ChemComm

COMMUNICATION

View Article Online
View Journal

Cite this: DOI: 10.1039/c6cc10206a

Received 23rd December 2016,
Accepted 25th January 2017

DOI: 10.1039/c6cc10206a

rsc.li/chemcomm

Second sphere ligand modifications enable a recyclable catalyst for oxidant-free alcohol oxidation to carboxylates†

Eric W. Dahl, Thomas Louis-Goff and Nathaniel K. Szymczak*

Modification of the classic terpyridine pincer ligand with pendent NHR (R = mesityl) groups provides enhanced activity and stability in Ru-catalyzed dehydrogenation catalysis. These second sphere modifications furnish highly active catalysts for the oxidant-free dehydrogenative oxidation of primary alcohols to carboxylates and facilitate catalyst recycling.

Although the (re)development of homogeneous catalysts most commonly relies on steric/electronic changes to ligands that are directly coordinated to the metal, modifications that extend beyond the metal's primary sphere can provide additional opportunities for reaction tuning. Changes to a ligand's secondary environment can promote enhanced substrate activation, or alternatively be used to stabilize high-energy intermediates.[1] These principles are widely used in hydrogenase and dehydrogenase enzymes,[2] yet are underutilized in synthetic systems. Our group[3] and others[4] are working to uncover how these key design features can be rationally adapted to enhance synthetic hydrogenation and dehydrogenation catalysis.

Dehydrogenative alcohol oxidation has recently emerged as a new synthetic strategy to access carboxylates that avoids the use of stoichiometric oxidants and generates H_2 as a reduced byproduct.[5] Stability toward water, a common catalyst poison[6] and the source of one of the oxygen atoms in the product, is a challenge for catalyst development. Of the few reported examples of this reaction, most incorporate ligands known to facilitate 'metal–ligand cooperative' pathways;[5a–d,i] however, the general metal–ligand properties needed for this transformation have not been elucidated.

We previously introduced Ru complexes based on 6,6″-dihydroxy-terpyridine (dhtp), which contain design elements reminiscent of the active site of [Fe]-hydrogenase and promote transfer hydrogenation catalysis.[2b,3a,b] We found that although addition of pendent –OH groups increased catalyst activity compared to unsubstituted terpyridine (tpy), it also imparted new decomposition pathways. During catalysis, a kinetically inert aquo-bridged dimer formed that assembled through hydrogen bonds (H-bonds) between the appended hydroxyl groups and adventitious H_2O.[3a] This decomposition route highlights one of the challenges in the field of ligand (re)design: targeted ligand modifications can impact unforeseen and sometimes deleterious characteristics of a metal complex, even from a deceptively simple arrangement in the precatalyst.

We hypothesized that increasing the steric profile of the ligand's secondary sphere would prevent the formation of higher nuclearity aggregates and thus impart greater catalyst stability for hydrogenation and dehydrogenation reactions, particularly in the presence of water or hydroxide. Herein, we introduce a new ruthenium complex based on the 6,6″-bis(mesitylamino)-terpyridine (H_2Tpy^{NMes}) ligand,[7] and show that sterically

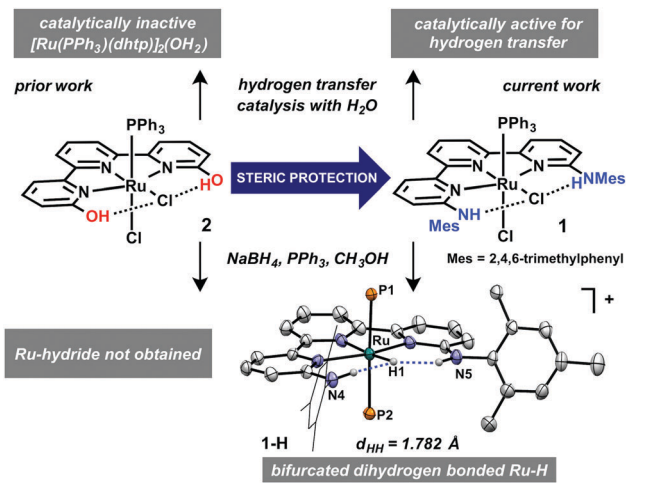


Fig. 1 Reactivity of Ru-tpy derivatives and X-ray structure of **1-H** (30% ellipsoids, H atoms not involved in H-bonding, PPh_3 and PF_6^- omitted for clarity).

Department of Chemistry, University of Michigan, 930 N. University Ave., Ann Arbor, MI 48108, USA. E-mail: nszym@umich.edu

† Electronic supplementary information (ESI) available: Synthetic and experimental procedures and spectral data. CCDC 1523509 and 1523510. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6cc10206a

encumbering mesityl amino groups impart unique stabilization of previously inaccessible Ru–H species. This new catalyst overcomes the decomposition pathway of related complexes and provides enhanced catalyst activity and stability in hydrogen transfer reactions containing water, including the oxidant-free dehydrogenative oxidation of primary alcohols to carboxylates.

The ruthenium complex $Ru(H_2Tpy^{NMes})(PPh_3)Cl_2$ (**1**) features an identical primary coordination environment compared to similar tpy and dhtp complexes, yet provides sterically protected –NH groups. Complex **1** was isolated as a purple powder from the reaction of $Ru(PPh_3)_3Cl_2$ with H_2Tpy^{NMes} in refluxing toluene for 18 h. Analogous *cis*-$Ru(L)(PPh_3)Cl_2$ complexes, where L = dhtp (**2**)[3a] and tpy (**3**),[8] were similarly prepared for comparative studies. The ^{31}P NMR spectra of **1–3** contain resonances at δ = 44.2, 45.9, and 43.1 respectively, consistent with similar ligand fields imposed on Ru by all tpy variants. The solid-state structure of **1** (see the ESI†) contains an equatorially bound chloride engaged in H-bonding interactions with the pendent –NH groups (average N–Cl distance = 3.07 Å). H-Bonding interactions were further evaluated by ^1H NMR spectroscopy. The ^1H NMR spectrum of **1** contains a resonance for the –NH groups at δ = 10.56 in $CDCl_3$, significantly downfield of the free ligand –NH (δ = 6.08), consistent with an H-bonding interaction with the chloride ligand. These data indicate that the –NH groups in **1** provide sterically protected H-bond donor groups in the secondary sphere that may be used to stabilize the reactive intermediates.

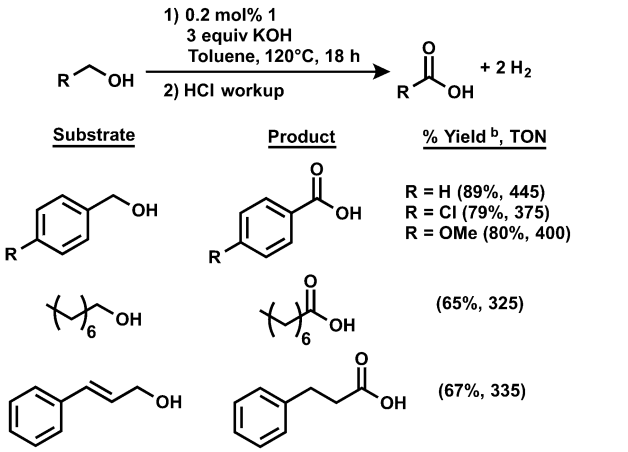
The pendent amine groups in the H_2Tpy^{NMes} ligand provide unique stabilization of a Ru-hydride. The reaction of **1** with PPh_3 and $[NH_4][PF_6]$ followed by $NaBH_4$ in CH_3OH afforded $[Ru(H_2Tpy^{NMes})(PPh_3)_2H]PF_6$ (**1-H**) after 48 h at room temperature (Fig. 1). This complex contains a Ru–H moiety that engages the pendent mesityl amino –NH groups in H-bonding interactions. Under identical reaction conditions, no Ru–H species were obtained when the H_2Tpy^{NMes} ligand was replaced with dhtp. Complex **1-H** contains a rare example of a bifurcated dihydrogen bond[3c,9] and was characterized in the solid- and solution-state. Within the crystal structure, H-atoms involved in dihydrogen bonding were located in the difference map and exhibited asymmetric dihydrogen bond lengths of 1.99 Å and 1.86 Å (average 1.92 Å). Due to the uncertainty of H–H distances obtained from X-ray diffraction, an ^1H NMR experiment was used to augment the XRD data. The ^1H NMR spectrum of **1-H** contains a Ru–H resonance at δ = −6.76 (t, J_{HP} = 21 Hz) in CD_2Cl_2. Evaluation of through-space dipole–dipole induced nuclear spin relaxation contributions[10] of the Ru–H afforded a dihydrogen bond distance of 1.78 Å at 283 K, consistent with persistent H-bonding interactions in solution.

One manifestation of the sustained H–H interactions in **1-H** is the lack of H/D exchange for either the Ru–H or the pendent –NH groups in the presence 100 equiv. D_2O after 24 h at 25 °C. For comparison, the free ligand (H_2Tpy^{NMes}) underwent complete H/D exchange of the –NH within three minutes under the same conditions. To the best of our knowledge, this is the first example of a dihydrogen bonded metal-hydride resistant to H/D exchange. The isolation of a H_2O stable Ru–H species with H_2Tpy^{NMes} highlights the stabilization imparted by incorporating bulky amine groups. We hypothesized that such stabilization could be exploited for enhanced stability in hydrogen transfer catalysis.

The appended amine donors in **1** dramatically improve both ketone transfer hydrogenation activity and catalyst stability. Heating a 500 μL ^iPrOH solution containing 0.05 mmol acetophenone, 0.05 mol% **1**, and 1 mol% KO^tBu in an NMR tube under N_2 at 40 °C for 24 h provided 1-phenylethanol in 95% yield (1900 TON). Catalyst stability toward H_2O was also enhanced. When reactions were heated to 80 °C for 12 h with 5% (w/v) exogenous H_2O, a minor drop in yield from 69% (1380 TON) to 56% (1120 TON) 1-phenylethanol was observed for **1**. In contrast, complex **2**, which contains *ortho*-OH, rather than –NH(Ar) groups showed a dramatic decrease in yield from 34% (680 TON) to 2% (40 TON) upon addition of H_2O. The transfer hydrogenation studies illustrate that a simple substitution of the pendent groups can have a dramatic effect on catalyst stability. Furthermore, the ability to operate in the presence of H_2O allows access to hydrogen transfer reactions that use H_2O as a reaction component/intermediate.

1 catalyzes the dehydrogenative oxidation of primary alcohols to carboxylates, a reaction that uses H_2O rather than stoichiometric oxidants. Aromatic and aliphatic primary alcohols are oxidized to their corresponding carboxylates in moderate to high yields (Table 1). Standard reaction conditions employed a 20 mL vial containing 0.5 mmol alcohol, 1.5 mmol KOH, 0.2 mol% **1**, and 2 mL toluene heated to 120 °C for 18 hours. After the reaction, the carboxylate product was isolated as the carboxylic acid following an acidic workup. The substrate, cinnamyl alcohol, containing both a primary alcohol and an olefin, was oxidized and hydrogenated to 3-phenylpropionic acid as the major product consistent with hydrogen transfer (hydrogen borrowing) from the alcohol to the internal olefin.[11] Functional group tolerance was evaluated by a substrate robustness screen.[12] We found that **1** tolerates thiophenes (62%), pyrroles (57%), pyridines (51%) and, to a lesser degree, furans (31%). The functional groups tolerated by **1** demonstrate the broader utility of this approach for alcohol oxidation.

Table 1 Dehydrogenative alcohol oxidation by **1**[a]



[a] Conditions: 0.5 mmol alcohol, 1.5 mmol KOH, 0.001 mmol **1**, 2 mL toluene, 120 °C, 18 h. HCl workup affords carboxylic acid. [b] Isolated yield.

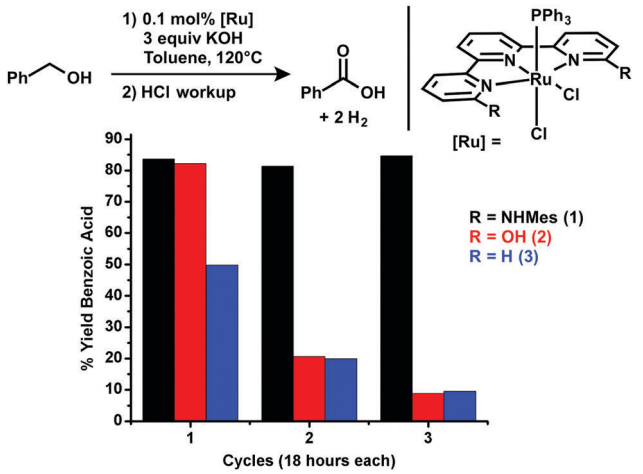


Fig. 2 Catalyst recycling experiments with **1**, **2**, and **3**. Yields calculated by GC and are the average of two independent runs.

One of the decomposition pathways that hindered hydrogen transfer reactions with **2** (formation of multinuclear aggregates) was overcome using **1** and demonstrated through catalyst recycling experiments. Catalysts **1–3** were subjected to three cycles of dehydrogenative oxidation of benzyl alcohol to assess the overall catalyst stability (Fig. 2). Complexes **2** and **3** show significant loss in activity over three cycles (total TON = 1120 and 790, cycle three = 9% and 10% yield, respectively). In contrast, the stability provided by the secondary mesityl amino groups in **1** allows for a fully recyclable catalyst (total TON = 2500, cycle three = 85% yield). These data illustrate that catalytic stability across a series of otherwise structurally analogous complexes is dramatically affected by modifications to the metal's secondary coordination sphere environment.

In conclusion, we have demonstrated that the simple substitution from –H to –OH to –NH(Ar) in the secondary sphere of the terpyridine framework can impart dramatic improvements in catalyst lifetime and activity for Ru-catalyzed hydrogen transfer reactions. This study outlines a design principle to use steric protection around polar secondary groups to stabilize reactive Ru–H intermediates and circumvent catalyst decomposition to impart markedly improved stability and activity for hydrogen transfer reactions. Further efforts will focus on the mechanistic underpinnings that govern these reactivity trends.

This work was supported by an NSF-CAREER grant (CHE-1350877) and an NSF grant CHE-0840456 for X-ray instrumentation. N. K. S. is an Alfred P. Sloan Research Fellow and a Camille Dreyfus Scholar. We thank Dr Jeff W. Kampf for X-ray assistance, and Dr Cameron M. Moore for helpful discussions.

Notes and references

1 (*a*) S. Werkmeister, J. Neumann, K. Junge and M. Beller, *Chemistry*, 2015, **21**, 12226–12250; (*b*) J. R. Khusnutdinova and D. Milstein, *Angew. Chem., Int. Ed. Engl.*, 2015, **54**, 12236–12273; (*c*) A. S. Borovik, *Acc. Chem. Res.*, 2005, **38**, 54–61; (*d*) M. R. DuBois and D. L. DuBois, *Chem. Soc. Rev.*, 2009, **38**, 62–72; (*e*) M. Zhao, H.-B. Wang, L.-N. Ji and Z.-W. Mao, *Chem. Soc. Rev.*, 2013, **42**, 8360–8375; (*f*) J. Rosenthal and D. G. Nocera, *Acc. Chem. Res.*, 2007, **40**, 543–553.

2 (*a*) W. Lubitz, H. Ogata, O. Rüdiger and E. Reijerse, *Chem. Rev.*, 2014, **114**, 4081–4148; (*b*) C. M. Moore, E. W. Dahl and N. K. Szymczak, *Curr. Opin. Chem. Biol.*, 2015, **25**, 9–17; (*c*) A. Dołga, *Coord. Chem. Rev.*, 2010, **254**, 916–937.

3 (*a*) C. M. Moore, B. Bark and N. K. Szymczak, *ACS Catal.*, 2016, **6**, 1981–1990; (*b*) C. M. Moore and N. K. Szymczak, *Chem. Commun.*, 2013, **49**, 400–402; (*c*) J. B. Geri and N. K. Szymczak, *J. Am. Chem. Soc.*, 2015, **137**, 12808–12814; (*d*) K.-N. T. Tseng, J. W. Kampf and N. K. Szymczak, *J. Am. Chem. Soc.*, 2016, **138**, 10378–10381.

4 (*a*) G. Zeng, S. Sakaki, K.-I. Fujita, H. Sano and R. Yamaguchi, *ACS Catal.*, 2014, **4**, 1010–1020; (*b*) K.-I. Fujita, R. Kawahara, T. Aikawa and R. Yamaguchi, *Angew. Chem., Int. Ed.*, 2015, **54**, 9057–9060; (*c*) K.-I. Fujita, W. Ito and R. Yamaguchi, *ChemCatChem*, 2014, **6**, 109–112; (*d*) K.-I. Fujita, Y. Tanaka, M. Kobayashi and R. Yamaguchi, *J. Am. Chem. Soc.*, 2014, **136**, 4829–4832; (*e*) W.-H. Wang, J. T. Muckerman, E. Fujita and Y. Himeda, *New J. Chem.*, 2013, **37**, 1860–1866; (*f*) S. Chakraborty, P. E. Piszel, W. W. Brennessel and W. D. Jones, *Organometallics*, 2015, **34**, 5203–5206; (*g*) D. DiMondo, M. E. Thibault, J. Britten and M. Schlaf, *Organometallics*, 2013, **32**, 6541–6554; (*h*) I. Nieto, M. S. Livings, J. B. Sacci, L. E. Reuther, M. Zeller and E. T. Papish, *Organometallics*, 2011, **30**, 6339–6342; (*i*) Y. Suna, M. Z. Ertem, W.-H. Wang, H. Kambayashi, Y. Manaka, J. T. Muckerman, E. Fujita and Y. Himeda, *Organometallics*, 2014, **33**, 6519–6530.

5 (*a*) T. Zweifel, J. V. Naubron and H. Grutzmacher, *Angew. Chem., Int. Ed.*, 2009, **48**, 559–563; (*b*) P. Sponholz, D. Mellmann, C. Cordes, P. G. Alsabeh, B. Li, Y. Li, M. Nielsen, H. Junge, P. Dixneuf and M. Beller, *ChemSusChem*, 2014, **7**, 2419–2422; (*c*) L. Zhang, D. H. Nguyen, G. Raffa, X. Trivelli, F. Capet, S. Desset, S. Paul, F. Dumeignil and R. M. Gauvin, *ChemSusChem*, 2016, **9**, 1413–1423; (*d*) J. H. Choi, L. E. Heim, M. Ahrens and M. H. Prechtl, *Dalton Trans.*, 2014, **43**, 17248–17254; (*e*) J. Malineni, H. Keul and M. Moller, *Dalton Trans.*, 2015, **44**, 17409–17414; (*f*) H. Li and M. B. Hall, *J. Am. Chem. Soc.*, 2014, **136**, 383–395; (*g*) C. Santilli, I. S. Makarov, P. Fristrup and R. Madsen, *J. Org. Chem.*, 2016, **81**, 9931–9938; (*h*) Z. Dai, Q. Luo, X. Meng, R. Li, J. Zhang and T. Peng, *J. Organomet. Chem.*, 2017, **830**, 11–18; (*i*) E. Balaraman, E. Khaskin, G. Leitus and D. Milstein, *Nat. Chem.*, 2013, **5**, 122–125.

6 R. H. Crabtree, *Chem. Rev.*, 2015, **115**, 127–150.

7 E. W. Dahl and N. K. Szymczak, *Angew. Chem., Int. Ed.*, 2016, **55**, 3101–3105.

8 B. P. Sullivan, J. M. Calvert and T. J. Meyer, *Inorg. Chem.*, 1980, **19**, 1404–1407.

9 S. Park, R. Ramachandran, A. J. Lough and R. H. Morris, *J. Chem. Soc., Chem. Commun.*, 1994, 2201–2202.

10 P. J. Desrosiers, L. Cai, Z. Lin, R. Richards and J. Halpern, *J. Am. Chem. Soc.*, 1991, **113**, 4173–4184.

11 Although a hydrogen borrowing mechanism is consistent with our data, isomerization of cinnamyl alcohol is an alternative plausible route to 3-phenyl propionic acid.

12 K. D. Collins and F. Glorius, *Nat. Chem.*, 2013, **5**, 597–601.