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TUTORIAL REVIEW

Chiral-at-metal complexes and their catalytic applications in organic synthesis

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This *tutorial review* provides an introduction to the synthesis and characterization of chiral-at-metal complexes and their catalytic application in organic transformations. The synthetic access to these architectures either *via* chiral resolution or by employment of chiral ligands is described, characterization techniques for the complexes are referenced and the application of the *R*/*S* nomenclature is explained. Racemization and epimerization processes are often observed for the title compounds; the article gives mechanistic insights to these processes and describes how to recognize and document them. Finally, key catalytic applications in organic synthesis are presented and how the molecular architectures of the chiral-at-metal complexes lead to stereodifferentiation and, thus to enantiomeric excesses in the products.

The synthesis and characterization of chiral metal complexes is one of the most intense research areas of current organometallic chemistry. This research interest is mainly driven by the potential application of chiral metal complexes as catalysts for enantioselective organic transformations.[1] A variety of chemical reactions can be catalyzed by chiral metal complexes to obtain organic products in high enantiomeric purity. These products can, in turn, find applications in pharmaceutical development and production.[2] Furthermore, chiral metal complexes are also increasingly investigated in the growing field of organometallic medicinal chemistry.[3]

Traditionally, chirality is established in metal complexes *via* chiral ligands, since the chiral information is then located in the coordination sphere of the complexes. The ligands can direct the orientation of substrates at the metal center for subsequent chemical transformations, thereby creating distinguishable faces on substrates to be attacked by a reagent, leading to stereodifferentiation and, finally, enantiomeric excesses in the products. Accordingly, enantioselective transition metal catalysis employing chiral ligands is powerful, and numerous applications have been reported both in academic and industrial settings.

However, there are organic transformations, for which, thus far, no metal complex with chiral ligands has been identified to obtain the targeted products in high enantioselectivity (*vide infra*).[4] Consequently, research efforts have been directed towards the exploration of other organometallic architectures, where the chiral information is not located at the ligand, but at the metal center, which is typically directly involved in catalytic transformations. Chiral-at-metal complexes exhibit a stereogenic metal center and the chirality parallels to a certain extent the very well known example from stereogenic carbon atoms in organic chemistry. As schematically shown for **1** in Fig. 1, compounds featuring tetrahedral carbon atoms with four different substituents are chiral. In much the same way, tetrahedral metal complexes with four different ligands are chiral as well as schematically shown for **2** in Fig. 1, and other coordination geometries also can exhibit stereogenic metal centers, as further outlined below. Such architectures have been systematically investigated since the 1960s. However, they are heavily underexplored compared to other chiral metal

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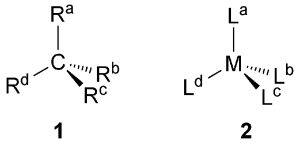


Fig. 1 Stereogenic carbon atom and organometallic analog.

complexes where the chiral information is located at the ligand. On the other hand, for some catalytic applications they turned out to be more efficient than "traditional" chiral metal complexes (*vide infra*).[4]

Herein, an introduction to the synthesis, characterization, reactivity and the catalytic application of chiral-at-metal complexes is presented. One of the objectives of this tutorial is the promotion of chiral-at-metal complexes to be employed in enantioselective organic transformations. The article is intended to inspire researchers to also consider these complexes in their own research, either in the area of organometallic synthesis or enantioselective catalysis. Rather than being comprehensive, some descriptive examples are selected from the literature to explain the concepts and to give a starting point for further reading. The topic has previously been intensely reviewed.[5–7]

Overview, challenge and the term "chiral-at-metal"

Two main types of chiral-at-metal complexes are typically encountered in the literature: complexes bearing four different ligands and complexes where multidentate, linear ligands are coordinated to the metal center, which will be separately described below. A major challenge is the potential racemization of an enantiopure metal complex over time.[8] For racemization, bond cleavage followed by bond re-formation is required. In organic compounds with stereogenic carbon atoms, such a process is, with a few exceptions, not a major problem, as carbon tends to form strong bonds to other atoms, which are not easily broken under ambient conditions. However, bonds from metal centers to ligand donor atoms are weaker; consequently, racemization or other forms of isomerizations can take place more easily under ambient conditions in solution. Racemization poses a problem, as a partial or fully racemized metal complex will give lower or no enantiomeric excess when employed as a catalyst in enantioselective reactions. Thus, chiral-at-metal complexes must be carefully designed and analyzed to recognize and prevent such racemization events.

Strictly speaking, the term "chiral-at-metal" is not correct. "Chirality" is the property of a whole molecule or metal complex, whereas "chiral-at-metal" suggests that only the metal center is chiral. A better description for the compound class described herein would be "stereogenic at metal", indicating that the complexes do have a stereogenic center, causing chirality of the whole compound. However, both terms are regularly used in the literature and will be employed in this article interchangeably.

The article will first describe a class of metal complexes bearing four different ligands; these complexes will also be used to demonstrate not only synthetic access and characterization but also *R*/*S* nomenclature and racemization or epimerization processes. Complexes with linear, polydentate ligands will be considered subsequently, followed by selected catalytic applications of these complexes and latest developments.

Chiral-at-metal complexes bearing four different ligands

The majority of chiral-at-metal complexes reported in the literature are constructed with four different ligands or donor atoms. The relevant coordination geometries for these complexes are tetrahedral and octahedral. As exemplified in Fig. 1, tetrahedral metal complexes **2** are reminiscent of compounds with tetrahedral carbon atoms, and the origin of chirality for the two systems is identical. However, tetrahedral metal complexes tend not to be configurationally stable.[9] Consequently, they are rarely investigated in the present context, albeit some progress has been made in recent years,[4] as discussed towards the end of the article.

Octahedral complexes are somewhat more stable, albeit these can racemize as well. However, assuming only monodentate ligands, the coordination chemistry of octahedral metal complexes can become very complex, as many different isomers with enantiomeric and diastereomeric relationships can form. For example, octahedral complexes with 6 different monodentate ligands can form 15 pairs of enantiomers.[10] Octahedral complexes can be chiral if they bear at least three different monodentate ligands, as exemplified for the complex **3a** and its mirror image **3b** in Fig. 2. These complexes are chiral and constitute a pair of enantiomers.

In the case of octahedral complexes with four different monodentate ligands, as in octahedral L_3Mabc, the complexes are chiral if they take a *fac*-arrangement (**4** in Fig. 1, *fac*-**4a** and *fac*-**4b** are a pair of enantiomers) whereas the *mer*-arrangement (**5** in Fig. 1) is achiral. In general, octahedral complexes with identical *trans* ligands are always non-stereogenic at the metal.

However, the synthesis of octahedral complexes bearing only monodentate ligands can be very cumbersome, as the

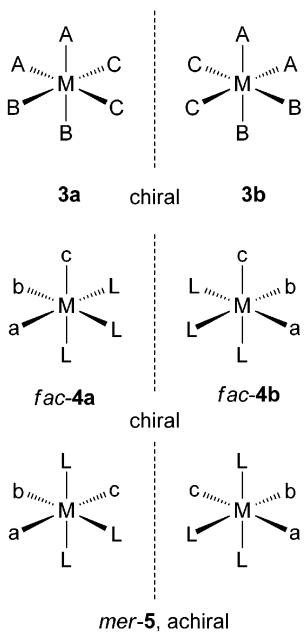


Fig. 2 Octahedral metal complexes.

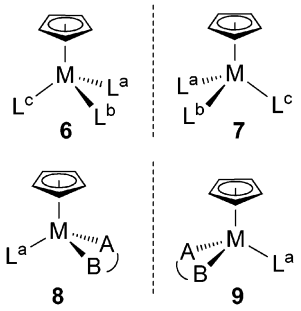
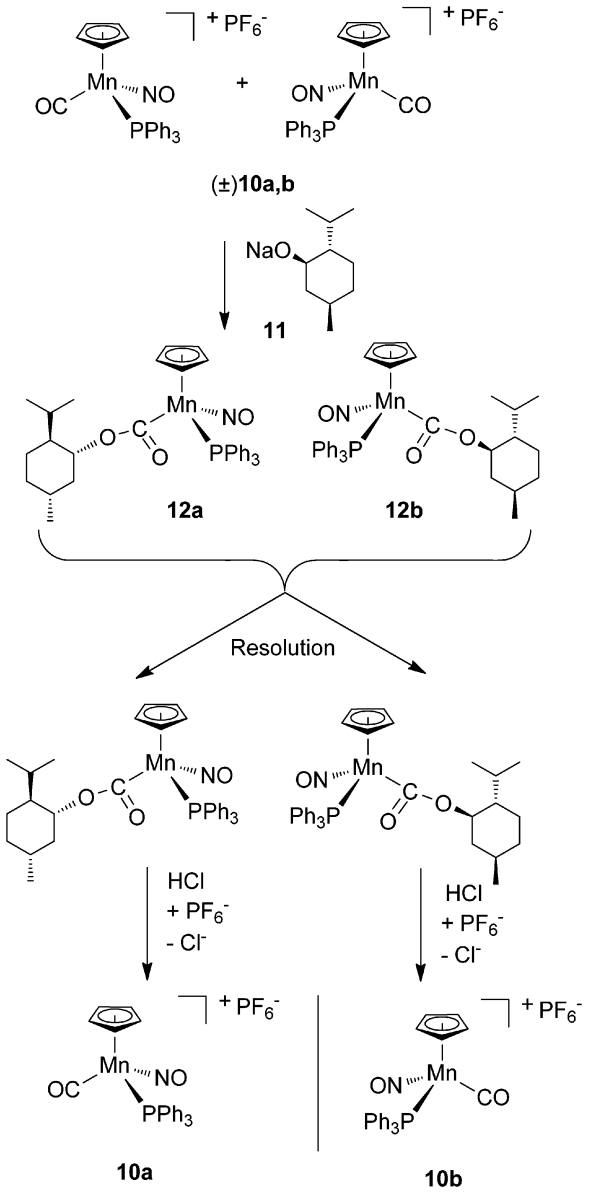


Fig. 3 Half sandwich metal complexes.

variety of possible isomers must be separated and can interconvert during or after workup. These complexes are, thus, difficult to access and are not good candidates for catalytic applications.

In octahedral half-sandwich complexes, one of the ligands is an aromatic ring system, mainly benzene or cyclopentadienyl (η^5-$C_5H_5^-$, Cp) and their derivatives (Fig. 3). When serving as ligands, they occupy a face of the six possible coordination sites of an octahedral metal complex; the other three sites can be occupied by other ligands; if these are all different (such as in **6**), or if unsymmetric bidentate ligands are employed (such as in **8**), the complexes are stereogenic at the metal. Half sandwich complexes can, thus, be viewed as octahedral architectures with a *fac*-arrangement of the three ligands L in **4** (Fig. 2), forcing the remaining three ligands a, b and c also into *fac*-positions, and the whole complex is consequently chiral.

In half-sandwich complexes, the number of ligands is restricted to a maximum of four, reducing the number of possible stereoisomers to two enantiomers. Permutation of two ligands (L^a and L^b in **6** and **7**) or the linking of the two different donor atoms in bidentate ligands (as in **8** and **9**) provides the other enantiomer just as is the case for a carbon atom with four different substituents. They are, therefore, a widely investigated compound class featuring a stereocenter at the metal. The most important features of the title compounds will be exemplified next with half-sandwich complexes.

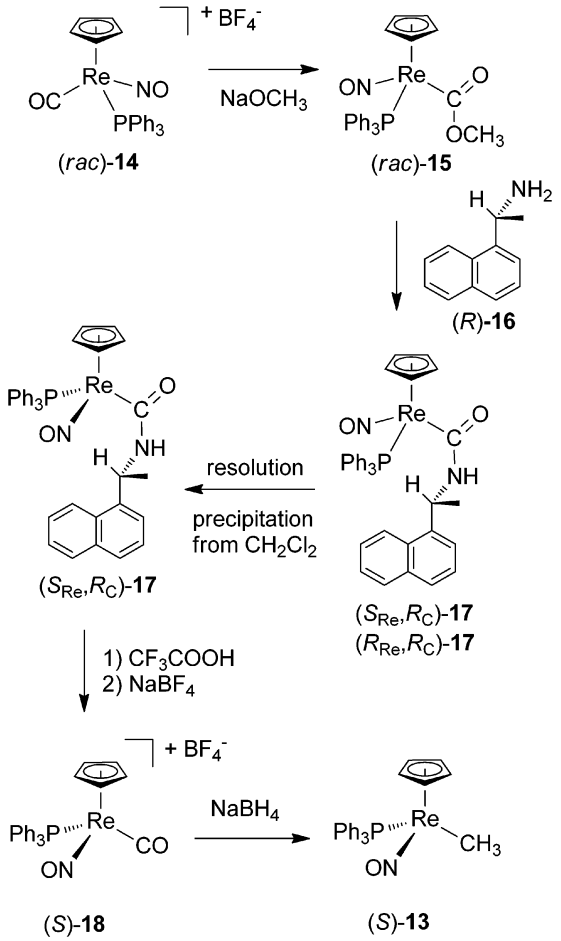


Scheme 1 Resolution of a chiral-at-metal manganese complex.[12,13]

Synthesis of enantiopure chiral-at-metal half sandwich complexes

Enantiopure chiral-at-metal complexes can be accessed by the resolution of a racemic mixture by means of a chiral auxiliary. In this approach, the racemic mixture of the metal complex is treated with a chiral, enantiopure agent that is capable of forming a covalent bond to one of the ligands. A mixture of two diastereomers forms, which differ only in the configuration at the metal. Diastereomers have different physical properties and can be separated, *e.g.* by fractional crystallization or by column chromatography. The chiral auxiliary can be subsequently removed, affording the chiral-at-metal complex in enantiopure form. This principle is exemplified by the first chiral-at-metal half sandwich manganese complex synthesized by Brunner (Scheme 1). The racemic, cationic manganese complex (±)$[Mn(Cp)(CO)(PPh_3)(NO)]^+PF_6^-$ (**10**) is accessible by exchange of the CO ligand in the achiral manganese complex $[Mn(Cp)(CO)_2NO]^+PF_6^-$ by PPh_3.[11] To resolve the two enantiomers, (±)-**10** was then reacted with the enantiopure sodium mentholate **11**, which attacks selectively the carbonyl ligand of **10** to give the mentholate complexes **12a** and **12b**.[12,13] They vary only in the configuration at the metal, have a diasteromeric relationship and exhibited significant solubility differences in pentane. Accordingly, the diastereomers were subsequently separated by fractional crystallization. The menthol auxiliary was then removed by HCl, affording the enantiopure manganese complexes **10a** and **10b**, which exhibited opposite optical rotation;[13] in the original publication, an absolute configuration could not be assigned.[12,13]

In a similar approach, Gladysz *et al.* accessed the chiral rhenium methyl complex (*S*)-**13** (Scheme 2).[14] The racemic, cationic rhenium complex $\mathbf{14}^+BF_4^-$ was first converted to the corresponding methyl ester **15**, which was then converted to the amide complex **17** utilizing the commercial, enantiopure 1-(1-napthalene)ethylamine (*R*)-**16**. Again, a pair of diastereomers formed; the complex (S_{Re},R_C)-**17** showed significantly

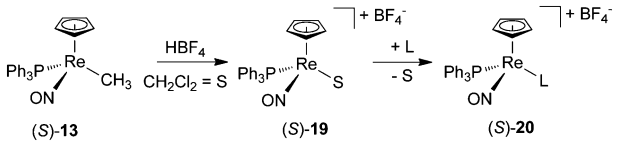


Scheme 2 Resolution of a chiral-at-metal rhenium complex.[14]

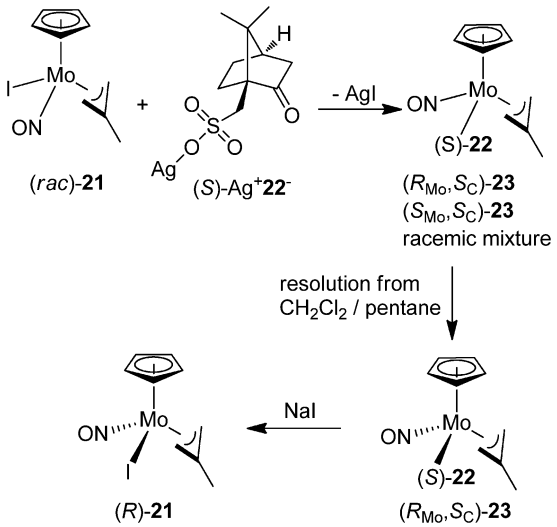
reduced solubility in CH_2Cl_2, and was selectively precipitated out of solution. The chiral auxiliary (*R*)-**16** was removed by CF_3COOH; in the resulting salt, the counterion was exchanged by BF_4^- and the CO ligand reduced by $NaBH_4$ to afford the neutral methyl complex (*S*)-**13** as a single enantiomer, whose absolute configuration was established by X-ray crystallography.[15]

The methyl complex (*S*)-**13** is a valuable precursor for a variety of other chiral-at-metal complexes; the methyl group can be removed upon treatment with HBF_4 in CH_2Cl_2 to give the chiral-at-metal solvate complex (*S*)-**19**, where the solvent molecule can be replaced by a variety of ligands L with retention of the configuration at the rhenium center (Scheme 3).[16] A diphosphine derivative of the chiral rhenium fragment (*S*)-**13** was applied in rhodium-catalyzed enantioselective ketone hydrosilylations and alkene hydrogenation reactions.[17]

Faller *et al.* used the silver salt of the chiral (*S*)-(+)-10-champhorsulfonate (*S*)-Ag^+**22**$^-$ to access enantiopure molybdenum complexes of the general formula [Mo(Cp)X(η^3-methallyl)(NO)]



Scheme 3 Further reactivity of complex (*S*)-**13**.[16]



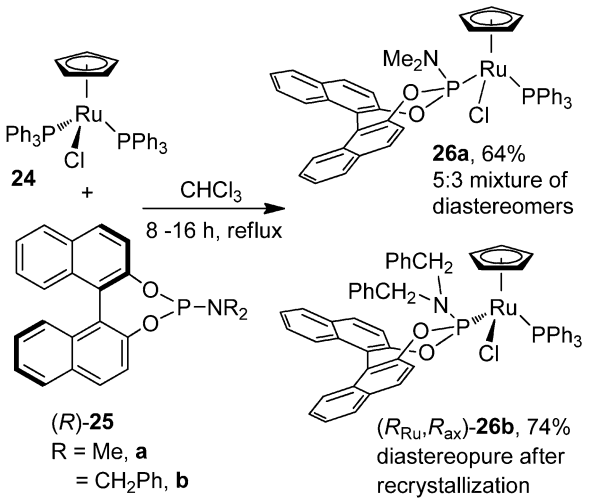
Scheme 4 Resolution of complex **21**.[18]

(X = Cl, Br, I).[18] In this approach, racemic [Mo(Cp)I-(η^3-methallyl)(NO)], (*rac*)-**21**, was first treated with (*S*)-Ag^+**22**$^-$ to replace the iodide ligand to obtain a diastereomeric mixture of [Mo(Cp)**22**(η^3-methallyl)(NO)] (Scheme 4). One of the diastereomers exhibited significantly reduced solubility in pentane, and precipitated from a CH_2Cl_2 solution by addition of pentane. The diastereopure complex (R_{Mo},S_C)-**23** was then treated with NaI to replace the (*S*)-**22** auxiliary by iodide with retention of configuration to obtain the enantiopure molybdenum complex (*R*)-[Mo(Cp)I(η^3-methallyl)(NO)], (*R*)-**21**. The absolute configuration was determined by X-ray crystallography.

Synthesis of diastereopure chiral-at-metal half sandwich complexes with chiral monodentate ligands

The complexes described in the previous section were stereogenic at the metal and featured achiral ligands. If such complexes bear a chiral ligand, they exhibit stereogenic centers both at the metal and at the ligand, giving rise to the formation of diastereomers. In cases where a chiral, enantiopure ligand is employed during the synthesis of corresponding complexes, only two diastereomers result, which differ in the configuration at the metal. These can be separated to afford single diastereomers, and as opposed to enantiomers, they typically do not form in a 1 : 1 ratio. Diastereomeric metal complexes are somewhat easier to handle than enantiomeric ones. Their stereochemical purity can be quickly assessed by NMR spectroscopy, because diastereomers typically give distinguishable signals in their spectra.[19] For phosphorus containing complexes, ^{31}P NMR spectroscopy has especially been useful for rapid assessment of stereochemical purity.[19]

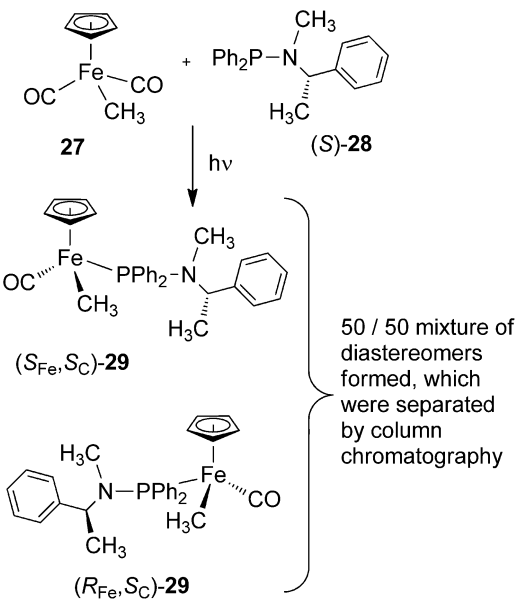
The author's laboratory published the isolation of a diastereopure ruthenium complex featuring a chiral phosphoramidite ligand in the coordination sphere (Scheme 5).[20] When the known, achiral ruthenium complex [RuCl(Cp)(PPh_3)$_2$] (**24**) was heated with chiral, enantiopure phosphoramidite ligands (*R*)-**25**, one of the two PPh_3 ligands was replaced by the phosphoramidite to afford ruthenium complexes of the general formula [RuCl(Cp)(PPh_3)((*R*)-**25**)] (**26**). These complexes are stereogenic at the metal and at the ligand and form a mixture



Scheme 5 Synthesis of diastereomeric ruthenium complexes with monodentate chiral ligands.[20]

of diastereomers. Interestingly, the phosphoramidite ligand (*R*)-**25a** with NMe_2 units gave complex **26a** as an inseparable 5 : 3 mixture of diastereomers, whereas the ligand (*R*)-**25b** with $N(CH_2Ph)_2$ units gave an 8 : 1 crude diastereomeric mixture. It appears that the size of the ligand has an impact on the diastereomeric ratio that forms during synthesis. The larger ligand (*R*)-**25b** favors the formation of one of the diastereomers. Subsequently, the diastereomeric mixture [RuCl(Cp)(PPh_3)((*R*)-**25b**)] (**26b**) was separated by fractional crystallization to obtain the diastereopure complex (R_{Ru},R_{ax})-[RuCl(Cp)(PPh_3)**25b**], (R_{Ru},R_{ax})-**26b**, in 74% isolated yield. The absolute configuration was determined by X-ray crystallography.

In a related ligand exchange reaction, Brunner *et al.* converted the achiral iron precursor complex [Fe(Cp)$(CO)_2CH_3$] (**27**) by photolysis promoted CO ligand exchange with the chiral aminophosphane (*S*)-**28** to the chiral-at-metal complex [Fe(Cp)(CO)((*S*)-**28**)] (**29**).[21] It was obtained as a 1 : 1 mixture of diastereomers, which could be separated by column chromatography (Scheme 6). The two complexes (S_{Fe},S_C)-**29** and (R_{Fe},S_C)-**29** are not configurationally stable at 70 °C and epimerize in solution with a $\tau_{1/2}$ value of 70 minutes (*vide infra*).



Scheme 6 Separable diastereomeric iron complexes with a chiral monodentate ligand.[21]

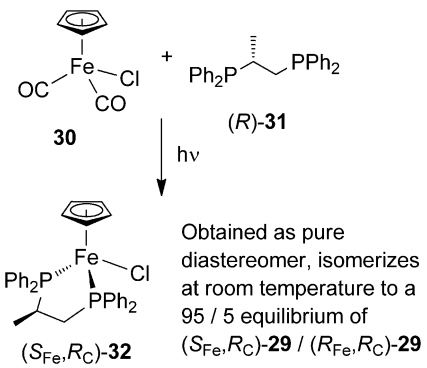
Synthesis of diastereopure chiral-at-metal half sandwich complexes with chiral bidentate ligands

This class of complexes is common and a number of examples are known. Bidentate ligands can increase the rigidity of a metal complex, and therefore prevent or retard isomerization processes. They are often applied to avoid the erosion of the stereochemical information of a metal complex through racemization or epimerization.

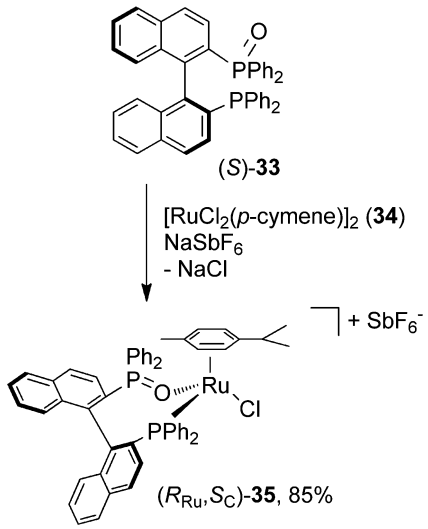
When a mixture of the iron precursor [Fe(Cp)$Cl(CO)_2$] (**30**) and the "Prophos" ligand (*R*)-**31** were irradiated in toluene, both CO ligands were replaced and the complex [Fe(Cp)Cl((*R*)-**31**)] (**32**) was obtained as a 95/5 mixture of diastereomers (Scheme 7).[22] The major diastereomer could be separated by fractional crystallization from a toluene/hexane mixture at −20 °C to obtain the diastereopure complex (S_{Fe},R_C)-[Fe(Cp)Cl(**31**)], (S_{Fe},R_C)-(**32**), whose absolute configuration was determined by X-ray crystallography. Complex (S_{Fe},R_C)-(**32**) epimerizes in benzene at room temperature to a 95/5 equilibrium of (S_{Fe},R_C)-(**32**)/(R_{Fe},R_C)-(**32**) with a $\tau_{1/2}$ value of 43 minutes.

The bisphosphine monoxide ligand "BINPO" (*S*)-**33** afforded upon reaction with the ruthenium precursor [$RuCl_2$(*p*-cymene)]$_2$ (**34**) in the presence of $NaSbF_6$ the complex (R_{Ru},S_{ax})-[RuCl(*p*-cymene)**33**]$^+$ SbF_6^-, (R_{Ru},S_{ax})-**35**, which was isolated by crystallization as a single diastereomer in 85% yield (Scheme 8).[23]

An example of a "four-legged" half-sandwich complex was reported by Scott *et al.*[24] Four-legged half-sandwich complexes can be stereogenic at the metal and a variety of geometrical isomers are possible depending on the type and arrangements of the "legs" of such complexes, and not all of them are chiral, such as **38** (Fig. 4). If three of the four ligands L are different, the complex can be chiral as in **36**, if the two identical ligands (here L^c) are aligned mutually *cis*. The two ligands L^c can be "forced" in the *cis* position by employing an asymmetric, bidentate ligand. In other words, asymmetric,



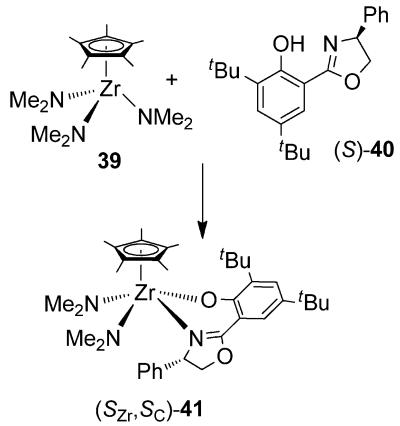
Scheme 7 Separable diastereomeric iron complexes with a chiral bidentate ligand.[22]



Scheme 8 Diastereomeric ruthenium complex with a chiral bidentate ligand.[23]

chelating ligands can give four-legged, half sandwich, chiral-at-metal complexes, even if the other two "legs" of the half-sandwich complex are identical.

Accordingly, when the precursor $[Zr(NMe_2)_3Cp^*]$ (**39**, Cp* = pentamethylcyclopentadienyl) was reacted with the oxazoline-based ligand (*S*)-**40**, the half-sandwich oxazoline complex (S_{Zr},S_C)-$[Zr((S\text{-}\mathbf{40})(NMe_2)_2Cp^*]$ (**41**, which is an example of complex **36** in Fig. 4) was obtained in diastereopure form.[24] This complex features, besides the Cp* ring system, four coordinated donor atoms but is nonetheless stereogenic at the metal (Scheme 9).



Scheme 9 Synthesis of a four-legged half-sandwich complex.[24]

Characterization of chiral-at-metal complexes

Enantiomeric and diastereomeric metal complexes can be characterized in a manner similar to the corresponding organic compounds. As described below, optically pure compounds can racemize or epimerize over time in solution, and consequently, special care must be taken when analyzing data.

Metal complexes that are only stereogenic at the metal center form a pair of enantiomers with identical physical properties. Different enantiomers can be identified by polarimetry, and a pair of enantiomers will give opposite optical rotation.[9,13,18] Circular dichroism (CD) spectroscopy is also commonly applied and the spectra of two enantiomers are mirror images of each other with opposite sign.[18,25] Often, the same absolute configuration is assigned to structurally related compounds with similar CD spectra, and similar compounds with mirror image of CD spectra can exhibit opposite absolute configuration.[5] However, extreme care must be taken as it cannot be generally assumed that similar compounds with the same absolute configuration about the metal give similar CD spectra or the same optical rotation.[26,27] Also, if CD or optical rotation is used to assess optical purity, comparison with an authentic, enantiopure sample must be made. The presence of an optical rotation alone is no sufficient proof for an enantiopure sample, as it also could indicate a scalemic mixture of a pair of enantiomers.[28] Chiral-at-metal complexes are often intensely colored, and in such cases the optical rotation can either be determined only at very high dilutions or not at all.[5] Chiral NMR shift reagents are an alternative to determine the enantiomeric purity of a sample.[29]

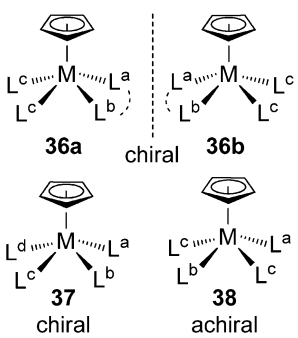


Fig. 4 Representative coordination geometries of four-legged half-sandwich complexes.

The absolute configuration of an enantiopure metal complex can be assigned by X-ray crystallography for crystalline samples.[19] If the absolute configuration is assigned based on X-ray, it is crucial that the crystals were grown from an optically pure sample, whose bulk identity and purity has been established by other spectroscopic methods such as NMR and optical rotation.

Diastereomeric complexes with a stereogenic metal center do have different physical properties and can be analyzed by NMR spectroscopy.[8,19] Typically, the chiral ligands are configurationally stable. In case an enantiopure, chiral ligand was employed in synthesis, two diastereomers form that differ only in the configuration at the metal center. Diastereoisomers that have the opposite configuration at only one of two or more stereocenters are called epimers. If a diastereomeric mixture of complexes is observed by NMR, it can be assumed that it consists of two epimers differing in the absolute configuration at the metal center only. The diastereomeric ratio can be calculated from the intensities of corresponding diastereomeric signals in ^1H or $^{31}P\{^1H\}$ NMR spectra,[8,19] albeit some care has sometimes to be taken when analyzing ^{31}P NMR spectra at low temperatures.[30] In case the absolute configuration of a diastereomer is assigned by X-ray, it is as crucial to grow the crystal from a diastereopure sample. It cannot

generally be assumed that the major diastereomer in a mixture crystallizes out of solution more easily than the minor diastereomer, as what is the most insoluble will precipitate first.[28,31]

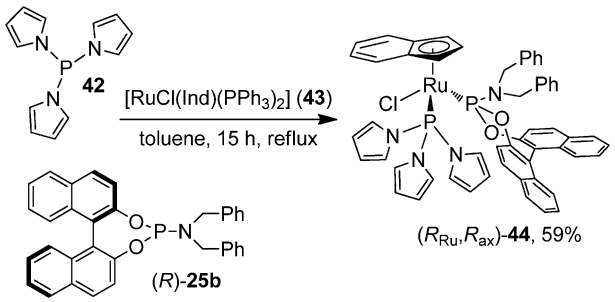
R/*S* Nomenclature

The absolute configuration of a stereogenic metal center is specified in a way similar to chiral organic compounds exhibiting a stereogenic carbon atom following the well-known Cahn–Ingold–Prelog (CIP) priority rules. The problem of assigning priorities to polyhapto ligands, *i.e.* to ligands that bond through more than one atom to a metal center, such as the η^5-cyclopentadienyl ligand (Cp), where five carbon atoms are coordinated to the metal was first addressed by Tirouflet *et al.*[32] He suggested that the sum of the *atomic number* of all atoms of a polyhapto ligand connected to the metal center should be considered. Stanley and Baird later suggested a similar modification of the CIP priority rules to determine the absolute configuration of a stereogenic metal center based on the sum of the *atomic weights* of the atoms in polyhapto ligands coordinated to a metal center.[33] They stated: "*In keeping with the suggestion that polyhapto ligands be assigned high priorities, we suggest that such ligands be considered pseudo-atoms of atomic weight equal to the sum of the atomic weights of all the atoms bonded to the metal atom*".[33] For example, the η^5-$C_5H_5^-$ cyclopentadienyl ligand would be considered a pseudo-atom of molecular weight 60 (five carbon atoms bonded to the metal), and the η^6-C_6H_6 benzene ligand of molecular weight 72 (six carbon atoms bonded to the metal center; *p*-cymene such as in complex **35** in Fig. 8 would be assigned the same molecular weight). As a consequence, the following priority sequence applies:

I > Br > η^6-C_6H_6 > η^5-$C_5H_5^-$ > η^3-$C_3H_3^-$ > Cl > P (such as in PPh_3) > O > (such as in alkoxides) > N (such as in amines or oxazolines) > η^1-C (such as in CH_3)

The determination of *R* or *S* configuration takes place in the same way as for stereogenic carbon atoms applying the CIP rules. In the previous sections, these rules already have been applied and the absolute configurations are given in schemes and figures (*e.g.* for the rhenium complex (*S*)-**13** in Scheme 2).

In metal complexes with more than one stereocenter, they are listed in front of the name or the compound number. Typically the configuration of the metal center is listed first followed by that of the ligand and subscripts are applied for clarification. These rules are exemplified with the ruthenium indenyl complex **44** synthesized by the authors own laboratory in a one pot procedure in 59% isolated yield (Scheme 10).[34] The complex features a chiral phosphoramidite ligand with *R* configuration and is in addition stereogenic at the metal. Only one diastereomer was isolated after workup, as seen by ^{31}P NMR, and the absolute configuration was determined by X-ray. According to the rules, the η^5-$C_9H_7^-$ indenyl ligand has a pseudo molecular weight of 60 (it is bonded through 5 carbons to the metal) and has, thus a higher priority than the chloro ligand. The phosphoramidite ligand (*R*)-**25b** to be employed in the synthesis has a higher priority than the tris(pyrrolyl)phosphine ligand $PPyrl_3$. The priority row is, thus, indenyl > Cl > (*R*)-**25b** > $PPyrl_3$, giving the metal an



Scheme 10 Syntheses of a chiral-at-metal tris(*N*-pyrrolyl)phosphine phosphoramidite complex.[34]

R configuration, which can be denoted either as (R_{Ru},R_{ax})-**44** or as (R_{Ru},R_{ax})-[RuCl(indenyl)**25b**$(PPyrl)_3$].

Racemization and epimerization

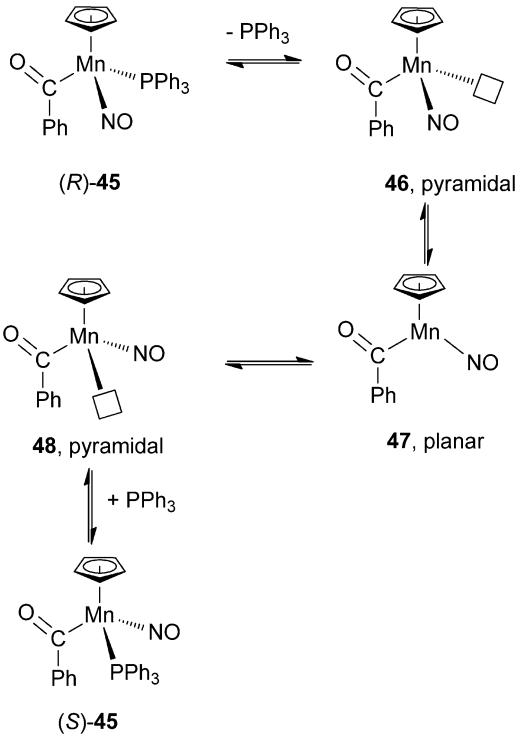
In the solid state, chiral-at-metal complexes are configurationally stable. However, in solution a change in configuration can occur. Metal–ligand bonds tend to be weaker than bonds in purely organic compounds; as a consequence, they could break more easily, leading to isomerization processes.[8]

Chiral metal complexes that are only stereogenic at the metal can racemize over time. Starting with an enantiopure sample, a racemization process eventually leads to a 1 : 1 mixture of the two possible enantiomers (as they are equal in energy). Such racemization processes can be followed by measurements of the optical rotation of a sample, which decreases for configurationally labile complexes in solution over time until it reaches zero for the fully racemized complex.[35]

The complex $[Mn(Cp)(CO)(PPh_3)(NO)]^+PF_6^-$ (**10**) described above (Scheme 1) appeared to be configurationally stable; the optical rotation of a CH_2Cl_2 solution of an enantiopure sample did not change over the course of several weeks.[8] On the other hand, the structurally related complex [Mn(Cp)(COPh)(PPh_3)(NO)] (**45**) racemizes over time, as determined by polarimetric measurements.[35,36] The racemization follows a first order rate law and is slowed after addition of PPh_3 to the sample. These findings suggest a dissociative mechanism as shown in Scheme 11.

First, the PPh_3 ligand leaves to give the pyramidal intermediate **46**, which can isomerize through the planar species **47** to give the enantiomeric pyramidal species **48**. The PPh_3 ligand can subsequently coordinate to the species **45** resulting in an inverted stereochemistry at the metal.

Many isomerization processes in the present context follow a first order rate law, and the half-life $\tau_{1/2}$ is, thus, a good measure to assess the configurational stability (or lability) of a complex.[8] The $\tau_{1/2}$ value can be related to the structure of the corresponding complexes which can, in turn, give important information about the mechanism of the isomerization process. For example, the complex [Mn(Cp)(COPh)(PPh_3)(NO)] (**45**) has a half-life of 50 minutes at 20 °C in toluene (Fig. 5).[36] If CF_3 substituents are present in the *para* position of the phenyl rings of the PPh_3 ligand, the half-life for the racemization process decreases to 5.9 minutes while it increases to 337 minutes, if a OCH_3 group is placed in that position.[8]



Scheme 11 Racemization mechanism.[35,36] The squares denote an open coordination site.

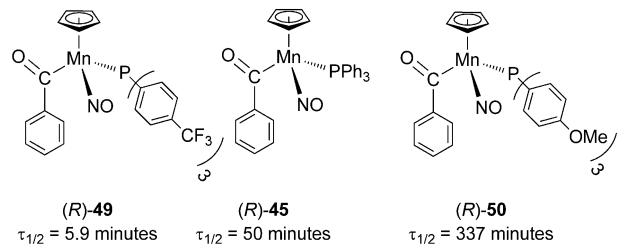
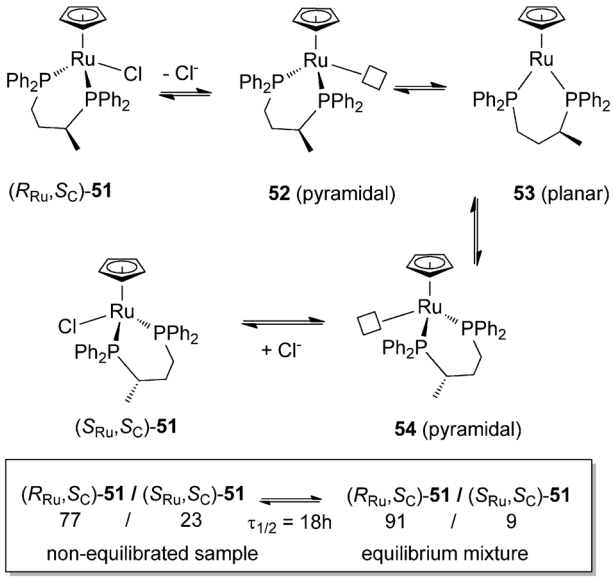


Fig. 5 Half-life of different manganese complexes.[8,36]

Accordingly, the Mn–P bond must be broken in the rate-determining step, as the CF_3 substituent in the *para* position weakens that bond, while the OCH_3 group strengthens it.

As stated previously, chiral ligands are typically configurationally stable. In the case of metal complexes that are stereogenic at the metal and at the ligand, isomerizations typically only take place at the metal, and as outlined above, a pair of epimers results. A configurational change at the metal thus provides the other of two possible epimers, and the process is consequently named epimerization.

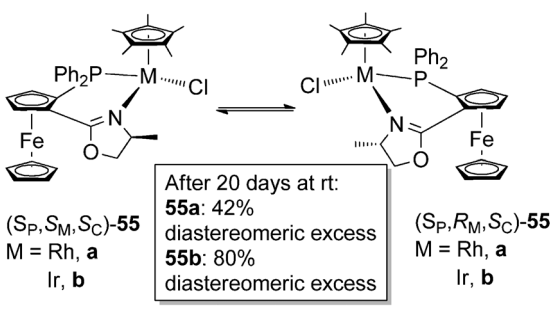
As epimers are diastereomers that differ in their physical properties, epimerization processes can be easily followed by NMR spectroscopy.[8] The process is exemplified with the ruthenium "Chairphos" complex [RuCl(Cp)(Chairphos)] (**51**) reported by Brunner *et al.* (Scheme 12).[37] It was first isolated as a (R_{Ru},S_C)/(S_{Ru},S_C)-**51** 76 : 24 mixture of diastereomers. Two recrystallizations from CH_2Cl_2 gave a sample with a 95 : 5 ratio of (R_{Ru},S_C)/(S_{Ru},S_C)-**51**. The epimerization of a 77 : 23 (R_{Ru},S_C)/(S_{Ru},S_C)-**51** mixture of diastereomers was followed over time by NMR, until a 91 : 9 equilibrium was



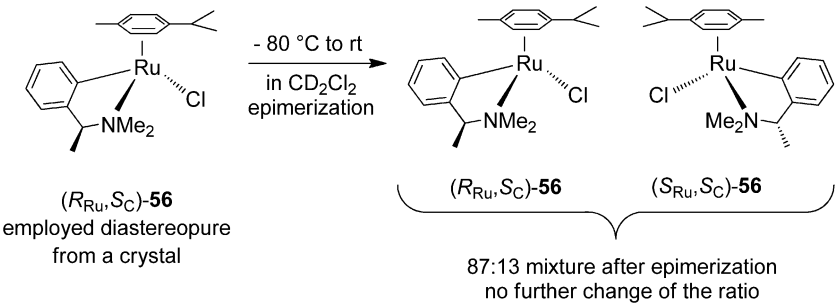
Scheme 12 Epimerization mechanism for complex **51**.[37] The squares denote an open coordination site.

reached at 293 K, leading to a $\tau_{1/2}$ value of 18 h (Scheme 12). The reaction proceeds through a pyramidal intermediate **52** afforded through chloride dissociation from (R_{Ru},S_C)-**51**, which is the rate-determining step of the reaction. Subsequent inversion of the pyramidal intermediate through the planar species **53** gives **54** with inverted stereochemistry at the metal and the chloride coordinates to give the epimer (R_{Ru},S_C)-**51**. The geometry of the cationic intermediates after chloride abstraction is a topic of current research.[38] Cationic main group compounds with three substituents (such as CMe_3^+) are planar, whereas corresponding transition metal species tend, with some exceptions, to be pyramidal. In the case where pyramidal intermediates form, their stability might have an impact on the stereochemistry of ligand exchange reactions. Stable pyramidal intermediates not only would inhibit epimerization processes; they might also promote ligand exchange reactions with retention of absolute configuration.

Similarly, Carmona *et al.* reported the synthesis of the complexes [MCl(C_5Me_5)L] (M = Rh, **55a**; M = Ir, **55b**; L = (*S*)-2-[(S_P)-2-(diphenylphosphino)ferrocenyl]-4-isopropyloxazoline).[39] By fractional crystallization, samples with a diastereomeric excess (de) of 98% were obtained and structurally characterized by X-ray to show an S_M configuration about the metal (Scheme 13). After 20 days at room temperature



Scheme 13 Epimerization at Rh and Ir in half sandwich complexes.[39]



Scheme 14 Epimerization of a diastereomeric ruthenium complex with a chiral bidentate ligand.[31,40,41]

in $CDCl_3$, the diastereomeric excesses decreased to 42% for **55a** and to 80% for **55b**, indicating epimerization at the metal.

Racemization and epimerization processes of new chiral-at-metal complexes should be carefully investigated and documented, as these will have an impact on the enantioselectivities when employed as chiral catalysts in enantioselective organic transformations. In this context, knowledge of the configurational stability (or lability) is a requirement. The configurational stability of complexes can, in fact, only properly be assessed, when potential isomerization processes are monitored over time.[8,35] For chiral metal complexes, that are only stereogenic at the metal, loss of the optical rotation of an enantiopure sample in solution indicates configurational instability and can be quantified by $\tau_{1/2}$ values.

For diastereomeric complexes with stereogenic centers at the metal and at the ligand, potential epimerization processes can be followed over time in solution by NMR spectroscopy to give information about configurationally stability.[8] Here, it is important to use non-equilibrated diastereomeric mixtures of complexes for investigations in order to avoid wrong conclusions, as exemplified by the complex **56** (Scheme 14) published by Nelson *et al.*[40] It was originally reported to form under *kinetic* control (*i.e.* one epimer forms faster than the other one and do not interconvert); a $CDCl_3$ solution was reported to contain the two epimers (R_{Ru},S_C)-**56** and (S_{Ru},S_C)-**56** in an 83 : 17 ratio.[31] However, Brunner and Zwack repeated the synthesis of this complex and obtained crystals, that at −80 °C in CD_2Cl_2 showed only (R_{Ru},S_C)-**56** in the NMR spectrum.[31] Upon warming of the solution to room temperature, the other epimer (S_{Ru},S_C)-**56** appeared in the spectrum. Thus, the complex at or near room temperature is configurationally not stable, as epimerization of the diastereopure sample leads to the appearance of the other isomer (a configurationally stable compound would not epimerize at all). Consequently, the 83 : 17 mixture of epimers observed in the NMR spectrum at room temperature is the product of a thermodynamically driven reaction, and at room temperature the two epimers exist in a dynamic equilibrium. After Brunner published his findings, Hansen and Nelson revoked his previous statement that the mixture obtained during synthesis was a product of kinetic control and that the complex is configurationally stable.[41]

If repeated attempts to separate two diastereomers fail, it is possible that the corresponding metal complex is configurationally not stable and continually reestablishes or keeps its thermodynamic equilibrium. On the other hand, a diastereomeric mixture that does not change its composition at different temperatures is not necessarily configurationally stable, if a thermodynamically equilibrated sample was used for investigations.[31]

Octahedral complexes with linear polydentate ligands that are stereogenic at the metal

The synthesis and fundamental properties of chiral-at-metal complexes were exemplified in the previous sections with half-sandwich complexes, which are very common. There are octahedral, organometallic architectures without η^5 or η^6 aryl ligands that are also stereogenic at the metal; their coordination chemistry is somewhat more complex than that of the half-sandwich complexes explained above. Only a few representative examples are described in this section; interested readers are referred to more comprehensive review articles that have previously appeared in the literature.[7,10,42]

As shown in Fig. 6, linear, tetradentate donor molecules can coordinate to an octahedral metal center in different ways. The *trans* coordination mode is achiral, whereas the *cis*-α and *cis*-β isomers exist as a pair of enantiomers that are stereogenic at the metal.[42] Additional isomers are possible if the ligands L are not identical. Bidentate ligands can give similar isomers, and show an even more complex structural diversity.

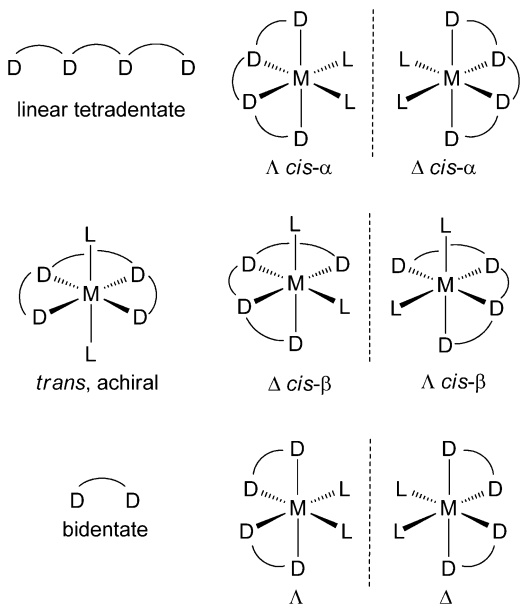


Fig. 6 Coordination modes for linear, multidentate ligands.

Isomerization processes between the isomers have been documented,[42] which reveal a rich coordination chemistry of these architectures.

Linear, tetradentate or bidentate ligands in the *cis*-α and *cis*-β configuration arrange around the metal in a helical manner, rendering the molecules chiral, and the metal atom can be considered as a stereogenic center.[43] The stereochemical specification is based on the orientation of the helices, and are termed Δ and Λ as shown in Fig. 6.[44] The Δ and Λ isomers are non-superimposable mirror images and are, thus, a pair of enantiomers.

As for the half sandwich complexes described previously, the multidentate ligands to be employed in synthesis can be achiral or chiral. In case achiral ligands are utilized, the Δ and Λ enantiomers form in a 1 : 1 ratio. The isomers can be resolved utilizing a chiral auxiliary. Most frequently, a cationic complex is treated with a chiral anion to form diastereomeric ion pairs; fractional crystallization of these ion pairs affords optically pure diastereomeric salts, and the anionic auxiliary can subsequently be removed by anion exchange to afford the optically pure metal complex.

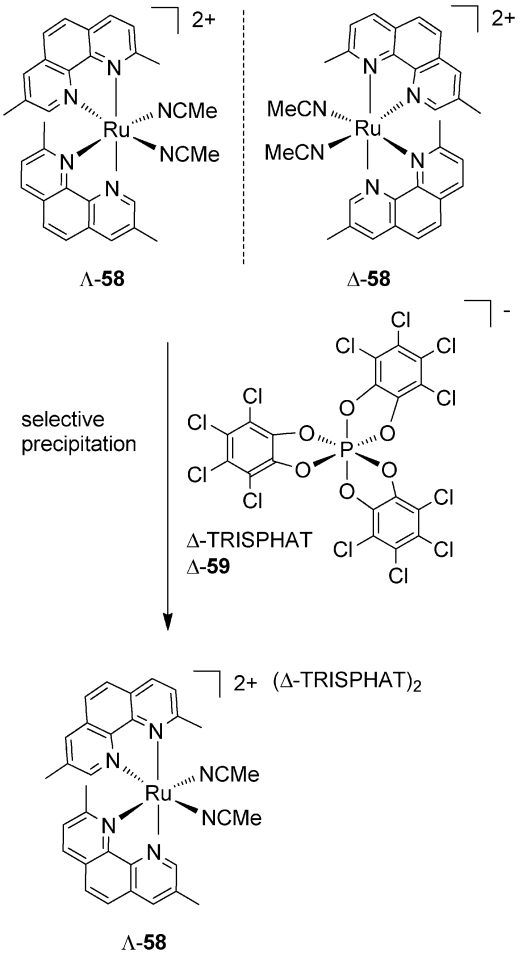
Fontecave *et al*. applied this principle to resolve a racemic mixture of a ruthenium phenanthroline complex utilizing the chiral TRISPHAT counterion **59**$^-$ (Scheme 15).[45] The ruthenium complex **58**$^{2+}$(PF$_6^-$)$_2$ is stereogenic at the metal and bears the achiral, bidentate phenanthroline ligand 2,9-dimethyl-1,10-phenanthroline. When a racemic mixture of this complex was treated with the chiral salt [*n*-Bu$_3$NH]$^+$ [Δ-TRISPHAT]$^-$, a yellow precipitate immediately formed, that consisted of the heterochiral, diastereomeric ion pair [Λ-**58**][Δ-TRISPHAT]$_2$. The other TRISPHAT isomer Λ-**59** forms a precipitate with Δ-**58**, allowing for resolution of a racemic mixture of **58**.This class of complexes was demonstrated to be catalytically active in chiral sulfide oxidation reactions employing H_2O_2 as the oxidant, albeit with low enantiomeric excesses.[45]

In the case where chiral ligands are employed, separable epimers can form that differ only in the configuration at the metal. Sometimes, one epimer forms almost exclusively. Meggers *et al*. showed that the diastereopure complex Λ-(*R*)-**61** could be accessed in a one-pot reaction of commercial [Ru(η^6-C$_6$H$_6$)Cl$_2$]$_2$, 2,2′-bipyridine and the bidentate chiral diphenylphosphino hydroxyl ligand (*R*)-**60** (Scheme 16).[46] The Λ isomer formed almost exclusively, and the complex Λ-(*R*)-**61** was isolated in 84% yield in a 34 : 1 diastereomeric ratio. Thus, the chiral ligand determined the absolute configuration at the metal, and such selectivities are currently under intense investigation as reflected in the number of recent publications on this topic.[10,42]

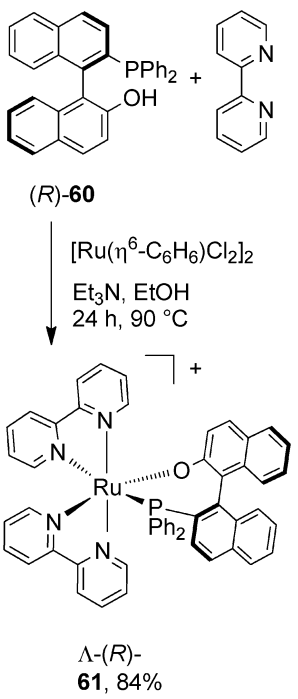
The architectures described in this section might find application in areas other than catalysis. They are also of interest in a bioinorganic and medicinal context,[3] as selective recognition of biomacromolecules such as proteins or nucleic acids is possible.[10] For example, Meggers *et al*. reported that ruthenium complexes similar to **61** are selective inhibitors of protein kinases.[47]

Applications in catalysis

The employment of chiral-at-metal complexes in catalysis is somewhat less common than that of other chiral organometallic



Scheme 15 Resolution of a racemic mixture of ruthenium complex **58** by precipitation with the chiral counterion TRISPHAT.[45]

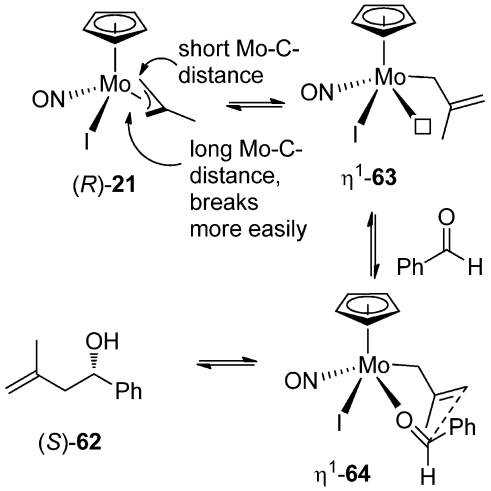


Scheme 16 Selective synthesis of complex Λ-(*R*)-**61** employing the chiral ligand (*R*)-**60**.[46]

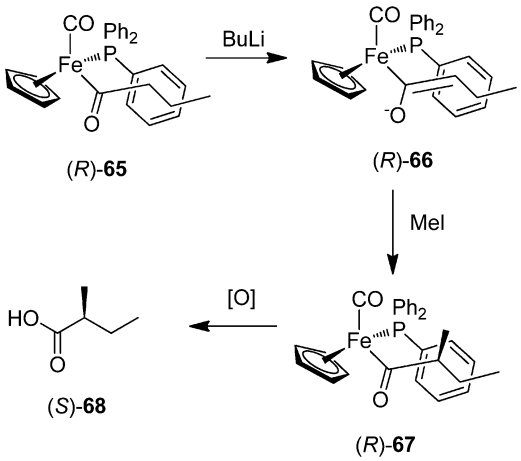
architectures, where the chiral information is located at the ligand. However, chiral-at-metal complexes can provide a unique electronic or steric environment about the metal center, which is crucial for the production of enantiomeric excesses in catalyzed organic transformations.

The principle of "electronic differentiation" can be exemplified by the reactivity of the molybdenum η^3-methallyl complex (*R*)-**21** reported by Faller; its preparation was described above (Scheme 4). As shown in Scheme 17, (*R*)-**21** reacts in a stoichiometric reaction with benzaldehyde to give the chiral alcohol (*S*)-**62** with 90 to >98% enantiomeric excess.[18] Mechanistically, the reaction was suggested to proceed through a η^1-methallyl intermediate **63** that opens a coordination site at the metal, where the benzaldehyde can coordinate through the carbonyl oxygen atom. As there are four different ligands in the coordination sphere, the distances between the molybdenum center and the two terminal carbon atoms of the methallyl ligand are not of equal length, as revealed by X-ray diffraction; the Mo–C bond *cis* to the halide is much longer than the Mo–C bond *cis* to the NO ligand. Consequently, the Mo–C-bond *cis* to the halide breaks more easily to form the η^1 intermediate **63**. It features an open coordination site with a unique steric environment at the stereogenic metal center; the incoming benzaldehyde can approach the methallyl ligand only from one face (**64**), which predetermines the stereochemical outcome of the reaction. As stated by Faller, *the stereochemistry of the products is controlled by the electronic asymmetry at the metal center rather than by the steric effects of the aldehyde substituents*.

Steric factors of chiral-at-metal complexes can also give high stereoselection when employed in organic syntheses. Chiral-at-metal iron acetyl complexes such as (*R*)-**65** have been extensively used as chiral auxiliaries in stoichiometric, enantioselective aldol-type alkylation reactions (Scheme 18).[48] As shown by the solid state structure, one of the phenyl rings of the PPh_3 ligand is arranged approximately parallel to the acetyl ligand. As shown in Scheme 18, the coordinated acetyl unit can be deprotonated with BuLi at −78 °C to afford the corresponding enolate (*R*)-**66**. In this enolate, one face is more



Scheme 17 Reactivity of complex (*R*)-**21**. The square in **63** denotes an open coordination site.[18]



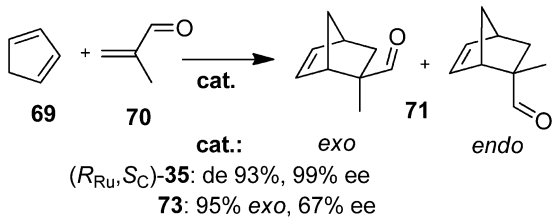
Scheme 18 Reactivity of complex (*R*)-**65**.[48]

efficiently shielded by one of the phenyl rings of PPh_3 than the other. Consequently, subsequent alkylation with E^+ (such as MeI) takes place selectively from the sterically less hindered side to give the corresponding methylated iron complex (*R*)-**67**, which is typically obtained as a single diastereomer, as shown by NMR spectroscopy. Oxidative cleavage of the alkylated acyl group afforded the corresponding alkylation products (such as the acids) in high enantiomeric excesses. A range of acyl ligands and alkylating agents can be employed in synthesis, and a wide variation of products can be accessed in high stereoselectivity.

Diels–Alder reactions[49] were reported to be efficiently catalyzed by chiral-at-metal complexes in a stereoselective manner. The reaction between cyclopentadiene **69** and methacrolein **70** gives the corresponding Diels–Alder product **71** (Scheme 19). The adduct can exhibit *exo* and *endo* configuration (which are diastereomers), each of which exists as a pair of enantiomers. Consequently, "double selectivity" is required in order to obtain a single, optically pure product.

After chloride abstraction with $AgSbF_6$, the ruthenium complex (R_{Ru},S_C)-$[RuCl(p\text{-cymene})(BINPO)]^+SbF_6^-$ (**35**, Scheme 8) was reported by Faller *et al.* to selectively catalyze the reaction at −78 °C to afford the Diels–Alder product **71** quantitatively with a diastereomeric excess of 93% in favor of the *exo* adduct and an enantiomeric excess of 99%.[23] When the chiral complex $[RuCl(p\text{-cymene})(S)\text{-BINAP}]^+SbF_6^-$ was employed for the reaction under identical conditions, an enantiomeric excess of only 19% was observed. Complex $[RuCl(p\text{-cymene})(S)\text{-BINAP}]^+SbF_6^-$ is not stereogenic at the metal and the chiral-at-metal complex (R_{Ru},S_C)-$[RuCl(p\text{-cymene})(BINPO)]^+$ is, thus, a more efficient catalyst for that reaction. The catalyst activates the aldehyde by coordination of the carbonyl oxygen atom. The stereogenic metal center appears to create a unique steric environment for the aldehyde adduct **72** as shown in Fig. 7. The binaphthyl and aryl rings block one face of the coordinated aldehyde more efficiently, which is approached by the cyclopentadiene from the opposite side. Thus, the stereogenic metal center provides an organized, well-defined catalyst–substrate structure.

Carmona *et al.* reported a series of iridium and rhodium phosphinooxazoline (PHOX) complexes of the general formula



Scheme 19 Diels–Alder-reaction.[23,26,50]

$[MCp^*Cl(PHOX)]^+SbF_6^-$ to be catalytically active in the Diels–Alder reaction.[26,50] The complexes were isolated as a mixture of epimers. After abstraction of the chloro ligand, the complexes catalyzed the reaction between methacrolein **70** and cyclopentadiene **69** to give the adduct **71** in 75–100% yield; the *exo* isomer was formed in 81–95%, and the enantiomeric excesses ranged from 4 to 67%. Again, the unique steric environment about the metal centers accounted for the stereoselection. The methacrolein coordinates s-*trans* type to the metal center (**73** in Fig. 7), and one face of the coordinated unit is more efficiently shielded by the oxazoline ligand than the other.[26]

The related 1,3-dipolar cycloaddition reaction between α,β-unsaturated aldehydes **74** and nitrones **75** to give isoxazolidine **76** can also be catalyzed by chiral-at-metal complexes, as investigated by Carmona and Lamata.[51,52] One example is shown in Scheme 20. The catalyst activates the aldehyde substrate through coordination, and makes it more susceptible towards attack by the nitrone. The cationic complexes (S_M,R_C)-$[M(\eta^5\text{-}C_5Me_5)(enal)(Prophos)]^+$, (S_M,R_C)-**77** (M = Rh, Ir) were found to be catalytically active in the transformation, with yields between 18 and 100% and enantiomeric excesses ranging from 66 to 94%. As shown for the rhodium complex **78**, the chiral pocket around the stereogenic metal center coordinates the unsaturated aldehyde substrate in an organized way: it takes a s-*trans* conformation and an *E*-configuration about the C=O bond; in addition, rotation about the M–O bond is restricted.[52] The highly organized catalyst–substrate adduct might be responsible for the high enantioselectivities obtained for the transformation. Structurally related

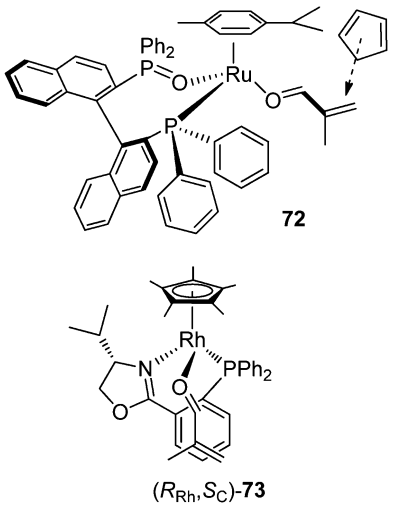
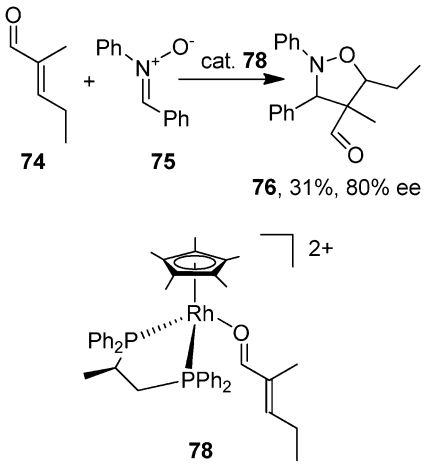


Fig. 7 Catalyst substrate complexes for chiral-at-metal Diels–Alder catalysts.[23,26]

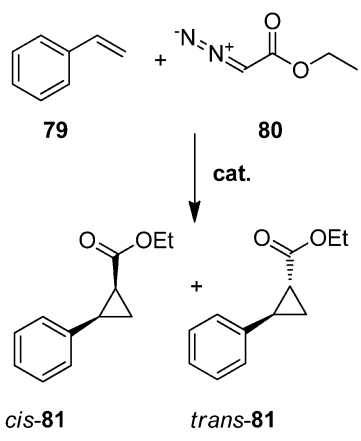


Scheme 20 1,3-Dipolar cycloaddition reaction between α,β-unsaturated aldehydes and nitrones.[51,52]

α,β-unsaturated nitrile complexes were reported by the same authors to catalyze the addition of nitrones to α,β-unsaturated nitriles.[53]

Ruthenium phosphinooxazoline complexes were demonstrated to be catalytically active in the asymmetric cyclopropanation of styrene **79** with ethyl diazoacetate **80** to obtain *cis* and *trans* isomers of cyclopropane **81**, as reported by López *et al.* (Scheme 21).[54] For example, the CH_3CN complex **82** (Fig. 8) was obtained as a single stereoisomer, but the absolute configuration about the metal center could not be established. After activation with AgOTf (OTf = $CF_3SO_3^-$), the complex catalyses the cyclopropanation of styrene with up to 74% *cis* selectivity and an enantiomeric excess of up to 68% for the *cis* isomer.

Scott *et al.* showed that for the same cyclopropanation reaction, a chiral-at-metal ruthenium complex bearing the tetradentate ligand (*R*)-**83** was also catalytically active for that reaction.[55] The ligand shown in Fig. 8 coordinates to the ruthenium center to give (*R*)-β-*cis*-[Ru(**83**)$(CH_3CN)_2$]; the coordination geometry of the *cis*-β isomer was shown earlier



Scheme 21 Cyclopropanation reactions.[54,55]

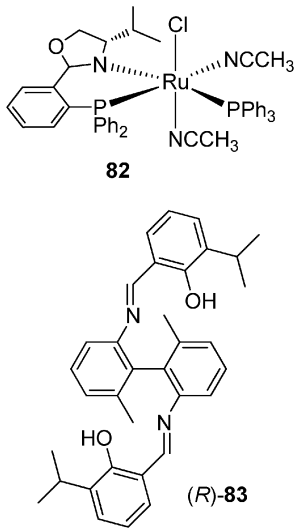
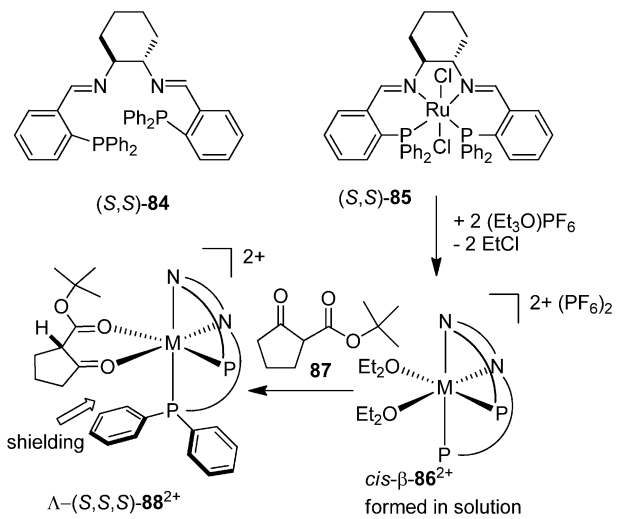


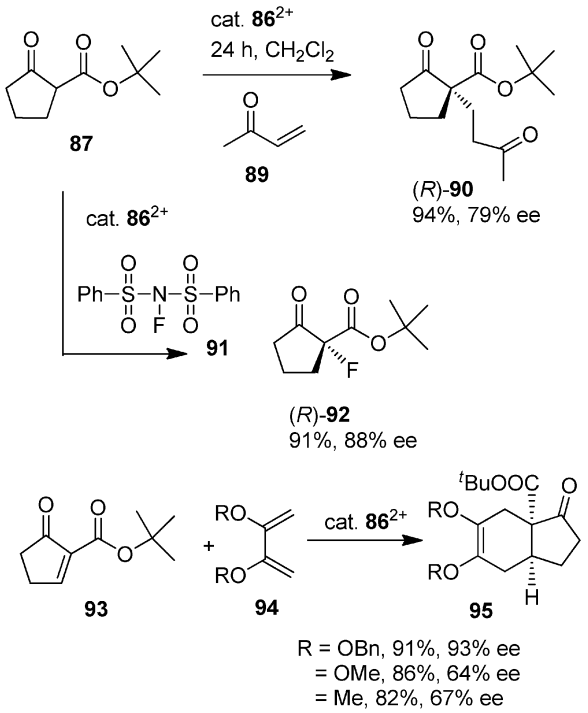
Fig. 8 Complex **82** and ligand (*R*)-**83** employed in cyclopropanation reactions.[54,55]

in Fig. 6. This complex catalyzes the cyclopropanation of styrene with ethyl diazoacetate in 94% yield; the product contained 98% of the *trans* isomer with an enantiomeric excess of 95% (Scheme 21). Scott identified electronic factors for the selective binding of the ethyldiazo acetate to the metal center, which predetermined the stereoselectivity of the reaction.

Another tetradentate ligand was employed by Mezzetti in a variety of catalytic applications (Scheme 22).[56] The tetradentate PNNP ligand (*S*,*S*)-**84** can be employed in the synthesis of the ruthenium complex (*S*,*S*)-[$RuCl_2$(**84**)] (**85**).[56] This complex is not chiral at the metal, but chiral at the ligand. The complex changes from the *trans* to the *cis* configuration when the two chloro ligands are removed by the chloride scavenger $(Et_3O)PF_6$ to afford *cis*-β-[$Ru(Et_2O)_2$(**84**)]$^{2+}$ $(PF_6)_2$ (**86**$^{2+}$).[57] The two coordination sites formerly occupied by the chloro ligands now bear Et_2O from the chloride scavenger. The complex **86**$^{2+}$ can bind 2-*tert*-butoxycarbonylcyclopentanone **87** in its non-enolized form to give the complex



Scheme 22 Chiral-at-metal ruthenium complex **86**$^{2+}$ created by double chloride abstraction.[56]



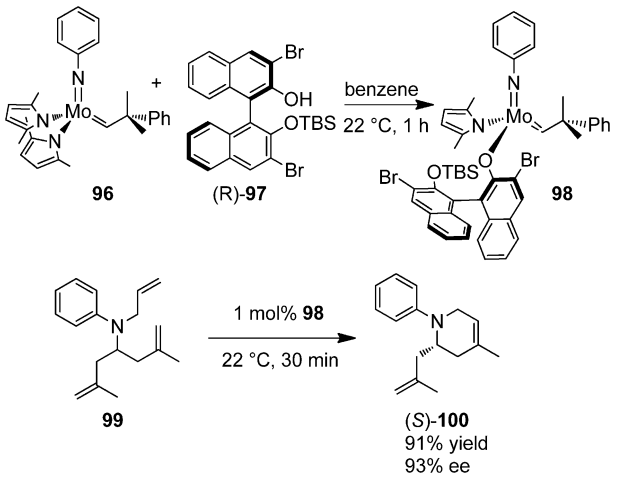
Scheme 23 Catalytic application of the chiral-at-metal complex **86**$^{2+}$ in a variety of transformations.[57–59]

(Λ)-(*S*,*S*,*S*)-[Ru(**84**)(**87**)]$^{2+}$ $(PF_6)_2$ (**88**$^{2+}$).[58] This complex is chiral-at-metal and it activates 2-*tert*-butoxycarbonylcyclopentanone **87** for further transformations.

The dicationic complex **86**$^{2+}$ can be generated in solution and is catalytically active in a variety of asymmetric transformations of 1,3-dicarbonyl compounds (Scheme 23).[56] Examples include the Michael addition[58] of **87** to methyl vinylketone **89** to give the aldol adduct (*R*)-**90** and the fluorination of **87** with *N*-fluoro-*N*-(phenylsulfonyl)benzenesulfonamide **91** to give **92**.[57] Diels–Alder reactions between the unsaturated dicarbonyl compound **93** and a variety of dienes **94** are also catalyzed by **86**$^{+}$ (examples are shown in Scheme 23).[59] The high enantiomeric excesses were attributed to the fact that one face of the coordinated dicarbonyl compound is more efficiently shielded by the PPh_2 group than the other one, as indicated for Λ-(*S*,*S*,*S*)-**88**$^{2+}$ in Scheme 22.[56]

Latest development: configurationally stable tetrahedral complexes for enantioselective metathesis reactions

The principles explained in the previous sections are finally demonstrated with the latest development in the field. The alkene metathesis reaction is a powerful C–C bond forming reaction. Ring closing metathesis (RCM) especially is widely used in organic synthesis, and ruthenium and molybdenum catalysts have been developed for the reaction. However, enantioselective metathesis reactions are still the objective of current research. Hoveyda and Nobel laureate Schrock developed a chiral-at-metal molybdenum catalyst to promote the reaction enantioselectively.[4] When the bis-pyrrolide complex **96** was treated with the chiral and enantiopure alcohol (*R*)-**97**,



Scheme 24 Chiral-at-metal molybdenum complex and catalytic activity in ring closing metathesis (RCM).[4]

the chiral-at-metal complex **98** was obtained with 95% conversion in a 7 : 1 diastereomeric ratio; the identity of the major diastereomer was established by X-ray diffraction (Scheme 24). Complex **98** is in the present context remarkable. It features only monodentate ligands in its coordination sphere, but is nevertheless configurationally stable and was obtained in enantiomerically enriched form. This complex catalyzed the RCM reaction of the substrate **99** to obtain the cyclized product (*S*)-**100** in 91% isolated yield and 93% enantiomeric excess (Scheme 24, bottom). The monodentate ligands provide an asymmetric electronic environment and are flexible enough to accommodate trigonal–bipyramidal intermediates, which were proposed during the course of the reaction. The chiral-at-metal complex **98** is superior over other catalytically active complexes where the chiral information is located at the ligands. These findings outline again the great potential of complexes with stereogenic metal centers.

Conclusion

This tutorial review provided an overview of the synthesis, characterization, properties and the catalytic application of complexes that are stereogenic at metal. Such complexes are still underexplored. However, the organometallic community has started to recognize the great potential in enantioselective catalysis. The synthesis of these unique architectures has made great progress in the past, and should and will be explored in more depth in the future. The pool of readily available chiral-at-metal complexes must become somewhat more diverse in the future.

The systems presented herein produce a minimum of stereoisomers, and future developments in the area should focus on such relatively simple systems. As potential isomerization processes at the metal center pose a problem, novel architectures should be carefully designed to suppress or minimize the configurational lability of the complexes. This can be accomplished either by using sterically demanding ligands (such as in Scheme 5) or by investigating chelate complexes (such as in Scheme 12).

There are already a number of catalytic processes known to be promoted by chiral-at-metal complexes, and this number will grow once more suitable complexes are synthetically available. This article is meant to inspire researchers at all levels of their career to also consider the title compounds in their own research. The preliminary data are promising and are hopefully a driving force to further investigate these interesting and challenging systems.

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