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Cobalt-Catalyzed Asymmetric Hydrogenation: Substrate Specificity and Mechanistic Variability

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Abstract: Asymmetric hydrogenation finds widespread application in academia and industry. And indeed, a number of processes have been implemented for the production of pharma and agro intermediates as well as flavors & fragrances. Although these processes are all based on the use of late transition metals as catalysts, there is an increasing interest in the use of base metal catalysis in view of their lower cost and the expected different substrate scope. Catalysts based on cobalt have already shown their potential in enantioselective hydrogenation chemistry. This review outlines the impressive progress made in recent years on cobalt-catalyzed asymmetric hydrogenation of different unsaturated substrates. We also illustrate the ligand dependent substrate specificity as well as the mechanistic variability in detail. This may well guide further catalyst development in this research area.

1. Introduction

Asymmetric hydrogenation (AH) is one of the most fundamental transformations in enantioselective catalysis offering excellent atom economic and high-yielding solutions for the preparation of chiral molecules.\[1\] The field of AH has already experienced a huge advancement since the ground-breaking discoveries of Knowles’s Rh/DIPAMP\[2\] and Noyori’s Ru/BINAP\[3\] for C=C and C=O reductions, respectively. Various transition metal catalysts, mostly based on rhodium, ruthenium, or iridium in combination with chiral ligands have shown excellent chemo-, regio- and enantioselectivity in the AH of different unsaturated compounds.

As a result, a number of large-scale processes have been developed for the synthesis of pharmaceutically relevant chiral molecules involving AH as the key step.\[4\] However, the high cost (Ir: \(\approx 147 \$/g\), Rh: \(\approx 175 \$/g\) vs. Co: \(\approx 0.02 \$/g\)) fluctuating prices, and limited supply of the late transition metals has encouraged researcher to search for alternatives.\[5\]

An increasing interest in the reactivity and catalytic activity of 3d-metals in hydrogenation has been observed since the last decade (Figure 1 shows the increasing trend on the use of cobalt-catalysts in hydrogenation). Being the most abundant element of the group in earth’s geosphere (Co: Rh: Ir = 10\(^{3}\): 5: 1)\[6\] cobalt offers a unique and alternative opportunity opening the gate to a novel field of catalysis especially in enantioselective hydrogenation chemistry.\[7\]

Cobalt has been investigated with respect to its organo-metallic chemistry and its use in homogeneous catalysis since the first half of the twentieth century.\[8\] The cobalt hydride complex HCo(CO)\(_5\) was already applied as catalyst by Otto Roelen\[9\] in the “oxo process”\[10\] (now better known as hydroformylation). Although nowadays rhodium complexes are also used, cobalt complexes are still applied in a number of hydroformylation processes.\[11\] Simultaneously, cobalt-based hydrogenation catalysts have also been applied during the early 1960s, when K\(_2\)Co(CN)\(_5\) and Co\(_2\)(CO)\(_8\) were tested on olefins where moderate to excellent yields were obtained depending on the substrates.\[12\] Based on the findings on H\(_2\) activation by aqueous potassium pentacyanocobaltate(II),\[13\] Kwiatek\[14\] Orchin\[15\] and many more\[7\] groups have developed a number of Co-catalyst for hydrogenation of activated and simple olefins.\[16\]

On the other hand, the development of Co-based catalysts for enantioselective hydrogenation was slow-moving (Figure 2) in comparison to its 4d (Rh) and 5d (Ir) congeners. Similar to other 1\(^{st}\) row metals, the low crystal field stabilization energy (CFSE), variable spin states, tendency towards 1e chemistry and lack of predictability of catalytic activity, makes cobalt catalysis more challenging as compared to the 4d or 5d metals. For example, it took more than 40 years after the discovery of the rhodium catalyst to develop a cobalt-based catalyst for the AH of the L-DOPA precursor (Figure 3).

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Soumyadeep Chakrabortty received his M.S. in chemistry at the Indian Institute of Science Education and Research, IISER Mohali, India in 2019 under the supervision of Prof. Dr. Sanjay Singh on NHC chemistry and catalysis. He joined as a PhD student with the late Prof. Paul C. J. Kamer and has obtained his PhD under the supervision of Prof. Johannes G. de Vries at the Leibniz Institute für Katalyse in Rostock, Germany. He was also awarded a DAAD Scholarship to visit the Van’t Hoff Institute for Molecular Science (HIMS), University of Amsterdam (UvA) during PhD studies. His research focuses on development and application of (chiral) phosphines in homogeneous (enantioselective) catalysis.

Figure 2. Selected examples of the development of cobalt catalysts (top) and ligands (bottom) for the AH of unsaturated substrates.

Johannes G. de Vries obtained a PhD in bioorganic chemistry from the University of Groningen in 1979. After a postdoc at Brandeis University, Waltham, USA, his first job was as a medicinal chemist with Sandoz in Vienna and in London. From 1988–2013 he worked for DSM in Geleen, The Netherlands, lastly as a Principal Scientist in the area of Homogeneous Catalysis. From 1999–2018 he was part-time professor homogeneous catalysis at the University of Groningen. In 2014 he became Department Head Catalysis with Renewables at the Leibniz Institut für Katalyse e. V. in Rostock, Germany. In 2013 he received the Paul N. Rylander Award for outstanding contributions in the field of catalysis as it applies to organic synthesis. He retired in 2021 but is still active as editor for Advanced Synthesis & Catalysis.

Bas de Bruin obtained his Ph.D. at the University of Nijmegen in the area of metal-mediated olefin oxygenation reactions. He did his postdoc in the group of Wieghardt at the Max-Planck Institut für Bioorganische Chemie (Mülheim a/d Ruhr, Av-Humboldt fellowship). After his postdoc he returned to the University of Nijmegen as an Assistant Professor. In November 2005 he moved to the University of Amsterdam (UvA), where he was promoted to Associate Professor (UHD) in 2008 and to Full Professor in 2013. He presently focuses on the fundamental development of homogeneous catalysis with metals in unconventional oxidation states and with unconventional ligands, specifically aiming at the development of new catalytic reactions.
1. Brief History on Co-Catalyzed Asymmetric Hydrogenation

In one of the earliest approaches, the combination of an achiral Co-complex with a chiral base led the foundation of Co-catalyzed stereoselective hydrogenation (the work of the Yoshimura and Takeuchi group). A number of C–C and C-heteroatom double bonds were hydrogenated with moderate to high optical yields using bis(dimethylglyoximato)cobalt(II)-Chiral cocatalyst.\[17]\]

The nitrogen-based semicorrin ligand was also found to be quite effective in the cobalt-catalyzed C–C hydrogenation of unsaturated esters (the work of the Pfaltz group).\[19]\] Utilization of bisphosphines in functionalized alkenes hydrogenation was introduced in 2004.\[19]\] The bis(imino)pyridine based cobalt complexes were quite successful in (endo and exo) cyclic alkene hydrogenation (the work of the Chirik group).\[19]\] After the discovery of the Co/phosphine catalyzed AH of methyl-2-acetamidoacrylate (MAA) and methyl-(Z)-a-acetamidocinnamate (MAC) via high throughput screening,\[21]\] this field has become an important area of research in asymmetric catalysis and organic synthesis. The use of readily available cobalt precursors and enantiopure ligands has generated (in situ) highly active catalysts for the hydrogenation of different types of unsaturated substrates with high enantioselectivity. Figure 2 shows the major milestones of the chiral cobalt catalyst development for AH.

Here the literature on cobalt-catalyzed enantioselective hydrogenation is reviewed from the point of view of substrate conversion. In addition, the mechanistic aspects are discussed in detail.

2. C–C Hydrogenation

The Co-catalyzed AH of alkenes (C=C) has experienced the most advancement since the last decades (Figure 2). The metal catalyzed addition of molecular hydrogen across C=C is a simple, efficient, and sustainable method for the preparation of enantioenriched compounds. However, the catalytic activity strongly depends on the chiral ligand used and the substituents/groups present on the alkene. As a result, the “catalyst-substrate specificity” is found to be the key factor behind obtaining excellent activity and selectivity.

The pro-chiral alkenes can be classified into two categories: (1) unfunctionalized (or, non-coordinating) and (2) functionalized (or, coordinating) alkenes based on the substituents (or, functional groups) attached to the C=C double bond. In this section, the development of Co-catalysts in the AH of C=C bonds will be described.

2.1. Unfunctionalized Alkenes

The term unfunctionalized alkene is not an absolute expression in the field of AH (Scheme 1).\[23]\] In general, alkyl- and aryl- substituted alkenes are that devoid of further coordinating entities are described as “unfunctionalized alkenes”. Enantioselective reduction of these alkenes is considered to be the most challenging due to the lack of proper coordinating/directing groups. First results in the AH of this class of substrates was achieved with the Ir-based catalysts developed by Pfaltz\[23]\] and Andersson\[25]\] and a few more groups resulting in quite remarkably high turnover numbers (TON) and ee’s.\[22]\]

In 2012, Chirik and co-workers synthesized a C1-symmetric bis(imino)-pyridine ligand (originally developed by the Bianchini group\[25]\] and applied in hydrogenation by Budzelaar and co-workers\[26]\] which was introduced in the AH of unfunctionalized olefins using well defined Co-catalysts.\[20]\] The diamagnetic cobalt(I)-chloride complexes were prepared from the dichloro complexes by reduction using NaBEt\(_3\)H (Scheme 2).

Following this, the alkyl cobalt complexes were synthesized by reacting (NNN)Co(Cl) with LiCH\(_2\)SiMe\(_3\) (for (NNN)Co-1) and MeLi (for (NNN)Co-2) (Scheme 2).\[20]\] The latter complex was evaluated in the AH of several alkenes. High enantioselectivities (up to 98 %) were achieved using mild reaction conditions (4 bar of H\(_2\), 22 °C, in benzene). The less hindered 1-methylindene was hydrogenated in high yield and 39 % ee.\[20]\]

The hydrogenation pathway was investigated via deuterium labelling experiments using (NNN)Co-2.\[27]\] Interestingly the AH of alkenes by (NNN)Co-2 was found to proceed via a substrate-dependent isomerization-hydrogenation process. The stereochemical outcome of the hydrogenation was also influenced by the ring size of the carbocyclic olefin (Scheme 3). The (R)- and (S)-alkanes were produced from their respective endo and exo olefins in the case of both the six- and seven-membered olefins, whereas...
only the (R)-alkane was produced from both endo- and exo-1-methyl-indene (five-membered). It was proposed that alkene isomerization (likely promoted by a Co-hydride species) is relatively fast in the case of the five-membered ring and only (R)-alkane was formed via kinetically accessible β-hydrogen elimination step that led to the formation of endocyclic indene followed by hydrogenation. This phenomenon is less probable in the case of six and seven-membered rings (Scheme 3). Deuterium labeling experiments showed that β-hydrogen elimination occurred preferentially from the methyl position over the ring methylene position, in the seven-membered ring. Research on the mechanism of the AH of the hindered alkenes found that the activation step. Then the substrate co-ordinates to the coordinated Co-hydrides. A non-classical σ-bond metathesis with silane is proposed to release the alkane, followed by the formation of a Co–Si intermediate (E, Scheme 6). Finally the co-hydride A can be regenerated via another σ-bond metathesis with hydrogen (Scheme 6) closing the loop.28

2.2. Functionalized Alkenes

Alkenes in which the C=C is directly substituted by functional groups (except alkyl/aryl) such as NHCOR, COOR, B(OR)₃, SiR₃, in which at least one additional coordinating atom is present (oxygen in most cases) can be described as functionalized alkenes (Scheme 7). The coordinating atom actively takes part in the catalyst-substrate complex form-

Use of Co/bisphosphine catalysts resulted in high ee’s albeit with moderate conversions in the AH of tri-substituted alkenes.21 The catalytic activity was investigated using E,1-diphenylpropene as substrate and an in situ prepared catalyst from (py)₂Co(LiCH₂SiMe₃)₂ and several bisphosphines via high-throughput experimentation (HTE), achieving up to 93.8 % ee (Scheme 4) at 23 °C. However, the Co/bisphosphine catalyst was not so successful in chiral induction for fully aliphatic non-coordinating alkenes.

In 2014, Lu and co-workers modified the imino-pyridine backbone with a chiral oxazoline motif resulting in the class of OIP ligands (OIP = oxazolinyl iminopyridine) in a synthetically simple two-step process.30

The bench-stable iron30 and cobalt31 complexes were quite successful in hydroboration and hydrosilylation of unfunctionalized olefins. Later, they applied the (NNN)-Co-3 in the hydrogenation of unsymmetrical diarylalkenes.32 A range of chiral diaryleneethanes were prepared using 0.5 mol % (NNN)-Co-3, activated with 15 mol % of NaBEt₃H, using a H₂ balloon at room temperature. High yields and enantiore-lectivities (96 %) were obtained with a range of substrates. However, high enantioselectivity was only obtained if one of the two aryl groups possesses an ortho-chloro substituent. (Scheme 5).32

Hong, Lu and co-workers proposed a mechanism (Scheme 6) for the OIP–Co catalyzed enantioconvergent hydrogenation of “minimally functionalized” E/Z isomeric olefins using additives.33 In the presence of 5 mol % (NNN)-Co-3 pre-catalyst, 1 bar of H₂, 1-(but-2-en-2-yl)-4-methoxybenzene (E:Z = 2:1) as model substrate and NaBEt₃H as reductant, 81 % conversion and 75 % ee was achieved. Interestingly, the ee was increased to 94 % using 10 mol % of diphenyl silane (P₂SiH₂) or PMHS (poly-methyl hydroxy silane) as additive. More than 45 (E/Z) isomeric alkenes were hydrogenated in excellent yield and ee (Scheme 6).

To gain more insight in the hydrogenation pathway, several deuteration labelling experiments were carried out. A rapid H–D exchange was noticed between P₂SiD₂ and H₂. The reaction with pure D₂ resulted in d-incorporation with scrambling, which revealed a fast alkene isomerization process, likely promoted by a Co-hydride species. Based on several control experiments, a plausible mechanistic pathway (Scheme 6) was proposed for the hydrogenation of 1-aryl-1-isopropyl-propene. Formation of the Co-hydride (A, Scheme 6) from the dihalide precursor was thought to be the activation step. Then the substrate co-ordinates to the cobalt followed by isomerization in which cobalt binds to the more substituted carbon. At this point β-hydride elimination could lead to the formation of two isomeric alkene-coordinated Co-hydrides. A non-classical σ-bond metathesis with silane is proposed to release the alkane, followed by the formation of a Co–Si intermediate (E, Scheme 6).

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Scheme 3. Substrate scope (top left), deuterium labelling (top right), mechanism (middle right) and stereochemical model (bottom right) of Co/BIP catalyzed alkene hydrogenation.\(^{[27]}\)

Scheme 4. Use of commercial bisphosphines in Co-catalyzed AH of methyl stilbene.\(^{[21]}\)

Scheme 5. Co/OIP catalyzed AH of 1,1-diaryl alkenes.\(^{[32]}\)
tion resulting in high selectivity in the hydrogenation reaction (Scheme 7, bottom).

2.2.1. Functionalized Cyclic Olefins

Cyclic amines are frequently occurring motifs in pharmaceuticals. Very often AH is applied to prepare amide/amide-derivatives from the corresponding enamides. A number of catalysts based on mostly Rh, Ru, and Ir are known to reduce cyclic trisubstituted enamides with high ee. Recently, de Vries and co-workers reported the preparation of chiral (exo)cyclic amides via cobalt-catalyzed AH. After a thorough screening of readily available chiral bisphosphines, (S,S)-PDE was chosen for further optimization, delivering better ee. Several other 1st row metals such as Ni(II)-halides, Mn(II)-salts, Fe(II)-salts were also tested, but no activity was observed. The CoCl₂/(S,S)-PDE precatalyst was fairly active in most alcoholic solvents, resulting in up to 90% ee. A number of chiral 1- or 2-tetrahydronaphthylamides were synthesized from the dihydronaphthalene compounds using 5 mol% of CoCl₂/(S,S)-PDE precatalyst in MeOH at 60 bar of H₂ pressure (Scheme 8). Interestingly, the enantioselectivity was improved from 88% to 98% by changing the amide group from NHAc to NHC(O)tBu ("amide effect"). However, the catalyst failed to hydrogenate 3-benzoylaminocoumarin, which is presumably caused by its additional oxo-functionality (Scheme 8). Tetra-substituted enamides derived from cyclohexanones could also not be hydrogenated using the CoCl₂/(S,S)-PDE catalyst. These results show that the specific mode of substrate coordination is crucial for the catalytic activity of the Co²⁺PDE catalyst. To elucidate the hydrogenation pathway, a number of experiments were performed. A deuterium labelling experiment revealed that the double bond is hydrogenated directly without isomerization. The homogeneous nature of the hydrogenation was supported by a (sub-stoichiometric) PMe₃ poisoning experiment, where complete inhibition of hydrogenation was not observed. A pre-hydrogenation experiment also supported that hydrogen activation/ligation does not happen prior to substrate coordination. Product inhibition was suspected in this hydrogenation. Its existence was proven when it was shown that the rate of the reaction was reduced upon addition of 20 eq. of the product. A series of EPR experiments was carried out to identify the possibly involved Co-species. Only cobalt(II) (S = 3/2) species were detected throughout the catalytic cycle, even in a high-pressure EPR experiment. This suggested the involvement of a redox neutral cycle in the cyclic enamide hydrogenation. The proposed catalytic cycle starts with the formation of monochloro complex A (Scheme 8) either by (i) reaction with H₂ by losing one proton or, (ii) σ-bond metathesis of H₂ over the Co–Cl bond. Next the hydrogen complex is formed, which undergoes a non-classical σ-bond metathesis pathway that results in the amide coordinated Co-species (D, Scheme 8). Finally, the product is released by reaction of the complex with the substrate forming A closing the catalytic cycle. This example shows the possibility of a non-classical...
and redox neutral pathway in Co-catalyzed asymmetric olefin hydrogenation. W. Zhang and co-workers also reported the use of CoCl$_2$/(-)-DTBM-SegPhos and CoCl$_2$/(-)-PhBPE as catalysts for the hydrogenation of tetralone derived β-enamide and α-enamide, respectively, using TFE as solvent in excellent ee's.

In 2021, X. Zhang and co-workers synthesized cyclic and acyclic chiral carboxylic acids via enantioselective hydrogenation of tetrasubstituted cyclic olefins. During the initial optimization, they found that the use of (-)-S,S)-PhBPE with Co(stearate)$_2$ resulted in formation of the saturated acid in up to 91 % ee. Use of other axially chiral bisphosphines and P*-stereogenic bisphosphines resulted in lower conversions and ee's. A number of enantioenriched six membered cyclic acids were synthesized using 5 mol % Co(stearate)$_2$/(-)-PhBPE in t-BuOH under 80 bar of H$_2$ pressure in 3 days reaction time (Scheme 9). The methodology was also applied to five- and seven-membered tetrasubstituted cyclic olefins although an irregular trend in ee's was observed. α,β,β-Trisubstituted acrylic acids were also hydrogenated using the Co(stearate)$_2$/(-)-PhBPE precatalyst maintaining the same activity (Scheme 9). Interestingly, the ester derivative could not be hydrogenated, which confirmed the role of the carboxylic acid in the catalyst activation as was previously observed in the case of trisubstituted olefins. EPR measurements confirmed the presence of high spin Co(II) (S = 3/2) throughout the catalytic cycle. No deuterium incorporation was detected by using tert-BuOD as solvent. Detailed DFT studies showed that the migratory insertion of the olefin into the cobalt hydride is the rate-, regio- and stereo-determining step. The hydrogen activation proceeds through a σ-bond metathesis pathway (Scheme 9) rather than via oxidative addition of H$_2$. Most importantly, the steric effect of the phenyl group also plays an crucial role in the enantio-control of the hydrogenation as observed by the DFT calculations.

Employing a similar catalyst with cyclic enamides as substrate de Vries and co-workers recently reported the synthesis of (-)-Rasagiline (Azilect: treatment of Parkinson’s disease) via Co/PhBPE-catalyzed asymmetric hydrogenation as the key step for enantio-induction (Scheme 10). The “amide effect” in enamide hydrogenation was also investigated by varying the alkyl and aryl part at the carbonyl group of the amides (Scheme 10). A modest variation in ee was found (NHCO$_i$Pr (88 %) < NHCO$_Me$ (89 %) < NHCO$_Ph$ (94 %)). The hydrogenation of indane-derived enamide using Co/PhBPE was found to proceed as an isomerization (enamide-imide) free direct C=C-H bond insertion.

**Scheme 8.** AH of tri-substituted cyclic enamides. Substrate scope (left), deuterium labelling experiments (top right) and proposed catalytic cycle (bottom right). 

**Scheme 9.** Deuterium labelling experiments. 

**Scheme 10.**AH of tri-substituted cyclic enamides. Substrate scope (left), deuterium labelling experiments (top right) and proposed catalytic cycle (bottom right).
hydrogenation with molecular $H_2$. Several control experiments and electron paramagnetic resonance (EPR) results also showed the involvement of a redox active Co(0)/Co(II) catalytic cycle promoted by Zn as 2e\textsuperscript{-} reductant.

### 2.2.2. Functionalized Acyclic Olefins

In 1962, Kwiatek and co-workers reported the hydrogenation of ketones and many olefins using $[\text{Co(CN)}_5]^3^-$ as catalyst in aqueous solution at atmospheric $H_2$ pressure.\[14\] A few years later, T. Suzuki and Kwan found that a combination of $[\text{Co(CN)}_5]^3^-$ and $\alpha$-amino acids can reduce dienes to mono-enes in the absence of hydrogen.\[44\] Following a similar concept, Takeuchi and co-workers attempted to reduce a number of pro-chiral ketones, olefins and dienes using Co/amino-acid as catalysts. Best results were obtained with atropic acid sodium salt (nearly quantitative yield), although no enantioselectivity was observed (Scheme 11).\[45\] The authors found that the actual catalyst is hydridopentacyanocobaltate anion which does not carry an amino acid as ligand, thus explaining the absence of enantioselectivity.

Previous reports showed that a number of prochiral olefins can be hydrogenated by using $\text{Co}^{II}$ (dimethylglyoximato) (abbreviated as Co(dmg)) complex under atmospheric pressure of hydrogen at room temperature in aqueous solution.\[38\]

Scheme 9. Synthesis of chiral carboxylic acids via Co-catalyzed AH.\[40\]

Scheme 10. Asymmetric hydrogenation of 1- indanone derived enamides and Azilect synthesis using Co/BPE.\[41\]
nearly quantitative yield. A breakthrough was achieved in 1981 by Ohgo and co-workers, when they combined the Co(dmg) with chiral amino alcohols such as the cinchona alkaloids, which allowed the asymmetric hydrogenation of diketones, \( \alpha \)-keto-esters, \( \alpha,\beta \)-unsaturated ketones and esters and acylated dehydroamino acid esters (Scheme 12).\(^{[16]}\) The AH of benzil gave \( S -(+)- \) benzoin in quantitative yield in 71 % ee (Scheme 12). The reduction of methyl phenyl diketone to the acyloan was also achieved in 56 % ee. Olefins could also be reduced although, in general, the ee’s were lower. The enantioselectivity was higher with the \( \beta \)-unsaturated ketones than with the esters.\(^{[46]}\) The effect of the chiral amine was thoroughly investigated and quinine, quinidine, cinchonidine, ephedrine, N-methyl-ephedrine, \( S -(1,2R)-2 \)-amino-1,2-diphenylethanol were all tested. The authors found that the alkaloid does not bind to the cobalt, and the chiral co-catalyst (B*) (Scheme 13). The effect of the substituent R of the hydantoins was also investigated. The 5-aryl methylene) substrates were reduced with higher enantioselectivity than the alkyl derivatives (Scheme 13). The authors proposed an interesting pathway, where Co(H-dmg),PR\(_3\), acts as an electron donor to the substrate and the protonated chiral base acts as chirality-recognizing \( H^+ \) donor to the prochiral intermediate.\(^{[47]}\)

Pfalz and co-workers used a chiral semicorrin ligand in the Co-catalyzed enantioselective reduction of \( \alpha,\beta \)-unsaturated esters with NaBH\(_4\).\(^{[18a]}\) The reduction could be performed with a catalyst prepared in situ from 1 mol % CoCl\(_2\) and 1.2 mol % of the semicorrin ligand. The E- and Z-isomers each afford products of opposite configuration (Scheme 14). It is worth mentioning that the enantioselectivities, which are up to 96 %, lie in the same range as those achieved with Noyori’s Ru-BINAP\(^{[48]}\) catalyst. In follow-up work, they also showed that the same Co/semicorrin complex can be utilized for the AH of electrophilic \( \text{C} = \text{C} \) bonds substituted with nitrile, sulfones, phosphonates, or amides (Scheme 14, bottom). The best ee’s were obtained with carboxamides and carboxylates (up to 93 %).\(^{[49]}\)

Shainyan and co-workers utilized neomenthyldiphenylphosphine (L1) and \( (R,R)\)-2,2-Dimethyl-4,5-bis(diphenylphosphinomethyl)-1,3-dioxolane (DIOP) (L2) in the AH of methyl 2-acetamido-acrylate (MAC) using CoCl\(_2\) and Co(OTf), as metal precursors.\(^{[19]}\) NaBH\(_4\) was used to reduce the Co-complex to the catalytically active form. The hydrogenation was performed in a 1:2 mixture of toluene-EtOH at 80 °C at 30 bar H\(_2\). Low conversions of...
MAC were achieved using $\text{LI}/\text{CoCl}_2$ (1:1), and the product was obtained with 8\% ee (Scheme 15). The ee could be improved to 35\% employing 1.7:1 ($\text{LI}/\text{Co}$) ratio using triflate as counterion.

Using $\text{Co(OTf)}_2$, the conversion was improved when ($R, R$)-DIOP as bidentate ligand was employed, although the product was obtained with low ee (Scheme 15).$^{[10]}$

In 2013, the Chirik group together with Merck disclosed the potential of commercially available/easily accessible cobalt/bisphosphines in the AH of functionalized alkenes.$^{[21]}$ Using a HTE set-up of 192 chiral phosphate ligands and different [Co]-precursors, a number of commercial bisphosphines such as QuinoxP*, BPE, BenzP* and Duphos (the R designates various alkyl groups) were identified that resulted in high yields and enantiomericities in the hydrogenation of the benchmark substrate MAA (Scheme 16). Two other benchmark olefins, MAC and N-(1-phenylvinyl)acetamide were also hydrogenated using 10 mol\% of molecularly defined (Duphos)-Co(LiCH$_2$SiMe$_3$)$_2$ and (Duphos)-Co(LiCH$_3$SiMe$_3$)$_2$ respectively in 92.7 \% ee and 82.0 \% ee (Scheme 16, left).$^{[21]}$ After this discovery, cobalt-based catalysts based on commercially available phosphine ligands gained more interest for the AH of olefins.

Later, the same group reported the application of CoBPE in the synthesis of the drug Levetiracetam, a treatment for epilepsy, on 200 g scale using only 0.08 mol\% of catalyst (Scheme 16, right).$^{[49]}$ Using HTE it was found that a number of benchmark chiral phosphines were successful in delivering high ee’s. Interestingly, the dehydrolevetiracetam hydrogenation can be performed in the presence of Zn, which reduces Co(II) first to Co(I) and thereafter to Co(0), and without Zn without affecting the enantiomericity. This observation suggested either (i) the involvement of a common catalytic intermediate or, (ii) two different hydrogenation pathways resulting in the same product formation. Deuterium labelling experiments with [(BPE)Co(μ-Cl)], as catalyst showed the production of 1,2-dilevetiracetam in MeOH supporting the formation of COD dihydride via homolytic cleavage of H$_2$, a different path compared to the Co(riphos)$^{[50]}$ catalyst for hydrogenation of carboxylic acids where a heterolytic H$_2$ splitting was proposed.

Cationic Rh(I)/bisphosphine complexes have been extensively investigated in organometallic chemistry and homogeneous catalysis with a wide range of applications. On the other hand, the cobalt analogue of the Schrock-Osborn type catalyst ([Rh(COD)L$_2$]$^-$X$^-\text{X}^-$) remained evasive for several decades possibly due to its high lability and tendency to 1e chemistry. Chirik and co-workers reported the synthesis of a range of cationic Co-complexes bearing a chiral bidentate phosphine ligand (R,R$_{\text{DuPhos}}$).$^{[21]}$ In contrast to the distorted T$_{d}$ geometry of the neutral $\text{[(R,R)DuPhos]-Co(COD)]}$ (d$^*$, 17e$^\circ$, S = 1/2), the cationic $\text{[(R,R)-DuPhos]-Co(COD)]BArF}$ (d$^*$, 16e$^\circ$) shows distorted planar geometry in which an elongated Co-C bond was observed resulting from stronger back-bonding from the first row metal (Scheme 17). Interestingly, the COD can be easily substituted in the cationic complex with an arene or a coordinating solvent showing the lability of the $\text{[(R,R)-DuPhos]-Co(COD)]BArF}$ complex. The 18e cationic $\text{[(R,R)-DuPhos]-Co(t^1-arene)]BArF}$ is air stable. It is noteworthy to mention that the lability of COD ligand can easily be affected by altering the 1e chemistry at the metal center (COD inert in neutral Co(0) vs. COD labile in cationic Co(I)). The cationic Co(I)/arene complex was used for the hydrogenation of MAA with excellent conversion.

Scheme 14. Co-semicolon in asymmetric enantiodivergent olefin hydrogenation.$^{[14c]}$

Scheme 15. Co/phosphine in MAC hydrogenation.$^{[9]}$
and > 99% ee. The enantioselectivity is even higher with the Co(I)-precatalyst as compared to the reported Co(II)-dialkyl precatalyst (99% vs. 92%). This established the difference in the origin of enantioselection and perhaps divergent catalytic pathways for Co(I) and Co(II) precatalysts. An analogous model to the Rh/hydrogenation for enantioselection has also been proposed (Scheme 17), where substrate coordination is fast and reversible to the oxidative addition of H₂ (k₂ > k₁) leading to the (S)-product formation following the Curtin–Hammett principle.

Chirik, Hopmann and co-workers extensively studied the mechanism of cobalt catalyzed AH of substituted dehydroamino acids. Four possible pathways were proposed: (a) A redox mechanism, (b) metathesis, (c) a mechanism via a metallocycle, and (d) an imine pathway. Most importantly, the hydrogenation mechanism is strongly influenced by the solvent and the (bisphosphine) ligand used in the catalysis. Initially, it was observed that the hydrogenation of dehydrolevetiracetam (DHL) can be performed under both Zn and Zn-free conditions (Scheme 16). This observation indicated the involvement of a common intermediate which was proposed to be the transient chloro-bridged Co(I) dimeric complex, that can be formed either via single electron reduction (with Zn) or a ligand re-binding pathway (shown in Scheme 18, bottom) using CoCl₂/PhBPE only in MeOH. The Co(I) complex can undergo further one electron reduction to form a Co(0) complex (S = 1/2) in the presence of Zn. On the other hand, the substrate (dehydrolevetiracetam) induced disproportionation of Co(I) (EPR silent) into Co(II) (S = 3/2) and Co(0) (S = 1/2) as was proposed based on the EPR results in MeOH. Recently, they found through DFT studies that the formation of DHL from the Co(0)-substrate complex is energetically more favorable through an aza-metallocycle intermediate (Scheme 18) with an overall energy barrier of 24.6 kcal mol⁻¹ for the (S)-path. On the contrary, the classical redox path appears to be within the barrier of 27.4 kcal mol⁻¹ for the (S)-path. However, a different scenario was observed upon changing the ligand in the (iPrDuPhos)-Co-catalyzed dehydroamino acid (MAA) hydrogenation. The computational results are consistent with the experimental studies, where no distinct Co–H species formation was observed. Additionally, it was also found that the (iPrDuPhos)-Co(0)-MAA (catalyst-substrate complex) is the lowest energy species in the cycle and addition of dihydrogen to the substrate is the rate limiting step. Overall, the (iPrDuPhos)-Co-catalyzed dehydroamino acid hydrogenation involves a redox active Co(0)/Co(II) cycle. These studies have shown that the Co-catalyzed asymmetric olefin hydrogenation...
The reaction pathway (redox active or, redox neutral) is highly ligand influenced. The mechanistic distinction will be discussed in detail in Section 5.

Performing similar chemistry with dehydro-amido esters as substrate, Chirik and co-workers reported the synthesis of 4-aniline- and indazole-containing amido ester derivatives based on the interest of active pharmaceutical synthesis via Co-catalyzed AH as the key step for enantioselection. Surprisingly, both the Co(II)/Zn method and the cationic Co(I) catalyst were active in the hydrogenation of functionalized olefins although a substrate specificity was recognized upon altering either acid/ester or amide substituents (Scheme 19). As an example, the conversion and ee significantly dropped upon changing the aryl part from the aniline-derivative (>99 % conversion, 99 % ee) to the indazole-containing- amido esters (15 % conversion, 74 % ee) by using the same Co(I) complex. This is an excellent example of substrate specificity related to the aryl part of dehydro-amido esters in asymmetric hydrogenation. The catalytic activity followed the same trend as the Rh-catalysis, however, the trifluoroacetylated substrate showed similar conversion as the acetylated substrate with the Co(II)-precatalyst, whereas lower conversion was obtained using the Co(I) complex without affecting the ee much. Most interestingly, the cationic Co(I)/BenzP* failed to hydrogenate the corresponding acid derivative, probably coordinating to Co(I) through the (free) carboxylate functional group arresting the hydrogenation (Scheme 19). Finally, the hydrogenation of the model indazole- derived dehydroamino acid was scaled up to 20 g using 0.4 mol % of Co(II)/BenzP*-Zn in >99 % conversion and >99 % ee. This results showed how (coordinating) substrates indeed play an important role in Co-catalyzed AH by altering one electron chemistry at the metal center.

Chiral carboxylic acids are present in several pharmaceuticals, agrochemicals, fragrances, and flavors. Development of an efficient method for the synthesis of chiral carboxylic acid is always in demand in both academia and industry. In 2020, Chen, X. Zhang and co-workers found an active cobalt catalyst (up to 1860 TON) for the synthesis of chiral carboxylic acid via hydrogenation of the \( \alpha, \beta \)-unsaturated acids. After screening of several commercial bisphosphines and [Co]-precursors, PhBPE and Co(acac)\(_2\) delivered high conversion (98 %) and ee (97 %) using trans-2,3-diphenylacrylic acid as model substrate in iso-propanol using Zn (10 mol %) as additive. A number of \( \alpha \)-chiral acids bearing alkyl, aryl, -CF\(_3\), thiophene, N-Boc derivatives were synthesized in excellent yields and ee’s (Scheme 20). Interestingly, a similar yield (98 %) and ee (94 %) could also be obtained under Zn-free conditions. Substrate dependent catalyst activation was also observed in this case.
conversion was found using the corresponding (ethyl) ester derivative (Scheme 20), which suggested that the carboxylic acid acts as activator (via the free OH group) which helps to mediate the activation process. Dissociation of one acac group from Co(acac)$_2$ by the substrate led to formation of the Co(II)-substrate complex which eventually forms the Co-H (A, Scheme 20) under Zn-free conditions. Alternatively, the substrate-Co$_2$H (A) can also be formed via the classical Zn-reduction pathway. A deuterium labelling experiment showed the existence of a direct hydrogenation (ADH) pathway without isomerization. The formation of the substrate-Co$_2$H complex (A) is the crucial step which is followed by the migratory insertion of the alkene into Co-H bond. This is followed by hydrogen complex formation and thereafter the hydrogen splitting occurs via a sigma-bond metathesis pathway.

The same class of substrates was also hydrogenated by Chirik and co-workers\textsuperscript{[56]} A high-throughput experimentation (HTE) was conducted using 192 chiral bidentate ligands, trans-α-Me-cinnamic acid as model substrate, 10 mol % Co-precursor, 100 mol % Zn, 1 eq. of triethylamine in methanol at 34 bar of H$_2$ pressure, where (R,R)-P$_2$BPE was found to be the best ligand. The hydrogenation of di- and tri substituted α,β-unsaturated carboxylic acids can also be performed using a molecularly defined Co(0) precatalyst (Scheme 21).

A number of di-, tri- and cyclic carboxylic acids were synthesized using the neutral [(R,R)-P$_2$BPE-Co(COD)] complex (2 mol %) using Zn and Et$_3$N as additives (Scheme 21) in excellent ee’s. To gain more insight in the hydrogenation pathway, (P–P)–Co$_2$H(pivalate)$_2$ complexes were synthesized and characterized. Interestingly, the Sin-gle-crystal X-ray Diffraction of the P$_2$BPE–Co(II)-pivalate complex shows octahedral geometry (O$_6$) with helical chirality resulting from the two k'–pivalate ligands. The

Scheme 20. Chiral carboxylic acid synthesis and proposed pathway for Co/BPE catalyzed AH.\textsuperscript{[21]}

Scheme 21. AH of α,β-unsaturated acids.\textsuperscript{[56]}

Bisphosphines impart a strong enough ligand field to enable the Co(II) low spin state (Scheme 21). Deuterium labelling studies were performed to distinguish between homolytic and heterolytic splitting of dihydrogen. Identical results were obtained using Zn and Zn/Et$_3$N-free conditions accentuating the exclusive role of (R,R)-BPE-Co(COD) in promoting the homolytic cleavage of D$_2$ with $>98\%$ 1,2-$d$-incorporation in the product.[56] Based on the experimental evidence, an oxidative addition of H$_2$ to the Co(0) was proposed to form a transient Co(II)-diydride to which the olefin inserted followed by C–H reductive elimination to afford the alkane (dihydride pathway).[56]

Amézquita-Valencia and Cabrera developed the Co$_2$(CO)$_8$-catalyzed hydrogenation of $\beta$-enamine esters using a mixed ligand (achiral-chiral) approach (Scheme 22).[57] Using 1 mol % Co/BINAP/PPh$_3$ (1:2:2) as pre-catalyst a number of $\beta$-amino esters was synthesized by AH using syngas (CO:H$_2$ = 1:3) at 120 $^\circ$C. They also isolated the non-symmetrical Co/PPh$_3$/BINAP complex from the reaction of Co$_2$(CO)$_8$, PPh$_3$, and (R)-BINAP. The pre-catalyst A (Scheme 22) can be dissociated into two hydride species (Scheme 22) B (chiral) and C (non-chiral) in the presence of syngas. (R-BINAP)-(PPh$_3$(CO)Co–H) was proposed to be the active species for enantio-induction in the hydrogenation.[57]

When an alkene and alkyne are present in the same molecule as in conjugated enynes, competitive hydrogenation pathways may be observed due to the similar coordination and activation modes of the alkene and the alkyne to the metal center. Alkynyl group activation was observed as unwanted side-reaction using Rh(I)-catalysis,[58] where the large atomic radius and more electron localizing ability to the Rh enables this, thus losing stereo control. On the other hand, the smaller atomic radius of 1st row transition metals could lead to higher selectivity by preferring the alkynyl functional group with the stronger amide coordination. In 2021, W. Zhang and co-workers reported the chemo- and enantioselective hydrogenation of conjugated enynes keeping the alkyne bond intact by using a Co-catalyst.[59] CoCl$_2$/(R,R)-QuinoxP* was found to be the best pre-catalyst the use of which resulted in up to 99 % ee using the model alkynyl enamide N-(4-phenylbut-1-en-3-yn-2-yl)acetamide as substrate and Zn (10 mol %) as additive in CH$_3$CN at 40 bar of H$_2$ pressure (Scheme 23). Activity and enantioselectivity were maintained with >25 alkynyl enamides bearing different substituents (OMe, CO$_2$Me, CF$_3$, heterocycles and many more) at the aryl group. Interestingly, complete conversion with >99 % ee was also achieved using 10 mol % ZnCl$_2$ as additive with Co(II)Cl(PPh$_3$)$_3$ as the [Co]

\[ \text{Scheme 22. AH of $\beta$-enamine esters.}\]

\[ \text{Scheme 23. Chemo-, regio-, and enantioselective hydrogenation of conjugated enynes.}\]
source. This result suggested the possibility of formation of cationic Co(I) species via one electron reduction of Co(II) by Zn, after which the hydrogenation reaction follows a Co(I)/Co(III) cycle. Deuterium labelling also showed the existence of an asymmetric direct hydrogenation (ADH) pathway with >99 % d-incorporation from D₂. It is noteworthy to mention that the reduction of alkene was also observed in up to 23 % yield during control experiments using CoCl₂(PPh₃)₂/ZnCl₂ as precatalyst. This showed the possibility of double hydrogenation of the same substrate which was further explored by the same group in follow-up studies (Scheme 23). After careful optimization CoCl₂(PPh₃)₂/(S,S)-PPh₆-BPE was found to be the optimal pre-catalyst for the asymmetric sequential hydrogenation of the alkynyl enamides for the synthesis of chiral allyl amides. Use of other electron-rich phosphines such as (R,R)-BenzP* and (R,R)-QuinoxP* resulted only in the AH of the enamide as previously observed. Interestingly, the use of 1 mol % of CoCl₂(PPh₃)₂ and 1.1 mol % of (S,S)-PPh₆-BPE resulted in the highest yields and ee’s in methanol using 10 bar of H₂ (Scheme 23). More than 28 Z-allyl amides were synthesized in this way. Deuterium labelling experiments showed that molecular hydrogen is the only source of the two equivalents of hydrogen used for the hydrogenation of the alkyn and the enamide. A few control experiments were performed to elucidate the mechanistic pathway. First, ZnCl₂ and NaSbF₆ were used as activator which resulted in similar reactivity and enantio-selectivity (>99 % conversion, >99 % ee). Altering the solvent to acetonitrile (CH₃CN) led to a significant decrease in selectivity, where only enamide hydrogenation was observed as in the previous publication. This showed the importance of MeOH as solvent in the “double hydrogenation” of conjugated enynes, possibly helping the chloride dissociation from the precatalyst (Scheme 23). A plausible Co(I)/Co(III) pathway was proposed aided by density functional theory (DFT) calculations consisting of two catalytic cycles: (1) 1° enamide hydrogenation, (2) 2° semi-hydrogenation of alkene. The transfer of the hydrogen atom going from C to D (in Scheme 23) is proposed to be the stereo-determining step (SDS) with a difference in Gibbs free energy (ΔΔG°) of 3.0 kcal mol⁻¹ (corresponding to an enantioselectivity of 99 %). After the first cycle (enamide hydrogenation), the product enters into the second cycle. The alkyn reacts with the cobalt complex to form the metallacyclopentene complex B, which reacts with hydrogen to form the hydrogen complex C, which rearranges to form the alkylcobalt hydride D. Reductive elimination forms the product complex E which releases the product by forming the Co(I)-species (A), closing the catalytic cycle. Additionally, the possibility of a third hydrogenation (alkene saturation) was also calculated and found to have a high free energy barrier (ΔΔG°, 24.2 kcal mol⁻¹) and hence the semi-hydrogenation can be adjusted by fine tuning of the H₂ pressure and the reaction time. Most importantly, the reactivity difference between (R,R)-QuinoxP* and (S,S)-PPh₆-BPE was also investigated via Gibbs free energy calculations (Scheme 24). By careful inspection of the 3D-optimized structures, it was found that the carbonyl group in the amide part (substrate) in the (R,R)-QuinoxP* coordinated Co-complex is bound more tightly as compared to the corresponding (S,S)-PPh₆-BPE Co-complex, thus making the carbonyl dissociation (substrate dissociation) more difficult in the Co/QuinoxP* catalyst which slows down the binding of the substrate for further semi-hydrogenation (Scheme 24 shows the energy comparison).

Shelvin, Chirik and co-workers utilized air-stable Co(I)-precursors in the AH of an enamine for the synthesis of Sitagliptin (Scheme 25). The authors prepared the Co(I)-precatalysts via an oxidatively induced reductive elimination pathway in the presence of the biphosphines. A series of cationic cobalt bisphosphine complexes such as [(PH₂BPE)Co(η⁶-C₆H₆)][BAR₄], [(PH₂DuPhos)Co(η⁶-C₆H₆)][BAR₄], [(QuinoxP*)Co(η⁶-C₆H₆)][BAR₄], [(BenzP*)Co(η⁶-C₆H₆)][BAR₄] were synthesized for evaluating the catalytic activity. All the prepared Co(I) complexes were active in the hydrogenation, resulting in up to >99 % yield of the product. After a thorough screening, it was found that the cobalt complexes bearing an DuPhos ligand showed better conversion and enantioselectivity. Interestingly, with the increase in steric bulk in the Diphos-phospholane motif, the enantioselectivity increased: Me (64 % ee) < Et (70 % ee) < iPr (89 % ee). The other precatalysts (PH₂BPE)Co(I), (QuinoxP*)Co(I) and (BenzP*)Co(I) resulted in 77 % ee (96 % yield), 67 % ee (97 % yield) and 70 % ee (74 % yield) respectively in THF using 34 bar of H₂ pressure (Scheme 25). A comparison was also made between the performance of the in situ prepared and preformed catalysts. Neither the combination of (py)Co(CH₂SiMe₃)₂(DuPhos) nor (DuPhos)Co(CH₂SiMe₃)₂ was active for the enamine hydrogenation (Scheme 25) without oxidant. However, a low product yield (39 %) was observed with 92 % ee using the [(PH₂DuPhos)-Co(µ-Cl)]₂ dimer as pre-catalyst. Similar enantioselectivity was found using (DuPhos)-Co(CH₂SiMe₃)₂ with the oxidant with >99 % conversion and 94 % ee. To gain further insight into the mechanism, deuteration (31 bar of D₂) was carried out in THF at 25 °C resulting in full conversion with 89 % ee. By careful NMR and mass analysis, deuteration incorporation was observed at both α- and β- positions in a 1:0.5 ratio. An increased d-incorporation (α: β = 1.0:3 to 1.0:15) was observed at the α-position when the deuteration was carried out at 5 bar of D₂-pressure. This resulted suggested that the Co(I) catalyzed AH of sitagliptin-enamine does not follow the asymmetric direct hydrogenation (ADH) pathway but rather is a combination of enamine-imine tautomerization and AH. Indeed, an imine hydrogenation was already invoked in the earlier publication on the use of Rh/JosiPhos for the same hydrogenation by the Solvias/Merck collaboration (Scheme 25). The stereochemical outcome of the C=C hydrogenation is largely influenced by the geometry of the alkene. As an example, Ir-catalyzed AH of the (Z)-alkenes often results in lower enantioselectivity than the AH of the corresponding E-alkenes. Very often, the most generally observed outcome in the hydrogenation of isomeric alkenes is that the E- and the Z-isomers result in formation of the opposite enantiomers (enantiodivergent hydrogenation). In contrast

to that, the less frequent, but synthetically more useful enantioconvergent hydrogenation, in which both isomers are converted to the product with the same configuration, has also been observed using different Rh, Ir and Ru catalysts.

W. Zhang and co-workers have shown that Co/bisphosphine catalysts can also be used for the enantioconvergent hydrogenation of E/Z- aryl enamides (Scheme 26). Excellent yields (up to 96%) and enantioselectivity (up to 99%) were observed using CoCl$_2$/(R)-DTBM-SegPhos or, CoCl$_2$/(S,S)-Ph$_2$BPE as precatalyst in the presence of 20 mol % Zn as additive at 40 bar of H$_2$ pressure. The enantioselection was found to be in the similar range for either the E-isomer or the E/Z (1 : 1) mixture. A number of β-aryl amides with different functional groups (Me, i-Pr, OMe, F, Cl, CF$_3$) were prepared using the CoCl$_2$/(R)-DTBM-SegPhos via the hydrogenation of both E and E/Z enamides (Scheme 26). A number of cyclic amides were also prepared following the same conditions. The same Co/Ph$_2$BPE system was also used for the enantioconvergent hydrogenation of acyclic and cyclic enamides (Scheme 26). The authors showed that the Co$_{\text{PhBPE}}$ catalyzed β-aryl enamide hydrogenation is a direct AH process by performing deuterium labelling experiments which showed that neither H/D scrambling nor deuterium transfer from the solvent TFE-d$_1$ was observed. This was confirmed for both E- and Z-isomers (Scheme 26). DFT calculations were also performed to clarify the mechanism. A Co(0)/Co(II) catalytic cycle was proposed, where the active (Ph$_2$BPE)-Co(0) is formed from the (Ph$_2$BPE)-Co(II) precursor via a two electron Zn-reduction process. Two possible substrate coordination and H$_2$-ligation modes were computed for both E- and Z-enamides. The Cobalt-substrate hydrogen complex reacts to form the Alkyl-Co-hydride directly (Scheme 26). It remains unclear if this is a concerted reaction or that oxidative addition of hydrogen to the dihydride is followed by an alkene insertion without barrier. The Gibbs free energy difference between the transition state of the S-cycle and the R-cycle was also calculated (2.7 kcal mol$^{-1}$ for the Z-conformer and 0.7 kcal mol$^{-1}$ for the E-conformer). It was proposed that the aryl and methyl group on the alkenyl enamide cause a steric hindrance with the chiral ligand as shown in the four-quadrant diagrams (Scheme 27). For the E-enamide, the substrate bearing a p-tolyl group provides similar steric hindrance and van der Waals interactions for the (E,R) and (E,S)- configurations, pushing the substrate away from the chiral ligand, thereby weakening the discrimination of the Me group in the transition state for the (E,R) and (E,S)- configurations (0.7 kcal mol$^{-1}$). Whereas for the Z-isomer the (Z,R)-and (Z,S)-configura-

Scheme 25. Synthesis of Sitagliptin via Co-catalyzed AH.\textsuperscript{[61]}

Scheme 26. Enantioconvergent hydrogenation of enamides.\textsuperscript{[40]}
tions are distinguishable by 2.7 kcal mol⁻¹. However, the transition states arising from E- and Z-isomers indicate the same trend in stereoselectivity, which can indirectly explained the “enantioconvergent” nature of the hydrogenation. This work showed the potential of 3d-metal catalysts in enantioconvergent alkene hydrogenation.

Deuterated drugs are commonly used for the elucidation of metabolic rates during the process development stage before the final approval. During this research it was found that deuterated drugs can be more slowly metabolized in the body allowing lower dosage. As a result, a number of deuterated compounds are currently under investigation in clinical trials. In this context, deuterated amino acids are useful compounds but also in biomedical research, such as conformational studies of proteins, insight in enzyme catalysis or interpretation of biosynthetic pathways. Qin, Zhou and co-workers recently developed a methodology for the synthesis of α,β-dideuterio-α-amino-esters via cobalt catalyzed asymmetric (transfer) hydrogenation. They used relatively cheap deuterium sources such as methanol (d₁) or deuterated acetic acid which can have an advantage over the use of high pressure deuterium gas. After careful screening, the combination of CoL₂ and P-chiral QuinoxP* was found to be the best for hydrogenation/deuteration using AcOH/MeOH or AcOD/MeOD. Indium powder was the most efficient reductant in the protic solvents. Other deuterated solvents such as DMSO-d₆ acetone-d₆ and DMF-d₃ resulted in poor yields. A number of α-amino-esters were synthesized in good to excellent yields with up to 95 % ee. However, the effect of the catalyst-substrate complex.

Interestingly, no reaction was observed when the acetamide group in the substrate was replaced by a trifluoroacetamide (NHCOCF₃), a sulfonamide (NHSO₃Ph) or a cyano (CN) group. This indicates that the electronics at the amide oxygen is an important factor in the formation and/or reactivity of the catalyst-substrate complex.

The catalytic cycle starts with the formation of the Co(II) complex (A, Scheme 29) via a two electron reduction by indium from the Co(II) complex. The Co(II)-complex oxidatively reacts with the excess AcOD to the Co–D complex (B, Scheme 29). Next, the substrate coordinates through the C–C and amide oxygen to the cobalt complex, followed by insertion of the alkene to form the benzyl cobalt species D. Finally, front-selective deuteration of the cobalt-carbon bond releases the syn-β-deutero product forming the Co(II)-acetate E. Indium reduces the Co(II)-acetate to Co(0) closing the catalytic cycle. A small amount of anti-β-deutero isomer was also observed.

Enantioenriched organoboron compounds can be used as building blocks for several stereo-selective transformations. Although enantioselective hydroboration[57] is the most useful method for their preparation, this often suffers from selectivity issues in the case of the di-boron analogues. In 2020, Chirik and co-workers exploited the reactivity of the Co/bis(imino)-pyridine catalyst for the preparation of 1,1'-disubstituted diborylalkanes (Scheme 30). A range of linear, alkyl substituted, 1,1-diborylalkanes was hydrogenated to their corresponding alkanes with up to 97 % ee and 98 % isolated yield using 5 mol % CoCM, Co-b₄ 4 bar H₂ pressure in benzene. The boryl substituent is important for the hydrogenation as the CoCM, Co-b failed to hydrogenate the non-borylated 1,1-disubstituted styrenes. The effect of the boronate substituents was also further investigated by varying the B-group although no general trend could be observed (Scheme 30). Hydrogenation of the catechol borane (BCat) derived indene resulted in the highest conversion and ee (76 %). Isotope labelling studies confirmed that the different boronates promoted distinct hydrogenation pathways. The less sterically hindered boronates (such as -BCat, -Beg) preferred the d-incorporation in 1,2-fashion through an α-boryl cobalt intermediate (Scheme 31) whereas the larger substituents on boron

[Scheme 27. The quadrant scheme. Reprinted with permission from Ref. [40]. Copyright 2023, Wiley-VCH.]

(--BPin) favored scrambling of the deuterium through isomerization via a $\beta$-boryl cobalt intermediate (up to 77% d-incorporation was observed to the $\beta$ carbon). In this particular study, better yield and ee were observed in the case of 1,1-diboryl alkene as compared to the indenyl-boronates (Scheme 31).

W. Zhang and co-workers reported the synthesis of enantioenriched pyrazole compounds via the AH of prochiral azole-functionalized alkenes. After careful screening of different chiral ligands, CoCl$_2$/Me$\text{DuPhos}$ and CoCl$_2$/Ph$\text{BPE}$ resulted in the highest conversion and up to 98% ee in MeOH using Zn as additive. Similar activity and selectivity were observed in other alcoholic solvents such as EtOH, iPrOH, tBuOH. More than 40 different $\beta$-chiral pyrazole, triazole and tetrazole derivatives were synthesized using 1 mol % CoCl$_2$, 1.1 mol % ((S,S)-Ph$\text{BPE}$, Zn (10 mol %) employing ethanol as solvent in 2 h (Scheme 32). However, $\gamma$-chiral pyrazoles could not be synthesized under these optimized conditions. This implies the importance of the 5-membered cobaltacycle for the catalyst-substrate complex formation and migratory insertion to the olefin (Scheme 32).

Isotope labelling experiments confirmed the asymmetric direct hydrogenation pathway. Based on literature observations, a plausible redox active Co(0)/Co(II) cycle was proposed for the hydrogenation (Scheme 32).

In 2019, Liu, Huang and co-workers also utilized a C1-symmetric pyridine-based phosphine-oxazoline (PPO) ligand in the cobalt-catalyzed AH of alkynylsilanes. More than 30 different organosilanes were synthesized using CoCl$_2$, $\text{NaBHEt}_3$, and TMSCH$_2$Li as activator in pentane (Scheme 33). Other activators such as MeLi and TMSCH$_2$Li also resulted in similar yields and enantioselectivities. No reaction was observed using Zn as activator. A Co-catalyst based on a pyridine-imino-oxazoline ligand was earlier applied in a one-pot hydroboration/
hydrogenation reaction\(^\text{[69]}\) and in the hydrosilylation/hydrogenation\(^\text{[72]}\) of alkynes, Lu and co-workers also reported the synthesis of chiral \(\beta,\beta\)-disubstituted ketones via chemo- and enantioselective 1,4-hydroboration of enones in up to 97% yield and 98% ee.\(^\text{[73]}\)

3. \(\text{C}=\text{O}\) Hydrogenation

Chiral alcohols are versatile building blocks for pharmaceuticals, agrochemicals, and flavours and fragrances. Enantioselective hydrogenation of \(\text{C}=\text{O}\) offers the most atom economical pathway for the preparation of such chiral alcohols (Scheme 34). Excellent progress has been made since the discovery of Noyori’s Ru/BINAP catalyst in the field of asymmetric ketone hydrogenation, mostly based on the utilization of 4d and 5d metals because of their superior activity and high TON’s.\(^\text{[74]}\) Several catalysts based on first row metals such as Fe and Mn have also been used in combination with chiral tridentate and tetradeutate ligands during the last decade.\(^\text{[74c,75]}\) In this section, the development of Co-catalyst in the AH of cyclic and acyclic ketones will be discussed.

Initial studies on cobalt-catalyzed \(\text{C}=\text{O}\) hydrogenation were based on using a combination of an achiral cobalt-complex with a chiral base. Takeuchi and co-workers reported asymmetric induction using Co/dmg and a chiral co-catalyst in the hydrogenation of benzil (and other diketones) with up to 78% ee.\(^\text{[17a,g]}\) However, more advancement was noticed in the hydrogenation of functionalized alkenes using this catalytic system (See also section 2.2.2).

In 1985 Simonneaux and co-workers utilized an in situ combination of Co\(_2\)(CO)\(_8\) and chiral phosphines in the AH of alicyclic ketones where negligible ee (max. 5%) was observed.\(^\text{[78]}\) In 1995, Mukaiyama and co-workers utilized the chiral Co/\(\beta\)-oxoaldiminato complex (NNOO)-Co-I as catalyst for the synthesis of chiral alcohols from their corresponding ketones using NaBH\(_4\). A number of exocyclic enantiocenriched alcohols were prepared in excellent yields and 68–94% ee using 1.5 eq of borohydride (Scheme 35, top).\(^\text{[76a]}\) Addition of 1 eq. of furfuryl alcohol (FA) derivatives in combination with NaBH\(_4\) and EtOH improved the TON and ee’s significantly. Furfuryl alcohol and methoxy ethanol also enhanced the yield and enantioselectivity (Scheme 35). Higher enantiomeric excess was obtained upon addition of tetrahydrofurfuryl alcohol (THFA).\(^\text{[79]}\) The same catalytic conditions were also used for the dynamic
kinetic resolution of β-keto esters in 97 % yield (cis product) and 92 % ee (Scheme 35, bottom).\[76b\]

Following this, Kim and co-workers also reported the application of unsymmetrical Co(II)-salen complexes in cyclic and acyclic ketone hydrogenation, where moderate ee’s were observed (12 %–67 %).\[80\] The symmetric Co/salen complexes were also applied in the reduction of aromatic ketones resulting in up to 70 % ee at room temperature using NaBH₄/EtOH.\[81\] In follow-up studies, Yamada and co-workers prepared the premodified borohydride with THFA and used this for the catalytic reduction of cyclic ketones.\[77a\] The reduction was completed in 20 mins resulting up to 94 % ee. It was proposed that the addition of THFA presented interesting features (1) making the reaction mixture homogeneous (2) activated in situ borohydride formation by liberating H₂ and thus forming the Co-hydride species (3) influencing the reactivity and enantio-induction in the hydrogenation (Scheme 36, top). Based on the experimental evidence, DFT calculations were performed to give support to the proposed reaction pathway.\[77b\] A sodium-ion (Na⁺) ligated anionic dichloromethyl Co-hydride species was proposed as the key intermediate (Scheme 36, bottom).
It is assumed that the ketone coordinates to the Na+ leading to the activation and stereochemical alignment of the C–O group. The Co/salen complexes were also used for the AH of 2-fluoro-benzophenones resulting in up to 96 % ee using pre modified lithium borohydride. Other halocarbons (CCl₄, CBr₄, CHI₃) did not improve the catalytic activity which indicated that CHCl₃ plays a specific role in the catalyst activation by forming the more active HCo-CHCl₂ complex, which was characterized by mass spectrometry.

The methodology was also used in continuous flow using the Co/salen complex for the reduction of cyclic and acyclic ketones (Scheme 37). In 12 min residence time, the reactions proceeded smoothly in up to 96 % yield and 90 % ee (comparable with the batch conditions). A gram-scale synthesis was also performed (3.0 g of substrate) using the flow setup as shown in Scheme 35, where the corresponding alcohol was isolated in 96 % yield in 92 % ee with a total operating time of 9.75 h. High chemo- and enantioselectivities were also obtained in the reduction of di-ketones. Yamada and co-workers also prepared a catalyst by reacting (NNOO)Co-1 with ethyl diazoacetate assuming this would lead to a cobalt carbene complex. They observed similar activity and ee’s in halogen-free solvents in the NaBH₄ reduction of ketones as compared to the previous results in chloroform.

In 2007, Nindakova and co-workers synthesized a new C-2 symmetric naphthyl substituted salen ligand. The cobalt complexes based on this ligand were applied in ketone hydrogenation, obtaining moderate yields and enantioselectivities.

Li and co-workers synthesized cobalt complexes based on a chiral aminophosphine (PNNP) ligand (Scheme 38). They employed the complexes (PNNP)-Co-1 and (PNNP)-Co-2 in asymmetric ketone hydrogenation using 400 mol % of KOH at 100 °C and 60 bar of H₂. (PNNP)-Co-1 and the semi-oxidized complex (PNNP)-Co-2 showed comparable activity (95 % yield, 81 % ee vs 99 % yield 82 % ee) using propiophenone as model substrate. A substrate dependent yield and enantioselectivity was noticed in the hydrogenation.
tion of benzylic ketones. As an example, hydrogenation of 2-chloro-acetophenone resulted in 90% yield and 54% ee, whereas the 2-Br derivative could not be hydrogenated (Scheme 38). Moderate to high ee's were obtained.

Tang and co-workers prepared chiral NNP ligands varying their steric and electronic properties (Scheme 39) and the corresponding divalent cobalt complexes. The EPR data indicated the (NNP)-Co-1 is a penta-coordinated low spin cobalt(II) (S = 1/2) complex. The complex was further investigated in the AH of ketones. No conversion was achieved using 2 mol % (NNP)-Co-1 employing acetophenone, 40 bar H_2 and NaOMe as base. Surprisingly, the catalytic activity was tremendously increased using a trivalent phosphine as additive. It was assumed that the phosphine helps to stabilize the penta-coordinated Co-hydride in the catalytic cycle (Scheme 40).

A number of chiral alcohols were prepared from their corresponding ketones tolerating a range of sensitive functional groups such as -SMe, -CF_3, -CN. Up to 84% ee was achieved using aryl-alkyl ketones.

Zuo and co-worker synthesized the cobalt complex of the amine(imine)diphosphine ligand PN(H)NP, which they found to have a square pyramidal geometry (Scheme 41). Several chiral secondary alcohols were synthesized with good to moderate conversions and ee's by using 0.164 mol % of (PNNP)-Co-1 and 1.3 mol % of base in the transfer hydrogenation of ketones using isopropanol as reductant.

Chiral macrocyclic P,N-ligands have attracted considerable attention in AH chemistry since the past decade. The P_N_N-type aminophosphine ligands possess the interesting property of having a "soft" P-atom with α-acceptor properties as well as a "hard" N-atom with σ-donor ability. Yuan, Li and co-workers synthesized the Co-complex of the chiral macrocyclic iminophosphine ligand (R,R,R',R')CyP_2N_4. The six coordinated CyP_2N_4Co-1 was applied in the asymmetric transfer hydrogenation of alkyl-aryl ketones using iPrOH/KOH (Scheme 42). An increase in ee was observed with the increase of steric bulk of the alkyl group of the substrate (Me(53%) < Et(83%) < n-Pr(81%) < n-Bu(80%) < i-Pr(95%) < Cy(95%)). More than 18 enantioenriched chiral secondary alcohols were synthesized in 85–99% yield and with ee's ranging from 29–99%. Lu and co-workers also utilized their Co/imino-oxazoline catalyst for the preparation
of chiral alcohols from the corresponding ketones using organoborane and NaBEt₃H as reductants.\[93\]

W. Zuo and co-workers developed an enantiodivergent ketone hydrogenation catalyst based on Co/amidoen-(amido) diphosphine complexes.\[94\] Interestingly, the charge of the metal center determined the enantioselectivity and configuration of the hydrogenation product (Scheme 43). In depth DFT calculations showed that the stereoselective outcome was defined by the net balance between the π–π attractive interaction between the ene(amido) group of the amino(hydrido) intermediate and the aryl group of the substrate and the CH–π attractive interaction between the substrate and the catalyst in the competitive diastereomeric transition states. This “metal charge directed enantiodivergent” catalysis was shown to function with more than 54 prochiral ketones bearing diverse functional groups.\[94\]

Wen, X. Zhang and co-workers synthesized a bis-ferrocene based secondary phosphine oxide ligand (Fc-SPO) starting from commercially available Ugi’s amine.\[95\] Interestingly, the solid-state structure of the cobalt complex based on this ligand (PO)Co-1 was found to be a bischelated tetrahedral complex in high spin state (μₑffective = 4.19 μB), in which the P=O and only one of the two phosphines is coordinated to the cobalt center (Scheme 44). The (PO)Co-1 complex was applied in the asymmetric hydrogenation of 2-methoxy-substituted diaryl ketones giving the alcohols in excellent yield with ee’s up to 92 %.\[95\]

Z. Zhang, W. Zhang and co-workers developed an efficient method for the synthesis of benzylic-β-aminoalcohols via asymmetric hydrogenation of protonated aromatic aminoketones using Co(R,R)BenzP* as catalyst.\[96\] They proposed a specific substrate coordination mode through the amino group (–NH₂) assisted by H₂CO₃ (Scheme 45), which is quite different from the conventional catalyst-substrate complex formation/activation via coordination of the hydroxy (–OH), amide, acid or ester groups (NHCOR, COOR, COOH) to the metal center in Co-catalyzed asymmetric hydrogenation. The catalytic activity was dramatically reduced by altering the carbon chain length between the NH₂ and the C=O group which confirmed the specific mode of catalyst/substrate activation. A range of α-primary amino alcohols were prepared bearing different functional groups on the aromatic ring (–OMe, –Me, –F, CF₃, –OH etc.) in excellent yields with up to 99 % ee.
Deuterium labelling experiments established that (1) molecular H$_2$ is the hydrogen source not MeOH (2) there is no equilibrium between ketone and enol or enamine tautomers. DFT calculations further supported a non-redox Co$^{II}$ catalytic cycle (Scheme 45). At first, H$_2$ is coordinated to the Co$^{II}$ complex A (in Scheme 45) which undergoes a heterolytic cleavage (assisted by acetate) forming the Co$^{II}$-H species C. Then, the substrate is coordinated through the amino (-NH$_2$) group assisted by carbonic acid resulting in the formation of D. The C=O is reduced to a single bond through a hydride-proton synergistic addition via carbonic acid assisted C=O activation and proton transfer (Scheme 45). Finally, the alcohol is released, regenerating the initial Co$^{II}$-species A. This mechanism does not resemble the “NH effect” activated outer-sphere mechanism as the C=O activation occurs via the proton shuttle of carbonic acid and not via the interaction with the metal-NH bond.

In the Co-catalyzed asymmetric reduction of prochiral ketones, most reports described the use of (sodium) borohydride as reducing agent (most likely due to faster active catalyst formation), whereas the use of molecular H$_2$ was limited.

4. C=N Hydrogenation

Chiral amines are privileged structural motifs found mostly in pharmaceuticals and agrochemicals. In addition, chiral primary and secondary amines are used as building blocks for asymmetric synthesis, and as chiral auxiliaries or as resolving agents. A number of efficient and practical approaches have been developed for the synthesis of α-chiral amines during the last decades. Of these, the AH of imines (C=N) is one of the most powerful and direct methods to construct the α-chirality in amines, particularly in N-alkylated and arylated amines that are not easily accessible by enzymatic reactions (Scheme 46). Many efficient catalysts that were designed for asymmetric C=C or C=O reduction showed poor activity in C=N reduction. Several factors, such as a possible imine-enamine tautomerization, as well as the presence of an E/Z isomeric mixture in the case of acyclic imines, can have an effect on the activity and enantioselectivity of the hydrogenation reaction.

The progress of Co-catalysis in (asymmetric) imine hydrogenation has been rather slow, possibly due to the frequent occurrence of catalyst deactivation. The imine (as substrate) or the amine (the product) can bind strongly to the Co-center forming Co-imine or Co-amine complexes (Scheme 47), retarding the hydrogenation. However, this challenge can be tackled by introducing electron-withdrawing functional groups on the imine N-atom.

Okamoto and co-workers utilized the Co(dmg)/quinine complex for the AH of imines. The catalytic activity in...
THF/MeOH was improved by altering the N-substituent from Ph (12 % yield) to the p-toluenesulfonyl (p-Ts) group (82 % yield). Up to 20 % ee was achieved in the hydrogenation of methyl 2-phenyl-2-(tosylimino)acetate (Scheme 48).[100]

In 2003, Yamada and co-workers applied their chiral β-ketoiminato Co(II) complexes for the preparation of chiral amine derivatives via imine reduction using NaBH₄ as reductant.[77] Acetophenone oxime or the oxime-methyl ether could not be reduced but the N-tosylimine derivative was reduced to give 95 % of the product with 78 % ee (Scheme 49). The ee’s were further improved by changing the N-protecting group to the N-phosphinyl group. The (NNOO)-Co-2 catalyst successfully hydrogenated a number of cyclic and acyclic N-phosphinylimines in excellent yields with up to 99 % ee (Scheme 49).[77] The phosphinyl group could be removed under mild conditions (HCl/MeOH, rt) without affecting the ee (98 %, Scheme 49). The α-deuterated chiral primary amine was also prepared using NaBD₄ in THFA-d as reductant.[101]

Amézquita-Valencia and Cabrera used Co₂(CO)₈ in combination with BINAP as catalyst for the hydrogenation of unsymmetrical benzophenone imines. Up to 99 % ee was obtained using N-benzyl imines, and up to 83 % ee with aniline derivatives (Scheme 50).

The catalytic activity was increased at elevated temperatures (120 °C) whereas no conversion was achieved at room temperature. Most importantly, imine reduction was not observed using H₂ only. An excellent yield was obtained using a 1:3 CO/H₂ mixture. This suggested that the stabilization of the cobalt-species with CO is a crucial factor. They characterized the possible Co-species via mass and IR spectroscopy and matched these results with data originally reported by the Gibson group.[103] Initially (BINAP)(CO)-Co-μ-(CO)₂Co(CO)₃ forms by the dissociation of 2 molecules of CO, which eventually undergoes another BINAP substitution via another CO liberation (Scheme 51). Also, the hydride complex was prepared by reacting with molecular hydrogen which was characterized via IR spectroscopy.

Scheme 48. Co(dmg)/quinine as catalyst for the asymmetric reduction of the C=N bond.[79]

Scheme 49. Enantioselective borohydride reduction of N-diphenylphosphinylimines using a β-ketoiminato Co(II) complex.[77]

Scheme 50. Co/BINAP catalyzed AH of N-benzyl imines.[102]
(2063 cm\(^{-1}\)) and mass spectrometry. Based on this information, the proposed mechanism starts with the formation of the cobalt-hydride intermediate (A) which converts into the active catalyst B via CO elimination. Next, the substrate imine is coordinated to the hydrido-complex (B) forming the intermediate adduct C. Subsequently, addition of CO leads to migratory insertion of the C\(=\)N double bond into the Co-H bond, giving the adduct D, which reacts with hydrogen to release the product and regenerates the catalyst (A) (Scheme 51).\(^{[102]}\)

W. Zhang and co-workers reported an efficient method for the preparation of chiral hydrazines via Co-catalyzed AH of N-functionalized hydrazones.\(^{[104]}\) Imine hydrogenation was also investigated. The hydrogenation activity is strongly influenced by the activating group present at the imine N-atom. No reactivity was observed with imines bearing a -Ts, -SO\(_2\)Bu, -NHTs or -NHAc group except with the -NHBz group (Scheme 52). Presumably, the carbonyl group of the -NHBz takes part in the catalyst activation by additional coordination to the Co atom. (S,S)-PhBPE provided the best activity in combination with CoBr\(_2\) and Zn (10 mol %) in the hydrogenation of N-benzoyl-hydrazones. More than 25 different chiral hydrazines were prepared in excellent yields and ee’s (Scheme 52) even at S/C = 2000. A deuterium labelling experiment also confirmed the direct hydrogenation of the C\(=\)N bond. A mechanistic cycle was computed via DFT calculations. Initially, a BPE ligated Co(0) is formed via 2e reduction by Zn. This complex undergoes oxidative addition of H\(_2\) to form Co-dihydride A (Scheme 53). The substrate N-NHBz coordinates to the Co-dihydride though the amide oxygen of the benzoyl group and the Co-N bond resulting in formation of the catalyst-substrate complex B (Scheme 53). After the insertion step a Co-H intermediate C is formed (where the transition state for the (S)-cycle is lower than that for the (R)-cycle by 13.6 kcal mol\(^{-1}\)) (Scheme 53). The C\(=\)N bond is hydrogenated directly by the catalyst B yielding the product D. A deuterium labelling experiment also confirmed the direct hydrogenation of the C\(=\)N bond. A mechanistic cycle was computed via DFT calculations. Initially, a BPE ligated Co(0) is formed via 2e reduction by Zn. This complex undergoes oxidative addition of H\(_2\) to form Co-dihydride A (Scheme 53). The substrate N-NHBz coordinates to the Co-dihydride through the amide oxygen of the benzoyl group and the Co-N bond resulting in formation of the catalyst-substrate complex B (Scheme 53). After the insertion step a Co-H intermediate C is formed (where the transition state for the (S)-cycle is lower than that for the (R)-cycle by 13.6 kcal mol\(^{-1}\)) (Scheme 53).
3.1 kcal/mol). The DFT calculation shows this as a concerted reaction although a two-step sequence via oxidative addition of hydrogen followed by a low-barrier insertion cannot be excluded. Reductive elimination leads to formation of the product-coordinated Co-species D (Scheme 53). It is noteworthy to mention that the amide coordination of the benzoyl group is present throughout the catalytic cycle and the π–π interactions between the two Ph groups (PBP and NHBz) is proposed to be the key factor behind the high selectivity in the C=N hydrogenation.

5. Mechanistic Aspects

Acquiring better knowledge of the reaction mechanism in asymmetric catalysis is important, as it provides the direction for catalyst optimization. The mechanistic pathway of AH is one of the most studied catalytic cycles. Initial investigations on Rh/bisphosphine catalyzed AH of dehydroamino esters by Kagan[106] and Knowles[105] established the oxidative addition of dihydrogen to the cationic (P=P)Rh(I)-substrate complex via classical oxidative addition, known as the unsaturated pathway (Figure 4, top) where 1:1 d-insertion across the C=C bond was observed exclusively. Gridnev and Imamoto proposed a complementary dihydride mechanism, which is operative with the strongly electron-donating bisphosphate ligands, where the oxidative addition of hydrogen precedes substrate coordination.[107]

The kinetics and mechanism of the Ru/BINAP catalyzed AH of unsaturated carboxylic acids were studied by Halpern and co-workers in 1991. There findings supported the heterolytic cleavage of dihydrogen to form the metal hydride (Figure 4, bottom).[108]

Major progress in AH has been achieved by identifying the possible reaction intermediates (mostly with precious metals) supported by computational studies of the various possible catalytic cycles. However, it is clear that not a single unified mechanism exists due to the reaction specificity based on the nature of the metal, the ligand, the type of substrate and even the solvent used. The mechanistic scenario is even more complicated for the AH using catalysts based on 1st row metals. Several mechanistic studies have been performed on enantioselective hydrogenation with earth-abundant metal catalysts, but it seems each catalyst has its own hydrogenation pathway depending on oxidation states, coordinating ligands and substrates.

Due to the lower electronegativity, smaller d-orbital splitting (Figure 5 shows a comparison), and propensity towards one electron chemistry, cobalt possesses unique properties in organometallic chemistry and homogeneous catalysis. To identify the active cobalt species in AH is rather challenging because of its unclear oxidation state(s) and geometry (Figure 5 bottom) in many cases. It becomes difficult to spot the exact oxidation state of cobalt in the presence of Zn or any reductants that are capable of doing 1e and/or 2e redox chemistry to the metal center. Another property that makes cobalt catalysis puzzling is the spin state. Both high (S = 3/2) and low (S = 1/2) spin states can be found for the most commonly observed cobalt(II) oxidation state during catalysis, which makes the mechanistic cycle even more complicated. The spin state of a metal complex can largely affect the overall geometry of the organometallic complex involved in the catalytic cycles. As a result, the stereo-determining step (S.D.S.) becomes more difficult to predict. Moreover, the divergence between the redox active or redox neutral pathways can easily be affected by the nature of the solvent, the ligand or the substrate used in the hydrogenation. As an example, three different alcohols,
MeOH, phenol and pinacol exhibited different coordination chemistries upon reaction with $^{3b}$DuPhos-Co(CH$_3$TMS)$_2$.$^{[109]}$ Phenols tend to form a Co(II) bis(aryloxide) complex in tetrahedral geometry with a magnetic moment of 3.9 μ$_B$ suggesting an S = 3/2 ground state, consistent with the X-band EPR spectrum (Scheme 54). In contrast, the reaction with pinacol (bearing β-H) resulted in the corresponding Co(II)-pinacolato complex exhibiting a square planar structure. The magnetic moment (1.6 μ$_B$) and the X-band EPR result also suggested the presence of a low spin S = 1/2 Co(II) species.

A completely different scenario was observed for the reaction with (excess) MeOH. Protonation of the alkyl ligands followed by dehydrogenation of methanol to CO led to the formation of a (CO)$_2$ bridged dimeric Co-species with a Co–Co bond (2.300(1) Å). The EPR spectrum suggested the presence of both S = 3/2 and S = 1/2 Co(II)-species.$^{[109]}$ In spite of these differences, the hydrogenation performances were identical using all three Co(II) species using MAA as substrate, although the pressure needed to be increased from 4 to 34 bar when using the CO-bridged dimer.

Recently, the electronic structure of both the diamagnetic cationic cobalt(I) complex [P$_2$Co(COD)]$^+$ and the neutral, formally Co(0) complex [P$_2$Co(COD)] have been computed by full molecule density functional theory (DFT) using the B3LYP function.$^{[110]}$ The qualitative d-orbital splitting diagram (Figure 6, left) showed that the highest occupied molecular orbital (HOMO) of [P$_2$Co(COD)]$^+$ has mainly $d_{yz}$ character, which is expected for a diamagnetic, low spin square planar d$^9$ metal complex with σ-donating phosphines and π-accepting alkene (here COD) ligands. On the other hand, the HOMO of neutral [P$_2$Co(COD)] was found to have the shape of a $d_{yz}$ orbital (Figure 6), which is basically the singly occupied molecular orbital (SOMO) as observed by the qualitative d-orbital splitting and Mulliken spin density distribution. This fact does not agree with the expected d$^9$ Co(0) complex, where Jahn–Teller distortion would result in a D$_{2h}$ geometry with more energetic $d_{xz}$ and $d_{yz}$ orbitals and filled $d_{xy}$ and $d_{yz}$. However, the elongated bond length in the solid-state structure also supports the distortion from expected D$_{2h}$ geometry to the square pyramidal structure. Hence, these formally [P$_2$Co(–COD)] complexes$^{[110]}$ are better described as five coordinated, d$^9$, Co(II) complexes where cyclooctadiene can be considered to be a LX$_2$ type ligand (i.e. the metallacyclopentane limit resonance structure in the Dewar-Chatt-Duncanson binding model of metal-bound alkenes).

Ligand and solvent can strongly influence the hydrogenation pathway of a Co-catalyst. A difference in hydrogenation pathways was observed by altering the catalyst from Co$^{3b}$BPE$^{[5a]}$ to Co$^{3b}$DuPhos$^{[5b]}$ using the same substrate (MAA) in MeOH. The solid state structure of neutral (R,R)-$^{3b}$DuPhos-Co(COD) showed distorted square pyramidal geometry, where the alkene occupies the basal plane and the amide oxygen binds at the axial position which is in contrast to the square planar cationic Rh(III)$^{[111]}$ and Co(II)$^{[5b]}$ bisphosphine complexes where both alkene and amide-oxygen reside at the basal plane. This finding highlighted that the enantioselective mode is strongly influenced by the geometry of the catalyst-substrate complex. As a result, the S.D.S (stereo-determining step) can easily be influenced by altering the redox properties (1electron difference) using Co(I) and Co(0)-catalysts even with the same pro-chiral substrate. The magnetic moment of (R,R)-$^{3b}$DuPhos-Co(COD) in solution (2.0 μ$_B$) and the X-band EPR spectrum identified it as having an S = 1/2 ground state.

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![Scheme 54. Difference in reactivity of Co(II)-complexes in alcoholic solvents.][52] X-ray structure reprinted with permission from Ref [109]. Copyright 2019 American Chemical Society

![Figure 6. Qualitative molecular orbital diagram of cationic [P$_2$Co–(COD)]$^+$ and neutral [P$_2$Co(COD)] possessing significant d-orbital character computed by DFT at B3LYP/def2-SVP/def2-TZVP theory.][53]

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Deuterium labeling studies and KIE data are consistent with the **unsaturated pathway**, in which substrate binding precedes hydrogen activation, and the \( ^{19} \)DuPhos-Co catalyzed MAA hydrogenation. Extensive DFT calculations have been performed to compute the hydrogenation pathway further (Scheme 55). The hydrogenation begins with the neutral Co-substrate complex A (Scheme 55) followed by \( \text{H}_2 \) ligation to form B. In contrast with the rhodium-catalyzed reaction, here, the oxidative addition of \( \text{H}_2 \) to the Co(II)-dihydride is less favored. Instead, oxidative hydride transfer (R.D.S.) from the intermediate B to the \( \beta \)-carbon was preferred, generating the Co(II)-alkyl hydride intermediate C. In the last step, the product coordinated Co complex D (stabilized by electrostatic interactions, C–H–O attraction) is formed via reductive elimination (Scheme 55). The Gibbs free energy calculation for the dissociation of MAA from the Co-catalyst (Scheme 55, middle) also indicated the stronger binding of the Co-enamide through C=C and amide oxygen (56.6 kcal mol\(^{-1}\)). The higher value (> 30 kcal mol\(^{-1}\)) of the overall computed energy barriers also ruled out the possibility of the formation of 6-membered metallacycle intermediates.

On the other hand, a metallacycle pathway is energetically favorable in the case of Co\(^{10}\)BPE catalyzed MAA hydrogenation along with the classical redox pathway\(^{[53a]}\) Formation of a six-membered Co(II)-metallacycle (B, Scheme 56) is energetically accessible via hydride transfer from the Co(0)-MAA to the \( \alpha \)-carbon of MAA. Then N-coordinated Co(II)-hydride (D) is formed through a Co-imine transition state followed by the coordination of another substrate molecule (E). Then the proton transfer (through a four membered cyclic transition state F, as shown in Scheme 56) would result in the formation of the starting Co-enamide (A), releasing the product. MeOH as solvent plays an important role by stabilizing (through H-bond formation) the possible intermediates in both the Co\(^{10}\)BPE\(^{[53a]}\) and the Co\(^{10}\)DuPhos\(^{[53b]}\) catalyzed AH of MAA. This also highlighted the importance of the solvent in asymmetric (hydrogenation) catalysis.

Initial reports showed that the development of cobalt catalysts already started as early as that of the heavier congeners, but the progress stayed behind, mostly because of its uncertain spin states which often makes the understanding of the reaction mechanism more challenging.\(^{[112]}\)

**Scheme 55.** Proposed (redox) active mechanistic pathway (top), catalyst-substrate dissociation energy calculation (middle), optimized (S)-transition state (bottom) in Co/PrDuPhos catalyzed MAA hydrogenation.\(^{[53h]}\) Reprinted with permission from Ref. [53b]. Copyright 2022 American Chemical Society.

**Scheme 56.** Proposed metallacycle pathway and computed free energies (B3LYP–D3/(IEFPCM(methanol))) for BPE–Co-catalyzed hydrogenation of MAA. Adapted with permission from ref [53a]. Copyright 2022 American Chemical Society.
The open shell electronic configurations make it even more difficult for the chemists. However, these challenges can be tackled by either (1) using strong field ligands such as phosphines, CO or isocyanide, thereby increasing the crystal field stabilization energy of the complex, or (2) employing redox-active ligands such as the bisimino-pyridine ligand (3), which can take part in metal-ligand cooperativity (MLC) and can act as electron reservoir (Figure 7).

6. Conclusion and outlook

Compared with the vast number of (existing and developing) chiral ligands available for 4d and 5d metal catalyzed AH, ligand selection is much more limited for cobalt catalysts. To date, electron rich cyclic bisphospholanes (e.g., R(Me, Et, iPr, Ph)-BPE and R(Me, Et, iPr)-DuPhos) and P*-bisphosphines (QuinoxP* and BenzP*) have been quite successful in the majority of cases.

The challenges and points of attention for further development of cobalt-catalyzed AH can be outlined in a few key points:

1. Solvent: In general, use of polar protic solvents resulted in better activity and selectivity with few exceptions. In most of the reports, industrially friendly solvents such as MeOH, t-BuOH, EtOAc or 2-MeTHF were used, which allows scale up of these processes. However, the solvent can also displace the phosphine ligand (BPE substitution by MeOH) by forming solvato-complexes which could be a potential catalyst deactivation pathway. Hence, proper solvent selection is a critical parameter behind achieving high activity and selectivity.

2. Chiral ligand: Clearly, the choice of ligand is vitally important for designing new catalysts for Co-catalyzed AH. Thus far, the use of electron-rich bidentate phosphines has dominated this area. Nevertheless, excellent yields and ee’s have also been obtained with N-based bis(imino)pyridine, oxazolinyl/imidazolyl iminopyridine ligands especially in minimally functionalized alkene hydrogenations. The price of the chiral ligand is an issue, but possibly catalyst separation and recycling could improve the economics for scale-up of the process, at least in the case of air-stable phosphines. The development of new classes of low-cost ligands for cobalt is seen as an important area for development.

3. Substrate specificity: It is quite evident from the existing literature that the substrate is also a key factor in Co-catalyzed AH. Altering the functional groups present at the C=C or C=N bond can completely change the reactivity. To date, di and tri-substituted and very few tetra-substituted alkenes have been explored. Finding good catalysts for tetra-substituted cyclic and acyclic olefins is another area where more research is needed. It should also be realized that substrate and product inhibition are quite common in Co-catalyzed AH. In particular, the polar groups that can coordinate to the metal are problematic. However, this opens opportunities to increase the reaction rate by modifying the substrate. Use of solvents in which substrate and product have low solubility would offer another method to solve this problem.

4. Mechanistic aspects: Solvent influence, substrate specificity and the “correct” chiral ligand contribute to the mechanistic pathway. Different alcohols such as p-methoxy-phenol, pinacol and MeOH can promote the formation of divergent Co-species with non-identical spin states and geometries, which makes the mechanistic cycle even more uncertain. Presence of both high spin \((S=3/2)\) and low spin \((S=1/2)\) states of Co\(^{II}\) species often makes the cycle more complex. Thus far, (1) Classical Co(0)/Co(II), (2) Co(I)/Co(III) and (3) non-classical “e-bond metathesis” mechanisms have been described and supported by experimental and analytical techniques. Several variations have been noticed between the Co(0/II) and Rh(III) catalytic cycles, in particular involving the mode of \(H_2\) activation, charge of the complexes, oxidation states, geometry of the intermediates and non-covalent interactions for enantioselection. The synthesis, isolation, and characterization of intermediates (such as catalyst-substrate complexes) is definitely helpful to understand the mechanism and provides better guidance for new catalyst design in Co-catalyzed asymmetric hydrogenation.

Although first reports of the use of chiral cobalt catalysts go back to the 1980’s, major advances have been realized in the last ten years. More efforts have been placed on “in situ” catalyst formation as compared to the usage of isolated molecular complex as precatalyst. Further expansion of the substrate classes will expand the usefulness for organic synthesis.

The question remains if cobalt-catalyzed AH can move beyond a research tool into a widely applied synthetic method for industrial production method for enantiopure fine chemicals.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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