Synthesis of (*R*)-Sulforaphane Using [CpRu((*R*,*R*)-CHIRAPHOS)]$^+$ as Chiral Auxiliary**

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Abstract: A new enantioselective (80% *ee*) synthesis of (*R*)-sulforaphane and its epimer (*S*)-sulforaphane is described, which makes use of the pseudo-tetrahedral complex fragment [CpRu(CHIRAPHOS)]$^+$ as a chiral auxiliary. Reaction of the chloride complexes [CpRu(L–L)Cl] [L–L = 1,2-bis(diphenylphosphino)ethane (dppe), (2*S*,3*S*)- and (2*R*,3*R*)-bis(diphenylphosphino)-butane ((*S*,*S*)- and (*R*,*R*)-CHIRAPHOS, respectively)] with phthalimidobutyl methyl sulfide gives the thioether complexes [CpRu(L–L)(MeSC$_4$H$_8$NPhth)]PF$_6$. Oxygen transfer from dimethyldioxirane (DMD) produces the corresponding sulfoxide complexes in high yield and high diastereoselectivity. Cleavage of the phthaloyl group with aqueous hydrazine and subsequent reaction with thiophosgene yields the sulforaphane complexes [CpRu(L–L)(MeS(O)C$_4$H$_8$NCS)]PF$_6$. Treatment of these with sodium iodide finally liberates the sulforaphane without noticeable racemization.

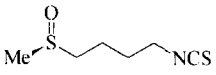
Keywords
asymmetric synthesis · dioxiranes · ruthenium · sulforaphane · sulfoxides

Introduction

Enantiomerically pure sulfoxides are important intermediates in organic syntheses.[2] They also often have interesting biological properties.[3] Consequently, the number of enantioselective syntheses of sulfoxides has increased steadily over the past decades.[4] We have recently been able to show that, in complexes of the type [CpRu(PR'$_3$)$_2$(SMeR)]$^+$, the coordinated thioether can be oxidized to the corresponding sulfoxide without rupture of the Ru–S bond (Scheme 1). The use of enantiomerically pure

Scheme 1.

complexes [CpRu((*S*,*S*)-CHIRAPHOS)(SMeR)]$^+$ (CHIRAPHOS® is 2,3-bis(diphenylphosphino)butane) has led to a highly enantioselective synthesis (up to 98% *ee*) of chiral sulfoxides RS(O)Me.[1] If this methodology is to be of any practical use, the ruthenium complexes must be able to survive the often rigorous conditions of multistep organic syntheses. In order to demonstrate this, we set out to synthesize (*R*)-sulforaphane [(*R*)-**1**], a constituent of broccoli, cauliflower, and related species. (*R*)-**1** has recently attracted considerable attention due to its ability to activate so-called phase II detoxication enzymes in mammals and thus counteract the detrimental effects of chemical carcinogens.[5]



(*R*)-**1**

Results and Discussion

The synthesis of sulforaphane is outlined in Scheme 2, it closely follows the original route published by Karrer.[6] Owing to the high cost of both enantiomers of CHIRAPHOS, we considered it advisable to test and optimize crucial steps using the achiral analogues [CpRu(dppe)(SMeR)]PF$_6$ (dppe = 1,2-bis(diphenylphosphino)ethane, Scheme 2). Thus, reaction between ruthenium complex **2a** and phthalimidobutyl methyl sulfide (**3**)[6] in boiling methanol gave the ionic thioether complex **4a** in quantitative yield. Complex **4a** is a lemon-yellow crystalline compound, which is completely air-stable and readily soluble in polar organic solvents. Its ^{1}H and ^{13}C NMR spectra display signals corresponding to all groups present. The ^{31}P NMR spectrum at room temperature consists of a sharp singlet, indicating rapid pyramidal inversion at sulfur.[7] Treatment of a solution of **4a** with a threefold excess of dimethyldioxirane (DMD)[8] in the same solvent gave near-quantitative yields of the corresponding sulfoxide. Complex **5a** is a light-yellow crystalline compound, similar in appearance to **4a**. Spectroscopically, the oxidation of the thioether to a sulfoxide functionality is evident from a marked downfield shift of the adjacent CH_3 and CH_2 groups.

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[**] Enantioselective Organic Syntheses Using Chiral Transition Metal Complexes, Part 3. For Part 2 see ref. [1].

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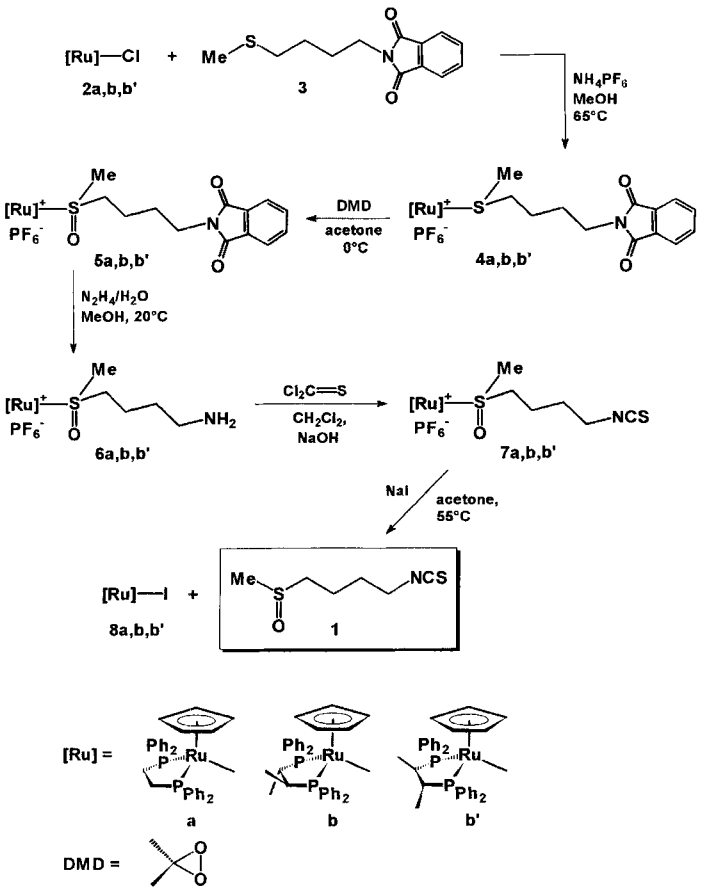

Scheme 2. Synthesis of sulforaphane.

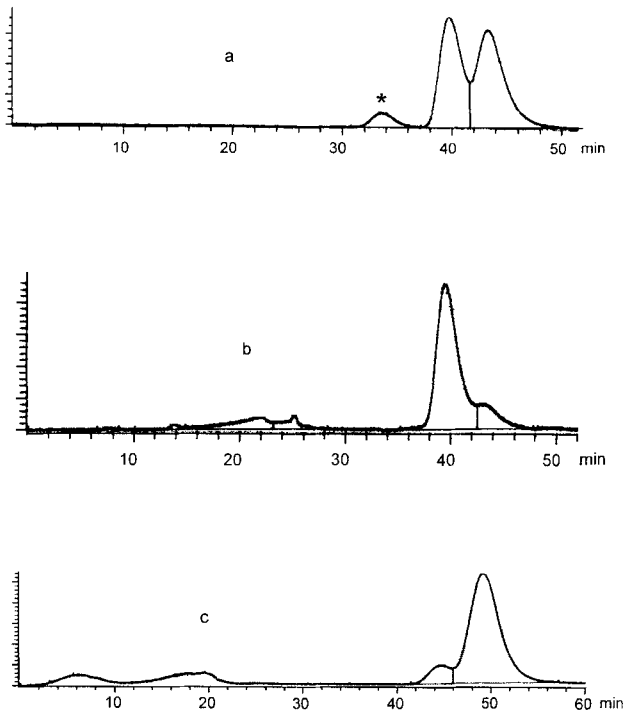

Figure 1. HPLC separation of (*R*,*S*)-**1** (a), (*S*)-**1** (b), and (*R*)-**1** (c). Column: Ceramosphere Ru-1, 4.6 × 250 mm, eluent: methanol, 0.6 mL min^{-1}, $T = 20$ °C (a, b), 35 °C (c); * denotes a slight impurity; the longer retention time in trace c is due to the higher column temperature.

The ^{31}P NMR spectrum now consists of an AB system, indicating a fixed configuration at the sulfur atom.

The amino group of **5a** was readily deprotected by the standard treatment with hydrazine in methanol/water. Amine **6a** was isolated as a light-yellow crystalline material. Treatment of **6a** at 0 °C with thiophosgene and sodium hydroxide in a two-phase system (CH_2Cl_2/H_2O) gave 45% yield of the racemic sulforaphane complex **7a**. The use of anhydrous sodium carbonate as a base instead of sodium hydroxide resulted in a slightly improved yield (54%). Complex **7a**, again, is a yellow solid, readily soluble in most polar organic solvents. In its ^{13}C NMR spectrum a weak signal at $\delta = 133.1$, which is absent in the DEPT 135 spectrum, may be attributed to the NCS group. The IR spectrum clearly shows the two typical isothiocyanate bands at 2180 and 2105 cm^{-1}, only marginally shifted from the values of uncoordinated **1**.[5a] Release of the sulforaphane ligand was readily achieved by boiling **7a** with sodium iodide in acetone. After chromatographic workup racemic **1** was isolated as an almost colorless oil with identical spectroscopic properties to those reported for (*R*)-sulforaphane.[5a, 9] HPLC analysis on a chirally modified Ceramospher column with combined UV and optical rotation detection gave a reasonable resolution of both enantiomers with (*S*)-(+)-**1** having the shorter retention time (Figure 1a).

With slight modifications this synthesis can be extended to the analoguous complexes of (*S*,*S*)-CHIRAPHOS or (*R*,*R*)-CHIRAPHOS (**b** and **b'**, respectively; Scheme 2). The yields of the various steps are similar to those in the achiral system; CHIRAPHOS complexes, however, are usually somewhat more soluble and tend to crystallize more readily than their dppe counterparts. The NMR spectra of **4b,b'**–**7b,b'** reflect the introduction of additional chirality into the molecule. Thus, in **4b,b'** all the protons of the C_4H_8 chain and the two phosphorus atoms are nonequivalent. The ^{1}H and ^{13}C NMR signals of the CH_2 and CH_3 groups at sulfur are broad, owing to the slightly restricted inversion of the coordinated thioether.[7] Oxidation of the thioether functionality of **4b** gave **5b** as an 89:11 mixture of (S_C,S_C,S_S) and (S_C,S_C,R_S) diastereomers. Similar treatment of **4b'** yielded **5b'** as a 90:10 mixture of (R_C,R_C,R_S) and (R_C,R_C,S_S) diastereomers. During the next steps care was taken to avoid any loss of product, so as to ensure that the enantiomer ratio of the isolated **1** closely mirrored the diastereoselectivity of the crucial oxidation step. As can be seen from Figures 1b,c, this was in fact achieved: the enantiomers of sulforaphane were each isolated with 80 ± 10% *ee*.

Concluding Remarks

As has been outlined previously,[1] use of the complex fragment [CpRu((*S*,*S*)-CHIRAPHOS)]$^+$ as chiral auxiliary allows the highly diastereoselective oxidation of coordinated methyl thioethers MeSR, even if the group R is sterically only slightly more demanding than a methyl group. This is again demonstrated by the remarkable stereoselectivity of the oxidation of **4b,b'** to **5b,b'**. Furthermore, the well-known inertness of second- and third-row d^6-octahedral complexes in general and of ruthenium(II) complexes in particular means that this and similar

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systems lend themselves to use as stereodirecting protective groups, which can be attached to (and readily removed from) a number of organic functionalities. It is probable that this auxiliary type can be exploited for other types of reactions as well, such as nucleophilic additions or cycloadditions. This has, for isolated examples, been demonstrated successfully[10] and will be further elaborated in our laboratory.

Experimental Section

General: All preparations were carried out in an inert atmosphere by using standard Schlenk techniques. The phosphine ligands dppe, (*S,S*)-CHIRAPHOS, and (*R,R*)-CHIRAPHOS were obtained from Strem Chemicals and used without further purification. DMD was employed as a freshly prepared 0.08–0.12 M solution in acetone [8]. The ruthenium complexes **2** were obtained by published methods or adaptations thereof [11]. Phthalimidobutyl methyl sulfide (**3**) was prepared as described by Karrer [6]. IR spectra were run on a Perkin-Elmer 283 instrument. ^{1}H, ^{13}C{^{1}H}, and ^{31}P{^{1}H} NMR spectra were recorded using a Bruker AMX 400 instrument. The ^{1}H and ^{13}C NMR signals of the chelate phosphine ligand are very similar for all compounds and have therefore been omitted from the lists of spectral data. HPLC analyses were carried out on a Ceramosphere Ru-1 column, with methanol as eluent and combined UV and ChiraLyzer detection. Melting and decomposition points were determined by differential scanning calorimetry using a DuPont 9000 instrument.

[CpRu(dppe)(MeSC$_4$H$_8$NPhth)]PF$_6$ (4a): A solution of [CpRu(dppe)Cl] (500 mg, 0.83 mmol), MeSC$_4$H$_8$NPhth (225 mg, 0.90 mmol), and NH_4PF_6 (150 mg, 0.92 mmol) in methanol (40 mL) was heated under reflux (2 h). After removal of the solvent the yellow residue was taken up in dichloromethane and chromatographed over silica with dichloromethane/acetone 20:1 as an eluent. The yellow fraction, which was collected, gave, after evaporation, 770 mg (97%) of **4a**. Lemon-yellow crystalline powder, decomp. 160 °C; ^{1}H NMR (400 MHz, [D$_6$]acetone, 25 °C, TMS): δ = 1.30 (s, 3H; SCH_3), 0.95 (m, 2H; CH_2), 1.08 (m, 2H; CH_2), 1.70 (m, 2H; CH_2), 3.42 (t, ^3J(H,H) = 6.8 Hz, 2H; NCH_2), 5.32 (s, 5H; Cp); ^{13}C NMR (100 MHz, [D$_6$]acetone, 25 °C, TMS): δ = 25.4 (t, ^3J(P,C) = 2.8 Hz, SCH_3), 27.5 (s; CH_2), 28.5 (s; CH_2), 37.8 (s; NCH_2), 46.0 (s; SCH_2), 83.4 (s; Cp); ^{31}P NMR (162 MHz, [D$_6$]acetone, 25 °C, 85% H_3PO_4): δ = 73.0 (s). $C_{44}H_{44}F_6NO_2P_3RuS$ (958.9): calcd C 55.11, H 4.63, N 1.46, S 3.34; found C 55.21, H 4.73, N 1.42, S 3.36.

[CpRu(CHIRAPHOS)(MeSC$_4$H$_8$NPhth)]PF$_6$ (4b, 4b′): Both enantiomers were prepared as described for **4a**, yield 95%. Lemon-yellow crystalline powder, decomp. 175 °C; ^{1}H NMR (400 MHz, [D$_6$]acetone, 25 °C, TMS): δ = 1.25 (m, 4H; CH_2CH_2), 1.57 (s, br, 3H; SCH_3), SCH_2 signal not detected, 3.48 (t, ^3J(H,H) 6.5 Hz, 2H; NCH_2), 4.81 (s, 5H; Cp); ^{13}C NMR (100 MHz, [D$_6$]acetone, 25 °C, TMS): δ = 26.0 (brs; SCH_3), 27.5 (s, CH_2), 28.4 (s, CH_2), 37.5 (s, NCH_2), 46.2 (brs; SCH_2), 85.2 (s, Cp); ^{31}P NMR (162 MHz, [D$_6$]acetone, 25 °C, 85% H_3PO_4): δ = 66.8 (d, J(P,P) = 40 Hz), 82.9 (d, J(P,P) = 40 Hz). $C_{46}H_{48}F_6NO_2P_3RuS$ (986.9): calcd C 55.89, H 4.90, N 1.42, S 3.25; found C 55.84, H 5.25, N 1.41, S 3.23.

[CpRu(dppe)(MeS(O)C$_4$H$_8$NPhth)]PF$_6$ (5a): To a solution of **4a** (200 mg, 0.21 mmol) in acetone (10 mL) was slowly added at 0 °C a solution of DMD in the same solvent (10 mL, 0.8 mmol). After 2 h at this temperature the solvent was stripped off and the residue chromatographed (silica, dichloromethane/acetone 20:1). The yellow fraction, after evaporation, gave analytically pure **5a**. Yield 195 mg (96%). Light yellow crystalline powder, decomp. 126 °C; ^{1}H NMR (400 MHz, [D$_6$]acetone, 25 °C, TMS): δ = 1.0–1.3 (m, 4H; CH_2CH_2), 2.31 (s, 3H; $S(O)CH_3$), 2.7 (m, 2H; $S(O)CH_2$), 3.45 (t, ^3J(H,H) = 6.5 Hz, 2Hz; NCH_2), 5.41 (s, 5H; Cp); ^{13}C NMR (100 MHz, [D$_6$]acetone, 25 °C, TMS): δ = 19.4 (s; CH_2), 27.8 (s; CH_2), 37.5 (s; NCH_2), 49.6 (s; $S(O)CH_3$), 64.7 (s; $CH_2S(O)$), 85.5 (s; Cp); ^{31}P NMR (162 MHz, [D$_6$]acetone, 25 °C, 85% H_3PO_4): δ = 73.2, 74.4 (AB system, J(P,P) = 22 Hz). $C_{44}H_{44}F_6NO_3P_3RuS$ (974.9): calcd C 54.21, H 4.55, N 1.44, S 3.29; found C 53.91, H 5.01, N 1.37, S 3.26.

[CpRu(CHIRAPHOS)(MeS(O)C$_4$H$_8$NPhth)]PF$_6$ (5b, 5b′): Both enantiomers were prepared as described for **5a**, yield 90%. Light-yellow crystalline powder, decomp. 118 °C; ^{1}H NMR (400 MHz, [D$_6$]acetone, 25 °C, TMS): major diastereomer: δ = 1.2–1.5 (m, 4H; CH_2CH_2), 2.22 (s, 3H, $S(O)CH_3$), 2.85 (m, 2H; $S(O)CH_2$), 3.52 (brt, ^3J(H,H) = 6.7 Hz; NCH_2), 5.02 (s, 5H; Cp); minor diastereomer: δ = 2.48 (s, 3H; $S(O)CH_3$), 5.04 (s, 5H; Cp); ^{13}C NMR (100 MHz, [D$_6$]acetone, 25 °C, TMS): major diastereomer: δ = 19.5 (s; CH_2), 27.6 (s; CH_2), 37.5 (s; NCH_2), 48.7 (s; $S(O)CH_3$), 64.9 (s; $S(O)CH_2$), 86.6 (s; Cp); minor diastereomer: δ = 49.9 (s; $S(O)CH_3$), 86.5 (s; Cp); ^{31}P NMR (162 MHz, [D$_6$]acetone, 25 °C, 85% H_3PO_4): major diastereomer: δ = 62.5 (d, J(P,P) = 36 Hz), 81.6 (d, J(P,P) = 36 Hz); minor diastereomer: δ = 63.1 (d, J(P,P) = 36 Hz), 81.5 (d, J(P,P) = 36 Hz). $C_{46}H_{48}F_6NO_3P_3RuS$ (1002.9): calcd C 55.09, H 4.82, N 1.40, S 3.20; found C 54.91, H 5.09, N 1.67, S 3.25.

[CpRu(dppe)(MeS(O)C$_4$H$_8$NH$_2$)]PF$_6$ (6a): Hydrazine hydrate (1.0 mL, 16 mmol) was added to a solution of **5a** (200 mg, 0.20 mmol) in methanol (20 mL) and allowed to react for 24 h at 20 °C. All volatiles were then removed under vacuum, the resulting yellow residue was dissolved in a minimum amount of dichloromethane and filtered over Celite. The product was precipitated by addition of hexane. Yield 160 mg (95%). Light-yellow crystalline powder, m.p. 92 °C (decomp.); ^{1}H NMR (400 MHz, [D$_6$]acetone, 25 °C, TMS): δ = 1.0–1.4 (m, 4H, CH_2CH_2), 2.31 (s, 3H; $S(O)CH_3$), 2.65 (m, 1H; S(O)CH), 2.95 (brt, ^3J(H,H) = 6.4 Hz, 2H; NCH_2), 3.2–3.4 (m, 3H; $S(O)CHCH_2$), 5.40 (s, 5H; Cp). ^{13}C NMR (100 MHz, [D$_6$]acetone, 25 °C, TMS): δ = 19.8 (s; CH_2), 29.6 (s; CH_2), 49.2 (s; $S(O)CH_3$), 50.6 (s; NCH_2), 65.1 (s; $S(O)CH_2$), 85.3 (s; Cp). ^{31}P NMR (162 MHz, [D$_6$]acetone, 25 °C, 85% H_3PO_4): δ = 74.1, 74.3 (AB system, J(P,P) = 22 Hz). $C_{36}H_{42}F_6NOP_3RuS$ (844.8): calcd C 51.18, H 5.01, N 1.66, S 3.80; found C 50.85, H 5.46, N 1.76, S 3.62.

[CpRu(CHIRAPHOS)(MeS(O)C$_4$H$_8$NH$_2$)]PF$_6$ (6b, 6b′): Both enantiomers were obtained in almost quantitative yield as described for **6a**. Light-yellow crystalline powder, m.p. 200 °C (decomp.); ^{1}H NMR (400 MHz, [D$_6$]acetone, 25 °C, TMS): major diastereomer: δ = 1.25 (m, 2H; CH_2), 1.47 (m, 2H; CH_2), 2.24 (s, 3H; $S(O)CH_3$), 2.60, 2.85 (m, 2H; $S(O)CH_2$), 3.00 (brt, ^3J(H,H) = 6.4 Hz, 2H; NCH_2), 4.98 (s, 5H; Cp); minor diastereomer: δ = 2.48 (s, 3H; $S(O)CH_3$), 5.02 (s, 5H; Cp). ^{13}C NMR (100 MHz, [D$_6$]acetone, 25 °C, TMS): major diastereomer: δ = 20.1 (s; CH_2), 30.3 (s; CH_2), 48.4 (s; $S(O)CH_3$), 50.8 (s; NCH_2), 65.7 (s; $S(O)CH_2$), 86.6 (s; Cp); minor diastereomer: δ = 48.8 (s; $S(O)CH_3$), 86.4 (s; Cp); ^{31}P NMR (162 MHz, [D$_6$] acetone, 25 °C, 85% H_3PO_4): major diastereomer: δ = 61.8 (d, J(P,P) = 36 Hz), 81.5 (d, J(P,P) = 36 Hz); minor diastereomer: δ = 62.8 (d, J(P,P) = 36 Hz), 81.5 (d, J(P,P) = 36 Hz). $C_{38}H_{46}F_6NOP_3RuS$ (872.8): calcd C 52.29, H 5.31, N 1.60, S 3.67; found C 52.68, H 6.15, N 2.14, S 3.34.

[CpRu(dppe)(MeS(O)C$_4$H$_8$NCS)]PF$_6$ (7a): To a solution of **6a** (200 mg, 0.24 mmol) in dichloromethane (20 mL) was added, at 0 °C, thiophosgene (20 μL, 0.27 mmol) and 2 M aqueous sodium hydroxide (2.0 mL, 4.0 mmol). The mixture was stirred 1.5 h at 0 °C and 0.5 h at 20 °C. The organic layer was then dried with magnesium sulfate, filtered over celite, and evaporated to dryness. The residue was chromatographed over silica using dichloromethane/acetone 20:1 as eluent. The yellow band, after evaporation, gave 80 mg (45%) of yellow crystalline **7a**. Use of anhydrous sodium carbonate instead of aqueous sodium hydroxide gave a slightly improved yield (88 mg, 54%). m.p. 196 °C (decomp.); ^{1}H NMR (400 MHz, [D$_6$]acetone, 25 °C, TMS): δ = 1.1–1.4 (m, 4H; CH_2CH_2), 2.35 (s, 3H; $S(O)CH_3$), 2.85 (m, 2H; $S(O)CH_2$), 3.42 (t, ^3J(H,H) = 6.0 Hz, 2H; NCH_2), 5.44 (s, 5H; Cp). ^{13}C NMR (100 MHz, [D$_6$]acetone, 25 °C, TMS): δ = 19.4 (s; CH_2), 29.0 (s; CH_2), 45.0 (s; NCH_2), 49.9 (s; $S(O)CH_3$), 64.3 (s; $S(O)CH_2$), 85.9 (s; Cp), 133.1 (s; NCS). ^{31}P NMR (162 MHz, [D$_6$]acetone, 25 °C, 85% H_3PO_4): δ = 73.4, 74.1 (AB system, J(P,P) = 22 Hz). $C_{37}H_{40}F_6NOP_3RuS_2$ (886.9): calcd C 50.11, H 4.55, N 1.58, S 7.23; found C 49.81, H 4.79, N 1.76, S 8.46.

[CpRu(CHIRAPHOS)(MeS(O)C$_4$H$_8$NCS)]PF$_6$ (7b, 7b′): Both enantiomers were prepared as described above and with sodium carbonate as a base. Yield 45–50%, orange-yellow crystalline powder, m.p. 105 °C (decomp.); ^{1}H NMR (400 MHz, [D$_6$] acetone, 25 °C, TMS): major diastereomer: δ = 1.27 (m, 2H; CH_2), 1.39 (m, 2H; CH_2), 2.25 (s, 3H; $S(O)CH_3$), 2.47, 2.86 (m, 2H; $S(O)CH_2$), 3.51 (t, ^3J(H,H) = 5.9 Hz, 2H; NCH_2), 5.00 (s, 5H; Cp); minor diastereomer: δ = 2.53 (s, 3H; $S(O)CH_3$), 5.04 (s, 5H; Cp). ^{13}C NMR (100 MHz, [D$_6$]acetone, 25 °C, TMS): major diastereomer:

δ = 20.3 (s; CH_2), 29.7 (s; CH_2), 45.8 (s; NCH_2), 49.2 (s; $S(O)CH_3$), 65.5 (s; $S(O)CH_2$), 87.2 (s; Cp), 133.2 (s; NCS); minor diastereomer: δ = 50.5 (s; $S(O)CH_3$, 87.0 (s; Cp). ^{31}P NMR (162 MHz, [D_6]acetone, 25 °C, 85% H_3PO_4): major diastereomer: δ = 62.3 (d, J(P,P) = 36 Hz), 81.5 (d, J(P,P) = 36 Hz); minor diastereomer: δ = 62.9 (d, J(P,P) = 36 Hz), 81.4 (d, J(P,P) = 36 Hz). $C_{39}H_{44}F_6NOP_3RuS_2$ (914.9): calcd C 51.20, H 4.85, N 1.53, S 7.01; found C 51.37, H 4.94, N 1.85, S 6.87.

Liberation of sulforaphane (1): A solution of **7a** (89 mg, 0.10 mmol) and sodium iodide (150 mg, 1.00 mmol) in acetone (10 mL) was heated under reflux (40 h). The solvent was then removed under vacuum, and the residue chromatographed over a silica column. With dichloromethane/acetone 10:1 as eluent a yellow band was recovered, which contained the iodo complex **8a**. Sulforaphane was then eluted with methanol and isolated after evaporation of the solvent as a slightly yellowish oil. Yield 17 mg (96%); similar treatment of **7b** or **7b′** gave near quantitative yields of (*S*)-**1** and (*R*)-**1**, respectively. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.9 (m, 4H; CH_2CH_2), 2.58 (s, 3H; $S(O)CH_3$), 2.72 (m, 2H; $S(O)CH_2$), 3.58 (t, ^3J(H,H) = 6.4 Hz; NCH_2). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 20.4 (s; CH_2), 29.3 (s; CH_2), 39.0 (s; $S(O)CH_3$), 44.9 (s; NCH_2), 53.8 (s; $S(O)CH_2$).

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