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

Angèle Monney, a Flavia Nastri b and Martin Albrecht a*

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The NαNγ-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 SMe2C5H4–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.

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 Nγ or Nα. 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 biometalorganic chemistry, 3 as the metal-carbene complex enables the exploitation of typical organometallic function such as catalysis, while the peptide backbone offers opportunities for peptidic transformations and hence biochemical engineering of the hydride. 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-imidazolylidenes, 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 tautomerationism to the imidazole isomer. 7 Such an approach has been used previously to prepare peptide-based imidazol(in)ylidene 8 and thiazolylidene 9 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 monopeptide organometallic complexes thus allows modifications of the biochemical scaffold to be targeted. Here we report the functionalisation of the histidylidene backbone with a small oligopeptide 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 peptide 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 known 13 Nγ-methylated histidine Boc–Hist(Me)–OMe 1 (Scheme 1). Cleavage of the Boc protecting group at the N-terminal was effected with methanolic HCl thus providing the dihydrochloride salt H–Hist(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 DCC 16 or N-mesyI-benzotriazole 17 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-dioxane\textsuperscript{18} and a further alanine residue was introduced to give the tripeptide Boc–Ala–His(Me)–OMe 3a. The deprotection-coupling sequence was repeated to synthesise the tetrapeptide Boc–Ala–

\( \text{His}^*\)–OMe 3b. Successful coupling was indicated by high-resolution mass spectrometry and by the presence of three distinct carbonyl signals in the \( ^{13}C\{^1H\}\) NMR spectrum of 3a in CDCl\(_3\) for the two amide functionalities and one ester group in the \( \delta_C\) 172–173 ppm range, and a carbamide resonance at \( \delta_C\) 155 ppm.

Likewise, the tetrapeptide 3b showed three different amide and one amide carbonyl resonances in the \( \delta_C\) 173–176 ppm range as well as a carbamide resonance at higher field (\( \delta_C\) 158 ppm, CD\(_3\)OD solution).

Alternatively, the oligopeptide tether can be synthesised first (route B). Thus deprotection of the alanine dipeptide Boc–Ala–OMe or tripeptide Boc–Ala–His(Me)–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 \( N_xN_y\)-dimethylated histidinium oligopeptides Boc–Ala–His(Me)–OMe 4a (n = 2) and 4b (n = 3). The formation of the imidazolium salts was indicated by the diagnostic downfield shift of the \( \delta_C\) His and \( \delta_C\) C\(_\text{H}\) resonances in the \( ^1H\) NMR spectrum, e.g. from \( \delta_H\) 6.99 to 7.39 ppm and from \( \delta_H\) 7.70 to 8.85 ppm, respectively, for 4b (in CD\(_3\)OD). 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, \( \alpha\) = \(-43^\circ\) and \(-37^\circ\) for 4a and 4b, respectively (\( e = 1\) in MeOH).

The histidinium salts 4a–b were successfully metallated using a standard transmetallation procedure via the \textit{in situ} formation of a silver carbene intermediate. As described previously,\textsuperscript{11} ambient temperature and short reaction times were crucial for the full retention of the configuration at the \( \alpha\)-carbon of histidine. Subsequent transmetallation with [Ir(Cp*)Cl\(_2\)] 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\(_\text{H}\) bound proton in the \( ^1H\) NMR spectra and by the downfield shift of the carbone signal in the \( ^{13}C\{^1H\}\) NMR spectra to \( \delta_C\) 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 M-C\(_\text{carbone}\) bond.\textsuperscript{11,19} The resonances attributed to C\(_\text{H}\) and COOCH\(_\text{3}\) are most diagnostic and appeared as two sets of signals each. For example in 6a, two signals for C\(_\text{H}\) were observed at \( \delta_H\) 6.56 and 6.60 ppm (1:0.9 integral ratio) and the methylester was resolved at \( \delta_H\) 3.67 and 3.70 ppm. The enantiopurity of the peptide histidylidene ligand was confirmed by \( ^{31}P\) NMR spectroscopy after coordination of \( (S)\)-Ph-binepine\textsuperscript{20} 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 \( ^{31}P\{^1H\}\) NMR spectrum, corresponding to the rotamer ratio observed for 6a. This pattern is consistent with related enantiopure histidylidene rhodium complexes.\textsuperscript{11b} In contrast, when the silver carbene intermediate was formed using reflux temperature and longer reaction times, the rhodium complex 6a

\begin{align*}
\text{scheme 1} & \quad \text{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 \degree C; v) LiOH, THF/MeOH/H\textsubscript{2}O, rt, then HCl aq.; vi) 2, HATU, DIEA, THF, rt.}
\end{align*}
displayed a more complicated $^1$H NMR spectrum. Four distinct signals were observed for $\text{C}_\text{u}$H 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 $\alpha$-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 Ir–C$_{\text{NH}2}$ bond.

Synthesis of histidyldiene 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 histidyldiene ligand. Methionine (Met) and tyrosine (Tyr) were chosen to induce a potentially coordinating amino acid residue on the histidyldiene ligand. Methionine (Met) and potentially coordinating functionality were essential for the successful formation of the silver carbene complex 8. The use of freshly prepared Ag$_2$O$^{22}$ and the addition of [NEt$_3$Me]$_2$PF$_6$ as a source of iodide were essential for the successful formation of the silver carbene intermediate prior to transmetallation with [Rh(cod)Cl]$_2$. Analyses by NMR spectroscopy revealed the disappearance of the $\text{C}_\text{u}$H signal in the $^1$H NMR spectra and the appearance of a low field doublet in the $^{13}$C NMR spectra at $\delta_{\text{C}}$ 182 ppm ($J_{\text{HCC}} = 51$ Hz).

Comparison with model compounds by NMR spectroscopy indicated no spontaneous chelation of the tyrosine residue. While with the Met homologue, KP$_2$-mediated chlorination abstraction induced the formation of the macrocyclic chelate complex 11 (Scheme 4), no signals of phenol binding to the rhodium centre were observed by $^1$H 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 $\text{i}+\text{3}$ 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 for rhodium coordination, which will result in ring-opening of the metallo-
smoothly over 2 h or less. According to Ph\textsubscript{4}P of 4 performs the effect of the peptide scaffold on the catalytic activity and selectivity towards 15 (within experimental error) as complex 6b comprising three Ala units (Table 2, 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 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.

As the major product along with small quantities of the enol ether 16 (Table 1)\textsuperscript{7,11} 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 2, 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.

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4 Table 1 Hydroisilylation of 4'-fluoroacetophenone with rhodium complexes

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<tr>
<th>Entry</th>
<th>[Rh]</th>
<th>% Conversion (% Selectivity)</th>
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<tr>
<td>1</td>
<td>6a</td>
<td>n/a 77 (93) 94 (90) 98 (87)</td>
</tr>
<tr>
<td>2</td>
<td>6b</td>
<td>n/a 76 (94) 83 (91) 92 (87)</td>
</tr>
<tr>
<td>3</td>
<td>11</td>
<td>n/a 79 (93) 86 (90) 97 (86)</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>39 (77) 64 (73) 99 (71) n/a</td>
</tr>
<tr>
<td>5</td>
<td>12</td>
<td>n/a 33 (71) 53 (68) 80 (67)</td>
</tr>
<tr>
<td>6</td>
<td>13</td>
<td>56 (83) 100 (82) 100 (79) 100 (79)</td>
</tr>
<tr>
<td>7</td>
<td>14</td>
<td>77 (90) n/a 90 (97) 94 (95) 100 (92)</td>
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* General conditions: 4'-fluoroacetophenone (1 mmol), diphenylsilane (2 mmol), and rhodium complex (1 mol%) in CD\textsubscript{2}Cl\textsubscript{2} (1 mL) at rt.\textsuperscript{5}

Conversion (selectivity towards 15 in parentheses) determined by \textsuperscript{1}H and/or \textsuperscript{19}F NMR spectroscopy; \textsuperscript{5} with addition of AgOTf (1 mol%).

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 NEt\textsubscript{3}P\textsubscript{2} (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

Catalytic hydrosilylation

Based on the established activity of NHC rhodium complexes such as 14 in hydrosilylation catalysis,\textsuperscript{11b,26} we investigated the effect of the peptide scaffold on the catalytic performance of the rhodium centre. Hydrosilylation of 4'-fluoroacetacetophenone as model substrate with Ph\textsubscript{2}SiH\textsubscript{2} using 1 mol% of catalyst precursor occurred smoothly over 2 h or less. According to in situ \textsuperscript{1}H and \textsuperscript{19}F NMR spectroscopy, the silyl ether 15 was formed

![Scheme 4 Caption methionine analogues 12 and 13 featuring a monodentate and chelating bidentate bonding mode of the histidyldiene, respectively](image)

![Fig. 1 CD spectra of complex 6b, 12, and the chelate 13 in MeCN and of 13 in TFE](image)

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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 metalloenzyme 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 Cα in a carbene binding mode, thus inducing new reactivity patterns.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Synthetic procedures for all new compounds. See DOI: 10.1039/b000000x/

12 Preliminary results of this work have been communicated: A. Monney and M. Albrecht, Chem. Commun. 2012, 48, 10960–10962.
16 M. D’Almeida and F. Paradisi, unpublished results.
Side-chain alkylated histidine was tethered to oligopeptides and metallated with iridium and rhodium to afford efficient peptide-based catalysts for the hydrosilylation of ketones.