Asymmetric Sulfoxidation by *C₁*-symmetric V(IV)O(ONO) (*S*)-NOBIN Schiff-base Vanadyl Complexes

Sanmitra Barman[a], Christopher J. Levy[b]*

Department of Chemistry, BML Munjal University, 67 Milestone, NH-8, HR-122413, India [a]
Department of Chemistry, The University of Western Ontario, 1151 Richmond Street, London, Ontario, Canada, N6A 5B7 [b]

E-mail: clevy9@uwo.ca & sanmitra.barman@bmu.edu.in

ABSTRACT

C_1-symmetric vanadyl Schiff-base complexes were synthesized by reacting vanadium(IV) acetylacetonate with (S)-3-[(1-(2-hydroxynaphthalen-1-yl)naphthalen-2-ylimino]methyl]-phenanthrene-4-ol and (S)-2-{[1-(2-hydroxynaphthalen-1-yl)naphthalen-2-ylimino]methyl}tetraphene-1-ol. The complexes were characterized by MALDI-TOF-MS, UV-Vis, and circular dichroism (CD) spectroscopy. The catalysts showed moderate activity for the oxidation of thioanisole to methyphenylsulfoxide with hydrogen peroxide, *tert*-butyl hydroperoxide and cumene hydroperoxide as the oxidants.

Keywords: C_1-symmetric, Schiff-base, Asymmetric Sulfoxidation, Vanadyl, NOBIN

Introduction

Chiral sulfoxides are important building blocks in pharmaceutical and fine chemical industries. The asymmetric catalytic oxidation of prochiral sulfides is an attractive and efficient pathway to chiral sulfoxides that has garnered significant interest.[1-4] There majority of studies have focused on titanium and vanadium catalysts to affect the oxidation, with hydrogen peroxide or molecular oxygen as preferred benign oxidants.[5] Vanadium complexes have commonly had chiral tridentate or tetradentate ligands in these systems.[6] Previously we have described monohelical tetradentate (ONNO) vanadyl salen complexes as catalysts for asymmetric sulfoxidations with hydrogen peroxide.[7] In keeping with other mechanistic proposals for non-radical oxidation, dissociation of one ligand donor was deemed necessary to accommodate peroxide and substrate addition to the vanadium center during catalysis. In these systems it has been proposed that the sulfide undergoes direct nucleophilic attack by the hydroperoxo ligand (Fig. 1).[6]
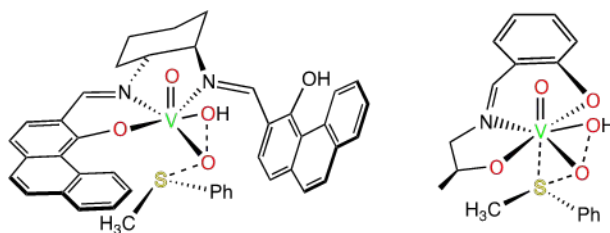

Fig. 1. Direct HOO⁻ nucleophilic attack (left, O to *si* face) and S-V precoordination (right, O to *re* face) reaction models for vanadyl complex catalyzed thioanisole oxidation with hydrogen peroxide.

Discussion

Tridentate ligands offer a more open coordination sphere and opportunity for direct sulfide coordination to the metal center, as described by Romanowski (Fig. 1).[8] This promotes stronger

and more predictable interaction with the ligand framework. Notably, the dominant enantiomer produced is reversed for the two mechanisms given similar steric topographies.

The majority of vanadium complexes with tridentate ligands that have been reported incorporate Schiff-base and phenoxide/alkoxide donors in an ONO pattern.[5] In this article, we describe the syntheses of vanadyl complexes whose ligands are based on Schiff-base condensation of a polyaromatic aldehyde to (*S*)-2-amino-2'-hydroxy-1,1'-binaphthyl [(*S*)-NOBIN]: these are the first vanadium complexes based on NOBIN to be reported. Previously, we have described titanium(IV) complexes of these ligands.[9] Thus, the synthesis and characterization of (*S*)-**1** and (*S*)-**2** have been reported.[8]

The new vanadyl (*S*)-NOBIN derived complexes (*S*)-**3** and (*S*)-**4** were produced from VO(acac)$_2$ under forcing conditions. Refluxing with the corresponding ligands (*S*)-**1** or (*S*)-**2** in the presence of excess base (10 eq. NaOMe) were required to produce adequate yields. The best results were obtained with 6 h of reflux in a 2:1 mixture of dry ethanol and dichloromethane. The complexes were isolated as brown powders after Soxhlet extraction and solvent removal *in vacuo* (Scheme 1). The compounds were air sensitive: solutions exposed to air darkened rapidly. The presumed oxidation products are μ-oxo bridged OV(V)–O–V(V)O dimers, such as those crystallographically-characterized by Correia et al. for related complexes under similar conditions.[10]

(S)-**1**, phenanthryl
(S)-**2**, benz[a]anthryl

(S)-**3**, phenanthryl, 72%
(S)-**4**, benz[a]anthryl, 74%
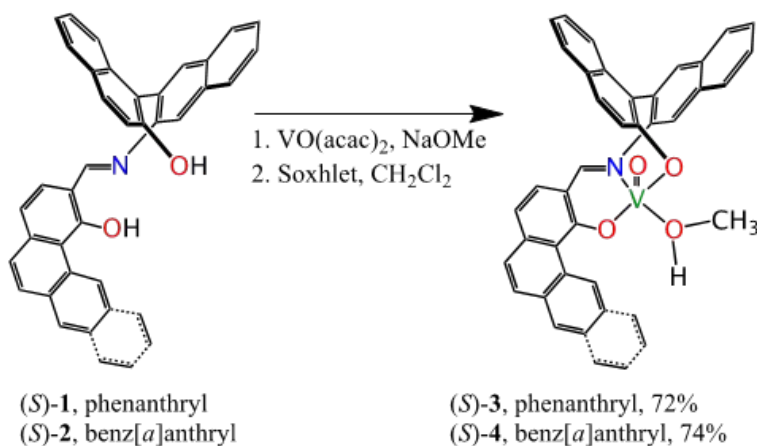
Scheme 1. Synthesis of V(IV) complexes (**S**)-**3** and (**S**)-**4**

The vanadyl complexes showed broad ^{1}H NMR spectra, consistent with the presence of paramagnetic V(IV) centers rather than d^0 V(V) complexes. Despite this, the chemical shifts are comparable to those for diamagnetic complexes, consistent with previous observations.[11] The MALDI-TOF-MS spectra show the [M]$^+$ ion peaks with the expected isotopic mass distributions. No dinuclear species were detected in the MS, pointing to mononuclear complexes. The ligands and complexes showed electronic absorption and CD spectra characteristic of 2,2′ substituted 1,1′ binaphthyls (Fig. 2).[12] Three absorption bands are observed, which corresponds to three basic absorption bands of β-mono-substituted naphthalene, and they can be conventionally assigned to three transitions of naphthalene: ^{1}B$_b$, ^{1}L$_a$, and ^{1}L$_b$ in order of decreasing energy. The intensities and signs of the absorptions in the CD spectra follow the pattern expected for chromophores in the (S)-NOBIN unit. The is significant red-shifting (*ca*. 20 nm) of the ^{1}B$_b$ band for the complexes compared to the ligands: (S)-**1** → (S)-**3**, 232 → 253 nm; (S)-**2** → (S)-**4,** 236 → 253 nm; negative 1La 282 → 289 nm. This reflects delocalization of frontier orbitals to both the metal center and the polyaromatic unit. This latter effect is the result of a reduction in the naphthyl to phenanthryl/benz[a]anthryl angle upon ligand coordination. The 267 nm bands of (S)-**1** and (S)-**2**

5

are due to the phenanthryl/benz[a]anthryl units. These become shoulders (253 nm) on the ^1B_b
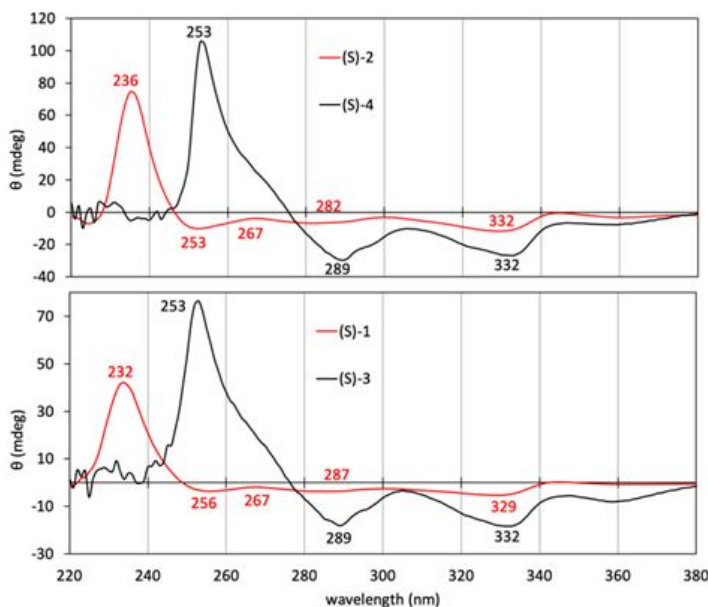
bands in the complexes. [9]

Fig. 2. Electronic CD spectra from THF solutions of the ligands (red) and vanadyl complexes (black).

Preliminary studies were carried out with (S)-**3** and (S)-**4** as catalysts for the oxidation of

thioanisole with three oxidants: hydrogen peroxide, *tert*-butyl hydroperoxide and cumene

hydroperoxide. The reaction conditions were optimized for solvent, temperature, oxidant and

reaction time. Selectivity was solvent dependent, with improved selectivity in methylene chloride.

Reactions were homogeneous, except with hydrogen peroxide. In this case the reaction takes place

under biphasic conditions: CH_2Cl_2 and H_2O_2 (*aq*). The reaction temperature was also an important

factor, with 0° C producing the best selectivity observed. Conversion of thioanisole to sulfoxide

reached 70% after 4 h and continued to increase up to *ca*. 12 h. Yields of sulfoxide decreased at

longer reaction times due to over-oxidation to sulfone. However, the selectivity (%ee) did not

change over the course of the reaction, suggesting that the stereochemical outcome is unaffected

6

by any changes in catalyst structures, such as the formation of V(V)–O–V(V) dimers. The substrate to oxidant ratio was varied to establish the effect of oxidant on conversion and selectivity. There was a distinct increase in the sulfone production and a decrease in selectivity when excess oxidant was used.
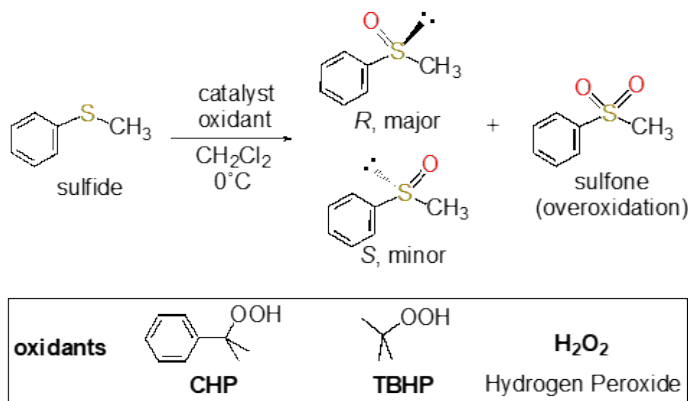
Scheme 2. Asymmetric sulfoxidation of thioanisole with vanadyl catalysts (major configuration *R*-sulfoxide).

The results of catalytic oxidation of thioanisole are presented in Table 1. In all cases the major enantiomer obtained from (*S*)-**3** and (*S*)-**4** was (*R*)-methylphenylsulfoxide. Moderate enantioselectivity (*ca*. 30%ee) was achieved with H_2O_2 as the oxidant. In comparison, *tert*-butyl hydroperoxide (~15%ee) and cumene hydroperoxide (~20%ee) are less selective oxidants under the conditions examined. This observation can be attributed to the homogeneous reaction conditions for TBHP and CHP: oxidant concentrations are higher and non-catalytic oxidation can become competitive. This phenomenon is supported by the observation that the conversions are higher for these oxidants in comparison to H_2O_2.

7

Table 1. Sulfoxidation of thioanisole catalyzed by (**S**)-**3** and (**S**)-**4**[a]

catalyst	oxidant	conv./%	SO/%	ee/%	SO$_2$/%
3	H$_2$O$_2$	84	81	29	19
3	TBHP	90	84	16	16
3	CHP	92	86	14	14
4	H$_2$O$_2$	82	82	18	18
4	TBHP	95	84	16	16
4	CHP	94	85	15	15

[a]1% cat., 12 h at 0 ˚C in CH$_2$Cl$_2$. [b]SO: PhSOMe. [c]Enantiomeric excess measured by HPLC with DIACEL OD-H column. [d]SO$_2$: PhSO$_2$Me

The proposed mechanism for catalytic sulfoxidation is consistent with that previously presented for other vanadyl complexes with tridentate ligands.[8] A key sequence is the coordination of sulfide to the vanadyl center followed by oxygen transfer from the hydroperoxo group. The stereochemical outcome is determined by whether the *re* or *si* prochiral face of the sulfide receives the oxygen (Fig. 3). Selectivity for the *R*-sulfoxide is consistent with preferred delivery of oxygen to the *si* face due to reduced steric repulsion between the sulfide and the polyaromatic ligand unit. The moderate enantioselection suggests only modest facial discrimination. This finding is supported molecular modelling (MM3) of the two possible intermediates, which indicated that binding to the *si* face of thioanisole is favored by 1.38 kJ/mol. This translates to a maximum ee% of 30%, without considering possible kinetic resolution effects often observed in similar systems.[13]
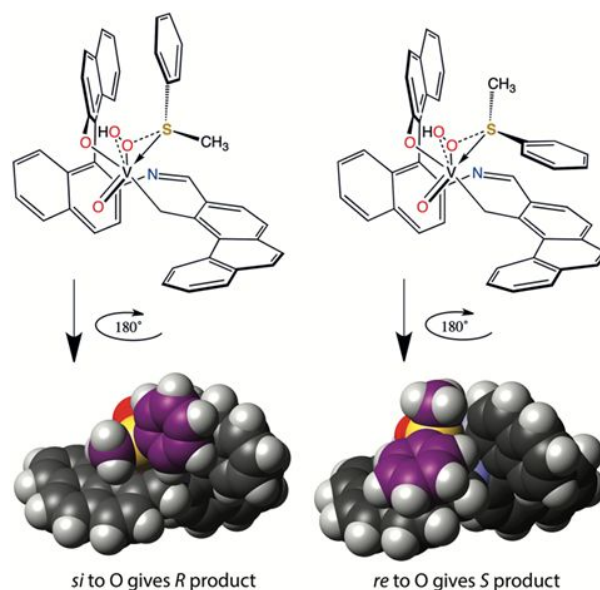
Fig. 3. Proposed intermediates for thioanisole oxidation by [(*R*)-**3**(OOH)] (top) and MM3-generated space-filling models (bottom).

The MM3 models indicate that *si* coordination is favored since the S-**Me** group interacts with the large phenanthryl group, while the S-**Ph** group interacts with the smaller naphthyl group. The larger S-**Ph** group has closer aromatic centroid-centroid contacts (3.40 & 3.87 Å) for *re* coordination, than for *si* coordination (3.63 Å).

The sulfoxidation results are similar to those for vanadyl salen catalysts we have previously examined.[7] This indicates that the tridentate (ONO) ligand system employed is comparable to the tetradentate (ONNO) systems. This supports the idea that the second ligand arm of the C_2-symmetrical complexes does not impact selectivity in these systems. One notable difference, however, is the higher degree of overoxidation with the C_1-symmetrical vanadyl NOBIN catalysts. This can be partially explained by the formation of oxo-bridged dimers in solution due to the open nature of the coordination sphere. This effectively removes catalyst from the system and allows nonselective uncatalyzed oxidation of sulfide to compete. By comparison, the bulkier tetradentate

ligand systems do not allow for rapid dimer formation, giving the catalytic pathways a chance to dominate.

Conclusions

The general conclusion of the study is that the complexes did catalyze asymmetric sulfoxidation, however the anticipated increase in activity compared to previous systems was not realized. The observed enantioselectivity in this study supports mechanism involving coordination of sulfide to the metal center before oxygen transfer to sulfur (Figure 4): the opposite selectivity is expected from direct nucleophilic attack of sulfur by a hydroperoxo ligand. The modeling study suggest that the maximum possible selectivity (30%ee) has been achieved for the system. The planar nature of the phenyl group in thioanisole stacks with the planar naphthyl and phenanthryl/benz[a]anthryl ligand groups in both diastereomeric coordination modes, and neither is strongly favored. This result points to the possibility of higher enantioselectivity for substrates with more sterically demanding groups, especially those that are non-planar. Further studies with a wider array of sulfide substrates along with computational work are planned.
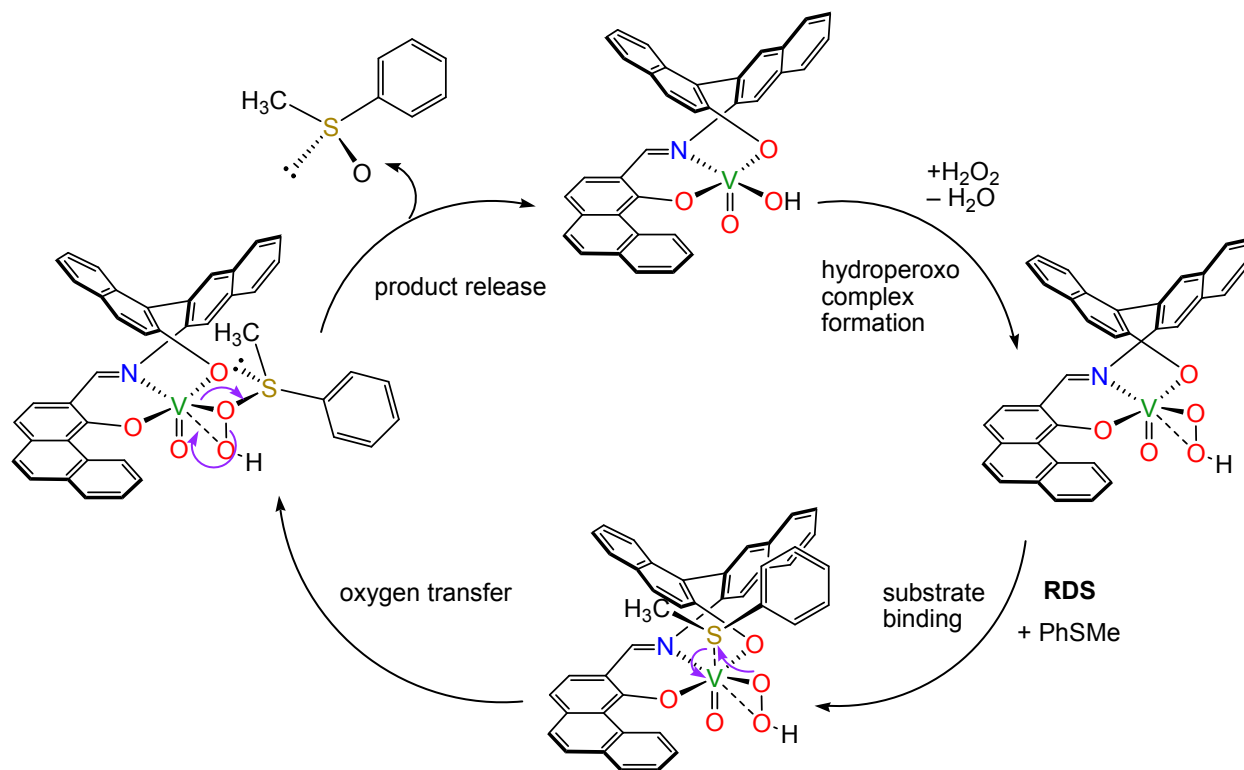
Fig. 4. Proposed mechanism for sulfoxidation reactions catalyzed by (*S*)-**3**.

Experimental procedure

General experimental methods

All the reactions were performed under inert atmosphere of nitrogen or argon unless otherwise mentioned. Solvents used were stored under calcium hydride or sodium benzophenone ketyl and degassed before using via Schlenk line technique. Synthesis and work up of the vanadyl complexes were done under rigorous inert atmosphere to avoid unwanted oxidation or decomposition. All mass spectra are recorded in Shimadzu MALDI TOF-TOF mass spectrometer. IR spectra are taken on neat samples using a Nicolet 380 FT-IR spectrometer with ZnSe ATR attachment. 1H and 13C NMR spectra were obtained on a Varian Unity 400 MHz spectrometer with residual solvent protons or TMS as an internal standard.

Synthesis of complexes

11

(*S*)-**3**: To the solution (composed of a mixture of CH_2Cl_2 (15 mL) and EtOH (7.5 mL)) of (*S*)-**1** (0.100 g, 0.205 mmol) was added vanadyl acetylacetonate (0.054 g, 0.205 mmol) and sodium methoxide (0.100 g, 2.04 mmol). The solution was refluxed for 6 h followed by filtration to obtain a brown colored precipitate. The compound was further purified by soxhlet extraction in CH_2Cl_2. Pure brown colored compound was obtained after solvent removal under reduced pressure (0.093 g, 72% yield). ^1H NMR ($CDCl_3$, 400 MHz): broad peaks suggest paramagnetic compound. MS: $[M+OMe]^{+1}$ $(C_{36}H_{24}N_1O_4V_1)^{+1}$ 586.261 (64%), 587.265 (24%), 588.272 (8%), 589.277 (4%). IR: $v_{V=O}$ 818.87 cm^{-1}, $v_{C=N}$ 1612.72 cm^{-1}. UV: 245 nm sharp high intensity peak is due to the absorption of the NOBIN backbone and the 275 nm peak is due to the interaction between the naphthyl ring of the NOBIN backbone and the phenanthryl side arm. L →M charge transfer at 365 nm (broad peak). CD: The chiral information in the complex is similar to the that of the ligand with CD peaks have shifted to longer wavelength.

(*S*)-**4**: To the solution (composed of a mixture of CH_2Cl_2 (8 mL) and EtOH (4 mL)) of **(*S*)-2** (0.063 g, 0.116 mmol) was added vanadyl acetyl acetonate (0.031g, 0.116 mmol) and sodium methoxide (0.063 g, 1.16 mmol). The solution was refluxed for 6 h followed by filtration to obtain a deep brown colored precipitate. The compound was further purified by soxhlet extraction in CH_2Cl_2. Deep brown colored compound was obtained after solvent removal under reduced pressure (0.059 g, 74% yield). ^1H NMR ($CDCl_3$, 400 MHz): broad peaks in the aromatic region suggest paramagnetic compound. MS: $[M+OMe]^{+1}$ $(C_{40}H_{26}N_1O_4V_1)^{+1}$ 636.169 (66%), 637.174 (26%), 638.183 (7%), 639.189 (1%). IR: $v_{V=O}$ 816.91 cm^{-1}, $v_{C=N}$ 1613.33 cm^{-1}. UV: The two sharp peaks for the ligand at 225 nm and 275 nm has become broad after complex formation. This shows higher interaction between the naphthyl rings in the NOBIN backbone and the benz[a]anthryl ring on the side arm. Characteristic broad peak at 365 nm for more delocalization of the Π electrons from

ligand to metal. CD: The chiral information for the complex is similar to that of the ligand with red shift of the CD peaks.

General procedure for sulfoxidations

All sulfoxidation reactions are carried out by 1 mol% of catalyst. The catalyst was dissolved in CH_2Cl_2 (3 mL) inside a two-neck round bottom flask under argon. After stirring for 10 minutes, thioanisole was added and then the reaction mixture was stirred for 15 minutes. The system was cooled to 0 ˚C in a regulated bath and 1.1 equivalents of oxidant (hydrogen peroxide, tert-butyl hydroperoxide, cumene hydroperoxide) was added for a period of 2 h. The mixture was additionally stirred for 10 h at 0 ℃ after the addition of the oxidant was complete. A saturated solution of sodium sulfite was added to quench the reaction. The reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL) and then combined extracts were dried over sodium sulfate. The solution was filtered, and the solvent evaporated. The product was purified by flash column chromatography in 10% ethyl acetate in hexane. Thioanisole, methylphenylsulfoxide and methylphenylsulfone can be identified from their signature peaks in ^{1}H NMR. The enantiomeric excess (*ee*) of the methylphenylsulfoxide was determined by HPLC analysis with a Daicel Chiralcel OD-H column using hexane and isopropanol mixture (90:10) as the eluent. The *R* isomer and the *S* isomer elutes at 17.2 and 20.8 minutes, respectively.

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Supporting Information is available on http://dx.doi.org/

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(14) NMR, IR, UV-Vis spectra and MS data for the complexes is provided as Supporting Information which is available electronically.