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Synthesis and catalytic activity of histidine-based NHC ruthenium complexes†

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Main-chain *C*,*N*-protected histidine has been successfully alkylated at both side-chain nitrogens. The corresponding histidinium salt was metallated with ruthenium(II) by a transmetalation procedure, thus providing histidine-derived NHC ruthenium complexes. These bio-inspired comsxsxsplexes show appreciable activity in the catalytic transfer hydrogenation of ketones.

The use of naturally abundant products as versatile starting materials for ligand development is an appealing concept in homogeneous catalysis and is an increasingly popular strand of bioinorganic and bioorganometallic chemistry.[1] A variety of biologically relevant classes of compounds have been functionalised for transition metal coordination, including DNA,[2] carbohydrates,[3] steroids,[4] alkaloids[5] and vitamins such as biotin.[6] Proteins constitute a particularly attractive platform for ligand synthesis, partly because of the diversity of the functional groups in the amino acid side chains.[7] Both covalent and supramolecular anchoring of complexes onto peptidic scaffolds has successfully been demonstrated.[8] Covalent linkers may be established, for example, *via* side chain functionalisation of the amino acids.[9] Histidine is remarkable in this respect, since imidazole has been widely employed as a precursor for N-heterocyclic carbenes,[10] which are probably the most popular class of ligands during the last decade.[11]

Alkylation of the histidine side chain and the subsequent metallation of the histidinium salt hence constitutes an attractive approach to bioorganometallic chemistry.[12] This provides potential catalyst precursors with activity and selectivity properties that may be tailored by biochemical principles inherent to enzymes, such as second coordination sphere modification or side-chain-directed substrate recognition. Towards this end, we report here a straightforward synthesis of catalytically active ruthenium centres anchored covalently to a histidine side chain through a histidine-derived NHC spectator ligand.

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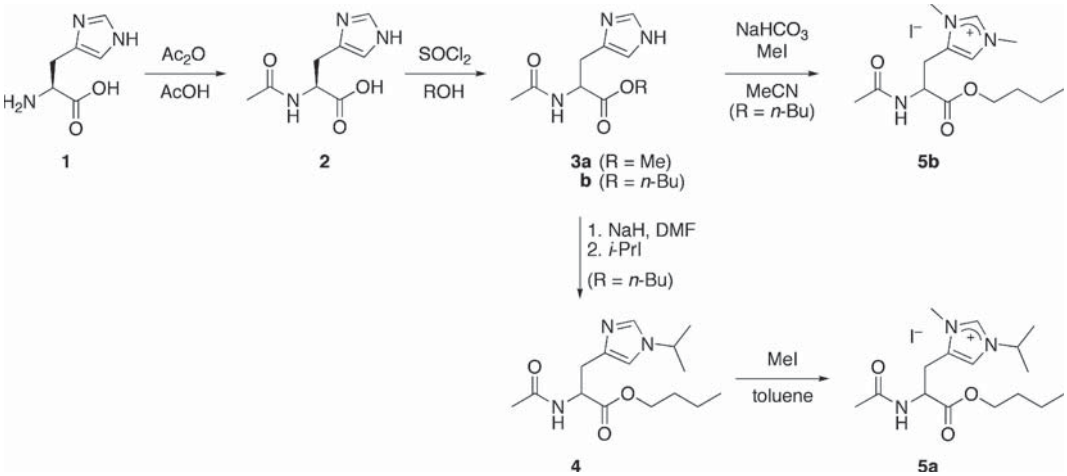
The synthesis of the histidine-derived carbene ligand precursors started with the protection of the amine and the acid group of native histidine (Scheme 1). An acetyl unit was chosen as the amine protecting group because of its facile introduction and high chemical stability. Acetyl histidine **2** was obtained according to known procedures[13] and subsequently esterified at the *C*-terminus.[14] The corresponding methyl ester **3a** was only soluble in highly polar solvents, which hampered the subsequent transformations considerably. Therefore, the corresponding butyl ester **3b**, comprising a longer alkyl chain, was prepared by esterification in *n*-BuOH. While the yields were high, racemisation at the α-carbon occurred during the work-up, as demonstrated by the loss of any optical rotation of **3** at the sodium D-line. Attempts to avoid the racemisation, by using milder bases or a phosphate buffer (pH = 7.2) for the neutralisation, have not been successful thus far. Optical instability of the *N*-acetyl protected amino acids is well-established[15] and often an undesired process. In our case, it may provide straightforward access to both L- and D-histidine-derived ligand precursors, which may be easily resolved when coordinated to a metal centre through the formation of diastereomeric complexes. Hence, racemisation is not necessarily disadvantageous and it has been claimed to be suppressed when using different protecting groups.[12a]

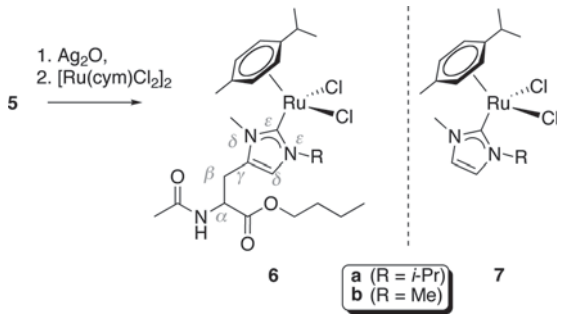
Functionalisation of the racemic *N*,*C*-protected histidine **3b** included the alkylation of the side chain by deprotonation, using NaH in DMF followed by the addition of 2-iodopropane. Selective N_ε-alkylation and the exclusive formation of the regioisomer **4** was confirmed by NMR spectroscopy, which showed a single set of signals and a NOE cross-correlation of $C_\delta H$ and the *i*-Pr protons. This alkylation method allows, thus, two different wingtip groups to be selectively introduced on the imidazole ring. Quaternisation at N_δ, by refluxing **4** and MeI in toluene, afforded the histidinium salt **5a** as a hygroscopic white solid. Introduction of two identical wingtip groups at the imidazole ring was performed in a single step by refluxing **3b** in the presence of excess alkyl halide and $NaHCO_3$ as proton scavenger, thus yielding the N_δ,N_ε-dimethylated histidinium salt **5b**. Apart from saving one synthetic step, this route also uses milder reaction conditions, which might be beneficial when enantiomerically pure ligands are sought.

Metallation of the histidine-derived imidazolium salts was accomplished by using a transmetallation procedure.[16] Accordingly, Ag_2O-mediated proton abstraction and subsequent transruthenation with $[Ru(cym)Cl_2]_2$ afforded the two ruthenium complexes **6a** and **6b**.‡ Both complexes are air and moisture stable and were purified by flash chromatography on silica gel, using a mixture



Scheme 1 Synthesis of the histidine-based ligand precursors **5**.

of acetonitrile and water (9 : 1). The disappearance of the signal due to the C_ε-bound proton in the ^{1}H NMR spectrum, as well as the downfield carbene signal in the ^{13}C NMR spectrum (δ_C = 173.6 and 172.9 ppm for **6a** and **6b**, respectively), supported the formation of complexes **6**. Notably, the NMR spectra in $CDCl_3$ are broad at room temperature, presumably due to rotation about the Ru–$C_{carbene}$ and the Ru-cymene bonds, which causes epimerisation at Ru. The resonances are markedly better resolved upon moderate warming. Variable temperature NMR spectroscopy revealed (de)coalescence of the wingtip groups, which allows for estimating the energy barrier for rotation about the Ru–$C_{carbene}$ bond. From these measurements, a distinct influence of the amino acid residue was noted as the activation barrier ΔG = 65(±2) kJ mol^{-1} for **6a** was higher than that determined for the model complex **7a** (ΔG = 60(±2) kJ mol^{-1}). This significant difference suggests that functionalisation at the imidazole C4 position (*i.e.* C_γ in Scheme 2) has a marked influence on the Ru–C bond, despite being remote.



Scheme 2 Synthesis of the histidine-based ruthenium carbene complexes and model complexes.

Both complexes are stable as solids at ambient conditions, but decompose within minutes in DMSO and within a few days in most common organic solvents (*e.g.* MeCN, toluene, CH_2Cl_2, $CHCl_3$). A single crystal of complex **6a**, obtained by layering a concentrated $CHCl_3$ solution with pentane, was analysed by single-crystal X-ray diffraction. The complex crystallised in a centrosymmetric space group ($P2_1/c$), implying the co-crystallisation of both the *R* and the *S* stereoisomers, as a racemate. The molecular structure (Fig. 1) features a ruthenium centre in a piano-stool-type arrangement. The Ru1–C1 bond length is 2.067(10) Å and hence is within the typical observed range.[17]

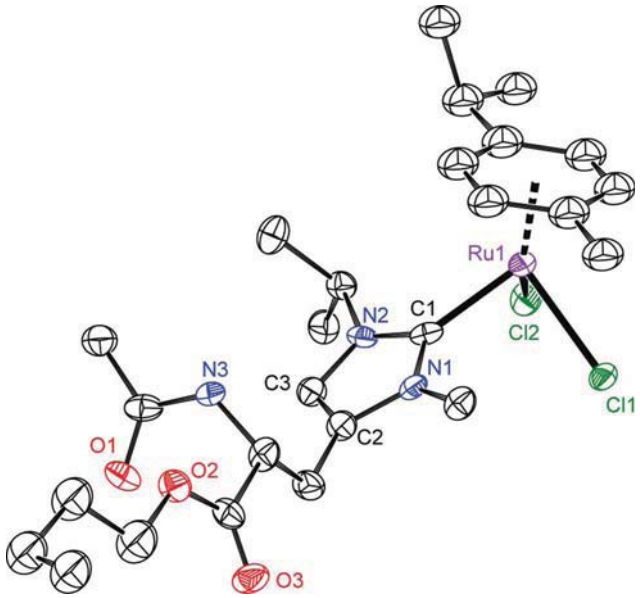
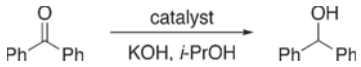


Fig. 1 ORTEP plot of complex **6a** (50% probability, hydrogen atoms omitted for clarity). Selected bond lengths (Å) and angles (°): Ru1–C1 2.067(10), Ru1–Cl1 2.407(3), Ru1–Cl2 2.430(3), Ru1–$C_{centroid}$ 1.691(5), C1–Ru1–Cl1 88.4(3), C1–Ru1–Cl2 89.1(3), Cl1–Ru1–Cl2 84.0(1).

Complexes **6** were evaluated as catalyst precursors for the transfer hydrogenation of ketones. Benzophenone was used as substrate and *i*-PrOH as hydrogen donor (Table 1). The known unfunctionalised analogues of complexes **6**, *i.e.* complexes **7** (*cf* Scheme 2),[18] were included as a reference. Under standard conditions, *i.e.* using KOH as a co-catalyst in refluxing *i*-PrOH (substrate/base/catalyst 100 : 10 : 1), the reference complexes **7** showed generally higher catalytic activity than the corresponding histidine-based complexes **6** (Table 1, entries 1–4). While these activity differences were observed in most runs, it should be noted that the catalytic performance of these monodentate carbene complexes showed very poor reproducibility in our hands.[19] For example, in some runs the catalytic activity of complex **7a** ceased after 5 min at conversion below 5%, while in other runs

Table 1 Transfer hydrogenation using Ru-carbene complexes **6** and **7**[a]



entry	catalyst	additive	conversion	
			0.5 h	2 h
1	**7a**	—	10–16%[b]	—
2	**7b**	—	31–47%[b]	—
3	**6a**	—	21%	56%
4	**6b**	—	20%	60%
5	**7a**	PPh_3	39%	88%
6	**7a**	$P(n\text{-}Bu)_3$	56%	93%
7	**7b**	$P(n\text{-}Bu)_3$	87%	99%
8	**6a**	$P(n\text{-}Bu)_3$	17%	50%
9	**6b**	$P(n\text{-}Bu)_3$	39%	85%

[a] General conditions: benzophenone (1 mmol), KOH (100 μmol), catalyst (10 μmol), and where indicated, additive (10 μmol) in refluxing *i*-PrOH (5 mL); [b] After 10 min with limited reproducibility, see text for details.

under seemingly identical reaction conditions, 97% conversions were reached after identical periods, which would place these ruthenium complexes amongst the most active transfer hydrogenation catalysts known to date ($TOF_{50} \sim 10^5\ h^{-1}$).[20] Possibly, the heterogeneisation of the catalyst precursor to catalytically active ruthenium nanoparticles may occur.[21]

Stabilisation of the catalytic intermediate was sought by using phosphines as additives.[22] In the presence of PPh_3 (1 : 1 ratio of Ru and PR_3), the transfer hydrogenation activity of complex **7a** was slightly lower (Table 1, entry 5), yet the reproducibility was significantly better. Addition of $P(n\text{-}Bu)_3$ improved both catalytic activity and reproducibility. The effect was particularly pronounced for the catalytic performance of complexes **6b** and **7b**, containing two methyl wingtip groups (entries 7 and 9). In contrast, complexes **6a** and **7a**, comprising an isopropyl wingtip group, were slightly less active (entries 6 and 8), presumably due to steric congestion at the ruthenium centre. As a general trend, the histidine-derived carbene ruthenium complexes displayed a lower catalytic activity than the model complexes prepared from simple imidazolium salts. Since the first coordination sphere of the metal centre is identical in both the histidine-derived complexes **6** and their model complexes **7**, these activity differences suggest that the remote amino acid residue has an impact on the (catalytic) properties of the metal centre, thus corroborating NMR spectroscopic analyses. Such remote tunability may provide interesting opportunities for catalyst optimisation through bio-inspired concepts.

In summary, histidine was successfully used as a starting material for two new NHC ruthenium complexes. The histidine-derived complexes were readily accessible in five to six steps using a final transmetallation procedure and, depending on the wingtip substitution pattern, they exhibit moderate to good catalytic performance in transfer hydrogenation. An attractive feature of these complexes is based on the fact that the catalytic activity differs from that of simple imidazol-2-ylidene ruthenium complexes, thus allowing the activity to be tailored both *via* wingtip group modification and *via* remote substitution at the amino acid moiety of the complex. Work along these lines is currently in progress.

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Notes and references

‡ *Typical procedure*: A mixture of **5a** (500 mg, 1.14 mmol) and Ag_2O (265 mg, 1.14 mmol) in dry CH_2Cl_2 (25 mL) was stirred at reflux for 15 h in the dark. After filtration of the cold mixture through Celite, solid $[Ru(cym)Cl_2]_2$ (350 mg, 0.57 mmol) was added to the filtrate and stirring in the absence of light was continued for 2.5 h. The reaction mixture was subsequently filtered through Celite and the volatiles were removed under reduced pressure. The residue was purified by flash chromatography (SiO_2, MeCN–H_2O 9 : 1), thus affording pure **6a** as a brown-orange solid (353 mg, 50% yield).
^1H NMR (500 MHz, $CDCl_3$, 50 °C) δ 6.92 (br, 1H, $C_\delta H$), 5.39–5.49 (m, 2H, $C_{cym}H$), 5.22 (septet, $^3J_{HH}$ = 6.7 Hz, 1H, $NCHMe_2$), 5.09 (d, $^3J_{HH}$ = 5.7 Hz, 2H, $C_{cym}H$), 4.78 (br, 1H, $C_\alpha H$), 4.09–4.18 (m, 2H, $COOCH_2$), 3.87 (br, 3H, NCH_3), 3.07–3.10 (m, 1H, $C_\beta H_2$), 2.96 (septet, $^3J_{HH}$ = 7.0 Hz, 1H, $C_{cym}CHMe_2$), 2.79 (br, 1H, $C_\beta H_2$), 2.05 (s, 3H, $C_{cym}CH_3$), 1.96 (br, 3H, CH_3CO), 1.60–1.64 (m, 2H, $CH_2CH_2CH_3$), 1.35–1.40 (m, 2H, CH_2CH_3), 1.37 (d, $^3J_{HH}$ = 6.7 Hz, 6H, $NCH(CH_3)_2$), 1.29 (d, $^3J_{HH}$ = 7.0 Hz, 6H, $C_{cym}CH(CH_3)_2$), 0.93 (t, $^3J_{HH}$ = 7.3 Hz, 3H, CH_2CH_3), NH not resolved; $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$, 50 °C) δ 173.6 ($C_{carbene}$), 171.1 (C═O), 170.3 (C═O), 131.5 (C_γ), 117.4 ($C_\delta H$), 108.8 (C_{cym}), 98.4 (C_{cym}), 86.5 ($C_{cym}H$), 85.3 ($C_{cym}H$), 82.4 (br, 2 × $C_{cym}H$), 65.9 ($COOCH_2$), 52.4 ($NCHMe_2$), 50.6 ($C_\alpha H$), 36.8 (NCH_3), 31.0 ($C_{cym}CHMe_2$), 30.7 ($CH_2CH_2CH_3$), 28.3 ($C_\beta H_2$), 24.9 (2 × $NCH(CH_3)_2$), 23.4 ($C_{cym}CH(CH_3)_2$), 23.1 (CH_3CO), 21.9 ($C_{cym}CH(CH_3)_2$), 19.2 (CH_2CH_3), 18.9 ($C_{cym}CH_3$), 13.7 (CH_2CH_3); Elem. anal. calcd for $C_{26}H_{41}N_3O_3Cl_2Ru$ (615.60): C 50.73, H 6.71, N 6.83; found: C 50.50, H 6.50, N 6.77.
Crystal data for **6a**: yellow rod, $C_{26}H_{41}Cl_2N_3O_3Ru$, M_r = 615.59, monoclinic, a = 11.1246(13), b = 10.9646(9), c = 24.403(3) Å, α = 90.00, β = 92.472(10), γ = 90.00 Å, V = 2973.8(6) Å^3, T = 173(2) K, space group $P2_1/c$, Z = 4, 19 658 measured reflections, 5293 unique reflections (R_{int} = 0.2063), R_1 = 0.0679, wR_2 = 0.1384 for $I > 2\sigma(I)$.

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