

Peptide-tethered monodentate and chelating histidylidene metal complexes: synthesis and application in catalytic hydrosilylation†

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The N_δ/N_ϵ -dimethylated histidinium salt (His⁺) was tethered to oligopeptides and metallated to form Ir(III) and Rh(I) NHC complexes. Peptide-based histidylidene complexes containing only alanine, Ala-Ala-His⁺-[M] and Ala-Ala-Ala-His⁺-[M] were synthesised ([M] = Rh(cod)Cl, Ir(Cp⁺)Cl₂), as well as oligopeptide complexes featuring a potentially chelating methionine and tyrosine residue, Met-Ala-Ala-His⁺-Rh(cod)Cl and Tyr-Ala-Ala-His⁺-Rh(cod)Cl. Chelation of the methionine-containing histidylidene ligand was induced by halide abstraction from the rhodium centre, while tyrosine remained non-coordinating under identical conditions. High catalytic activities in hydrosilylation were achieved with all peptide-based rhodium complexes. The cationic $S_{\text{Met}}, C_{\text{His}^+}$ -bidentate peptide rhodium catalyst outperformed the monodentate neutral peptide complexes and constitutes one of the most efficient rhodium carbene catalysts for hydrosilylation, providing new opportunities for the use of peptides as *N*-heterocyclic carbene ligands in catalysis.

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Introduction

Histidine is ubiquitous in metalloenzymes because its imidazole side chain is able to coordinate to a vast array of metal centres in various oxidation states.¹ Typically, the imidazole is coordinated through one of its nitrogen atoms, either N_δ or N_ϵ . In addition, imidazole and its substituted derivatives constitute versatile precursors for the formation of *N*-heterocyclic carbenes (NHCs), a powerful class of spectator ligands for transition metal chemistry.² Hence, modification of histidine to a NHC precursor provides a straightforward approach to bio-organometallic chemistry,³ as the metal-carbene complex enables the exploitation of typical organometallic function such as catalysis, while the peptidic backbone offers opportunities for peptidic transformations and hence biochemical engineering of the hybrid. For example, specific structural conformations may be induced that affect the organometallic site. Peptide-based organometallic conjugates have been successfully employed,⁴ for example for enzyme-controlled enantioselective catalysis.⁵

While protic metal complexes of NH,NH-imidazolylienes, *i.e.* tautomers of imidazole, are known,⁶ their synthesis often

involves formation of the heterocycle within the metal coordination sphere, which precludes the use of histidine as a starting material. Alternatively, alkylation of the side-chain nitrogens of histidine constitutes a straightforward process to generate NHC derivatives that will not suffer from potential tautomerisation to the imidazole isomer.⁷ Such an approach has been used previously to prepare peptide-based imidazol-(in)ylidene⁸ and thiazolylidene⁹ metal complexes. Building on pioneering work by Erker,¹⁰ we have developed a synthetic protocol to histidylidene (*i.e.* histidine-derived NHC) complexes as catalyst precursors for transfer hydrogenation and for the catalytic hydrosilylation of ketones.¹¹ The availability of appropriate stereospecific methodologies for the preparation of mono-peptide organometallic complexes thus allows modifications of the biochemical scaffold to be targeted. Here we report the functionalisation of the histidylidene backbone with small oligopeptides using peptide coupling and the impact of these modifications on the (catalytic) activity of the metal centre.¹² This approach provides access to catalytically active NHC complexes with a peptidic environment around the metal centre as novel models of metalloenzymes.

Results and discussion

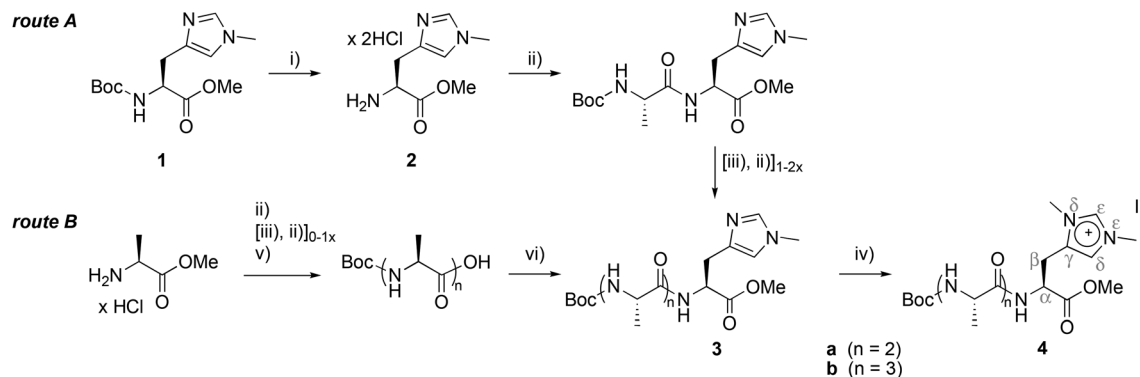
Synthesis of alanine-based histidylidene metal complexes

The synthesis of the alanine-containing histidinium ligand precursors **4a** and **4b** started from the known¹³ N_ϵ -methylated histidine Boc-His(Me)-OMe **1** (Scheme 1). Cleavage of the Boc

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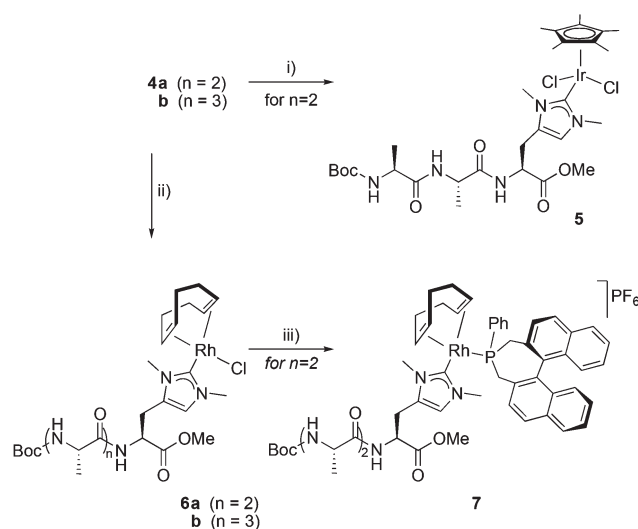
Scheme 1 Synthesis of the histidinium tripeptide **4a** and tetrapeptide **4b**. Reagents and conditions: (i) HCl/MeOH, reflux; (ii) Boc-Ala-OH, HATU, DIEA, THF, rt; (iii) HCl/1,4-dioxane, rt; (iv) MeI, MeCN, 40 °C; (v) LiOH, THF/MeOH/H₂O, rt, then HCl aq.; (vi) **2**, HATU, DIEA, THF, rt.

protecting group at the N-terminus was effected with methanolic HCl thus providing the dihydrochloride salt H-His(Me)-OMe·2HCl **2**. Deprotection with TFA was equally successful,¹⁴ however the obtained trifluoroacetate salt was significantly more hygroscopic than the chloride salt and hence less easy to handle. The C-protected methyl-histidine **2** was subsequently used for amino acid coupling reactions. These reactions were all performed using HATU as the coupling agent according to a modified literature procedure.¹⁵ Other standard and less costly agents such as DCC¹⁶ or *N*-mesyl-benzotriazole¹⁷ were also evaluated, though these methods failed to give the desired peptide bond. According to route A (Scheme 1), the free amine **2** was reacted with commercially available Boc-L-alanine to give the desired dipeptide Boc-Ala-His(Me)-OMe. The Boc protecting group was then removed using a solution of HCl in 1,4-dioxane¹⁸ and a further alanine residue was introduced to give the tripeptide Boc-Ala₂-His(Me)-OMe **3a**. The deprotection-coupling sequence was repeated to synthesise the tetrapeptide Boc-Ala₃-His(Me)-OMe **3b**. Successful coupling was indicated by high-resolution mass spectrometry and by the presence of three distinct carbonyl signals in the ¹³C{¹H}-NMR spectrum of **3a** in CDCl₃ for the two amide functionalities and one ester group in the δ_C 172–173 ppm range, and a carbamide resonance at δ_C 155 ppm. Likewise, the tetrapeptide **3b** showed three different amide and one ester carbonyl resonances in the δ_C 173–176 ppm range as well as a carbamide resonance at higher field (δ_C 158 ppm, CD₃OD solution).

Alternatively, the oligopeptide tether can be synthesised first (route B). Thus deprotection of the alanine dipeptide Boc-Ala₂-OMe or tripeptide Boc-Ala₃-OMe at the C-terminus using LiOH followed by careful neutralisation and subsequent coupling to the free amine **2** yielded the oligopeptides **3a–b**. Even though both routes gave the desired oligopeptides **3** in the same number of steps, route B presents the significant advantage to be convergent rather than a completely linear reaction sequence. The imidazole ring was then alkylated by gently heating **3** with MeI in MeCN to give the *N*_δ,*N*_ε-dimethylated histidinium oligopeptides Boc-Ala_n-His⁺-OMe **4a** (*n* = 2) and **4b** (*n* = 3). The formation of the imidazolium salts was indicated by the diagnostic downfield shift of the C₆H and

C_εH resonances in the ¹H NMR spectrum, e.g. from δ_H 6.99 to 7.39 ppm and from δ_H 7.70 to 8.85 ppm, respectively, for **4b** (in CD₃OD). Both ligand precursors **4a** and **4b** were highly hygroscopic solids and were obtained as single enantiomers as demonstrated by the presence of one set of signals in the NMR spectra. They both displayed optical activity, $[\alpha]_D^{20} = -43^\circ$ and -37° for **4a** and **4b**, respectively (*c* = 1 in MeOH).

The histidinium salts **4a–b** were successfully metallated using a standard transmetalation procedure *via* the *in situ* formation of a silver carbene intermediate. As described previously,¹¹ ambient temperature and short reaction times were crucial for the full retention of the configuration at the α -carbon of histidine. Subsequent transmetalation with [Ir(Cp*)Cl₂]₂ or [Rh(cod)Cl]₂ afforded the corresponding peptide-based histidylidene iridium(III) and rhodium(I) complexes **5a** and **6a–b**, respectively (Scheme 2). Formation of the complexes was supported by the disappearance of the signal for the C_ε-bound proton in the ¹H NMR spectra and by the downfield



Scheme 2 Synthesis of alanine-containing histidylidene iridium **5** and rhodium **6–7** complexes. Reagents and conditions: (i) Ag₂O, [Ir(Cp*)Cl₂]₂, CH₂Cl₂, rt; (ii) Ag₂O, [Rh(cod)Cl]₂, CH₂Cl₂, rt; (iii) (*S*)-Ph-binepine, KPF₆, CH₂Cl₂/H₂O, rt.

shift of the carbene signal in the ^{13}C NMR spectra to δ_{C} 156.9, 182.9 and 182.3 ppm for **5a**, **6a** and **6b**, respectively. Of note, the NMR spectra of all three complexes showed the presence of two rotamers, as expected from the slow rotation about the $\text{M}-\text{C}_{\text{carbene}}$ bond.^{11,19} The resonances attributed to C_δH and COOCH_3 are most diagnostic and appeared as two sets of signals each. For example in **6a**, two signals for C_δH were observed at δ_{H} 6.56 and 6.60 ppm (1:0.9 integral ratio) and the methylester was resolved at δ_{H} 3.67 and 3.70 ppm. The enantiopurity of the peptidic histidylidene ligand was confirmed by ^{31}P NMR spectroscopy after coordination of (*S*)-Ph-binepine²⁰ to the rhodium centre in **6a** in the presence of KPF_6 (Scheme 2). The resulting cationic phosphine complex **7** displayed two doublets in a 1:0.9 integral ratio in the $^{31}\text{P}\{^1\text{H}\}$ -NMR spectrum, corresponding to the rotamer ratio observed for **6a**. This pattern is consistent with related enantiopure histidylidene rhodium complexes.^{11b} In contrast, when the silver carbene intermediate was formed using reflux temperature and longer reaction times, the rhodium complex **6a** displayed a more complicated ^1H NMR spectrum. Four distinct signals were observed for C_δH as well as for the COOCH_3 group, which is consistent with the presence of two diastereomers (both existing as two rotamers) due to partial epimerisation at the histidylidene α -carbon.

In addition, single crystals were obtained for the tripeptide iridium complex **5**. While the organometallic residue was clearly identified, the Ala-Ala residue was significantly disordered and did not allow refinement to converge. Nonetheless, this diffraction analysis supports the formation of the organometallic entity and the presence of a $\text{Ir}-\text{C}_{\text{NHC}}$ bond.

Synthesis of histidylidene complexes containing a remote potentially coordinating amino acid residue

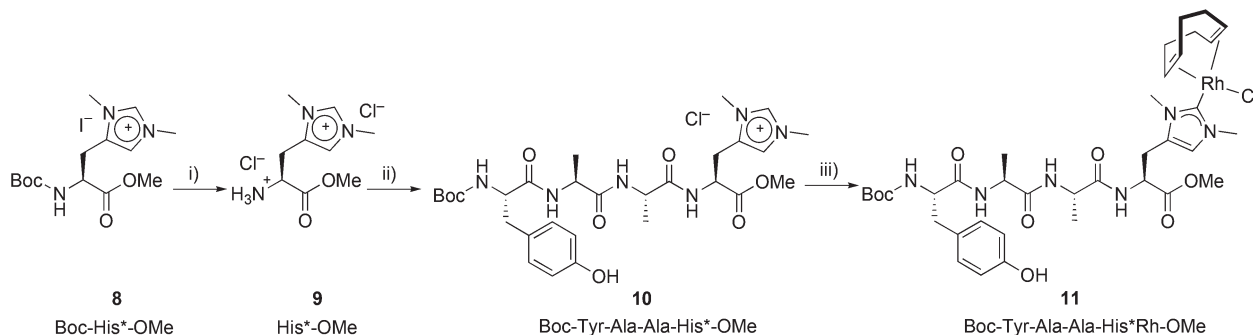
In order to promote chelation, amino acids containing a potentially coordinating functionality in the side chain were introduced on the histidylidene ligand. Methionine (Met) and tyrosine (Tyr) were chosen to induce a C,S- and a C,O-bidentate binding mode of the histidylidene oligopeptide, respectively.¹² An alanine dipeptide linker was placed between the coordination sites in order to promote the formation of an α -helix.²¹ Since a complete turn in a peptidic α -helix contains 3.6 amino

acid residues, the resulting tetrapeptides may adopt a conformation that is suitable for chelation where the side chain of the $i+3$ residue (*i.e.* Met/Tyr) is positioned almost eclipsed to the metal-bound histidylidene unit.

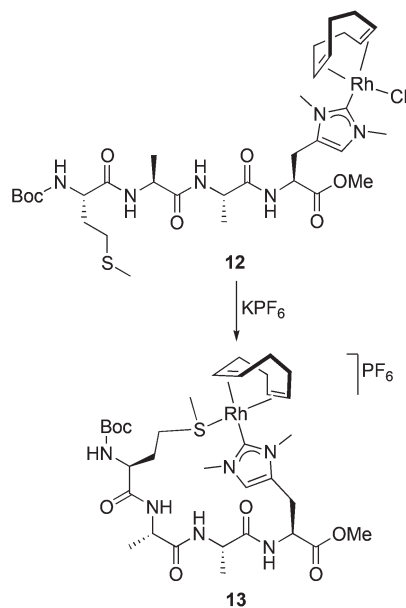
Because the side chains of tyrosine comprise a nucleophilic phenol group, the imidazole ring of histidine was alkylated prior to the coupling with the oligopeptide.¹¹ The N_δ,N_ϵ -dimethylated histidinium salt **8** was deprotected at the N-terminus using a solution of HCl in 1,4-dioxane, followed by an ion exchange to yield compound **9** in excellent yield (Scheme 3). The N-deprotected histidinium salt was subsequently coupled to the tripeptides Boc-Tyr-Ala-Ala-OH, which was synthesised in a manner similar to that described for Boc-Ala₃-OH (*cf.* Scheme 1, route B). This coupling reaction afforded the tyrosine-containing histidinium tetrapeptide **10** as a highly hygroscopic solid. The formation of the oligopeptide was confirmed by high-resolution mass spectrometry, which showed the expected signal for the cationic $[\text{M}-\text{Cl}]$ fragment at 603.3135 amu (calculated 603.3142 amu). Furthermore the presence of four low field signals for the amide carbonyl functionalities and the ester in $^{13}\text{C}\{^1\text{H}\}$ NMR spectroscopy supported successful coupling. In the ^1H NMR spectrum, the signal for the C_ϵ -bound proton appeared at δ_{H} 8.79 ppm for **10**, which is at slightly higher field than in the deprotected mono-peptide **9** (δ_{H} 9.00 ppm).

Similar to its Met homologue,¹² the histidinium tetrapeptide Boc-Tyr-Ala-Ala-His⁺-OMe was successfully rhodated under mild conditions to yield complex **11**. The use of freshly prepared Ag_2O ²² and the addition of $[\text{NEt}_3\text{Me}]\text{I}$ ²³ as a source of iodide were essential for the successful formation of the silver carbene intermediate prior to transmetallation with $[\text{Rh}(\text{cod})\text{Cl}]_2$. Analyses by NMR spectroscopy revealed the disappearance of the $\text{C}_\epsilon\text{H}$ signal in the ^1H NMR spectra and the appearance of a low field doublet in the ^{13}C NMR spectra at δ_{C} 182 ppm ($J_{\text{RhC}} = 51$ Hz). Two sets of signals were observed, which were attributed to the presence of two rotamers. No epimerisation at C_α was observed when the metallation reaction was carried out at room temperature and for a short time only (1 h).^{11b}

Comparison with model compounds by NMR spectroscopy indicated no spontaneous chelation of the tyrosine residue.



Scheme 3 Synthesis of the peptide-embedded histidylidene-rhodium complex **11** containing a tyrosine residue. *Reagents and conditions:* (i) HCl/1,4-dioxane, rt, then ion-exchange resin; (ii) Boc-Tyr-Ala-Ala-OH, HATU, DIEA, THF, rt, then ion-exchange resin; (iii) $[\text{NEt}_3\text{Me}]\text{I}$, Ag_2O , $[\text{Rh}(\text{cod})\text{Cl}]_2$, CH_2Cl_2 , rt.



Scheme 4 Methionine analogues **12** and **13** featuring a monodentate and chelating bidentate bonding mode of the histidylidene, respectively.

While with the Met homologue **12**, KPF_6 -mediated chloride abstraction induced the formation of the macrocyclic chelate complex **13** (Scheme 4), no signs of phenol binding to the rhodium centre were observed by ^1H NMR spectroscopy when subjecting **11** to analogous conditions or after addition of AgPF_6 in the presence or absence of DIEA as proton scavenger.

The effect of potentially chelating amino acid residues in $i + 3$ position was examined by CD spectroscopy in the far UV region for the rhodium tetrapeptides **6b**, **12**, and **13**. The CD spectra of all the complexes in MeCN solution display a strong negative band at 198 nm and a small positive shoulder at 220 nm (Fig. 1). This typical random coil signature indicates an unordered secondary structure for all three complexes.²⁴ In MeCN, the solvent may potentially compete with methionine

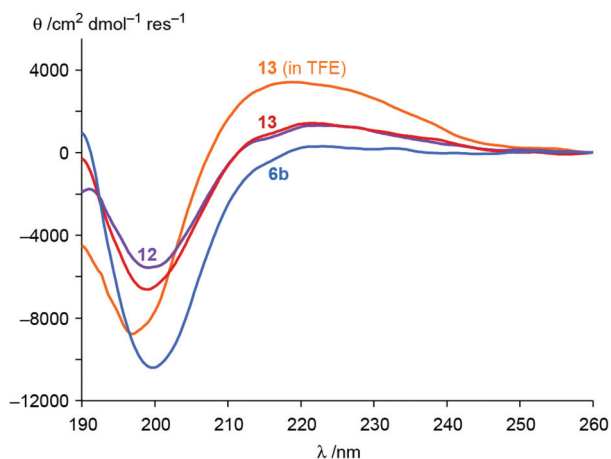


Fig. 1 CD spectra of complex **6b**, **12**, and the chelate **13** in MeCN and of **13** in TFE.

for rhodium coordination, which will result in ring-opening of the metallo-macrocyclic in **13**, thus entailing an oligopeptide structure reminiscent of **12**. To prevent such ring-opening, analysis of the chelate tetrapeptide **13** were also performed in TFE as a non-coordinating and helix-inducing solvent.²⁵ This solvent change did not have any noticeable impact on the CD spectrum and the general features of an unordered peptide structure are still persistent. Introduction of a pronounced α -helical or β -turn motive therefore requires a longer oligopeptide scaffold.

Catalytic hydrosilylation

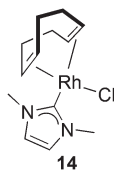
Based on the established activity of NHC rhodium complexes such as **14** in hydrosilylation catalysis,^{11b,26} we investigated the effect of the peptide scaffold on the catalytic performance of the rhodium centre. Hydrosilylation of 4-fluoroacetophenone as model substrate with Ph_2SiH_2 using 1 mol% of catalyst precursor occurred smoothly over 2 h or less. According to *in situ* ^1H and ^{19}F NMR spectroscopy, the silyl ether **15** was formed as the major product along with small quantities of the enol ether **16** (Table 1).²⁷ Monitoring the course of the reaction spectroscopically indicated a strong influence of the peptide scaffold on both the activity and the selectivity of the catalytically active rhodium centre. Complex **6a** containing two alanine residues bound to the histidylidene ligand displayed identical catalytic activity and selectivity towards **15** (within experimental error) as complex **6b** comprising three Ala units (Table 1, entries 1 and 2). With both precursors, 77% conversion with 94% selectivity was reached within 30 min. Under the same conditions, the model complex **14** exhibited higher activity (entry 7), achieving the same conversion level in only 5 min with similar selectivity. The peptidic backbone in **6** appears to hamper the efficiency of the catalysts, perhaps because of diffusion limitations due to the bulk imparted by the oligopeptide moiety. These observations are in line with

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

Entry	[Rh]	% conversion (% selectivity) ^b				
		5 min	10 min	0.5 h	1 h	2 h
1	6a	<i>n/a</i>	<i>n/a</i>	77 (93)	84 (90)	98 (87)
2	6b	<i>n/a</i>	<i>n/a</i>	76 (94)	83 (91)	92 (87)
3	11	<i>n/a</i>	<i>n/a</i>	79 (93)	86 (90)	97 (86)
4 ^c	11	39 (77)	64 (73)	99 (71)	<i>n/a</i>	<i>n/a</i>
5	12	<i>n/a</i>	<i>n/a</i>	33 (71)	53 (68)	80 (67)
6	13	56 (83)	100 (82)	100 (80)	100 (79)	100 (79)
7	14	77 (90)	<i>n/a</i>	90 (97)	94 (95)	100 (92)

^a General conditions: 4'-fluoroacetophenone (1 mmol), diphenylsilane (2 mmol), and rhodium complex (1 mol%) in CD_2Cl_2 (1 mL) at rt; ^b Conversion (selectivity towards **15** in parentheses) determined by ^1H and/or ^{19}F NMR spectroscopy; ^c With addition of AgOTf (1 mol%).

the previously noted lower catalytic activity of histidylidene ruthenium and rhodium complexes when compared to their imidazolylidene counterparts with identical first coordination spheres yet lacking the remote amino acid functionality.¹¹



Under identical conditions, the tyrosine-containing rhodium complex **11** showed catalytic activity and selectivity similar to complexes **6a,b** containing only alanine residues, converting 79% of the ketone in 30 min with 93% selectivity towards **15** (entry 3). The phenol group present in the side chain of the tyrosine residue seems to have no impact on the catalytic properties of the rhodium complex. In contrast, the methionine side chain in complex **12** is inhibiting catalytic turnovers (33% conversion after 30 min, entry 5) and decreases the selectivity from >90% to around 70%. Apparently, the coordinating ability of the thioether side chain efficiently competes with substrate coordination to the catalytically active centre.

Attempts to enhance the catalytic activity of **11** by inducing *in situ* chelation were unsuccessful. For example, addition of NEt₃Pr₂ (2 mol%) as a base for potentially scavenging HCl from complex **11** was unfavourable and gave only 57% conversion after 30 min. However, modification of the rhodium coordination sphere by abstracting the metal-bound chloride increased the catalytic activity of the rhodium complexes substantially. In the presence of a tyrosine side chain, essentially complete conversion was achieved within 30 min upon activation of the catalyst precursor with AgOTf (entry 4, cf. 97% conversion after 2 h with the RhCl unit). Interestingly, though, this enhanced catalytic activity is accompanied by a loss in selectivity from around 90% towards formation of **15** to only 70%. In contrast, chloride abstraction from the methionine-containing oligopeptide rhodium complex **12** and generation of the macrocyclic rhodium cation **13** increased the selectivity (entry 6). Moreover, the activity is markedly higher than that of the AgOTf-activated complex **11** as full conversion was accomplished within 10 min. This activity corresponds to an approximately four-fold increase of turnover rates, which is presumably not only induced by the cationic nature of the rhodium centre, but also by the beneficial effect of methionine coordination. Since tyrosine chelation was not detected, similar effects due to intramolecular stabilisation of the metal centre are absent with complex **11**. These results underline the relevance of chelation and indicate the unique behaviour of the methionine-containing catalyst. Further optimisation of the peptide scaffold may thus allow catalyst performance to be further improved.

Conclusions

Based on appropriate histidine functionalisation, a synthetic methodology has been devised to form carbene complexes on

an oligopeptide scaffold. Incorporation of an amino acid with a donor site in the side chain in the *i* + 3 position allows for the generation of a bidentate system, mimicking a metallo-enzyme active site with two coordinated amino acids. Chelation has a beneficial effect on the catalytic activity of the metal centre. These principles may be extended to introduce functional sites also at the C-terminus of the oligopeptide and to eventually engineer a second coordination site by biochemical methods through incorporation of appropriate amino acids that induce, for example, α -helical or β -turn conformations. Such an approach provides active site models in which the histidine is forced to bind *via* C_ε in a carbene binding mode, thus inducing new reactivity patterns.

Acknowledgements

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