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

Angèle Monney, a,b Galmari Venkatachalam b and Martin Albrecht a,b

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Main-chain C,N-protected histidine has been successfully alkylated at both side-chain nitrogens. The corresponding histidinium salt hence constitutes an attractive approach to bioorganometallic chemistry, providing 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 on a straightforward synthesis of catalytically active ruthenium centres anchored covalently to a histidine side chain through a histidine-derived NHC spectator ligand.

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 amine protecting group because attractive appr

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

19 Alkylation of the histidine side chain and subsequent metallation of the histidinium salt hence constitutes an
histidine-derived ligand precursors that 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.\(^{12}\)

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 \(N\)-alkylation and exclusive formation of the regioisomer \(4\) was confirmed by NMR spectroscopy which showed a single set of signals and a NOE cross-correlation of \(C\alpha\) and the \(i\)-Pr protons. This alkylation method allows thus two different wingtip groups to be selectively introduced on the amidazole ring. Quaternisation at \(N\_2\) by refluxing \(4\) and Mel in toluene afforded the histidinium salt \(5a\) as a hygroscopic white solid. Introduction of two identical wingtip groups at the amidazole 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 \(N\_N\)-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\(_2\)O-mediated proton abstraction and subsequent transreuthenation 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 of acetonitrile and water (9:1). Disappearance of the signal due to the \(C\gamma\)-bound proton in the \(^1\)H NMR spectrum as well as the downfield carbene signal in the \(^{13}\)C NMR spectrum (\(\delta_{C} = 173.6\) 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\(_\text{carbene}\) and the Ru–cyocene 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\(_\text{carbene}\) bond. From these measurements, a distinct influence of the amino acid residue was noted as the activation barrier \(\Delta G^\ddagger\) = 65(±2) kJ mol\(^{-1}\) for \(6a\) was higher than that determined for the model complex \(7a\).

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transfer hydrogenation of ketones. Benzophenone was used as substrate and i-propanol as hydrogen donor (Table 1). The known unfunctionalised analogues of complexes 6, i.e. complexes 7 (c’/ 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 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 ~ 10^5 h⁻¹).20 Possibly, heterogenisation 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 PPh₃ (1:1 ratio of Ru and PR₃), the transfer hydrogenation activity of complex 7a was slightly lower (Table 1, entry 5), yet the reproducibility was significantly better. Addition of PBU₃ 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 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

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3 Electronic Supplementary Information (ESI) available: CCDC 804412 and experimental and analytical details; see DOI: 10.1039/b0000000/c
4 Typical procedure: A mixture of 5A (500 mg, 1.14 mmol) and AgO (265 mg, 1.14 mmol) in dry CH2Cl2 (25 mL) was stirred at reflux for 15 h in the dark. After ﬁltration of the cold mixture through Celite, solid [Ru(cym)Cl2] (350 mg, 0.87 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 (SiO2, MeCN/H2O 9:1), thus affording pure 6a as a brown-orange solid (353 mg, 50% yield).
5 ¹H NMR (500 MHz, CDCl3, 50 °C) δ 6.92 (br, 1H, C₆H), 5.39–5.49 (m, 2H, C₆H₂, C₅H₅), 5.22 (septet, J = 6.7 Hz, 1H, NCHMe), 5.09 (d, J = 5.7 Hz, 2H, C₅H₅), 4.78 (br, 1H, C₆H), 4.09–4.18 (m, 2H, COOCH₂), 3.87 (br, 3H, NCH), 3.07–3.10 (m, 1H, C₆H), 2.96 (septet, J = 7.0 Hz, 1H, C₅H₂CH₂Me), 2.79 (br, 1H, C₆H₂), 2.05 (s, 3H, C₆H₂CH₂), 1.96 (br, 3H, CH₂O), 1.60–1.64 (m, 2H, CH₂CH₂CH₂), 1.35–1.40 (m, 2H, CH₂CH₂).
6 13C NMR data for 6a: yellow rod, C₆H₄N₃O₃Ru, M = 615.59, monomeric, 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) Å³, T = 173(2) K, space group P2₁/n, Z = 4, 19658 measured reﬂections, 5293 unique reﬂections (Rint = 0.2063), R1 = 0.0679, wR2 = 0.1384 for > 2σ(I).


Synthesis and catalytic activity of histidine-based NHC ruthenium complexes

Angèle Monney,¹,² Galmari Venkatachalam³ and Martin Albrecht*¹,²

Histidine has been successfully used as a bio-relevant precursor for the synthesis of catalytically active ruthenium NHC complexes. The activity of the metal centre in hydrogen transfer catalysis is considerably affected by the remote C,N-protected amino acid functionality.

[Chemical structure diagram]