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ARTICLE TYPE

Stereospecific Synthesis and Catalytic Activity of *L*-Histidylidene Metal Complexes †‡

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We report on the synthesis, metal coordination, and catalytic impact of histidylidene, a histidine-derived N-heterocyclic carbene ligand. The histidinium salt **3**, comprising methyl substituents at both heterocyclic nitrogens and protected at the C- and N-terminus of the amino acid, was rhodated and iridated by a transmetallation protocol using Ag₂O. Ambient temperature and short reaction times were pivotal for full retention of configuration at the α carbon. The stereospecificity of the reaction was conveniently probed by ³¹P NMR spectroscopy after transmetallation with rhodium(I) and coordination of enantiopure (*S*)-Ph-binepine. The histidylidene rhodium complexes are highly efficient catalysts for the hydrosilylation of ketones under mild reaction conditions. For the cationic complexes [Rh(cod)(histidylidene)(phosphine)]⁺, lowering the temperature shifted the rate-limiting step of the catalytic reaction to an earlier stage that is not enantioselective. Hence the asymmetric induction—which is governed by the chiral phosphine—did not improve at low temperature.

Introduction

Due to their abundance and chirality, biomolecules such as enzymes,¹ carbohydrates,² and nucleic acids³ provide a very attractive pool of ligand precursors for the synthesis of organometallic complexes.⁴ Slight modifications are generally required to introduce a metal-carbon bond and to access this area of bioorganometallic chemistry.⁵ Peptides are a particularly versatile class of precursors,⁶ since the chiral amino acid building blocks are readily available. In addition, the different side chain functionalities allow a variety of modifications and linkages to classical organometallic ligands to be introduced. Because of the imidazole side chain, histidine—ubiquitous as ligating amino acid in the active site of metalloenzymes—constitutes a particularly intriguing ligand precursor for bioorganometallic complexes, especially when considering the high and steadily growing popularity of imidazolium-derived N-heterocyclic carbenes (NHCs)⁷ as ligands for transition metals.⁸ Alkylation of both nitrogens of the imidazole side chain of naturally occurring *L*-histidine provides straightforward access to the synthesis of bio-inspired N-heterocyclic carbenes and to peptide-derived NHC complexes (Scheme 1).^{9,10}

Histidine alkylation has previously been reported to give functionalised ionic liquids.¹¹ We have used a non-stereospecific protocol to prepare histidinium salts and the corresponding histidylidene ruthenium complexes.^{12,13} Through a careful choice of protecting groups¹⁴ and metallation conditions, we have now developed a protocol for the preparation of chiral *L*-histidylidene

complexes. Here we report the stereospecific synthesis of rhodium and iridium complexes and their catalytic activity in the hydrosilylation of ketones. These investigations pertain to recent work directed towards using NHC ligands as mimics of histidine in metalloenzyme active sites.¹⁵

Scheme 1 Retrosynthetic approach to histidylidene metal complexes.

Results and discussion

Synthesis of the ligand precursor

The *N*_ε-methylated histidine methyl ester **2** with a Boc-protected amino function was prepared according to a recently published procedure.^{11b} A key step in this synthesis is the formation of the bicyclic urea **1**, which is obtained in a solvent-free reaction of the histidine methyl ester and 1,1'-carbonyldiimidazole at 80 °C with a flow of nitrogen using a mechanical stirrer (Scheme 2). The neat reaction was equally successful in a ball mill¹⁶ without a nitrogen flow or external heating. Slightly heating of **2** and MeI in MeCN induced quaternisation at N_δ and afforded after column chromatography the histidinium salt **3** as a hygroscopic white solid (Scheme 2). Formation of an imidazolium unit was

indicated by the diagnostic downfield shift of the C δ H and C ϵ H resonances in the ^1H NMR spectrum from δ_{H} 6.64 to 7.44 and from 7.32 to 8.96 ppm respectively.

Scheme 2 Synthesis of histidylidene iridium and rhodium complexes.

All compounds **1–3** were optically active at the sodium D-line and the enantiomeric purity of **2** was previously assessed by chiral HPLC.^{11b} We applied an amino acid coupling protocol to confirm the full retention of chirality throughout the synthesis. Therefore, the histidinium salt **3** was deprotected at the *N*-terminus using methanolic HCl and subsequently coupled with Boc-*L*-methionine using HATU as coupling agent.^{11a} Only one set of signals was recorded by ^1H NMR spectroscopy, consistent with the presence of one diastereomer. In comparison, the corresponding dipeptide revealed two sets of resonances in the ^1H NMR spectrum when **3** was synthesised following a non-stereospecific protocol.¹³ These sets are clearly distinguishable by two resonances around δ_{H} 7.2 and 4.8 ppm, attributed to the C δ - and C α -bound protons, respectively. Integration of these signals suggests a diastereomeric excess of about 25%.

Synthesis of the metal complexes

Metallation of the optically pure histidinium salt **3** was performed using a standard transmetallation procedure,¹⁷ involving the *in situ* formation of a silver carbene intermediate by refluxing **3** with Ag₂O in CH₂Cl₂ in the dark. Subsequent transmetallation with Ir(Cp*)Cl₂ or [Rh(cod)Cl]₂ afforded the corresponding histidylidene iridium(III) and rhodium(I) complexes **4** and **5** in good yields (Scheme 2). Both complexes are air- and moisture-stable as solids and were purified by flash chromatography on SiO₂. Formation of the complexes was supported by the disappearance of the signal for the C ϵ -bound proton in the ^1H NMR spectrum and by the downfield shift of the carbene signal in the ^{13}C NMR spectrum to δ_{C} 155.2 and 183.3 ppm for **4** and **5**, respectively.^{18,19} In the case of **5**, the latter resonance appeared as a doublet due to coupling with ^{103}Rh ($^2J_{\text{RhC}} = 51$ Hz). Two full sets of signals were observed for complex **5** both by ^1H and ^{13}C NMR spectroscopy, indicating the presence of two rotamers in approximate 0.8:1 ratio as a consequence of hindered rotation about the Rh–C ϵ bond.^{18b,c} For example, four distinct singlets appeared in the 3.9–4.0 ppm range for the *N*-bound methyl protons. In the ^{13}C NMR spectrum, the largest shift was observed

for the stereogenic C α nucleus, which resonates in one rotamer at 52.6 ppm and at 52.1 ppm in the other rotamer. No coalescence was observed upon moderate heating to 50 °C (CDCl₃ solution).

Fig. 1 ORTEP plot of complex **4** (50 % probability, hydrogen atoms omitted for clarity). Selected bond lengths (Å) and angles (°): Ir–C11 2.041(3), Ir–C11 2.152 (3), Ir–Cl2 2.146 (3), Ir–C_{centr} 1.809(3), C11–Ir–C11 90.21(8), C11–Ir–Cl2 94.36(8), C11–Ir–Cl2 85.30(2).

A single crystal of the iridium complex **4** was analysed by X-ray diffraction. The molecular structure (Fig. 1) features an iridium centre in a piano-stool-type arrangement. The Ir–C_{carbene} bond length is 2.041(3) Å and hence within the typical range observed for NHC iridium(III) species.^{19,20} The complex crystallised in the triclinic non-centrosymmetric space group *P*–1, implying the co-crystallisation of both the *L*- and *D*-histidylidene complexes as a racemate. In agreement with racemisation, amorphous samples of the iridium and the rhodium complex did not display any optical rotation at the sodium D-line. Since the ligand precursor **3** was enantiopure (see above), racemisation at C α must have occurred under the reaction conditions used for (trans)metallation. Most likely, proton exchange at the α -carbon of the amino acid is induced by the strong basicity of Ag₂O or of intermediate hydroxides, leading to partial or full loss of enantiomeric purity. The lability of acidic protons *e.g.* α to the heterocyclic nitrogen, in the presence of a base has been documented.²¹ This lability is obviously closely associated with the racemisation of various chiral NHC ligand precursors upon metallation via base-mediated proton abstraction (free carbene route) or via transmetallation involving Ag₂O,²² and it may also account for the low performance of many NHC complexes in enantioselective catalysis.²³ Such racemisation processes also have direct implications for catalytic reactions involving strong bases, such as KOH-assisted transfer hydrogenation.²⁴ Due to the observed racemisation, we investigated the transmetallation reaction in more detail. For this purpose, the chiral phosphine (*S*)-Ph-binepine²⁵ was coordinated to the histidylidene-bound rhodium centre, thus providing a diagnostic spectroscopic probe for the presence of diastereoisomers due to racemisation at the C α centre. Hence, treatment of complex **5** with (*S*)-Ph-binepine in the presence of KPF₆ afforded the cationic complex **6** (Scheme 3). Displacement of cod under a CO atmosphere yielded the corresponding di(carbonyl) complex **7**. Both complexes *rac*-**6** and *rac*-**7** feature a seemingly similar resonance pattern in the ^{31}P NMR spectrum (Fig. 2), consisting of a low-field doublet and two partially overlapping doublets at higher field. Four distinct resonances would be expected in *rac*-**6** and *rac*-**7** due to the presence of two diastereoisomers (originating from *L*- and *D*-histidylidene), both existing as two rotamers in almost equimolar ratio (*cf* NMR discussion of **5**). Integration of the signals of *rac*-**6** revealed a 1:1 ratio between the low-field and the two high-field signals at δ_{P} 39.95 and 39.73

ppm ($^1J_{\text{RhP}}$ 153 Hz), suggesting two superimposed resonances at lower field. Variation of the metallation conditions further revealed (see below) that the two rotamers are separated in the spectrum of *rac*-**6**, but not the two epimers.† In contrast, the 1:1 integral ratio of the signals of *rac*-**7** ensues from mutual overlap of the rotamers, indicating distinct signals for the two epimers. The two rotamers of *L*-**7** thus each display a doublet (δ_{P} 42.03 and 42.08 ppm; $^1J_{\text{RhP}}$ 123 Hz), while the resonance for *D*-**7** appears as a single doublet at lower field, δ_{P} 42.47 ($^1J_{\text{RhP}}$ 122 Hz; rotamers unresolved). Hence, the carbonyl complex **7** provides a direct probe for the C_{α} configuration and thus offers an indirect measure for the stereospecificity of the (trans)metallation reaction.

Fig. 2 Relevant section of the ^{31}P NMR spectrum of a) *rac*-**6** and b) *rac*-**7**; c) the ^{31}P NMR spectrum of *L*-**6** displays only two doublets in 0.8:1 ratio, corresponding to the rotamer ratio observed for **5**; d) disappearance of one of the signal sets indicates diastereomerically pure *L*-**7**.

Table 1 Impact of metallation conditions on the configurational stability at C_{α}

entry	silver salt	molequiv.	solvent	temperature	time	ee ^a
1	Ag_2O	0.7	CH_2Cl_2	reflux	16 h	0%
2	Ag_2CO_3	0.7	CH_2Cl_2	reflux	16 h	0%
3	Ag_2O	0.7	MeOH	50 °C	13 h	0%
4	Ag_2CO_3	0.7	MeOH	50 °C	13 h	0%
5	Ag_2O	0.5	CH_2Cl_2	20 °C	1 h	96%
6	Ag_2CO_3	1.1	CH_2Cl_2	20 °C	3 h	0%
7	Ag_2O	0.5	CH_2Cl_2	20 °C	21 h	74%

^a ee determined by ^{31}P NMR spectroscopy from the diastereomeric excess in **7**.

Different reaction conditions for the formation of the silver carbene intermediate were then evaluated by using the diagnostic ^{31}P NMR signals of complexes **6** and **7** (Table 1). Due to the potential basicity of the intermediate AgOH released in reactions with Ag_2O ,²⁶ Ag_2CO_3 was considered as an alternative source of silver that would release bicarbonate as a significantly less basic

side product. While Ag_2CO_3 successfully mediated the deprotonation of **3**, the rhodium complex obtained after transmetalation was fully racemised (Table 1, entry 2). Lowering the basicity of the anion in the silver precursor even further was detrimental to the reaction outcome, and neither silver(I) triflate nor silver(I) acetate were reactive enough to form the corresponding carbene complex. Attenuation of the base strength was thus attempted by using protic MeOH as solvent (entries 3, 4), and by lowering the reaction temperature from reflux to ambient (entries 5, 6). Only the latter modification had an impact, and an ee up to 96% was obtained for the histidylidene ligand in complex **7** when Ag_2O was used as silver(I) source.²⁷ Short reaction times were critical, as stirring the reaction for extended periods of time induced substantial racemisation (6.4:1 integral ratio in the ^{31}P NMR spectrum of **7**, corresponding to 74% ee after 21 h, entry 7). In agreement with the suggested assignments of the resonances, the ^{31}P NMR spectrum of the essentially enantiopure **6** (entry 5) displayed a 0.8:1 ratio of the two sets of signals, while the spectrum of the corresponding carbonyl complex **7** reflected a 45:1 ratio and allowed the ee to be determined. In support of the ^{31}P NMR probe, the CD spectrum of *rac*-**5** (cf. entry 1) showed no optical activity, while *L*-**5** prepared under milder conditions (cf. entry 5) displayed a CD signal with a maximum around 390 nm and inverse activity below 370 nm (Fig. 3).

Fig. 3 CD spectra of *rac*-**5** (dotted grey line) and *L*-**5** (solid red line; 10^{-3} M in MeCN).

Alternative rhodation procedures met little success. Reaction of the enantiopure histidinium salt **3** with *in situ* prepared $[\text{Rh}(\text{cod})(\text{OEt})_2]$ ²⁸ yielded, after ligand exchange, the complex **7** as a 1:1 diastereomeric mixture. Metallation of **3** with $[\text{Rh}(\text{cod})\text{Cl}]_2$ in the presence of a mild base such as NaOAc , NEt_3 or Cs_2CO_3 failed in our hands,²⁹ as did attempts to thermally induce cleavage of the *in situ* formed CHCl_3 adduct.³⁰

Catalytic hydrosilylation

The histidylidene rhodium complexes **5** and **6** were tested as catalyst precursors for the asymmetric hydrosilylation of ketones. Their performance was compared with the analogous NHC rhodium complexes **8** and **9** which lack the amino acid backbone. *Para*-fluorinated acetophenone was chosen since its consumption as well as product formation can be readily monitored by ^{19}F NMR spectroscopy without the need for any work-up. In a typical reaction, 4'-fluoroacetophenone **I** and diphenylsilane were stirred

in the presence of 1 mol% rhodium catalyst, producing the silyl ether **II** together with minor quantities of the silylated enol ether **III** (Table 2).^{31,32} Release of gaseous H₂, was generally observed.

Table 2 Hydrosilylation of fluoroacetophenone with rhodium complexes^a

entry	[Rh]	conversion (selectivity) ^b			
		5 min	0.5 h	1 h	2 h
1	5	77 (90.0)	90 (97.0)	94 (94.7)	100 (91.6)
2	6	57 (98.7)	98 (97.9)	100 (98.0)	100 (98.4)
3	8	89 (99.4)	92 (96.2)	95 (93.7)	100 (90.5)
4	9	82 (98.7)	100 (98.0)	100 (98.3)	100 (98.5)

^a General conditions: ketone (1 mmol), silane (2 mmol), catalyst (10 μmol, 1 mol%) in CD₂Cl₂ (1 mL) at rt.

^b Conversion (selectivity towards **II** in parentheses) determined by ¹H and

¹⁹F NMR spectroscopy.

With all four catalysts high conversions were accomplished within 5 minutes (Table 2). This performance corresponds to a turnover frequency at 50% conversion (TOF₅₀) around 1000 h⁻¹ and places these complexes amongst the most active NHC-based hydrosilylation catalysts known to date.^{22a,33} The amount of silylenol ether (**III**) formed during the reaction was consistently lower in runs catalysed by the cationic complexes **6** or **9** (entries 2, 4), than in reactions with the neutral complexes **5** and **8** (entries 1, 3). This higher selectivity is in agreement with recent mechanistic studies which propose the bonding of the substrate ketone to a silylene-rhodium dihydride species as a critical step.³² According to such a model, keto-enol tautomerisation and ensuing formation of the silylenol ether side product strongly depends on the Lewis acidity of the silicon atom and thus indirectly on the electronic properties of the rhodium centre. Electron-rich neutral rhodium centres as in **5** and **8** increase the electron density at the silylene and hence facilitate substrate bonding in its tautomeric enol form. In contrast, the cationic nature of the rhodium centre in **6** and **9** enhances the Lewis acidity of the silicon nucleus and thus favors substrate bonding in the keto form, reflected in the almost exclusive formation of **II**. It is interesting to note that the product selectivity eroded at the later stages of the reaction when using the neutral complexes **5** and **8**. This lower selectivity may be compensated for to some degree by extending the reaction time beyond full conversion. For example, the product selectivity obtained with the histidylidene complex **5** raised to 92.7% after 5 h, presumably due to slow tautomerisation of the enol ether.

Lowering the catalyst loading to 0.1 mol% decelerated the reaction and allowed the activity of the different complexes to be evaluated (Fig. 4). The cationic complexes **6** and **9** displayed 3-5

times higher initial activity than their corresponding neutral complexes **5** and **8**, respectively. After 30 min, approximately 60% conversion was reached with the cationic species, corresponding to an estimated turnover frequency TOF₅₀ = 1300 h⁻¹. This value is closely related to the TOF₅₀ deduced at higher catalyst loading and suggests a molecularly based process. The phosphine-free neutral complexes required substantially longer reaction times to reach 50% conversion (ca. 2 h), corresponding to a TOF₅₀ around 250 h⁻¹ (for **5**) and even less for **8**. With all complexes, the product selectivity was significantly lower, yet again higher when the cationic complexes **6** and **9** were used (around 80%) than with the neutral complexes (ca. 60%). Of note, both **6** and **9** displayed identical activity within errors, indicating that the amino acid backbone of the histidylidene ligand does not have any substantial influence on the catalytic performance under these conditions.

Fig. 4 Catalytic hydrosilylation under the conditions described in Table 2, but using 0.1 mol% of **5** (■), **6** (□), **8** (●), and **9** (○).

Fig. 5 Catalytic hydrosilylation under the conditions described in Table 2, but performed at -18 °C with **5** (■), **6** (□), **8** (●), and **9** (○).

Experiments performed at low temperature revealed a different behaviour. In contrast to the catalytic runs at room temperature, conversions at -18 °C were substantially slower with the cationic complexes **6** and **9** than with their corresponding neutral analogues **5** and **8** (Fig. 5). This change of relative activity may be a consequence of a different rate-limiting step in the cationic complexes. Dissociation of a weakly bound ligand, for example, may become increasingly difficult at low temperature, in particular with electron-deficient metal centres.³⁴ Possibly,

catalyst pre-activation may thus be the rate-determining process in catalytic hydrosilylation using **6** or **9**.

At these low temperatures, the histidylidene ligand induced consistently lower activity than the simple imidazolylidene homologue, both with the cationic and the neutral catalyst precursors. This result corroborates previous observations with related ruthenium complexes, which demonstrated a direct impact of the remote amino acid functionality on the properties of the metal centre.¹² It is interesting to note that a decreased catalyst loading had a much stronger impact on the performance of the neutral complex **5** than on the cationic phosphine carbene complex **6**, while a decrease in reaction temperature had an inverse effect and reduced the activity of **6** more substantially than that of **5**. Irrespective of the catalyst precursor, however, the product selectivity was considerably higher in hydrosilylation reactions performed at $-18\text{ }^{\circ}\text{C}$ and only traces of silylenoether were detected (selectivity > 99%).

Table 3 Enantioselectivity of hydrosilylation with complexes **5**, **6**, and **9**^a

entry	catalyst precursor	temperature	ee (%) ^a
1	<i>L</i> - 5	rt	0
2	<i>rac</i> - 6	rt	26 (<i>S</i>)
3	9	rt	31 (<i>S</i>)
4	<i>L</i> - 5	$-18\text{ }^{\circ}\text{C}$	0
5	<i>rac</i> - 6	$-18\text{ }^{\circ}\text{C}$	34 (<i>S</i>)
6	9	$-18\text{ }^{\circ}\text{C}$	37 (<i>S</i>)

^a See Table 2 for general conditions; ee determined by chiral HPLC after hydrolysis of the silylether **II** with methanolic TFA.

Since complexes *L*-**5**, *rac*-**6** and **9** are comprised of at least one chiral ligand, the potential for asymmetric hydrosilylation was investigated. To this end, the formed silylether **II** was hydrolysed with methanolic TFA and the corresponding alcohol was analysed by chiral HPLC (Table 3). As expected from the remote position of the stereocentre, the histidylidene ligand did not induce any enantioselectivity, neither at room temperature nor at $-18\text{ }^{\circ}\text{C}$ (entries 1, 4). In contrast, complexes **6** and **9** containing (*S*)-Ph-binepine as an enantiopure phosphine ligand generated a moderate 30% enantiomeric excess (ee) in the product alcohol (entries 2, 3).³⁵ The enantioselectivity did not improve significantly when lowering the temperature to $-18\text{ }^{\circ}\text{C}$ (entries 5, 6). The independence of the ee on temperature is in agreement with a rate-limiting step that is stereoselectively not relevant. This result corroborates the conclusions from NMR analyses, which suggest a shift of the rate-limiting step to an early stage upon lowering the temperature (see above).

Conclusions

We have developed a synthetic protocol towards chiral histidylidene iridium and rhodium complexes starting from *L*-histidine. The full retention of configuration at the stereogenic amino acid carbon is strongly dependent on the conditions used for the metallation, in particular for the instalment of the silver(I) centre for subsequent transmetallation. Coordination of a chiral phosphine has double advantage, firstly in serving as a diagnostic and straightforward probe for the stereospecific course of the metallation, and secondly as stereo-discriminating ligand in the asymmetric hydrosilylation of ketones catalysed by the histidylidene rhodium complexes. Although the chiral amino acid functionality of the histidylidene ligand did not induce any

enantiomeric excess, vast opportunities emerge from modification of the complex by classic concepts of peptide synthesis to induce, *e.g.*, chelation. Moreover, the versatility of the transmetallation route will also allow transition metals of direct biological relevance to be coordinated to the histidylidene ligand.

Experimental section

We thank S. L. James (Queen's University Belfast) and F. O'Meara (University College Dublin) for technical assistance. The authors gratefully acknowledge financial support from the Swiss National Science Foundation and the European Research Council.

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- † Electronic Supplementary Information (ESI) available: Experimental details for all new compounds and crystallographic data for *rac*-**4** (CCDC No. 870836). See DOI: 10.1039/b000000x/
- ‡ Dedicated to Professor David Cole-Hamilton on the occasion of his retirement and for his outstanding contribution to transition metal catalysis
- § In a typical catalytic procedure, the catalyst (10 μmol) and 4'-fluoroacetophenone (0.12 mL, 1.0 mmol) were dissolved in CD_2Cl_2 (1 mL). Diphenylsilane (0.37 mL, 2.0 mmol) was added and the mixture was placed in an NMR tube. Conversions were determined by ^1H and ^{19}F NMR spectroscopy. Hydrolysis was performed by addition of TFA in MeOH (1%, 0.5 mL). The solution was stirred for 10 min and then filtered through a small pad of SiO_2 , eluting with pentane/ Et_2O (3:1). The enantiomeric excess was determined by chiral HPLC (IA or OBH column, heptane/ EtOH 99:1, 1 mL min^{-1}).
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Histidine-derived NHC rhodium and iridium complexes were synthesized and used as catalyst precursor in (asymmetric) hydrosilylation reaction. The stereospecific course of the reaction
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