Asymmetric Catalysis

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Isomerization-Induced Asymmetric Coordination Chemistry: From Auxiliary Control to Asymmetric Catalysis**

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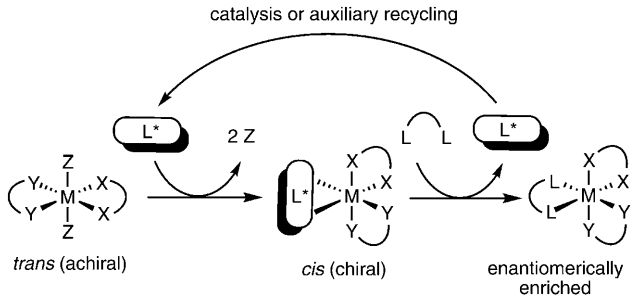
Dedicated to Professor Bernd Giese on the occasion of his 70th birthday

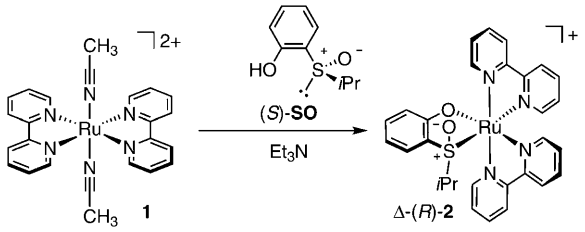
Methods for the synthesis of enantiopure chiral-at-metal octahedral coordination compounds are strongly in demand to fully exploit the structural opportunities of octahedral coordination spheres in the areas of catalysis, materials sciences, and life sciences. However, compared to the availability of highly sophisticated methods for the asymmetric synthesis of organic molecules, the synthetic control of metal-centered chirality is still in its infancy.[1] For example, to the best of our knowledge, not a single report exists of the catalytic asymmetric synthesis of a chiral octahedral metal complex.

Herein we show that tailored chiral sulfoxide ligands are capable of inducing a stereocontrolled ligand isomerization within an octahedral coordination sphere, which can be exploited for the auxiliary-mediated[2] and even the catalytic asymmetric synthesis of chiral ruthenium complexes (Scheme 1).



Scheme 1. Asymmetric coordination chemistry by asymmetric *cis–trans* isomerization induced by a chiral auxiliary or catalyst.

We selected *trans*-$[Ru(bpy)_2(MeCN)_2](CF_3SO_3)_2$[3] (**1**, Scheme 2) as our achiral model complex in which a *trans–cis* isomerization of the two 2,2′-bipyridine (bpy) ligands would afford a chiral coordination sphere. It was envisioned that certain bidentate ligands might be capable of inducing such an isomerization as they will only be able to coordinate to the *cis* complex in a bidentate fashion but not the *trans* starting compound. Furthermore, if chiral, such a ligand might lead to the asymmetric formation of predominately one metal-centered stereoisomer (Scheme 1).



Scheme 2. Highly diastereoselective conversion of prochiral *trans*-$[Ru(bpy)_2(MeCN)_2]^{2+}$ (**1**) into chiral *cis*-Δ-$[Ru(bpy)_2\{(S)\text{-}\mathbf{SO}\}]^{+}$ (Δ-(*R*)-**2**). According to the Cahn–Ingold–Prelog priority rules, the assignment of the absolute stereochemistry at the sulfur changes upon coordination from *S* to *R*.

Surprisingly, although initial efforts with our previously reported chiral salicyloxazoline auxiliary[4] were not successful at all, we discovered that the reaction of the *trans* complex **1** with (*S*)-(isopropylsulfinyl)phenol, (*S*)-**SO**,[5] in DMF or ethylene glycol in the presence of 10 equiv Et_3N, led to the completely diastereoselective formation of Δ-(*R*)-**2** without any detectable Λ-(*R*)-**2** (Scheme 2 and Table 1).[6]

Table 1: Asymmetric *trans–cis* isomerization of achiral complex **1** into Δ-(*R*)-**2**.[a]

Entry	Solvent	[**1**]	Yield	d.r.[b]
1	MeCN, acetone, or C_6H_5Cl	200 mM	no product	–
2	DMF	200 mM	80%	only Δ-(*R*)
3	$HOCH_2CH_2OH$	200 mM	81%	only Δ-(*R*)
4	$HOCH_2CH_2OH$	25 mM	72%	50:1

[a] Conditions: Reaction of **1** with 2 equiv of (*S*)-**SO** and 10 equiv Et_3N at 95 °C in a sealed brown glass vial. [b] Diastereomeric ratios determined by ^1H NMR spectroscopy.

It is noteworthy that yields and diastereoselectivities of this conversion are very sensitive to reaction conditions. For example, no product is formed with the solvents MeCN, acetone, or C_6H_5Cl, whereas in the preferred solvents DMF and ethylene glycol the d.r. value decreases slightly when the reaction is executed at lower concentrations (Table 1). This latter observation can be rationalized with a competition between a thermal background isomerization of the *trans* complex **1** into its thermodynamically more stable *cis* isomer and the (*S*)-**SO**-induced reaction to Δ-(*R*)-**2**.

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A crystal structure of the monocation Δ-(*R*)-**2** (Figure 1) confirms the Δ-configuration at the ruthenium center. The chiral bidentate (*S*)-(isopropylsulfinyl)phenol auxiliary was initially chosen because it positions the sulfur-centered chirality in direct vicinity to the metal center and is thus

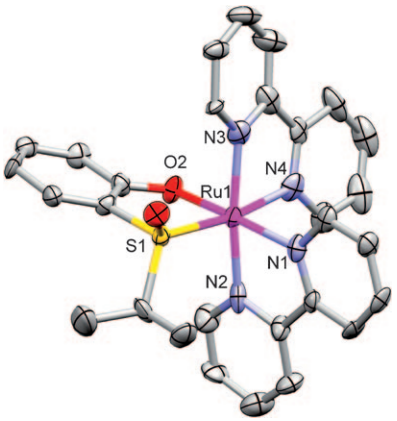
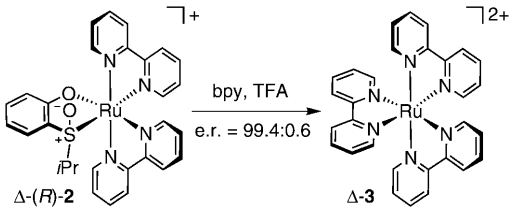


Figure 1. Crystal structure of Δ-(*R*)-**2** (ellipsoids set at 50% probability; the PF_6^- counterion and a water molecule are omitted for clarity). Selected bond lengths [Å] and angles [°]: Ru1—S1 2.237(3), Ru1—O2 2.071(7), Ru1—N1 2.049(8), Ru1—N2 2.047(10), Ru1—N3 2.070(10), Ru1—N4 2.084(10); N1-Ru1-O2 173.4(3), N2-Ru1-N3 179.8(3), N4-Ru1-S1 170.5(2), O2-Ru1-N4 86.9(3), N3-Ru1-O2 85.2(3).

expected to have an especially strong influence on controlling the absolute metal-centered configuration. Indeed, the crystal structure demonstrates that the isopropyl group comes in very close proximity to one of the bpy ligands.[7] The complex appears to release some strain by distorting the five-membered sulfoxide chelate ligand out of planarity. It is apparent that in the disfavored opposite diastereomer the isopropyl substituent would sterically clash with the CH group in the 6-position of one bpy ligand, thus explaining why Λ-(*R*)-**2** is not observed under optimized reaction conditions.[8] Interestingly, the Ru–N bond in *trans* position to the sulfoxide ligand is elongated to 2.084 Å. It can be speculated that this structural *trans* effect of the sulfoxide ligand might go along with a kinetic *trans* effect, thus helping to release the second acetonitrile ligand after the initial coordination of (*S*)-**SO** in the course of the reaction **1**→Δ-(*R*)-**2**.[9]

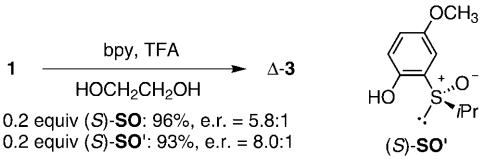
We then investigated the removal of the chiral sulfoxide ligand (*S*)-**SO** from Δ-(*R*)-**2**. A protonation of the phenolate ligand should decrease the chelate strength,[4] and indeed, when we treated Δ-(*R*)-**2** with 5 equiv of trifluoroacetic acid (TFA) in the presence of 15 equiv of bpy in freshly distilled dry acetonitrile at 110 °C (sealed vial) for 2 h, (*S*)-**SO** was replaced smoothly by bpy under retention of configuration, affording Δ-$[Ru(bpy)_3]^{2+}$ (Δ-**3**) in a yield of 63% with an enantiomeric ratio e.r. = 99.4:0.6, as determined by chiral HPLC (Scheme 3).[10,11] Thus, it can be concluded that (*S*)-(isopropylsulfinyl)phenol serves as a powerful chiral auxiliary for converting the achiral *trans* complex **1** into a virtually enantiomerically pure ruthenium polypyridyl complex.

Beyond its function as a chiral auxiliary, we envisioned that (*S*)-**SO** might even be able to serve as a catalyst for



Scheme 3. Acid-induced substitution of the chiral sulfoxide ligand (*S*)-**SO** for bpy under retention of configuration.

isomerization-induced asymmetric synthesis. Revealingly, after some optimization we found that the reaction of **1** at a high concentration in ethylene glycol (300 mM) with 0.2 equiv (*S*)-**SO** in the presence of TFA and bpy afforded Δ-**3** with a yield of 96% and an e.r. = 5.8:1 (Scheme 4). In the same system, the more electron-rich methoxy derivative (*S*)-**SO′** even afforded an e.r. of 8.0:1 with a yield of 93%.[12] This



Scheme 4. Catalytic synthesis of enantiomerically enriched Δ-$[Ru(bpy)_3]^{2+}$ (Δ-**3**) with the chiral ligands (*S*)-**SO** or (*S*)-**SO′** as catalysts.

corresponds to turnover numbers of more than 3 and demonstrates that these sulfinylphenols constitute true catalysts for the asymmetric conversion **1**→Δ-**3**. Apparently, (*S*)-**SO** and even more so the more nucleophilic (*S*)-**SO′** react significantly faster with **1** than bpy, which will be monoprotonated and thus less reactive under the acidic reaction conditions, and be subsequently recycled through an acid-promoted replacement by bpy, thus allowing a full catalytic cycle (Scheme 1).[13] It is noteworthy that along with the right amount of TFA, the nature of the solvent is crucial for a successful catalysis in this system. We recognized that in ethylene glycol the *trans* complex **1** 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 **1** at all times during the catalysis.[14]

In conclusion, we have presented an example of highly efficient isomerization-induced asymmetric coordination chemistry. Chiral (*S*)-(isopropylsulfinyl)phenol is capable of converting achiral *trans*-$[Ru(bpy)_2(MeCN)_2]^{2+}$ into chiral *cis*-Δ-$[Ru(bpy)_2\{(S)\text{-(isopropylsulfinyl)phenolato}\}]^+$ under substitution of two acetonitrile ligands and accompanied by a chirality-generating *trans–cis* isomerization of the bpy ligands. The ligand (*S*)-(isopropylsulfinyl)phenol constitutes a chiral auxiliary as it can be replaced by bpy under complete retention of configuration in an acid-induced manner. Furthermore, this study culminated in what is probably the first example of catalytic asymmetric coordination chemistry, with a small organic molecule serving as an asymmetric catalyst for

the enantioselective, organocatalytic synthesis of an octahedral metal complex.

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[8] This is consistent with the observed high chemical instability of the minor diastereomer Λ-(*R*)-**2**.

[9] For structural and kinetic *trans* effects in octahedral complexes, see: B. J. Coe, S. J. Glenwright, *Coord. Chem. Rev.* **2000**, 203, 5–80.

[10] Optimized reaction conditions: 50 mM Δ-(*S*)-**2**, 15 equiv bpy, 5 equiv TFA, distilled and dry MeCN, 110 °C in a sealed brown-glass vial, 2 h. See the Supporting Information for more details.

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[12] Optimized reaction conditions for the asymmetric catalysis with chiral sulfoxides: 300 mM **1**, 0.2 equiv (*S*)-**SO** or (*S*)-**SO′**, 1.0 equiv bpy, 6.0 equiv TFA, ethylene glycol, 95 °C in a sealed brown-glass vial under air, 48 h; thereafter addition of 10 equiv bpy and another 2 h at 95 °C to replace the ruthenium-bound catalyst. See the Supporting Information for more details.

[13] The chiral sulfoxides are configurationally stable under the acidic reaction conditions.

[14] The ruthenium complex intermediates and products were tested to be configurationally stable and soluble under the applied reactions conditions, which excludes mechanistic explanations for the observed enantiomeric excess involving chiral ion-pairing interactions or solubility differences of the intermediate ruthenium diastereomers.

