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ARTICLE TYPE

A chelating tetrapeptide rhodium complex comprised of a histidylidene residue: biochemical tailoring of a NHC-Rh hydrosilylation catalyst †‡

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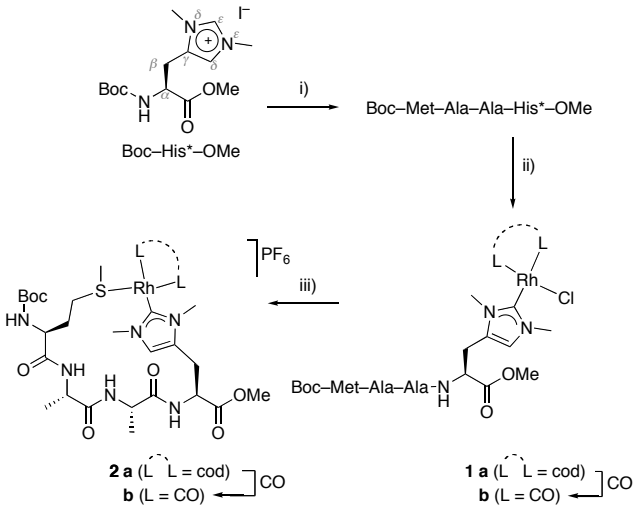
Coupling of histidinium salt with a MetAlaAla amino acid sequence followed by metallation with $[RhCl(cod)]_2$ yields a rhodium(I) NHC complex with a pending peptide residue. Methionine chelation, induced by chloride abstraction from the metal coordination sphere, affords an efficient hydrosilylation catalyst precursor comprised of a peptidic macrocyclic chelate backbone.

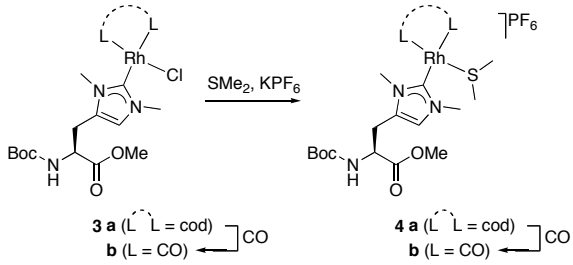
The combination of organometallic entities and peptides offers attractive opportunities in bioorganometallic chemistry.[1] Peptides provide a biocompatible scaffold, and they induce structural conformations that impact the organometallic site.[2] This approach has furnished, for example, peptide-decorated organometallic complexes[3] and enantioselective organometallic catalysts from achiral complexes deeply buried in enzymatic pockets,[4] and it spurred the development of artificial (organometallic) amino acids for de-novo peptide synthesis.[5]

Based on earlier work by Erker,[6] we have recently disclosed a route to modify histidine stereospecifically to access *C*-bound histidine metal complexes.[7] These histidylidene complexes combine the fields of N-heterocyclic carbene (NHC)[8] and peptide chemistry,[9] thus providing new opportunities for catalysis. We have become particularly interested in functionalising the amino acid moiety to tailor the catalytic activity of the histidylidene-bound metal centre. Here we have introduced methionine (Met) as potentially chelating amino acid. Chelation through *C,S*-bidentate bonding was anticipated in a *i*+3 arrangement with Met separated by two amino acids from histidylidene. Alanine (Ala) residues were selected as spacers as they promote α-helix formation,[10] thus positioning the two metal-binding amino acids on the same side of two adjacent loops.

The histidinium-containing tetrapeptide was synthesised from the corresponding *N*- and *C*-protected histidinium salt Boc-His*-OMe and the Met-Ala-Ala tripeptide (Scheme 1). Histidine methylation before coupling to the oligopeptide circumvented potential complications arising from partial methylation of the thioether in methionine. The Boc protecting group in the N_δ,N_ε-dimethylated histidinium salt Boc-His*-OMe (Scheme 1)[7b] was removed in excellent yield using a solution of HCl in 1,4-dioxane[11] followed by an ion exchange. Subsequent coupling to Boc-Met-Ala-Ala-OH was achieved by *O*-(7-Azabenzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium hexafluorophosphate (HATU) activation in THF.[12] The histidinium-containing tetrapeptide Boc-Met-Ala-Ala-His*-OMe was isolated as a highly hygroscopic solid. Successful coupling was indicated by the expected high-resolution mass for the cationic portion, and by the presence of four distinct carbonyl signals in the ^{13}C NMR spectrum for the three different amid functionalities and the terminal ester in the 171–176 ppm range. The C_ε-bound proton appeared at δ_H 8.86 ppm. Subsequent carbene formation and installation of rhodium(I) was accomplished under mild conditions using a transmetallation protocol. The use of freshly prepared Ag_2O and the addition of a source of iodide was essential for the formation of the silver carbene intermediate, which was then transmetallated with $[RhCl(cod)]_2$ to yield **1a**.‡ The NMR spectra of **1a** revealed the disappearance of the signal due to the C_ε-bound proton and a characteristic 0.1–0.15 ppm downfield shift of the methyl wingtip groups of the NHC ligand. Two sets of signals were observed, which was attributed to the formation of two rotamers (*e.g.* δ_H 4.01, 3.97, 3.96, 3.92 ppm for the NMe groups).[7b] The carbene resonance was poorly resolved and was only detectable indirectly through long-range C–H correlation spectroscopy as a broad resonance at δ_C 182 ppm (J_{CRh} not resolved), indicative for



Scheme 1 Synthesis of the rhodium tetrapeptides. *Reagents:* i) HCl, dioxane; then Boc-Met-Ala-Ala-OH, HATU, NEt*i*Pr$_2$, THF; ii) $[NEt_3Me]I$, Ag_2O, CH_2Cl_2, then $[RhCl(cod)]_2$; iii) KPF_6, CH_2Cl_2/H_2O.



Scheme 2 Synthesis of histidylidene complexes **4** as models of **2** for establishing sulfur coordination.

rhodium bonding at the C_ε position. No epimerisation at C_α was observed provided the reaction with Ag_2O was carried out at room temperature and for short time only (1 h).

Comparison of the NMR data of **1a** with those of the monopeptide histidylidene complexes **3a** and **4a** (Scheme 2) indicated no spontaneous chelation of the methionine. However, KPF_6-mediated chloride abstraction induced the formation of the macrocyclic cationic complex **2a**.‡ Sulfur coordination was most diagnostically indicated by the characteristic shift of the signals due to the cod ligand. Specifically the olefinic $C_{cod}H$ resonances moved from δ_H 4.9 and 3.3 ppm in the neutral complex **1a** to 4.7 and 4.0 ppm in **2a**. Similar behaviour was observed upon exchange of Cl^- in **3a** for a neutral SMe_2 in **4a**. The chemical shift of the S–CH_3 protons provides a further—though less diagnostic—probe for sulfur bonding, as the corresponding signal undergoes a small highfield shift from 2.09. in **1a** to 2.05 ppm in **2a**.

Further confirmation of sulfur coordination was obtained when displacing the cod ligand with CO. In both cationic thioether complexes **2b** and **4b**, the asymmetric stretch vibration appears at approximately 30 cm^{-1} higher energy than in the corresponding neutral precursors **1b** and **3b**, respectively, as expected for the transformation of a formally neutral rhodium center into a cationic residue (Fig. 1).[13] Methionine binding was also supported by NMR spectroscopy, which was facilitated by using isotopically labeled ^{13}CO for cod displacement. In the chelate **2b** ^{13}C NMR spectroscopy showed two doublets for the rhodium-bound carbonyl groups located at 188.8 and 187.5 ppm ($^1J_{RhC}$ = 84 and 79 Hz, respectively). These signals are at distinctly lower field than in the monodentate carbene tetrapeptide **1b** (δ_C 187.2 and 183.8 ppm, $^1J_{RhC}$ = 53 and 75 Hz, respectively, $^2J_{CC}$ = 5 Hz). Both the downfield shift of the resonances as well as the increased coupling constants[14] reflect the lower electron density at rhodium in the cationic complex **2b** due to bonding of a neutral methionine as opposed to the anionic chloride in **1b**.

Chelation was supported by ESI MS, which indicates a monomeric structure, and spectroscopically by the broad NMR resonances of **2a**, which were much poorer resolved compared to **1a** and which suggest conformational flexibility. Preliminary CD spectroscopy does not reveal a pronounced α-helical peptide conformation, despite the propensity of alanines to stabilise such secondary structural motifs. Molecular modeling studies (mm2 geometry optimisaton‡) also support a macrocyclic structure as depicted in Scheme 1.

The rhodium complexes **1a–4a** were evaluated as catalyst

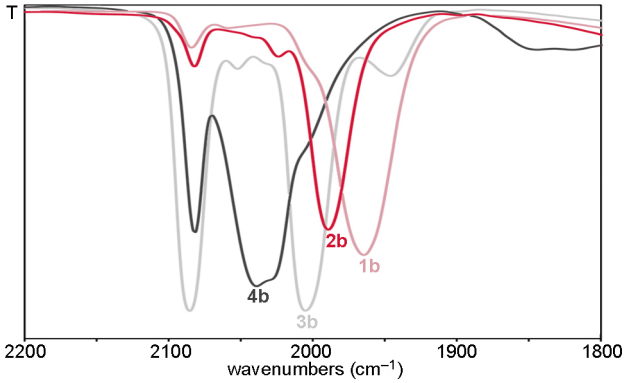
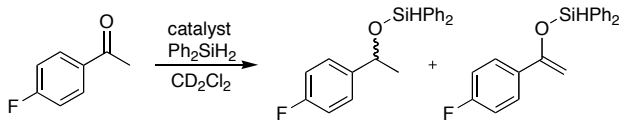


Fig. 1 Relevant section of the IR spectra of the Rh(histidylidene) dicarbonyl complexes.

precursors for the hydrosilylation of ketones.‡ Para-fluoroacetophenone was chosen as substrate since conversion is readily detectable by ^1H and ^{19}F NMR spectroscopy. Hydrosilylation with diphenylsilane in the presence of 1 mol% of rhodium tetrapeptide **1a** produced about 80% of the silylether **II** together with minor quantities of the silylenolether **III** and gaseous H_2 within 2 h (entry 1, Table 1).[15] Under the same conditions, the histidylidene rhodium complex **3a** showed substantially higher activity and selectivity (entry 3). With this precursor, the same level of conversion was achieved within 5 min with high selectivity towards **II**, even though the first coordination sphere around rhodium is identical in **1a** and **3a**. The strong influence of the peptidic backbone in **1a** supposedly originates from a limited diffusion of the oligopeptide-thethered catalyst and suggests a remote tunability of these carbene metal complexes.[7] In addition, coordination of the dangling thioether of methionine to the catalytically active species may compete in occupying one of the coordination sites available for substrate coordination after cod dissociation, thus leading to severe deactivation. A similar effect was observed when catalytic runs with **3a** were carried out in the presence of SMe_2 (1 equiv), resulting in a mere 59% conversion after 30 min. In contrast, the *C,S*-bidentate chelating tetrapeptide rhodium complex **2a** exhibits very high catalytic activity and induced full conversion within less than 10 min (entry 2). This performance corresponds to a turnover frequency at 50% conversion TOF_{50} ~ 1200 h^{-1}. The selectivity is slightly improved when compared with the neutral complexes, and it is also higher than when using the SMe_2-containing monodentate histidylidene complex **4a**, the most active complex in this series (TOF_{50} ~ 3200 h^{-1}, entry 4). The thioether group has thus an ambivalent role: it is a catalytic poison when coordinating to the neutral [RhCl(carbene] fragment as in **1a** and **3a**, yet a strong promotor when coordinating to the cationic [Rh(carbene)]+ unit (*cf.* activity of **2a** and **4a**).

Lowering the catalyst loading to 0.1 mol% decelerated the reaction significantly and allowed for a better comparison of the catalytic activity of cationic complexes **2a** and **4a**. The monopeptide complex **4a** is moderately better performing than the chelating tetrapeptidic catalyst derived from **2a**, reaching TOF_{50} values of 910 h^{-1} *vs* 610 h^{-1} under these conditions (entries 5, 6).[16] It is worth noting that a lower catalyst loading

Table 1 Hydrosilylation of 4'-fluoroacetophenone with rhodium complexes[a]



I **II** **III**

entry	complex	% conversion (selectivity)			
		5 min	10 min	30 min	2 h
1	**1a**	n.d.	n.d.	33 (71)	80 (67)
2	**2a**	56 (83)	100 (82)	100 (80)	100 (79)
3	**3a**	77 (90)	n.d.	90 (97)	100 (92)
4	**4a**	91 (75)	100 (75)	100 (71)	100 (70)
5[c]	**2a**	n.d.	n.d.	16 (68)	59 (53)
6[c]	**4a**	n.d.	n.d.	23 (69)	77 (65)

[a] General conditions: ketone (1 mmol), silane (2 mmol), catalyst precursor (1 mol%) in CD_2Cl_2 (1 mL) at rt.
[b] Conversion (selectivity towards **II** in parentheses) determined by ^1H and ^{19}F NMR spectroscopy; n.d. = not determined.
[c] 0.1 mol% catalyst precursor.

reduced the product selectivity of **2a** and afforded a 3:1 ratio of silylether and silylenolether (*cf* 9:1 ratio at 1 mol% **2a**). In contrast, the selectivity of the histidylidene complex **4a** is consistently about 70%, independent of the catalyst loading.

Despite the α-helical backbone of the catalyst precursors, no asymmetric induction was observed when analysing the hydrolysed silylether by chiral HPLC. The bidentate coordination mode apparently fails to induce stereoselective binding of prochiral substrates, even in catalytic reactions carried out at −18 °C, possibly because the chirality of the peptidic macrocycle is too remote from the active metal centre.[17] Better stereo-discrimination may become accessible through biochemical optimisation, *e.g.* by further modification of the tetrapeptide backbone particularly at the *C*-terminus.

In conclusion, we disclosed a convergent de-novo synthesis of a metalloenyzme analogue featuring a *C*-bound histidylidene amino acid and a chelating methionine residue. Chelation substantially enhanced the catalytic competence of the bound rhodium centre, affording highly active hydrosilylation catalysts. Biochemical strategies such as peptide modifications provide interesting routes to further optimise the activity of the organometallic entity, thus providing new organometallic/peptide hybrid systems with vast opportunities in catalysis and for novel active site models of metalloenzymes.

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Notes and references

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‡ Electronic Supplementary Information (ESI) available: Synthetic and catalytic procedures and model of **2b** . See DOI: 10.1039/b000000x/

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