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Chiral-Auxiliary-Mediated Asymmetric Synthesis of Ruthenium Polypyridyl Complexes

LEI GONG,[†] MARIANNE WENZEL,[‡] AND ERIC MEGGERS*[,†,‡]

[†]*Fujian Provincial Key Laboratory of Chemical Biology, Department of Chemical Biology, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen, Fujian 361005, People's Republic of China, and* [‡]*Fachbereich Chemie, Philipps-Universität Marburg, Hans-Meerwein-Strasse, 35043 Marburg, Germany*

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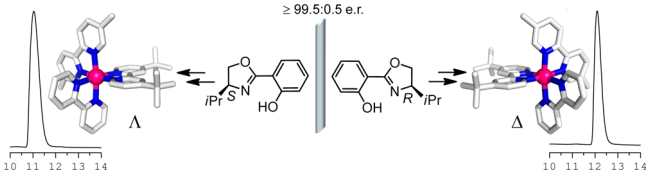
CONSPECTUS



An octahedral metal complex with 6 different monodentate ligands can form 15 diastereomers as pairs of enantiomers. As a result, the elaborate stereochemistry of octahedral coordination geometries provides tremendous opportunities in the fields of catalysis, the materials sciences, and the life sciences. The demand for enantiomerically pure coordination complexes for tasks related to the selective molecular recognition of biomacromolecules led us to develop synthetic methods to control the absolute stereochemistry at octahedral metal centers. A few years ago our laboratory therefore embarked on a project exploring new and general synthetic strategies for the asymmetric synthesis of inert octahedral transition metal complexes. We initially used the example of thermally inert ruthenium polypyridyl complexes and developed a family of chiral bidentate ligands, including salicyloxazolines, (mercaptophenyl)oxazolines, sulfinylphenols, *N*-acetylsulfinamides, a phosphinohydroxybinaphthyl, and even the amino acid proline to serve as chiral auxiliaries for asymmetric coordination chemistry. All these chiral auxiliaries strongly coordinate to ruthenium(II) in a bidentate, deprotonated fashion, allowing them to control the absolute metal-centered configuration in the course of subsequent ligand exchange reactions. Finally, we can remove them from the metal without any loss of chiral information and without leaving a chemical trace. A key feature of these chiral auxiliary ligands is their switchable binding strength. A chelate effect ensures 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. At the same time a coordinating phenolate, carboximidate, carboxylate, or thiophenolate moiety makes the coordination reversible by weakening the binding strength through protonation or methylation. Following this strategy, we synthesized a large number of homoleptic, bis-heteroleptic, and tris-heteroleptic ruthenium polypyridyl complexes in an asymmetric fashion with enantiomeric ratios that routinely reached or exceeded 96:4. Our approach should serve as a blueprint for the asymmetric synthesis of different classes of ruthenium complexes and chiral coordination complexes of other metals

Introduction

This year marks the 100th anniversary of the Nobel Prize in Chemistry awarded to Alfred Werner in recognition of his pioneering contributions to coordination chemistry, in particular the chemistry and theory of octahedral coordination complexes.[1] The elaborate stereochemistry of six-coordinate octahedral coordination geometries is nowadays a key feature for many applications in different areas of chemical research, ranging from catalysis to the materials sciences and the life sciences. In the life sciences, for instance, substitutionally inert octahedral coordination complexes have been established as versatile structural templates for the design of highly selective binders of nucleic acids[2−5] and proteins,[6,7] thereby exploiting the sophisticated globular and, due to chelation-induced conformational restrictions, often rigid coordination structures. As to be expected, for such applications of molecular recognition of chiral biomacromolecules, the chirality-at-metal plays an important role.[8−19] In fact, the influence of the metal-centered chirality for the molecular recognition of

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proteins was noticed already more than half a century ago in a landmark study by the Australian chemist Francis P. Dwyer.[20,21] Namely, Dwyer reported a significant stereodifferentiation in the binding of the enantiomers of $[Ru(bpy)_3](ClO_4)_2$, bpy = 2,2′-bipyridine, to the enzyme acetylcholine esterase with the Δ-enantiomer (right-handed propeller) showing 90% inhibition, yet the Λ-enantiomer (left-handed propeller) only 20% inhibition at a concentration of 100 μM. For this study, the optically pure ruthenium polypyridyl complexes were obtained from the resolution of a racemic mixture by using the different solubilities of the diastereomeric antimonyl tartrate salts.[22] In fact, until today, most reported nonracemic synthetic octahedral metal complexes, such as chiral ruthenium polypyridyl complexes synthesized for biological investigations,[8−22] are derived through chiral resolution of racemic mixtures into their Λ- and Δ-antipodes at some stage during the synthesis routes. To circumvent such often time-consuming and uneconomical chiral separation techniques, the development of general synthetic methods for the asymmetric synthesis of chiral metal complexes is an important goal in contemporary coordination chemistry and will ultimately facilitate to take full advantage of the sophisticated stereochemistry of octahedral coordination geometries.

Background: From Diastereoselective Coordination Chemistry to Chiral Auxiliaries

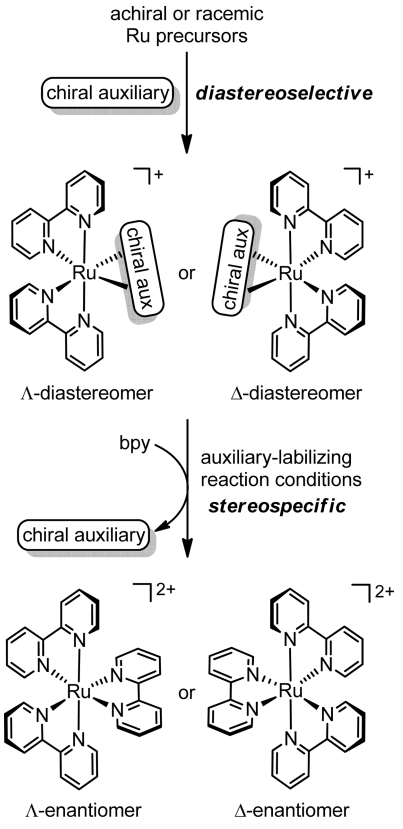
Over the last decades, many laboratories made important contributions to the development and understanding of chirality transfer from chiral coordinating ligands to transition metal centers, typically by employing carefully tailored chiral multidentate ligands that provide high diastereoselectivities in the course of coordination reactions.[23−27] On the other hand, much less effort has been dedicated to the more challenging asymmetric synthesis of nonracemic chiral-at-metal complexes devoid of any chirality in the metal coordinating ligands. The previously reported examples into this direction exploited mainly one of three distinct strategies: the temporary coordination of chiral monodentate or bidentate ligands, the attachment of cleavable chiral groups or linkers to the periphery of coordinating ligands, and the utilization of chiral counterions.[28] Bailar was the first to describe such a chiral-auxiliary-mediated asymmetric synthesis of octahedral transition metal complexes[29] and applied it to the synthesis of enantiomerically enriched $[Ru(bpy)_3]^{2+}$ by reacting K_2RuCl_5 hydrate first with the chiral auxiliary (*R*,*R*)-(+)-tartrate, affording *in situ* an undefined "tartratoruthenium complex", followed by the reaction with an excess of bpy to yield the nonracemic ruthenium complex $[Ru(bpy)_3]^{2+}$, albeit with a very modest enantiomeric Λ/Δ ratio of merely around 2:1.[30] More recently, Inoue and coworkers reported the use of a monodentate chiral sulfoxide as chiral auxiliary. The reaction of (*R*)-(+)-methyl *p*-tolyl sulfoxide with either *trans*- or *cis*-$[Ru(pp)_2Cl_2]$ in DMF at 120 °C afforded *cis*-$[Ru(pp)_2\{(R)$-(+)-methyl *p*-tolyl sulfoxide$\}$-Cl]Cl with a Δ/Λ-ratio of 2.8:1 for pp = bpy and a Δ/Λ-ratio of 4:1 for pp = 4,4′-dimethyl-2,2′-bipyridine.[31] A subsequent substitution of the coordinated chiral sulfoxide and chloride against bipyridyl ligands under retention of configuration yielded enantiomerically enriched tris(2,2′-bipyridine) complexes, thus rendering the chiral sulfoxide a true chiral auxiliary for ruling the absolute configuration at the metal center. Starting from racemic *cis*-$[Ru(pp)_2Cl_2]$, Aït-Haddou and co-workers improved the diastereoselective coordination of the chiral sulfoxide by performing the reactions under microwave irradiation to afford d.e. values of up to 76% (Δ/Λ = 7.3:1) with yields reaching 99%.[32] Because of different solubilities of the two formed diastereomers, the diastereomeric purity of the major isomer could be further improved by washing or crystallization protocols.

Although these reports of using transiently coordinated chiral ligands as chiral auxiliaries are not applicable in a general fashion to the asymmetric synthesis of enantiomerically pure ruthenium(II) polypyridyl complexes, they are pointing into a promising direction but at the same time reveal the challenges associated with the asymmetric synthesis of inert transition metal complexes: the typically required harsh reaction conditions for inducing ligand substitutions limit available strategies for efficient asymmetric inductions while permitting later removal of the transient chirality-inducer without loss of chiral information. Bailar et al.,[29,30] Inoue et al.,[31] and Aït-Haddou et al.[32] addressed this issue with relatively weak but reversibly coordinating ligands but at the cost of obtaining only moderate asymmetric inductions.

Our Strategy and Overview

We developed a new approach for the chiral-auxiliary-mediated asymmetric synthesis of inert transition metal complexes, using the example of ruthenium(II) polypyridyl complexes, by applying a class of tailored chiral coordinating bidentate ligands which provide excellent asymmetric inductions during coordination chemistry and can afterward be removed in a traceless fashion from the metal without loss of chiral information.[33−42] A key aspect of these new chiral auxiliary ligands is their switchable binding

SCHEME 1. Overall Strategy for the Chiral-Auxiliary-Mediated Asymmetric Synthesis of Ruthenium Polypyridyl Complexes Using the Example of $[Ru(bpy)_3]^{2+}$ [a]



[a]Note that the chiral auxiliary deprotonates upon coordination.

strength: a chelate effect ensures 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 effectively control the absolute metal-centered configuration during highly diastereoselective ligand substitution chemistry, whereas a coordinating phenolate, enolate, carboxylate, or thiophenolate moiety warrants that the coordination can be made reversible by weakening the binding strength through protonation or methylation and thus permits a stereospecific replacement of the chiral auxiliary ligand against an achiral ligand under retention of configuration (Scheme 1). The developed and/or applied chiral auxiliaries such as salicyloxazolines (**Salox**, **Salox'**),[33−36] 2-diphenylphosphino-2′-hydroxy-1,1′-binaphthyl (**HO-MOP**),[37] sulfinylphenols (**SO**, **SO'**),[38,39] *N*-acetylsulfinamides (**ASA**),[40] (mercaptophenyl)oxazolines (**TS**),[41] and even the natural amino acid proline[42] in combination with a variety of achiral or racemic ruthenium precursors allowed us to asymmetrically synthesize a large number of homoleptic, bis-heteroleptic, and tris-heteroleptic ruthenium(II) polypyridyl complexes with

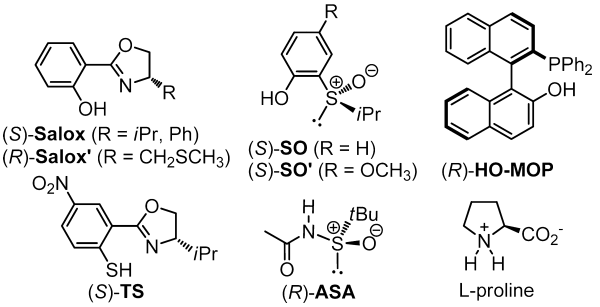


FIGURE 1. Collection of chiral auxiliaries developed and/or applied by Meggers and co-workers for asymmetric coordination chemistry.

enantiomeric ratios routinely exceeding 96:4 e.r. and often reaching e.r. values of above 99:1 (Figure 1 and Table 1).

Auxiliary-Mediated Diastereoselective Coordination Chemistry

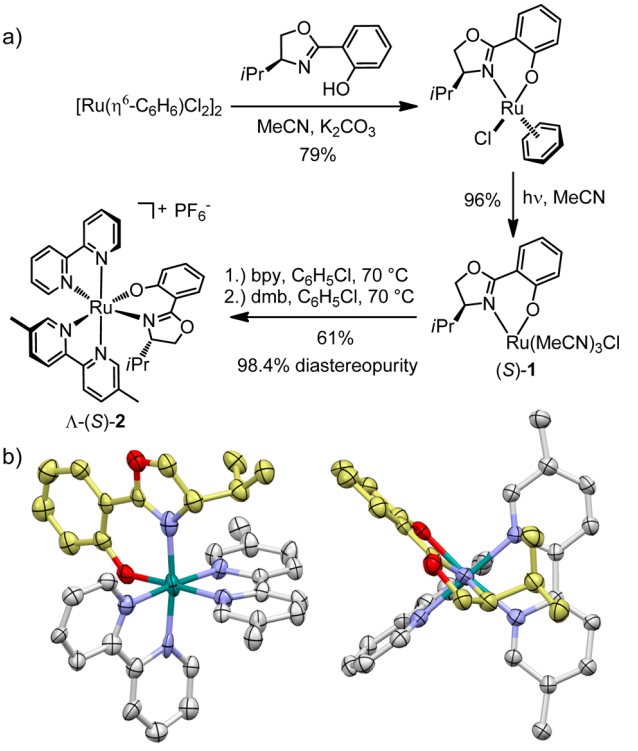
Our studies began with investigating the scope of chiral salicyloxazolines as chiral auxiliaries for asymmetric coordination chemistry because chiral oxazolines are not only excellent coordinating ligands but also readily available from chiral α-amino acids.[33−35] In our initial attempts to influence the chiral ruthenium center with the carbon-based chirality of the oxazoline moiety, we investigated the diastereoselectivity of ligand substitution reactions of the precursor complex (*S*)-**1**, which harbors a deprotonated (*S*)-4-isopropyl-2-(2′-hydroxyphenyl)oxazoline ligand {(*S*)-**Salox**} in addition to four monodentate ligands.[33] Revealingly, as shown in Scheme 2, 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*)-**1** with first 1 equiv of bpy in chlorobenzene at 70 °C and subsequently with 5,5′-dimethyl-2,2′-bipyridine (dmb) again in chlorobenzene at 70 °C afforded complex Λ-(*S*)-**2** with virtually complete diastereoselectivity (diastereopurity >98% as determined by ^{1}H NMR). A crystal structure of the monocation Λ-(*S*)-**2** is shown in Scheme 2 and reveals a Λ-configuration at the ruthenium center with the *i*Pr-group stacking on the dmb ligand. Thus, the formation of Λ-(*S*)-**2** can be rationalized by the stereoselective incorporation of the first added ligand bpy at the two coordination sites pointing the farthest away from the *i*Pr-group, with the following second bidentate ligand dmb filling the remaining two vacant coordination sites. 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

TABLE 1. Compilation of Ruthenium Complexes Used in Our Studies As Direct Starting Materials for Diastereoselective Coordination Chemistry and Overview of Synthesized Nonracemic Ruthenium Polypyridyl Complexes[a]

entry	ruthenium precursors	chiral auxiliaries	synthesized polypyridyl complexes[b,c]	remarks
1	$[RuCl_2(dmso)_4]$	**Salox**, **Salox′**	Λ- and Δ-$[Ru(bpy)_3]^{2+}$	diastereoselective ligand substitutions
2	$RuCl_3 \cdot 3H_2O$	**Salox′**	Δ-$[Ru(bpy)_3]^{2+}$	diastereoselective ligand substitutions
3	[Ru(aux)$(MeCN)_3$Cl][d]	**Salox**, **ASA, TS**	Λ-$[Ru(bpy)_3]^{2+}$, Λ-$[Ru(phen)_3]^{2+}$, Λ-$[Ru(dmb)_3]^{2+}$, Λ-$[Ru(bpy)_2(dmob)]^{2+}$, Λ-$[Ru(phen)_2(dmob)]^{2+}$, Λ-$[Ru(dmb)_2(dmob)]^{2+}$, Λ-[Ru(bpy)(dmb)(dbb)]$^{2+}$, Λ-[Ru(bpy)(dmb)(dmob)]$^{2+}$, Λ-[Ru(bpy)(dmb)(phen)]$^{2+}$	diastereoselective ligand substitutions
4	[Ru(bpy)$(MeCN)_3$Cl]Cl	**HO-MOP**	Λ-$[Ru(bpy)_3]^{2+}$, Λ-[Ru(bpy)(dmb)(dmob)]$^{2+}$	diastereoselective ligand substitutions
5	[Ru(bpy)(η^6-C_6H_6)Cl]Cl	**Salox′**, **HO-MOP**	Λ- and Δ-$[Ru(bpy)_3]^{2+}$, Δ-[Ru(bpy)(dmb)(phen)]$^{2+}$	removal of η^6-coordinated benzene
6	$[Ru(\eta^6\text{-}C_6H_6)Cl_2]_2$	**HO-MOP, ASA**	Λ-$[Ru(bpy)_3]^{2+}$	removal of η^6-coordinated benzene
7	racemic *cis*-$[Ru(pp)_2Cl_2]$[e]	**SO**, **SO′**, **ASA**, proline	Λ-$[Ru(bpy)_3]^{2+}$, Λ-$[Ru(dmb)_3]^{2+}$, Λ-$[Ru(phen)_3]^{2+}$, Δ-$[Ru(bpy)_2(dppz)]^{2+}$, Λ-[Ru(bpy)(dmb)(phen)]$^{2+}$, Λ-[Ru(bpy)(dmb)(dbb)]$^{2+}$	dynamic thermodynamic resolution
8	*trans*-$[Ru(bpy)_2(MeCN)_2]$-$(CF_3SO_3)_2$	**SO**, **SO′**	Δ-$[Ru(bpy)_3]^{2+}$	asym. trans → cis isomerization

[a]See refs 33−42 for detailed reaction conditions. [b]bpy = 2,2′-bipyridine, dmb = 5,5′-dimethyl-2,2′-bipyridine, dmob = 4,4′-dimethoxy-2,2′-bipyridine, dbb = 4,4′-di-*tert*-butyl-2,2′-bipyridine, dppz = dipyrido-[3,2-a:2′,3′-c]-phenazine, phen = 1,10-phenanthroline. [c]Complexes were isolated as their hexafluorophosphate salts. [d]Aux = deprotonated chiral auxiliary coordinated in a bidentate fashion. [e]pp = bidentate polypyridyl ligands.

SCHEME 2. (a) Diastereoselective Synthesis of Salicyloxazoline Complex Λ-(*S*)-**2** from Precursor (*S*)-**1** and (b) Crystal Structure of the Cation Λ-(*S*)-**2** from Two Different Perspectives[a] and ORTEP Drawing with 50% Probability Thermal Ellipsoids

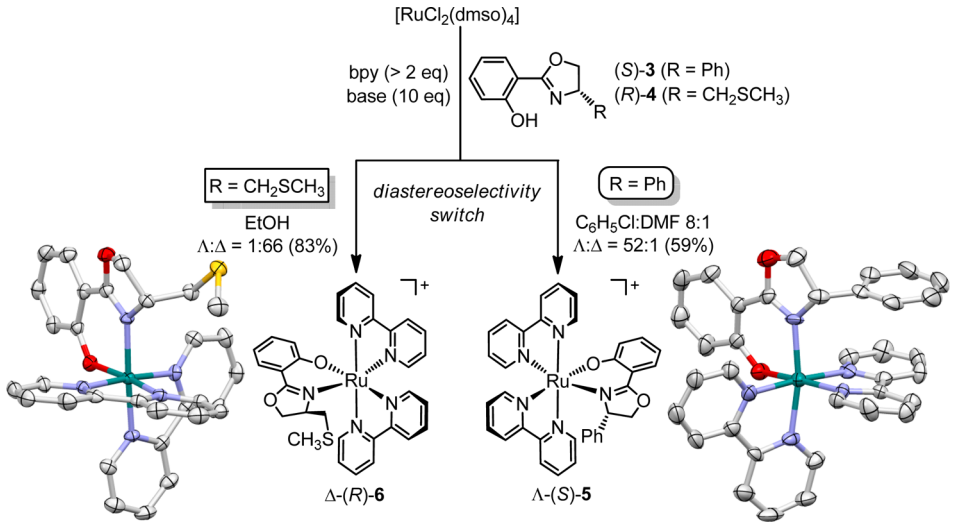


[a]With the carbon atoms of the auxiliary ligand colored in yellow.

modest d.r. values. It is worth noting that a combination of computational and experimental results revealed that the observed stereoselectivities are in fact under thermodynamic control favoring the formation of the thermodynamically most stable diastereomer, although additional kinetic effects are likely to play a significant role as well. Additional insight into the scope and limitation of this synthetic method plus an empirical guide to optimal standard reaction conditions has been reported by us recently.[34]

In the quest for straightforward and economical asymmetric syntheses of chiral octahedral metal complexes, we were seeking alternatives to precursor complexes such as (*S*)-**1** as they are not only relatively unstable and therefore must be prepared freshly but also because their synthesis involves one photochemical step which requires more specialized equipment (Scheme 2). Fortuitously, we very recently found that the reaction of the readily accessible ruthenium precursor complex $[RuCl_2(dmso)_4]$ with (*S*)-4-phenyl-2-(2′-hydroxyphenyl)oxazoline {(*S*)-**3**} in the presence of bpy (8 equiv) and K_2CO_3 (10 equiv) in C_6H_5Cl/DMF (8:1) at 140 °C for 2 h afforded in a one-pot procedure the thermodynamically favored diastereomer Λ-(*S*)-**5** (59%) in a single step and with high diastereocontrol (52:1 d.r.).[35] The crystal structure in Scheme 3 reveals a favorable stacking of the phenyl substituent on one of the bpy ligands. However, to our big surprise, when we employed the oxazoline derivative (*R*)-**4** instead, in which the phenyl substituent is replaced by a thioether, the stereochemical outcome of this reaction was completely switched, providing the Δ-diastereomer (Δ-(*R*)-**6**) smoothly in 83% yield with 66:1 d.r. under optimized conditions with EtOH as the solvent, Et_3N (10 equiv) as the base, 2.2 equiv of bpy, and reflux overnight (Scheme 3).[35] A crystal structure of the thioether complex Δ-(*R*)-**6** is displayed in Scheme 3 and confirmed an opposite stereochemistry with a Δ-configuration at the metal (right-handed propeller) and unambiguously demonstrating that the thioether ligand, although essential for the stereochemical outcome of the reaction, is indeed not

SCHEME 3. Controling Chirality-at-Metal by the Substituent of the Salicyloxazoline Auxiliaries in a Convenient Diastereoselective One-Pot Formation of Salicyloxazolinate Complexes[a]

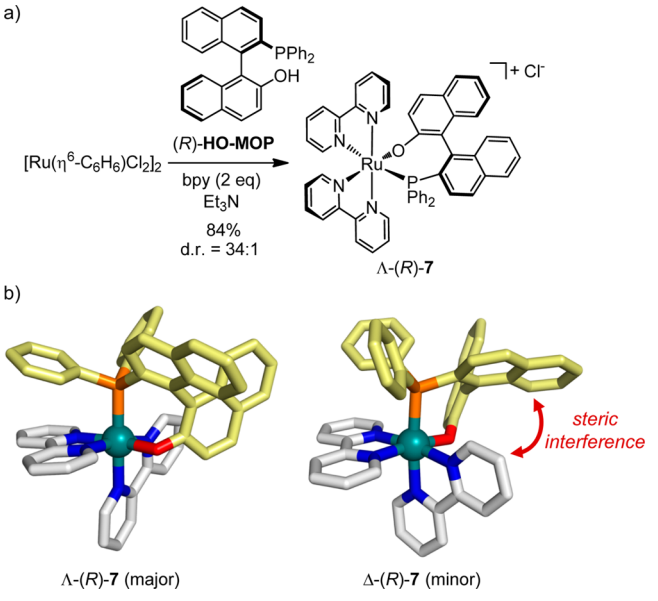


[a]Shown are the X-ray crystal structures of the monocations Λ-(*S*)-**5** and Δ-(*R*)-**6**. Note that according to the Cahn-Ingold-Prelog priority rules, the formal assignment of the absolute stereochemistry at the oxazoline moiety changes from *S* to *R* upon introduction of the sulfur into the substituent.

coordinated to the ruthenium in the product. This surprising sulfur-effect for the chirality transfer from carbon to metal most likely relies on the active participation of a transiently coordinating thioether substituent, causing a reversal of the stereochemical outcome compared to the commonly applied passive steric control of chiral moieties such as in (*S*)-**1** and (*S*)-**3**. This work therefore reveals a new mechanism for the stereocontrolled synthesis of octahedral metal complexes. From a purely practical perspective, the here reported reaction sequence provides a highly convenient access to nonracemic ruthenium polypyridyl complexes starting from the common precursor $[RuCl_2(dmso)_4]$ which can be synthesized from $RuCl_3$ in a single step. In fact, the thioether-assisted diastereoselective synthesis of Δ-(*R*)-**6** can even be executed starting directly from $RuCl_3 \cdot 3H_2O$, albeit in a somewhat lower yield (53% with 36:1 d.r.).

Whereas the **Salox** and **Salox**′ systems enable the transfer of chirality from a stereogenic carbon atom to a ruthenium center, related ligands that provide a different source of chirality, such as the bidentate ligand (*R*)-2-diphenylphosphino-2′-hydroxy-1,1′-binaphthyl {(*R*)-**HO-MOP**} possessing axial chirality,[43] can be used in an analogous fashion.[37] For example, we found that (*R*)-**HO-MOP** serves as an effective chiral auxiliary starting from different metal precursor complexes, most notably 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

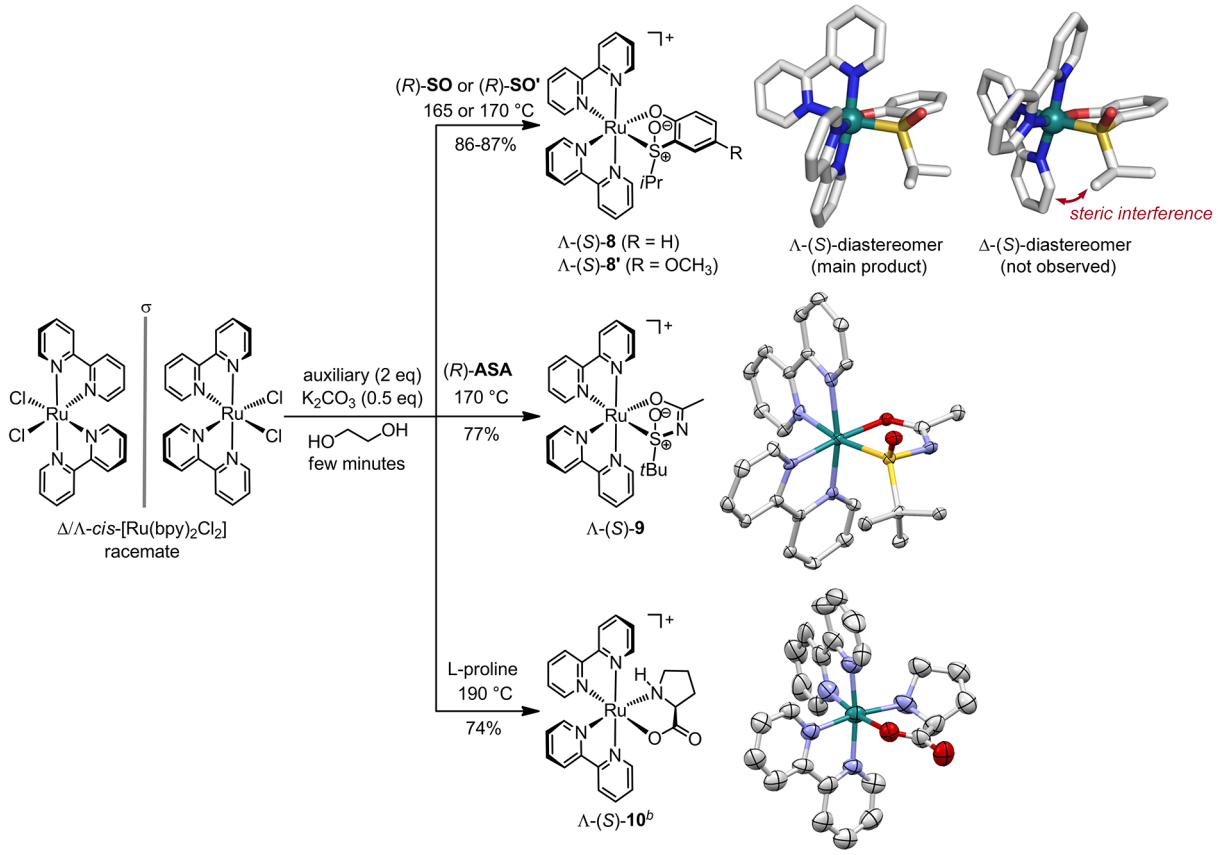
SCHEME 4. Transfer of Axial Chirality of (*R*)-**HO-MOP** to Metal-Centered Chirality in an Auxiliary-Mediated Asymmetric Synthesis[a]



[a](a) Example reaction for the application of (*R*)-**HO-MOP** and (b) DFT-calculated geometries of the major and minor diastereomer.

the complex Λ-[Ru(bpy)$_2${(*R*)-**HO-MOP**}]Cl (Λ-(*R*)-**7**) in a yield of 84% and with a satisfactory diastereoselectivity of 34:1 d.r. (Scheme 4). Density functional theory calculations verified that the preferentially formed Λ-(*R*)-diastereomer is thermodynamically more stable in analogy to the thermodynamically controlled diastereoselective coordination chemistry with the **Salox** chiral auxiliary. The structures shown in Scheme 4 demonstrate that this is apparently due to a direct

SCHEME 5. Dynamic Resolution under Thermodynamic Control Allows the Use of the Racemic Starting Material *cis*-$[Ru(pp)_2Cl_2]$[a]



[a]Note that according to the Cahn-Ingold-Prelog priority rules, the formal assignment of the absolute stereochemistry at the sulfur changes from *R* to *S* upon coordination to the ruthenium center. [b]Crude d.r. ≥ 20:1, after purification d.r. ≥ 100:1.

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*)-**7**, one naphthalene moiety is instead favorably stacked face-to-face with a bpy ligand. Overall, **HO-MOP** is an interesting auxiliary for performing diastereoselective coordination chemistry starting with ruthenium(II) half-sandwich complexes. However, some drawbacks limit the general applicability of **HO-MOP** as chiral auxiliary for asymmetric coordination chemistry. First, the observed diastereoselectivities are only modest compared to the **Salox** and **Salox**′ auxiliaries, and second all investigated complexes containing the deprotonated **HO-MOP** ligand are quite labile and therefore need to be handled with great care by avoiding proton sources and Lewis acids. This instability is most likely due to the unfavorable seven-membered chelate in combination with a large steric crowding within the coordination sphere.

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. With this anticipation, we designed (*R*)- and (*S*)-2-(isopropylsulfinyl)phenols (**SO** and **SO**′, Figure 1) as auxiliaries for asymmetric coordination chemistry.[38,39] Indeed, these auxiliaries turn out to be highly valuable reagents for several applications. For example, we 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 *cis*-$[Ru(bpy)_2Cl_2]$ into single diastereomers Λ-$[Ru(bpy)_2\{(R)$-**SO**$\}]PF_6$ (Λ-(*S*)-**8**) and Λ-$[Ru(bpy)_2\{(R)$-**SO**′$\}]PF_6$ (Λ-(*S*)-**8**′), respectively, in a thermodynamically controlled dynamic transformation, in analogy to the discussed work with monodentate sulfoxides by Inoue and Aït-Haddou but with significantly higher diastereoselectivities (Scheme 5).[38] 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, leading to a large difference in the stabilities of the intermediate Λ-(*S*) and Δ-(*S*) diastereomers and thereby providing 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 racemic starting materials *cis*-[Ru(pp)$_2$Cl$_2$], with pp = 1,10-phenanthroline (phen) or dmb and should be of practical value for the asymmetric synthesis of ruthenium polypyridyl complexes because of readily available racemic ruthenium complexes as starting materials.

However, the chiral 2-sulfinylphenols **SO** and **SO′** are somewhat cumbersome to synthesize in a highly enantiomerically pure fashion and thus of limited practical value. Seeking readily accessible, atom-economical chiral sulfoxide auxiliaries, we envisioned that the *N*-acetylsulfinamide shown in Figure 1 might be an interesting candidate by coordinating reversibly as a bidentate ligand through its deprotonated *N*-sulfinylcarboximidate form.[40] Conveniently, (*R*)-*N*-acetyl-*tert*-butanesulfinamide {(*R*)-**ASA**} can be synthesized in a single step by acetylation of commercially available enantiomerically pure *tert*-butanesulfinamide (Ellman's sulfinamide), a compound that is well established in organic synthesis as a chiral auxiliary for asymmetric transformations involving carbonyl groups.[44] We reacted (*R*)-**ASA** with racemic *cis*-[Ru(bpy)$_2$Cl$_2$] in the presence of 0.5 equiv of K_2CO_3 in ethylene glycol at 170 °C for 90 s, analogous to the above outlined procedure developed for chiral sulfinylphenol auxiliaries, and to our delight obtained Λ-[Ru(bpy)$_2${(*R*)-**ASA**}]PF$_6$ (Λ-(*S*)-**9**) as a single diastereomer in a yield of 77% (Scheme 5).

In order to further simplify the generation of nonracemic ruthenium complexes, we turned our attention to the amino acid proline because it has been demonstrated over the past decade or so that proline is a highly versatile catalyst for asymmetric organic transformations (asymmetric organocatalysis),[45] and we imagined that it could also serve as a cheap and readily available powerful chiral auxiliary for asymmetric coordination chemistry. Our strategy was inspired by investigations of Williams and co-workers, who reported that in (*S*)-aminoacidate complexes of the type Δ,Λ-[Ru(pp)$_2${(*S*)-aminoacidate}]$^+$, pp = bidentate polypyridyl ligand, the Λ-diastereomer is typically thermodynamically more stable and the authors explained this observation with an interligand repulsion between the α-pyridyl proton of one diimine ligand and the α-side chain of the aminoacidate ligand in the less favored Δ-propeller.[46] We speculated that this thermodynamic difference between the Λ- and Δ-diastereomer should be most pronounced in the related ruthenium-prolinate complexes which might enable us to develop an asymmetric synthesis of ruthenium polypyridyl complexes by a dynamic transformation based on an equilibrium between two diastereomers of significantly different stabilities. Indeed, when racemic *cis*-[Ru(bpy)$_2$Cl$_2$] was reacted with 2 equiv of L-proline in ethylene glycol and in the presence of 0.5 equiv of K_2CO_3 at 190 °C for a few minutes, Λ-[Ru(bpy)$_2$(L-pro)]PF$_6$ (Λ-(*S*)-**10**) formed as the main product with a crude diastereoselectivity between the Λ- and Δ-diastereomer of ≥20:1.[42] Silica gel column chromatography then afforded Λ-(*S*)-**10** in an isolated yield of 74% and a d.r. value of at least 100:1 as determined by ^{1}H NMR. In contrast to the reactions with (*S*)-**SO**/**SO′** and (*R*)-**ASA**, in the L-proline system the minor diastereomer Δ-(*S*)-**10** could be isolated in small quantities.

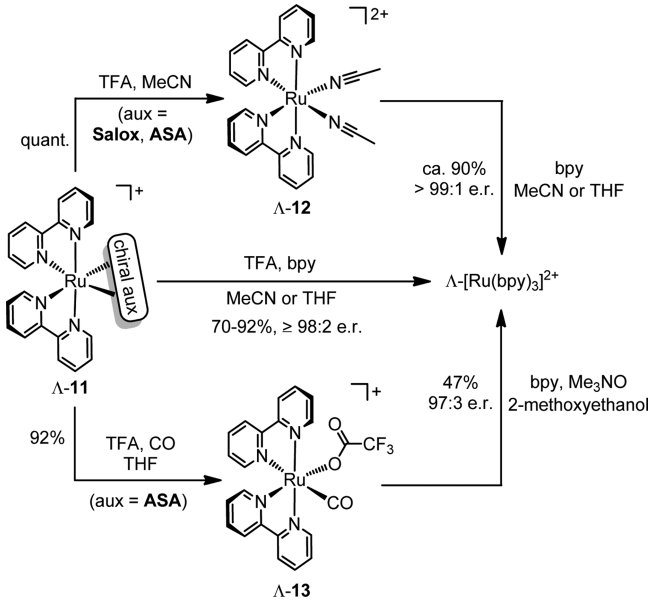
We assume that these three outlined diastereoselective reactions of (*R*)-**SO**/**SO′**, (*R*)-**ASA**, and L-proline with racemic *cis*-[Ru(bpy)$_2$Cl$_2$] all proceed through the same reaction mechanism in which probably initially both diastereomers Λ-(*S*) and Δ-(*S*) are formed but that under the optimized high temperature reaction conditions, the thermodynamically less favored diastereomer Δ-(*S*) is unstable and reversibly releases the auxiliary ligand. Since under these conditions the two enantiomers of the starting material must be in an equilibrium with each other through the dissociation of one or two chlorides and the formation of coordinatively unsaturated intermediates, the unstable and reversibly formed diastereomer Δ-(*S*) can convert to the more stable diastereomer Λ-(*S*). This would constitute a dynamic resolution under thermodynamic control.[47] This proposed mechanism is supported by an experiment in which we heated the minor diastereomer Δ-(*S*)-**10** in ethylene glycol at 190 °C under argon for 10 min and found a conversion to the major diastereomer Λ-(*S*)-**10** with a crude d.r. of ≥20:1 and an isolated yield of 60% (d.r. > 100:1). This thermally induced Δ → Λ conversion most likely involves the dissociation or at least labilization of the L-prolinate ligand because the yield for this isomerization increased to 82% if the Δ → Λ conversion was performed in the presence of additional L-proline (10 equiv) for 20 min, thereby most likely suppressing side reactions of coordinatively unsaturated ruthenium intermediates after the dissociation of proline from Δ-(*S*)-**10**. These methods exploiting a dynamic asymmetric transformation under thermodynamic control are attractive because they draw from the readily available racemic starting material *cis*-[Ru(pp)(pp′)Cl$_2$].

Stereospecific Auxiliary Removal under Retention of Configuration

A chiral auxiliary for the asymmetric synthesis of metal complexes has not only the task to control the metal

centered chirality in the course of ligand exchange reactions but must also be removable without affecting the metal centered configuration.[48,49] Our strategy of auxiliary-mediated asymmetric coordination chemistry therefore relies on the ability to trigger a labilization of the coordinated, deprotonated auxiliaries. In fact, we found that all auxiliaries which coordinate through a basic oxygen ligand such as phenolate (**Salox**, **Salox**′, **HO-MOP**, **SO**, **SO**′),[33−39] carboximidate (**ASA**)[40] or carboxylate (proline)[42] can be replaced smoothly against polypyridyl ligands in the presence of a strong acid, preferably trifluoroacetic acid (TFA). Under our standard reaction conditions (15 equiv of polypyridyl ligand, 5 equiv of TFA, MeCN, closed vessel, 110 °C), the substitution occurs under complete retention of configuration without any noticeable loss of chiral information (70−92% yields, ≥98:2 e.r.) (Scheme 6). It is worth noting that other acids such as HCl gave inferior results, revealing that the conjugate base affects the reaction outcome.[34] Crucial for a suppression of any racemization in the course of the substitution reaction is also the use of a coordinating solvent such as MeCN or THF, presumably to stabilize the reactive, more labile intermediate that is formed after TFA-induced dissociation of the auxiliary.[34] Indeed, treating auxiliary complexes Λ-$[Ru(pp)_2(aux)]^+$ (aux = deprotonated chiral auxiliary coordinated in a bidentate fashion), such as Λ-**11**, with TFA in MeCN at 50 °C provides in quantitative yields the complexes Λ-$[Ru(pp)_2(MeCN)_2]^{2+}$, such as Λ-**12**, which can subsequently be converted to enantiomerically pure ruthenium polypyridyl complexes.[33,34,40] We also recently disclosed a variation of this two step procedure by first reacting Λ-$[Ru(bpy)_2\{(R)$-**ASA**$\}]^+$ with TFA under a saturated CO-atmosphere to afford the surprisingly stable complex Λ-**13** in which the auxiliary was replaced by CO and one trifluoroacetate ligand, followed by a conversion into Λ-$[Ru(bpy)_3]^{2+}$ (47%, 97:3 e.r.) by reacting it with bpy and Me_3NO in 2-methoxyethanol at room temperature, in analogy to a method developed by Keene and co-workers.[40,48]

SCHEME 6. TFA-Mediated Routes for the Substitution of the Coordinated, Deprotonated Chiral Auxiliaries against bpy under Retention of Configuration with the Chiral Auxiliaries **Salox**, **Salox**′, **HO-MOP**, **SO**, **SO**′, **ASA**, and Proline

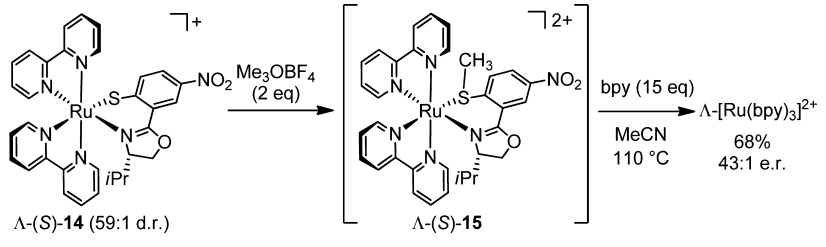


All thus far discussed reaction sequences involve the use of the strong acid TFA at elevated temperature, but not all functional groups can withstand these conditions. We were therefore seeking auxiliaries that permit the final replacement under different conditions. Indeed, in a recent study we found that coordinated, deprotonated (mercaptophenyl)oxazolines[41] can be weakened and subsequently substituted by first methylating the thiophenolate ligand with Meerwein salt *in situ*, followed by a replacement of the thioether ligand with a bipyridyl ligand under retention of configuration and with only a slight loss of chiral information (Λ-(*S*)-**14** → {Λ-(*S*)-**15**} → Λ-$[Ru(bpy)_3]^{2+}$, Scheme 7).

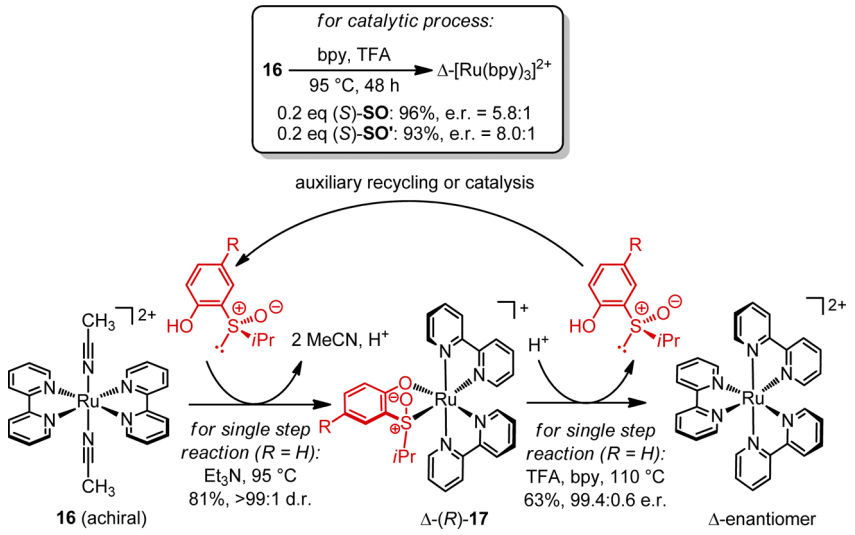
Conclusions and Outlook

Over the last several years, our laboratory developed a series of chiral auxiliaries which permit the asymmetric synthesis of virtually enantiomerically pure ruthenium polypyridyl complexes bearing only achiral polypyridyl ligands, thus circumventing the need for the resolution of stereoisomers at any stage during the synthesis. The developed

SCHEME 7. Replacement of a Thiophenolate Ligand under Retention of Configuration Induced by Methylation with the Meerwein Salt



SCHEME 8. From Auxiliary-Controlled Asymmetric Coordination Chemistry Based on a Chirality-Inducing trans−cis Isomerization to the Catalytic Asymmetric Synthesis of Δ-$[Ru(bpy)_3]^{2+}$ with the Chiral Ligands (*S*)-**SO** or (*S*)-**SO′** as Catalysts



strategy relies on tailored chiral bidentate ligands, the chiral auxiliaries, with tunable binding strength so that after a sequence of auxiliary-controlled diastereoselective coordination chemistry, the release of the auxiliary ligands is triggered and replaced by achiral bidentate ligands under complete retention of configuration. We recommend the auxiliary proline as our currently most straightforward and economical method for the asymmetric synthesis of polypyridyl complexes $[Ru(pp)(pp')(pp'')](PF_6)_2$ since it is based on readily available starting materials and can easily be applied to large scale synthesis.[42] Overall, we believe that the here outlined auxiliary-mediated asymmetric synthesis scheme, which was initially developed for ruthenium(II) polypyridyl complexes, might serve as a blueprint for developing asymmetric coordination chemistry of other transition metals. However, the typically required harsh reaction conditions for the final removal of the auxiliaries currently limits the scope of this strategy. Future work will also need to address the asymmetric synthesis of structurally more complicated coordination complexes with lower symmetry which, unfortunately, is not possible with the here discussed auxiliary ligands.

Finally, beyond chiral auxiliaries, organic chemistry has demonstrated over the last decades the power of catalysis for the resource-efficient and economical synthesis of chiral compounds and this will become an important direction for the asymmetric synthesis of metal complexes as well. In a first step into this direction, our laboratory recently demonstrated that the sulfinylphenols (*S*)-**SO** and (*S*)-**SO′** under carefully optimized reaction conditions can serve as catalysts for the isomerization-induced asymmetric synthesis of Δ-$[Ru(bpy)_3]^{2+}$.[39,50] Accordingly, the chiral (*S*)-(isopropylsulfinyl)phenols are capable of converting achiral *trans*-$[Ru(bpy)_2(MeCN)_2]^{2+}$ (**16**) to chiral *cis*-Δ-[Ru(bpy)$_2${(*S*)-(isopropylsulfinyl)phenolate}]$^+$ (Δ-(*R*)-**17**) under substitution of two MeCN ligands and accompanied by a chirality-generating trans−cis isomerization of the bpy ligands. The coordinated (*S*)-(isopropylsulfinyl)phenolates can subsequently become replaced by bpy under complete retention of configuration in a TFA-induced fashion (Scheme 8). This reaction sequence can be executed stepwise or as a one-pot reaction with catalytic amounts of the (*S*)-(isopropylsulfinyl)-phenols (insert in Scheme 8) so that in this latter one-pot reaction a small organic molecule serves as an asymmetric catalyst for the enantioselective, organocatalytic synthesis of an octahedral metal complex.

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BIOGRAPHICAL INFORMATION

Lei Gong is Associate Professor in the College of Chemistry and Chemical Engineering of Xiamen University, P. R. China.

Marianne Wenzel is a doctoral student in the Chemistry Department of the Philipps-University Marburg, Germany.

Eric Meggers is Professor and Chair of Chemical Biology at the Chemistry Department of the Philipps-University Marburg, Germany, and Professor in the College of Chemistry and Chemical Engineering of Xiamen University, P. R. China.

FOOTNOTES

*E-mail: meggers@chemie.uni-marburg.de, meggers@xmu.edu.cn.
The authors declare no competing financial interest.

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