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6,6′-Dihydroxy terpyridine: a proton-responsive bifunctional ligand and its application in catalytic transfer hydrogenation of ketones†

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The ligand 6,6′-dihydroxy terpyridine (dhtp) is presented as a bifunctional ligand capable of directing proton transfer events with metal-coordinated substrates. Solid-state analysis of a Ru(II)-dhtp complex reveals directed hydrogen-bonding interactions of the hydroxyl groups of dhtp with a Ru-bound chloride ligand. The utility of dhtp was demonstrated by chemoselective transfer hydrogenation of ketones.

Metal–ligand cooperativity is a key aspect of H_2 activation/transfer by bifunctional catalysts. These systems exploit intramolecular proton transfer as a means to (a) store proton equivalents in the ligand periphery and/or (b) utilize the protonation/deprotonation event to modulate the structural and electronic properties of the ligand.[1] Biological systems similarly engage metal–ligand cooperativity to mediate multi-electron redox events, proton-coupled electron-transfer reactions, and substrate activation.[2] A biologically-relevant M–L platform for bifunctional activation was recently visualized following the discovery of a 2-hydroxypyridine-derived cofactor in the active site of the hydrogenase metalloenzyme, [Fe]-hmd,[3] and subsequently, synthetic transition-metal complexes supported by 2-hydroxypyridine (2-HP)-derived ligands have been demonstrated to promote (de)hydrogenation catalysis.[4] While the intimate details of the role of the 2-HP unit in [Fe]-hmd are still under investigation, the tautomeric pair 2-HP and 2-pyridone likely function to facilitate H_2 cleavage and transfer.[3b,5]

Approaches to synthetic systems that seek to emulate a cooperative H_2 activation pathway, reminiscent of [Fe]-hmd, have targeted bidentate ligand frameworks, such as bipyridine and bipyrimidine, that incorporate 2-HP units.[6] Piano-stool type complexes containing such appended 2-HP structural units have shown promising hydrogenation activity; however, the orientation of the appended OH groups with respect to the metal-bound substrate limits their utility as efficient hydrogenation catalysts due to a necessary reorganization required for H_2 heterolysis. Accordingly, we targeted hydrogen-transfer reactivity using a ligand framework that promotes directed interactions between the secondary coordination sphere environment and metal-bound substrates.

The ligand, 6,6′-dihydroxy terpyridine was selected as a rigid, pincer-based framework that enforces interactions of the ligand hydroxyl groups with metal-bound substrates, and is capable of promoting bifunctional catalysis.[7]

The tautomerism of 6,6′-dihydroxy terpyridine(dhtp) provides accessible proton donors and acceptors in the secondary coordination sphere of the metal center, when maintaining a meridonal *N,N,N*-coordination mode. The ligand binding modes of the two tautomeric forms of dhtp also present drastically different ligand fields; the hydroxy-tautomer serving as an L_3-type ligand, while the deprotonated pyridone tautomer (dhtp′) acting as an LX_2-type ligand (Fig. 1). Such proton-responsive ligand-field dependence is a common feature of catalysis involving proton-transfer events.[1c,d,8]

We targeted a straightforward synthesis of dhtp, amenable to gram quantity scalability. Because this compound was previously synthesized using F_2-derived reagents[9] and multi-step ring-closing metathesis routes,[10] we devised an alternative two-step route that proceeds from the commercially-available 6,6′-dibromo terpyridine (Scheme S1, ESI†). Palladium(II)-catalyzed coupling of 6,6′-dibromo terpyridine with sodium *tert*-butoxide afforded 6,6′-di-*tert*-butoxy terpyridine in 81% yield. Conveniently, hydrolysis of the *tert*-butoxide groups proceeds within minutes at room temperature upon addition of formic acid, and cleanly provides dhtp in 80% yield as a microcrystalline powder; the preparation can be scaled to gram quantities.

The ability of metal-dhtp adducts to promote hydrogen-transfer reactivity was probed by examining Ru(II) complexes containing PPh_3 as an auxiliary ligand. Reaction of equimolar

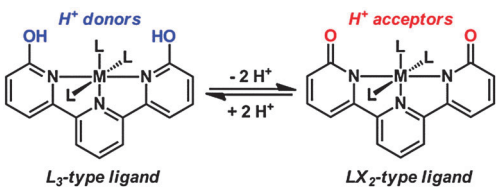

Fig. 1 Dhtp as a proton-responsive ligand.

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† Electronic supplementary information (ESI) available: Detailed synthetic and experimental procedures as well as ^1H and ^{31}P NMR spectra of **1**. CCDC 902601. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc36927c

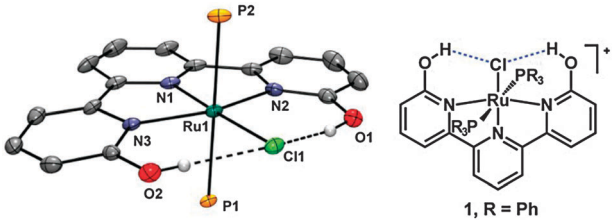


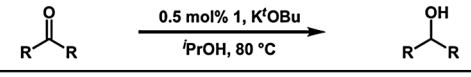
Fig. 2 Solid-state structure of **1** (30% thermal ellipsoids: hydrogen atoms not involved in hydrogen bonds, phenyl rings on PPh_3 ligands and PF^- anion omitted for clarity).‡ Selected bond distances (Å) and angles (°): Ru1-N1 1.974(3), Ru1-N2 2.129(3), Ru1-N3 2.116(3), Ru1-Cl1 2.4926(8), Ru-P1 2.4403(9), Ru1-P2 2.415(1), N2-Ru1-N3 158.05(12), N1-Ru1-Cl1 177.29(8), P1-Ru1-P2 178.31(3).

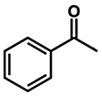
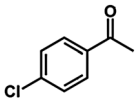
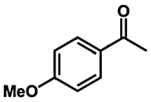
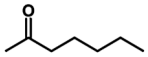
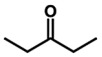
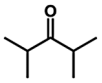
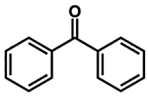
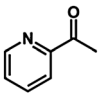
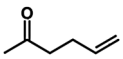
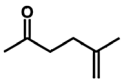
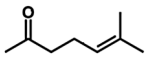
quantities of $RuCl_2(PPh_3)_3$ and dhtp in refluxing methanol under an inert atmosphere provided *trans*-RuCl(dhtp)$(PPh_3)_2PF_6$ (**1**) after anion metathesis with $[NH_4][PF_6]$. The solid state structure of **1** (Fig. 2) reveals octahedral coordination around ruthenium(II), with mutually *trans* PPh_3 ligands. Notably, both of the pendant hydroxyl groups engage in close-contact interactions to the Ru-bound chloride (O1-Cl1 and O2-Cl of 3.017(3) and 2.966(3) Å, respectively); consistent with intramolecular hydrogen-bonding interactions. Additionally the solid-state structure of **1** reveals C–O distances of the terpyridine fragment (1.336(5) and 1.335(5) Å) consistent with C–O single bonds and a neutral ligand scaffold.[11]

The orientations of the hydroxyl groups in **1** with respect to the Ru-bound chloride can be used to approximate subsequent M-substrate interactions. For a relevant comparison, Ru-based piano-stool complexes featuring 6,6′-dihydroxy bipyridine (dhbp), $[(\eta^6\text{-arene})Ru(dhbp)Cl]^+$,[6d] were selected. In **1**, the torsion angles between the Ru–Cl and C–O bond vectors are 2.93° and 4.22° (avg. 3.58°), which demonstrates that the two bond vectors lie nearly co-planar. In contrast, the torsion angles are significantly greater in the case of the dhbp adduct: 65.45° and 62.44° (arene = C_6Me_6, avg. 63.95°), and 82.71° and 82.31° (arene = *p*-cymene, avg. 82.51°). The OH···Cl interaction was further investigated by comparison of the average distances between the hydroxyl groups and the Cl atom between **1** and the $[(\eta^6\text{-arene})Ru(dhbp)Cl]^+$ complexes; 3.007 Å for **1**, 3.489 Å (arene = C_6Me_6) and 3.773 Å (arene = *p*-cymene), the former is consistent with an intramolecular hydrogen-bonding interaction. The differences in distances, as well as geometry, between hydroxyl groups and the ruthenium-bound chloride atom (a surrogate for a metal-bound hydride) suggest that the ligand geometry imposed by **1** is predisposed to offer a strongly coupled hydride/hydroxyl system for hydride and proton transfer.

To confirm the utility of the favorable orientations of the hydroxyl groups in **1**, we examined transfer hydrogenation reactivity of acetophenone using complex **1** as a catalyst. Using 0.5 mol% **1** and 10 mol% KO^{t}Bu in neat 2-propanol, acetophenone is reduced to 1-phenylethanol in nearly quantitative (98%) yield over the course of 12 hours at 80 °C (Table 1, entry 1).[12,13] Substitution of the 4-position with electron donating groups (entry 3) was found to slightly decrease hydrogenation, while electron withdrawing groups (entry 2) slightly promoted hydrogenation. Aliphatic ketones were hydrogenated with yields highly sensitive to the ketone steric environment (entries 4–6). Additionally, when benzophenone is used as a substrate no hydrogenation product is observed (entry 7). The catalytic system of **1** and KO^{t}Bu

Table 1 Scope of transfer hydrogenation catalyzed by **1** and KO^{t}Bu[a]



Entry	Substrate	Yield[b] (%)	TOF[c] (h^{-1})
1		98	82
2		100	100
3		92	42
4		100	64
5		78	66
6		17	10
7		0	0
8[d]		79	26
9[d]		57[e,f]	n.d.
10[d]		66[e]	n.d.
11[d]		95[e]	n.d.

[a] General conditions: 0.05 mmol ketone, 0.00025 mmol **1**, 0.005 mmol KO^{t}Bu, 0.500 mL ^{i}PrOH, 0.029 mmol PhTMS, 80 °C, 12 h. [b] NMR yield calculated against PhTMS internal standard. [c] TOF calculated after 2 h, TOF = 0.5 × [(mmol ketone)$_0$ − (mmol ketone)$_{t=2}$]/(mmol 1). [d] Reaction time 24 h. [e] Yield determined by GC/MS; yield of carbonyl hydrogenation product. Note other products are observed, see text. [f] 1 mol% PPh_3 added.

tolerates heteroaromatics such as 2-acetylpyridine, which can be reduced to the corresponding alcohol in good yield (79%) over 24 h (entry 8). This finding is noteworthy because the product, 1-(2-pyridinyl)ethanol, is a strongly chelating bidentate ligand,[14] which could coordinate an active hydrogenation catalyst that contains more than one accessible coordination site.

Given that one of the hallmarks of outer-sphere hydrogenation catalysts is the ability to perform chemoselective hydrogenations, we examined the transfer hydrogenation of unsaturated ketone substrates by **1** and KO^{t}Bu. Using our general conditions for transfer hydrogenation, 5-hexen-2-one is converted to a mixture of hydrogenation products with high conversion (95%) over 24 h; the ratio of 1 : 0.55 : 0.71 obtained for 5-hexen-2-ol, 2-heptanone and 2-hexanol, respectively, with a 42% yield of 5-hexen-2-ol. We hypothesized that this low observed selectivity may be due to a competitive *inner-sphere* hydrogenation pathway which could be suppressed using PPh_3. In support, addition of

1 mol% PPh_3 provided an increase in selectivity for the carbonyl hydrogenation product, giving a ratio of the aforementioned products of 1 : 0.16 : 0.30 after 24 h, with 57% yield of 5-hexen-2-ol (Table 1, entry 9).[15] This finding is consistent with suppression of an alternative, non-selective hydrogenation mechanism, however further studies are merited to elucidate the intimate details.

Based on our results illustrating a high steric dependence on hydrogenation, we hypothesized that the chemoselectivity of transfer hydrogenation by **1**/KO^{t}Bu could be further increased by introducing steric differentiation between the carbonyl and olefin groups. We tested this by performing the transfer hydrogenation of 5-methyl-5-hexen-2-one (entry 10). Transfer hydrogenation of this substrate proceeds to 81% conversion after 24 h to afford a mixture of 5-methyl-5-hexen-2-ol, 5-methyl-5-hexen-2-one and 5-methyl-5-hexen-2-ol in a 1 : 0.09 : 0.13 ratio, respectively, with a 66% yield of 5-methyl-5-hexen-2-ol. Further increasing the steric environment around the olefin provides high chemoselectivity. Transfer hydrogenation of 6-methyl-5-hexen-2-one provides 6-methyl-5-hexen-2-ol as the exclusive transfer hydrogenation product in 95% yield (entry 11). This highlights the ability of the catalytic system **1**/KO^{t}Bu to differentiate between steric environments and double bonds, and consistent with prior reports of metal-mediated bifunctional catalysis.[1b,e]

Ligand dissociation is a common initiation step for most Ru-based *inner-sphere* hydrogenation catalysts.[16] Thus, we examined whether exogenous PPh_3 hindered catalytic transfer hydrogenation mediated by **1**. We hypothesized that, for an *outer sphere* mechanism, conditions suited to suppress the loss of PPh_3 would not inhibit catalysis. Indeed, when an excess of PPh_3 (2–8 eq.) is added to the reaction mixture, the rate of transfer hydrogenation catalyzed by the **1**/KO^{t}Bu system is not significantly affected (Fig. S7, ESI†). This result suggests that PPh_3 dissociation is not involved in the rate-limiting step of transfer hydrogenation, and is consistent with a catalytically-active species that retains both PPh_3 ligands.[17] The stoichiometry of transfer hydrogenation was also examined by quantifying the formation of acetone, relative to 1-phenylethanol, during the reduction of acetophenone, which revealed that equimolar quantities of acetone and 1-phenylethanol are produced concomitantly during the transfer hydrogenation.

In conclusion, we have presented dhtp as a rigid bifunctional ligand that promotes directed interactions with metal-bound substrates, such as chloride (a surrogate for hydride). The ruthenium(II) complex **1** efficiently catalyzes the transfer hydrogenation of a variety of ketones in the presence of KO^{t}Bu in 2-propanol. High chemoselectivity was realized in the presence of substituted alkenes, and **1** selectively catalyzes the reduction of carbonyl groups in the presence of non-polar olefins. A potential catalytic cycle for this transformation may involve an outer sphere transfer of hydride/proton equivalents from the metal and ligand backbone (respectively) to a ketone substrate. Further experiments to isolate potential catalytic intermediates, as well as detailed mechanistic analyses, are currently underway.

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Notes and references

‡ Crystal data for **1**·**Et$_2$O**: $C_{55}H_{51}ClF_6N_3O_3P_3Ru$, M_w = 1145.42, Triclinic; Space group $P\bar{1}$; a = 9.8116(2), b = 13.4845(3), c = 20.0259(14) Å, α = 107.241(7)°, β = 95.644(7)°, γ = 94.671(7)°; V = 2501.09(19) Å^3; Z = 2; ρ_{calcd} = 1.521 Mg m^{-3}; F(000) 1172; Crystal size 0.13 × 0.02 × 0.02 mm^3, reflections collected: 69 525; independent reflections: 9002 [$R_{(int)}$ = 0.1001]; θ range 2.33 to 68.25°; goodness-of-fit on $F2$ 1.152; final R indices [$I > 2\sigma(I)$]: R_1 = 0.0521, wR_2 = 0.1406; R indices (all data): R_1 = 0.0546, wR_2 = 0.1434.

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13 The maximum TOF for acetophenone reduction catalyzed by **1**/KO^{t}Bu (82 h^{-1}) surpasses that observed for the [(η^6-arene)Ru(dhbp)Cl]$^+$ system (7.33 h^{-1}), however the electronic dissimilarity between the two catalysts limits the applicability of comparison based on geometry alone (see ref. 6*d*).

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15 See ESI†.

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17 The addition of Hg^0 (*ca.* 1.4 × 10^4 eq.) during transfer hydrogenation has no effect on the reaction profile. The mercury poisoning experiment, as well as the highly reproducible reaction kinetics (see SI) provide evidence consistent with a homogeneous ruthenium catalyst: see J. A. Widegren and R. G. Finke, *J. Mol. Catal. A: Chem.*, 2003, **198**, 317–341.

