Atropo-Enantioselective Ring Cleavage of Lewis Acid Modified Biaryl Thionolactones†,‡

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*Summary: Attachment of an achiral, ruthenium-based Lewis acid fragment to configurationally unstable biaryl thionolactones **1a**−**1c**, atropo-enantioselective reductive lactone cleavage of the resulting complexes with chiral hydride reagents, and subsequent decomplexation leads to axially chiral thioethers **3a**−**3c** with enantiomeric ratios of up to 92:8.*

Introduction

The directed preparation of axially chiral biaryls, such as biologically active natural products[1] or chiral auxiliaries for asymmetric synthesis,[2] is an important task. During the past two decades only a few methods[3−8] have emerged that guarantee high chemical and optical yields in the biaryl coupling step. In an extension of our "lactone methodology"[9] for the synthesis of axially chiral biaryls, we have recently shown that, similar to the corresponding oxolactones, the likewise configurationally unstable thionolactones **1a**−**1c**[10] (see Scheme 1) are rewarding substrates for atropisomer-selective ring cleavage reactions, too: attached to a chiral Ru−CHIRAPHOS fragment as in **2a**−**2c**, they can be cleaved atropo-diastereoselectively by the use of achiral H-nucleophiles in good diastereomeric ratios of up to 87:13,[11] ultimately giving the demetalated thioethers **3a**−**3c** in high enantiomeric purity. In this paper, we report on the first atropo-*enantioselective* reduction of thionolactone complexes **4a**−**4c** that are equipped with an achiral Ru fragment, using chiral H-nucleophiles.

Results and Discussion

In a first attempt, we tested the CBS reduction[12] of complex **4c** using (*S*)-oxazaborolidine-activated borane. In previous atropo-enantioselective reductions of the corresponding metal-free oxo analogues of **1a**−**1c**, this reagent combination had given excellent results (enantiomeric ratio (er) up to 98.5:1.5).[9,13] For **4c** as a substrate, however, no reaction took place with this chiral H-nucleophile. Further investigations using other nucleophiles such as DipCl[14] and the even more reactive Alpine-Hydride[15] showed that borane-based hydride transfer reagents are not able to reduce the C═S bond and cleave the ring. The aluminum-based reagent BINAL-H,[16] by contrast, proved to be an excellent chiral agent for the smooth reductive ring opening of the thionolactone complexes **4a**−**4c** (see Scheme 2 and Table 1).

Exploratory reactions were performed at room temperature, showing an immediate color change from

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‡ Part 12 in the series Enantioselective Organic Syntheses Using Chiral Transition Metal Complexes; for part 11 see: Schenk, W. A.; Bezler, J.; Burzlaff, N.; Hagel, M.; Steinmetz, B. *Eur. J. Inorg. Chem.* **2000**, 287.

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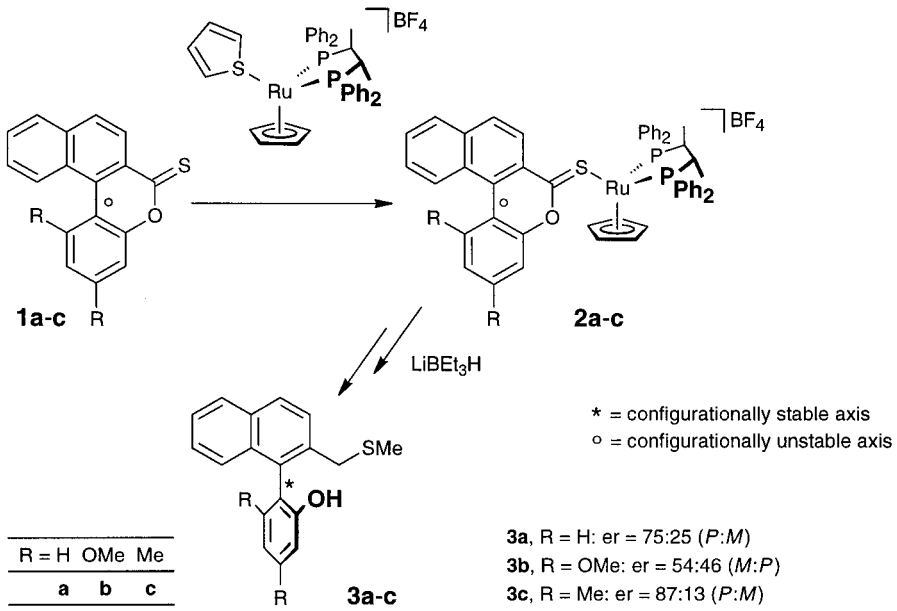
Scheme 1. Atropo-Diastereoselective Ring Cleavage of Chirally Modified Biaryl Thionolactones 2a−2c with Achiral H-Nucleophiles



3a, R = H: er = 75:25 (*P*:*M*)
3b, R = OMe: er = 54:46 (*M*:*P*)
3c, R = Me: er = 87:13 (*P*:*M*)

Table 1. Enantiomeric Ratios Obtained for Thioethers 3a−3c at Different Temperatures

thioether	*T* [°C]	(*M*)-**3**:(*P*)-**3**
3a	23	56:44
3b	23	47:53
3c	23	61:39
3a	0	59:41
3b	0	46:54
3c	0	68:32
3a	−78	66:34
3b	−78	42:58
3c	−78	92:8

violet (complexes **4a**−**4c**) to yellow in each case, a significant hint at a successful reduction to the ring-opened products **5a**−**5c**, which are compounds already known from previous work.[10]

For the determination of the stereoselectivity in the reduction step to **5a**−**5c**, the complexes were *S*-alkylated with MeI to give the cationic ruthenium complexes **6a**−**6c**, and the biaryls were then, after thermal cleavage, isolated as the thioethers **3a**−**3c** in 85−89% yield. The ruthenium fragment was recovered as the complex **7** in about 90% yield. The enantiomeric ratios of **3a**−**3c** were determined by HPLC on a chiral phase (Chiralcel OD-H), giving a poor to low er (Table 1, 61:39, *M:P* for **3c**).[17] As also experienced in previous ring cleavage reactions of the oxolactones[18] and for other BINAL-H reductions,[16] better asymmetric inductions were obtained at lower temperature, here leading to an er of up to 92:8 (*M:P*) for **3c**.

Compared with the atropo-*diastereoselctive* reduction of chirally modified ruthenium complexes **2a**−**2c** with achiral nucleophiles (see Scheme 1),[10] the atropo-*enantioselective* reduction reported here, using BINAL-H as a chiral H-nucleophile, leads to higher selectivities and represents the cheaper alternative, too.

The application of this novel variant of transition metal assisted atropo-enantioselective ring cleavage reactions on configurationally unstable biaryl thionolactones to the synthesis of axially chiral natural products and reagents is under investigation.

Experimental Section

All experimental manipulations were performed under an argon atmosphere with dried and distilled solvents using Schlenk techniques. The thionolactones **1a**−**1c** and the corresponding ruthenium complexes **4a**−**4c** were synthesized according to literature procedures.[10] NMR spectra were recorded on a Bruker AM 250 spectrometer at the Institut für Organische Chemie, Universität Würzburg. Elemental analyses were carried out by the microanalytical laboratory of the Institut für Anorganische Chemie, Universität Würzburg.

General Procedure for the Atropo-Enantioselective Reduction of Biaryl Thionolactone Complexes 4a−4c with (*M*)-BINAL-H. An (*M*)-BINAL-H solution, freshly prepared from 4.0 equiv of a 1.0 M solution of $LiAlH_4$ (in THF), 4.4 equiv of a 0.2 M solution of (*M*)-BINOL (in THF), and 4.4 equiv of ethanol, was adjusted to the reaction temperature indicated in the Table in Scheme 2, treated with 1.0 equiv of complex **4** (dissolved in THF), and stirred until completion of the reaction (TLC).[19]

Cleavage of the Thioethers 5a−5c. After evaporation of the solvent in vacuo, the residue was dissolved in acetone, treated with 5.0 equiv of MeI, and stirred for 1 h. The solvent was removed by distillation, and benzene was added to the precipitate. The obtained suspension was heated to reflux for 6 h and then dried in vacuo. Column chromatography on silica gel (hexane/ethyl acetate, 1:1) yielded the thioethers **3a**−**3c** and, as a slowly moving yellow band, the iodo complex **7**.

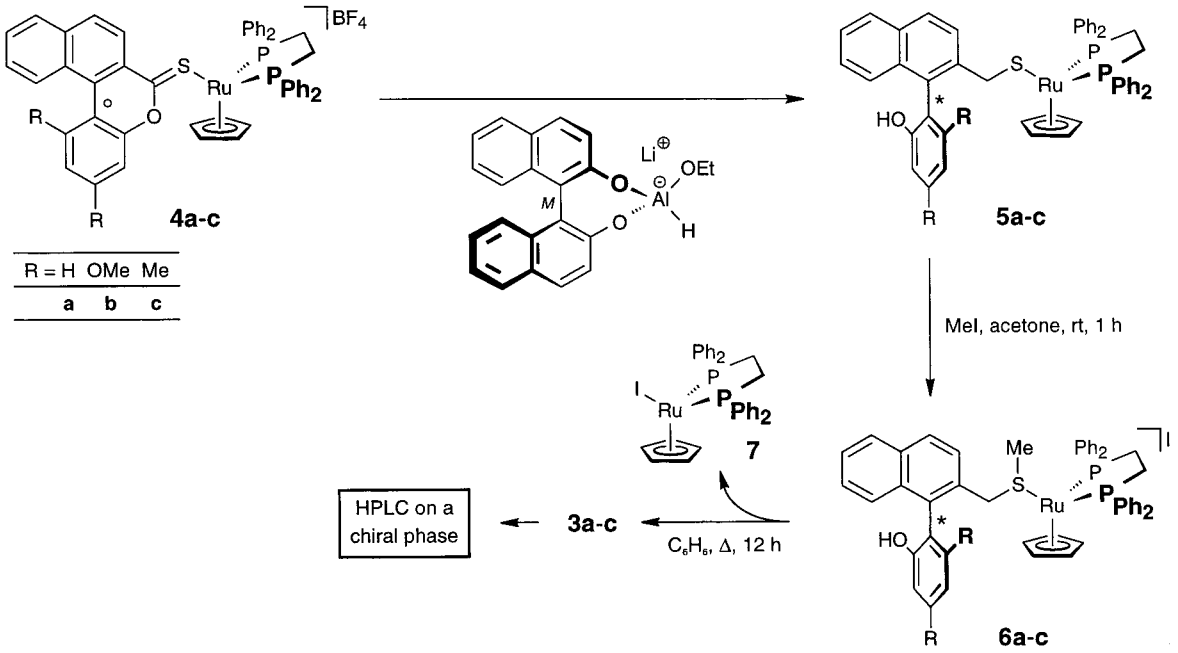
Preparation of 3a. According to the general procedure described above, 200 mg (219 μmol) of complex **4a** gave 52.8 mg (86%) of the thioether **3a** as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.92 (d, ^3J = 8.4 Hz, 1 H), 7.88 (m, 1 H), 7.65 (d, ^3J = 8.4 Hz, 1 H), 7.35−7.52 (m, 4 H), 7.03−7.20 (m, 3 H), 4.72 (s, 1 H), 3.68 (d, ^2J = 15.3 Hz, 1 H), 3.61 (d, ^2J = 15.3 Hz, 1 H), 1.97 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ 153.5 (CH), 136.0 (CH),

(17) The configuration at the biaryl axis was assigned by an independent synthesis of the thioether (*M*)-**3c** in enantiomerically pure form.[11]

(18) Bringmann, G.; Breuning, M. *Tetrahedron: Asymmetry* **1999**, *10*, 385.

(19) The (*M*)-BINAL-H solution had to be discarded if a large quantity of material precipitated.

Scheme 2. Atropo-Enantioselective Ring Cleavage of 4a−4c with (*M*)-BINAL-H and Analysis of the Resulting Products



133.0 (CH), 132.1 (CH), 131.5 (CH), 129.8 (CH), 129.0 (CH), 128.1 (CH), 127.6 (CH), 126.9 (CH), 126.1 (CH), 126.0 (CH), 124.5 (CH), 120.9 (CH), 116.2 (CH), 36.5 (CH_2S), 15.6 (SCH_3). IR (film): ν 3400 (m), 1600 (m), 1590 (m), 1200 (s), 1170 (s) cm^{-1}. MS (EI, 70 eV): *m/e* 280 (22, M^+), 233 (44, $M^+ - SCH_3$). Anal. Calcd for $C_{18}H_{16}OS$: C, 77.11; H, 5.75; S, 11.44. Found: C, 76.54; H, 5.65; S, 11.15.

Preparation of 3b. Following the general procedure, 200 mg (205 μmol) of complex **4b** gave 59.4 mg (85%) of the thioether **3b**. Recrystallization from CH_2Cl_2/Et_2O yielded **3b** as colorless needles. Mp: 138−139 °C. ^{1}H NMR ($CDCl_3$): δ 7.90 (d, ^3J = 8.6 Hz, 1 H), 7.86 (m, 1H), 7.69 (d, ^3J = 8.6 Hz, 1 H), 6.32 (d, ^3J = 2.3 Hz, 1 H), 6.25 (d, ^3J = 2.3 Hz, 1 H), 4.66 (s, 1 H), 3.88 (s, 3 H), 3.60 (s, 2 H), 3.58 (s, 3 H), 1.94 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ 161.7 (CH), 158.7 (CH), 154.9 (CH), 137.4 (CH), 133.0 (CH), 128.9 (CH), 128.3 (CH), 128.1 (CH), 127.5 (CH), 126.7 (CH), 125.9 (CH), 125.7 (CH), 105.7 (CH), 93.3 (CH), 91.9 (CH), 55.6 (OCH_3), 55.4 (OCH_3), 36.4 (CH_2S), 15.3 (SCH_3). IR (KBr): ν 3440 (m), 1605 (s), 1570 (s), 1130 (s), 1105 (s) cm^{-1}. MS (EI, 70 eV): *m/e* 340 (842, M^+), 325 (8, $M^+ - CH_3$), 293 (100, $M^+ - SCH_3$), 278 (15, 293 − CH_3), 261 (39, 293 − CH_3OH). Anal. Calcd for $C_{20}H_{20}O_3S$: C, 70.56; H, 5.92; S, 9.42. Found: C, 70.50; H, 5.66; S, 9.23.

Preparation of 3c. According to the general procedure described above, 200 mg (212 μmol) of complex **4c** gave 58.3 mg (89%) of the thioether **3c** as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.91 (d, ^3J = 8.4 Hz, 1 H), 7.87 (m, 1 H), 7.67 (d, ^3J = 8.4 Hz, 1 H), 7.30−7.53 (m, 3 H), 6.78 (s, 1 H), 6.77 (s, 1 H), 4.51 (s, 1 H), 3.64 (d, ^2J = 16.0 Hz, 1 H), 3.57 (d, ^2J = 16.0 Hz, 1 H), 2.40 (s, 3 H), 2.00 (s, 3 H), 1.82 (s, 3 H). ^{13} C NMR ($CDCl_3$): δ 153.2 (CH), 139.3 (CH), 138.0 (CH), 136.2 (CH), 133.1 (CH), 132.8 (CH), 131.2 (CH), 128.8 (CH), 128.2 (CH), 127.5 (CH), 127.0 (CH), 126.1 (CH), 125.6 (CH), 123.4 (CH), 114.1 (CH), 36.6 (CH_2S), 21.3 (CH_3), 19.9 (CH_3), 15.9 (SCH_3). IR (film): ν 3460 (m), 1610 (m), 1560 (m), 1170 (s), 1150 (s) cm^{-1}. MS (EI, 70 eV): *m/e* 308 (5, M^+), 261 (8, $M^+ - SCH_3$), 205 (79, 261 − C_3H_8O). Anal. Calcd for $C_{20}H_{20}OS$: C, 77.88; H, 6.54; S, 1040. Found: C, 78.01; H, 6.38; S, 10.17.

Determination of the Enantiomeric Ratios of the Thioethers 3a−3c. The enantiomer analysis of the biaryls **3a−3c** were achieved by HPLC on a chiral phase (Chiralcel OD-H Column, DAICEL Chem. Ind. Ltd., 4.6 × 250 mm, detection at 270 nm, flow rate 0.5 mL/min, eluent petroleum ether/PrOH, 98:2).

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