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Phosphine-imine and-enamido ligands for acceptorless dehydrogenation catalysis

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A highly tunable phosphine-imine ligand family is introduced. Following metallation with ruthenium, deprotonation of the ligand affords a phosphine-enamido species. Complexes with the ligand in both the imine and enamido forms are active toward acceptorless dehydrogenation reactions.

Metal-ligand cooperative (MLC) catalysts[1-3] give chiral alcohols and amines by hydrogenation,[4, 5] and carboxylic acids, esters, amides and imines by acceptorless dehydrogenation reactions.[6, 7] These catalysts contain an acid/base site on the ligand that shuttles protons to or from the metal active site. In the highly successful Milstein-type catalysts (Figure 1), the driving force for protonation is ligand aromatization to give a central pyridyl moiety.[7-14] However, aromatization is not essential since acceptorless dehydrogenation is achieved with phosphine enamido complexes that give non-aromatic imine moieties on ligand protonation.[15-17] H_2 activation reactions confirm that a cooperative pathway is accessible. Since relatively few phosphine enamido catalysts have been studied, the extent to which non-aromatic systems follow cooperative pathways is unknown. Additionally, the performance of the known phosphine-enamido catalysts is limited, thus improvements in catalyst design are warranted. We report here a new ligand family that contains phosphine and imine moieties, and deprotonation gives a phosphine-enamido species. Catalytic performance of complexes with the ligand in both enamido and imine forms is evaluated.

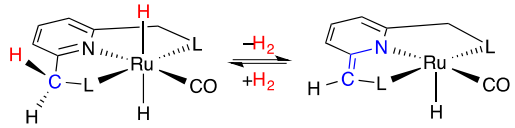
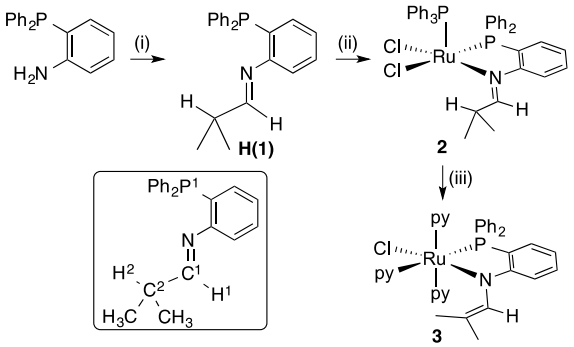


Figure 1. Cooperative H_2 formation and activation with a general Milstein pincer catalyst, showing aromatic pyridyl and dearomatized enamido species.

The phosphine-imine pro-ligand, **H(1)** was obtained on condensation of 2-diphenylphosphinoaniline with isobutyraldehyde (Scheme 1). Formation of **H(1)** is evident from a ca. 5 ppm downfield shift of the ^{31}P resonance relative to the starting material. The alpha-imine proton (H^1; see Scheme 1 for label assignments) is found at 7.29 ppm as confirmed by a ^1H-^1H COSY NMR correlation to the unique isopropyl proton (H^2).

Scheme 1. Synthesis of ligand **H(1)**, and Ru complexes **2** and **3**.[a]



[a] Reaction conditions: (i) 2 equiv. isobutyraldehyde, 5% formic acid, toluene, RT, 24 h, 72% yield; (ii) $RuCl_2(PPh_3)_3$, THF, RT, 2 h, 70% yield. (iii) 1.15 equiv. $Li[N(SiMe_3)_2]$, pyridine, RT, 2 h, 85% yield (95% purity).

Treatment of $RuCl_2(PPh_3)_3$ with **H(1)** in THF results in a colour change from purple to green (Scheme 1), consistent with a switch to a weaker-field donor (i.e. PPh_3 to imine). Isolation and analysis by $^{31}P\{^1H\}$ NMR spectroscopy revealed a set of two doublets at δ_P 89.0 and 46.0 for the phosphine atoms of **H(1)** and PPh_3 ligands, respectively. The coupling constant ($^2J_{PP}$ = 35 Hz) indicates a cis disposition.[18] Crystallization from DMF gives an octahedral solvent adduct (Figure 2a) where the N-C1 bond length of 1.285(4) Å is in the expected range for an imine moiety.

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Addition of pyridine to **2** resulted in an immediate colour change from green to amber (presumably due to the 6-coordinate solvate) and a change to red occurred on addition of one equivalent of the base Li[N(SiMe$_3$)$_2$] (Scheme 1). X-ray diffraction of the octahedral product **3** shows ligand **1** is bound in a bidentate κ^2-PN fashion (Figure 2b). Deprotonation to give an enamido is indicated by an increase of the N-C1 bond length by 0.12 Å and a decrease in the C^1-C^2 distance by 0.06 Å versus the imine complex **2**. The planarity about C^2 in **3** further confirms the sp^2 nature of this centre. In the solution state, **3** is characterized by a singlet in the ^{31}P{^{1}H} NMR spectrum at δ 71.6, ca. 17 ppm upfield of the analogous signal in **2**. The signal for C^2 (δ_C 118.8) is shifted 82 ppm downfield relative to **2**, a location diagnostic for a κ^1-N enamido.[16, 17, 19, 20] Deprotonation is accompanied by halide abstraction of one chloride ligand, giving LiCl as a byproduct, and pyridine occupies the vacated coordination site.

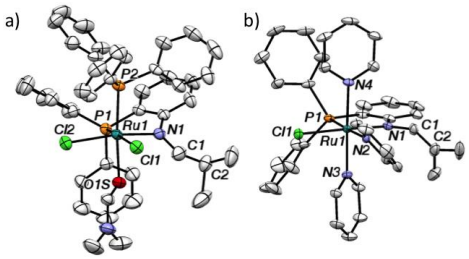

Figure 2. Displacement ellipsoid diagrams of a) **2** as a DMF solvate (CCDC 1470534); and b) **3** (CCDC 1470535). Ellipsoids are shown at 50% probability and hydrogen atoms are removed for clarity. Selected bond lengths for: **2** = Ru-P1 2.2403(10), Ru-N1 2.087(2), N1-C1 1.285(4), C1-C2 1.396(5); **3** = Ru-P1 2.2406(14), Ru-N1 2.091(4), N1-C1 1.400(6), C1-C2 1.332(7).

Acceptorless dehydrogenation (AD) of benzyl alcohol (BnOH; Scheme 2) can directly give benzaldehyde (**A**) or an ester (**B**), which is formed via nucleophilic attack of **A** by additional alcohol, followed by a second AD step.[21] Dehydrogenation of BnOH with **3** (1 mol%) over 48 h gave **A** as the sole product in 33% yield (Table 1, Entry 2). Increasing the catalyst loading gives marginal improvement with a 46% yield (Entry 3). Under the same conditions, phosphine-imine complex **2** gave only minimal (7%) conversion (Entry 4). Surprisingly, 54% conversion is achieved on halide-abstraction from **2** with KPF_6 (Entry 5). Aldehyde **A** is the major product, but mass balance is not achieved indicating a side reaction does occur. Since the ligand in **2** is already in the protonated imine form it cannot mediate a concerted MLC dehydrogenation of BnOH. Likely, **2** operates via a non-MLC mechanism and this raises the possibility that **3** may also follow a non-MLC pathway. In addition to KPF_6, pyridine was added to **2** to more closely mimic the ancillary ligands of **3** (Entry 6). Poor turnover was observed suggesting the added pyridine inhibits substrate binding to the catalyst. In situ treatment of **2** with Li[N(SiMe$_3$)$_2$] likely gives a species analogous to **2**/KPF_6, except the ligand is deprotonated to the phosphine-enamido form. This is supported by the similar performance of **2**/Li[N(SiMe$_3$)$_2$] and the isolated phosphine-enamido complex **3** (Entry 7). Monitoring the three best catalysts (**3**; **2**/KPF_6; **2**/Li[N(SiMe$_3$)$_2$]) over time revealed that maximum conversion is reached within 24 h and no obvious induction period is observed (ESI).

Scheme 2. Acceptorless Dehydrogenation (AD) of benzyl alcohol (BnOH) to give aldehyde (**A**) or ester (**B**) products.[a]

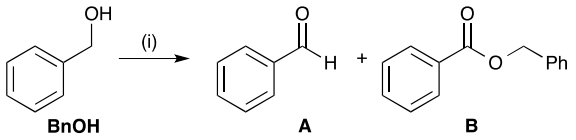

Table 1. Catalyst comparison and optimization for AD of **BnOH** with **2** and **3**.[a]

Entry	[Ru] (mol%)	Additive	Conv. (%)	%A	%B
1	**3** (0.1)	-	3	3	0
2	**3** (1)	-	34	33	0
3	**3** (5)	-	49	46	1
4	**2** (5)	-	7	3	0
5	**2** (5)	KPF_6[b]	54	27	2
6	**2** (5)	Py[c] + KPF_6[b]	17	12	0
7	**2** (5)	Li[N(SiMe$_3$)$_2$][b]	59	44	1

[a] Conditions: (i) BnOH (250 mM), Tetralin (120 mM), toluene (0.5 mL), 100 ˚C, 48 h. Substrate conv. and product yields were determined by analysis of reaction samples (diluted to 20 mM) by calibrated GC-FID, values are an average of 2 or 3 runs and errors are <±5%. [b] 5 mol% relative to BnOH. [c] 15 mol% relative to BnOH.

Acceptorless dehydrogenative coupling (ADC) of BnOH with benzyl amine ($BnNH_2$; Scheme 3) is known to give different products depending on the nature of the catalyst.[21, 22] AD of BnOH gives aldehyde **A**, which undergoes coupling with $BnNH_2$ to give imine **C** with release of H_2O. Rehydrogenation of the imine gives amine **D** via a hydrogen-borrowing pathway. Alternatively, imine **C** can be formed through dehydrogenation of $BnNH_2$ and coupling with a second amine equivalent.[23, 24] Or a double AD of $BnNH_2$ gives nitrile **E**.[25-27] The intermediate hemiaminal on route to **C** (from ACD of BnOH with $BnNH_2$) can undergo a second AD to give amide **F**. ADC of BnOH and $BnNH_2$ was assessed with 5 mol% the three catalysts: **3**, **2**/Li[N(SiMe$_3$)$_2$] and **2**/KPF_6 (Table 2). Catalyst **3** consumed all of the starting amine and nearly half of the alcohol (Table 2, Entry 1) to give a mixture of aldehyde (**A**), imine (**C**) and nitrile (**E**) in a 1:3:2 ratio. The consumption values and prevalence of **C** and **E** suggests that AD of $BnNH_2$ competes with that of BnOH. This is contrary to nearly all reported catalysts for this reaction that favour reaction with alcohol over amine. Only one reported system preferentially dehydrogenates amines over alcohols.[23] This feature of catalyst **3** could be exploited through future ligand derivatives that may further improve selectivity. In situ generation of the phosphine-enamido catalyst (**2**/Li[N(SiMe$_3$)$_2$]) gives a very similar selectivity profile to **3** (Entry 2). On the other hand, the phosphine-imine catalyst (**2**/KPF_6; Entry 3) consumes nearly equal amounts of BnOH and $BnNH_2$ to give **A**, **C** and **E** in a 2:1:2 ratio. While the limited selectivity of the catalysts precludes application to other substrates, the product distribution provides some insight into the catalyst performance. Notably, the distinct selectivity between the phosphine-imine catalyst and the phosphine-enamido catalysts suggests different dehydrogenation

pathways are dominant when the ligand is in the protonated or deprotonated forms.

Scheme 3. Possible products from acceptorless dehydrogenative coupling (ADC) of BnOH and $BnNH_2$.[a]

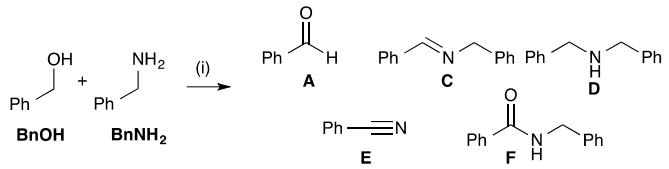

Table 2. Catalyst performance in the dehydrogenation of BnOH and/or $BnNH_2$.[a]

			Conv. (%)[b]		Yield (%)[b]				
Entry	[Ru]	Additive	**BnOH**	**$BnNH_2$**	**A**	**C**	**D**	**E**	**F**
1	**3**	-	40	100	10	31	0	20	0
2	**2**	Li[N(SiMe$_3$)$_2$][c]	32	96	1	29	1	34	0
3	**2**	KPF_6[c]	76	86	24	12	3	26	0
4	**3**	-	-	87	-	46	0	41	-
5	**2**	Li[N(SiMe$_3$)$_2$][c]	-	91	-	25	0	33	-
6	**2**	KPF_6[c]	-	98	-	57	0	35	-

[a] Conditions: (i) BnOH (250 mM), $BnNH_2$ (250 mM), Tetralin (120 mM), 5 mol% [Ru], toluene (0.5 mL), 100 ˚C, 48 h. [b] Substrate consumption and product yields were determined by analysis of reaction samples (diluted to 20 mM) by calibrated GC-FID, values are an average of 2 or 3 runs and errors are <±5%. [c] 1 equiv. relative to **2**.

All three catalysts give nearly quantitative conversion toward the dehydrogenation of benzylamine to give imine (**C**) or nitrile (**E**) (Table 2, Entries 4-6). Phosphine-enamido **3** gives a 1:1 mixture of the two products while phosphine-imine **2** gives the imine as the preferred product in nearly a 2:1 ratio. None of the catalysts are capable of the hydrogen borrowing reaction, despite that these reactions were conducted in sealed containers, suggesting H_2 release (whether through an MLC or non-MLC mechanism) from the catalyst is favourable. This is supported by the fact that the reverse reaction, addition of H_2 to **3** at 75 ˚C, does not proceed over prolonged times (ESI). All three catalysts generate nitrile **E**, an uncommon AD product. Selective formation of **E** is found only for a small group of catalysts that operate via a non-MLC mechanism.[25-27]

Conclusions

A new phosphine-imine ligand family is presented with **H(1)** as the first entry. A ruthenium complex (**2**) with **H(1)** can be deprotonated to give a phosphine enamido complex (**3**) that is analogous to known cooperative catalysts. Compound **3** is an active acceptorless dehydrogenation catalyst, showing preferential reaction with amines over alcohols. Phosphine-imine **2** is inactive, but halide abstraction or ligand deprotonation both give an active catalyst, which likely operates through a non-cooperative mechanism. The synthetic accessibility of the ligand in both imine and enamido forms suggests cooperative proton shuttling is feasible without ligand aromatization as a driving force. However, the catalytic competency of the phosphine-imine complex raises the possibility that, non-cooperative mechanisms may be operative and they will be considered in due course.

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