J|A|C|S COMMUNICATIONS

Published on Web 06/25/2009

Chiral-Auxiliary-Mediated Asymmetric Synthesis of Tris-Heteroleptic Ruthenium Polypyridyl Complexes

Lei Gong, Seann P. Mulcahy, Klaus Harms, and Eric Meggers*

Fachbereich Chemie, Philipps-Universität Marburg, Hans-Meerwein-Strasse, 35032 Marburg, Germany

Received April 21, 2009; E-mail: meggers@chemie.uni-marburg.de

As molecular recognition involving metal complexes continues to gain importance, for example, in the design of nucleic acid probes or enzyme inhibitors, so does the demand for efficient syntheses of enantiopure chiral-at-metal coordination compounds. However, compared with the availability of highly sophisticated methods for the asymmetric synthesis of organic molecules, synthetic control of metal-centered chirality, particularly in kinetically inert metal complexes, is still in its infancy.[1−4] For example, the generation of enantiopure ruthenium polypyridyl complexes lacking additional chirality in the organic ligand sphere relies solely on chiral resolution techniques[5] and thus does not differ conceptually from the first report on the optical resolution of chiral complexes by Werner almost a century ago.[6]

We here introduce a method for the asymmetric synthesis of enantiopure $[Ru(pp)(pp')(pp'')]^{2+}$ complexes in which pp, pp′, and pp″ are achiral 2,2′-bipyridines.[4] Our strategy employs salicyloxazolines as chiral auxiliaries,[7] which upon deprotonation serve as bidentate ligands that provide excellent asymmetric induction in the course of the coordination chemistry and, importantly, can thereafter become substituted stereospecifically with complete retention of configuration in the presence of acid.

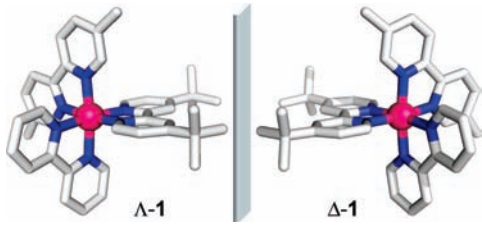


Figure 1. Λ and Δ enantiomers of the chiral Ru complex dication **1**.

We began by selecting complex dication **1** as a representative model system for a typical tris-heteroleptic ruthenium complex (Figure 1). This complex contains 2,2′-bipyridine (bpy), 5,5′-dimethyl-2,2′-bipyridine (Me_2bpy), and 4,4′-di-*tert*-butyl-2,2′-bipyridine (tBu_2bpy) as ligands and can form Λ and Δ enantiomers.

With $[(\eta^6\text{-}C_6H_6)RuCl_2]_2$ as the ruthenium source, the reaction with (*S*)-5-isopropyl-2-(2′-hydroxyphenyl)oxazoline [(*S*)-**2**] in the presence of K_2CO_3 afforded (*S*)-**3**[7b] (79%), which was photolyzed in acetonitrile with UV light to provide (*S*)-**4** in 96% yield (Scheme 1). Precursor (*S*)-**4** contains four labile ligands, all of which are accessible for substitution. Accordingly, heating of (*S*)-**4** with 1 equiv of bpy in chlorobenzene at 70 °C for 1 h and subsequently with Me_2bpy again in chlorobenzene at 70 °C for 2.5 h afforded Λ_{Ru}-S_C-**5** (61% yield) as the main diastereomer, with a diastereopurity of 98.4% (Table 1, entry 1). Changing the order of ligands by first adding the larger Me_2bpy ligand followed by bpy afforded complex Λ_{Ru}-S_C-**6** with a further improved diastereopurity of 99.3% (Table 1, entry 2). Even more, the reaction of (*S*)-**4** with first

Scheme 1. Diastereoselective Synthesis of Salicyloxazoline Complexes Λ_{Ru}-S_C-**5**−**7** (See Table 1 for the Compositions of these Complexes; **L1**, **L2** = Achiral 2,2′-Bipyridines)

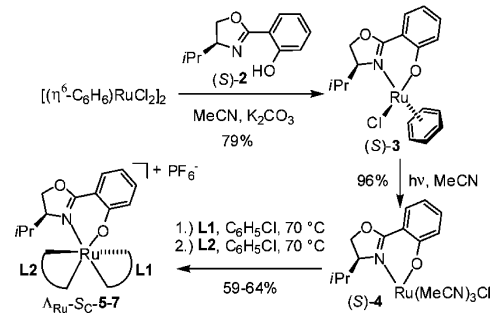


Table 1. Diastereoselectivity in the Formation of Salicyloxazoline Complexes Λ_{Ru}-S_C-**5**−**7** Starting from Precursor (*S*)-**4**[a]

entry	L1	L2	main product	yield	diastereopurity[b]
1	bpy	Me_2bpy	Λ_{Ru}-S_C-**5**	61%	98.4%
2	Me_2bpy	bpy	Λ_{Ru}-S_C-**6**	59%	99.3%
3	tBu_2bpy	Me_2bpy	Λ_{Ru}-S_C-**7**	64%	99.6%

[a] Conditions: Reaction of (*S*)-**4** in C_6H_5Cl at 70 °C first with 1 equiv of **L1** (1.0 h) and then with 1 equiv of **L2** (2.5 h). [b] Determined by ^1H NMR.

tBu_2bpy and then Me_2bpy yielded Λ_{Ru}-S_C-**7** with almost exclusive formation of only a single diastereomer (Table 1, entry 3).

The crystal structure of the monocation Λ_{Ru}-S_C-**5** shown in Figure 2 reveals a Λ configuration at the ruthenium center and steric interference between the *i*Pr group and the Me_2bpy ligand. Thus, the formation of Λ_{Ru}-S_C-**5**−**7** can be rationalized by the stereoselective incorporation of the first added ligand (**L1**) at the two coordination sites pointing farthest away from the *i*Pr group, with the second bidentate ligand (**L2**) filling the remaining two vacant coordination sites. According to this mechanism, the first ligand addition determines the chirality at the metal center. Theoretically,

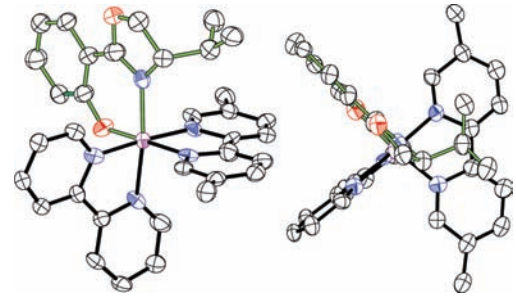
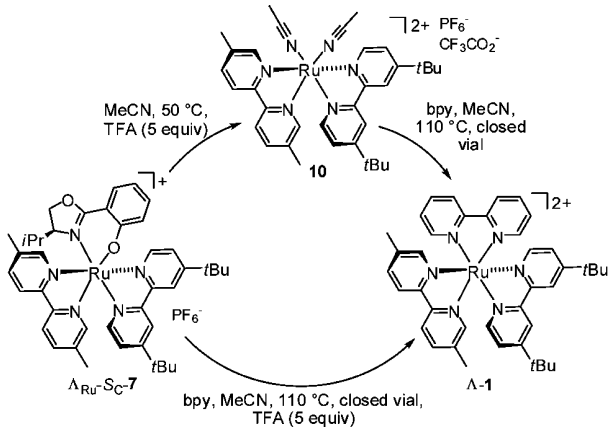


Figure 2. Crystal structure of Λ_{Ru}-S_C-**5** from two different perspectives (ORTEP drawings with 50% probability thermal ellipsoids). Only one complex of the unit cell is shown, and the PF_6^- counterion and solvent molecules have been omitted for clarity.

10.1021/ja9031665 CCC: $40.75 © 2009 American Chemical Society

Scheme 2. Stereospecific Synthesis of Complex Λ-**1** (PF_6^- Counterions) from Λ_{Ru}-S_C-**7**



in the course of the reaction of (*S*)-**4** with **L1** and subsequently **L2**, a total of four diastereomers can be formed if **L1** ≠ **L2**: two with Λ and two with Δ configuration at the ruthenium center. To our surprise, in each of the discussed conversions, virtually no Δ diastereomer was detectable. The predominant minor diastereomer in the formation of Λ_{Ru}-S_C-**5** (Table 1, entry 1) was Λ_{Ru}-S_C-**6** (Table 1, entry 2) and vice versa. Thus, the coordinated salicyloxazoline in precursor complex (*S*)-**4** provides excellent control over the configuration at the metal center. This high Λ/Δ diastereoselectivity is crucial for the enantiopure formation of the final tris-heteroleptic ruthenium complexes.

Next, we continued with the highly diastereopure complex Λ_{Ru}-S_C-**7** and set out to synthesize Λ-**1** by replacing the salicyloxazoline ligand with bpy with retention of configuration.[8] In preliminary experiments we recognized the acid lability of the salicyloxazoline ligand in complexes of type Λ_{Ru}-S_C-**5**−**7**. Gratifyingly, after several rounds of optimization, we found that treatment of Λ_{Ru}-S_C-**7** with 5 equiv of trifluoroacetic acid (TFA) at 50 °C in freshly distilled dry acetonitrile for 3.5 h led to smooth replacement of the salicyloxazoline ligand by two acetonitriles to afford intermediate **10**, which could be followed by the subsequent reaction with bpy to afford Λ-**1** with complete retention of configuration as determined by chiral HPLC analysis (Scheme 2 and Table 2, method A).[9] Even more conveniently, complex Λ_{Ru}-S_C-**7** could be converted into virtually enantiopure Λ-**1** in a one-pot procedure by the reaction with 15 equiv of bpy in the presence of 5 equiv of TFA in dry MeCN at 110 °C in a closed vessel for just 2 h (Scheme 2 and Table 2, method B). The chiral HPLC traces of Λ-**1** and Δ-**1** synthesized according to this protocol from the chiral oxazolines

Table 2. Stereospecific Formation of Λ-**1** from Λ_{Ru}-S_C-**7**

method	conditions	yield	e.r.[a]
A	(*i*) synthesis of intermediate **10**: MeCN, 50 mM Λ_{Ru}-S_C-**7**, 5 equiv of TFA, 50 °C, 3.5 h. (*ii*) formation of Λ-**1**: MeCN, 10 mM **10**, 15 equiv of bpy, 110 °C in a closed vial, 2 h.	88%	99.4:0.6
B	one-step substitution: MeCN, 50 mM Λ_{Ru}-S_C-**7**, 5 equiv of TFA, 15 equiv of bpy, 110 °C in a closed vial, 2 h.	91%	99.6:0.4

[a] Enantiomeric ratios determined by chiral HPLC analysis.

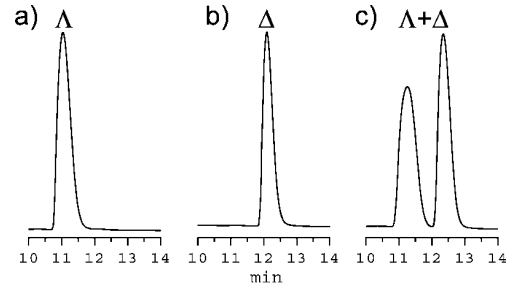


Figure 3. HPLC traces demonstrating the enantiopurity of synthesized Λ-**1** and Δ-**1**: (a) Λ-**1** synthesized from (*S*)-**2**; (b) Δ-**1** synthesized from (*R*)-**2**; (c) Λ/Δ-**1** synthesized from *rac*-**2**. All of the complexes were synthesized according to method B (Table 2). HPLC conditions: Daicel Chiralcel OD-R, 250 × 4 mm; flow rate, 0.5 mL/min; eluent, 0.087% H_3PO_4(aq) and MeCN (30 → 60% in 20 min).

(*S*)-**2** and (*R*)-**2**, respectively, are shown in Figure 3 and demonstrate the enantiopurity of the complexes Λ-**1** and Δ-**1**. The scope of this stereospecific replacement of the chiral auxiliary with retention of configuration was verified by applying it to the incorporation of 1,10-phenanthroline and 4,4′-dimethoxy-2,2′-bipyridine (≥99.3:0.7 e.r. in both cases; see the Supporting Information for more details).

In conclusion, we here have introduced salicyloxazolines as powerful chiral auxiliaries for the synthesis of enantiopure chiral-at-metal ruthenium polypyridyl complexes. We are convinced that this work will pave the way to control of the stereochemistry in even more complicated metal complexes. Work along these lines as well as the application of this method to the asymmetric synthesis of bioactive ruthenium complexes is in progress.

Acknowledgment. We thank the Philipps-University Marburg for financial support of this project.

Supporting Information Available: Experimental details, analytical data, HPLC traces, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For reviews of stereoselective synthesis in coordination chemistry, see: (a) Knof, U.; von Zelewsky, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 302. (b) Knight, P. D.; Scott, P. *Coord. Chem. Rev.* **2003**, *242*, 125.
(2) For control of ruthenium-centered chirality with a chiral tetradentate ligand, see: (a) Hayoz, P.; von Zelewsky, A.; Stoeckli-Evans, H. *J. Am. Chem. Soc.* **1993**, *115*, 5111.
(3) For examples of asymmetric coordination chemistry using chiral auxiliaries, see: (a) Jonassen, H. B.; Bailar, H. C.; Huffman, E. H. *J. Am. Chem. Soc.* **1948**, *70*, 756. (b) Hesek, D.; Inoue, Y.; Ishida, H.; Everitt, S. R. L.; Drew, M. G. B. *Tetrahedron Lett.* **2000**, *41*, 2617. (c) Warr, R. J.; Willis, A. C.; Wild, S. B. *Inorg. Chem.* **2006**, *45*, 8618.
(4) For the first asymmetric synthesis of enantiomerically enriched $[Ru(bpy)_3]^{2+}$, see: Liu, C. F.; Liu, N. C.; Bailar, J. C. *Inorg. Chem.* **1964**, *3*, 1085.
(5) For example, see: (a) Rutherford, T. J.; Pellegrini, P. A.; Aldrich-Wright, J.; Junk, P. C.; Keene, F. R. *Eur. J. Inorg. Chem.* **1998**, 1677. (b) Lacour, J.; Torche-Haldimann, S.; Jodry, J. J.; Ginglinger, C.; Favarger, F. *Chem. Commun.* **1998**, 1733.
(6) Werner, A. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 1887.
(7) For stereoselective coordination of chiral salicyloxazolines in half-sandwich complexes, see: (a) Brunner, H.; Nuber, B.; Prommesberger, M. *Tetrahedron: Asymmetry* **1998**, *9*, 3223. (b) Davenport, A. J.; Davies, D. L.; Fawcett, J.; Russell, D. R. *Dalton Trans.* **2004**, 1481. (c) Gott, A. L.; Clarke, A. J.; Clarkson, G. J.; Munslow, I. J.; Wade, A. R.; Scott, P. *Organometallics* **2008**, *27*, 2706.
(8) For substitution of two pyridines or two CO ligands with retention of configuration, see: (a) Rutherford, T. J.; Quagliotto, M. G.; Keene, F. R. *Inorg. Chem.* **1995**, *34*, 3857. (b) Hua, X.; von Zelewsky, A. *Inorg. Chem.* **1995**, *34*, 5791.
(9) The absolute configuration of Λ-**1** was determined by X-ray crystallography and independently verified by circular dichroism analysis.

JA9031665