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In situ generation of sulfoxides with predetermined chirality *via* a structural template with a chiral-at-metal ruthenium complex†

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The reaction of Δ/Λ-$[Ru(bpy)_2(py)_2]^{2+}$ with a prochiral sulfide ligand, and then *in situ* oxidation, provide the corresponding Δ-$[Ru(bpy)_2\{(R)\text{-OSO-iPr}\}]^+$ and Λ-$[Ru(bpy)_2\{(S)\text{-OSO-iPr}\}]^+$ (OSO-iPr = 2-isopropylsulfonylbenzonate) enantiomers in a yield of 83% with 98% ee. The chiral sulfoxides were obtained by treatment of the sulfoxide complexes with TFA in a yield of 90% with 88–91% ee.

Chiral sulfoxides are widely used as intermediates, auxiliaries, and ligands in asymmetric synthesis, and commercial pharmaceuticals.[1] Three principal approaches can be utilized to prepare chiral sulfoxides, including separation of a racemic mixture, transformation of a reagent from the chiral pool, or the use of chiral catalysts for enantioselective synthesis. Since the first enantioselective catalyst for the oxidation of sulfides to sulfoxides was reported in 1984 by the groups of Kagan[2] and Modena,[3] some excellent asymmetric sulfoxidation reactions have been developed.[4–6] However, they still have certain disadvantages, such as low turnover numbers and ee values, the need to precisely control the reaction conditions and the water content, and overoxidation to sulfones, which stimulate the search for other catalytic systems.[1]

Traditionally, the metal-dependent asymmetric catalysts are based on a combination of a metal ion and a chiral ligand responsible for the asymmetric environment. Therefore, the stereoselective processes often rely on the chirality transfer from a chiral ligand to a catalytically active center.[7] Contrarily, the chiral-at-metal complexes with achiral ligands (for example Δ and Λ enantiomers in octahedral complexes) as a source of the asymmetric environment for catalysis have been still very rarely exploited.[8] This depends mostly on the available approaches for the preparation of the chiral-at-metal complex in an enantiopure form and its configurational stability in a catalytic reaction.[9] To the best of our knowledge, only one instance of the enantioselective oxidation of sulfides to sulfoxides mediated by the chiral-at-metal complex has been reported so far with chemoselectivity (sulfoxide/sulfone = 9 : 1) and the enantiomeric excess in the range of 7–18%.[10] Although its stereoselectivity was modest, the chirality mediated by the "chiral-at-metal" opened a new approach for asymmetric synthesis of sulfoxides. This encouraged us to observe the *in situ* oxidation of prochiral sulfides to chiral sulfoxides *via* a structural template with a chiral-at-metal ruthenium complex.

Early studies have shown that the diastereoselectivity has been found in the reaction of $[Ru(bpy)_2Cl_2]$ (bpy = 2,2′-bipyridine) and chiral sulfoxides.[9b,c,11] We perceived that octahedral stereocenters permit the straightforward generation of Δ and Λ enantiomers, which may serve as rigid scaffolds for *in situ* generation of the enantiomeric sulfoxides. To examine this hypothesis, a prochirally chelated sulfide was chosen to coordinate to Δ/Λ-$[Ru(bpy)_2(py)_2]^{2+}$, generating Δ/Λ-$[Ru(bpy)_2(OS\text{-}R)]^+$ (OS-R = 2-alkylthiobenzonate) enantiomers. We found that the bulky alkyl group of the sulfide always keeps away from the α-pyridyl proton to avoid steric congestion (see Scheme 1).[12] If this site was blocked by the alkyl group, the oxygen atom was only positioned on the other site and hydrogen bonded to the α-pyridyl proton when the sulfide was oxidated to the sulfoxide OSO-R (OSO-R = 2-alkylsulfonylbenzonate), leading to the predetermined chirality of the sulfoxide. Moreover, the overoxidation to sulfones can also be avoided by the coordination of the sulfur atom to ruthenium. The oxidation-adducts can be converted to the corresponding sulfoxides in good yields without a loss of their enantiopurity. Herein, we report our preliminary results on generation of enantiomeric sulfoxides with predictable stereospecificity *via* a chiral-at-metal complex.

The chiral precursors Δ/Λ-$[Ru(bpy)_2(py)_2]^{2+}$ were prepared according to the literature.[13] The synthesis procedures for sulfoxides are briefly summaried in Scheme 2. When Δ/Λ-$[Ru(bpy)_2(py)_2]^{2+}$ reacted with 2-(isopropylthio)benzoic acid (OS-iPr) in ethylene glycol at 120 °C for 4 h under argon protection, the corresponding products Δ/Λ-$[Ru(bpy)_2(OS\text{-}iPr)]^+$ (Δ-**1** and Λ-**1**) were afforded in a yield of *ca.* 81% after a chromatographic separation (see ESI†). The absolute metal-centered configuration of the Δ-**1** enantiomer was

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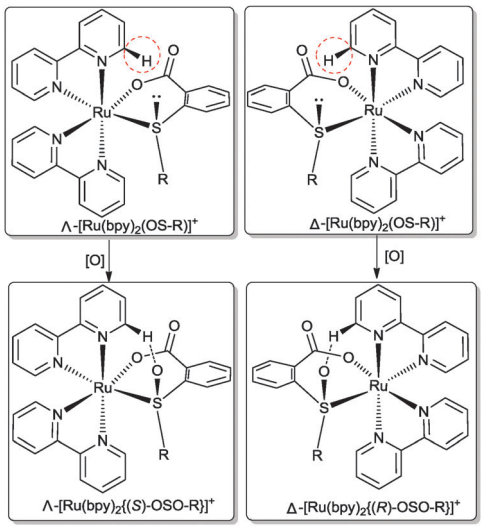
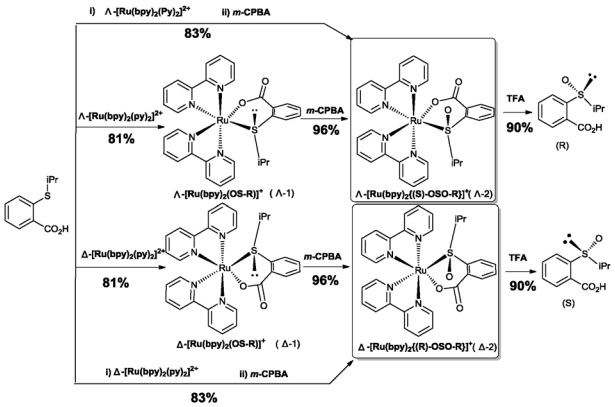


Scheme 1 Generation of enantiomeric sulfoxides from prochiral sulfides.



Scheme 2 An outline of the asymmetric synthesis of sulfoxides.

determined by X-ray crystallography[14] and is shown in Fig. 1. It crystallizes in a chiral space group *C*2. The structure verifies a *Δ* configuration at the ruthenium center and the Flack parameter (−0.015(6)) is close to zero, demonstrating that the assignment of chirality at the metal center is correct and the absolute configuration at the metal center is preserved during the reaction. Moreover, the sulfur atom indeed coordinates to the Ru atom and the isopropyl group keeps away from the α-pyridyl proton to avoid steric congestion. The optical properties of *Δ*-**1** and *Λ*-**1** were investigated *via* circular dichroism (CD). The CD spectra of the enantiomers are almost mirror images with a negative Cotton effect at 282 nm and a positive Cotton effect at 297 nm for *Δ*-**1**, and a positive Cotton effect at 281 nm and a negative Cotton effect at 297 nm for *Λ*-**1** (see Fig. S1, ESI†), suggesting that the configuration at the metal center is the dominant factor in the appearance of the spectra. The NMR spectra of *Δ*-**1** and *Λ*-**1** are almost the same, however, the two enantiomers become distinguishable in the presence of (*S*)-1,1′-binaphtol (*S*-binol) as a chiral NMR shift reagent.[15] The resonance peak at 9.47 ppm in the **rac-1** was split into two peaks and shifted to 9.30 and 9.22 ppm (see Fig. S2, ESI†). Which can be assigned to the α-H of the py ring in bpy of *Λ*-**1** and *Δ*-**1** enantiomers, and used for

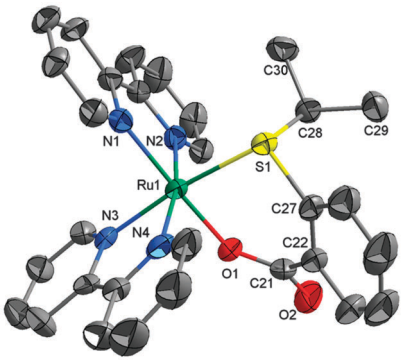


Fig. 1 Crystal structure of *Δ*-**1** (ellipsoids set at 50% probability; the anion and solvent molecules are omitted for clarity).

determining enantiomeric excesses. The spectra (Fig. S2, ESI†) show very high enantiopurity in both cases and the enantiopurity was found to be >98% ee from the ratio of the integrals of the α-H peaks of the two enantiomers.

The sulfoxide complexes, *Δ*-[Ru(bpy)$_2${(*R*)-OSO-iPr}]$^+$ (OSO-iPr = 2-(isopropylsulfonyl)benzonate, *Δ*-**2**) and *Λ*-[Ru(bpy)$_2${(*S*)-OSO-iPr}]$^+$ (*Λ*-**2**), were prepared by reaction of the ruthenium thioether complexes *Δ*-**1** and *Λ*-**1** with *m*-CPBA in methanol, respectively. The excess *m*-CPBA and the reduced product, 3-chlorobenzonate, were removed by ultrasonic extraction of the solid ruthenium product with ether. The yield was almost quantitative (96%) and no over-oxidation to sulfones was found. The absolute metal-centered and sulfoxide configurations in *Δ*-**2** and *Λ*-**2** were determined by X-ray crystallography[16] and are shown in Fig. 2. They crystallize in a pair of chiral space groups $P4_12_12$ and $P4_32_12$. Structural analyses show that the *Δ* and *Λ* configurations at the ruthenium center are consistent with their parent configurations, indicating that the absolute configuration at the metal center is unchanged during the oxidation reaction. Interestingly, the isopropyl group is far away from the α-pyridyl proton and the oxygen atom of the sulfoxide group indeed sits on the site near the α-pyridyl proton with a hydrogen bond between them (O···H = 2.6 Å), leading to enantioselective oxidation. According to the Cahn–Ingold–Prelog priority rules, the absolute stereochemistry at the sulfur atom is assigned an *R* configuration in the *Δ* complex, and an *S* configuration in the *Λ* complex. That is, the *Δ* complex gave an *R* configuration sulfoxide and the *Λ* complex gave an *S* configuration sulfoxide, resulting in predetermined chirality of the sulfoxides. The CD spectra of *Δ*-**2** and *Λ*-**2** are almost mirror images with a negative Cotton effect at

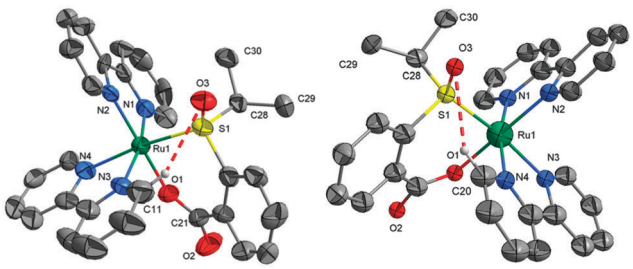


Fig. 2 Crystal structure of *Δ*-**2** (left) and *Λ*-**2** (right) (ellipsoids set at 50% probability; the anion and solvent molecules are omitted for clarity).

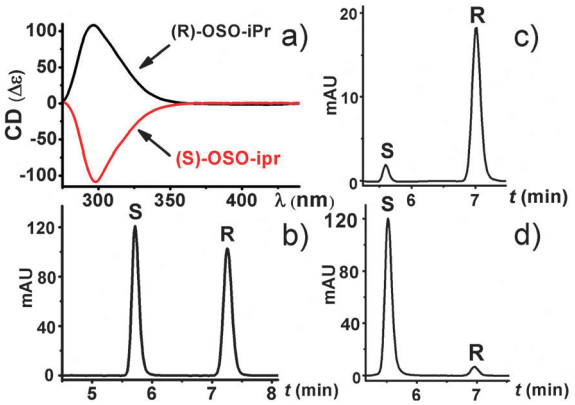


Fig. 3 (a) CD spectra of (*R*)-OSO-iPr and (*S*)-OSO-iPr in CH_2Cl_2 (40 μM); (b) HPLC traces of racemic OSO-iPr, (c) (*R*)-OSO-iPr and (d) (*S*)-OSO-iPr.

276 nm and a positive Cotton effect at 292 nm for *Δ*-**2**, and a positive Cotton effect at 277 nm and a negative Cotton effect at 293 nm for *Λ*-**2** (see Fig. S3, ESI†). The enantiopurity of *Δ*-**2** and *Λ*-**2** enantiomers is also determined by NMR spectroscopy using *S*-binol as a chiral NMR shift reagent. The peak assigned to the α-H of the pyridine ring at 9.22 ppm of the **rac-2** was split into two peaks and high-field shifted to 9.10 and 9.05 ppm in the presence of 40 equiv. of *S*-binol, which are consistent with those of *Λ*-**2** and *Δ*-**2** enantiomers (see Fig. S4, ESI†). The ee values were found to be >98% from the ratio of the integrals of the α-H peaks of the two enantiomers.

To optimize the synthetic procedure, a one-step approach was also developed. After the reaction of the chiral precursors Δ/*Λ*-$[Ru(bpy)_2(py)_2]^{2+}$ and OS-iPr in ethylene glycol for 4 h, 2 equiv. of oxidant *m*-CPBA in methanol was directly added to the above reaction mixture. The corresponding products *Δ*-**2** and *Λ*-**2** were obtained in yields of *ca.* 83% after a several-step separation process (see ESI†). The CD spectra show that they are optically active. Their enantiopurity was determined by NMR spectroscopy in the presence of *S*-binol as a chiral shift reagent. The ee values were found to be >98%, demonstrating that the chiral configurations at the metal center were retained under the reaction conditions.

Upon treatment of *Δ*/*Λ*-**2** with TFA in CH_3CN at 80 °C for 2 h in the dark, the pure (*S*/*R*)-OSO-iPr were isolated in yields of 90% (see ESI†). As shown in Fig. 3, their CD spectra are mirror images with a Cotton effect at 296 nm. The enantiopurity of (*S*)-OSO-iPr and (*R*)-OSO-iPr were determined by chiral HPLC analysis (see ESI†) and found to be 91.6 and 88.2% ee, respectively. To determine the stability of the chirality at the metal centre, *Λ*-**2** was reacted with TFA in the presence of bpy to form *Λ*-$[Ru(bpy)_3]^{2+}$, in a yield of 80% with 91.2% ee (Fig. S5, ESI†). Thus, the processes of removal of the chiral sulfoxide ligands occurred with retention of chiral configuration at the metal center.

It should be pointed out that the absolute stereochemistry at the sulfur atom changes from *R* to *S* upon removal of coordination. Although the direct oxidation of metal-bound thiolato ligands has been reported,[17] the oxidation *in situ* generation of enantiomeric sulfoxides is unprecedented. The results described herein may provide a novel approach for asymmetric synthesis of sulfoxides.

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14 Crystal data for [*Δ*-**1**]$(PF_6)\cdot 0.25CH_2Cl_2\cdot 0.25H_2O$: $C_{30}H_{27}RuN_4O_2SPF_6\cdot 0.25CH_2Cl_2\cdot 0.25H_2O$, M = 779.35, monoclinic, space group $C2$, a = 37.5718(9) Å, b = 10.8548(2) Å, c = 16.9834(4) Å, β = 113.393(4)°, V = 6357.1(2) Å^3, T = 160(2) K, Z = 8, 54 163 reflections measured, 10 100 independent reflections (R_{int} = 0.0644). The final R_1 values were 0.0379 ($I > 2\sigma(I)$). The final w$R(F^2)$ values were 0.0995 ($I > 2\sigma(I)$). The final R_1 values were 0.0385 (all data). The final w$R(F^2)$ values were 0.1005 (all data). Flack parameter = −0.015(6).
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16 Crystal data for [*Δ*-**2**]$(PF_6)\cdot 0.5H_2O$: $C_{30}H_{28}RuN_4O_{3.5}SPF_6$, M = 778.66, tetragonal, space group $P4_12_12$, a = 9.4645(5) Å, b = 9.4645(5) Å, c = 68.310(4) Å, V = 6119.0(5) Å^3, T = 163(2) K, Z = 8, 16 030 reflections

measured, 4881 independent reflections (R_{int} = 0.0720). The final R_1 values were 0.0884 ($I > 2\sigma(I)$). The final w$R(F^2)$ values were 0.1878 ($I > 2\sigma(I)$). The final R_1 values were 0.0910 (all data). The final w$R(F^2)$ values were 0.1890 (all data). Flack parameter = 0.07(3). Crystal data for [*Λ*-**2**](PF$_6$)·0.5H$_2$O: $C_{30}H_{28}RuN_4O_{3.5}SPF_6$, M = 778.66, tetragonal, space group $P4_32_12$, a = 9.4537(4) Å, b = 9.4537(4) Å, c = 68.322(12) Å, V = 6106.1(11) Å^3, T = 153(2) K, Z = 8, 8861 reflections measured, 3907 independent reflections (R_{int} = 0.0545). The final R_1 values were 0.1040 ($I > 2\sigma(I)$). The final w$R(F^2)$ values were 0.2233 ($I > 2\sigma(I)$). The final R_1 values were 0.1079 (all data). The final w$R(F^2)$ values were 0.2255 (all data). Flack parameter = 0.08(4).

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