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Asymmetric Synthesis of Octahedral Coordination Complexes

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In memory of the 100th anniversary of metal-centered chirality manifested by Alfred Werner

Keywords: Chirality / Asymmetric synthesis / Coordination modes / Octahedral complexes / Ligand design

In contrast to stereoselective organic chemistry, which has established sophisticated synthetic strategies to control the relative and absolute configuration at tetrahedral carbon atoms, the stereochemical control of octahedral coordination spheres is much less understood. This microreview reflects on the state of the art of asymmetric coordination chemistry of octahedral complexes within the historical context, including asymmetric coordination chemistry evolved by nature, the predetermination of metal-centered chirality with tailored chiral ligands, chiral-anion-mediated asymmetric synthesis, chiral-auxiliary-mediated asymmetric coordination chemistry, and finally, very recent work on the catalytic asymmetric synthesis of an octahedral coordination complex. The stereocontrolled synthesis of octahedral metal complexes is an important problem of contemporary coordination chemistry and will ultimately provide the necessary synthetic tools to fully exploit the opportunities provided by the rich stereochemistry of octahedral coordination geometries.

1. Introduction

It is now 100 years ago that Alfred Werner experimentally demonstrated for the first time the existence of metal-centered chirality.[1,2] In 1911, Werner reported the resolution of the enantiomers of the octahedral coordination compounds $[Co(en)_2X(NH_3)]^{2+}$ (**1**), X = Cl or Br, en = ethylenediamine, into their individual mirror-imaged Δ- and Λ-enantiomers (right and left-handed propeller twist, respectively), verified their predicted optical activities, and a few years later extended this validation to the carbon-free tetranuclear complex $[Co_4(NH_3)_{12}(OH)_6]^{6+}$ (**2**) (Figure 1).[1,3] These studies regarding the absolute stereochemistry of metal complexes represented a final powerful evidence to validate Werner's coordination theory, since there was no satisfactory alternative explanation for the existence of the observed metal-centered chirality other than arranging the ligands in an octahedral fashion around the central metal ion.

The fascination for the octahedral geometry of six-coordinate metal complexes does not only arise from the aesthetic beauty of the octahedron as a platonic solid, but is rather founded in its stereochemical complicatedness. In fact, an octahedral coordination compound possessing six individual monodentate ligands, as shown for complex **3** in Figure 1, can adopt the incredible number of up to 30 individual stereoisomers (15 diastereomers as pairs of enantiomers).[4] Although this elaborate octahedral stereochemistry is a constant curse for experimental coordination chemists, it ultimately promises enormous opportunities in the fields of catalysis,[5] materials science,[6] and the life sciences.[7] In the life sciences, for instance, octahedral coordination compounds have been established as powerful structural scaffolds for the selective recognition of nucleic acids[8,9] and proteins[10,11] by exploiting the globular nature and stereochemical options of octahedral compounds. As an illustration, the rhodium complex Δ-(*R*,*R*)-**4** was demonstrated by Barton and co-workers to be a sequence-selective

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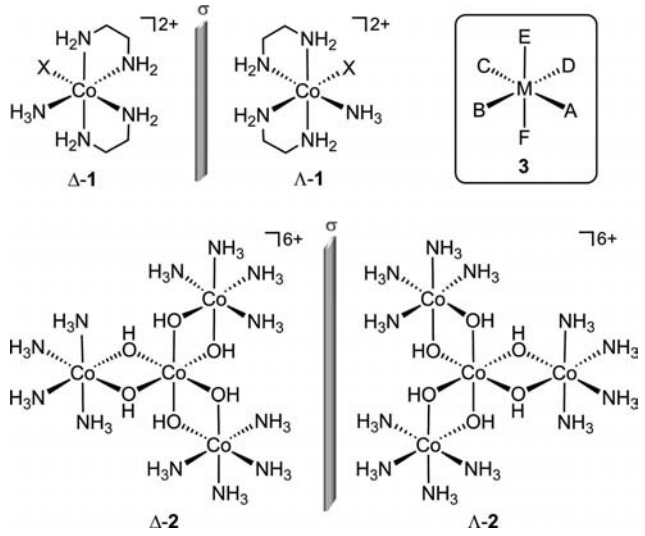

Figure 1. Alfred Werner's discovery of optically active octahedral coordination compounds by the resolution of $[Co(en)_2X(NH_3)]^{2+}$ (**1**) (X = Cl, Br; en = 1,2-ethylenediamine) into their Δ- and Λ-enantiomers. The tetranuclear complex $[Co_4(NH_3)_{12}(OH)_6]^{6+}$ (**2**) was the first example of an optically active coordination complex devoid of any carbon atoms.

DNA intercalator (Figure 2a),[12] whereas Meggers et al. recently reported the optically active ruthenium complex Λ-**5** as a highly potent and selective inhibitor of the protein kinase GSK3 (Figure 2b).[13]

In comparison to organic compounds, for which the established sophisticated synthetic strategies of organic chemistry can be used to control the configuration at tetrahedral carbon atoms, the stereochemistry of octahedral coordination compounds is much less understood. Clearly, a strong demand exists for general synthetic methods to control relative and absolute stereochemistry at octahedral metal centers – if possible simultaneously – in order to take full advantage of the stereochemical richness of six-coordinate coordination compounds. This review will reflect on the state of the art of asymmetric coordination chemistry of octahedral complexes within the historical context, including highly diastereoselective reactions to control the metal-centered chirality, emerging tools of chiral-auxiliary-mediated synthesis, and, finally, very recent work on the catalytic asymmetric synthesis of coordination compounds.

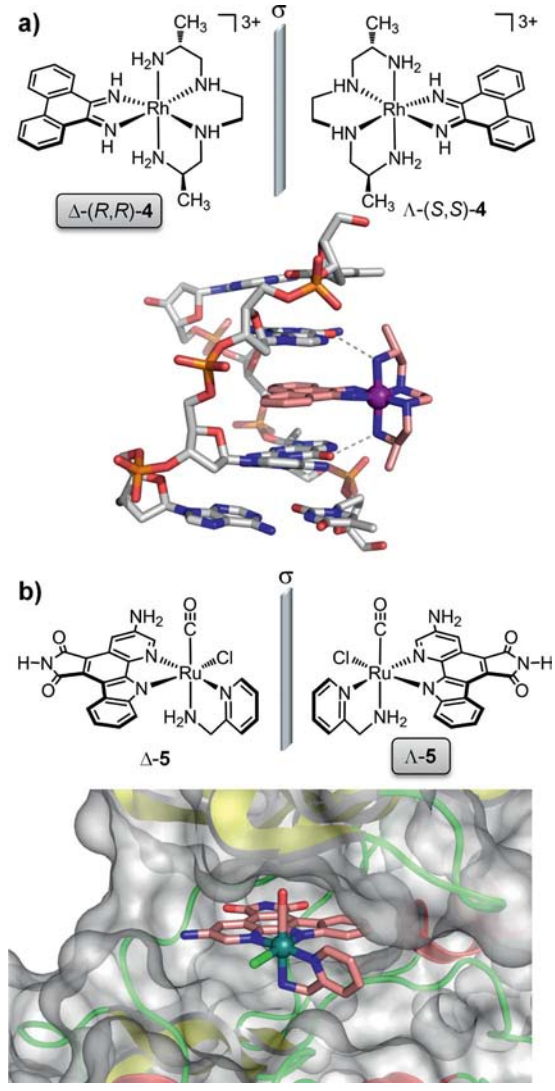

Figure 2. Selective molecular recognition of chiral octahedral coordination compounds by biomacromolecules. (a) The rhodium complex Δ-(*R*,*R*)-**4** is a sequence-selective DNA intercalator. Shown is also the intercalation of Δ-(*R*,*R*)-**4** between two GC base pairs of a duplex DNA segment (PDB code 454D). (b) The ruthenium complex Λ-**5** is a potent and selective inhibitor of glycogen synthase kinase 3 (GSK3) in contrast to the almost inactive mirror-image complex Δ-**5**. Shown is also the binding of Λ-**5** to the active site of GSK3 (PDB code 3PUP).

2. Controlling Metal-Centered Chirality with Chiral Ligands

Excellent reviews covering the control of the metal-centered configuration with chiral coordinating ligands – leading to diastereoselective coordination chemistry – are available.[14] Here, only some selected aspects including historical work, examples of asymmetric coordination chemistry applied by nature, and recently designed tailored chiral ligands that provide efficient control of the metal-centered configuration will be discussed. It is also important to note that several mechanisms exist for diastereoselectivity in coordination chemistry, ranging from thermodynamic and kinetic control to solubility differences of diastereomers. The mechanisms will be emphasized wherever possible.

2.1 Smirnoff's First Report of Chirality Transfer from a Stereogenic Carbon to a Metal Center

The first reported asymmetric synthesis of a chiral coordination compound can be traced back to work by Alexander P. Smirnoff, research that apparently was executed in large parts in Werner's laboratory.[15] In 1920, Smirnoff described the reaction of enantiomerically pure propane-1,2-diamine (pn) with H_2PtCl_6 in EtOH under reflux to form

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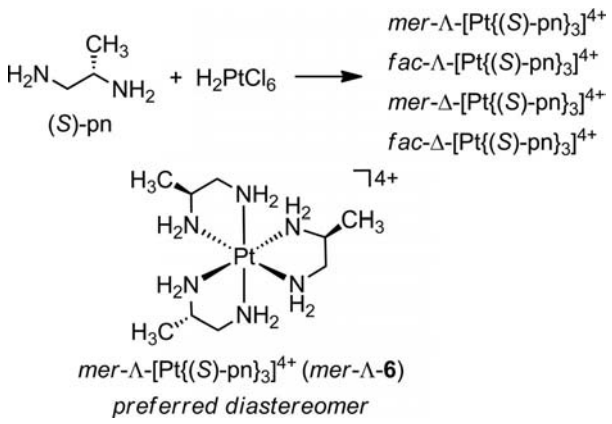
octahedral complexes and concluded from the analysis of the optical rotations that the reaction occurred diastereoselectively. A. von Zelewsky carefully reinvestigated this reaction 85 years later and confirmed that the reaction of (*S*)-pn with H_2PtCl_6 indeed leads to the favored formation of *mer*-Λ-[Pt{(*S*)-pn}$_3$]$^{4+}$ (*mer*-Λ-**6**) out of four possible diastereomers (Scheme 1), albeit with a very modest diastereoselectivity, which, however, could be further improved by precipitation and crystallization steps.[16] Thus, the work by Smirnoff can be considered the first report of an asymmetric synthesis of a chiral octahedral metal complex by transfer of chirality from a stereogenic carbon to a metal center.



Scheme 1. Smirnoff's first report of an asymmetric coordination reaction which was later reinvestigated in detail by von Zelewsky.

2.2 Asymmetric Coordination Chemistry Evolved by Nature

Nature has learned to master the control of metal-centered chirality already millions of years ago. For example, siderophores – microbial iron chelators that facilitate iron acquisition and transport – coordinate iron with high affinity and predetermined chirality.[17] One of the best understood siderophores, enterobactin, coordinates Fe^{III} in a hexadentate fashion through three catecholates that are connected by amide linkages to a cyclic tri(L-serine) lactone (Figure 3a).[18] The iron(III)–enterobactin complex is optically active and possesses the Δ-configuration, as has been revealed by CD spectroscopy. The crystal structure of a vanadium(IV)–enterobactin complex is shown in Figure 3a and is considered a closely representative model of the ferric enterobactin complex.[19] In this model structure, the vanadium ion is coordinated in the Δ-configuration and has a geometry that is intermediate between trigonal prismatic and octahedral. The preference for the Δ-isomer in metal–enterobactin complexes can be explained by the preferred conformation of the chiral trilactone backbone, mediated to the catecholate ligands through three intramolecular hy-

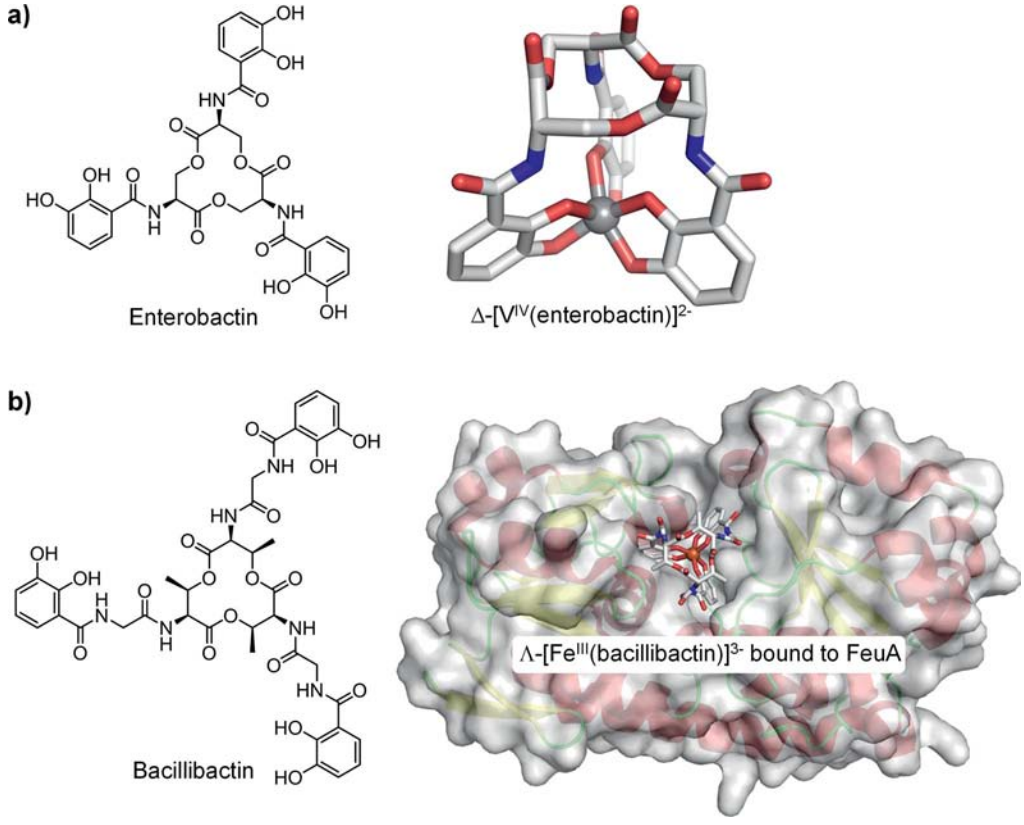


Figure 3. Siderophores as natural iron chelators that coordinate iron(III) in an asymmetric fashion. (a) Enterobactin and the corresponding structure of the chiral complex Δ-[V^{IV}(enterobactin)]$^{2-}$, which is considered a model for the analogous Fe^{III} complex. (b) Bacillibactin and the corresponding chiral complex Λ-[Fe^{III}(bacillibactin)]$^{3-}$ bound to the siderophore binding protein FeuA (PDB code 2WHY). Water molecules are omitted.

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drogen bonds between amide protons and catecholate oxygen atoms.

Interestingly, while enterobactin forms the Δ-ferric complex, the closely related siderophore bacillibactin (corynebactin) possesses the Λ-configuration (Figure 3b).[20] Bacillibactin is built from a trilactone out of three L-threonines which are linked to three catechole amides through glycine spacers. These structural changes relative to enterobactin are sufficient to switch the predetermined chirality of the ferric complex. A recently reported cocrystal structure of $[Fe^{III}$(bacillibactin)$]^{3-}$ bound to the siderophore-binding-protein FeuA revealed that FeuA specifically recognizes the left-handed propeller (Λ-configuration) of the ferric tris(catecholate) complex (Figure 3b).[21] Interestingly, FeuA is even capable of switching the metal-centered configuration of ferric tris(catecholate) complexes: the ferric complex of enterobactin which adopts the Δ-configuration in solution binds to FeuA in its energetically unfavorable Λ-configuration.

2.3 Predetermining Metal-Centered Configuration with Tailored Chiral Ligands

Nature's strategy to control metal-centered configuration with chiral multidentate ligands has been mimicked by synthetic chemists. In pioneering work, von Zelewsky developed terpene-derived chiral tetradentate bis(2,2′-bipyridine)s – so called CHIRAGENs (from CHIRAlity GENerator) – to generate the metal stereogenic center in a completely asymmetric fashion. For example, the reaction of (+)-chiragen[6] with $[Ru(DMSO)_4Cl_2]$, which was first converted in situ into $[Ru(MeCN)_4Cl_2]$, followed by the reaction with 4,4′-dimethyl-2,2′-bipyridine (Me_2bpy) and workup, afforded the complex Δ-[Ru{(+)-chiragen[6]}(Me_2bpy)]-$(CF_3SO_3)_2$ (Δ-**7**) as a single diastereomer, albeit in low yields of only 25% (Scheme 2a).[22] Geometrical and conformational constraints of the chiral terpenoid linker apparently allow only the formation of one metal-centered configuration. Interestingly, the crystal structure of Δ-**7** reveals a significantly distorted octahedral coordination sphere around the ruthenium, indicating that even the preferred Δ-configuration is under strain, therewith explaining the modest yields in the formation of Δ-**7**. According to the authors, this work marked the first report of an asymmetric synthesis of an enantiomerically pure octahedral ruthenium complex without the need for chiral resolution.

Recent work by several groups has introduced new chiral motifs in multidentate ligands to efficiently control relative and absolute configurations upon metal complexation.[23–28] For example, Yamamoto and co-workers reported tethered bis(8-quinolinolato) metal complexes in which 1,1′-binaphthyl serves as a chiral linker between two 8-hydroxyquinoline (8-HQ) ligands {(*S*)-**8**H_2} (Scheme 2b).[23,24] Because of the rotational restrictions of the binaphthyl backbone and 8-HQ chelators, the reaction of (*S*)-**8**H_2 with $CrCl_2$ followed by air oxidation provides *cis*-β-Λ-[Cr{(*S*)-**8**}$(EtOH)_2$]Cl (*cis*-β-Λ-(*S*)-**9**) in almost quantitative yield as a single stereoisomer with *cis*-β (*fac-mer*) configuration of the tetradentate ligand and Λ-configuration at the Cr^{III} center (Scheme 2b).[24] This complex has been applied as an efficient catalyst for asymmetric organic transformations.[23,24] 2,2′-Bipyrrolidine is another privileged chiral motif as part of designed tetradentate ligands which "helically wrap" around metal ions in a highly asymmetric fashion.[25–27] For example, Que Jr. et al. recently reported that the reaction of bipyrrolidine ligand (*R*,*R*)-**10** with $Fe(OTf)_2$·2MeCN provides exclusively the iron complex *cis*-α-Δ-[Fe{(*R*,*R*)-**10**}$(OTf)_2$] (*cis*-α-Δ-(*R*,*R*)-**11**), which itself serves as a catalyst for asymmetric olefin *cis*-dihydroxylation (Scheme 2c).[25] In a related example, Kol and coworkers reported that the 2,2′-bipyrrolidine-derived Salan ligand (*S*,*S*)-**12**H_2, upon reaction with $Zr(OtBu)_4$, afforded the single stereoisomer *cis*-α-Λ-[Zr{(*S*,*S*)-**12**}$(OtBu)_2$] (*cis*-α-Λ-(*S*,*S*)-**13**) in high yield (Scheme 2d).[26] The geometrically and conformationally constrained 2,2′-bipyrrolidine moiety apparently only allows one predetermined helical sense.[27]

Instead of relying on highly preorganized geometries of chiral multidentate ligands, aromatic face-to-face π-stacking can be exploited for the control of the absolute metal-centered configuration. The Scott group reported a one-pot reaction to generate with high diastereoselectivity *fac*-Δ-$[Fe(A\text{-}B)_3]^{2+}$ complexes from chiral iminopyridines, which were synthesized in situ from chiral benzylamines and 2-pyridinecarbaldehyde.[29] For example, the reaction of iminopyridine (*R*)-**14** with $Fe(ClO_4)_2$·$6H_2O$ in MeCN afforded the single diastereomer *fac*-Δ-[Fe{(*R*)-**14**}$_3$]$(ClO_4)_2$ (*fac*-Δ-**15**) (Scheme 3a). ^{1}H NMR spectroscopic analysis demonstrated that this single diastereomer is present at all accessible temperatures. The origin of the impressive stereoselectivity is readily apparent from the crystal structure of *fac*-Δ-**15** shown in Scheme 3a: each of the three pyridine units forms a face-to-face π-interaction with a phenyl unit on a neighboring ligand. This work represents a rare case in which relative (*fac* vs. *mer*) and absolute (Δ vs. Λ) stereochemistry are controlled simultaneously in a one-pot reaction. On the basis of the same principle, Constable, Housecroft, and co-workers recently reported a one-pot reaction of 2,2′-bipyridine-6-carbaldehyde with enantiopure chiral amines and Fe^{II} to generate octahedral Fe^{II} complexes in a highly diastereoselective fashion. For example, the reaction of in situ generated iminobipyridine (*S*)-**16** with $FeCl_2$·$4H_2O$ led to the formation of the single stereoisomer Δ-[Fe{(*S*)-**16**}$_2$]$(PF_6)_2$ (Δ-**17**).[30] The crystal structure shown in Scheme 3b reveals an efficient stacking between the 2,2′-bipyridine and naphthyl moieties, thus explaining the high preference of the Δ- over the Λ-configuration at the Fe^{II} center.

The examples presented here demonstrate that carefully tailored chiral nonracemic multidentate ligands are capable of efficiently controlling the stereochemistry of octahedral coordination complexes. Tetradentate ligands restrict the number of possible diastereomers (relative configuration), and the geometrical and conformational constraints imposed by the chiral backbone result in the predetermination

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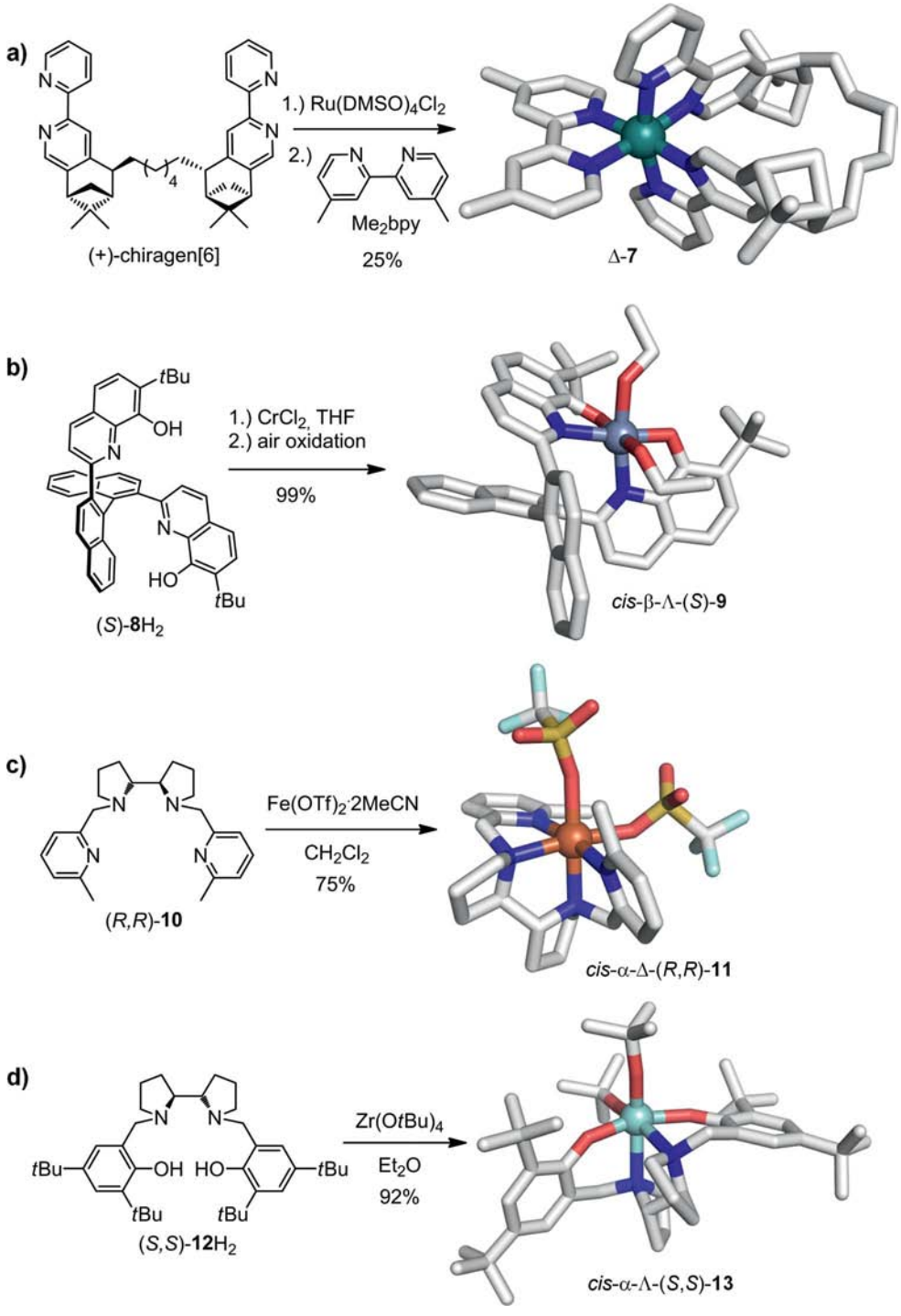

Scheme 2. Tailored multidentate ligands with chiral backbones designed for highly diastereoselective coordination chemistry with predetermined metal-centered configurations. (a) von Zelewsky's highly diastereoselective control of Ru^{II}-centered chirality by using the tetradentate (+)-chiragen[6] ligand. (b) Binaphthyl-tethered bis(8-hydroxyquinoline) ligand for the control of metal-centered configuration in a Cr^{III} complex (CCDC-254819). (c) Rigid 2,2′-bipyrrolidine backbone for diastereoselective formation of a Fe^{II} catalyst (CCDC-657098). (d) "Helical wrapping" around Zr^{IV} with a 2,2′-bipyrrolidine-derived Salan ligand (CCDC-715079). Counterions and solvent molecules are omitted in the shown crystal structures.

of the absolute metal-centered configuration. When ligands with lower denticity are used, multiple tailored chiral ligands are introduced into the coordination sphere at the same time to generate the necessary control of relative and absolute metal-centered stereochemistry. It is with high certainty that in all examples discussed here the thermodynamically most stable diastereoisomer is formed. However, it is worthwhile to distinguish between labile and inert metal complex formation: whereas the asymmetric synthesis of labile metal complexes is based on a straightforward

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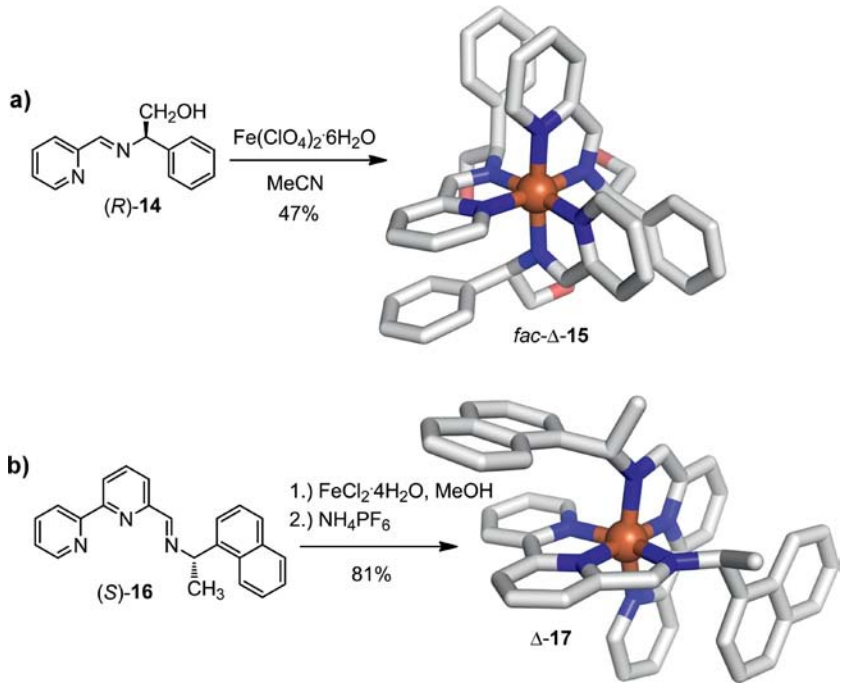
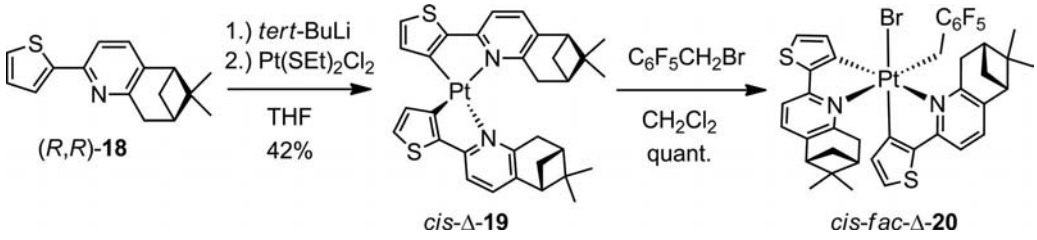


Scheme 3. Diastereoselective coordination chemistry with Fe^{II} directed by aromatic face-to-face π-stacking. The imines were formed in situ from (a) 2-pyridinecarbaldehyde and (*R*)-2-phenylglycinol or (b) 2,2′-bipyridine-6-carbaldehyde and (*S*)-1-(1-naphthyl)ethylamine. Counterions and solvent molecules are omitted in the shown crystal structures (CCDC-711828 for *fac*-Δ-**15** and CCDC-759473 for Δ-**17**).

thermodynamically controlled reaction in which the individual diastereomers are in equilibrium (e.g. Figure 2b–d, Figure 3a,b),[31] this is a little bit more complicated for inert metal complexes in which the individual stereoisomers typically cannot reach equilibrium (e.g. Figure 2a). It can be expected that in the latter cases it is often the faster rate of the formation of the thermodynamically more stable stereoisomer that accounts for the observed diastereoselectivity, maybe sometimes in combination with a formation of unidentified side products resulting from the reaction of the strained minor diastereomer or its intermediates, thereby leading to low overall yields. This could, for example, explain the low yields observed for the diastereoselective formation of the chiragen ruthenium complex Δ-**7**. Because of such complications, the asymmetric synthesis of inert metal complexes of Ru^{II}, Os^{II}, Rh^{III}, and Ir^{III} is especially challenging and needs further investigation. In fact, only few examples have been reported for the asymmetric synthesis of octahedral Rh^{III} complexes,[32] and, to the best of the author's knowledge, not a single example exists for the asymmetric synthesis of inert octahedral Ir^{III} compounds.

Last but not least, it is noteworthy that octahedral metal complexes can be synthesized asymmetrically not only through ligand-substitution reactions, but also by means of oxidative addition. An example of this approach is displayed in Scheme 4.[33] Accordingly, the Pt^{II} starting complex *cis*-Δ-**19** was obtained by cyclometalation of the chiral thienylpyridine ligand (*R*,*R*)-**18**, which was synthesized from (–)-α-pinene. Due to steric constraints, this tetracoordinate Pt^{II} complex is chiral and adopts a distorted square-planar, Δ-configured, two-bladed helix. This Δ-configuration is preserved upon oxidative addition with, for example, $C_6F_5CH_2Br$, which leads to the single stereoisomer *cis*-*fac*-Δ-**20**.



Scheme 4. Asymmetric synthesis of an octahedral Pt^{IV} complex by oxidative addition.

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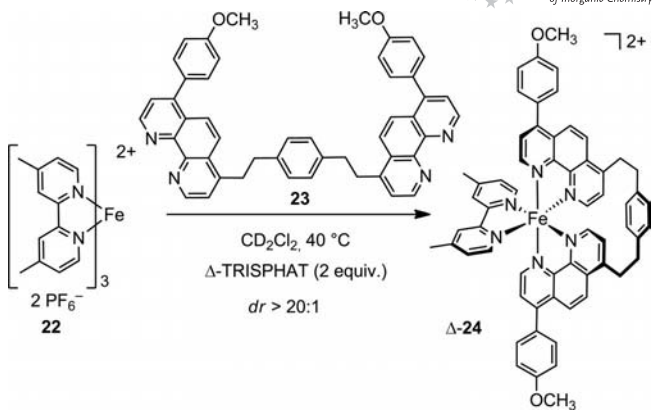
3. Chiral-Anion-Mediated Asymmetric Synthesis

Because metal complexes are frequently positively charged, the formation of metal-centered chirality can be influenced by asymmetric ion pairing with chiral counterions. In such systems, the asymmetric transformation is merely induced by weak intermolecular interactions within an ion pair.[34] The Lacour group developed a particularly powerful chiral anion, the so-called TRISPHAT anion, a chiral tris(tetrachlorobenzenediolato)phosphate(V) anion in which the phosphorus is coordinated in a hexacoordinate octahedral fashion (Scheme 5).[35] TRISPHAT is configurationally stable at room temperature and can be resolved into its Δ- and Λ-enantiomers. Due to its propeller shape, it is capable of discriminating strongly between the Δ- and Λ-enantiomers of chiral metal complex cations. For example, Δ-TRISPHAT shifts the equilibrium between the configurationally labile iron(II)–tris(diimine) enantiomers Λ-**21** and Δ-**21** towards the Δ-enantiomer to reach a diastereomeric ratio greater than 50:1.[36]

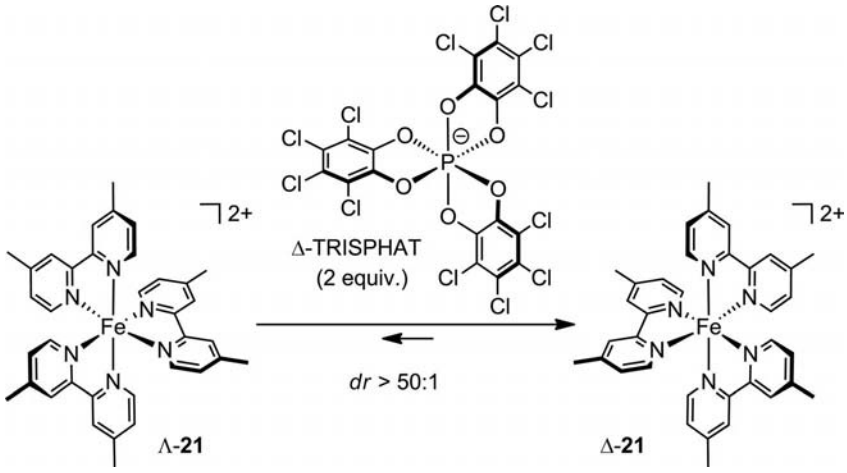
Under ideal circumstances, TRISPHAT is even able to influence the metal-centered chirality in configurationally more stable coordination compounds. Scheme 6 shows a recent example from Lacour et al., in which the reaction of the iron(II) source $[Fe(Me_2bpy)_3]^{2+}$ (**22**) with the tetradentate ligand **23** in CD_2Cl_2 at 40 °C yielded the iron complex Δ-**24** with high diastereoselectivity in the presence of the chiral counteranion Δ-TRISPHAT.[37] However, when the reaction was performed at 20 °C, as opposed to 40 °C, no asymmetric induction was observed at all, presumably because Λ-**24** and Δ-**24** cannot reach an equilibrium in this thermodynamically controlled reaction. Apparently, the observed stereoselectivity results from the preferred homochiral association of the three-bladed propellers Δ-**24** and Δ-TRISPHAT, as opposed to the heterochiral propellers Λ-**24** and Δ-TRISPHAT. Since the iron complex is configurationally stable at room temperature, the TRISPHAT counteranion can be removed without loss of stereochemical information, thus rendering TRISPHAT in this example a chiral auxiliary.



Scheme 6. Ion-pair-mediated asymmetric synthesis of a configurationally stable tris(diimine) iron(II) complex.

Asymmetric ion pairing can even be applied to the asymmetric synthesis of highly inert ruthenium polypyridyl complexes. In such a rare example, Fontecave and co-workers exploited the large solubility differences of TRISPHAT-containing diastereomeric ion pairs in a photo- and crystallization-induced asymmetric transformation.[38] Accordingly, the irradiation of a racemic mixture of $[Ru(dmp)_2(MeCN)_2](PF_6)_2$ (dmp = 2,9-dimethyl-1,10-phenanthroline), [**25**]$(PF_6)_2$, with a 40 W tungsten filament lamp for 3 h in CH_2Cl_2 and in the presence of [nBu$_3$NH][Λ-TRISPHAT] (2.1 equiv.) afforded virtually optically pure [Δ-**25**][Λ-TRISPHAT]$_2$ (Scheme 7). This method is based on a dynamic resolution process, in which the photochemically established equilibrium between the enantiomers of ruthenium complex **25** is completely shifted towards Δ-**25** as a result of the low solubility of the heterochiral ion pair [Δ-**25**][Λ-TRISPHAT]$_2$ in CH_2Cl_2, which precipitates out of solution.

Finally, the TRISPHAT anion can be further functionalized in order to modify its molecular recognition properties or improve the synthetic implementation of the stereogenic phosphorus center.[35,39–42] For example, replacing one tetrachlorocatecholate ligand of TRISPHAT by a dou-



Scheme 5. Shifting the equilibrium between the Λ- and Δ-configurations of a labile iron complex with Δ-TRISPHAT.

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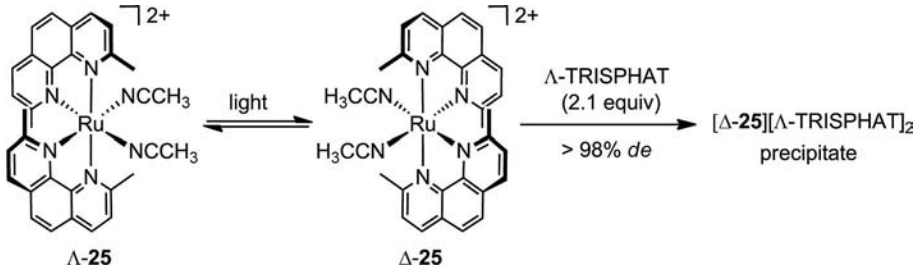

Scheme 7. Photo- and crystallization-induced asymmetric synthesis with the chiral anion Λ-TRISPHAT as a chiral auxiliary.

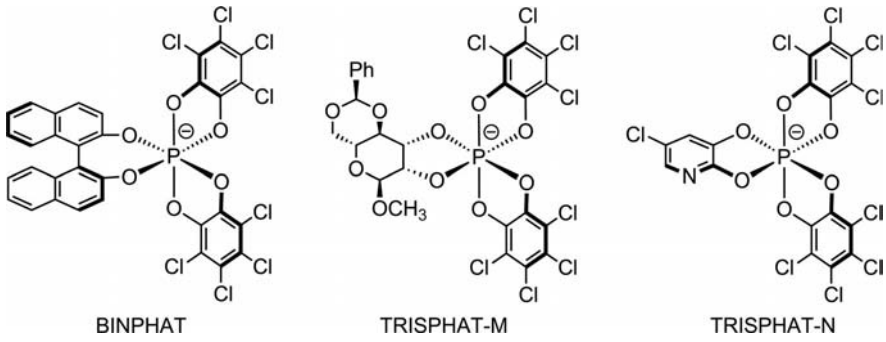

Figure 4. Functionalized TRISPHAT derivatives.

bly deprotonated 1,1′-naphthalene-2,2′-diol or a mannopyranoside-derived ligand, leads to BINPHAT or "TRISPHAT-M", respectively (Figure 4).[40,41] Both of these chiral phosphate anions can be synthesized in a one-pot procedure without the need for a subsequent resolution of isomers. Figure 4 also shows the ligand TRISPHAT-N, which incorporates a pyridine ligand and thus facilitates asymmetric inductions through a combination out of asymmetric ion pairing followed by asymmetric coordinative bond formation through the pyridine.[42]

It can be concluded that chiral counterions such as TRISPHAT are not only useful for the resolution of enantiomers of racemic cationic substrates or chiral shift reagents, but can be exploited for efficient asymmetric coordination chemistry based on energy or solubility differences between tightly associated diastereomeric ion pairs. However, due to the intrinsic weakness of such intermolecular forces, there is a limitation for the asymmetric synthesis of inert metal complexes.

4. Chiral-Auxiliary-Mediated Asymmetric Coordination Chemistry with Chiral Ligands

Chiral auxiliaries are utilized extensively as work horses in organic chemistry for the synthesis of enantiomerically pure compounds in a predictable and time-efficient fashion. In this strategy, a chiral compound or moiety – the chiral auxiliary – is temporarily linked to a substrate to direct the stereochemical course of a diastereoselective reaction, before being detached afterwards. Applied to metal complexes, a chiral auxiliary may constitute a transiently metal-coordinating chiral ligand, which directs the stereochemical course of ligand substitutions and is removed after the reaction from the coordination sphere of the metal to leave behind an enantiomerically enriched metal complex. Significant efforts have been devoted to diastereoselective coordination chemistry with chiral ligands, and this important body of research has provided important insight into strategies to control metal-centered chirality.[14] However, the current challenge lies in the development of tailored chiral ligands that are capable of efficiently ruling the metal-centered configuration and are at the same time removable afterwards without compromising the induced metal-centered stereochemistry.[43]

4.1 Initial Work: Tartrate and Monodentate Sulfoxides as Chiral Auxiliaries

The first example of a chiral auxiliary for coordination chemistry was introduced by Bailar Jr. and co-workers. In 1948, Bailar Jr. demonstrated that (*R*,*R*)-(+)-tartrate can be employed as a chiral auxiliary for the synthesis of (+)-$[Co(en)_3]^{3+}$, (+)-$[Co(en)_2Cl_2]^+$, and (+)-$[Co(en)_2(NO_2)_2]^+$, en = 1,2-ethylenediamine, in dynamic kinetic resolutions.[44] For example, the reaction of racemic $[Co(en)_2CO_3]^+$ first with (*R*,*R*)-(+)-tartrate and subsequently with en, afforded the complex (+)-$[Co(en)_3]^{3+}$ (the Λ-enantiomer)[45] in a yield of 70% and with an enantiomeric purity of up to 90%. Bailar Jr. et al. unraveled that the asymmetric formation of (+)-$[Co(en)_3]^{3+}$ is apparently the result of a faster reaction of the more reactive diastereomer (+)-$[Co(en)_2\{(R,R)$-(+)-tartrate$\}]^+$ with en, while the more stable diastereomer (–)-$[Co(en)_2\{(R,R)$-(+)-tartrate$\}]^+$ remained unreacted in solution and slowly converted into the (+)-diastereomer as the latter was depleted in the course of the reaction with en. Bailar Jr. later also reported the first auxiliary-mediated

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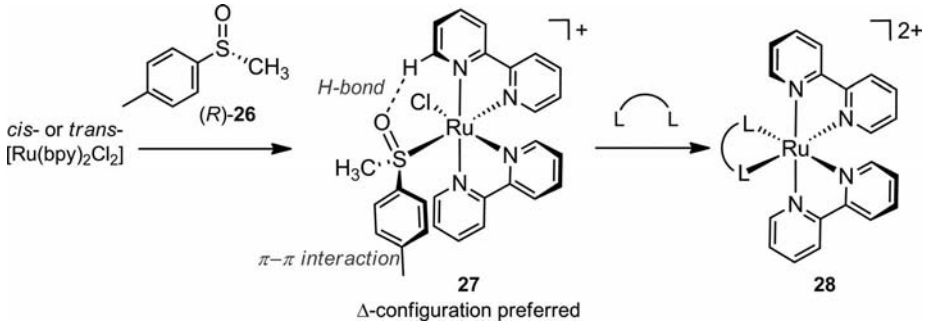

Scheme 8. Monodentate methyl *p*-tolyl sulfoxide as a chiral auxiliary for the asymmetric synthesis of ruthenium polypyridyl complexes.

asymmetric synthesis of enantiomerically enriched configurationally inert $[Ru(bpy)_3]^{2+}$, bpy = 2,2′-bipyridine, by reacting K_2RuCl_5 hydrate first with (*R*,*R*)-(+)-tartrate, which afforded in situ an undefined "tartratoruthenium complex", followed by the addition of an excess of bpy to yield the ruthenium complex $[Ru(bpy)_3]^{2+}$ with a modest enantiomeric ratio of 63:37.[46,47] Enantiomerically enriched complexes $[Ru(phen)_3]^{2+}$ (phen = 1,10-phenanthroline) and $[Os(bpy)_3]^{2+}$ were synthesized in an analogous fashion.[46]

Several decades later, Inoue and co-workers reported the use of monodentate chiral sulfoxides as chiral auxiliaries.[48,49] For example, the reaction of (*R*)-(+)-methyl *p*-tolyl sulfoxide, (*R*)-**26**, with $[Ru(pp)_2Cl_2]$ in DMF at 120 °C afforded *cis*-$[Ru(pp)_2\{(R)$-**26**$\}Cl]Cl$ with a Δ/Λ ratio of 2.8:1 for pp = bpy (complex **27**) and a Δ/Λ ratio of 4:1 for pp = 4,4′-dimethyl-2,2′-bipyridine (Scheme 8). Interestingly, the observed diastereoselectivities were independent of the choice of the *cis* (chiral, racemic) or *trans* (achiral) starting materials, indicating that the two enantiomers of the *cis* complex are in equilibrium, maybe through the intermediate formation of the thermodynamically less stable *trans* complex. One can expect that under the reaction conditions the coordination of the monodentate sulfoxide ligand is reversible, so that the observed diastereomeric ratios reflect the stability differences of the two diastereomers (thermodynamic control). NMR spectroscopic experiments, molecular modeling, and the X-ray crystallographic analysis of related sulfoxide complexes suggest that the preferred diastereomer is stabilized by a combination of face-to-face π-stacking of the tolyl group with a bidentate ligand and a hydrogen bond between the sulfoxide oxygen and a pyridyl *ortho*-proton.[48,50,51] Starting from racemic *cis*-$[Ru(pp)_2Cl_2]$, Aït-Haddou and co-workers improved this asymmetric synthesis by performing the reactions under microwave irradiation to afford *de* values of up to 76% (Δ/Λ = 7.3:1) with yields reaching 99%.[51] Due to different solubilities of the two formed diastereomers, the diastereomeric purity of the major isomer could be further improved by washing or crystallization protocols. Overall, the observed only modest diastereoselectivities in this system can be traced back to the reversibility of the sulfoxide coordination, together with a rotational freedom around the Ru–S bond of the coordinated chiral sulfoxide. Finally, as demonstrated by Inoue and co-workers, the optically active sulfoxide complexes can subsequently be converted to ruthenium polypyridyl complexes with substitution of the chiral sulfoxide by a third bidentate ligand with almost complete retention of the metal-centered configuration, thus rendering the sulfoxide a true chiral auxiliary for ruling the absolute configuration at the metal center (**27**→**28** in Scheme 8).[49,52–54]

4.2 Chiral Bidentate Ligands with Switchable Coordination Strength as Auxiliaries

Design Principle

The typical high inertness of coordination compounds of the d^6 metals Ru^{II}, Os^{II}, Rh^{III}, and Ir^{III} results in very stable absolute metal-centered configurations, often even under harsh conditions, which is a desired feature for applications that rely on the persistence of their absolute stereochemistry. However, at the same time this poses significant challenges for the asymmetric synthesis of such inert complexes. For example, reaction conditions for ligand substitutions typically require high temperatures, which limit available strategies for efficient asymmetric inductions and the subsequent removal of the transient chirality-inducer. Bailar Jr. et al., Inoue et al., and Aït-Haddou et al. addressed this issue with relatively weak but reversibly coordinating ligands, but at the cost of only obtaining moderate asymmetric inductions.[44,46,48,51] The Meggers group recently provided a somewhat different solution to this problem by developing a class of tailored chiral coordinating bidentate ligands, which provide excellent asymmetric inductions during coordination chemistry and can be removed afterwards in a traceless fashion from the metal without any loss of chiral information.[55–59] A key aspect of these chiral-auxiliary ligands is their switchable binding strength: a chelate effect ensures on the one hand that the chiral ligands coordinate very tightly to the metal center, placing their carbon-based, sulfur-based, or axial chirality in a well-defined position close to the metal center to efficiently establish the absolute metal-centered configuration, and on the other hand a coordinating phenolate moiety warrants that the coordination can be made reversible by weakening the binding strength through protonation (Figure 5).

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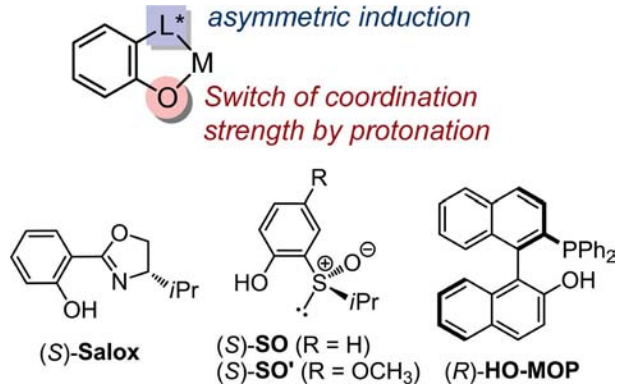
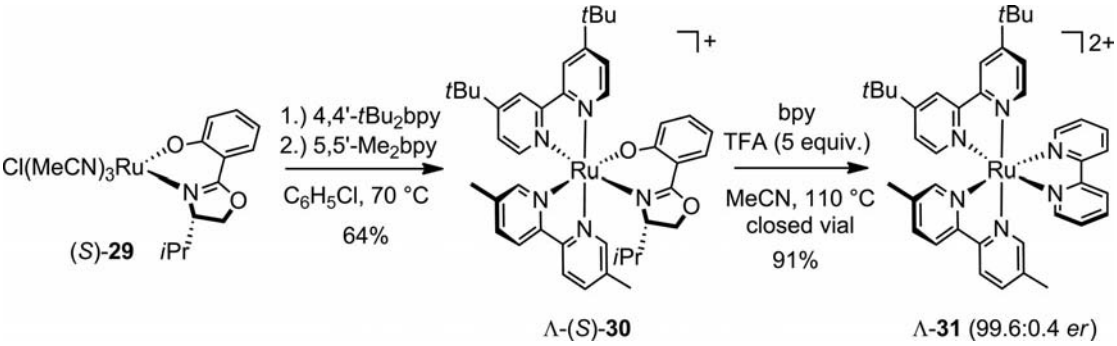


Figure 5. Chelating chiral auxiliaries with switchable binding strength designed for asymmetric coordination chemistry according to refs.[55–59]

Chiral Salicyloxazolines as Auxiliaries

The scope of such carefully tailored bidentate chiral auxiliaries was first demonstrated for the efficient asymmetric synthesis of virtually enantiopure tris-heteroleptic ruthenium polypyridyl complexes $[Ru(pp)(pp')(pp'')]^{2+}$, in which pp, pp′, pp′′ = achiral 2,2′-bipyridines.[55,56] For example, starting from complex (*S*)-**29**, which harbors a deprotonated (*S*)-5-isopropyl-2-(2′-hydroxyphenyl)oxazoline ligand {(*S*)-**Salox**} in addition to three acetonitriles and one chloride, the chiral salicyloxazolinate ligand provided an excellent asymmetric induction in the course of the substitution of the three acetonitriles and the chloride for two bipyridine ligands: the reaction of (*S*)-**29** with first one equivalent of 4,4′-di-*tert*-butyl-2,2′-bipyridine (4,4′-tBu$_2$bpy) in chlorobenzene at 70 °C and subsequently with one equivalent of



Scheme 9. Example of the asymmetric synthesis of a tris-heteroleptic ruthenium polypyridyl complex by utilizing (*S*)-**Salox** as a chiral auxiliary.

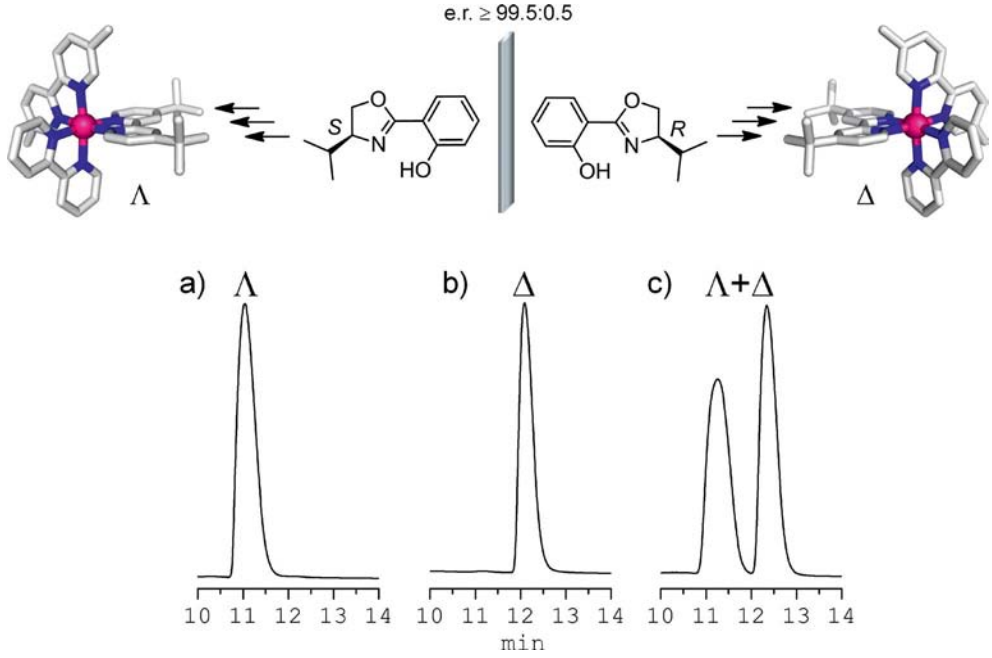


Figure 6. HPLC traces demonstrating the enantiopurity of the synthesized complexes Λ-**31** and Δ-**31**: (a) Λ-**31** synthesized from (*S*)-**Salox**; (b) Δ-**31** synthesized from (*R*)-**Salox**; (c) Λ/Δ-**31** synthesized from *rac*-**Salox**. HPLC conditions: Daicel Chiralcel OD-R, 250 × 4 mm, flow rate = 0.5 mL/min, 0.087% aq. H_3PO_4 and MeCN as eluent (30→60% in 20 min).

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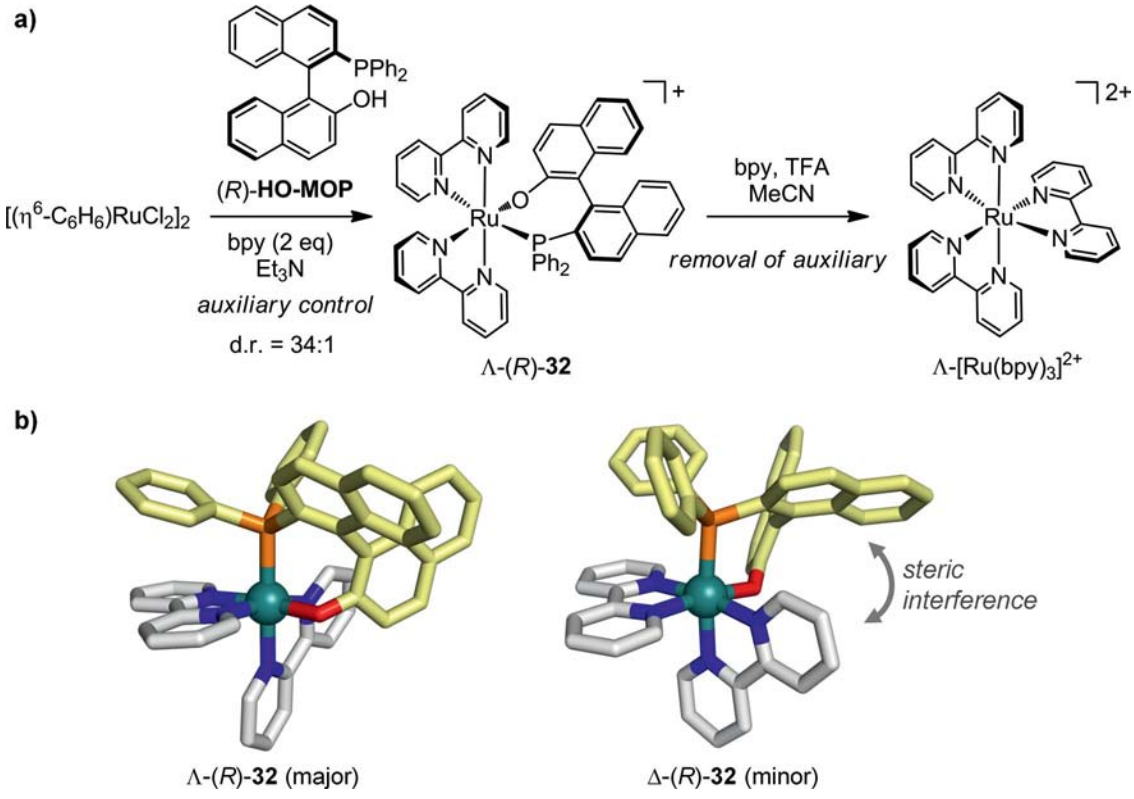
5,5′-dimethyl-2,2′-bipyridine (5,5′-Me_2bpy) again in chlorobenzene at 70 °C afforded complex Λ-(*S*)-**30** with virtually complete diastereoselectivity (diastereopurity > 99.5%) (Scheme 9). Interestingly, the diastereoselectivity of this reaction step is highly solvent-dependent: aprotic solvents such as chlorobenzene or THF provided the most favorable diastereoselectivities, whereas alcohols led to only very modest *dr* values. It is worth noting that a combination of computational and experimental results revealed that the observed stereoselectivities are in fact under thermodynamic control, although additional kinetic effects may also play a role.[56] Subsequently, treatment of Λ-(*S*)-**30** with bpy in acetonitrile at 110 °C in a closed vial in the presence of 5 equiv. of TFA afforded the tris-heteroleptic complex Λ-**31** stereospecifically by replacement of the salicyloxazolinate with bpy under complete retention of configuration and with a high enantiopurity of 99.6:0.4 *er*. It is here apparently the protonation of the phenolate oxygen that is responsible for diminishing the coordinative strength of the coordinated salicyloxazolinate ligand. For this reaction step, the choice of solvent also plays a crucial role in the stereochemical outcome of the reaction: only coordinating solvents such as MeCN or THF are capable of suppressing racemization at the applied elevated reaction temperature.[56]

Thus, this method constitutes an inexpensive and rapid asymmetric synthesis of ruthenium polypyridyl complexes in which the chiral auxiliary is obtained from readily available chiral α-amino acids. As exemplified by the HPLC traces in Figure 6, (*S*)-**Salox** cleanly generates the Λ configuration and (*R*)-**Salox** the Δ configuration at the asymmetric ruthenium center. A detailed investigation of this reaction sequence, revealing the scope and limitations of this method, and providing a guide to optimal standard reaction conditions, has been reported recently.[56]

2-Diphenylphosphanyl-2′-hydroxy-1,1′-binaphthyl as Chiral Auxiliary

The strategy of using chiral chelating ligands with switchable binding strength for chiral-auxiliary-mediated asymmetric coordination chemistry, as reported initially for the **Salox** system, can be applied to related ligands that provide a different source of chirality, such as the bidentate ligand (*R*)-2-diphenylphosphanyl-2′-hydroxy-1,1′-binaphthyl (**HO-MOP**) possessing axial chirality.[59] It was found, among others, that (*R*)-**HO-MOP** serves as an effective chiral auxiliary starting from different metal precursor complexes, most notably by using the commercially available half-sandwich complex $[Ru(\eta^6\text{-}C_6H_6)Cl_2]_2$. Accordingly, the reaction of $[Ru(\eta^6\text{-}C_6H_6)Cl_2]_2$ with 1.25 equiv. of (*R*)-**HO-MOP** and 2 equiv. of bpy in dry ethanol and in the presence of Et_3N at 95 °C in a sealed vial afforded in one step and after workup and purification complex Λ-[Ru(bpy)$_2${(*R*)-**HO-MOP**}]Cl (Λ-(*R*)-**32**) in a yield of 84% and with a satisfactory diastereoselectivity of 34:1 *dr* (Scheme 10). Density functional theory calculations verified that the prefer-



Scheme 10. Transfer of axial chirality of (*R*)-**HO-MOP** to metal-centered chirality in a chiral-auxiliary-mediated asymmetric synthesis. (a) Example for the application of (*R*)-**HO-MOP**. (b) Calculated geometries of the two possible diastereomers formed in the reaction of $[Ru(\eta^6\text{-}C_6H_6)Cl_2]_2$ with (*R*)-**HO-MOP** and bpy.

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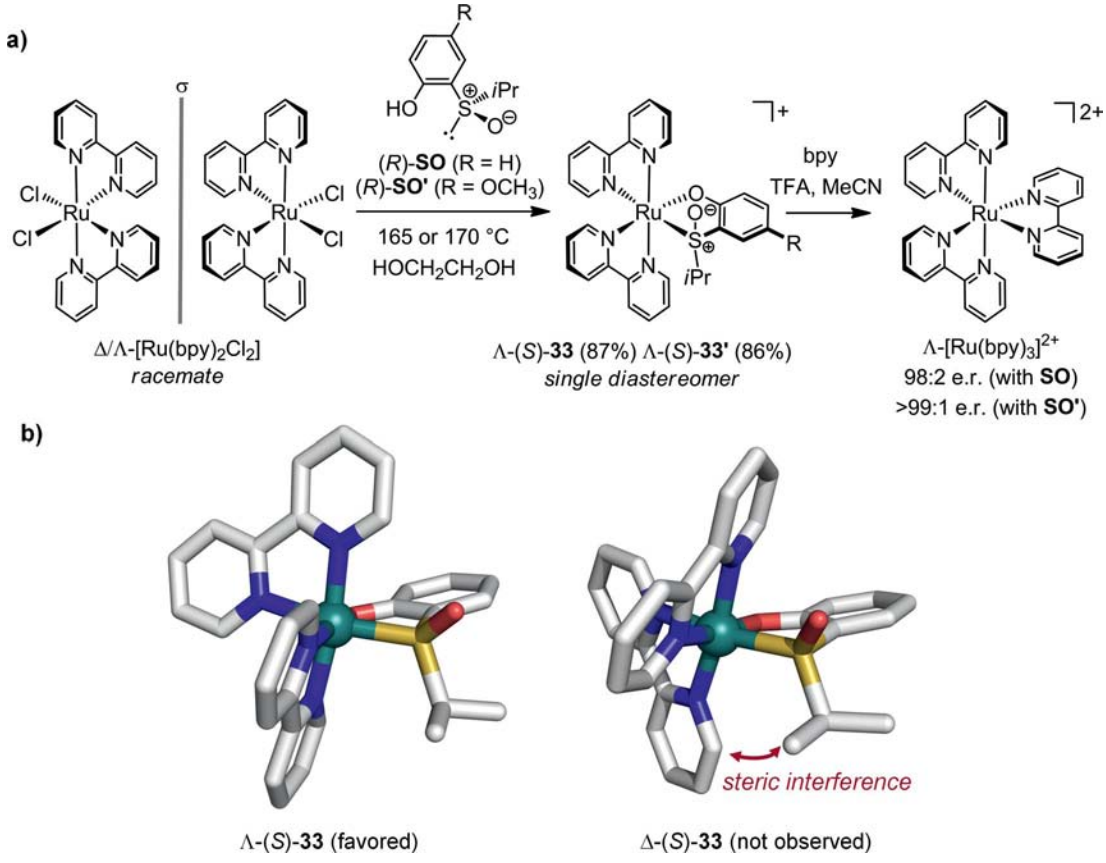
entially formed Λ-(*R*)-diastereomer is thermodynamically more stable in analogy to the thermodynamically controlled diastereoselective coordination chemistry with the **Salox** chiral auxiliary. Scheme 10 demonstrates that this is mainly due to a direct steric hindrance between one of the naphthalene moieties and a bpy ligand in the minor Δ-(*R*)-diastereomer, whereas in the more stable diastereomer Λ-(*R*)-**32**, one naphthalene moiety is instead favorably stacked face-to-face with a bpy ligand. Overall, **HO-MOP** is an attractive tool for the straightforward synthesis of bis-heteroleptic complexes of the type $[Ru(pp)_2(pp')]^{2+}$ starting directly from the commercially available half-sandwich complex $[Ru(\eta^6\text{-}C_6H_6)Cl_2]_2$.

Dynamic Asymmetric Transformation with Chiral 2-(Isopropylsulfinyl)phenols

Chiral sulfoxides are especially attractive ligands as components of chiral auxiliaries because sulfoxides place their center of asymmetry – the coordinating sulfur – in direct proximity to the metal, thus promising an especially facile transfer of chirality from the auxiliary to the metal.[48–52] With this anticipation, Meggers and co-workers designed (*R*)- and (*S*)-2-(isopropylsulfinyl)phenols (**SO** and **SO′**, Figure 5) as auxiliaries for asymmetric coordination chemistry.[57,58] Indeed, these auxiliaries turn out to be highly valuable reagents for several applications. For example, it was recently discovered that (*R*)-2-(isopropylsulfinyl)phenol, (*R*)-**SO**, and preferably the more electron-rich derivative (*R*)-2-(isopropylsulfinyl)-4-methoxyphenol, (*R*)-**SO′**, are capable of converting the racemic starting complex *rac*-$[Ru(bpy)_2Cl_2]$ into single diastereomers Λ-$[Ru(bpy)_2\{(R)\text{-}\mathbf{SO}\}]PF_6$ (Λ-(*S*)-**33**) and Λ-$[Ru(bpy)_2\{(R)\text{-}\mathbf{SO'}\}]PF_6$ (Λ-(*S*)-**33′**), respectively, in a thermodynamically controlled dynamic transformation, in analogy to the discussed work with monodentate sulfoxides by Inoue[48–50,52] and Aït-Haddou[51] but with significantly higher diastereoselectivities (Scheme 11).[58,60] Complexes Λ-(*S*)-**33** and Λ-(*S*)-**33′** themselves are direct precursors for the generation of optically active ruthenium polypyridyl complexes by TFA-induced stereospecific replacement of the sulfinylphenolate auxiliaries under retention of configuration, with, for example, bpy, to afford Λ-$[Ru(bpy)_3]^{2+}$ with high enantiomeric ratios (98:2 *er* with **SO** and >99:1 *er* with **SO′**). Thus, in this method, the high steric crowding of an octahedral coordination sphere is exploited by placing a bulky sulfur-based stereocenter in direct proximity to the ruthenium stereocenter, which leads to a large difference in the stabilities of the intermediate Λ-(*S*) and Δ-(*S*) diastereomers and thereby



Scheme 11. Dynamic asymmetric transformation with chiral 2-(isopropylsulfinyl)phenols. (a) Synthesis of Λ-$[Ru(bpy)_3]^{2+}$ from racemic $[Ru(bpy)_2Cl_2]$ with (*R*)-**SO** or (*R*)-**SO′** as the chiral auxiliaries. Note that according to the Cahn–Ingold–Prelog priority rules, the assignment of the absolute stereochemistry at the sulfur atom changes from *R* to *S* upon coordination. (b) Calculated geometries of the two theoretically possible diastereomers formed in the reaction of $[Ru(bpy)Cl_2]_2$ with (*R*)-**SO** from which only Λ-(*S*)-**33** was observed, while Δ-(*S*)-**33** appears to be too labile.

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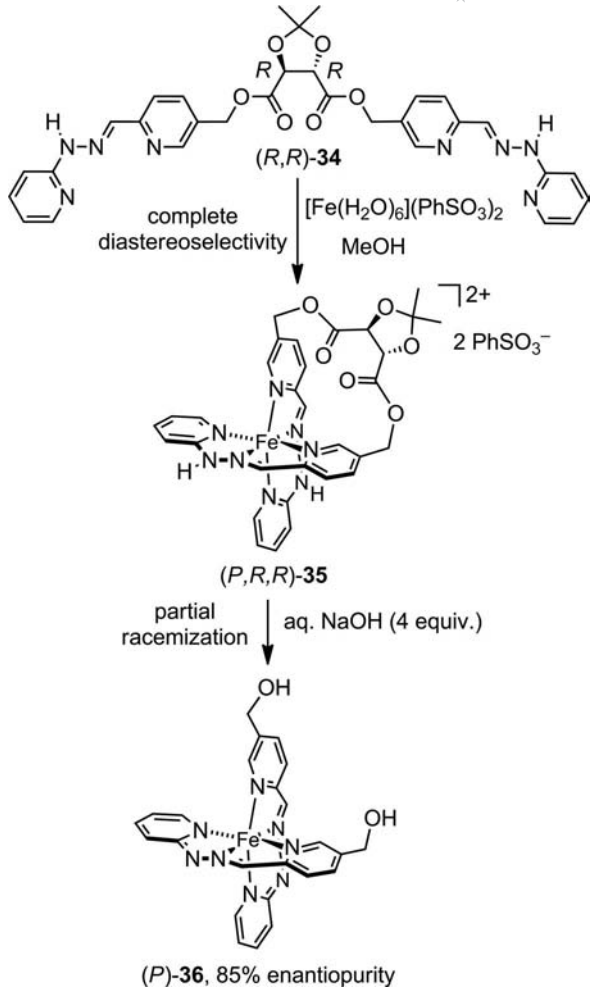
provides the opportunity to find suitable reaction conditions for converting the destabilized diastereomer into the thermodynamically more stable one. In fact, the unobserved Δ-(*S*) diastereomer appears to be too labile for isolation. This method was also applied to the related starting materials *rac*-[Ru(pp)$_2$Cl$_2$], with pp = phen or 5,5′-Me$_2$bpy, and should be of practical value for the asymmetric synthesis of ruthenium polypyridyl complexes because of readily available racemic ruthenium complexes as starting materials.

4.3 Cleavable Chiral Linkers as Auxiliaries

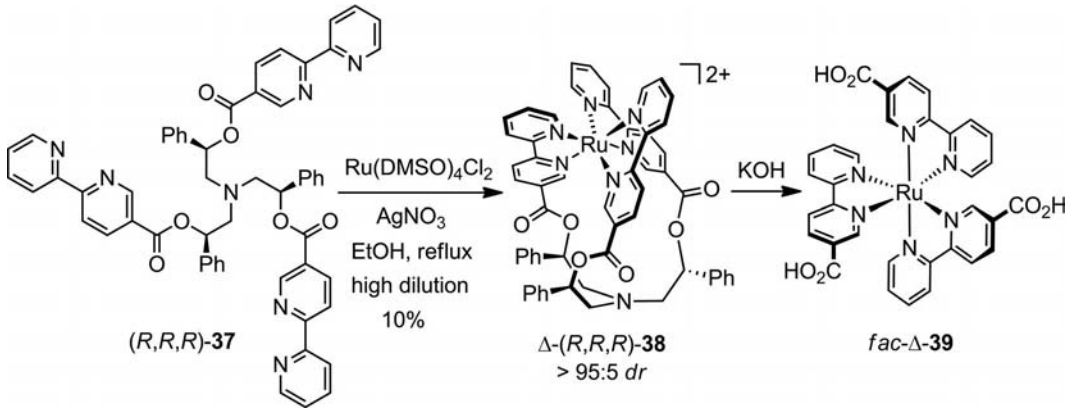
In a different approach, the chiral auxiliary can be a transient, cleavable linker between two or more multidentate ligands. For example, Wild and co-workers developed the C_2-symmetrical hexadentate ligand (*R*,*R*)-**34**, in which two tridentate pyridine-2-carbaldehyde 2′-pyridylhydrazones are bridged by a base-cleavable chiral (*R*,*R*)-tartrate linker (Scheme 12).[61,62] When reacted with iron(II), the hexadentate ligand (*R*,*R*)-**34** afforded an octahedral, two-bladed propeller complex (*P*,*R*,*R*)-**35** with complete diastereoselectivity. Unfortunately, removal of the auxiliary by hydrolysis of the ester linkages and deprotonation of the hydrazone NH groups provided the corresponding neutral iron complex (*P*)-**36** only with an *er* of 85:15. The loss of configurational integrity during the cleavage step was attributed to partial racemization of the metal-centered configuration in the configurationally labile iron complex.

In a variation of this strategy, Fletcher et al. made use of a chiral tripodal linker system which not only allowed controlling the metal stereocenter but also the relative orientation of C_s-symmetrical bidentate ligands in favor of the facial (*fac*) isomer.[63,64] For example, the reaction of the enantiopure tripodal hexadentate ligand (*R*,*R*,*R*)-**37** with [Ru(DMSO)$_4$Cl$_2$] in the presence of AgNO$_3$ under reflux in EtOH and high dilution, afforded the ruthenium complex Δ-(*R*,*R*,*R*)-**38** as mainly one diastereomer (> 95:5 *dr*) albeit in very low yields of only 10% (Scheme 13). The low yields were attributed to the hydrolytic instability of the ester



Scheme 12. Chiral auxiliary ligand with a cleavable tartrate linker for the asymmetric synthesis of a chiral two-bladed propeller complex. The iron-centered configuration is described with the helix nomenclature.

bonds. The subsequent cleavage of the ester bonds with aqueous KOH then provided the complex *fac*-Δ-**39**. Unfortunately, the low yields of the coordination step and prob-



Scheme 13. Asymmetric synthesis of a *fac*-Δ ruthenium polypyridyl complex with the cleavable linker approach. Complex Δ-(*R*,*R*,*R*)-**38** was isolated in low yields as the PF_6 salt. The diastereomeric excess was estimated by ^{1}H NMR spectroscopy. The isolation of *fac*-Δ-**39** proved difficult due to the high hydrophilicity of the complex.

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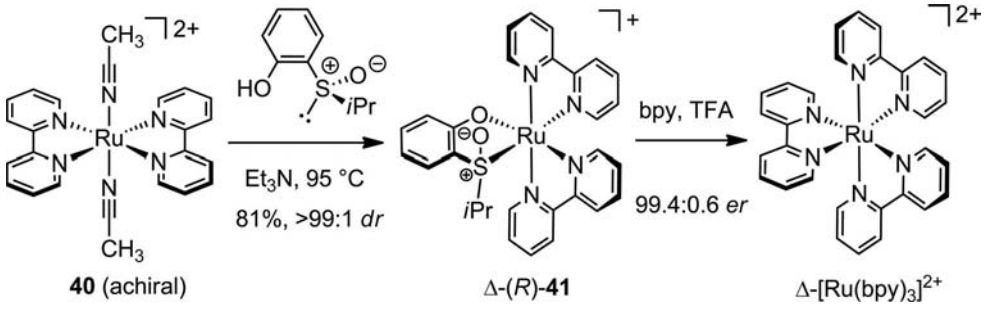
lems with the workup of the highly hydrophilic ruthenium polypyridyl complex *fac*-Δ-**39** render this method rather unattractive.

It can be concluded that the cleavable-chiral-linker-strategy has the appealing advantage that it allows to control the relative and absolute stereochemistry of the metal complex simultaneously. However, at the same time it poses a significant restriction on the choice of ligands since the ligand–spacer–ligand constructs need to be designed very carefully in order to warrant a proper coordination site for the metal.

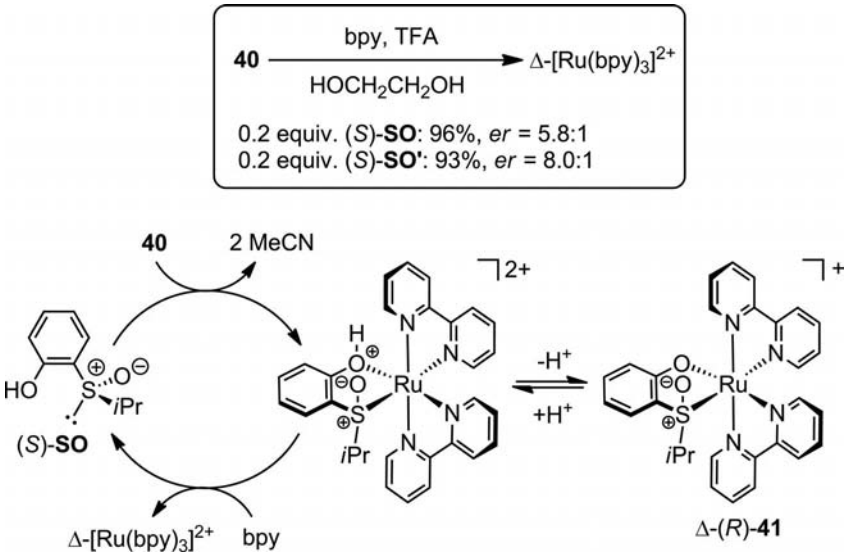
5. Catalytic Asymmetric Synthesis of Coordination Compounds

Catalysis plays a central role in the resource-efficient and economical asymmetric synthesis of chiral organic compounds. This is, however, not yet the case for the asymmetric synthesis of coordination complexes. Surprisingly, but illustrating the state of the art of asymmetric coordination chemistry, the first example of a catalyst for an asymmetric generation of metal-centered chirality has been reported only recently.[57] In this work, it was disclosed that the tailored chiral sulfoxide ligands **SO** and **SO′** are capable of efficiently inducing a stereocontrolled *trans–cis* isomerization of two bidentate ligands within an octahedral coordination sphere, which was exploited for the auxiliary-mediated and even the catalytic asymmetric synthesis of a chiral ruthenium complex. Accordingly, the reaction of the achiral complex *trans*-$[Ru(bpy)_2(MeCN)_2](CF_3SO_3)_2$ (**40**) with (*S*)-**SO** in the presence of Et_3N led to the clean and completely diastereoselective formation of only Δ-(*R*)-**41** with substitution of the two acetonitrile ligands and a simultaneous chirality-inducing *trans–cis* isomerization of the two bpy ligands (Scheme 14). The **SO**-auxiliary was subsequently replaced by bpy under complete retention of configuration in the presence of TFA to afford Δ-$[Ru(bpy)_3]^{2+}$ (99.4:0.6 *er*). It is worth noting that the asymmetric *trans–cis* isomerization outlined here did not work well with other chiral auxiliaries such as **Salox** or **HO-MOP** (Figure 5).

Beyond its function as a chiral auxiliary, it was demonstrated that, under carefully optimized conditions, (*S*)-**SO** can even serve as a catalyst for isomerization-induced asymmetric synthesis. Accordingly, it was found that the reaction of **40** at a high concentration in ethylene glycol (300 mM) with 0.2 equiv. (*S*)-**SO** in the presence of TFA and bpy afforded Δ-$[Ru(bpy)_3]^{2+}$ with a yield of 96% and an *er* of 5.8:1 (Scheme 15). The more electron-rich methoxy derivative (*S*)-**SO′** even afforded an *er* of 8.0:1 with a yield of



Scheme 14. Auxiliary-controlled asymmetric coordination chemistry based on a chirality-inducing *trans–cis* isomerization.



Scheme 15. Catalytic asymmetric synthesis of Δ-$[Ru(bpy)_3]^{2+}$ with the chiral ligands (*S*)-**SO** or (*S*)-**SO′** as catalysts. Shown is the proposed mechanism with the catalyst **SO**.

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93%. This corresponds to turnover numbers of more than 3 and demonstrates that these sulfinylphenols constitute true catalysts for the asymmetric conversion **40**→Δ-[Ru(bpy)$_3$]$^{2+}$. Apparently, (*S*)-**SO** and even more so the more nucleophilic (*S*)-**SO′** react significantly faster with **40** than bpy and are subsequently recycled through a TFA-promoted replacement by bpy, thus allowing a full catalytic cycle (Scheme 15). It is noteworthy that, in addition to the right amount of TFA, the nature of the solvent is crucial for a successful catalysis in this system. It was recognized that in ethylene glycol the *trans* complex **40** forms a suspension and is dissolved only to about 10% at 300 mM. This is apparently an important requirement for observing turnover, probably because it allows the catalysts (*S*)-**SO** or (*S*)-**SO′** to be in excess of the substrate **40** at all times during the catalysis. Thus, in these reactions a small organic molecule serves as an asymmetric catalyst for the enantioselective, organocatalytic synthesis of an octahedral metal complex.

6. Conclusions and Outlook

This review provided an overview of the asymmetric synthesis of octahedral coordination compounds from initial attempts to the current state of the art. Although significant progress has been made in controlling metal-centered chirality by carefully tailored ligands, chiral counterions, chiral auxiliaries, and even catalysts, important challenges lie ahead in the field of stereocontrolled coordination chemistry. Most importantly, novel methods are sought that enable the simultaneous control of both the relative and absolute metal-centered configuration. Considering that for octahedral metal complexes with low symmetry a large number of diastereomers are possible, more sophisticated auxiliaries or even combinations of auxiliaries will be necessary to solve this problem in a general fashion. The stereocontrolled synthesis of octahedral metal complexes is a central and exciting problem of modern coordination chemistry and will ultimately provide the necessary tools to fully exploit the opportunities provided by the rich stereochemistry of octahedral coordination geometries.

Acknowledgments

I would like to thank all my past and present co-workers who contributed to this area of research. Financial support from the German Research Foundation (DFG) is gratefully acknowledged. Images of crystal structures and calculated structures were created with PyMOL (DeLano Scientific LLC).

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