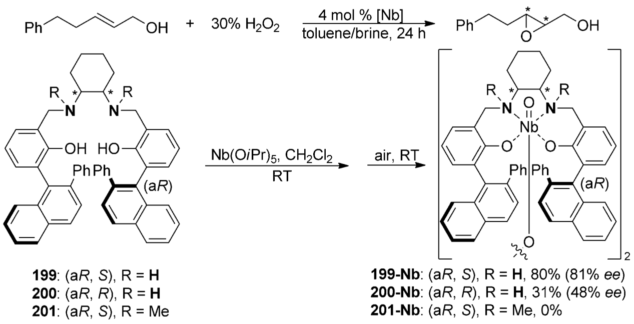


Scheme 84. Ti-catalyzed asymmetric epoxidation of 1,2-dihydronaphthalene: ligand effect.

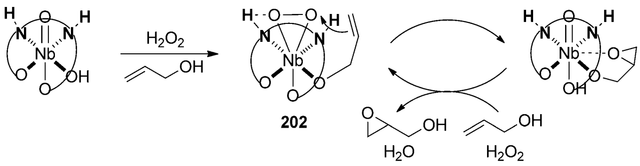


Scheme 85. Asymmetric epoxidation of various olefins catalyzed by **197**-Ti.

A similar NH effect was also observed in Nb(salan)-catalyzed asymmetric epoxidation of allylic alcohols using aqueous H_2O_2 as the oxidant.[111] As shown in Scheme 86, Nb complexes with NH moieties, such as **199-Nb** and **200-Nb**, were active and enantioselective for the epoxidation. However, complex **201-Nb** generated from *N,N'*-dimethyl salan **201** did not show any catalytic activity in the reaction. Monomeric peroxo niobium species **202** was proposed to be an active intermediate for the asymmetric epoxidation of allylic alcohols. The NH moiety in the catalyst activates the niobium peroxo by intramolecular hydrogen bonding, which facilitates the oxygen transfer from the niobium peroxo to the double bond of the allylic alcohol, leading to the dramatic NH effect observed in this epoxidation (Scheme 87).



Scheme 86. Nb-catalyzed asymmetric epoxidation of allylic alcohols: ligand effect.

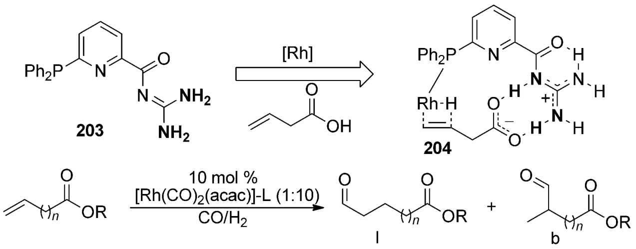


Scheme 87. The proposed mechanism for Nb-catalyzed epoxidation of allylic alcohols using aqueous H_2O_2 as oxidant.

3. M···NH Catalysis

The additional functions of the NH moiety in a ligand have also been found in the M···NH catalytic system in which the N atom usually does not directly coordinate to the metal center (Figure 1 b). The NH moiety in the ligand can activate and/or recognize substrate by hydrogen bonding (M···NH catalysis). The selectivities and activities could be significantly improved if the NH moiety selectively recognizes the substrate and renders the substrate in a favorable orientation close to the metal center. Thus the distance and the relative orientation between the metal center and the NH moiety are extremely important for the M···NH catalysis. This catalysis concept has received much attention recently and already been successfully applied to many reactions.

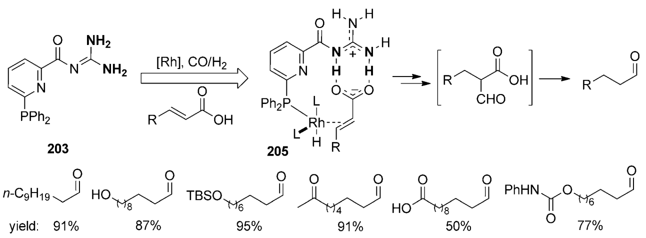
An elegant example of the M···NH catalysis was contributed by Breit and co-workers.[112] A phosphine ligand **203** containing a guanidine moiety was designed for Rh-catalyzed hydroformylation of unsaturated carboxylic acids (Scheme 88).[112] The guanidine unit recognizes carboxylic acid by hydrogen bonding and brings the C−C double bond of the substrate close to the Rh center, as shown in the proposed transition state **204**. When the Rh supramolecular catalyst and olefin substrate match well, improved catalytic activity and regioselectity would be expected. In fact, as shown in Scheme 88, this concept works very well for the hydroformylation of functionalized olefins. Ligand **203** showed much better performance in terms of activity and regioselectivity than PPh_3 in the Rh-catalyzed hydroformylation of but-3-enoic acid under otherwise identical conditions (Scheme 88, entry 1 vs 2). The carboxylic acid moiety in the olefin substrate is crucial for the high efficiency and regioselectivity in the hydroformylation. For example, the corresponding methyl ester of vinylacetic acid showed much lower activity and worse regioselectivity in the reaction (Scheme 88, entry 1 vs 3). γ,δ-Unsaturated acid, such as penta-4-enoic acid, which is one carbon longer between the C=C double bond and the carbonyl group than β,γ-unsaturated acid, exhibited much lower activities and worse regioselectivities under the identical experimental conditions (Scheme 88, entry 1 vs 4), indicating the critical importance of harmonious match between supramolecular catalyst and substrate for the activity and regioselectivity of the catalysis.



Entry	L	Substrate	Conv. [%]	l/b	TOF [h^{-1}]
1	**203**	*n* = 1, R = H	100	23	250
2	PPh_3	*n* = 1, R = H		1.3	30
3	**203**	*n* = 1, R = Me	50	1.1	29
4	**203**	*n* = 2, R = H	73	3.6	49

Scheme 88. Rh-catalyzed hydroformylation of unsaturated carboxylic acids: effect of guanidine moiety.

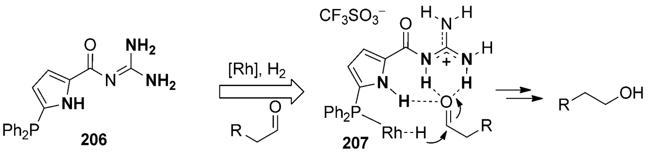
This concept was also applied to the Rh-catalyzed decarboxylative hydroformylation of α,β-unsaturated carboxylic acids (Scheme 89).[113] Hydroformylation forms an α-formyl cayboxylic acid intermediate, which undergoes imme-

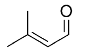
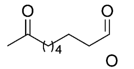
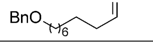


Scheme 89. Rh-catalyzed decarboxylative hydroformylation of α,β-unsaturated carboxylic acids.

diate decarboxylation to give the corresponding aldehyde product. Various aldehydes with different functional groups were prepared in high yields on the basis of this approach.

Breit and co-workers further extended this concept by employing phosphine **206** as the ligand to construct Rh catalyst for hydrogenation of aldehydes (Scheme 90).[114] The

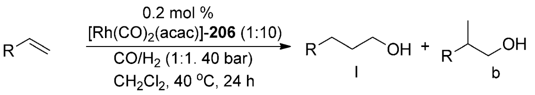


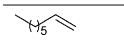
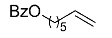
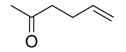
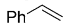
entry	ligand	substrate	conv. [%]	yield [%]
1	Ph_3	R = n-C_6H_{13}	0	0
2	**203**	R = n-C_6H_{13}	3	3
3	**206**	R = n-C_6H_{13}	100	97
4	**206**	R = i-Pr		90
5	**206**	R = Ph		98
6	**206**			99
7	**206**			98
8	**206**			96

Scheme 90. Rh-catalyzed hydrogenation of aldehydes to primary alcohols: effect of guanidine moiety.

guanidine moiety binds and activates aldehyde through hydrogen bonding as shown in the proposed transition state **207**, facilitating the transfer of hydride from Rh to aldehyde. PPh_3 is totally ineffective for the reduction under otherwise identical experimental conditions, demonstrating that the guanidine recognition unit is very important for the catalysis (Scheme 90, entry 1 vs 3). Various aldehydes were hydrogenated to give the corresponding primary alcohols in excellent yields by using this supramolecular Rh catalyst. It is worthy to note that readily reduced functional groups, such as ketones and activated C–C double bonds, are well tolerated by the hydrogenation (Scheme 90, entries 6 and 7). This supramolecular catalyst was also successfully extended to tandem hydroformylation/hydrogenation of simple terminal olefins, giving various primary alcohols that are one carbon longer in good yields and high regioselectivities (Scheme 91).

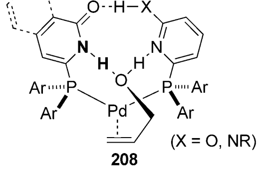
Breit and co-workers extended the M···NH supramolecular strategy to Pd-catalyzed allylation of *N*-heterocycles with

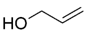
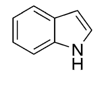
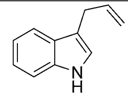
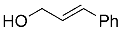
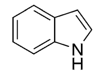
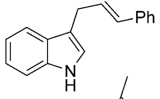
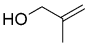
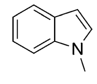
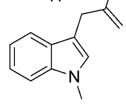
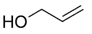
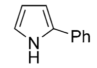
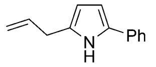
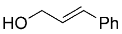
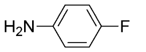
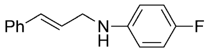


substrate	conv. [%]	yield [%]	l/b
	90	87	92:8
	95	93	83:17
	100	98	91:9
	95	90	7:93

Scheme 91. Rh-catalyzed tandem hydroformylation/hydrogenation of terminal olefins

unactivated allylic alcohols (Scheme 92).[115] Usually, allylic alcohols are not active enough to serve as an allylation reagent. The NH moieties in the self-assembled catalyst binds

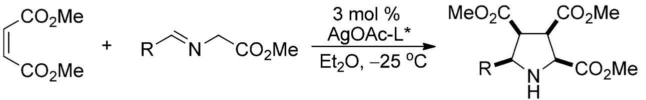


allylic alcohol	nucleophile	product	yield [%]
			80
			79
			94
			61
			92

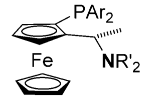
Scheme 92. Pd-catalyzed allylation of *N*-heterocycles with allylic alcohols.

and activates the allylic alcohols through hydrogen bonding with the hydroxy group of the allylic alcohol, as shown in intermediate **208** (Scheme 92). The allylation proceeds smoothly and yields various allylic indoles, allylic pyrrole, and allylic amines in good yields.

Zhou and Li also disclosed an interesting NH effect in Ag^I-catalyzed asymmetric [3+2] cycloaddition of azomethine ylides to dimethyl maleate (Scheme 93).[116a] Phosphine ligand **209** with an NH_2 moiety showed completely reverse enantiocontrol for the cycloaddition as compared to the related ligand **210** with NMe_2 group. Computational studies provided a rational explanation for the reversal of the asymmetric induction between the two ligands. As shown in Scheme 94, when NH_2-containing ligand **209** is applied to the catalysis, maleate is activated by the NH_2 unit through double hydrogen



R	L*	yield [%]	*ee* [%]
Ph	**209**	95	90
Ph	**210**	96	-85
p-anisyl	**209**	93	90
p-anisyl	**210**	98	-87
2-naphthyl	**209**	98	91
2-naphthyl	**210**	91	-87

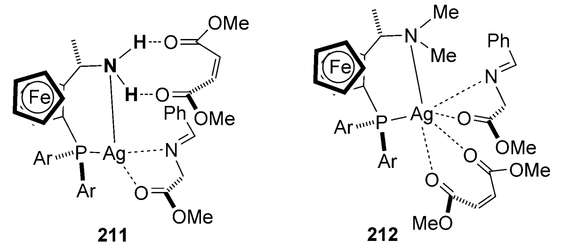


Ar = 3,5-$Me_2C_6H_3$

209: R' = **H**

210: R' = Me

Scheme 93. Ag^I-catalyzed asymmetric [3+2] cycloaddition of azomethine ylides to dimethyl maleate.

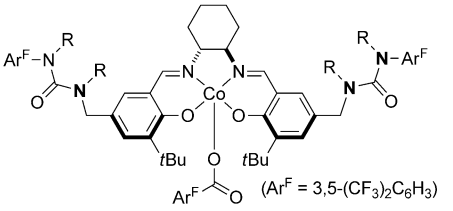


211 **212**

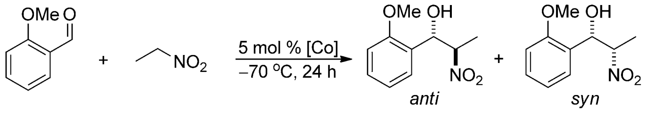
Scheme 94. NH effect in Ag^I-catalyzed asymmetric [3+2] cycloaddition.

bonding (intermediate **211**), thus the maleate approaches azomethine ylide from the top face. On the other hand, when NMe_2-containing ligand **210** is used, maleate coordinates to Ag^I center as shown in the intermediate **212**, thus the coordinated maleate approaches azomethine ylide from the down face, resulting in the reversal of enantioselectivity in the cycloaddition. Recently, Wang and co-workers also disclosed a similar cooperation between a NH group and the metal center in the Cu-catalyzed asymmetric 1,3-dipolar cycloaddition and conjugate addition of azomethine ylides.[116b–e] The computational analysis of the reaction mechanisms supported the activation of the electron-dificient olefins through hydrogen bonding between the NH group of the catalyst and the olefin substrate.[116b]

Very recently, Hong and co-workers showed that NH moieties were also significant in terms of activity and selectivity in the urea-modified salen/Co^{III} **213**-catalyzed asymmetric nitroaldol reaction (Scheme 95).[117] Structurally similar catalyst **214** with NMe instead of NH moieties showed much lower activity and worse diastero- and enantioselectivities than catalyst **213** in the nitroaldol reaction between 2-methoxybenzaldehyde and nitroethane (Scheme 95, entry 1 vs 2). By using Co complex **213** as catalyst, a series of nitro alcohols were obtained in good yields and high enantio- and diastereoselectivities through the nitroaldol reaction (Scheme 96). Mechanistic studies suggested a Co⋯NH bifunctional catalysis for this nitroaldol reaction (Scheme 97) in which the NH moieties bind and activate the nitroalkane by double hydrogen bonding with the nitro oxygen atoms, leading to the high activity and good selectivities.

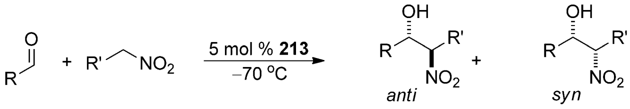


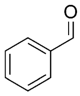
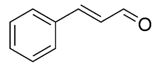
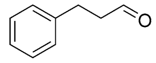
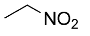
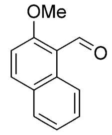
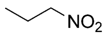
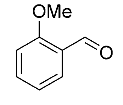
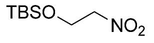
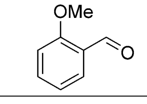
213, R = **H**, **214**, R = Me



catalyst	yield [%]	*anti*/*syn*	*ee* [%]
213	84	48:1	96/n.d.
214	14	4:1	85/82

Scheme 95. Co^{III}-catalyzed asymmetric nitroaldol reaction: effect of a urea side group.

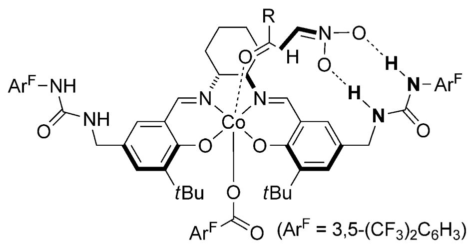


nitroalkane	aldehyde	yield [%]	*anti*/*syn*	*ee* [%]
—NO_2		85	–	97
—NO_2		88	–	92
—NO_2		89	–	91
		95	17/1	97/n.d.
		67	6/1	85/88
		88	>50/1	94/n.d.

Scheme 96. Asymmetric nitroaldol reaction catalyzed by Co^{III} complex **213**. TBS = *tert*-butyldimethylsilyl.

4. Assembly of Ligands by NH Interactions

Bidentate donor ligands have been widely used in organometallic catalysis. The two donor atoms in classic bidentate ligands are usually linked by covalent bonds, which might require laborious synthesis and limit the structural diversity of the ligands. It would be more facile if the generation of bidentate ligands occurs through in situ self-assembling monodentate ligands through NH-initiated hydrogen bonding around coordination sphere. The hydrogen-bonding connection provides spacial flexibility between the

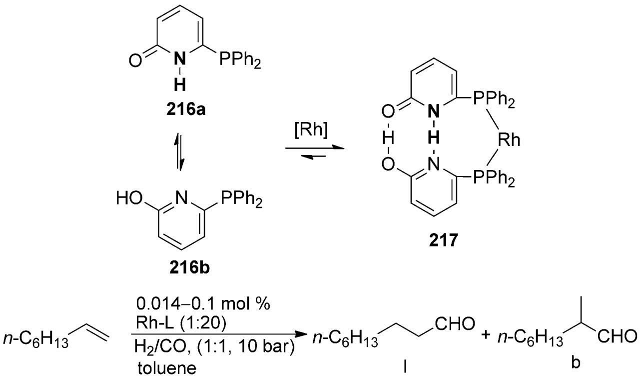


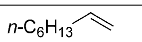
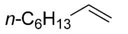
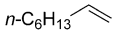
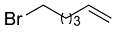
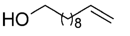
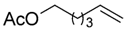
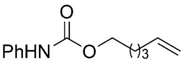
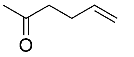
215

Scheme 97. The proposed working model for Co⋯NH bifunctional catalysis of the nitroaldol reaction.

two donor atoms, allowing the ligand to adjust the relative position between the two coordinating units to meet the different configuration requirements during all catalysis stages. Therefore, self-assembled bidentate ligands through NH hydrogen bonding might have unique catalytic performance as compared to structurally relatively rigid classic bidentate ligands. Moreover, the self-assembly strategy provides a quick method to dramatically enlarged libraries of bidentate ligands by employing combinatorial approach and thus accelerates catalyst discovery.

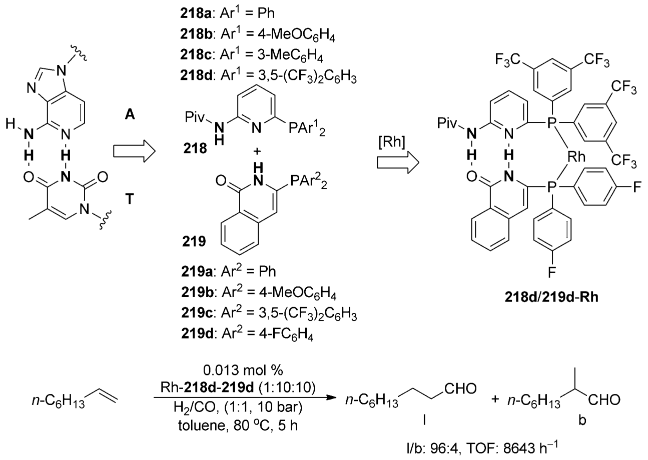
In 2003, Breit and co-workers reported a Rh-catalyzed hydroformylation of olefins using a self-assembled chelating diphosphine as the ligand. The ligand was generated from a tautomeric pair of monodentate phosphines **216a** and **216b**.[118a] As shown in Scheme 98, double hydrogen bonds have been assumed to be formed between the pyridone/hydroxypyridine tautomers in catalyst **217**. The self-assembled catalyst was applied to hydroformylation of 1-octene. The activity and linear regioselectivity were much higher in the reaction (entry 3) than those abtained in the hydroformylation using monodentate triphenylphosphine as the ligand (entry 1). Moreover, this self-assembled catalyst demonstrated even higher activity than the Rh^I complex of a well-known bidentate phosphine ligand (*t*Bu-XANTPHOS), albeit with similar regioselectivity (entry 3 vs 2). These results demonstrate that monodentate ligands **216a**,**b** should act as a bidentate chelating assembly in the hydroformylation of olefins, as assumed by the authors. Besides the excellent regioselectivity and high catalytic activity, the self-assembled Rh catalyst **217** also tolerated a variety of functional groups well in the olefin hydroformylation.[118]



entry	substrate	ligand	conv. [%]	l/b
1		PPh_3	22	73:27
2		*t*Bu-XantPhos	6	98:2
3		**216a-b**	56	97:3
4		**216a-b**	100	97:3
5		**216a-b**	100	96:4
6		**216a-b**	100	96:4
7		**216a-b**	100	96:4
8		**216a-b**	100	94:6

Scheme 98. Self-assembled Rh catalyst **217** for hydroformylation of various olefins.

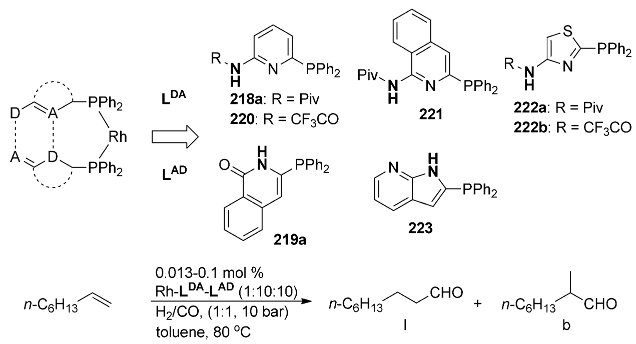
Inspired by the complementary hydrogen bonding between adenine (A) and thymine (T), Breit and Seiche designed an aminopyridine/isoquinolone system (**218**/**219**) to generate combinatorial library of self-assembled bidentate ligands (Scheme 99).[119] The ligand library was tested in Rh-catalyzed hydroformylation of 1-octene. The Rh complex generated from monodentate phosphines **218d** and **219d** was found to be the best in terms of both activity and regioselectivity.



Scheme 99. Complementary hydrogen bonding effect in the Rh-catalyzed hydroformylation of 1-octene.

The impact of the hydrogen-bond-forming units of the self-assembly system on the catalytic performance was also investigated by Breit and co-workers (Scheme 100).[120] Combinatorial screening disclosed that thiazole systems **222a**/**219a** and **222b**/**219a** showed very high linear regioselectivities in Rh-catalyzed hydroformylation of 1-octene. The high linear regioselectivity was maintained even in a protic solvent, such as MeOH, despite the fact that MeOH may interrupt the hydrogen bonding between the paired monodentate phosphines.

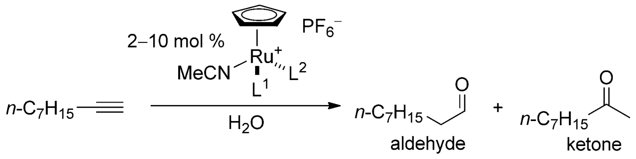
The self-assembly concept was also applied to the Ru-catalyzed anti-Markovnikov hydration of terminal alkynes (Scheme 101).[121] The Ru complex **224** generated in situ from self-assembled chelating ligand exhibited the highest regio-

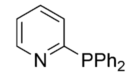
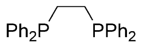
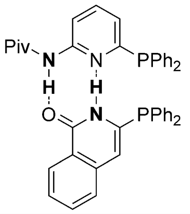


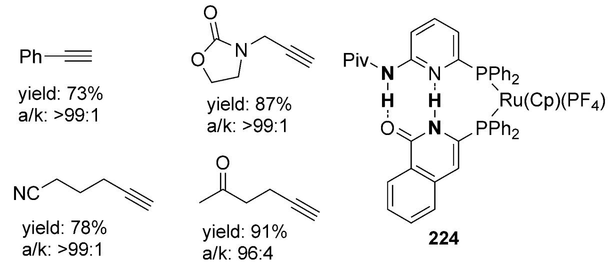
$L^{DA} \rightarrow$ / $L^{AD} \downarrow$	**218a** TOF [h^{-1}]	**218a** l/b	**220** TOF [h^{-1}]	**220** l/b	**221** TOF [h^{-1}]	**221** l/b	**222a** TOF [h^{-1}]	**222a** l/b	**222b** TOF [h^{-1}]	**222b** l/b
219a	2465	94:6	3396	96:4	2341	95:5	**3890**	**98:2**	**3888**	**>99:1**
213	2713	89:11	4356	96:4	3205	95:5	3233	95:5	2318	99:1

L^{DA}/L^{AD}	218a/219a	220/219a	222a/219a	222b/219a	222b/223
l/b (in toluene)	94:6	96:4	98:2	99:1	99:1
l/b (in MeOH)	82:18	79:21	**97:3**	**96:4**	85:15

Scheme 100. Hydrogen bonding effect in the Rh-catalyzed hydroformylation of 1-octene.



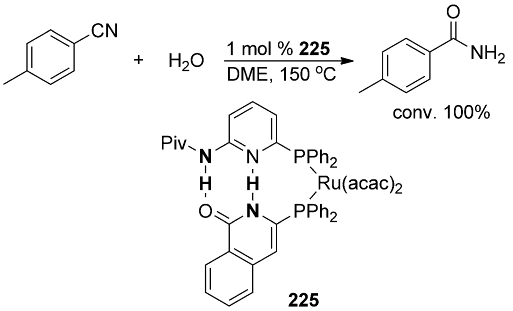
entry	L^1(L^2)	*t* [h]	aldehyde [%]	ketone [%]
1	PPh$_3$	140	1.2	18
2		168	4.0	2.4
3		168	2.1	20
4		26	94	0



Scheme 101. Complementary hydrogen bonding effect in Ru-catalyzed *anti*-Markovnikov hydration of terminal alkynes.

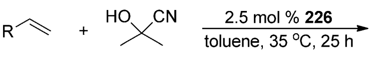
selectivity for the linear aldehyde production among the Ru catalysts of a variety of monodentate and bidentate ligands in the hydration of 1-nonyne (entry 4 vs entries 1–3). This catalyst was workable for the hydroformylation of a wide range of olefins with various functional groups. The structure of the Ru catalyst **224** was further identified by NMR studies and X-ray analysis, and the complementary hydrogen bonds between two monophosphines were clearly clarified.

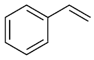
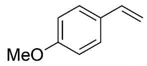
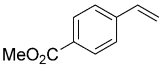
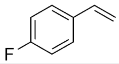
This self-assembly concept was further extended to Ru-catalyzed hydration of nitriles to amides (Scheme 102)[122a] and Ni-catalyzed hydrocyanation of alkenes (Scheme 103).[122b] The Ni catalyst **226** showed excellent regioselectivities for branched nitrile products in the hydrocyanation of styrenes with acetone cyanohydrin as cyanide source (Scheme 103).

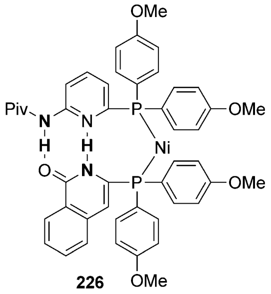


225

Scheme 102. Hydrogen-bonding-organized Ru catalyst for hydration of nitrile.



substrate	b/l	yield [%]
	>99:1	89
	>99:1	100
	>99:1	100
	>99:1	100

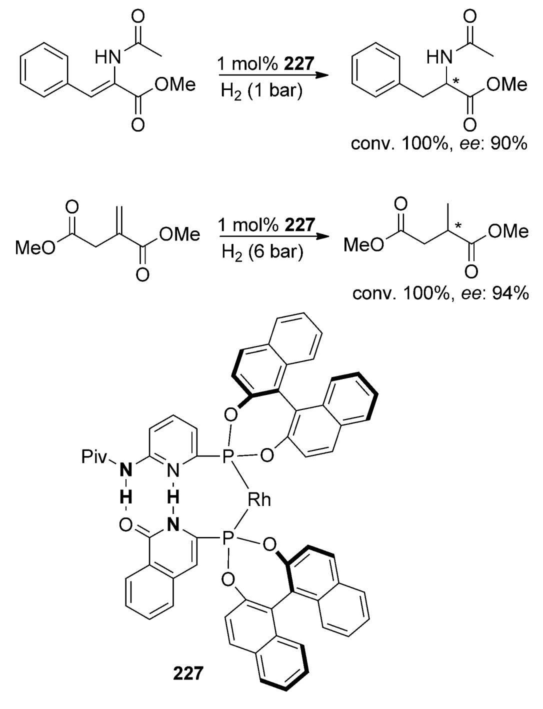


226

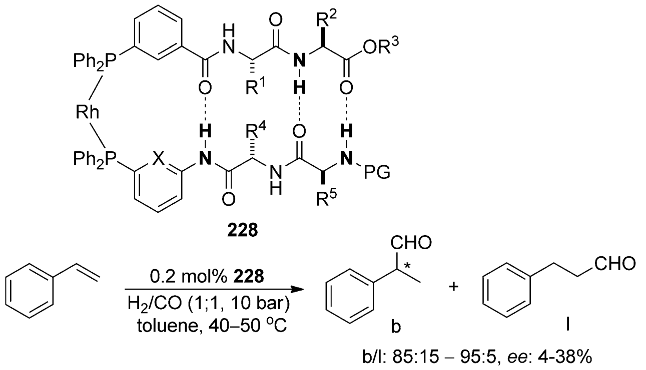
Scheme 103. Hydrogen-bonding-organized Ni catalyst for hydrocyanation of various styrenes.

When chiral elements are introduced to the self-assembled system, a catalytic asymmetric version would be expected. By using self-assembled chiral Rh catalyst **227** formed from monodentate (*S*)-BINOL-based phosphonites, asymmetric hydrogenation of functionalized alkenes was realized with complete conversion of the substrates and high enantiomeric excesses of products (Scheme 104).[123]

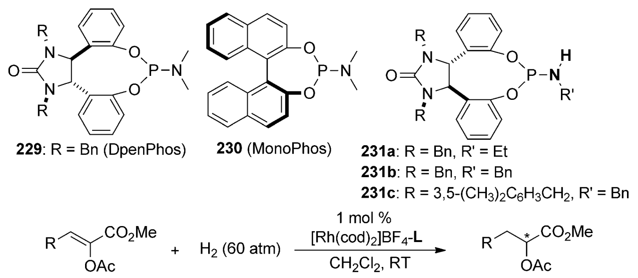
By imitating β-sheet structure in proteins, Breit and coworkers developed a chiral self-assembled Rh catalyst **228** (Scheme 105).[124] It was proposed that the chelating diphosphine in **228** was formed through hydrogen bonding between the peptides of the two monophosphines. Catalyst **228** showed asymmetric induction in hydroformylation of styrene with high regioselectivity for branched aldehydes.



Scheme 104. Hydrogen-bonding-organized Rh catalyst in asymmetric hydrogenation of functionalized olefins.



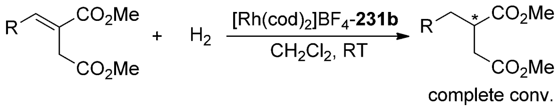
Scheme 105. Hydrogen-bonding-organized Rh catalyst for asymmetric hydroformylation of styrene.



entry	R	ligand	conv. [%]	*ee* [%]
1	Ph	**229**	0	
2	Ph	**230**	0	
3	Ph	**231a**	100	88
4	Ph	**231b**	100	>99
5	Ph	**231c**	100	93
6	$CH_3(CH_2)_2$	**231b**	100	99
7	4-FC_6H_4	**231b**	100	>99
8	3-ClC_6H_4	**231b**	100	96
9	2-BrC_6H_4	**231b**	100	96
10	2-naphthyl	**231b**	100	98

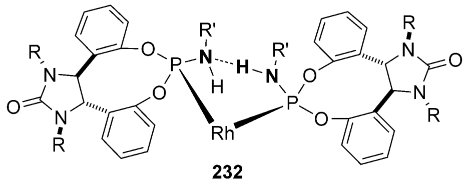
Scheme 106. NH effect in the asymmetric hydrogenation of (*Z*)-methyl α-(acetoxy)acrylates catalyzed by Rh-DepenPhos.

Ding and co-workers developed a type of structurally diverse monodentate phosphoramidites (DpenPhos) from enantiomerically pure *trans*-1,2-di(2-methoxyphenyl)-1,2-ethylenediamine (Scheme 106).[125] The structure of the ligand is highly tunable by changing the substituents on the N atoms, thus providing the opportunities to meet the requirements of various transition-metal-catalyzed reactions. Although DpenPhos ligands (**229**) showed high activities and excellent enantioselectivities in Rh-catalyzed asymmetric hydrogenation of dehydro-α-amino acid methyl esters and acetyl enamides, its Rh complex and commonly used Rh^I/MonoPhos (**230**) were found to be totally inactive for asymmetric hydrogenation of more challenging substrates, such as (*Z*)-methyl α-(acetoxy)acrylates (Scheme 106, entries 1 and 2).[126] Interestingly, the Rh^I complexes of phosphoramidites bearing NH moieties, such as ligands **231a–c**, showed very high catalytic activities and enantioselectivities in the hydrogenation of (*Z*)-methyl α-(acetoxy)acrylates (Scheme 105, entries 3–5). These results clearly indicated that the NH moiety in the ligand is critically important for the drastic improvement of catalytic activities from NH-free ligands **229** and **230** to NH-bearing ligands **231a–c**. Phosphoramidite **231b** turned out to be the best ligand for the Rh^I-catalyzed asymmetric hydrogenation of (*Z*)-methyl α-(acetoxy)acrylates, giving various α-hydroxy esters in excellent enantioselectivities and high yields (Scheme 106, entries 4 and 6–10). The catalyst is also very efficient for enantioselective hydrogenation of itaconates (Scheme 107). The hydrogenation was completed in 10 h with a TON up to 10^5 (Scheme 107, entry 6). The observed profound NH effect was explained on the basis of a hydrogen-bonding model between two NH-bearing monodentate phosphoramidites; this hydrogen-bonding attractive interaction renders the bite angle of P-Rh^I-P to be more close to the ideal angle of 90° (Scheme 108). Such



entry	R	H_2 [atm]	S/C	*ee* [%]
1	C_6H_5	40	4000	97
2	4-FC_6H_4	40	1000	99
3	3-$MeOC_6H_4$	40	100	99
4	2-BrC_6H_4	40	100	97
5	2-naphthyl	40	1000	96
6	H	30	10^5	94

Scheme 107. Enantioselective hydrogenation of itaconates catalyzed by Rh-**231b**.

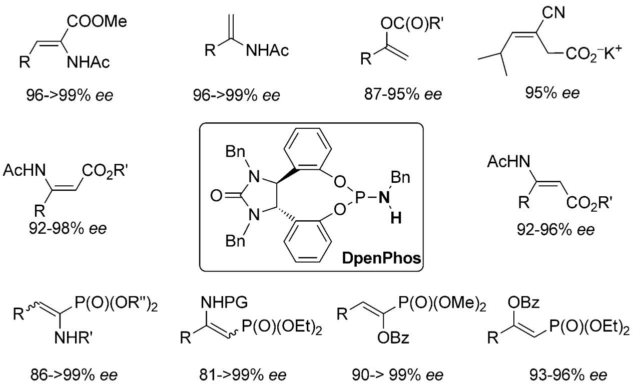


232

Scheme 108. Proposed hydrogen bonding model of Rh-**231** complex.

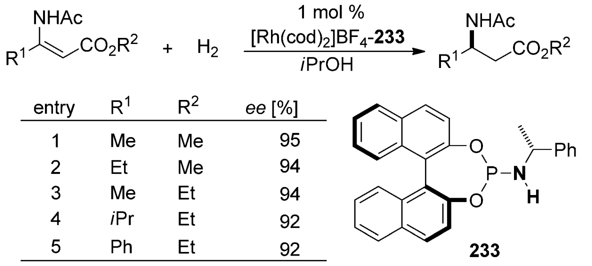
NH-initiated hydrogen bonds in coordination sphere were further evidenced in solution by ^{1}H NMR studies.[126]

The NH-bearing ligand DepenPhos was also successfully extended to Rh^I-catalyzed asymmetric hydrogenation of other functional olefins, including β-substituted α-enamido phosphonates,[127a] β-enamido phosphonates,[127a] α-acyloxy β-substituted α,β-unsaturated phosphonic acid dimethyl esters,[127b] dehydro β-amino acid esters,[127c] enol esters,[127d] potassium (*E*)-3-cyano-5-methylhex-3-enoate,[127d] and β-acyloxy β-substituted α,β-unsaturated phosphonic acid dimethyl esters,[127b] affording various hydrogenation products with high enantiopurities (Scheme 109). Similar NH effects were observed in the enantioselective hydrogenation of β-substituted α-enamido phosphonates and α-acyloxy β-substituted α,β-unsaturated phosphonic acid dimethyl esters.[127a,b]



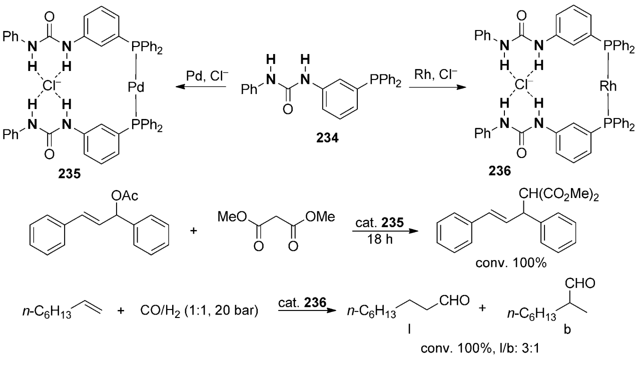
Scheme 109. Enantioselective hydrogenation of various functionalized olefins catalyzed by Rh-**231**.

The dramatic acceleration effect of the NH group was also observed in monodentate phosphoramidite-Rh catalyzed asymmetric hydrogenation of β-dehydroamino acid derivatives reported by Feringa in 2002 (Scheme 110).[128] The NH-bearing phosphoramidite **233** displayed comparable or even higher activity in asymmetric hydrogenation of dehydrophenylalanine methyl ester and (*Z*)-ethyl 3-acetamido-2-butenoate than some of the most successful bidentate phosphines used in asymmetric hydrogenation, including DuPhos, PhanePhos, and Josiphos.[128b] Steric effects were proposed to account for the extremely high activity of the NH-bearing monodentate ligand **233** in the asymmetric hydrogenation.[128]



entry	R^1	R^2	*ee* [%]
1	Me	Me	95
2	Et	Me	94
3	Me	Et	94
4	*i*Pr	Et	92
5	Ph	Et	92

Scheme 110. Asymmetric hydrogenation of β-dehydroamino acid derivatives catalyzed by Rh-**233**.

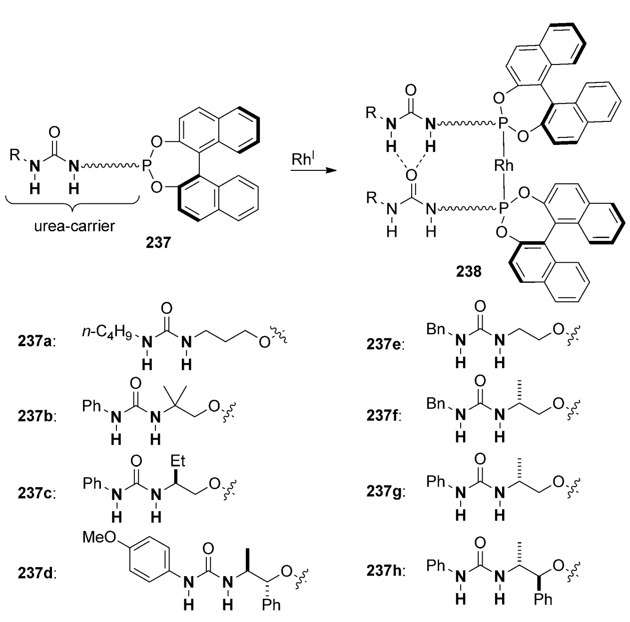


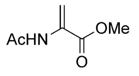
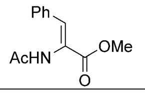
Scheme 111. Pd- and Rh-complexes **235** and **236** assembled from monodentate ureaphosphine **234**.

Love and co-workers reported self-assembled Pd- and Rh-complexes **235** and **236** generated from monodentate ureaphosphine **234** (Scheme 111).[129] The two monophosphines was linked together to form a chelate by a bound chloride ion between the two urea units. The Pd complex **235** and the Rh complex **236** showed catalytic activities for allylic alkylation and olefin hydroformylation, respectively.

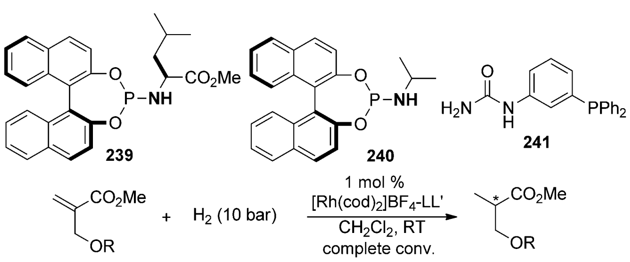
Reek and co-workers developed self-assembled chiral Rh catalyst **238** from monodentate ligand **237** (Scheme 112).[130,131] Catalyst **238** showed moderate to high enantioselectivities in asymmetric hydrogenation of dehydro α-amino acid ester derivatives.

Reek and co-workers found that the Rh complexes chelated by heterobidentate ligands could be generated in high purities from NH-bearing phosphoramidites **239** and **240** and urea-containing phosphine **241** by hydrogen-bond-facilitated self-assembly (Scheme 113).[132] On the basis of computational studies, the authors proposed that a single hydrogen bond was formed between the NH moiety of the phosphoramidite **239** or **240** and the urea carbonyl group of phosphine **241**, as shown in complex **242**. This was evidenced by comparing the percentage of the heteroligand complex in the mixture of [Rh(cod)$_2$]BF$_4$, phosphoramidite **239**, and a monodentate phosphine ligand in 1:1:1 ratio (Scheme 113). Urea phosphine **241** gave the highest purity (> 99 %) in the heterocomplex in combination with phosphoramidite **239** (Scheme 113, entry 9 vs entries 3–8), implicating that a hydrogen bond might be formed between mondentate ligands **239** and **241** in the coordination sphere as assumed by the authors. A very high enantioselectivity (> 99 % *ee*) was obtained in the asymmetric hydrogenation of methyl 2-hydroxymethylacrylate by using the **239**/**241** hetero Rh complex as catalyst

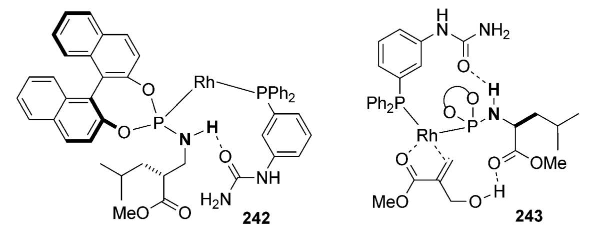


entry	ligand	substrate	conv. [%]	*ee* [%]
1	**237a**		0	–
2	**237b**		100	93
3	**237c**		100	92
4	**237d**		100	82
5	**237e**		34	47
6	**237f**		16	95
7	**237g**		23	96
8	**237h**		33	94

Scheme 112. Asymmetric hydrogenation of dehydro α-amino acid ester derivatives catalyzed by self-assembled Rh catalyst **238**.



entry	L	L'	R	*ee* [%]	heterocomplex (%)
1	**239**	**239**	H	31	–
2	**230**	**230**	H	13	–
3	**239**	PPh_3	H	94	91
4	**230**	PPh_3	H	34	85
5	**239**	$P(4\text{-}MeOC_6H_4)_3$	H	94	94
7	**239**	$P(4\text{-}MeC_6H_4)_3$	H	94	97
8	**239**	$P(3\text{-}MeC_6H_4)_3$	H	94	86
9	**239**	**241**	H	>99	>99
10	**230**	**241**	H	38	mixture
11	**240**	**241**	H	88	>99
12	**239**	**241**	TMS	52	>99



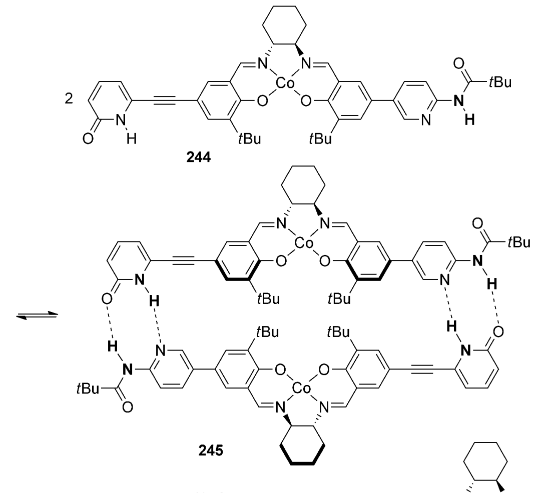
Scheme 113. Asymmetric hydrogenation of methyl 2-hydroxymethylacrylate and the TMS-protected derivative in the presence of self-assembled Rh catalysts.

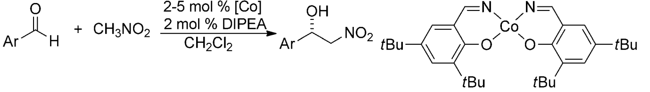
(Scheme 113, entry 9). In contrast, TMS protection of the hydroxy group of methyl 2-hydroxymethylacrylate resulted in a dramatic decrease of enantioselectivity under the same reaction conditions (Scheme 113, entry 12), implying that a hydrogen bond might be formed between the catalyst and the olefin substrate as shown in the intermediate **243**. The hydrogen bonding arranges the olefin substrate at a favorable position to achieve the excellent enantioselectivity.

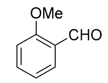
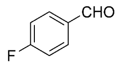
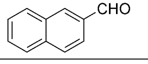
5. Assembly of Catalysts by NH Interactions

Cooperative catalysis between two metal centers has been recognized as a powerful way to improve activities and/or selectivities. To cooperate well in catalysis, the two monometallic units should be arranged in a close proximity. Conventional design of cooperative bimetallic catalysts uses covalent bonds to link the two monometallic units, which usually requires laborious synthesis. Automatic connection of the two monometallic units through NH-initiated self-assembly is an attractive way to construct bimetallic catalysts.

Hong and co-workers developed a bimetallic Co^{III}–salen catalyst **245** from monomeric Co^{III}–salen complex **244** by using self-assembly approach through hydrogen bonding interactions (Scheme 114).[133] The structure of a related Ni bimetallic complex was characterized by X-ray analysis. It was disclosed that the two monometallic units were closely connected through hydrogen bonding. Bimetallic catalyst

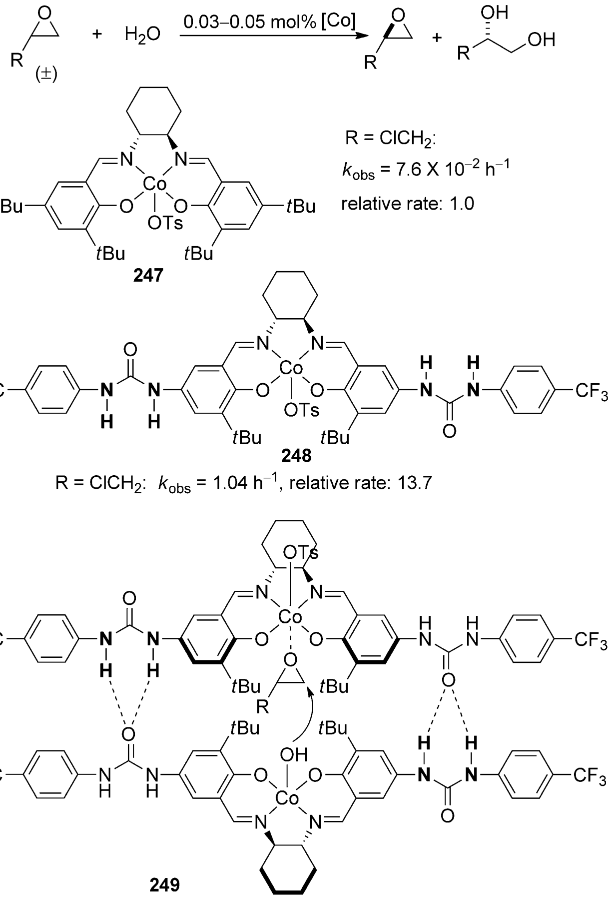




entry	aldehyde	cat.	yield [%]	*ee* [%]
1		**244**	87	96
2		**246**	11	55
3		**244**	65	90
4		**244**	88	87

Scheme 114. Asymmetric Henry reaction catalyzed by a self-assembled bimetallic catalyst.

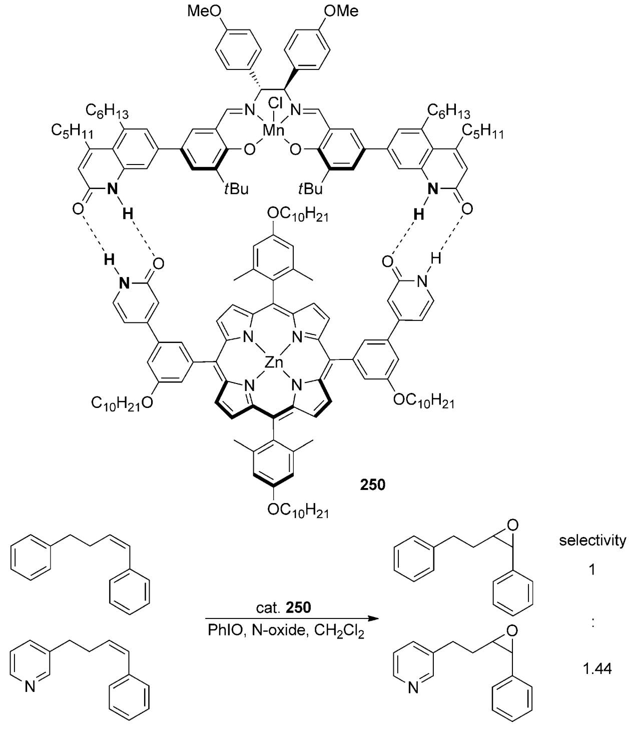
245 showed dramatically improved activity and enantioselectivity in the asymmetric Henry reaction as compared to the related monomeric Co^{II}–salen catalyst **246** (Scheme 114, entry 1 vs 2). Based on kinetic experiments, cooperative activation was proposed for the catalysis of bimetallic catalyst **245** in the Henry reaction, which accounts for the significantly enhanced activity and enantioselectivity. In the Co^{III}–salen catalyzed hydrolytic kinetic resolution of racemic epoxides, kinetic studies have shown that the reaction followed a second-order dependence on the concentration of Co^{III}–salen complex, indicating a mechanism wherein two discrete catalyst molecules cooperate to activate both the electrophile (epoxide) and the nucleophile (water).[134] On the basis of mechanistic understanding, the self-assembly strategy was also extended to hydrolytic kinetic resolution of epoxides by Hong and co-workers.[135] Bis(urea)-bearing Co–salen complex **248** was developed and tested in the hydrolytic kinetic resolution of *rac*-epoxides (Scheme 115). Dramatically improved catalytic activity was observed in the resolution as compared to Co^{III}–salen **247** without urea groups, indicating that the in situ formation of a dimeric Co^{III}–salen complex from **248** indeed occurred through urea–urea hydrogen bonding. The Co^{III}–salen dimer activated both the epoxide and the water in the hydrolytic kinetic resolution, as shown in transition state **249** (Scheme 115), which contributes the drastic rate acceleration.



entry	R	cat.	*t* [h]	yield [%]	*ee* [%]
1	CH_2Cl	**248**	14	41	99
2	CH_2Cl	**247**	71	42	96
3	CH_2O(allyl)	**248**	8	43	99
4	CH_2O(allyl)	**247**	32	43	98
5	Et	**248**	8	43	99
6	Et	**247**	24	43	99

Scheme 115. Cooperative catalysis in hydrolytic kinetic resolution of *rac*-epoxides in the presence of a self-assembled bimetallic Co catalyst.

Wärnmark and co-workers developed Mn^{III}(salen)–Zn^{II}(porphyrin) catalyst **250** for epoxidation of olefins by self-assembly of the component units through hydrogen bonding interactions (Scheme 116).[136] Modest selectivity for pyridine olefin over phenyl olefin was observed in the competitive expoxidation. The Zn^{II}(porphyrin) unit was proposed to selectively recognize the pyridine olefin through coordination interaction, leading to the olefin selectivity observed in the oxidation.



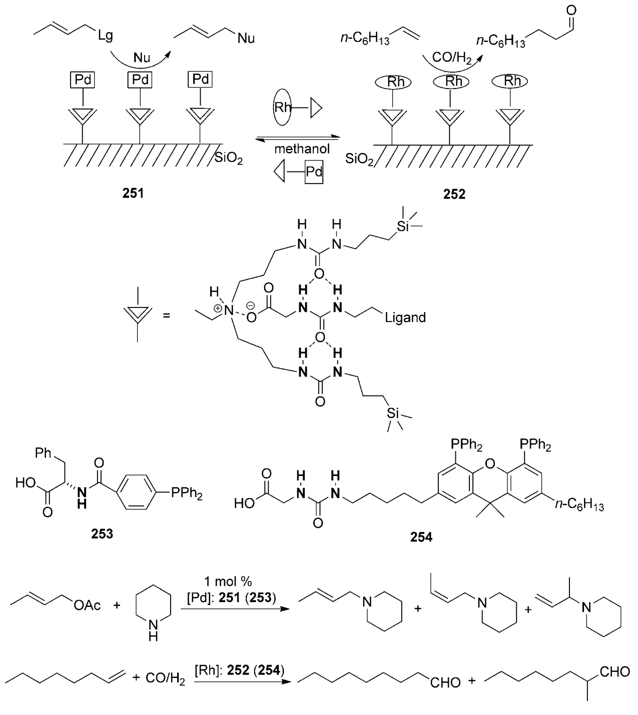
Scheme 116. Competitive expoxidation of olefins in the presence of a self-assembled bimetallic catalyst.

6. Immobilization of Homogeneous Catalysts

Immobilized homogeneous catalysts have the advantage of easy separation and convenient reuse over the corresponding homogeneous counterparts, which has stimulated the development of this area, and many immobilization methods have emerged.[137] In most immobilized systems developed to date, the catalysts are tagged to the supports by covalent linkages, which may need tedious organic synthesis. Recently, noncovalent interactions, such as hydrogen bonds, have provided a new strategy for immobilization of homogeneous catalysts. As good hydrogen bond donors, NH moieties have been frequently introduced to the catalysts and/or the supports to constitute the hydrogen bond sites.

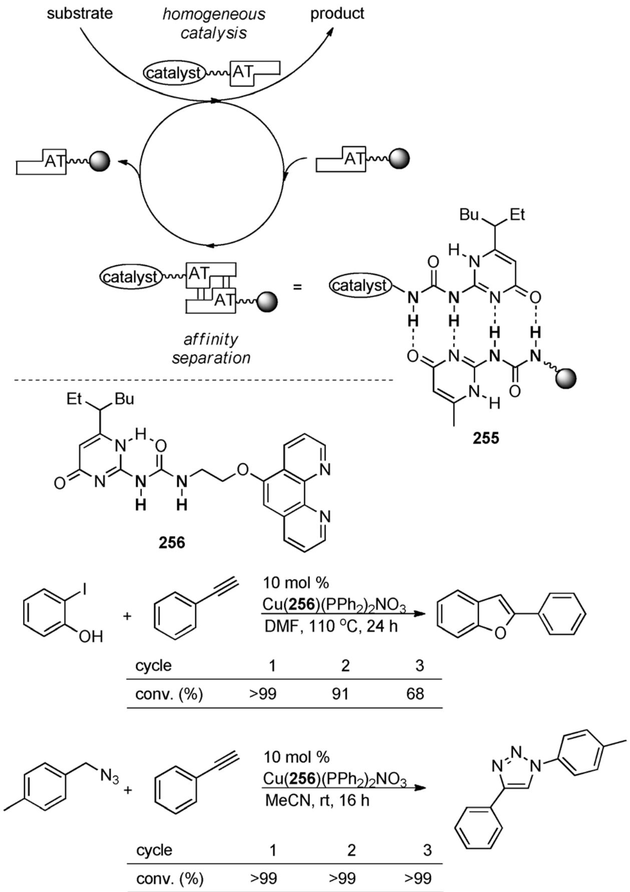
6.1. Anchoring of Homogeneous Catalysts to Inorganic Supports

Inorganic materials are most commonly used as supports for immobilization of homogeneous catalysts. NH-initiated hydrogen bonding has provided an attractive approach to attach homogeneous catalysts to insoluble inorganic supports. In 2004, Reek and co-workers elucidated this application by anchoring Pd and Rh catalysts to a silica support through hydrogen bonding and ionic interaction (Scheme 117).[138] The silica was functionalized with well-defined binding motifs, including two urea groups and a basic amine, which can selectively combine the catalysts through the quadruple hydrogen bonding between the three urea groups as well as the electrostatic interaction between the ammonium cation formed in situ and the acid anion. The reversible nature of the noncovalent binding allows the controlled up- and down-loading of catalysts by tuning the polarity of media, providing good opportunities to ultimately reuse the supramolecular support for different catalysis. After the guest catalyst is removed by washing with methanol, the new catalyst can be reloaded to the silica support by stirring them together in non-polar solvent. The immobilization system was used for both Pd-catalyzed allylic amination and Rh-catalyzed olefin hydroformylation. The immobilized palladium catalyst **251**, which was generated from glycine–urea phosphine ligand **253**, showed similar yields and product distributions as the homogeneous analogue in the allylic amination of crotyl acetate with piperidine. The catalyst could be reused at least four times with a slight decrease of activity. The rhodium catalyst **252** was prepared by simple stirring of the mixture of the silica support, urea phosphine **254**, and [Rh(acac)(CO)$_2$] in toluene. The immobilized catalyst has been recycled for eleven runs in hydroformylation of 1-octene without loss of either activity or selectivity. However, in comparison with its homogeneous counterpart, relatively lower activity and selectivity were observed for the immobilized rhodium catalyst.



Scheme 117. Anchoring of Pd and Rh catalysts to a silica support through hydrogen bonding and electrostatic interactions for organometallic catalysis.

Rutjes and co-workers used a resin functionalized with a hydrogen-bonding handle to fish out homogeneous catalyst equipped with complementary affinity tag from the crude reaction mixture after the reaction is completed (Scheme 118).[139] Four complementary hydrogen bonds are formed between the two ureido[1*H*]pyrimidinone units, as shown in **255**. The catalyst can be released from the resin by breaking the hydrogen bonds with protic solvent, such as methanol, and reused again for homogeneous catalysis. The recycling concept has been successfully applied to Cu-catalyzed tandem Sonogashira coupling/5-*endo*-dig cycliza-



cycle	1	2	3
conv. (%)	>99	91	68

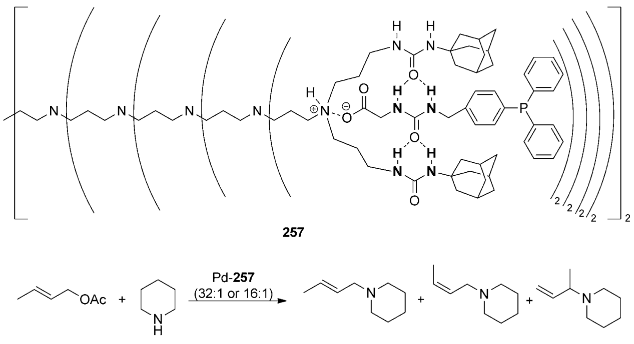
cycle	1	2	3
conv. (%)	>99	>99	>99

Scheme 118. Catalyst recycling based on NH interactions by using a well-defined resin support.

tion and Cu-catalyzed [3+2] Huisgen cycloadditions. The copper catalyst was recycled for three times with some extent of decrease in activity for the Sonogashira coupling/5-*endo*-dig cyclization but without obvious loss of activity in the [3+2] Huisgen cycloaddition.

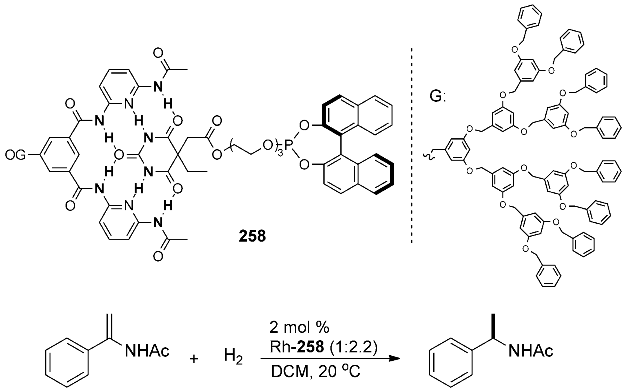
6.2. Anchoring of Homogeneous Catalysts to Dendrimers

Dendrimers, which are a type of well-defined hyperbranched macromolecules, have been extensively utilized as supports for immobilization of homogeneous catalysts. Reek and Meijer first demonstrated that NH-based hydrogen bonding interactions can be used for anchoring homogeneous catalysts to dendrimer supports in 2001 (Scheme 119).[140] The urea-functionalized poly(propylene imine) dendrimer selectively binds 32 phosphine ligands with complementary interaction motifs and a high binding constant through quadruple hydrogen-bonding and electrostatic interactions. The functionalized dendrimer was tested as multidentate ligand in Pd-catalyzed allylic amination of crotyl acetate with piperidine. The reaction showed approximately the same rate and product distribution as that catalyzed by monomeric palladium complex in absence of the dendrimer. The dendrimer catalyst was also applied to a Pd-catalyzed allylic amination in a continous-flow membrane reactor. The catalyst became slightly less active only after the amount of 13 reactor volumes of substrate solution had been pumped through the reactor, indicating that the noncovalently functionalized dendrimer is an excellent and highly recyclable support for immobilization of homogeneous catalysts.



Scheme 119. NH-based anchoring of a Pd catalyst to a dendrimer support for catalytic allylic amination of crotyl acetate.

Fan and co-workers developed self-assemblies of chiral monophosphite ligands with barbiturate units and dendrimers equipped with Hamilton receptors in 2009 (Scheme 120).[141] Six hydrogen bonds are formed between the Hamilton receptor and the barbiturate unit. The chiral dendritic ligands were examined in Rh-catalyzed asymmetric hydrogenation of enamides and α-dehydroamino acid derivatives. Good enantioselectivities were observed in the hydrogenation, which are comparable to those obtained by using dendrimer-free analogous catalyst. The dendritic catalyst could be recycled and reused at least 6 times in the asymmetric hydrogenation of enamide with a slight loss of activitity.

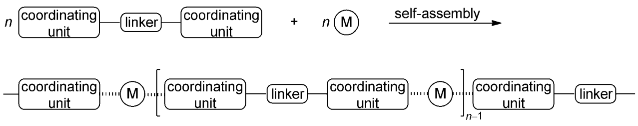


run	1	2	3	4	5	6
conv. [%]	100	100	100	100	100	88
ee [%]	85	86	85	85	85	84

Scheme 120. NH-based anchoring of a chiral Rh catalyst to dendrimer support for the asymmetric hydrogenation of functionalized olefins.

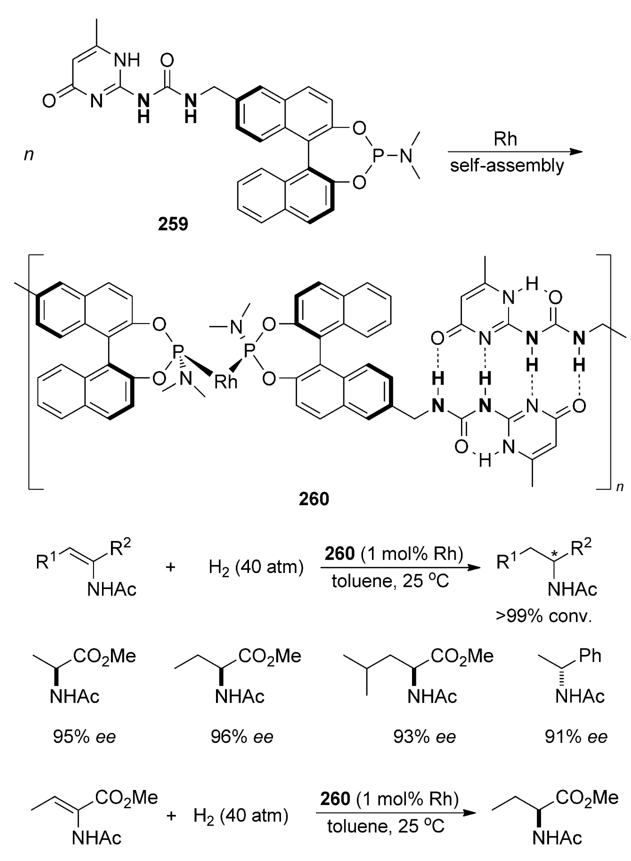
6.3. Self-Supported Catalysts by NH Interactions

Recently, a new immobilization concept, named a self-supported strategy, was introduced by the groups of Ding and Sasai (Scheme 121).[142,143] The self-assembly of metals and ligands bearing two or multiple separate coordinating units in situ generates insoluble metal–ligand polymers (or oligomers), which can be used as heterogeneous catalysts in asymmetric catalysis without using any supports. This immobilization method has been successfully applied to various reactions, including enantioselective Ti-catalyzed carbonyl-ene[142,143a] and sulfoxidation reactions,[143f] Ru and Rh-catalyzed hydrogenation of ketones and olefins,[143b–d,i,l] and La- and Zn-catalyzed epoxidation of α,β-unsaturated ketones.[143e,j] High catalytic activities, excellent enantioselectivities, facile recovery and reuse, and negligible catalyst leaching were realized in these reactions.



Scheme 121. Self-supporting strategy for catalyst immobilization.

Covalent linkers usually are employed to connect the different coordinating units in multitopic ligands (Scheme 121), which requires tedious synthesis. Ding and co-workers developed a new self-supported catalyst **260** by using a self-assembly approach through hydrogen bonding and metal–ligand coordination (Scheme 122).[144] A self-complementary hydrogen bonding unit was tethered to the monodentate phosphoramidite to give the ligand monomer



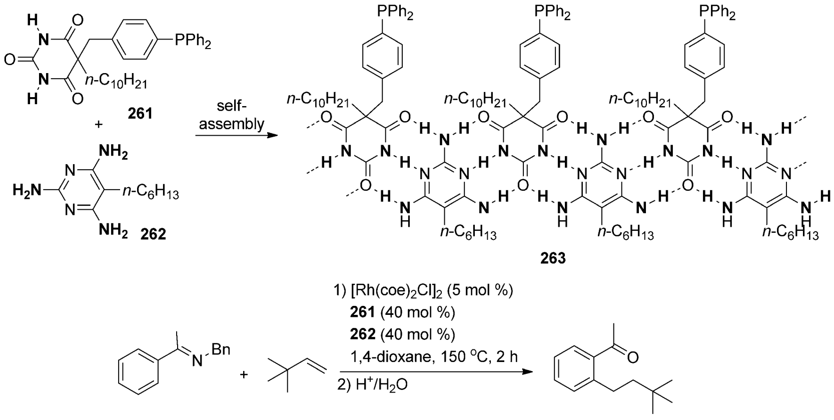
run	1	2	3	4	5	6	7	8	9	10
conv. [%]	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99
TOF [h^{-1}]	180	111	83	68	44	32	24	19	11	8
ee [%]	96	96	95	95	94	95	95	95	93	92

Scheme 122. NH-organized "self-supported" catalyst **260** for the asymmetric hydrogenation of dehydro-α-amino acid derivatives and enamides.

(**259**). Quadruple hydrogen bonds were formed between two monomeric ligands in the polymerized Rh catalyst (**260**). The heterogeneous catalyst **260** showed high activities and excellent enantioselectivities in the asymmetric hydrogenation of dehydro-α-amino acid derivatives and enamides (Scheme 122). The self-supported catalyst could be cycled and readily reused up to ten times without detectable Rh leaching in the hydrogenation (Scheme 122). The decreased TOF is most likely due to partial deactivation of the catalyst during the recycling manipulation. This work has shown the potential of the application of NH moieties in immobilization of homogeneous catalysts by forming hydrogen bonds.

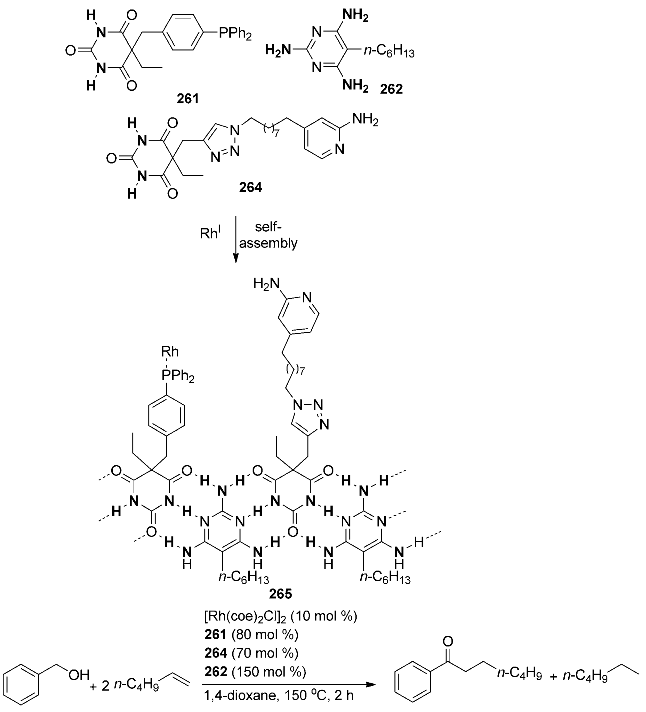
6.4. Homogeous Catalysis/Self-Assembly-Based Heterogeneous Recycling

Usually, a hydrogen-bond network is easily broken at high temperature or in polar solvents but can be reestablished at low temperature in less-polar solvents. Jun successfully applied this reversible nature of hydrogen bond to catalyst design.[145] Catalysts with appropriate interaction motifs can form insoluble self-assemblies at room temperature by forming a hydrogen bond network, thus realizing heterogeneous recycling of the catalysts. On the other hand, high reaction temperatures will break the hydrogen-bond network to render the self-assembled heterogeneous catalysts and reactants as one homogeneous phase, thereby achieving the maximum catalytic activity. This catalysis concept has been well elucidated by the **261**-**262**-Rh-catalyzed orthoalkylation of benzylimines with terminal olefins (Scheme 123).[145a] The rhodium catalyst was completely homogeneous with the reactants and highly active for the orthoalkylation, but it precipitated out as a yellow solid at room temperature upon addition of *n*-pentane when the reaction was complete. The precipitation of the rhodium catalyst is contributed to the formation of a NH-based hydrogen bond network between **261** and **262**, as shown in **263**. Recycling experiments showed that the recovered catalyst was still very active even after seven runs, demonstrating that the catalyst system is highly efficient and recyclable. The catalysis concept was also successfully extended to Rh-catalyzed chelation-assisted hydroacylation of olefins with primary alcohols (Scheme 124 and 125).[145b,c] Both **261**-**262**-**264**-Rh (Scheme 124) and **261**-**266**-Rh (Scheme 125) catalyst systems showed high activities and good recyclability in the reaction.



cycle	1	2	3	4	5	6	7	8
yield [%]	87	91	94	97	95	92	89	86

Scheme 123. Orthoalkylation of benzylimines with terminal olefins in the presence of **261**-Rh and **262**-Rh catalyst. coe = cyclooctene.



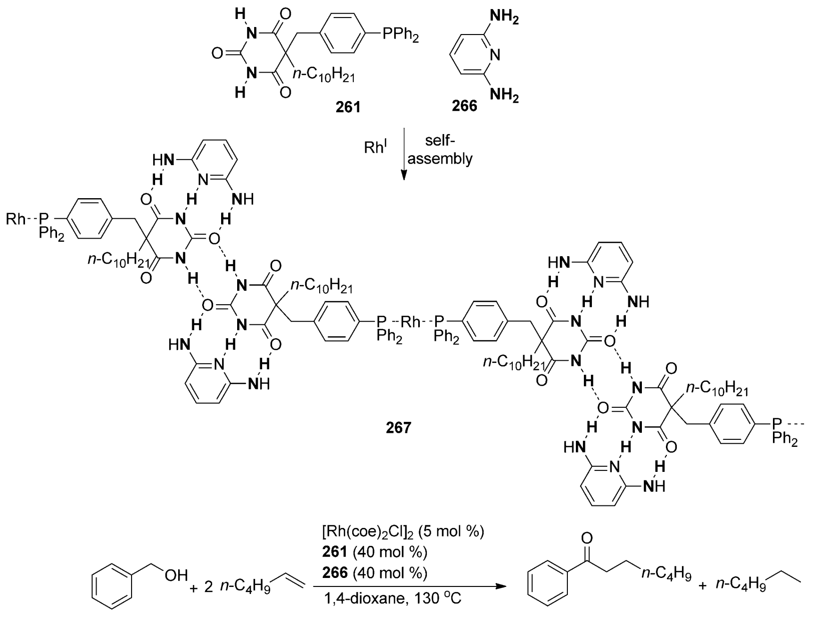
cycle	1	2	3	4	5	6	7	8
yield [%]	95	88	94	87	82	89	81	91

Scheme 124. Rh-catalyzed chelation-assisted hydroacylation of olefins with primary alcohols in the presence of **261**-**262**-**264**-Rh catalysts.

7. Conclusion

As shown in this Review, NH moieties of ligands have unique functions and wide applications in organometallic catalysis. One of the most important beneficial effects is the cooperation of NH moiety with metal center by the recognition and activation of substrates. Such cooperation may lead to dramatically improved catalytic activities and/or selectivities in organometallic catalysts. On the other hand, NH moieties can also initiate ligand–ligand, ligand–catalyst, and catalyst–catalyst interactions through hydrogen bonding. This has been widely used to generate self-assembled ligands and catalysts from relatively simple, easily prepared ligand and catalyst monomers. Accordingly, various combinatorial libraries of ligands and catalysts can be readily created on the basis of this concept, thus simplifying catalyst synthesis and accelerating catalyst discovery. Finally, as good hydrogen-bond donors, NH moieties have been extensively applied to the immobilization of homogeneous catalysts by hydrogen-bonding interactions, typically including the formation of inorganic- and dendritic-material-supported and self-supported catalysts. In contrast to the covalent approach for immobilization of homogeneous catalysts, the use of the hydrogen bonding interaction not only reduces laborious synthetic works, but also keeps high catalytic activities and facile recovery capabilities of the catalysts.

The combination of NH functions and metal catalysis has become an important and attractive topic of catalyst design. Although much success have been achieved in the application of NH functions in organometallic catalysis, this field is still in its early and active stage of development. The concepts and examples reviewed herein should stimulate future research on the development of organometallic catalysts on the basis of cooperative catalysis by taking advantage of NH functions.



cycle	1	2	3	4	5	6
yield [%]	70	84	84	78	75	80

Scheme 125. Rh-catalyzed chelation-assisted hydroacylation of olefins with primary alcohols in the presence of **261**-**266**-Rh catalysts.

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