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Asymmetric Oxidation Synthesis of Modafinil Acid by Use of a Recyclable Chiral-at-Metal Complex

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The enantioselective oxidation synthesis of chiral modafinil acid and its analogues with high enantiomeric excess has been developed by means of a chiral-at-metal strategy. Treatment of ruthenium complexes *cis*-[Ru(bpy)$_2$Cl$_2$] or Δ/Λ-[Ru(bpy)$_2$(MeCN)$_2$](PF$_6$)$_2$ (bpy is 2,2′-bipyridine) with the appropriate prochiral thioether ligands afforded thioether complexes *rac*-**1**, Δ/Λ-**1**, *rac*-**2**, Δ/Λ-**2**, *rac*-**3**, and Δ/Λ-**3**. Diastereoselective oxidation of the thioether complexes in situ produced the corresponding sulfoxide complexes *rac*-**1a**, Δ/Λ-**1a**, *rac*-**2a**, Δ/Λ-**2a**, *rac*-**3a**, and Δ/Λ-**3a**. The configuration at the metal center in each case is stable during the coordination and oxidation reactions, and dictates the chirality of the sulfoxide ligand in the oxidation process. The chiral modafinil acids were obtained with *ee* values greater than 98% upon their removal from the corresponding sulfoxide complexes in the presence of TFA/MeCN. Moreover, the chiral ruthenium precursors Δ/Λ-[Ru(bpy)$_2$(MeCN)$_2$](PF$_6$)$_2$ are recyclable and reusable with complete retention of the configurations.

Introduction

Modafinil [Provigil, 2-(diphenylmethylsulfinyl)acetamide], the most effective pharmaceutical agent for the treatment of excessive sleepiness caused by narcolepsy, shift work sleep disorder, and obstructive sleep apnea,[1] has been marketed in the United States by Cephalon since 1998.[2] However, recent studies suggest that (*R*)-modafinil has an apparent steady-state oral clearance three times slower than that of (*S*)-modafinil and shows a longer half-life than the racemate.[3] Therefore, (*R*)-modafinil was renamed as armodafinil (Nuvigil) and approved by the FDA in 2007.

Two main pathways have been developed for the synthesis of armodafinil. In the first, the key step is the enantioselective oxidation of (2-benzhydrylsulfanyl)acetamide to armodafinil.[4] In the second, the crucial process is the preparation of chiral modafinil acid. This involves either fractional crystallization with α-methylbenzylamine[5a] or chemical resolution by treatment with a chiral thiazolidinethione.[5b] Moreover, (diphenylmethylsulfinyl)acetic acid (modafinil acid) is also an essential intermediate for the synthesis of new structural analogue pharmaceuticals such as adrafinil [Olmifon, 2-(diphenylmethylsulfinyl)-*N*-hydroxyacetamide].[4g] Therefore, it is highly desirable to develop a general and effective approach to synthesize chiral modafinil acid and its analogues.

Recently, the asymmetric oxidation of thioethers to sulfoxides by a metal catalysis strategy has attracted great attention.[6,7] A new approach for the synthesis of chelate sulfoxide compounds with *ee* values of up to 98.9% by means of oxidation of a coordinated thioether to a sulfoxide in situ in a chiral-at-metal asymmetric environment, followed by release of the oxidized ligand, has been developed by our group.[8] In these processes, the absolute configuration at the metal center is each case completely retained during the formation of the thioether complex, the oxidation in situ to generate the sulfoxide complex, and the release of the sulfoxide ligand. The most interesting factor is that the configuration of the chiral metal center dictates the chirality of the formed sulfoxide during the oxidation process, thereby generating predictable chirality in the sulfoxide and allowing an enantioselective synthesis of sulfoxide compounds. As part of an ongoing study, we have extended the "coordination/oxidation in situ" approach to the enantioselective synthesis of (*R*)- and (*S*)-modafinil acid and its analogues, which are crucial intermediates for the preparation of modafinil, armodafinil, and adrafinil. In this article, the synthesis and structural characterization of the thioether complexes *rac*-**1**, Δ/Λ-**1**, *rac*-**2**, Δ/Λ-**2**, *rac*-**3**, and Δ/Λ-**3** (Scheme 1) and their corresponding oxidized products *rac*-**1a**, Δ/Λ-**1a**, *rac*-**2a**, Δ/Λ-**2a**, *rac*-**3a**, and Δ/Λ-**3a** are reported. Chiral variants of modafinil acid [(*R*)-**4** and (*S*)-**4**] and their analogues (*R*)-**5**, (*S*)-**5**, (*R*)-**6**, and (*S*)-**6** were obtained with *ee* values greater than 98% by acidolysis of the corresponding sulfoxide complexes in the presence of

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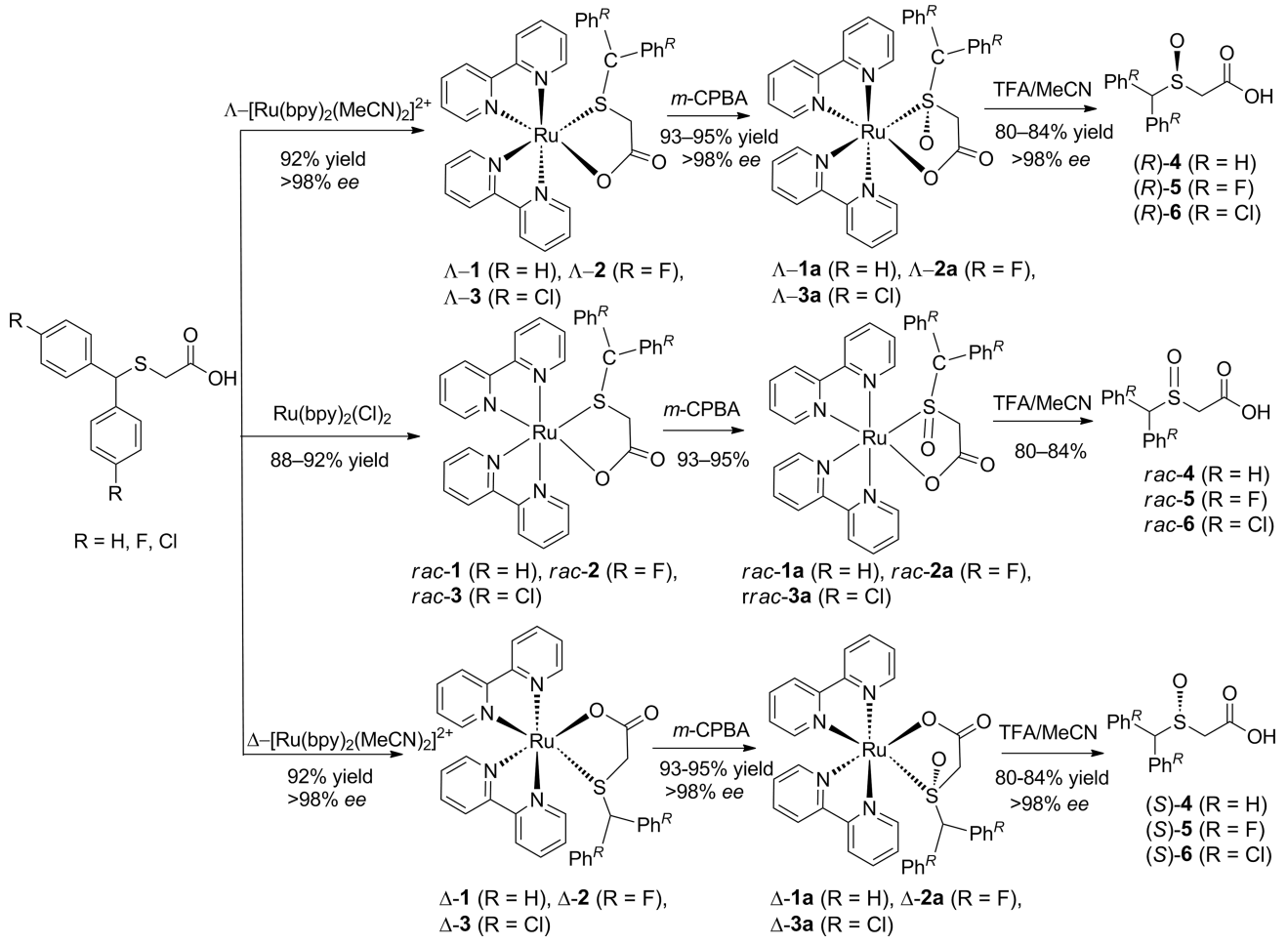


Scheme 1. Synthesis of complexes and of modafinil acid and its derivatives.

TFA/MeCN. Importantly, the chiral ruthenium precursors Δ/Λ-$[Ru(bpy)_2(MeCN)_2](PF_6)_2$ can be recovered and reused in at least three cycles. The approach reported here may offer a new pathway for the synthesis of chiral modafinil acid and its analogues.

Results and Discussion

Synthesis and Characterization of the Thioether Complexes

The thioether complexes were synthesized in yields of 88–93% by treatment of *cis*-$Ru(bpy)_2Cl_2$ or chiral precursors Δ/Λ-$[Ru(bpy)_2(MeCN)_2]^{2+}$ with the prochiral thioether ligands (diphenylmethylthio)acetic acid (HOSdp), 2-[bis-(4-fluorophenyl)methylthio]acetic acid (HOSdpF), and 2-[bis(4-chlorophenyl)methylthio]acetic acid (HOSdpCl) in ethylene glycol at 110 °C for 1 h, as shown in Scheme 1. NMR and MS as well as EA techniques were used to verify their compositions. CD spectra were also used to observe the optical activity. As shown in Figure 1, Λ-**1** and Δ-**1** show Cotton effects at 283, 296, and 346 nm. The spectra are almost mirror images. The CD spectra of Δ/Λ-**2** and Δ/Λ-**3** are described in Figures S1 and S2 in the Supporting Information.

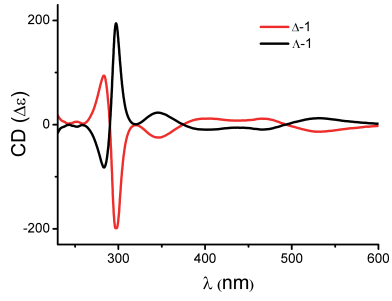


Figure 1. CD spectra of isomers Δ-**1** and Λ-**1** in MeCN (50 μM) at room temperature.

Although the ^1H NMR spectra of *rac*-**1**, Δ-**1**, and Λ-**1** are identical, they become distinguishable in the presence of (*S*)-BINOL as a chiral shift reagent.[8,9] As shown in Figure 2 and in Figures S3 and S4 in the Supporting Information, the resonance peaks of H_6 of bpy near to the carboxylate group of the thioether ligand, at δ = 9.18 ppm for *rac*-**1**, 9.17 ppm for **2**, and 9.16 ppm for **3**, are each split into two peaks, at δ = 9.14 and 9.07 ppm, 9.13 and 9.06 ppm, and 9.11 and 9.04 ppm, respectively, in the presence of 40 equiv. (*S*)-BINOL. The low-field signal can be assigned to the Λ enantiomer, whereas the peak at high field

is consistent with the Δ enantiomer. The spectra show very high enantiopurity in each case, indicating that the configuration at the metal center is stable and that no isomerization occurs during the formation of the thioether complex. The integrals of these peaks were used to calculate the *ee* values of the Δ and Λ enantiomers. They were found to be greater than 98%. Moreover, the resonance peaks of the methine component of the thioether ligands, at δ = 4.68 ppm for *rac*-**1**, 4.66 ppm for *rac*-**2**, and 4.63 ppm for *rac*-**3**, are shifted to higher field upon coordination to ruthenium ion and split into two singlet peaks, at δ = 4.67 and 4.64 ppm, 4.65 and 4.61 ppm, and 4.61 and 4.58 ppm, respectively. Similar observations are also made in each case for the low-field methylene proton of the thioether ligand, the signals of which shift from 3.22 ppm to 3.34 and 3.22 ppm for *rac*-**1**, from 3.23 ppm to 3.33 and 3.22 ppm for *rac*-**2**, and from 3.23 ppm to 3.33 and 3.21 ppm for *rac*-**3**.

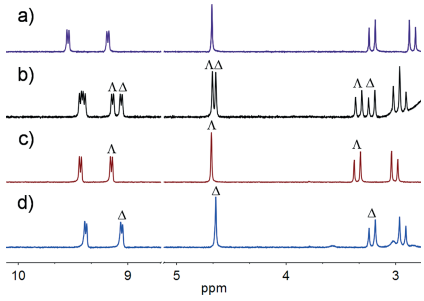


Figure 2. Excerpts from the ^{1}H NMR spectra of (a) *rac*-**1**, (b) *rac*-**1** with 40 equiv. (*S*)-BINOL, (c) Λ-**1** with 40 equiv. (*S*)-BINOL, and (d) Δ-**1** with 40 equiv. (*S*)-BINOL in CD_3CN at room temperature.

The crystal structure of *rac*-**3**·CH_3OH was determined by single-crystal X-ray diffraction. It crystallizes in the $P2_1/n$ space group. The chelating thioether ligand is indeed bound to the $[Ru(bpy)_2]^{2+}$ moiety, as shown in Figure 3.

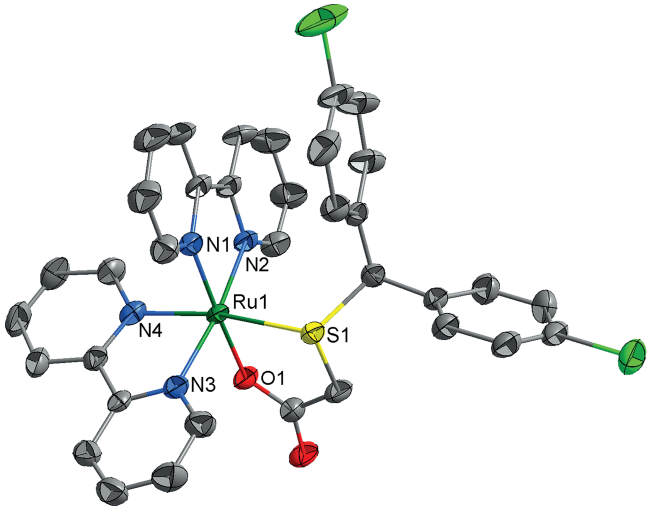


Figure 3. Crystal structure of *rac*-**3**. Selected interatomic distances and angles: Ru1–N1 2.039(3) Å, Ru1–N2 2.047(3) Å, Ru1–N3 2.065(4) Å, Ru1–N4 2.087(3) Å, Ru1–S1 2.326(1) Å, Ru1–O1 2.104(3) Å, O1–Ru1–S1 84.00(8)°. ORTEP drawing with 50% probability thermal elipsoids.

The Ru1–S1 distance is 2.326(1) Å, which is in accord with that reported.[8,10] The Ru1–N4 bond length is slightly longer than those of others, indicating that the sulfur atom has a strong *trans* effect. The phenyl group is engaged in π–π stacking with the py ring at a distance of 3.43 Å.

Synthesis and Characterization of the Sulfoxide Complexes

The sulfoxide complexes were obtained in yields of 93–95% by the oxidation of the thioether complexes in situ, with *m*-CPBA as oxidant in CH_2Cl_2 at room temperature, as shown in Scheme 1. It is noteworthy that the oxidation reaction was incomplete in methanol, ethanol, or ethylene glycol, indicating the oxidation reaction is highly solvent-dependent. Moreover, only single diastereomers were produced during the oxidation process: namely, the Δ configuration at the metal center gives rise to the *R* configuration of the sulfoxide ligand, whereas the Λ one produces the *S* configuration of the sulfoxide ligand (vide infra). Therefore, the in situ oxidation reaction is completely diastereoselective: only the Δ-*R* and Λ-*S* configurations were produced when the Δ and Λ metal centers, respectively, were present.[11] As expected, Λ/Δ-**1a**, Λ/Δ-**2a**, and Λ/Δ-**3a** are optically active. The CD spectra of the enantiomers show strong Cotton effects and mirror-image relationships, as can be seen in Figure 4 and in Figures S5 and S6 in the Supporting Information.

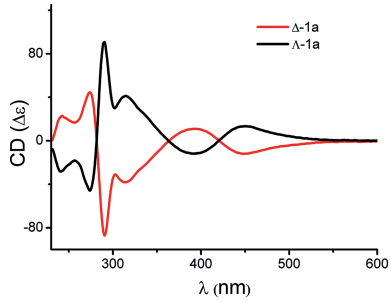


Figure 4. CD spectra of isomers Δ-**1a** and Λ-**1a** in MeCN (50 μM) at room temperature.

The chemical shifts of the methine and methylene components of the sulfoxide ligands, at δ = 4.84, 4.23, and 3.68 ppm for **1a**, 4.85, 4.18, and 3.68 ppm for **2a**, and 4.83, 4.20, and 3.66 ppm in **3a**, are markedly shifted to lower field in comparison with those at δ = 4.68, 3.22, and 2.85 ppm for **1**, 4.66, 3.23, and 2.86 ppm for **2**, and 4.63, 3.23, and 2.90 ppm for **3**. This indicates that the thioether ligands are indeed oxidized in situ to sulfoxide ligands, because the sulfoxide group is a strongly electron-withdrawing group. Moreover, the chemical shifts of H_6 of bpy, at δ = 10.24 ppm in **1a**, 10.21 ppm in **2a**, and 10.21 ppm in **3a**, are shifted significantly to lower field in comparison with those of the corresponding thioether complexes (9.55, 9.56, and 9.57 ppm). This is due to the hydrogen-bonding interaction between the sulfoxide group and the proton of bpy. The hydrogen-bonding interaction might assist in directing the added sulfoxide oxygen atom (vide infra).[12] Excerpts from

the ^{1}H NMR spectra of *rac*-**1a**, Λ-**1a**, and Δ-**1a** in the absence or in the presence of (*S*)-BINOL are shown in Figure 5. The peaks at δ = 8.96, 4.84, and 3.68 ppm are each split into two peaks at δ = 8.89 and 8.81 ppm, 4.81 and 4.78 ppm, and 3.77 and 3.65 ppm, respectively, in the presence of (*S*)-BINOL as a chiral shift reagent, which are consistent with the presence of Λ-**1a** and Δ-**1a** enantiomers. The *ee* values were calculated from the integrals of the peaks at δ = 8.89 and 8.81 ppm for the two enantiomers and found to be greater than 98%. Identical situations were also observed in the cases of *rac*-**2a** and *rac*-**3a** (see Figures S7 and S8 in the Supporting Information). These results demonstrated that the configuration at the ruthenium center is stable in each case and that no isomerization occurs during the oxidation reaction under the experimental conditions.

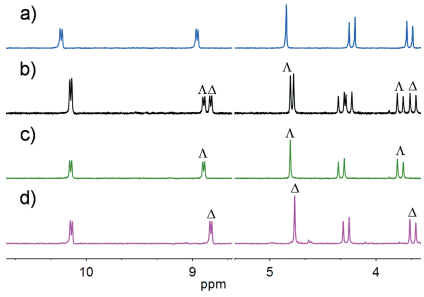


Figure 5. Excerpts from the ^{1}H NMR spectra of (a) *rac*-**1a**, (b) *rac*-**1a** with 40 equiv. (*S*)-BINOL, (c) Λ-**1a** with 40 equiv. (*S*)-BINOL, and (d) Δ-**1a** with 40 equiv. (*S*)-BINOL in CD_3CN at room temperature.

Single-crystal X-ray structural analysis of *rac*-**3a**·CH_3OH reveals that it crystallizes in the monoclinic space group $P2_1/n$. As shown in Figure 6, the sulfoxide ligand is indeed generated in situ. The sulfur atom is bound to Ru^{II} with a Ru1–S1 distance of 2.221(2) Å, which is shorter than that in *rac*-**3** [2.326(1) Å]. The S–O bond length of 1.484(5) Å indicates that it has a double bond character. The oxygen atom of the sulfoxide ligand is engaged in hydrogen bonding to H_6 of bpy with a C20···O3 distance of 3.105 Å, consistently with the NMR observations (vide supra). Although two pairs of diastereomeric configurations (Δ-*R* and Δ-*S*, Λ-*R* and Λ-*S*) would be generated in *rac*-**3a** in theory, because a pair of enantiomers Δ-**3** and Λ-**3** were used as the starting materials. Surprisingly, only two configurations Δ-*R* and Λ-*S* were observed in the crystal structure of *rac*-**3a**, indicating that the in situ oxidation reaction is completely diastereoselective and that the configuration of the metal center dictates the chirality of the sulfoxide in each case, with the Δ and Λ configurations at metal centers giving rise to the *R* and S configurations, respectively, of the sulfoxide. This can be used to synthesize sulfoxide compounds diastereoselectively.

Synthesis and Characterization of the Chiral Sulfoxide Compounds

The above experiments demonstrated that the configuration at the metal center dictates the chirality of the sulfoxide sulfur atom, thanks to which it can be employed to synthesize chiral sulfoxide compounds. Indeed, chiral modafinil acid [(*R*)- and (*S*)-**4**] and its analogues (*R*)- and (*S*)-**5** and (*R*)- and (*S*)-**6** were obtained by treatment of the corresponding sulfoxide complexes with TFA/CH_3CN at 60 °C for 3 h.[13] They are optically active and show strong Cotton effects (see Figures S9–S11 in the Supporting Information). Their enantiopurities were found to be greater than 98% through integration of the methine peaks in the ^{1}H NMR spectra in the presence of L-phenylglycinol as a chemical shift reagent (see Figure 7 and Figures S12–13 in the Supporting Information). When 2 equiv. of L-phenylglycinol were added to the solution of modafinil acid, the singlet peak at δ = 5.35 ppm was split and shifted upfield to 5.13 and 5.09 ppm. These signals are assigned to the chemical shifts of the methine component of (*S*)-**4** and (*R*)-**4**, respectively. We found that the other chemical shift reagents, such as (*S*)-BINOL and (*R*)-α-(methoxyphenyl)acetic acid, that have been used to discriminate (*R*/*S*)-modafinil in $CDCl_3$[14] were unable to differentiate between the two enantiomers of modafinil acid, although chiral modafinil acid has been prepared by fractional crystallization in the presence of a resolution reagent and chemical resolution.[5] However, the

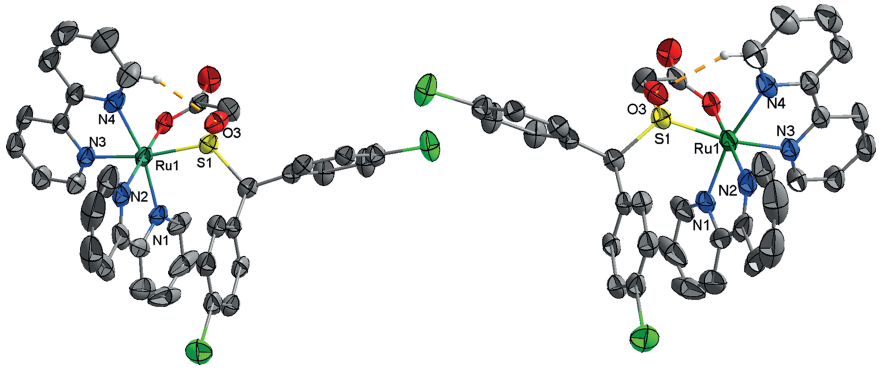


Figure 6. Crystal structures of a pair of cations (Δ-*R* and Λ-*S*) in *rac*-**3a**. Selected interatomic distances and angles: Ru1–N1 2.054(5) Å, Ru1–N2 2.053(6) Å, Ru1–N3 2.105(5) Å, Ru1–N4 2.089(3) Å, Ru1–S1 2.221(2) Å, Ru1–O1 2.075(4) Å, S1–O3 1.484(5) Å, O1–Ru1–S1 84.47(2)°. ORTEP drawing with 50% probability thermal elipsoids.

yields and *ee* values are moderate. Here we provide a new approach by which to synthesize chiral modafinil acid and its analogues with high yields and enantiopurities.

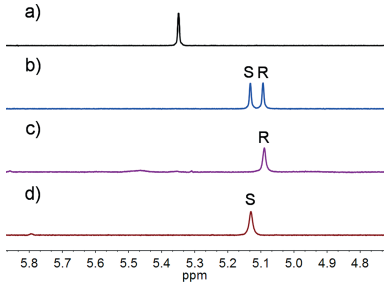


Figure 7. Excerpts (methine component) from the ^{1}H NMR spectra of (a) HOSOdp, (b) HOSOdp with 2 equiv. L-phenylglycinol, (c) (*R*)-HOSOdp with 2 equiv. L-phenylglycinol, and (d) (*S*)-HOSOdp with 2 equiv. L-phenylglycinol in $CDCl_3$ at room temperature.

Recovery and Reuse of the Chiral Ruthenium Complexes

The acidolysis reaction, affording chiral modafinil acid with high *ee* values, indicates that no isomerization occurred in this process. Thereby, the configuration of the metal centre upon removal of the chiral sulfoxide ligand was observed. It was found that the configuration of the metal center was completely retained under the experiment conditions. This inspired us to develop an approach to recycle and reuse the chiral ruthenium complex as a precursor. After addition of an excess of KPF_6 to the resulting aqueous solution to form a hexafluorophosphate salt, followed by extraction with CH_2Cl_2, Λ/Δ-[Ru(bpy)$_2$(MeCN)$_2$](PF$_6$)$_2$ was obtained in yields of ca. 91%. The recycled chiral ruthenium complex was used as the starting material to react with the prochiral thioether ligand in ethylene glycol at 110 °C, followed by oxidation in CH_2Cl_2 at room temperature. The enantiopurity of the obtained ruthenium complex was determined by ^{1}H NMR spectroscopy with (*S*)-BINOL as a chiral shift reagent (see Figure S14 in the Supporting Information) and found to be greater than 98%, demonstrating that the configuration of the recycled ruthenium complex had been completely retained. Three-cycle experiments were carried out (see Scheme 2). The enantiopurities were monitored by ^{1}H NMR spectroscopy of modafinil acid complexes in the presence of (*S*)-BINOL (see Figure S15 in the Supporting Information) and the configuration was found to have been completely retained.

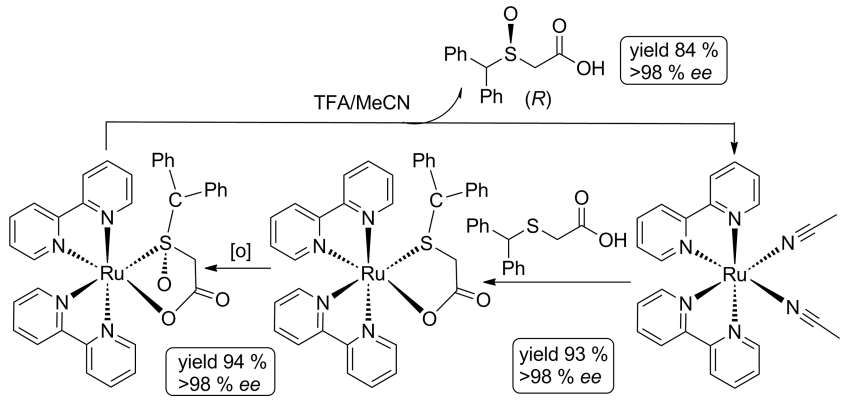
In addition, a one-pot method (thioether coordination and oxidation) was also employed to synthesize the sulfoxide complex; however, the yield was very low, because the oxidation reaction was highly solvent-dependent and incomplete in polar solvents such as ethylene glycol, methanol, and ethanol (vide supra).

Conclusions

The enantioselective oxidation synthesis of chiral modafinil acid and its analogues has been developed by use of a chiral-at-metal strategy. The configuration at the metal center is stable in each case and dictates the chirality of modafinil acid obtained during the reaction. Moreover, the chiral ruthenium precursors are recyclable and reusable with complete retention of their configurations. This provides a new choice for the synthesis of chiral modafinil acid, armodafinil, and their analogues.

Experimental Section

General Procedures: All chemicals were commercially available and used as purchased unless otherwise noted. The precursors [Ru(bpy)$_2$Cl$_2$]·2H$_2$O,[15] Λ-[Ru(bpy)$_2$(MeCN)$_2$](PF$_6$)$_2$,[8c] and Δ-[Ru(bpy)$_2$(MeCN)$_2$](PF$_6$)$_2$,[8c] and the thioether ligands HOSdp,[16,17] HOSdpF,[18] and HOSdpCl[18] were synthesized according to the literature. All manipulation were carried out under Ar or N_2 unless otherwise noted. The reactions involving the formation of chiral ruthenium complexes were carried out in the dark to protect against light-induced decomposition and isomerization. Column chromatography was performed with silica gel (300–400 mesh) under low light. Elemental (C, H, N, and S) analyses were carried out with an Elementar Vario EL analyzer. Electrospray ionization mass spectra (ESI-MS) were obtained with a Thermo LCQ DECA XP mass spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with a Varian Mercury-Plus 300 spectrometer and use of the solvent as internal standard. Circular dichroism (CD) spectra were measured with a JASCO J-810 CD spectropolar-



Scheme 2. Reaction cycle for the synthesis of chiral modafinil acid and recovery of the chiral precursor.

imeter (1 s response, 3.41 nm bandwidth, scanning speed of 200 nm min^{-1}, accumulation of three scans). The enantiomeric excess (*ee*) values of the ruthenium complexes and sulfoxide compounds were determined by ^{1}H NMR with use of (*S*)-1,1′-binaphthol (*S*-Binol) and L-phenylglycinol, respectively, as chiral shift reagents.

General Procedure for the Preparation of the Thioether Complexes: The appropriate ruthenium complex (0.5 mmol), the appropriate thioether ligand (1.0 mmol), K_2CO_3 (0.25 mmol), and ethylene glycol (2 mL) were placed in a three-necked flask. The mixture was magnetically stirred and heated at 110 °C for 1 h under argon. The reaction mixture was allowed to cool to room temperature, and the crude material was purified by silica gel chromatography with MeCN, MeCN/H_2O (10:1, *v*/*v*), and finally $CH_3CN/H_2O/KNO_3$ (sat) (100:1:0.2, *v*/*v*/*v*) as eluents. After removal of the solvent, water (20 mL) was used to dissolve the resulting product, and an excess of solid KPF_6 was added to the solution. Then, CH_2Cl_2 (15 mL) was added to the solution, and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic phase was dried with $MgSO_4$, filtered, concentrated, and dried under high vacuum.

[Ru(bpy)$_2$(OSdp)](PF$_6$) (*rac*-1): Yield 90%. [*cis*-Ru(bpy)$_2$Cl$_2$·2H$_2$O was used as the precursor, EtOH (18 mL) and H_2O (2 mL) were used as solvent at 90 °C for 2.5 h]. ^{1}H NMR (300.1 MHz, CD_3CN): δ = 9.55 (d, 1 H), 9.18 (d, 1 H), 8.43 (d, 1 H), 8.32 (d, 1 H), 8.11 (m, 2 H), 7.86 (m, 5 H), 7.65 (d, 1 H), 7.55 (t, 1 H), 7.41 (d, 2 H), 7.25 (m, 4 H), 7.08 (m, 2 H), 6.94 (t, 1 H), 6.72 (t, 2 H), 6.56 (d, 2 H), 4.68 (s, 1 H), 3.22 (d, 1 H), 2.85 (d, 1 H) ppm. ^{13}C NMR (75.5 MHz, CD_3CN): δ = 178.1, 159.2, 158.6, 158.3, 158.1, 153.5, 153.3, 151.2, 150.8, 140.2, 139.0, 138.0, 137.8, 137.7, 136.0, 129.7, 129.7, 129.5, 129.5, 129.0, 128.8, 128.8, 128.2, 128.2, 128.1, 127.0, 126.4, 126.1, 126.1, 124.6, 124.3, 124.2, 124.0, 56.9, 37.2 ppm. ESI-MS: *m*/*z* = 671 [M – PF$_6$]$^+$. $C_{35}H_{29}F_6N_4O_2PRuS$ (815.73): calcd. C 51.53, H 3.58, N 6.87, S 3.93; found C 51.31, H 3.72, N 6.79, S 3.80. Λ-[Ru(bpy)$_2$(OSdp)](PF$_6$) (**Λ-1**), yield 93% {Λ-[Ru(bpy)$_2$-(MeCN)$_2$](PF$_6$)$_2$ was used as the precursor}, *ee* 98%. CD (Δε/M^{-1}cm^{-1}, MeCN): 283 (–96), 296 (+201), 346 nm (+23). Δ-[Ru(bpy)$_2$-(OSdp)](PF$_6$) (**Δ-1**), yield 93% {Δ-[Ru(bpy)$_2$(MeCN)$_2$](PF$_6$)$_2$ was used as the precursor}, *ee* 98%. CD (Δε/M^{-1}cm^{-1}, MeCN): 283 (+94), 297 (–199), 346 nm (–24).

[Ru(bpy)$_2$(OSdpF)](PF$_6$) (*rac*-2): Yield 92% (the procedures were similar to those used for *rac*-**1**). ^{1}H NMR (300.1 MHz, CD_3CN): δ = 9.56 (d, 1 H), 9.17 (d, 1 H), 8.43 (d, 1 H), 8.32 (d, 1 H), 8.13 (t, 2 H), 8.05 (d, 1 H), 7.83 (m, 5 H), 7.60 (t, 1 H), 7.43 (m, 2 H), 7.19 (t, 1 H), 7.07 (m, 4 H), 6.60 (m, 2 H), 6.48 (t, 2 H), 4.66 (s, 1 H), 3.23 (d, 1 H), 2.86 (d, 1 H) ppm. ^{13}C NMR (75.5 MHz, CD_3CN): δ = 177.8, 164.2, 163.5, 161.8, 161.0, 159.2, 158.6, 158.3, 158.0, 153.7, 153.2, 151.4, 150.8, 138.2, 137.9, 137.8, 136.0, 130.8, 130.8, 128.4, 128.3, 128.2, 128.1, 127.1, 126.6, 124.7, 124.3, 124.1, 124.0, 116.7, 116.4, 116.3, 116.1, 55.2, 37.3 ppm. ESI-MS: *m*/*z* = 707 [M – PF$_6$]$^+$. $C_{35}H_{27}F_8N_4O_2PRuS$ (851.7): calcd. C 49.36, H 3.20, N 6.58, S 3.76; found C 49.50, H 3.32, N 6.51, S 3.73. Λ-[Ru(bpy)$_2$(OSdpF)](PF$_6$) (**Λ-2**), yield 92% {Λ-[Ru(bpy)$_2$(MeCN)$_2$]-(PF$_6$)$_2$ was used as the precursor}, *ee* 98%. CD (Δε/M^{-1}cm^{-1}, MeCN): 283 (–75), 297 (+175), 345 nm (+20). Δ-[Ru(bpy)$_2$-(OSdpF)](PF$_6$) (**Δ-2**), yield 92% {Δ-[Ru(bpy)$_2$(MeCN)$_2$](PF$_6$)$_2$ was used as the precursor}, *ee* 98%. CD (Δε/M^{-1}cm^{-1}, MeCN): 283 (+70), 297 (–160), 345 nm (–19).

[Ru(bpy)$_2$(OSdpCl)](PF$_6$) (*rac*-3): Yield 88% (the procedures were similar to those used for *rac*-**1**). ^{1}H NMR (300.1 MHz, CD_3CN): δ = 9.57 (d, 1 H), 9.16 (d, 1 H), 8.43 (d, 1 H), 8.32 (d, 1 H), 8.11 (m, 3 H), 7.82 (m, 5 H), 7.62 (t, 1 H), 7.41 (d, 2 H), 7.33 (d, 2 H), 7.19 (t, 1 H), 7.08 (m, 2 H), 6.73 (d, 2 H), 6.57 (d, 2 H), 4.63 (s, 1 H), 3.23 (d, 1 H), 2.90 (d, 1 H) ppm. ^{13}C NMR (75.5 MHz, CD_3CN): δ = 177.7, 159.2, 158.6, 158.3, 158.1, 153.8, 153.2, 151.5, 150.9, 138.5, 138.2, 138.0, 137.9, 137.4, 135.9, 134.6, 133.8, 130.4, 130.4, 129.9, 129.9, 129.5, 129.5, 128.4, 128.1, 128.1, 128.1, 127.2, 126.7, 124.7, 124.4, 124.1, 124.0, 55.4, 37.2 ppm. ESI-MS: *m*/*z* = 739 [M – PF$_6$]$^+$. $C_{35}H_{27}Cl_2F_6N_4O_2PRuS$ (884.6): calcd. C 47.52, H 3.08, N 6.33, S 3.62; found C 47.22, H 3.14, N 6.24, S 3.53. Λ-[Ru(bpy)$_2$(OSdpCl)](PF$_6$) (**Λ-3**), yield 92% {Λ-[Ru(bpy)$_2$(MeCN)$_2$]-(PF$_6$)$_2$ was used as the precursor}, *ee* 98%. CD (Δε/M^{-1}cm^{-1}, MeCN): 283 (–66), 296 (+181), 345 nm (+18). Δ-[Ru(bpy)$_2$-(OSdpCl)](PF$_6$) (**Δ-3**), yield 92% {Δ-[Ru(bpy)$_2$(MeCN)$_2$](PF$_6$)$_2$ was used as the precursor}, *ee* 98%. CD (Δε/M^{-1}cm^{-1}, MeCN): 283 (+68), 297 (–176), 345 nm (–19).

General Procedure for the Asymmetric Oxidation of Sulfoxide Complexes: A solution of the appropriate ruthenium thioether complex (0.05 mmol) and *m*-CPBA (0.075 mmol) in CH_2Cl_2 (2 mL) was stirred for 5 h at room temperature, and then ether was added to induce precipitation. The solid was isolated by vacuum filtration, rinsed with ether, and air-dried.

[Ru(bpy)$_2$(4)](PF$_6$) (*rac*-1a): Yield 94% (*rac*-**1** was used as the starting material). ^{1}H NMR (300.1 MHz, CD_3CN): δ = 10.24 (d, 1 H), 8.96 (d, 1 H), 8.46 (d, 1 H), 8.38 (d, 1 H), 8.17 (t, 1 H), 8.10 (t, 1 H), 7.98 (m, 2 H), 7.90 (d, 1 H), 7.82 (m, 2 H), 7.74 (m, 2 H), 7.45 (m, 2 H), 7.36 (m, 3 H), 7.25 (m, 2 H), 7.01 (t, 1 H), 6.82 (d, 1 H), 6.72 (m, 4 H), 4.84 (s, 1 H), 4.23 (d, 1 H), 3.68 (d, 1 H) ppm. ^{13}C NMR (75.5 MHz, CD_3CN): δ = 173.6, 158.6, 158.1, 157.9, 156.8, 156.3, 153.3, 151.8, 149.7, 139.9, 139.5, 139.1, 137.7, 137.6, 133.9, 131.6, 131.6, 129.8, 129.8, 129.6, 129.2, 129.2, 128.7, 128.6, 128.2, 127.6, 127.1, 127.0, 127.0, 124.9, 124.9, 124.8, 124.1, 73.5, 61.5 ppm. ESI-MS: *m*/*z* = 687 [M – PF$_6$]$^+$. $C_{35}H_{29}F_6N_4O_3PRuS$ (831.7): calcd. C 50.54, H 3.51, N 6.74, S 3.86; found C 50.38, H 3.77, N 6.79, S 3.74. Λ-[Ru(bpy)$_2${(*S*)-**4**}](PF$_6$) (**Λ-1a**), yield 94% (**Λ-1** was used as the starting material), *de* 98%. CD (Δε/M^{-1}cm^{-1}, MeCN): 274 (–45), 290 (+90), 392 (–11), 448 nm (+14). Δ-[Ru(bpy)$_2${(*R*)-**4**}](PF$_6$) (**Δ-1a**), yield 94% (**Δ-1** was used as the starting material), *de* 98%. CD (Δε/M^{-1}cm^{-1}, MeCN): 274 (+45), 290 (–88), 392 (+11), 448 nm (–13).

[Ru(bpy)$_2$(5)](PF$_6$) (*rac*-2a): Yield 95% (*rac*-**2** was used as the starting material). ^{1}H NMR (300.1 MHz, CD_3CN): δ = 10.21 (d, 1 H), 8.94 (d, 1 H), 8.45 (d, 1 H), 8.38 (d, 1 H), 8.17 (t, 2 H), 8.00 (m, 3 H), 7.82 (m, 4 H), 7.46 (m, 2 H), 7.26 (m, 2 H), 7.11 (t, 2 H), 6.80 (m, 3 H), 6.48 (t, 2 H), 4.85 (s, 1 H), 4.18 (d, 1 H), 3.68 (d, 1 H) ppm. ^{13}C NMR (75.5 MHz, CD_3CN): δ = 173.6, 164.9, 163.6, 162.4, 161.1, 158.5, 158.0, 157.9, 156.8, 156.2, 153.5, 152.1, 149.7, 140.0, 139.8, 139.2, 137.8, 133.6, 133.5, 129.3, 129.2, 128.9, 128.6, 127.7, 127.3, 124.9, 124.7, 124.5, 124.2, 116.6, 116.4, 116.2, 116.0, 71.7, 61.6 ppm. ESI-MS: *m*/*z* = 723 [M – PF$_6$]$^+$. $C_{35}H_{27}F_8N_4O_3PRuS$ (867.7): calcd. C 48.45, H 3.14, N 6.46, S 3.70; found C 48.38, H 3.27, N 6.33, S 3.64. Λ-[Ru(bpy)$_2${(*S*)-**5**}](PF$_6$) (**Λ-2a**), yield 95% (**Λ-2** was used as the starting material), *de* 98%. CD (Δε/M^{-1}cm^{-1}, MeCN): 275 (–36), 292 (+75), 393 (–90), 448 nm (+8). Δ-[Ru(bpy)$_2${(*R*)-**5**}](PF$_6$) (**Δ-2a**), yield 95% (**Δ-2** was used as the starting material), *de* 98%. CD (Δε/M^{-1}cm^{-1}, MeCN): 276 (+35), 292 (–77), 393 (+9), 448 nm (–7).

[Ru(bpy)$_2$(6)](PF$_6$) (*rac*-3a): Yield 93% (*rac*-**3** was used as the starting material). ^{1}H NMR (300.1 MHz, CD_3CN): δ = 10.21 (d, 1 H), 8.93 (d, 1 H), 8.45 (d, 1 H), 8.38 (d, 1 H), 8.18 (t, 2 H), 7.99 (m, 3 H), 7.82 (m, 4 H), 7.41 (m, 4 H), 7.28 (m, 2 H), 6.81 (d, 1 H), 6.74 (m, 4 H), 4.83 (s, 1 H), 4.20 (d, 1 H), 3.66 (d, 1 H) ppm. ^{13}C NMR (75.5 MHz, CD_3CN): δ = 173.3, 158.5, 158.0, 157.9, 156.7, 156.3, 153.6, 152.1, 149.7, 140.0, 139.9, 139.2, 137.7, 135.9, 135.5, 134.1,

133.1, 133.1, 132.1, 129.8, 129.8, 129.4, 129.4, 129.0, 128.9, 128.9, 128.6, 127.7, 127.5, 124.9, 124.8, 124.6, 124.2, 71.9, 61.6 ppm. ESI-MS: m/z = 755 $[M - PF_6]^+$. $C_{35}H_{27}Cl_2F_6N_4O_3PRuS$ (900.6): calcd. C 46.68, H 3.02, N 6.22, S 3.56; found C 46.60, H 3.14, N 6.12, S 3.51. Λ-[Ru(bpy)$_2${(*S*)-**6**}](PF$_6$) (Λ-**3a**), yield 93% (Λ-**3** was used as the starting material), *de* 98%. CD ($\Delta\varepsilon$/M^{-1}cm^{-1}, MeCN): 275 (–47), 292 (+104), 396 (–9), 451 nm (+5). Δ-[Ru(bpy)$_2${(*R*)-**6**}](PF$_6$) (Δ-**3a**), yield 93% (Δ-**3** was used as the starting material), *de* 98%. CD ($\Delta\varepsilon$/M^{-1}cm^{-1}, MeCN): 274 (+54), 293 (–98), 396 (+12), 449 nm (–7).

General Procedure for the Preparation of Sulfoxide Compounds and Recovery of the Chiral Precursors: A solution of the appropriate ruthenium sulfoxide complex (1 mmol) and trifluoroacetic acid (5 mmol) in CH_3CN (10 mL) was magnetically stirred and heated at 60 °C for 3 h under argon. The reaction mixture was allowed to cool to room temperature and concentrated to give an orange solid. After addition of H_2O (20 mL) to the orange solid, the aqueous phase was extracted with Et_2O (3 × 15 mL). The Et_2O solution was dried with $MgSO_4$ and then filtered. The solvent was removed under reduced pressure and dried under high vacuum to give the sulfoxide compound.

Moreover, an excess of solid KPF_6 was added to the resulting aqueous phase. CH_2Cl_2 (3× 15 mL) was used to extract the product from the aqueous phase, and the CH_2Cl_2 phase was combined and dried with $MgSO_4$. After filtration and concentration, Λ/Δ-[Ru(bpy)$_2$(MeCN)$_2$](PF$_6$)$_2$ was obtained in 91% yield.

(Diphenylmethanesulfinyl)acetic Acid (4): Yield 84% (*rac*-**1a** was used as the starting material). ^{1}H NMR (300.1 MHz, CD_3Cl): δ = 7.41 (m, 10 H), 5.35 (s, 1 H), 3.65 (d, 1 H), 3.31 (d, 1 H) ppm. (*S*)-**4**, yield 84% (Δ-**1a** was used as the starting material), *ee* 98%. CD ($\Delta\varepsilon$ /M^{-1}cm^{-1}, MeCN): 239 nm (–15). (*R*)-**4**, yield 84% (Λ-**1a** was used as the starting material), *ee* 98%. CD ($\Delta\varepsilon$ /M^{-1}cm^{-1}, MeCN): 239 nm (+12).

2-[Bis(4-fluorophenyl)methylsulfinyl]acetic Acid (5): Yield 80% (*rac*-**2a** was used as the starting material). ^{1}H NMR (300.1 MHz, CD_3Cl): δ = 7.45 (m 4 H), 7.12 (m 4 H), 5.45 (s 1 H), 3.66 (d 1 H), 3.33 (d 1 H) ppm. ^{13}C NMR (75.5 MHz, CD_3Cl): δ = 166.6, 131.4, 131.3, 130.6, 130.5, 116.8, 116.6, 116.2, 116.0, 69.0, 51.9 ppm. ESI-MS: m/z = 309 $[M - H]^-$. $C_{15}H_{12}F_2O_3S$ (310.3): calcd. C 58.06, H 3.90, S 10.33; found C 58.20, H 4.00, S 10.23. (*S*)-**5**, yield 80% (Δ-**2a** was used as the starting material), *ee* 98%. CD ($\Delta\varepsilon$ /M^{-1}cm^{-1}, MeCN): 240 nm (–13). (*R*)-**5**, yield 80% (Λ-**2a** was used as the starting material), *ee* 98%. CD ($\Delta\varepsilon$ /M^{-1}cm^{-1}, MeCN): 239 nm (+12).

2-[Bis(4-chlorophenyl)methylsulfinyl]acetic Acid (6): Yield 82% (*rac*-**3a** was used as the starting material). ^{1}H NMR (300.1 MHz, CD_3Cl): δ = 7.39 (m 8 H), 5.41 (s 1 H), 3.65 (d 1 H), 3.34 (d 1 H) ppm. ^{13}C NMR (75.5 MHz, CD_3Cl): δ = 166.3, 130.8, 130.1, 129.9, 129.3, 69.3, 51.5 ppm. ESI-MS: m/z = 341 $[M - H]^-$. $C_{15}H_{12}Cl_2O_3S$ (343.2): calcd. C 52.49, H 3.52, S 9.34; found C 52.61, H 3.63, S 9.25. (*S*)-**6**, yield 82% (Δ-**3a** was used as the starting material), *ee* 98%. CD ($\Delta\varepsilon$/M^{-1}cm^{-1}, MeCN): 242 nm (–20). (*R*)-**6**, yield 82% (Λ-**3a** was used as the starting material), *ee* 98%. CD ($\Delta\varepsilon$/M^{-1}cm^{-1}, MeCN): 242 nm (+19). CD ($\Delta\varepsilon$/M^{-1}cm^{-1}, MeCN): 300 nm (+126).

Crystallographic Analysis: The diffraction intensities for *rac*-**3**·CH_3OH and *rac*-**3a**·CH_3OH were collected with an Oxford Gemini S Ultra CCD Area detector diffractometer and use of graphite-monochromated Cu-K_α radiation (λ = 1.54178 Å) at 298 K. All of the data were corrected for absorption effect by the multi-scan technique.[19] The structures were solved by direct methods with SHELXS-97 programs[20] and refined by full-matrix, least-squares technique on F^2 with SHELXL-97 programs.[21] Anisotropic thermal parameters were applied to all non-hydrogen atoms. The organic hydrogen atoms of the ligands were generated geometrically. The crystal data and the details of data collection and refinement for the complexes are summarized in Table 1.

Table 1. Crystallographic data for complexes *rac*-**3** and *rac*-**3a**.

	rac-**3**·CH_3OH	*rac*-**3a**·CH_3OH
Molecular formula	$C_{36}H_{30}Cl_2F_6N_4O_3PRuS$	$C_{36}H_{30}Cl_2F_6N_4O_4PRuS$
Mr	915.64	931.64
Crystal system	monoclinic	monoclinic
Space group	$P2_1/n$	$P2_1/n$
a [Å]	12.0972(2)	11.1576(4)
b [Å]	21.4763(4)	21.9860(6)
c [Å]	14.5927(3)	15.5320(4)
°	97.124(2)	96.661(3)
V [Å^3]	3761.96(12)	3784.5(2)
Z	4	4
D_c [g cm^{-3}]	1.615	1.635
μ [mm^{-1}]	6.239	6.234
Data collected	19929	12435
Observed reflections	5756	5700
$R_1[I > 2\sigma(I)]$[a]	0.0460	0.0624
$_wR_2$ (F^2) $[I > 2\sigma(I)]$[b]	0.1141	0.1757
R_1 (all data)	0.0542	0.0716
wR_2 (all data)	0.1220	0.1852
GOF on F^2	1.039	1.074
$\Delta\rho_{max.}/\Delta\rho_{min.}$ [e Å^{-3}]	0.729/–1.398	1.577/–0.714

[a] $R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. [b] $wR = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$.

CCDC-1054697 (for *rac*-**3**·CH_3OH) and -1054698 (for *rac*-**3a**·CH_3OH) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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