Dalton Transactions

Accepted Manuscript

This is an *Accepted Manuscript*, which has been through the RSC Publishing peer review process and has been accepted for publication.

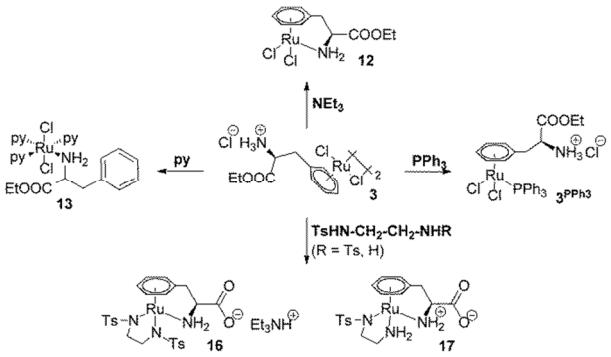
Accepted Manuscripts are published online shortly after acceptance, which is prior to technical editing, formatting and proof reading. This free service from RSC Publishing allows authors to make their results available to the community, in citable form, before publication of the edited article. This *Accepted Manuscript* will be replaced by the edited and formatted *Advance Article* as soon as this is available.

To cite this manuscript please use its permanent Digital Object Identifier (DOI®), which is identical for all formats of publication.

More information about *Accepted Manuscripts* can be found in the **Information for Authors**.

Please note that technical editing may introduce minor changes to the text and/or graphics contained in the manuscript submitted by the author(s) which may alter content, and that the standard **Terms & Conditions** and the **ethical guidelines** that apply to the journal are still applicable. In no event shall the RSC be held responsible for any errors or omissions in these *Accepted Manuscript* manuscripts or any consequences arising from the use of any information contained in them.

TOC graphic



Depending on the reaction conditions, phenylalanine derived ruthenium(II) half-sandwich complexes show a rich reactivity and coordination chemistry, which can be utilised for selective derivatisations.

Phenylalanine - a biogenic ligand with flexible η^6- and η^6:κ^1-coordination at ruthenium(II) centres†

Thomas Reiner,[a,b] Dominik Jantke,[c] Xiaohe Miao,[c] Alexander N. Marziale,[c] Florian Kiefer,[a] Jörg Eppinger*[c]

Received (in XXX, XXX) Xth XXXXXXXXX 201X, Accepted Xth XXXXXXXXX 201X
First published on the web Xth XXXXXXXXX 201X
DOI: 10.1039/b000000x

The reaction of (*S*)-2,5-dihydrophenylalanine **1** with ruthenium(III) chloride yields the μ-chloro-bridged dimeric η^6-phenylalanine ethyl ester complex **3**, which can be converted into the monomeric analogue, η^6:κ^1-phenylalanine ethyl ester complex **12** under basic conditions. Studies were carried out to determine stability and reactivity of complexes bearing η^6- and η^6:κ^1-chelating phenylalanine ligands under various conditions. Reaction of **3** with ethylenediamine derivatives N-*p*-tosylethylenediamine or 1,4-di-N-*p*-tosylethylenediamine results in the formation of monomeric η^6:κ^1-phenylalanine ethyl ester complexes **14** and **15**, which could be saponified yielding complexes **16** and **17** without changing the inner coordination sphere of the metal centre. The structure of η^6:κ^1-phenylalanine complex **17** and a N-κ^1-phenylalanine complex **13** resulting from the reaction of **3** with an excess of pyridine were confirmed by X-Ray crystallography.

Introduction

The well established stability of d^6 - sandwich complexes towards oxygen, water or even under physiological conditions[1] has triggered widespread interest for the application of such systems as biological probes[2,3] as well as pharmacologically active compounds (**A**, **B**).[4,5,6] In particular, the labelling of aromatic side chains of unprotected amino acids and peptides by introduction of CpM and Cp*M-moieties (M = d^6-metal cation) has been an active field with pivotal contributions by the groups of Moriart[7], Pearson,[8] Sheldrick[9] and others.[10] Conversion to half-sandwich complexes adds a further dimension to the chemistry of these systems due to the introduction of potentially labile coordination sites. Ward and co-workers recently tailored the labile coordination sphere of rhodium half-sandwich conjugates to generate an artificial enzyme.[11] In particular ruthenium(II) η^6-arene half sandwich complexes found a large variety of applications.[12] The *in vivo* and *in vitro* cytotoxic activities of this class of compounds has recently triggered intense research activity targeting the design of selective organometallic anticancer agents (**C**).[13,14] Further well-documented applications include building blocks for supramolecular structures,[15] catalysts for transfer hydrogenations (**D**, **E**),[16,17,18] hydrogenations[19] or C-C couplings[20]. Half sandwich ruthenium complexes were also successfully converted into catalytically active metal centres of organometallic enzyme hybrids.[21] Ruthenium η^6-arene complexes with pendant carboxylic,[22] amine[3,9,23] (**F**) or alcohol[24] functions have been synthesized. Side chains containing a coordinating moiety such as an alcohol,[25] amide[15] or carbene[26] group offer an easy entry to η^6:κ^1-arenes which provide a hemilabile tether at the metal centre. Multiple synthetic endeavours focused on the preparation of complexes with a chiral tether, targeting asymmetric induction in catalysis.[17,23] However, examples of η^6-ruthenium complexes with biogenic amino acids are scarce.[9,23]

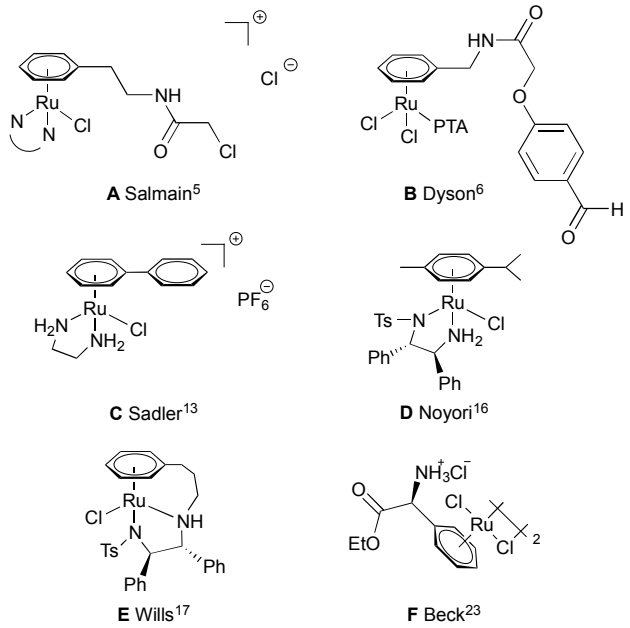


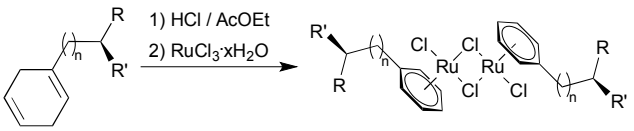
Fig. 1 Various η^6-arene Ru(II) half sandwich complexes applied in the selective inhibition of enzymes (**A**), biological probes (**B**), tumour therapy (**C**) or catalysis (**D**, **E**). Complex (**F**) represents the only Ru(II) half-sandwich complex with η^6-coordination of an amino acid side chain and unprotected amino group.

[a] Technische Universität München, Department Chemie, Lichtenbergstr. 4, D-85747 Garching, Germany.
[b] Present address: Department of Radiology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, New York 10065, USA.
[c] King Abdullah University of Science and Technology (KAUST) Division of Physical Sciences & Engineering and KAUST Catalysis Center (KCC), Thuwal 23955-6900, Saudi Arabia, E-mail: jorg.eppinger@kaust.edu.sa; Tel: (+) 996 2 808-2414.
† Electronic supplementary material available. CCDC reference numbers 721712–721713. For crystallographic data in CIF see DOI: 10.1039/b000000x/

Hence, we became interested in synthesis and exploration of complexes that feature biogenic amino acids. We present the synthesis of various novel η^6-phenylalanine, η^6:κ^1-phenylalanine and η^6:κ^1-phenylalanine ethyl ester complexes of ruthenium(II). The distinct coordination behaviour of side chain and external donors and complex stabilities are evaluated by ^{1}H NMR, ^{13}C NMR and ^{15}N NMR spectroscopy. X-Ray crystallography supports the spectroscopic results.

Results

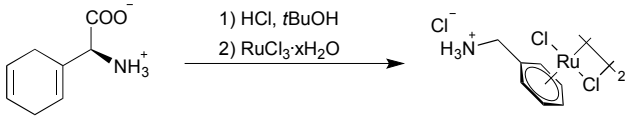
The particular orientation of carboxylic acid and amino moieties, which is characteristic for α-amino acids, is well suited to chelate cationic metal centres. Hence, a decrease in binding affinity of these functionalities is essential to prevent chelation and thus deactivation of metal centre binding sites. Beck *et al.* recently described an elegant procedure avoiding tedious protection/deprotection strategies by a simple *in situ* protonation (amino group) and esterification (carboxy group) in acidic solutions.[24] Using this strategy, the dihydro derivates **1**[27] and **2**[28], which were prepared from the artificial amino acid L-phenylglycine as well as the biogenic amino acid L-phenylalanine, respectively, can be converted with ruthenium(III) chloride hydrate in refluxing ethanol to the corresponding η^6-arene ruthenium(II) complexes **3** and previously described **4**[24] in high yields (scheme 1).



1 n = 1, R = COO^-, R' = NH_3^+ **3** (90%) n = 1, R = COOEt, R' = $NH3^+Cl^-$
2 n = 0, R = COO^-, R' = NH_3^+ **4** (78%) n = 0, R = COOEt, R' = $NH3^+Cl^-$

Scheme 1 Synthesis of η^6-arene ruthenium complexes **3** and **4**[24].

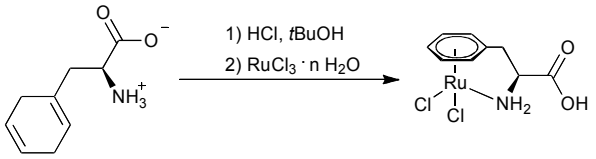
^{t}BuOH esters are unstable under the strongly acidic reaction conditions. Hence, changing the reaction medium from HCl/AcOEt to ^{t}BuOH prevents formation of the carboxylic acid ester. Also, the high proton concentration disfavours coordination of the carboxylic acid group. Nevertheless, reaction of 2,5-dihydro-phenylglycine **2** with $RuCl_3 \cdot n\ H_2O$ in the presence of ^{t}BuOH does not lead to the expected pendant η^6-half sandwich amino acid. Instead, we observe decarboxylation of phenylglycine at the α-CH position, resulting in the formation of the dimeric μ-chloro-bridged η^6-benzylammonium ruthenium(II) complex **5** (scheme 2), which has been synthesized via a different route earlier.[29] The combination of an ammonium function and an electron withdrawing η^6-coordinated Ru(II) centre at the aromatic side chain leads to an highly electron deficient α-carbon, which is known to favour decarboxylation under acidic conditions and elevated temperatures. Correspondingly, decarboxylation does not take place if 2,5-dihydro-phenylalanine **1** is used as the η^6-arene precursor (scheme 3). In this case, monomeric η^6:κ^1-phenylalanine complex **6** was isolated in 54% yield as a bright yellow powder. Spectroscopic data indicate that despite the acidic reaction conditions the side chain amino function coordinates to the metal centre, while the carboxylic acid function is protonated. IR spectra of the ruthenium(II)



2 **5** (69%)

Scheme 2 Synthesis of η^6-arene ruthenium complex **5** from 2,5-dihydro-L-phenylglycine in ^{t}BuOH.

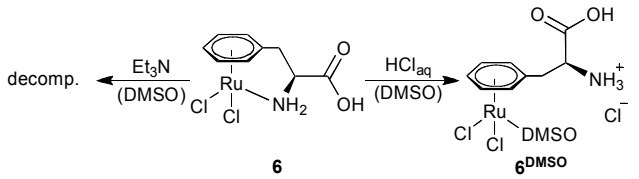
complexes **3**, **4** and **6** reveal strong bands between 1741 and 1746 cm^{-1}, which correspond to the respective CO stretching frequencies.[30] While IR sprectra of **6** in chloroform solution exhibit one carbonyl absorption at 1741 cm^{-1}, preparations in KBr display two sharp bands in the carbonyl region at 1734 cm^{-1} and 1726 cm^{-1}. The same two bands are present in nujol, hence halide exchange during sample preparation can be ruled out as possible reason for the double band structure. In agreement with the IR measurements described above ^{13}C MAS NMR spectra of **6** exhibited a double set of signals for α, β and carboxyl carbons. Hence, we assume that in the solid state packing effects and / or different hydrogen bonding patterns lead to different orientations and electron density for the carboxylic acid function. The ^{1}H and ^{13}C NMR spectra of the dimeric complexes **3**, **4** and **5** only show a single set of signals. ^{1}H NMR spectra of **6** recorded in $CDCl_3$ show two multiplets (at 4.69 ppm and 4.06 ppm) for the prochiral NH_2 protons. This confirms coordination of the amine to the metal centre. In contrast, the ammonium resonances of **3**, **4** and **5** are observed as broad singlets between 8.92 and 8.77 ppm. Complex **6** is only slightly soluble in most organic solvents other that DMSO-d_6, where it decomposes and the η^6-cordinated arene is lost. Decomposition is faster in the presence of 4% triethylamine in DMSO, whereas in the presence of 4% HCl in DMSO η^6-arene coordination is retained and no decomposition was detected within 48 h, however, the metal centre's inner coordination sphere is altered.



1 **6** (52%)

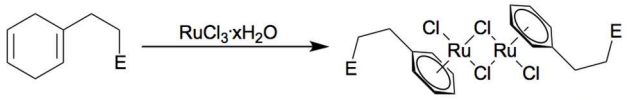
Scheme 3 Synthesis of η^6:κ^1-arene ruthenium complex **6** from 2,5-dihydro-L-phenylalanine in *t*-butanol.

Addition of HCl leads to protonation of the amine tether and concomitant dissociation of amine and metal centre. This results in the formation of $\mathbf{6}^{\mathbf{DMSO}}$, the first example of a non-derivatized η^6-arene phenylalanine ligand coordinated to a half sandwich Ru(II) complex (scheme 4). ^{13}C NMR spectra of $\mathbf{6}^{\mathbf{DMSO}}$ exhibited a single set of signals for all carbons, the ammonium signal in ^{1}H NMR spectra was observed as a broad singlet at 8.72 ppm. The specific optical rotation of $\mathbf{6}^{\mathbf{DMSO}}$ was determined to be $[\alpha]_D^{22}$ +44.0 (c 0.58 in HCl / DMSO = 1 / 25), indicating racemization of the phenylalanine ligand to be unlikely under reaction conditions.



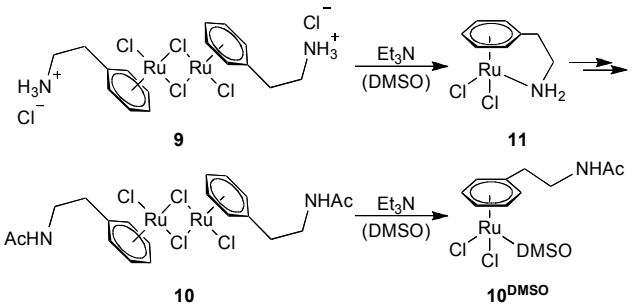
Scheme 4 Reactivity of **6** under acidic (HCl) and basic (Et_3N) conditions.

To understand the role of the pendant amine group of complex **6** in η^6-arene dissociation, two model compounds were synthesized: the previously reported ammonium functionalized complex **9**[31,32] and its acetamide analogue **10**. Both complexes were obtained from their 2,4-dihydro cyclohexadiene derivatives as brown and ochre powders in high yields (**9**: 88 % **10**: 92 %). In case of **9**, the NH_3^+ resonance was observed as a broad singlet at 8.15 ppm in ^{1}H NMR spectra. The amide signal of **10** resonates 2.37 ppm downfield from the free ligand at 7.94 ppm.



Scheme 5 Synthesis of η^6-arene ruthenium complex **9**[31,32] and **10** via re-aromatization of cyclohexadiene derivatives **7**[33] and **8**.

Both complexes **9** and **10** form deep red solutions in DMSO-d_6 and are stable in solution under aerobic conditions for days. Upon addition of triethylamine, the colour of complex **9** instantly changes from red to yellow. This colour change is indicative for the formation of complex **11** (scheme 6), which was characterized recently.[34] In ^{1}H NMR spectra, the ammonium signal of complex **9** is replaced by a NH_2 resonance at 4.39 ppm. Resonances of the η^6-coordinated arene ring are shifted upfield by up to 0.5 ppm, indicating a more electron deficient metal centre and a changed Ru(II) coordination sphere. When triethylamine is added to a solution of **10** in DMSO-d_6, ^{1}H NMR as well as ^{13}C NMR signals of **10** do not change. Therefore, only the primary amine tether is able to coordinate to the metal centre in the presence of triethylamine / DMSO (scheme 6). Complex **11** is highly unstable and approximately 20 % of complex **11** decomposed after 40 min in solution (figure 2). In ^{1}H NMR, decomposition intermediate **I** can be observed after just minutes. While compound **I** is not fully characterized, observed NMR shifts suggest that the phenyl ring remains metal-coordinated. Arene signals are shifted upfield (6.4 ppm – 5.5 ppm) in comparison to non-coordinated arenes. Beside these signals, we observe free 2-phenylethylamine **II**, and after 24 h, the decomposition was found to be complete (figure 2). This finding is in accordance with observations made for η^6:κ^1-coordinated complex **6**, which is unstable in DMSO-d_6 and highly unstable in DMSO-d_6 containing Et_3N. Protonated amine functions result in the prevention of decomposition (following HCl addition to complex **6** or **9** as isolated from synthesis). The combined observations from complexes **6**, **9** and **10** suggest that the η^6:κ^1-coordination mode of the amine tether is responsible for the observed instability.



Scheme 6 Reactivity under basic conditions depends on the side chain functionality of complexes **9** and **10**.

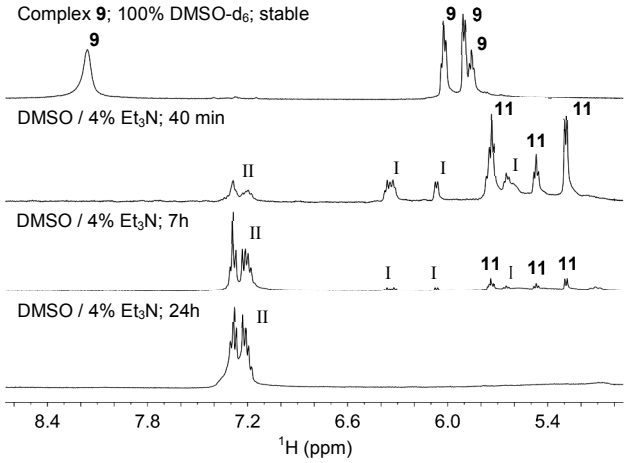
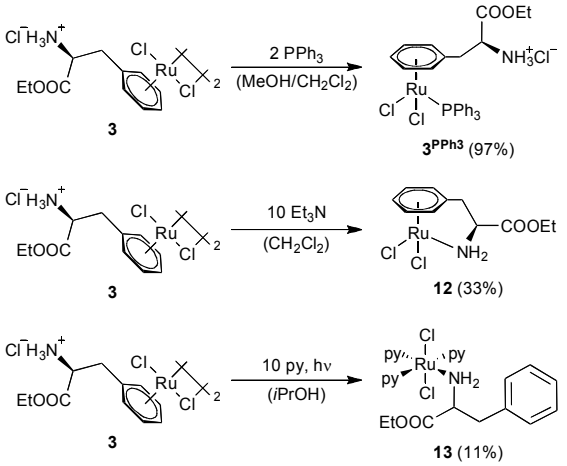


Fig. 2 Decomposition of complex **9** (^{1}H NMR, 400 MHz, Et_3N / DMSO-d_6 = (1 / 25)). Within minutes, the amine tether coordinates to the metal centre, forming complex **11** and thus initiating the decomposition. **I**: unisolated intermediate. **II**: free 2-phenyletylamine.

Correspondingly, complex **3**, which has a protonated (= non-coordinating) ammonium moiety, can be converted cleanly into the respective monomeric complex through addition of nucleophiles. Reaction with triphenylphosphine in a mixture of methanol and dichloromethane yielded adduct **3**^{PPh3}, which was highly soluble in polar media, in near-quantitative yield (97 %, scheme 7). No coordination of the pendant amino group was detected. The NH_3^+ resonance is observed as a broad singlet at 8.77 ppm. The deep red solid is stable for days in protic or coordinating organic solvents such as methanol and DMSO without apparent decomposition. When triethylamine was added to a suspension of **3** in dichloromethane, the colour of the reaction mixture changed from red to bright yellow within 2 h, resulting from the formation of η^6:κ^1-coordinated complex **12**. The ethyl ester group markedly increases solubility of complex **12** in non-coordinating organic solvents as compared to complex **6**.



Scheme 7 Reactivity of dinuclear η^6-arene complex **3** towards different nucleophiles.

In the ^{1}H NMR spectrum, two signals were observed for the diastereotopic NH_2 protons (triplet at 4.57 ppm and multiplet at 3.82 ppm). Complex **12** shares the typical instability in protic (methanol) and coordinating (DMSO) solvents of the other η^6:κ^1-coordinated complexes. In presence of an excess of pyridine, complex **3** rapidly decomposes into several products, two of which were characterized. Complex **13** (figure 3) was crystallized from the reaction mixture in 11 % yield, confirming the observations for η^6: κ^1-coordinated complexes described above. The ligand no longer coordinates via a η^6 – mode but is only bound through the amine side chain to the Ru(II) centre. The octahedral coordination geometry is completed by two axial chloride and three meridional pyridine ligands. Standard crystallographic data are compiled in table 1. The Ru-amine (Ru-N4) (2.1640(3) Å) bond is longer than the other Ru- $N_{pyridine}$ distances (2.053(3)-2.102(3) Å) (figure 3), indicating a higher Ru-N bond energy for the pyridine ligands. Correspondingly a second species could be crystallized from the reaction mixture: the octahedral complex $[(py)_4RuCl_2]$, which had been structurally characterized before.[35]

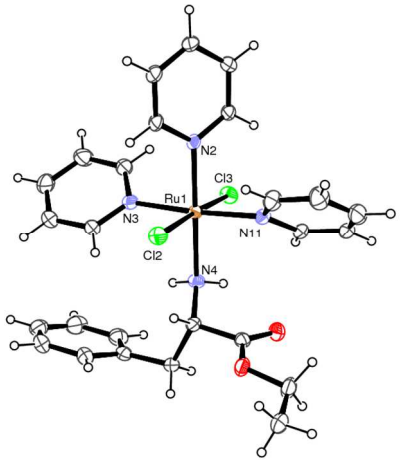


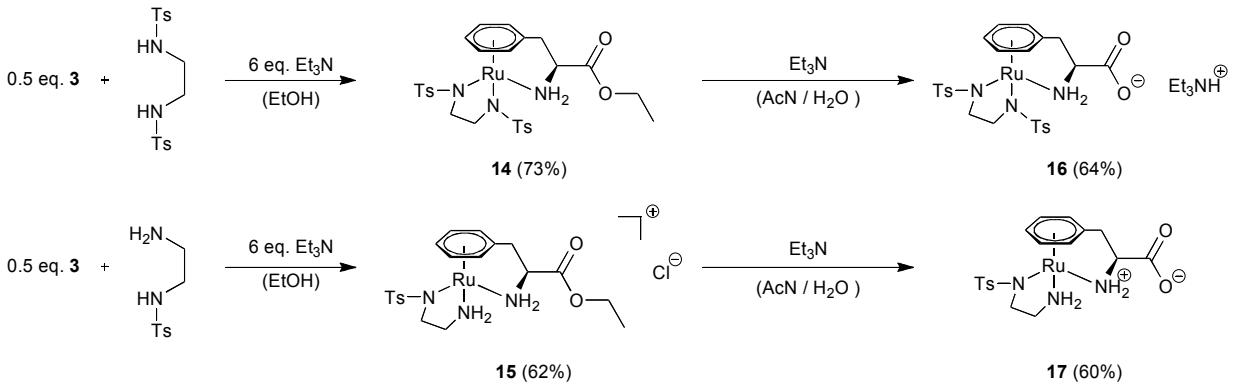
Fig. 3 ORTEP representation of complex **13** (50 % thermal ellipsoids). Selected bond lengths (Å): Ru-N1 2.102(3), Ru-N2 2.053(3), Ru-N3 2.090(3), Ru-N4 2.164(3).

Table 1 Crystallographic data for complexes **13** and **17**

	13	**17**
formula	$C_{26}H_{30}Cl_2N_4O_2Ru$	$C_{44}H_{68}N_6O_{12}Ru_2S_6$
formula wt	602.51	1267.54
cryst system	Orthorhombic	Triclinic
space group	$P2_12_12_1$	$P1$
cryst size (mm)	0.17 x 0.1 x 0.08	0.15 x 0.11 x 0.09
a (Å)	9.008(2)	10.390(1)
b (Å)	9.554(2)	12.136(1)
c (Å)	31.245(6)	12.916(1)
α (deg)	90	103.591(8)
β (deg)	90	111.663(9)
γ (deg)	90	108.650(8)
V (Å^3)	2688.9(9)	1313.9(2)
Z	4	1
D_{calc} (g cm^{-3})	1.488	1.602
no. of indep rflns	4868	8457
no. of params	318	626
R1 ($I > 2\sigma(I)$)	0.0323	0.0410
wR2 (all data)	0.0957	0.0910
goodness of fit	1.184	1.003

Diamine chelates of Ru(II) half-sandwich complexes have become particularly popular since Noyori and Ikariya described this type of complex as the prototype M/NH acid base synergy catalyst in 1995.[36] We therefore reacted the dimeric complex **3** with ethylenediamine derivatives N-*p*-tosylethylenediamine and 1,4-di-N-*p*-tosylethylenediamine, yielding chelate complexes **14** and **15** respectively (Scheme 8). Triethylamine was added to neutralize the hydrochloric acid formed. The basic conditions again lead to the coordination of the α-amino group tether. Complexes **14** and **15** possess markedly different solubility properties. Whereas complex **14** can be dissolved in dicloromethane and purified by washing with water, the monocationic[37] complex **15** is highly soluble in aqueous solution. In order to remove triethylammonium chloride from **15**, the complex was dissolved in cold dry tetrahydrofurane and the remaining salt was filtered off.

Both complexes **14** and **15** are stable towards daylight and air. When dissolved in a mixture of acetonitrile, water and triethylamine, their ethyl ester functionality can be saponified without changing the inner coordination sphere of the metal centre, leading to bright yellow complexes **16** and **17** in good yields. While complex **15** dissolves in water as well as in dichloromethane, the zwitterion **17** is insoluble in dichloromethane and only slightly soluble in water. It crystallizes readily from DMSO at room temperature. Both complexes **14** and **16** display a single set of signals in NMR spectra, as the α-CH carbon is their only chiral centre. However, for complexes **15** and **17**, which contain an unsymmetrically substituted diamine ligand, the ruthenium metal centre becomes a second stereocentre, resulting in formation of diastereomeric compounds. Hence, NMR spectra of **17** recorded in DMSO-d_6 / CD_3COOD (9 / 1) show the expected two diastereomers with R and S configuration of the Ru(II) centre. ^{13}C-NMR resonances corresponding to (R_{Ru}/$S_{α-CH}$)-α-*C*H and (S_{Ru}/$S_{α-CH}$)-α-*C*H carbons appear as 1:1:1 triplets, each separated by 0.1 ppm (10 Hz), a feature only observed for complex **17**. These triplets may result from slow



Scheme 8 Conversion of **3** with ethylenediamine ligands, yielding complexes **14** and **15**. Saponification with triethylamine leads to complexes **16** and **17**.

proton-deuterium exchange at the α-*C*H position. When recorded in DMSO-h_6 / CH_3COOH (9 / 1), only a singlet was observed for ($S_{Ru}/S_{α\text{-}CH}$)-α-*C*H and for ($R_{Ru}/S_{α\text{-}CH}$)-α-*C*H. All amine-bound hydrogen atoms show different ^{1}H-NMR shifts, which were all assigned by ^{1}H,^{1}H-COSY experiments. For complexes **14-17**, two magnetically inequivalent protons were observed that are coupling to the α-nitrogen.

For complex **15**, a ^{1}H^{15}N-HSQC NMR-spectrum could be obtained in $CDCl_3$ (Fig. 4). It confirms the data collected in ^{1}H, ^{1}H^{1}H-COSY and ^{13}C NMR spectra. ^{1}H^{15}N-HSQC NMR data show four inequivalent nitrogen atoms. Each of these nitrogen atoms is connected to two distinct proton resonances. These findings are in agreement with formation of two diastereomers. Each diastereomer is represented by two signals on the ^{15}N axis indicating two protonated nitrogen atoms per stereoisomer. The tosylated nitrogen does not give a signal which confirms its anionic / deprotonated state. Overall, NMR data confirm configurational stability of the η^6:κ^1-configuration on the NMR time scale as well as formation of (($S_{Ru}/S_{α\text{-}CH}$)- and the ($R_{Ru}/S_{α\text{-}CH}$)-diastereomers due to coordination of the α-nitrogen at the Ru centre.

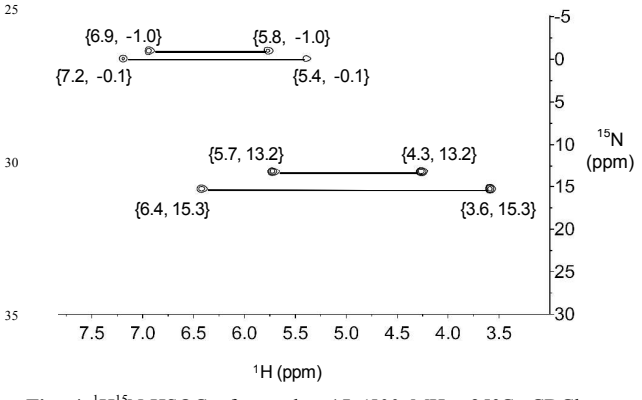


Fig. 4 ^{1}H^{15}N-HSQC of complex **15** (500 MHz, 25°C, $CDCl_3$, natural abundance).

The basic nature of the coordinated nitrogen and the different ligands and available counter ions lead to the formation of a cationic ruthenium complex in case of **15** and an anionic complex in case of **16**. In infrared spectra of complexes **14** and **15**, bands corresponding to ethyl ester functionalities can clearly be identified at 1738 and 1736 cm^{-1}, respectively. The IR spectra of complexes **16** and **17** show bands corresponding to a free carboxylate moiety at 1610 and 1619 cm^{-1} instead.

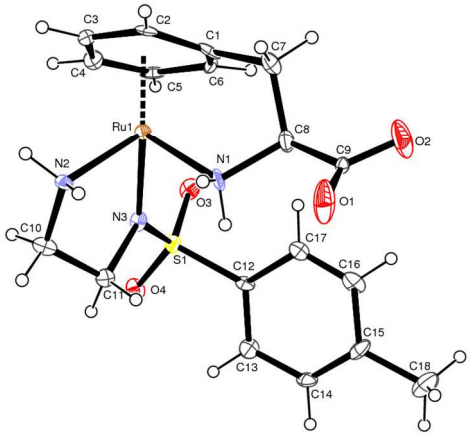


Fig. 5 ORTEP representation of complex **17** (50 % thermal ellipsoids). Selected bond lengths (Å) and angles (deg) ($R_{Ru}/S_{α\text{-}CH}$): Ru1-C1 2.094(11), Ru1-C2 2.173(10), Ru1-C3 2.175 (9), Ru1-C4 2.167(11), Ru1-C5 2.167(11), Ru1-C6 2.191(11), Ru1-N1 2.153(8), Ru1-N2 2.103(9), Ru1-N3 2.079(9), C9-O1 1.205 (12), C9-O2 1.226(13), Ru1-N1-C8 110.8(6) Ru1-N2-C10 111.3(6) ($S_{Ru}/S_{α\text{-}CH}$): Ru2-C19 2.126(12), Ru2-C20 2.151(12), Ru2-C21 2.172(11), Ru2-C22 2.240(9), Ru2-C23 2.195 (11), Ru2-C24 2.158 (11), Ru2-N4 2.148(9), Ru2-N5 2.137(8), Ru2-N6 2.130(8), C27-O5 1.325(16), C27-O6 1.211(11), Ru2-N4-C26 111.4(5) Ru2-N5-C28 111.7(6).

The molecular structure of complex **17** was confirmed by single crystal diffraction analysis (figure 5). Standard crystallographic data are compiled in table 1. The λ-(S_{Ru}, $S_{α\text{-}CH}$)- and δ-(R_{Ru}, $S_{α\text{-}CH}$) configurations of complex **17** co-crystallized from DMSO with four solvent molecules per unit cell. The crystal structure was solved in space group *P*1 with both complexes in the unit cell showing the original *S* stereochemsitry at the α-position of the phenylalanine ligand (figure 5).[38] Both the tosylated nitrogens (sum of bond angles for N3 358.6°; N6 357.3°) and the carboxylic groups (C-O bond length from 1.205(12) to 1.325(16)Å) are in the mono-anionic state. Since no other anions are present in the unit cell, both primary amine functions (N1, N2) have two N-H

bonds. The Ru-N distances of the tethers (Ru1-N1, 2.153(8); Ru2-N4 2.148(8)Å) are slightly elongated in comparison with the other Ru-N bonds. This indicates some conformational strain generated by the relatively short tether when coordinated to the metal centre. An analysis of the crystal structure reveals, that this strain induces a tilt of C1 towards the metal centre. The respective planes form an angle of 10.1(6)° (C2, C3, C4, C5 and C6 vs. C1, C2 and C6). The crystal structure further reveals some intermolecular interactions. The two diastereomeric complexes within one unit cell show a typical off-cantered parallel displaced π-stacking interaction[39] between the η^6-coordinated phenyl rings. Diastereomeric complexes of neighbouring unit cells pair in an antiparallel orientation via hydrogen bonding interaction between the two Ru-coordinated NH_2-moieties and the negatively charged carboxylate groups (see supplementary figure S2 and supplementary tables S3 - S5 for details). The observed hydrogen bonding interactions further confirm the protonation/deprotonation of the functionalities involved.

Discussion

Amino acids are attractive ligands for transition metal complexes since the combine sustainability, intrinsic chirality, low costs and a high degree of functionalization.[4] Ruthenium(II) η^6-arene half sandwich complexes have found numerous applications including artificial enzymes, reporters, and biomedical research.[12] Therefore it is important to investigate their reactivity in the presence of biogenic functional groups. Our study provides clear guidelines for the synthesis, stability and application of such complexes. Synthesis from the respective 2,5-dihydro amino acid precursors is straightforward. η^6-coordination of the metal centre to phenylglycine results in acidification and subsequent decarboxylation at the C_α, if the carboxylic moiety is not protected as an ester. For all other cases, the C_α configuration is maintained and no racemisation was detected under synthesis conditions. While it is obvious, that optimal enantioselectivities require enantiopure catalyst precursors it was shown recently, that also cytotoxicity of η^6-arene half sandwich complexes strongly depends on the chirality of the ligand.[40] Correspondingly, any synthetic strategy targeting the carboxylic moiety of a coordinated phenylglycine ligand should avoid acidic conditions.

Our data reveal surprisingly fast decomposition for several η^6-arene ruthenium(II) complexes in the presence of an excess of nucleophiles. Notably, decomposition does also proceed in the dark. The combined observations from complexes **3**, **6**, and **9** - **12** suggest that a η^6:κ^1-coordination mode of the amine tether is responsible for the observed instability. The strain resulting from coordination of the tether may induce ring slippage, which temporarily opens a coordination site. Donor coordination may lock the phenylethylamine ligand in a η^4:κ^1-coordination, which would be in agreement with the signals observed for intermediate **I** along a suggested decomposition pathway **9** → **11** → **I** → **II** (2-phenylethylamine). Here, successive DMSO coordination leads to fast decoordination of the arene. The hypothesis that ring strain (which is induced through η^6:κ^1-ligand coordination and is evident from the X-ray structure of complex **17**) induces this instability is supported by the observation that addition of nucleophiles to dimeric complex **3** results in clean formation of the respective monomeric complexes, as long as the primary ammonium group remains protonated. Under basic conditions, however, the complex decomposes rapidly. Isolation of complex **13** and $[(py)_4RuCl_2]$ from the conversion with 10 eq. of pyridine provides further insight into the decomposition pathway: the donor ligand first facilitates decoordination of the arene ligand (complex **13**). Excess of donors to formation of the terminal product $[(L)_4RuCl_2]$ (L= donor ligand, e.g. py, DMSO, …).

A marked increase in stability is observed, if the chloride anions are replaced by chelating ethylenediamine-derived ligands (complexes **14** – **16**). This stabilisation takes place despite coordination of the amine tether to the metal centre and is independent of the protonation state and charge of the diamine-ligand (mono- or di-anionic). Hence, electronic effects are not a likely cause for the stabilisation observed. We therefore assume that the increased stability is a result of steric shielding of the metal centre by the chelating ligands, which prevents donor coordination.

In summary, intramolecular coordination of a nucleophilic tether promotes decomposition of ruthenium(II) η^6-arene half sandwich complexes. Responsible are two factors: the ring strain induced and availability of additional donor ligands. Correspondingly, three elements can lead to increased stability: (i) appropriate tether length, (ii) masking of the donor (via protonation or temporary protecting groups) or (iii) steric shielding of the metal centre by chelating ligands. We therefore derive the following guidelines for applications of tethered half sandwich complexes: first, during derivatisations and bioconjugation of the tether nucleophile, excess of donors and donor solvents should be avoided, if basic conditions are required. Second, for most bioengineering and medical applications, neutral to basic conditions as well as an excess of donors ligands can not be excluded[11]. Hence tethers, which induce strain after coordination (e.g. by forming a five-membered ring) should be avoided. Alternatively, chelating ligands may be introduced to protect the metal centre. Third, for catalytic applications, the tether may provide protons (as e.g. required by the outer sphere mechanism in hydrogenations and transfer hydrogenations)[41] and induce enantioselectivity by formation of diastereomeric transition states. However, both functions require coordination of the tether to the metal centre and steric shielding would also diminish catalytic activity. A longer tether, which does not induce much strain or a tether with two metal binding donor moieties that prevent coordination of additional donors should be applied. This reasoning may explain the remarkable performance of the tethered ruthenium(II) half sandwich hydrogenation catalyst developed by Wills and others (figure 1E)[17], which combine these design elements.

Conclusion

Based on the appropriate synthetic conditions, the novel and known phenyl alanine and phenyl glycine derived η^6-arene

and tethered η^6:κ^1-arene ruthenium(II) complexes are accessible. The coordination behaviour of the flexible amine tether strongly depends on reaction conditions. Protonation leads to a decoordination of the tether, which can be reversed under basic conditions. The strain induced by the tether, which is also confirmed by the solid state structure of compound **17**, makes these complexes surprisingly unstable under basic conditions, particularly in the presence of coordinating nucleophiles. Excess of base can hence quickly lead to loss of the η^6–coordinated ligand. Reaction with ethylenediamine derivatives gave η^6:κ^1-phenylalanine ruthenium(II) complexes, which are stable under mild saponification conditions. Hence, the ester protecting group, which is required to achieve good synthetic yields, can be converted into a free carboxylate. This opens the possibility for further derivatisation of the amino acid derived η^6:κ^1-ruthenium(II) complexes. The stabilities and instabilities documented here provide as a guideline to design tethered as well as donor-functionalized complexes for future applications, e.g. as pharmaceutically, catalytically active compounds or contrast agents.

Experimental

Materials and Methods

Commercially available solvents and reagents were purified according to literature procedures. All reactions were carried out in degassed solvents under an argon atmosphere. $RuCl_3 \cdot n\ H_2O$ and triphenyl-phosphine were obtained from Sigma Aldrich and used without further purification. N-acetyl-1,4-cyclohexadiene-1-ethylamine **8**[42] was prepared similar to the route previously reported. 2,5-dihydro-L-phenylalanine **1**,[27] $[(\eta^6$-phenylglycineOEt)$RuCl_2]_2 \cdot 2$ HCl **4**,23 1,4-cyclohexadiene-1-ethylammonium chloride **7**,[33] 1,4-di-*p*-tosylethylenediamine,[43] N-*p*-tosylethylenediamine,[44] and $[(\eta^6$-$C_6H_5(CH_2)_2NH_3^+)\ RuCl_2]_2 \cdot 2$ HCl **9**[31,32] were prepared as previously reported.

Physical Measurements

Elemental analyses were obtained from the Microanalytical Laboratory of Technische Universität München. Spectroscopic data were recorded on the following instruments: IR spectra: Jasco FT/IR-460 PLUS (KBR pallets / nujol / $CHCl_3$ in KBr cell); optical rotations: Perkin-Elmer Polarimeter 341; mass spectra: Thermo Electron LCQ classic. MAS NMR spectra: Bruker Avance 300 (^{13}C NMR 75.43 MHz), T = 300 K; NMR spectra: JEOL JNM-GX 400 (^{1}H NMR 400.13 MHz, ^{13}C NMR 100.53 MHz, ^{31}P NMR 161.8 MHz), T = 300 K, or BRUKER DRX 500 (^{1}H NMR 500.13 MHz, ^{13}C NMR 125.76 MHz), T = 300 K. Signals were calibrated to the residual proton resonance and to the natural abundance ^{13}C resonance of the solvent (DMSO-d_6, δ_H = 2.50 ppm and δ_C = 39.52 ppm; $CDCl_3$, δ_H = 7.26 ppm and δ_C = 77.16 ppm). For ^{31}P spectra, H_3PO_4 was used as an external standard. Signal multiplicities are abbreviated as: s (singlet), d (doublet), t (triplet), m (multiplet), br (broad). For cases where diastereomers are formed, signal assignments for distinct spin systems are marked with a tilde (~).

Procedures

$[(\eta^6$-PheOEt)$RuCl_2]_2 \cdot 2$ HCl (3). *(R)*-2,5-dihydrophenyl-alanine **1** (1.02 g, 6.12 mmol) was stirred with 16 mL of a solution of $HCl_{conc.}$ in ethyl acetate (approx. 2M) for 1 h. To this suspension, $RuCl_3 \cdot n\ H_2O$ (400 mg, 1.53 mmol) and 60 mL of ethanol were added and the resulting mixture was heated to 80°C for 16 h. The resulting suspension was cooled to -78°C, the precipitate filtered off, washed with cold ethanol and dichloromethane (each 2 x 5 mL) and dried under reduced pressure. Pure product **3** (553 mg, 0.69 mmol, 90%) was obtained as an orange powder. – elemental analysis: calcd (%) for $C_{22}H_{32}Cl_6N_2O_4Ru_2$: C 32.9, H 4.0, N 3.5; found: C 32.9, H 4.0, N 3.4; IR (KBr): ν_{max}/cm^{-1} 1724vs (CO), 1487s, 1250s, 1073w, 856w; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 8.92 (s, 6H, NH_3^+), 6.08-5.87 (m, 10H, $C_{arene}H$), 4.39 (dd, $^3J_{H,H}$ = 6.8 Hz, $^3J_{H,H}$ = 6.8 Hz, 2H, $C_\alpha H$), 4.23-4.14 (m, 4H, CH_2CH_3), 3.05-2.90 (m, 4H, $C_\beta H_2$), 1.17 (t, $^3J_{H,H}$ = 7.0 Hz, 6H, CH_2CH_3); ^{13}C NMR (100.5 MHz, DMSO-d_6): δ (ppm) = 168.3 (*C*OO), 97.9 / 88.5 / 88.1 / 87.6 / 87.4 / 85.6 (C_{arene}), 62.1 (CH_2CH_3), 51.8 (C_αH), 33.8 ($C_\beta H_2$), 13.9 (CH_2CH_3).

$[(\eta^6$-PheOEt)$RuCl_2(PPh_3)]$ ($\mathbf{3^{PPh3}}$). To a suspension of $[(\eta^6$-PheOEt)$RuCl_2]_2 \cdot 2$ HCl **3** (39 mg, 0.05 mmol) in a solution of methanol / dichloromethane (4 mL, MeOH / DCM = 1 / 1), triphenylphosphine (31 mg, 0.12 mmol) was added and the mixture stirred at r.t. for 1.5 h, the solvent evaporated under reduced pressure. Then the residue was redissolved in dichloromethane (1.5 mL) and diethylether (9 mL) was added. The precipitate was filtered off and washed with diethylether and hexane. Pure product $\mathbf{3^{PPh3}}$ (62.8 mg, 0.09 mmol, 97%) was obtained as a red solid. – elemental analysis: calcd (%) for $C_{29}H_{31}Cl_3NO_2PRu$: C 52.5, H 4.7, N 2.1; found: C 52.3, H 4.6, N 2.1; IR (KBr): ν_{max}/cm^{-1} 1744vs (CO); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 8.77 (br s, 3 H, NH_3^+), 7.62 (m, 6 H, $C_{PPh3}H$), 7.32 (m, 9 H, $C_{PPh3}H$), 6.02 (m, 1 H, $C_{ortho}H_a$), 5.80 (m, 1 H, $C_{ortho}H_b$), 5.28 (m, 1 H, $C_{meta}H_a$), 5.18 (m, 1 H, $C_{meta}H_b$), 4.60 (m, 1 H, $C_\alpha H$), 4.46 (m, 1 H, $C_{ortho}H$), 4.10 (m, 2 H, CH_2CH_3), 3.53 (m, 1 H, $C_\beta H_a H_b$), 3.40 (m, 1 H, $C_\beta H_a H_b$), 1.03 (m, 3 H, CH_2CH_3); ^{13}C NMR (100.5 MHz, DMSO-d_6): δ (ppm) = 168.2 (*C*OO), 134.2 (d, J_{PC} = 9.2 Hz, C_{PPh3}), 133.1 (d, J_{PC} = 56.9 Hz, C_{PPh3}), 130.5 (s, C_{PPh3}), 128.3 (d, J_{PC} = 9.2 Hz, C_{PPh3}), 105.2 / 90.8 / 90.6 / 88.5 / 87.7 / 82.8 (C_{arene}), 63.1 (CH_2CH_3), 53.3 (C_αH), 33.8 ($C_\beta H_2$), 14.1 (CH_2CH_3); ^{31}P NMR (161.8 MHz, $CDCl_3$): δ (ppm) = 29.52 (s); MS (ESI): m/z (%) = 592.1 ([M-H-2Cl]$^+$) (100), 627.9 ([M-Cl]$^+$) (35).

$[(\eta^6$-benzylammonium)$RuCl_2]_2Cl_2$ (5). *(R)*-2,5-dihydro-phenylglycine **2** (1.17 g, 7.65 mmol) was added to 20 mL of a solution of $HCl_{conc.}$ in *tert*-butyl alcohol (approx. 2M). Thereafter, $RuCl_3 \cdot n\ H_2O$ (400 mg, 1.53 mmol) in 70 mL of *tert*-butyl alcohol were added and the resulting mixture heated at 80°C for 16 h. The precipitate formed was filtered off, washed with cold ethanol and dichloromethane (each 2 x 5

mL) and the residue dried under reduced pressure. Pure product **5** (320 mg, 0.51 mmol, 66%) was obtained as an ochre powder. – elemental analysis: calcd (%) for $C_{14}H_{20}Cl_6N_2Ru_2$: C 26.6, H 3.2, N 4.4; found: C 26.9, H 3.4, N 4.3; IR (KBr): ν_{max}/cm^{-1} 3052 vs, 2912 vs, 1594 s, 1489 s, 1455 m, 1384 m, 1203 w, 1111 w, 1088 w, 876 s; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 8.80 (br s, 3 H, NH_3^+), 6.23 (d, $^3J_{H,H}$ = 6.0, 2 H, C$_{ortho}H$), 6.13 (t, $^3J_{H,H}$ = 5.8, 2 H, C$_{meta}H$), 5.98 (t, $^3J_{H,H}$ = 5.6 1 H, C$_{para}H$), 3.81 (s, 2 H, CH_2); ^{13}C NMR (100.5 MHz, DMSO-d_6): δ (ppm) = 93.4 / 89.3 / 87.3 / 86.9 (C_{arene}), 40.6 (CH_2).

[(η^6:κ^1-PheOH)RuCl$_2$] (6). *(R)*-2,5-dihydrophenylalanine **1** (1.00 g, 6.25 mmol) was added to 20 mL of a solution of HCl$_{conc.}$ in *tert*-butyl alcohol (approx. 2M). Thereafter, RuCl$_3$ · n H$_2$O (342 mg, 1.25 mmol) in 100 mL of *tert*-butyl alcohol was added and the resulting mixture heated to 80°C for 16 h. The formed precipitate was filtered off, washed with 2-propanol (2 x 10 mL) and dried under reduced pressure. Pure product **6** (438 mg, 1.30 mmol, 52%) was obtained as a yellow powder. – elemental analysis: calcd (%) for $C_9H_{11}Cl_2NO_2Ru$: C 32.1, H 3.3, N 4.15, Cl 21.0; found: C 32.1, H 3.7, N 4.1, Cl 20.9; IR (KBr): ν_{max}/cm^{-1} 1747vs and 1739vs (CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.85 (t, 1 H, $^3J_{HH}$ = 5.4 Hz, C$_{meta}H_a$), 5.80 (t, 1 H, $^3J_{HH}$ = 5.6 Hz, C$_{meta}H_b$), 5.63 (d, 1 H, $^3J_{HH}$ = 5.8 Hz, C$_{ortho}H_a$), 5.52 (t, 1 H, $^3J_{HH}$ = 5.8 Hz, C$_{para}H$), 5.39 (d, 1 H, $^3J_{HH}$ = 5.8 Hz, C$_{ortho}H_b$), 4.75-4.62 (m, 2 H, C$_\alpha H$ / NH_aH$_b$), 4.06 (m, 1 H, NH$_a H_b$), 3.14 (dd, 1 H, $^2J_{HH}$ = 13.3 Hz, $^3J_{HH}$ = 6.2 Hz, C$_\beta$H$_a$H$_b$), 2.84 (dd, 1 H, $^2J_{HH}$ = 12.9 Hz, $^3J_{HH}$ = 12.0 Hz, C$_\beta$H$_a H_b$); ^{13}C NMR (12 kHz, CPMAS, HPDEC, 4mm ZrO_2 rotor): δ (ppm) = 171.4 / 168.6 (*C*O), 104.1 / 97.2 / 95.3 / 93.4 / 77.0 / 74.4 / 70.9 / 68.9 (C$_{arene}$ / C_αH), 40.2 / 39.1 ($C_\beta H_2$).

[(η^6-PheOH)RuCl$_2$(Me$_2$SO)]$_2$ (6^{DMSO}). [(η^7-PheOH)RuCl$_2$]$_2$ **6** (20 mg, 0.06 mmol) was dissolved in a solution of concentrated hydrochloric acid and deuterated dimethylsulfoxide (520 µL, HCl/DMSO-d_6 = 1/25) and stirred until the complex was completely dissolved, before product complex **6^{DMSO}** (quantiative) was analyzed in NMR. – $[\alpha]_D^{22}$ +44.0 (c = 0.58 g/ml in HCl$_{conc}$ / DMSO = 1 / 25); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 8.72 (br s, 3 H, NH_3^+), 6.05-5.96 (m, 3 H, C$_{arene}H$), 5.88 (d, 1 H, $^3J_{H,H}$ = 5.8 Hz, C$_{ortho}H$), 5.84 (t, 1 H, $^3J_{H,H}$ = 5.6 Hz, C$_{arene}H$), 4.28 (m, 1 H, CHCH$_2$), 2.95 (d, 1 H, $^3J_{H,H}$ = 6.6 Hz, CHCH_2); ^{13}C NMR (100.5 MHz, DMSO-d_6): δ (ppm) = 169.8 (*C*OO), 98.4 / 88.7 / 88.3 / 87.8 / 87.7 / 85.8 (C_{arene}), 52.1 (*C*H), 33.9 (CH*C*H$_2$).

N-acetyl-1,4-cyclohexadiene-1-ethylamine (8). 1,4-cyclohexadiene-1-ethylammonium chloride **7** (0.56 g, 3.50 mmol) was dissolved in a mixture of acetic anhydride and pyridine (4 mL, acetic anhydride / pyridine = 3 / 1) and stirred at 0°C for 2 h. Thereafter, the solvent was evaporated under reduced pressure, the residue redissolved in water (5 mL) and extracted with dichloromethane (3 x 5 mL). The organic phase was dried over $MgSO_4$ and the solvent removed under reduced pressure. Pure product **8** (0.54 g, 3.36 mmol, 96%) was obtained as a yellowish solid. Spectroscopic data are in accordance with literature.[39]

[(η^6-2'-phenylethylammonium)RuCl$_2$]$_2$Cl$_2$ (9). To a stirred solution of 1,4-cyclohexadiene-1-ethylammonium chloride **7** (1.10 g, 6.90 mmol) in a solution of HCl$_{conc}$ in ethyl acetate (20 mL, approx. 2 M), RuCl$_3$ · n H$_2$O (300 mg, 1.15 mmol) and ethanol (40 mL) were added and the resulting solution heated for 16 h at 80°C. The suspension was reduced to half the volume *in vacuo*, cooled to -10°C for 48 h, the precipitate filtered off and subsequently washed with cold pentane and ethanol (each 3 x 5 mL) and dried under reduced pressure. Pure product **9** (332 mg, 0.50 mmol, 88%) was obtained as a brown powder. – elemental analysis: calcd (%) for $C_{16}H_{24}Cl_6N_2Ru_2$: C 29.5, H 3.6, N 4.3; found: C 29.15, H 3.7, N 4.25; IR (KBr): ν_{max}/cm^{-1} 1583 s, 1485 s, 1455 vs, 1423 s, 1143 s, 1024 w, 996 w, 945 w, 854 s; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 8.15 (s, 3 H, NH_3^+), 6.02 (t, $^3J_{H,H}$ = 5.8 Hz, 2 H, C$_{meta}H$), 5.90 (d, $^3J_{H,H}$ = 5.6 Hz, 2 H, C$_{ortho}H$), 5.86 (t, $^3J_{H,H}$ = 5.6 Hz, 1 H, C$_{para}H$), 3.16 (m, 2 H, CH$_2$CH_2NH$_3^+$), 2.78 (t, $^3J_{H,H}$ = 7.6 Hz, 2 H, CH_2CH$_2$NH$_3^+$); ^{13}C NMR (100.5 MHz, DMSO-d_6): δ (ppm) = 101.1 / 87.6 / 87.2 / 84.9 (C_{arene}), 37.8 (CH$_2$*C*H$_2$NH$_3^+$), 30.4 (*C*H$_2$CH$_2$NH$_3^+$).

[(η^6-N-Acetyl-2'-phenylethylamine)RuCl$_2$]$_2$ (10). To a stirred solution of N-acetyl-1,4-cyclohexadiene-1-ethylamine **8** (1.14 g, 6.90 mmol) in ethanol (50 mL), RuCl$_3$ · n H$_2$O (300 mg, 1.15 mmol) was added and the resulting solution heated to reflux for 16 h. The suspension was reduced to half the volume *in vacuo*, cooled to -10°C for 48 h, filtered and the precipitate washed with cold pentane and ethanol (each 3 x 5 mL) and thereafter the residual solvent removed under reduced pressure. Pure product **10** (355 mg, 0.55 mmol, 92%) was obtained as an ochre powder. – elemental analysis: calcd (%) for $C_{20}H_{26}Cl_4N_2O_2Ru_2$: C 35.8, H 3.9, N 4.2; found: C 35.4, H 3.9, N 4.1; IR (KBr): ν_{max}/cm^{-1} 1643 vs (CO), 1567br, 1446s, 1376s, 1297vs, 1254w, 1194w, 1153w, 1103w; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 7.94 (m, 1 H, N*H*), 5.98 (t, $^3J_{H,H}$ = 5.6 Hz, 2 H, C$_{meta}H$), 5.76 (m, 3 H, C$_{ortho}H$, C$_{para}H$), 3.34 (m, 2 H, CH$_2$CH_2NH), 2.56 (t, $^3J_{H,H}$ = 6.8 Hz, 2 H, CH_2CH$_2$NH), 1.78 (s, 3 H, CH_3); ^{13}C NMR (100.5 MHz, DMSO-d_6): δ (ppm) = 169.4 (*C*ONH), 104.3 / 88.3 / 86.0 / 84.0 (C_{arene}), 38.0 (*C*H$_2$CH$_2$NH), 32.8 (CH$_2$*C*H$_2$NH), 22.6 (*C*H$_3$).

[(η^6:κ^1-C$_6$H$_5$(CH$_2$)$_2$NH$_2$)RuCl$_2$] (11). In a standard NMR tube, [(η^6-C$_6$H$_5$(CH$_2$)$_2$NH$_2$)RuCl$_2$] **9** (20 mg, 0.03 mmol) was dissolved in a solution of triethylamine and deuterated dimethylsulfoxide (520 µL, Et$_3$N/DMSO-d_6 = 1/25) and immediately analyzed. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 5.74 (t, 2 H, $^3J_{HH}$ = 5.4 Hz, C$_{meta}H$), 5.47 (t, 1 H, $^3J_{HH}$ = 5.4 Hz, C$_{para}H$), 5.29 (d, 2 H, $^3J_{HH}$ = 5.4 Hz, C$_{ortho}H$), 4.39 (m, 2 H, NH_2), 3.59 (t, 2 H, $^3J_{HH}$ = 5.2 Hz, CH$_2$CH_2NH$_2$), 2.67 (t, 2 H, $^3J_{HH}$ = 6.2 Hz, CH_2CH$_2$NH$_2$).

[(η^6:κ^1-PheOEt)RuCl$_2$] (12). [(η^6-PheOEt)RuCl$_2$]$_2$ · 2 HCl **3** (100 mg, 0.12 mmol) was suspended in dichloromethane (3 mL). After addition of triethylamine (174 µL, 1.24 mmol), the reaction mixture was stirred at room temperature for 2 h,

filtered, the solid washed with a small amount of cold dichloromethane and dried under reduced pressure to give a bright yellow powder **12** (30 mg, 0.08 mmol, 33%). – elemental analysis: calcd (%) for $C_{11}H_{15}Cl_2NO_2Ru$: C 36.2, H 4.1, N 3.8; found: C 35.8, H 4.1, N 3.55; IR (KBr): ν_{max}/cm^{-1} 1734vs and 1726vs (CO), 1575w, 1384w, 1288s, 1263s, 1206s; ν_{max}(nujol)/cm^{-1} 1733vs and 1725vs (CO); ν_{max}($CHCl_3$)/cm^{-1} 1741vs (CO); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 6.03 (t, 1 H, $^3J_{H,H}$ = 5.6 Hz, $C_{meta}H_a$), 5.91 (t, 1 H, $^3J_{H,H}$ = 5.4 Hz, $C_{meta}H_b$), 5.50 (t, 1 H, $^3J_{H,H}$ = 5.6 Hz, $C_{para}H$), 5.37 (d, 1 H, $^3J_{H,H}$ = 5.4 Hz, $C_{ortho}H_b$), 5.26 (d, 1 H, $^3J_{H,H}$ = 5.8 Hz, $C_{ortho}H_a$), 4.69 (m, 1 H, $C_\alpha H$), 4.57 (t, 1 H, $^3J_{HH}$ = 10.4 Hz, NH_aH_b), 4.30 (q, 2 H, $^3J_{H,H}$ = 7.1 Hz, CH_2CH_3), 3.82 (m, 1 H, NH_aH_b), 3.28 (dd, 1 H, $^2J_{H,H}$ = 14.1 Hz, $^3J_{H,H}$ = 6.2 Hz, $C_\beta H_aH_b$), 2.96 (dd, 1 H, $^2J_{H,H}$ = 14.1 Hz, $^3J_{H,H}$ = 11.2 Hz, $C_\beta H_aH_b$), 1.34 (t, 3 H, $^3J_{H,H}$ = 7.0 Hz, CH_2CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 169.9 (*C*OO), 99.9 / 93.9 / 93.4 / 78.5 / 75.8 / 72.4 (C_{arene}), 68.1 (CH_2CH_3), 63.0 (C_αH), 39.1 ($C_\beta H_2$), 14.3 (CH_2CH_3).

[(η^6:κ^1-PheOEt)Ru(enTs$_2$)] (14). Triethylamine (103 µL, 0.74 mmol) was added to a suspension of [(η^6-PheOEt)$RuCl_2$]$_2$ · 2 HCl **3** (100 mg, 0.14 mmol) and N,N'-di-*p*-tosylethylenediamine (101 mg, 0.24 mmol) in ethanol (15 mL) and refluxed for 80 min. The solvent was evaporated under reduced pressure; the crude compound was dissolved in dichloromethane (30 mL) and extracted with distillated water and brine (each 3 x 30 mL). The organic phase was dried over $MgSO_4$ and the solvent removed under reduced pressure to give the yellow product **14** (yield: 131 mg, 0.20 mmol, 73%). – elemental analysis: calcd (%) for $C_{27}H_{33}N_3O_6RuS_2$: C 49.1, H 5.0, N 6.4; found: C 49.0, H 5.0, N 5.9; IR (KBr): ν_{max}/cm^{-1} 1738vs (CO), 1261vs, 1133vs, 1091vs, 814vs, 662s; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.67 (d, 4 H, $^3J_{H,H}$ = 7.9 Hz, $C_{Ts}H$), 7.19 (m, 4 H, $C_{Ts}H$), 5.89 (t, 1 H, $^3J_{H,H}$ = 5.4 Hz, $C_{meta}H_a$), 5.67 (t, 1 H, $^3J_{H,H}$ = 5.4 Hz, $C_{meta}H_b$), 5.44 (d, 1 H, $^3J_{H,H}$ = 7.0 Hz, $C_{ortho}H_a$), 5.42 (d, 1 H, $^3J_{H,H}$ = 6.2 Hz, $C_{ortho}H_b$), 4.80 (t, 1 H, $^3J_{H,H}$ = 5.6 Hz, $C_{para}H$), 4.75 (m, 1 H, $C_\alpha H$), 4.36 (m, 1 H, $CHNH_aH_b$), 4.20 (q, 2 H, $^3J_{H,H}$ = 7.2 Hz, CH_2CH_3), 3.60 (m, 1 H, $CHNH_aH_b$), 3.26 (dd, 1 H, $^2J_{H,H}$ = 13.7 Hz, $^3J_{H,H}$ = 5.8 Hz, $C_\beta H_aH_b$), 2.70-2.34 (m, 5H, NCH_2 / $C_\beta H_aH_b$), 2.33 (s, 6 H, $C_{Ts}CH_3$), 1.27 (t, 3 H, $^3J_{H,H}$ = 6.9 Hz, CH_2CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 170.1 (*C*OO), 141.5 / 141.4 ($C_{Ts}CH_3$), 140.8 / 140.1 ($C_{Ts}SO_2$), 129.4 / 129.3 / 126.9 / 126.6 ($C_{Ts}H$), 103.4 ($C_{arene}CH_2$), 93.3 / 91.8 / 80.3 / 77.3 / 69.3 ($C_{arene}H$), 67.5 ($C_\alpha H$), 62.3 (CH_2CH_3), 53.0 / 52.2 (NCH_2), 38.4 ($C_\beta H_2$), 21.4 ($C_{Ts}CH_3$), 14.1 (CH_2CH_3); MS (ESI): m/z (%) = 662.1 ([M+H]$^+$) (100), 1322.6 ([2M+H]$^+$) (45).

[(η^6:κ^1-PheOEt)Ru(enTs)]Cl (15). Triethylamine (103 µL, 0.74 mmol) was added to a suspension of [(η^6-PheOEt)$RuCl_2$]$_2$ · 2 HCl **3** (100 mg, 0.14 mmol) and N-*p*-tosylethylenediamine (59 mg, 0.24 mmol) in ethanol (15 mL) and refluxed for 80 min. The solvent was evaporated under reduced pressure, the crude product suspended in sodium-dried tetrahydrofurane and left at -20°C for 16 h. Triethylammoniumchloride was filtered off and the filtrate evaporated under reduced pressure. The crude compound was dissolved in dichloromethane, precipitated by adding diethylether, washed with diethylether and hexane and dried *in vacuo* to give the yellow solid **15** (yield: 81.3 mg, 0.15 mmol, 62%) as mixture of diastereomers. – elemental analysis: calcd (%) for $C_{20}H_{28}ClN_3O_4RuS$ · H_2O requires C 42.8, H 5.4, N 7.5, Cl 6.3; found: C 42.3, H 5.4, N 7.3, Cl 6.1; IR (KBr): ν_{max}/cm^{-1} 1736vs (CO), 1263vs, 1133vs, 1079vs, 832s, 662s; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.74 (d, 4 H, $^3J_{H,H}$ = 7.9 Hz, $C_{Ts}H$ / $\tilde{C}_{Ts}\tilde{H}$), 7.28 (d, 2 H, $^3J_{H,H}$ = 7.8 Hz $C_{Ts}H$ / $\tilde{C}_{Ts}\tilde{H}$), 7.21 (m, 1 H, $CH_2NH_aH_b$), 6.77 (m, 1 H, $\tilde{C}\tilde{H}_2$-$\tilde{N}\tilde{H}_a\tilde{H}_b$), 6.66 (m, 1 H, $C_{meta}H_a$), 6.56 (m, 1 H, $\tilde{C}_{meta}\tilde{H}_a$), 6.44 (m, 1 H, $C_\alpha HNH_aH_b$), 6.03 (t, 1 H, $^3J_{H,H}$ = 5.5 Hz, $C_{meta}H_b$), 5.88 (t, 1 H, $^3J_{H,H}$ = 5.4 Hz, $\tilde{C}_{meta}\tilde{H}_b$), 5.77 (m, 1 H, $\tilde{C}\tilde{H}_2$-$\tilde{N}\tilde{H}_a\tilde{H}_b$), 5.73 (m, 1 H, $\tilde{C}_\alpha\tilde{H}\tilde{N}\tilde{H}_a\tilde{H}_b$), 5.60 (d, 1 H, $^3J_{H,H}$ = 5.4 Hz, $\tilde{C}_{ortho}\tilde{H}_b$), 5.58 (m, 1 H, $C_{ortho}H_a$), 5.54 (d, 1 H, $^3J_{H,H}$ = 5.7 Hz, $\tilde{C}_{ortho}\tilde{H}_a$), 5.48 (d, 1 H, $^3J_{H,H}$ = 5.7 Hz, $C_{ortho}H_b$), 5.41 (m, 1 H, $CH_2NH_aH_b$), 5.20 (dd, 1 H, $^3J_{H,H}$ = 4.4 Hz, $^3J_{H,H}$ = 4.4 Hz, $\tilde{C}_{para}\tilde{H}$), 5.11 (dd, 1 H, $^3J_{H,H}$ = 4.5 Hz, $^3J_{H,H}$ = 4.5 Hz, $C_{para}H$), 4.84 (m, 2 H, $C_\alpha H$ / $\tilde{C}_\alpha\tilde{H}$), 4.25 (m, 5 H, CH_2CH_3 / $\tilde{C}\tilde{H}_2\tilde{C}\tilde{H}_3$ / $\tilde{C}_\alpha\tilde{H}\tilde{N}\tilde{H}_a\tilde{H}_b$), 3.61 (m, 1 H, $C_\alpha HNH_aH_b$), 3.28 (dd, 1 H, $^3J_{H,H}$ = 5.5 Hz, $^2J_{H,H}$ = 14.5 Hz, $C_\beta H_aH_b$), 3.25 (dd, 1 H, $^3J_{H,H}$ = 5.6 Hz, $^2J_{H,H}$ = 14.2 Hz, $\tilde{C}_\beta\tilde{H}_a\tilde{H}_b$), 2.93 (dd, 1 H, $^3J_{H,H}$ = 13.1 Hz, $^2J_{H,H}$ = 13.1 Hz, $\tilde{C}_\beta\tilde{H}_a\tilde{H}_b$), 2.74-2.53 (m, 8 H, CH_2CH_2 / $\tilde{C}\tilde{H}_2\tilde{C}\tilde{H}_2$), 2.67 (m, 1 H, $C_\beta H_aH_b$), 2.43 (s, 6 H, $C_{Ts}CH_3$), 1.34 (t, 3 H, $^3J_{H,H}$ = 7.0 Hz, CH_2CH_3), 1.33 (t, 3 H, $^3J_{H,H}$ = 6.9 Hz, $\tilde{C}\tilde{H}_2\tilde{C}\tilde{H}_3$); ^{13}C NMR (100.5 MHz, DMSO-d_6): δ (ppm) = 170.5 / 170.4 (*C*OO / $\tilde{C}\tilde{O}\tilde{O}$), 141.3 / 141.1 / 140.9 / 140.7 ($C_{Ts}SO_2$ / $\tilde{C}_{Ts}\tilde{S}\tilde{O}_2$), 129.5 / 129.3 ($C_{Ts}H$ / $\tilde{C}_{Ts}\tilde{H}$), 126.3 / 126.0 ($C_{Ts}H$ / $\tilde{C}_{Ts}\tilde{H}$), 105.1 / 104.5 ($C_{arene}CH_2$ / $\tilde{C}_{arene}\tilde{C}\tilde{H}_2$), 94.7 / 93.0 / 90.8 / 90.2 / 80.0 / 77.7 / 77.3 / 74.5 / 70.2 / 69.5 / 68.1 / 67.1 ($C_{arene}H$ / $\tilde{C}_{arene}\tilde{H}$ / $C_\alpha H$ / $\tilde{C}_\alpha\tilde{H}$), 61.4 ($CH_2CH_3$ / $\tilde{C}\tilde{H}_2\tilde{C}\tilde{H}_3$), 50.2 / 46.2 / 46.1 ($NCH_2$ / $\tilde{N}\tilde{C}\tilde{H}_2$), 36.9 / 36.8 ($C_\beta H_2$ / $\tilde{C}_\beta\tilde{H}_2$), 20.9 / 20.8 ($C_{Ts}CH_3$ / $\tilde{C}_{Ts}\tilde{C}\tilde{H}_3$), 14.0 ($CH_2CH_3$ / $\tilde{C}\tilde{H}_2\tilde{C}\tilde{H}_3$); ^{1}H,^{15}N-HSQC (500 MHz, $CDCl_3$): {6.9, -1.0} / {5.8, -1.0} / {7.2, -0.1} / {5.4, -0.1} ($CH_2NH_aH_b$ / $CH_2NH_aH_b$ / $\tilde{C}\tilde{H}_2\tilde{N}\tilde{H}_a\tilde{H}_b$ / $\tilde{C}\tilde{H}_2\tilde{N}\tilde{H}_a\tilde{H}_b$), {5.7, 13.2} / {4.3, 13.2} / {6.4, 15.3} / {3.6, 15.3} ($CHNH_aH_b$ / $CHNH_aH_b$ / $\tilde{C}\tilde{H}\tilde{N}\tilde{H}_a\tilde{H}_b$ / $\tilde{C}\tilde{H}\tilde{N}\tilde{H}_a\tilde{H}_b$); MS (ESI): m/z (%) = 508.1 ([M+H]$^+$) (80), 1050.9 ([2M+HCl+H]$^+$) (100).

[(η^6:κ^1-PheO$^-$)Ru(enTs$_2$)] $HNEt_3^+$ · 2 H_2O (16). [(η^6:κ^1-PheOEt) Ru(enTs$_2$)] **14** (72 mg, 0.11 mmol) was dissolved in a mixture of triethylamine, water and acetonitrile (10 mL, Et_3N:H_2O:AcN = 1:1:4.5) and stirred at room temperature for 16 h before removing volatiles under reduced pressure. The crude product was dissolved in dichloromethane (20 mL) and extracted with distilled water (3 x 10 mL). The aqueous phase was lyophilized, giving the bright yellow solid **16** (yield: 39.8 mg, 0.07 mmol, 64%). – elemental analysis: calcd (%) for $C_{31}H_{44}N_4O_6RuS_2$ · 2 H_2O: C 48.4, H 6.3, N 7.0; found: C 47.9, H 5.9, N, 7.0; IR (KBr): ν_{max}/cm^{-1} 1610s (CO), 1259s, 1131vs, 1091vs, 815s, 661s; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.69 (m, 4 H, $C_{Ts}H$), 7.19 (d, 4 H, $^3J_{H,H}$ = 7.5 Hz, CTs*H*), 5.89 (t, 1 H, $^3J_{H,H}$ = 5.4 Hz, $C_{meta}H_a$), 5.72 (t, 1 H, $^3J_{H,H}$ = 5.2 Hz, $C_{meta}H_b$), 5.43 (d, 1 H, $^3J_{H,H}$ = 5.4 Hz, $C_{ortho}H_a$), 5.39 (d, 1 H, $^3J_{H,H}$ = 5.4 Hz, $C_{ortho}H_b$), 4.80 (t, 1 H, $^3J_{H,H}$ = 5.4 Hz, $C_{para}H$), 4.61 (m, 1 H, $C_\alpha H$), 4.33 (t, 1 H, $^3J_{H,H}$ = 10.4 Hz, $C_\alpha HNH_aH_b$),

3.31 (m, 1 H, $C_\alpha HNH_aH_b$), 3.27 (m, 1 H, $C_\beta H_aH_b$), 3.04 (q, 6 H, $^3J_{H,H}$ = 6.1 Hz, N-CH_2CH_3), 2.75 (dd, 1H, $^2J_{H,H}$ = 12.4 Hz, $^3J_{H,H}$ = 12.8 Hz, $C_\beta H_aH_b$), 2.58 (m, 2 H, $NCH_2CH'_2N'$), 2.50 (m, 2 H, $NCH_2CH'_2N'$), 2.35 (s, 6 H, $C_{Ts}CH_3$), 1.27 (t, 9 H, $^3J_{H,H}$ = 7.0 Hz, NCH_2CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 175.3 (*C*OO), 141.2 / 141.1 / 141.0 ($C_{Ts}CH_3$ / $C_{Ts}SO_2$), 129.3 / 127.0 / 126.9 ($C_{Ts}H$), 106.2 ($C_{arene}CH_2$), 92.8 / 91.6 / 79.4 / 77.0 / 71.6 (C_{arene}), 69.7 ($C_\alpha H$), 52.8 / 52.2 ($NCH_2CH'_2N'$), 45.4 ($N(CH_2CH_3)_3$), 39.7 ($C_\beta H_2$), 21.5 ($C_{tosyl}CH_3$), 9.0 ($N(CH_2CH_3)_3$); MS (ESI): m/z (%) = 634.1 ($[M+H]^+$) (100).

[(η^6:κ^1-Phe)Ru(enTs)] (17). [(η^6:κ^1-PheOEt)Ru(enTs)]Cl **15** (44 mg, 0.08 mmol) was dissolved in a mixture of triethylamine, water and acetonitrile (7 mL, Et_3N:H_2O:AcN = 1:1:4.5) and stirred at room temperature for 16 h before removing volatiles under reduced pressure. The residue was washed with diethylether, dichloromethane and methanol, giving the citric powder **17** (yield: 22.8 mg, 39.8 mg, 0.05 mmol, 60%). – elemental analysis: calcd (%) for $C_{18}H_{23}N_3O_4RuS \cdot 4\ H_2O$: C 39.3, H 5.7, N 7.6; found: C 39.3, H 5.0, N 7.2; IR (KBr): ν_{max}/cm^{-1} 1619s and 1597s (CO), 1399s, 1385s, 1247s, 1126s, 1092vs, 834vs, 593s; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.66 / 7.64 (d, 2 H, $^3J_{H,H}$ = 7.5 Hz, d, 2 H, $^3J_{H,H}$ = 7.0 Hz, $C_{Ts}H$ / $C_{Ts}\tilde{H}$), 7.30 / 7.28, (d, 2 H, $^3J_{H,H}$ = 6.2 Hz, d, 2 H, $^3J_{H,H}$ = 7.1 Hz, $C_{Ts}H$ / $C_{Ts}\tilde{H}$), 6.49 (m, 2 H, $CH_2NH_aH_b$ / $C\tilde{H}_2N\tilde{H}_a\tilde{H}_b$), 5.97 (t, 1 H, $^3J_{H,H}$ = 5.4 Hz, $C_{meta}H_a$), 5.94 (t, 1 H, $^3J_{H,H}$ = 5.0 Hz, $\tilde{C}_{meta}\tilde{H}_a$), 5.87 (t, 1 H, $^3J_{H,H}$ = 5.0 Hz, $C_{meta}H_b$), 5.72 (t, 1 H, $^3J_{H,H}$ = 4.1 Hz, $\tilde{C}_{meta}\tilde{H}_b$), 5.53 (d, 1 H, $^3J_{H,H}$ = 6.2 Hz, $\tilde{C}_{ortho}\tilde{H}_a$), 5.51 (d, 1 H, $^3J_{H,H}$ = 5.8 Hz, $\tilde{C}_{ortho}\tilde{H}_b$), 5.45 (d, 1 H, $^3J_{H,H}$ = 5.8 Hz, $C_{ortho}H_a$), 5.26 (d, 1 H, $^3J_{H,H}$ = 5.4 Hz, $C_{ortho}H_b$), 5.10 (t, 1 H, $^3J_{H,H}$ = 5.2 Hz, $\tilde{C}_{para}\tilde{H}$), 5.04 (t, 1 H, $^3J_{H,H}$ = 5.4 Hz, $C_{para}H$), 4.79 (m, 2 H, $C_\alpha HNH_aH_b$), 4.71 (m, 2 H, $\tilde{C}_\alpha\tilde{H}$-$\tilde{N}\tilde{H}_a\tilde{H}_b$), 4.61 / 4.26 (m, 2 H, $CH_2NH_aH_b$ / $C\tilde{H}_2\tilde{N}\tilde{H}_a\tilde{H}_b$), 4.26 (m, 2 H, $C_\alpha H$ / $\tilde{C}_\alpha\tilde{H}$), 3.61 (m, 2 H, $\tilde{C}H\tilde{N}\tilde{H}_a\tilde{H}_b$), 3.52 (m, 2 H, $C_\alpha HNH_aH_b$), 3.13 (dd, 1 H, $^2J_{H,H}$ = 13.7 Hz, $^3J_{H,H}$ = 5.8 Hz, $C_\beta H_aH_b$), 3.05 (dd, 1 H, $^2J_{H,H}$ = 13.7 Hz, $^3J_{H,H}$ = 6.2 Hz, $\tilde{C}_\beta\tilde{H}_a\tilde{H}_b$), 2.68 (m, 1 H, $\tilde{C}_\beta\tilde{H}_a\tilde{H}_b$), 2.50 (m, 1 H, $C_\beta H_aH_b$), 2.60 (m, 2 H, $CH_2CH_2NH_aH_b$ / $\tilde{C}\tilde{H}_2\tilde{C}\tilde{H}_2\tilde{N}\tilde{H}_a\tilde{H}_b$), 2.20 (m, 2 H, $CH_2CH_2NH_aH_b$ / $\tilde{C}\tilde{H}_2\tilde{C}\tilde{H}_2\tilde{N}\tilde{H}_a\tilde{H}_b$); ^{13}C NMR (100.5 MHz, 90 % DMSO-d_6, 10 % CD_3COOD): δ (ppm) = 173.1 / 173.0 (*C*OO / $\tilde{C}\tilde{O}\tilde{O}$), 141.3 / 141.1 / 141.0 ($C_{Ts}CH_3$ / $\tilde{C}_{Ts}\tilde{C}\tilde{H}_3$), 129.7 / 129.4 ($C_{Ts}SO_2$ / $\tilde{C}_{Ts}\tilde{S}\tilde{O}_2$), 126.5 / 126.2 ($C_{Ts}H$ / $\tilde{C}_{Ts}\tilde{H}$), 108.1 / 106.9 ($C_{arene}CH_2$ / $\tilde{C}_{arene}\tilde{C}\tilde{H}_2$), 94.7 / 93.3 / 90.8 / 90.2 / 79.8 / 77.7 / 76.2 / 74.5 ($C_{arene}H$ / $\tilde{C}_{arene}\tilde{H}$), 71.9 / 71.8 / 71.7 / 71.5 / 71.4 / 71.3 ($C_\alpha H$ / $\tilde{C}_\alpha\tilde{H}$), 70.6 / 70.0 ($C_{arene}H$ / $\tilde{C}_{arene}\tilde{H}$), 50.3 / 46.7 / 46.5 ($NCH_2$ / $\tilde{N}C\tilde{H}_2$), 38.2 / 38.0 ($C_\beta H_2$ / $\tilde{C}_\beta\tilde{H}_2$), 21.0 ($C_{Ts}CH_3$ / $\tilde{C}_{Ts}\tilde{C}\tilde{H}_3$); MS (ESI): m/z (%) = 480.2 ($[M+H]^+$) (100).

Crystal structure determinations†

Crystals suitable for single-crystal X-ray analysis of complex **13** were grown from the reaction solution at room temperature within several days. Complex **17** was crystallized in a solution of DMSO-d_6 (approx 40 mg/mL) at room temperature within several days. Diffraction data were collected on an Oxford Xcalibur3 and Nonius Kappa CCD diffractometer using MoK_α radiation (λ = 0.71073 Å, graphite monochromator). A Cryojet Controller from Oxford Diffractions allowed measurements at 150 K. The absorption correction (empirical) of the Oxford Xcalibur3 data set was carried out using the program CrysAlis RED (Oxford Diffraction Ltd). The structures were solved by Direct Methods and refined by least-squares and difference Fourier analysis, using least-squares cycles based on F^2 with the SHELXTL software package.[45] All the hydrogen atoms were geometrically fixed and refined using a riding model. CCDC-721713 (for **13**) and CCDC-721712 (for **17**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB21EZ, UK; Fax: +44-1223-336033; E-mail: deposit@ccdc.cam.ac.uk).

Acknowledgedemts

The authors thank Dr. Andreas O. Frank for help with NMR spectra and both Prof. Dr. Horst Kessler and Prof. Dr. Thomas F. Fässler for helpful discussions. This work was supported by KAUST-GCR (FIC/2010/07) and the KAUST baseline fund (J.E.). We thank the Elitenetzwerk Bayern (graduate fellowship for T.R. and A.N.M.) and the IDK NanoCat for funding.

References

1 (*a*) G. Winkhaus, H. Singer, *J. Organomet. Chem.* **1967**, *7*, 487-491; (*b*) G. Winkhaus, H. Singer, M. Kricke, *Z. Naturforsch.* **1966**, *21b*, 1109-1110; (*c*) R. Zelonka, M.C. Baird, *J. Organomet. Chem.* **1972**, *44*, 383-389; (*d*) R.A. Zelonka, M.C. Baird, *Can. J. Chem.* **1972**, *50*, 3063-3072; (*e*) M.A. Bennett, G.B. Robertson, A.K. Smith, *J. Organomet. Chem.* **1972**, *43*, C41-C43; (*f*) M.A. Bennett, A.K. Smith, *J. Chem. Soc. Dalton Trans.* **1974**, 233-241; (*g*) A.N. Nesmeyanov, A.Z. Rubezhov, *J. Organomet. Chem.* **1979**, *164*, 259-275; (*h*) T. Arthur, T.A. Stephenson, *J. Organomet. Chem.* **1981**, *208*, 369-387; (*i*) E. L. Muetterties, J. R. Bleeke, E. J. Wucherer, *Chem. Rev.* **1982**, *82*, 499-525; (*j*) R. M. Moriarty, U. S. Gill, Y. Y. Ku, *J. Organomet.. Chem.* **1988**, *350*, 157-190; (*k*) M.A. Bennett, *Coord. Chem. Rev.* **1997**, *166*, 225-254.

2 D. B. Grotjahn, *Coord. Chem. Rev.* **1999**, *190-192*, 1125-1141.

3 R. Krämer, *Angew. Chem. Int. Ed.* **1996**, *35*, 1197-1199.

4 (*a*) K. Severin, R. Bergs, W. Beck, *Angew. Chem. Int. Ed.* **1998**, *37*, 1634-1654; (*b*) G. Jaouen, A. Vessières, *Acc. Chem. Res.* **1993**, *26*, 361-369; (*c*) P. Köpf-Maier, H. Köpf, *Chem. Rev.* **1987**, *87*, 1137-1152; (*d*) R. Alberto, *J. Organomet. Chem.* **2007**, *692*, 1179-1186; (*e*) D. S. Williams, G. E. Atilla, H. Bregman, A. Arzoumanian, P. S. Klein, E. Meggers, *Angew. Chem. Int. Ed.* **2005**, *44*, 1984-1987; (*f*) H. Bregman, P.J. Carroll, E. Meggers, *J. Am. Chem. Soc.* **2006**, *128*, 877-884; (*g*) J. É. Debreczeni, A. N. Bullock, G. E. Atilla, D. S. Williams, H. Bergman, S. Knapp, E. Meggers, *Angew. Chem. Int. Ed.* **2006**, *45*, 1580-1585; (*h*) C. Streu, E. Meggers, *Angew. Chem. Int. Ed.* **2006**, *45*, 5645-5648; (i) A. L. Noffke, A. Habtemariam, A. M. Pizarro, P. J. Sadler, *Chem. Commun.* **2012**, *48*, 5219-5346.

5 P. Haquette, B. Talbi, S. Canaguier, S. Dagorne, C. Fosse, A. Martel, G. Jaouen, M. Salmain, *Tetrahedron Lett.* **2008**, *49*, 4670-4673.

6 W. H. Ang, E. Daldini, L. Juillerat-Jeanneret, P. J. Dyson, *Inorg. Chem.* **2007**, *46*, 9048-9050.

7 R. M. Moriarty, Y.-Y. Ku, U. S. Gill, *Chem. Commun.* **1987**, 1837-1838.

8 A. J. Pearson, K. Lee, *J. Org. Chem.* **1994**, *59*, 2304-2313.

9 (*a*) W. S. Sheldrick, A. Gleichmann, *J. Organomet. Chem.* **1994**, *470*, 183-187; (*b*) A. J. Gleichmann, J. M. Wolff, W. S. Sheldrick, *J.*

Chem. Soc., Dalton Trans. **1995**, 1549-1554; (*c*) J. M. Wolff, A. J. Gleichmann, C. Schmidt, W. S. Sheldrick, *J. Inorg. Biochem.* **1995,** *59*, 219; (*d*) J. M. Wolff, W. S. Sheldrick, *J. Organomet. Chem.* **1997**, *531*, 141-149; (*e*) J. M. Wolff, W. S. Sheldrick, *Chem. Ber. Recueil* **1997**, *130*, 981-988; (*f*) D. A. Herebian, C. S. Schmidt, W. S. Sheldrick, C. van Wüllen, *Eur. J. Inorg. Chem.* **1998**, 1991-1998. (*g*) R. Stodt, S. Gencaslan, A. Frodl, C. Schmidt, W. S. Sheldrick, *Inorg. Chim. Acta* **2003**, *355*, 242-253; (*h*) R. Stodt, S. Gencaslan, I. M. Müller, W. S. Sheldrick, *Eur. J. Inorg. Chem.* **2003**, 1873-1882.

10 (*a*) R. S. Koefod, K. R. Mann, *J. Am. Chem. Soc.* **1990**, *112*, 7287–7293; (*b*) J. W. Janetka, D. H. Rich, *J. Am. Chem. Soc.* **1995**, *117*, 10585–10586; (*c*) R. M. Fairchild, K. T. Holman, *Organometallics* **2007**, *26*, 3049-3053.

11 (*a*) T. K. Hyster, L. Knörr, T. R. Ward, T. Rovis, *Science* **2012**, *338*, 500-503; (*b*) D. Häusinger, F. Hollmann, N. J. Turner, T. R. Ward, *Nature Chem.* **2013**, *5*, 93-99.

12 B. Therrien, *Coord. Chem. Rev.* **2009**, *253*, 493-519.

13 (*a*) R.H. Fish, G. Jaouen, *Organometallics* **2003**, *22*, 2166-2177; (*b*) R.E. Morris, R.E. Aird, P. del S. Murdoch, H. Chen, J. Cummings, N.D. Hughes, S. Parsons, A. Parkin, G. Boyd, D.I. Jodrell, P.J. Sadler, *J. Med. Chem.* **2001**, *44*, 3616-3621; (*c*) R.E. Aird, J. Cummings, A.A. Ritchie, M. Muir, R.E. Morris, H. Chen, P.J. Sadler, D.I. Jodrell, *Br. J. Cancer* **2002**, *86*, 1652-1657. (*d*) S.J. Dougan, P. J. Sadler, *Chimia* **2007**, *61*, 704-715; (*e*) R. Schuecker, R.O. John, M.A. Jakupec, V.B. Arion, B.K. Keppler, *Organometallics* **2008**, *27*, 6587-6595; (*f*) W.F. Schmid, R.O. John, V.B. Arion, M.A. Jakupec, B.K. Keppler, *Organometallics* **2007**, *26*, 6643-6652.

14 (*a*) A. F. A. Peacock, A. Habtemariam, R. Fernandez, V. Walland, F. P. A. Fabbiani, S. Parsons, R. E. Aird, D. I. Jodrell, P. J. Sadler, *J. Am. Chem. Soc.* **2006**, *128*, 1739-1748; (*b*) A. F. A. Peacock, S. Parsons, P. J. Sadler, *J. Am. Chem. Soc.* **2007**, *129*, 3348-3357; (*c*) H. Kostrhunova, J. Florian, O. Novakova, A. F. A. Peacock, P. J. Sadler, V. Brabec, *J. Med. Chem.* **2008**, *51*, 3635-3643; (*d*) J. C. Gray, A. Habtemariam, M. Winnig, W. Meyerhof, P. J. Sadler, *J. Biol. Inorg. Chem.* **2008**, *13*, 1111-1120.

15 K. Severin, *Chem. Commun.* **2006**, 3859-3867.

16 K.-J. Haack, S. Hashiguchi, A. Fujii, T. Ikariya, R. Noyori, *Angew. Chem. Int. Ed.* **1997**, *36*, 285-288.

17 (*a*) J. Hannedouche, G. J. Clarkson, M. Wills, *J. Am. Chem. Soc.* **2004**, *126*, 986-987; (*b*) A. M. Hayes, D. J. Morris, G. J. Clarkson, M. Wills, *J. Am. Chem. Soc.* **2005**, *127*, 7318-7319; (*c*) D. J. Morris, A. M. Hayes, M. Wills, *J. Org. Chem.* **2006**, *71*, 7035-7044; (*d*) D. S. Matharu, G. J. Clarkson, D. J. Morris and M. Wills, *Chem. Commun.* **2006**, 3232; (*e*). 10) F. K. Cheung, M. A. Graham, F. Minissi and M. Wills, *Organometallics* **2007**, *26,* 5346-51; (*f*) M. Wills, D. S. Matharu and J. E. D. Martins, *Chemistry; An Asian Journal* **2008**, *3,* 1374-1383; (*g*) K. E. Jollis, A. Zanotti-Gerosa, F. Hancock, A. Dyke, D. M. Grainger, J. A. Medlock, H. G. Nedden, J. J. M. Le Paih, S. J. Roseblade, A. Seger, V. Sivakumar, D. J. Morris, M. Wills, *Adv. Synth. Catal.* **2012**, 2545-2555; (*h*) J. Li, Y. Tang, Q. Wang, X. Li, L. Cun, X. Zhang, J. Zhu, L. Li, J. Deng, *J. Am. Chem. Soc.* **2012**, *134*, 18522-18525; (i) K. M. Steward, M. T. Corbett, C. G. Goodman, J. S. Johnson, *J. Am. Chem. Soc.* **2012**, *134*, 20197-20206.

18 (*a*) W. Baratta, W.A. Herrmann, R.M. Kratzer, P. Rigo, *Organometallics* **2000**, *19*, 3664-3669; (*b*) W. Baratta, E. Herdtweck, W.A. Herrmann, P. Rigo, J. Schwarz, *Organometallics* **2002**, *21*, 2101-2106; (*c*) S. Gladiali, E. Alberico, *Chem. Soc. Rev.* **2006**, *35*, 226-236; (*d*) T. Reiner, F. N. Naraschewski, J. Eppinger, *Tetrahedron: Asymmetry* **2009**, *20*, 362-367.

19 C. Daguenet, R. Scopelliti, P.J. Dyson, *Organometallics* **2004**, *23*, 4849-4857.

20 (*a*) L. Ackermann, A. Althammer, R. Born, *Angew. Chem. Int. Ed.* **2006**, *45*, 2619-2622; (*b*) A. Fürstner, L. Ackermann, *Chem. Comm.* **1999**, 95-96.

21 (*a*) M. Creus, A. Pordea, T. Rossel, A. Sardo, C. Letondor, A. Ivanova, I. LeTrong, R. E. Stenkamp, T. R. Ward, *Angew. Chem. Int. Ed.* **2008**, *47*, 1400-1404; (*b*) J. Steinreiber, T. R. Ward, *Coord. Chem. Rev.* **2008**, *252*, 751-766; (c) T. Reiner, D. Jantke, A. N. Marziale, A. Raba. J. Eppinger, *ChemistryOpen*, doi: 10.1002/open.201200044.

22 R. Stodt, S. Gencaslan, I.M. Müller, W.S. Sheldrick, *Eur. J. Inorg. Chem.* **2003**, 1873-1882.

23 H. Dialer, P. Mayer, K. Polborn, W. Beck, *Eur. J. Inorg. Chem.* **2001**, 1051-1055

24 (*a*) J. Soleimannejad, A. Sisson, C. White, *Inorg. Chim. Acta* **2003**, *352*, 121-128; (*b*) G. Marconi, H. Baier, F.W. Heinemann, P. Pinto, H. Pritzkow, U. Zenneck, *Inorg. Chim. Acta* **2003**, *352*, 188-200; (*c*) J. Soleimannejad, C. White, *Organometallics* **2005**, *24*, 2538-2541.

25 T. Ohnishi, Y. Miyaki, H. Asano, H. Kurosawa, *Chem. Lett.* **1999**, *28*, 809-810.

26 (*a*) B. Çetinkaya, S. Demir, I. Özdemir, L. Toupet, D. Séméril, C. Bruneau, P.H. Dixneuf, *New J. Chem.* **2001**, *25*, 519-521; (*b*) B. Çetinkaya, S. Demir, I. Özdemir, L. Toupet, D. Séméril, C. Bruneau, P.H. Dixneuf, *Chem. Eur. J.* **2003**, *9*, 2323-2330; (*c*) I. Özdemir, S. Demir, Bekir Çetinkaya, L. Toupet, R. Castarlenas, C. Fischmeister, P.H. Dixneuf, *Eur. J. Inorg. Chem.* **2007**, 2862-2869.

27 A. Skolaut, J. Rétey, *Arch. Biochem. Biophys.* **2001**, *393*, 187-191.

28 G. Zvilichovsky, V. Gurvich, *Tetrahedron* **1995**, *51*, 5479-5490.

29 (a) T. Reiner, M. Waibel, A. N. Marziale, D. Jantke, F. J. Kiefer, T. F. Fässler, J. Eppinger, *J. Organomet. Chem.* **2010**, *695*, 2667-2672 (b) T. Reiner, D. Jantke, A. Raba, A. N. Marziale, J. Eppinger, *J. Organomet. Chem.* **2009**, *694*, 1934-1937.

30 Due to decarboxylation, the IR spectrum of **5** does not exhibit any CO bond stretching frequencies.

31 Y. Miyaki, T. Onishi, H. Kurosawa, *Inorg. Chim. Acta* **2000**, *300-302*, 369-377.

32 C. Scolaro, T. J. Geldbach, S. Rochat, A. Dorcier, C. Gossens, A. Bergamo, M. Cocchietto, I. Tavernelli, G. Sava, U. Rothilsberger, P. J. Dyson, *Organometallics*, **2006**, *25*, 756-765.

33 R. Grewe, H.-W. Otto, *Chem. Ber.* **1959**, *92*, 644-651.

34 M. Melchart, A. Habtemariam, O. Novakova, S. A. Moggach, F. P. A. Fabbiani, S. Parsons, V. Brabec, P. J. Sadler, *Inorg. Chem.* **2007**, *46*, 8950-8962.

35 (*a*) W.-T. Wong, T.-C. Lau, *Acta Cryst. Sect. C* **1994**, *C50*, 1406-1407; (*b*) M. R. J. Elsegood, D. A. Tocher, *Acta Cryst. Sect. C* **1995**, *C51*, 40-42.

36 For recent reviews see: (*a*) A. Robertson, T. Matsumoto, S. Ogo, *Dalton Trans.* **2011**, *40*, 10304-10310; (*b*) T. Ikariyy, *Top. Organomet. Chem.* **2011**, *37*, 31-35.

37 Coordination to the metal centre increases the N-H acidity enough to promote deprotonation of sulphonamides (pK_a approx. 16 for non-coordinated N-H in DMSO) under reaction conditions while primary amines remain protonated (pK_a > 40 for non-coordinated N-H in DMSO). For pK_a values of amines coordinated to late transition metals compare: A. N. Marziale, E. Herdtweck, J. Eppinger, S. Schneider, *Inorg. Chem.* **2009**, 48, 3699-3709 and references cited therein.

38 The crystal structure of compound **17** can be solved in space groups *P*1 (no inversion of chirality at the α-CH) or space group *P*-1 (partial inversion of chirality at the α-CH). Using space group *P*-1, however, leads to higher R-values and implies significant disordering. The solvent molecules cannot be refined in space group *P*-1.

39 G.B. McGaughey, M. Gagné, A. K. Rappé, *J. Biol. Chem.* **1998**, 15458-15463.

40 K. J. Kilpin, S. M. Cammack, C. M. Clavel, P. J. Dyson, *Dalton Trans.* **2013**, *42*, 2008-2014

41 S. E. Clapham, A. Hadzovic, R. H. Morris, *Coord. Chem. Rev.* **2004**, *248*, 2201-2237.

42 S. Sugasawa, R. Tachikawa, *Tetrahedron* **1958**, *4*, 205-212.

43 Y. Fukudome, H. Naito, T. Hata, H. Urabe, *J. Am. Chem. Soc.* **2008**, *130*, 1820-1821.

44 A. Dijksman, J.M. Elzinga, Y.-X. Li, I. W. C. E. Arends, R. A. Sheldon, *Tetrahedron: Asymmetry* **2002**, *13*, 879-884.

45 Bruker AXS Shelxtl, Version 6.14, **2000**.