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The first asymmetric synthesis of chiral ruthenium tris(bipyridine) from racemic ruthenium bis(bipyridine) complexes

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Abstract

The first 'one-pot' asymmetric synthesis of ruthenium tris(bipyridine) derivatives starting from corresponding racemic ruthenium bis(bipyridine) complexes is described. This is achieved through the stereocontrolled formation of reactive intermediates derived from (*R*)-(+)- or (*S*)-(−)-methyl *p*-tolyl sulfoxide, which can be easily converted to the products with a retention of configuration at the metal center.

Keywords: asymmetric synthesis; chirality; sulfoxides; ruthenium.

Optically active ruthenium tris(bipyridine) complexes are important synthetic targets,[1] yet their preparation through diastereoselective synthetic methods is only rarely found in the literature, requiring highly preorganized ligands which are not readily modified.[2] The Δ- and Λ-isomers of $[Ru(bpy)_3]^{2+}$ are most commonly prepared using a racemic synthesis, followed by a chiral resolution technique.[3] Alternatively, it is possible to prepare a racemic ruthenium bis(bipyridine) complex, which is then resolved, and used to prepare optically active $[Ru(bpy)_3]^{2+}$ derivatives.[4] However, these ruthenium bis(bipyridine) precursors are not easily handled, and their scope may be limited by this problem. For instance, *cis*- or *trans*-$Ru(dmbpy)_2Cl_2$ (**1**) (dmbpy=4,4′-dimethyl-2,2′-bipyridine) and $Ru(bpy)_2Cl_2$ (**2**) (bpy=2,2′-bipyridine) have only poor solubility, and the polar protic or harsh acidic reaction conditions required to dissolve **1** or **2** may result in racemization. Attempts to resolve **2** into its Δ- and Λ-isomers are not encouraging,[5] and the direct preparation of enantiopure materials from resolved **2** seems unlikely to succeed in the near future. We have recently reported that chromatographically resolved *cis*-Δ- and *cis*-Λ-$[Ru(bpy)_2(DMSO)(Cl)]^+$ react with bpy nucleophiles to give the corresponding ruthenium tris(bpy) products with almost complete retention (96% *ee*) of chirality at the metal center.[6,7] However, this procedure, when using optically resolved ruthenium bis(bipyridine) complexes by HPLC, is not

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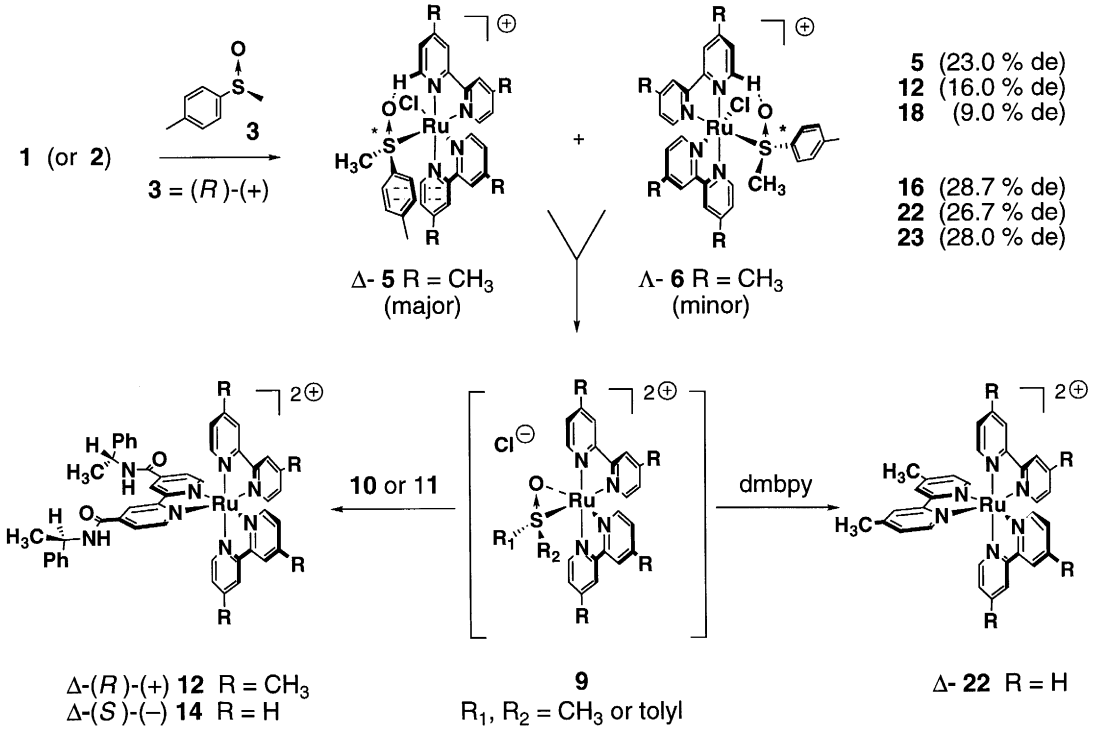
of real practical use as only a mg-scale sample is available for the synthesis. In order to simplify this method, we have developed the first asymmetric synthesis of novel, diastereomerically enriched ruthenium bis(bpy) *p*-tolyl sulfoxide ligands, derived from **1** and **2**. In this reaction[8] *cis*- or *trans*-$Ru(dmbpy)_2Cl_2$ (**1**) with either (*R*)-(+)-methyl *p*-tolyl sulfoxide (**3**) or (*S*)-(−)-methyl *p*-tolyl sulfoxide (**4**) leads to the preferential formation of *cis*-Δ-[$Ru(dmbpy)_2$**3**(Cl)]Cl (**5**) or *cis*-Λ-[$Ru(dmbpy)_2$**4**(Cl)]Cl (**7**), along with the formation of corresponding minor diastereomers *cis*-Λ-[$Ru(dmbpy)_2$**3**(Cl)]Cl (**6**) or *cis*-Δ-[$Ru(dmbpy)_2$**4**(Cl)]Cl (**8**), respectively. The highest *de*s were observed in dipolar aprotic solvents such as DMF (e.g. **5** of 59.5% *de* from **3**), which slightly decreased when the reaction was carried out in a refluxing polar protic solvent (e.g. **5** of 29.5% *de* from **3** in MeOH, or 23.0% *de* in MeOH:AcOH, 10:1). This important result[8] led us to investigate whether chiral $Ru(bpy)_3$ complexes could be prepared in a similar manner, particularly as the conventional synthetic methods were handicapped by difficulties such as the low reactivity and solubility of the $Ru(bpy)_2$ complexes used in the reaction.

In this paper, we wish to report that these new diastereomerically enriched precursors can be in situ converted to optically active $[Ru(bpy)_3]^{2+}$ complexes *without the need for isolation or resolution*, making them potentially invaluable in the syntheses of new optically active ruthenium tris(bipyridine) complexes (Scheme 1).



Scheme 1.

Ultimately, reaction to **5** and **6** could be carried out smoothly by treating an alcohol solution of **1** with **3** followed by warming to 60°C for a few hours, thereby affording **5** and **6** in quantitative yields. The isolation of these light sensitive sulfoxide precursors is not necessary as the unresolved, diastereomerically enriched mixture **5** and **6** can be readily converted by a 'one-pot' process to other complexes through the nucleophilic substitution of the sulfoxide and chloride ligands under very mild conditions (e.g. 20–30 min, refluxing MeOH). We have proposed that the mechanism of ligand exchange involves the establishment of the intermediate species **9**, in which the structure is intramolecularly

stabilized by bonding of the S–O group (Scheme 1), following the dissociation of Cl^- from **5** or **6**. This intermediate **9** retains the stereochemical information at the octahedral metal center during the thermally induced formation of ruthenium tris(bipyridine) complexes.

The absolute configuration of ruthenium tris(bipyridine) complexes can be determined by X-ray diffraction methods if one of the ligands contains known chiral centers. For this reason, both of the Δ- and Λ-isomers of [Ru(dmbpy)$_2$(4,4′-bis[(*R*)-(+)-α-phenylethylamido]-2,2′-bipyridine)]Cl$_2$ (**12** and **13**) were synthesized from a diastereomerically enriched mixture of *cis*-Δ-[Ru(dmbpy)$_2$**3**(Cl)]Cl (**5**) and *cis*-Λ-[Ru(dmbpy)$_2$**3**(Cl)]Cl (**6**) prepared in situ (**5**:**6**=61:38, 23.2% *de*) reacting with the 4,4′-bis[(*R*)-(+)-α-phenylethylamido]-2,2′-bipyridine nucleophile (**10**).† This gave products for which retention of chirality at the metal center was observed (**12**:**13**=58:42, 16.0% *de*; starting material **5**:**6**=23.0% *de*). Similar diastereoselectivities were seen for the reaction of *cis*-Δ-[Ru(bpy)$_2$**3**(Cl)]Cl (**16**) and *cis*-Λ-[Ru(bpy)$_2$**3**(Cl)]Cl (**17**) with **10** affording *cis*-Δ-[Ru(bpy)$_2$**10**]Cl$_2$ (**18**) and *cis*-Λ-[Ru(bpy)$_2$**10**]Cl$_2$ (**19**), although with a small decrease in selectivity (9.0% *de*). The decrease in diastereoselectivity was also seen when the opposite enantiomer 4,4′-bis[(*S*)-(−)-α-phenylethylamido]-2,2′-bipyridine (**11**) was employed yielding a diastereomeric mixture of *cis*-Λ-[Ru(bpy)$_2$**11**]Cl$_2$ (**20**) and *cis*-Δ-[Ru(bpy)$_2$**11**]Cl$_2$ (**21**). From the X-ray structure[9] of **13** (the details will be reported elsewhere), in the chiral spacegroup $P2_1$, we were able to fully assign the absolute configuration of the separated species. In combination with the HPLC retention times, it was then possible to assign the correct stereochemistry to the CD spectra of **18** and **19**, as shown in Fig. 1. The two CD spectra in CH_3CN are not mirror image reflections of one another, as they are a diastereomeric, rather than an enantiomeric, pair. We considered that the stereochemistry at the metal center is influenced by the chiral centers of the nucleophile as it approached the metal, as both of the chiral auxiliary bearing bipyridines 4,4′-bis[(*R*)-(+)-α-phenylethylamido]-2,2′-bipyridine (**10**) and 4,4′-bis[(*S*)-(−)-α-phenylethylamido]-2,2′-bipyridine (**11**) had been found to react with *cis*-Δ-[Ru(dmbpy)$_2$**3**(Cl)]Cl (**5**) and *cis*-Δ-[Ru(bpy)$_2$**3**(Cl)]Cl (**16**) to give products whose diastereomeric preferences showed only retention of stereochemistry at the metal center. However, in order to clarify the situation we synthesized **12**, **13** and **14**, or **15** from racemic *cis*-Ru(dmbpy)$_2$Cl$_2$ (**1**) by a direct process, simply by reacting the starting material with **10** or **11**, respectively. The products from this reaction showed Cotton effects in the CD spectrum, but chiral HPLC resolution of the product mixture demonstrated that only racemic (1:1) mixtures had been formed. This meant that the observed *de* arose through the retention of the chirality of the sulfoxide precursors (**5** and **7**), and not as a function of the chiral centers on the bipyridine nucleophile. Importantly, we were also able to carry out the diastereoselective synthesis of **12** or **14** in a ‘one-pot’ process.

When racemic *cis*-Ru(bpy)$_2$Cl$_2$ (**2**) was reacted with (*R*)-(+)-methyl *p*-tolyl sulfoxide **3**, and dmbpy subsequently added to the reaction mixture, [Ru(bpy)$_2$(dmbpy)]Cl$_2$ (**22**) was formed as the expected Δ-isomer with an increased *de* of 26.7%, as determined by HPLC. The Λ-isomer **23** could also be prepared following the same procedure, but using (*S*)-(−)-methyl *p*-tolyl sulfoxide **4** instead of **3**, and resulting in products with *de*=28.0% (see Scheme 1).

In conclusion, we have demonstrated for the first time an ability to control the chirality at the metal center in ruthenium tris(bipyridine) complexes through the use of chiral σ-bonded sulfoxide precursors. When (*R*)-(+)-methyl *p*-tolyl sulfoxide **3** reacts with racemic **1** or **2**, an excess of the Δ-isomer, both for the sulfoxide precursor, and for the Ru(bpy)$_3$ product, is observed. The complimentary synthesis of the

† Derivatives **10** and **11** are prepared from the 4,4′-dicarboxylic acid (Fluka), which is converted to the diacid chloride; this is quantitatively quenched with (*R*)- or (*S*)-α-phenylethylamine.

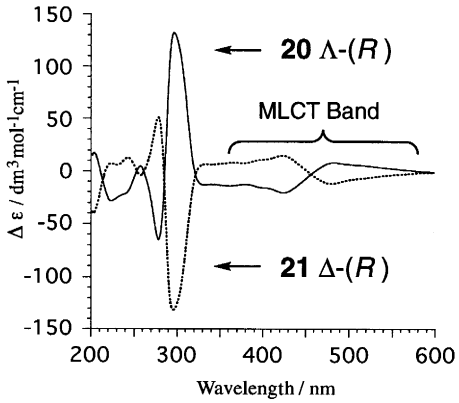


Fig. 1. CD spectra for **20** and **21** measured in CD_3CN

Λ-isomer is achieved when the (*S*)-(−)-sulfoxide **4** is used. This asymmetric synthesis represents the first direct approach to optically active ruthenium tris(bipyridine) complexes to be reported.

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