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DOI: 10.1039/C8CC10315A

Journal Name

COMMUNICATION

Aldehyde Effect and Ligand Discovery in Ru-Catalyzed Dehydrogenative Cross-Coupling of Alcohols to Esters

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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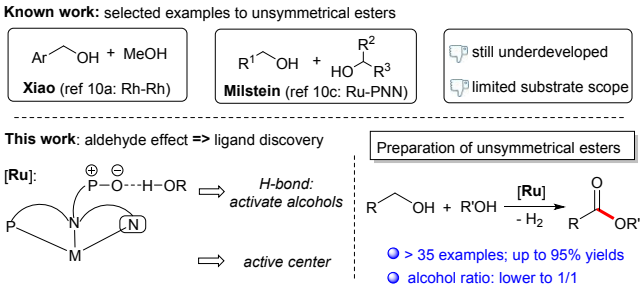
The presence of different aldehydes is found to have significant influence on the catalytic performance when using PN(H)P type ligands for dehydrogenation of alcohols. Accordingly, the hybrid multi-dentate ligands were discovered based on an oxygen-transfer alkylation of PNP ligands by aldehydes. The relevant Ru-PNN(PO) system provided desired unsymmetrical esters in good yields via acceptorless dehydrogenation of alcohols. Hydrogen bonding interactions between the phosphine oxide moieties with alcohol substrate likely assisted the observed high chemoselectivity.

Ester functional groups figure widely in both natural and synthetic compounds, and unsymmetrical esters are of important relevance to industrial commodities in foods, fragrance, pharmaceuticals and material sciences.[1,2] Traditional esterification methods are generally reliant on reaction of acids/aldehydes or their derivatives with alcohols, most of which use strong acid promoters or stoichiometric amounts of oxidants,[3,4] amongst other methods including Tishchenko and carbonylation reactions.[5] As a clean and convenient approach with hydrogen gas as sole by-product, acceptorless dehydrogenations of alcohols (ADA) for ester preparation have been recently developed.[6] In this regard, many types of phosphine/nitrogen ligands were developed for transition metal-catalyzed alcohol dehydrogenations.[7-10] To the best of our knowledge, efficient and general preparation of unsymmetrical esters remains illusive (Scheme 1).[10a,c]

Herein, we report a Ru-catalyzed highly selective dehydrogenative cross-coupling of alcohols to esters using serendipitously discovered phosphine oxide containing ligands based on the aldehyde effect in metal-pincer ligand catalysis. The introduction of phosphine oxide moiety accelerated the rate of alcohol dehydrogenation and in situ NMR showed the specific interaction of phosphine oxide moiety with alcohol substrate molecules leading to preparation of unsymmetrical esters with low excess amounts (1-15 equiv.) of the other alcohol substrate.

Ligand development is key for the transition metal-based catalysis regarding to both reactivity and selectivity. Phosphine oxides are strong electron donors with high dipole moment and known to engage in substantial hydrogen bonding interactions with alcohols,[11a] which have been applied to improve column separation efficiency in gas chromatography.[11b] Hence, we envisaged that the introduction of phosphine oxide moiety into PNN ligand would bring alcohol substrates closer to the active metal center and hence lead to higher reactivity (Scheme 1).

Scheme 1. Design of phosphine oxide ligands for selective preparation of unsymmetrical esters.



It is well known that the use of Ru-PNP catalyst for redox reactions of alcohols often generates aldehyde intermediates. Moreover, PN(sp^2)P pincer ligands can react with aldehydes through C-C bond formation.[12] *In order to ascertain possible side reactions and ligand degradation caused by the generated aldehydes*, we deliberately introduced aldehydes into the reaction as control experiments when using PN(H)P ligands. It was noticed that the reactivity and chemoselectivity had been influenced and hence we suspected an *in-situ* ligand structural modification via *N*-alkylation procedure.

Accordingly, we discovered that intramolecular reduction of the formed iminium intermediate by phosphine afforded (PNN(PO)) type ligands.[13] Specifically, new hybrid phosphine-phosphine oxide ligands **L3** and **L4** were synthesized through the

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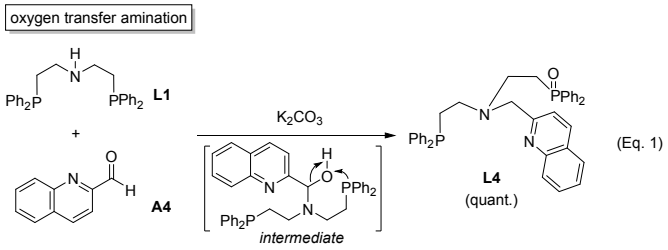
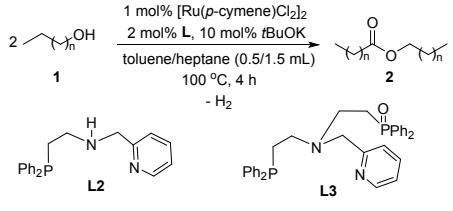
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

reaction of PNP^{Ph} ligand **L1** with picolinaldehyde (**A1**) and 2-quinolinecarboxaldehyde (**A4**), respectively (Eq. 1 for **L4**).



The newly prepared ligands, **L1** and the PNN ligand **L2** were tested *in situ* in the Ru-catalyzed dehydrogenative coupling of aliphatic alcohols (Scheme 2). To our delight, significant reactivity promotion was observed when using phosphine oxide ligand **L3** or **L4** based catalysts.[14] Much higher reactivity (up to 93% yield for reactions of 1-hexanol) was observed with **L3** and **L4** compared to **L1** and **L2** under same reaction conditions. Specifically, when quinoline-containing **L4** was used, the catalyst was found sensitive to the acidity of alcohol substrates and clear reactivity distinction could be obtained for 1-butanol *versus* 1-hexanol (15% *vs* 93% yield, Scheme 2).[15]

Scheme 2. Screening of new hybrid phosphine oxide ligands.



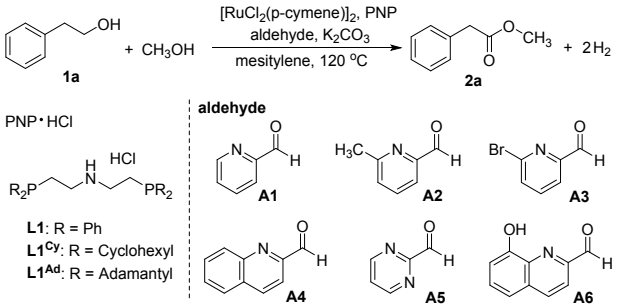
yield (%, **2**) / L / alcohol	L1	L2	L3	L4
	18	3	10	15
	21	22	41	88
	24	7	86	93

Encouraged by these initial results, we attempted to expand the repertoire of these ligands based on the intramolecular oxygen transfer amination procedure. We then developed a rapid screening method for these new ligands through an *in situ* preparation pathway by simply adding selected aldehydes to the reaction mixture. And, there is no need any more to synthesize all the phosphine oxide ligands from reaction of HCl salts of PNP ligands (PNP^{Ph}, **L1**; PNP^{Cy}, **L1**^{Cy} and PNP^{Ad}, **L1**^{Ad}) with selected aldehydes (**A1**-**A6**). Thus, we carried out Ru-catalyzed dehydrogenative coupling reaction of 2-phenylethanol (**1a**) with methanol in the absence/presence of aldehyde additives (Table 1).

We observed that the addition of different aldehydes clearly affected reactivity of alcohol substrates. Initially, Ru-catalyzed reaction with PNP^{Ph}, **L1** afforded the product methyl phenylacetate in 18% yield prior to the addition of aldehydes (entry 1, Table 1). The use of PNN **L2** led to even worse reactivity (entry 2, Table 1). To our delight, enhanced catalytic reactivity and better yields were achieved (35%, 41%) upon addition of picolinaldehyde (**A1**) and 6-methyl-2-picolinaldehyde (**A2**), respectively (entries 3-4, Table 1). Then, the reaction improved greatly in the presence of heterocyclic 2-quinolinecarboxaldehyde (**A4**) giving methyl phenylacetate in 60% yield (entry 6, Table 1). We also found that the addition of aldehydes **A5** and **A6** were less effective toward the desired reaction (entries 7-8, Table 1).

In addition, we noticed that the reaction is solvent dependent with higher yield obtained in non-polar solvent (SI, Table S1). And, we identified the combination of **L1** and **A4** as the best choice producing the flavor compound methyl phenylacetate in 75% yield in *n*-heptane (entry 10, Table 1).

Table 1. Conditions optimization by *in situ* ligand formation.[a]



Entry	PNP	Aldehyde	Conv. (%)[b]	Yield (%)[b]
1	**L1**	-	21	18
2	**L2**	-	12	8
3	**L1**	**A1**	39	35
4	**L1**	**A2**	48	41
5	**L1**	**A3**	9	7
6	**L1**	**A4**	66	60
7	**L1**	**A5**	36	31
8	**L1**	**A6**	19	18
9[c]	**L1**	**A4**	17	15
10[d]	**L1**	**A4**	**88**	**75**
11	**L1**^{Cy}	**A4**	2	Trace
12	**L1**^{Ad}	**A4**	2	Trace

[a]Reaction conditions: 1a (0.3 mmol), MeOH (4.5 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (1 mol%), PNP (2 mol%), aldehyde (2.5 mol%), K_2CO_3 (20 mol%), 16 h. [b]Determined by GC (internal standard: *n*-tetradecane). [c]Solvent: toluene. [d]Solvent: *n*-Heptane. Cy = Cyclohexyl group. Ad = Adamantyl group.

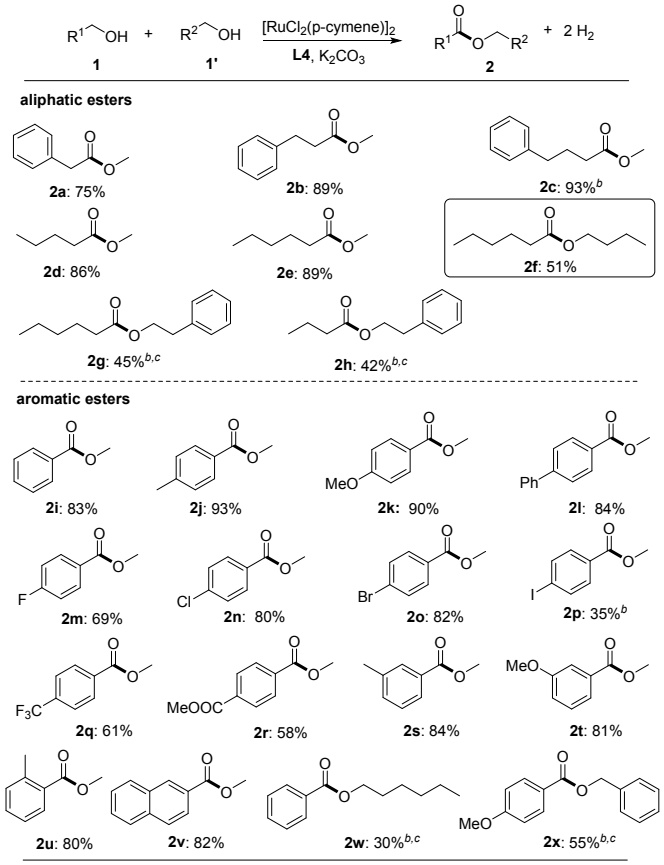
Furthermore, PNP ligands bearing cyclohexyl or adamantyl groups, **L1**^{Cy} or **L1**^{Ad} only gave traces of product in the presence of 2-quinolinecarboxaldehyde (**A4**), showing the crucial role of the phenyl groups in PNP^{Ph} ligand **L1** (entries 11-12, Table 1). Instead of **L1** and **A4** combining, when directly using the pre-formed ligand **L4**, similar catalytic results were obtained. Hence, such rapid ligand screening method based on the additive effect of aldehydes was shown to be valid.

With the optimized reaction conditions in hand, we turned our attention to examining substrate scope and limitations (Table 2). Opportunely, we found that it was suitable for the dehydrogenation of aliphatic chain alcohols as well as benzylic alcohols affording the corresponding ester products in moderate to excellent yields (42-93%, **2a**-**x**, Table 2). Notably, the challenging reaction of 1-hexanol with 1-butanol proceeded

smoothly and produced the fragrance compound butyl hexanoate **2f** in 51% yield.[16]

Methyl benzoates are important industry raw materials.[17] Testing our catalytic system toward benzylic alcohols with electron-donating groups on *para*-position gave ester products in excellent yields (90-93%, **2j-k**; Table 2). Meanwhile, benzylic alcohols with electron-withdrawing groups afforded ester products with relatively lower yields, especially for 4-iodobenzyl alcohol (35%, **2p**; Table 2). Furthermore, this exceptional approach produced trifluoromethyl and ester substituted benzoates from the corresponding alcohols (61%, **2q**; 58%, **2r**; Table 2). The hindered *ortho*-substituted alcohol also afforded good yield of desired product under the same reaction conditions (80%, **2u**; Table 2). Notably, moderate yields could be obtained when 1:1 ratio of alcohols was used (30-55% yields; **2g**, **2h**, **2w**, **2x**) and yield up to 55% was obtained for **2x**. Such unprecedented selectivity showed promising application potential of this system for the production of unsymmetrical esters.

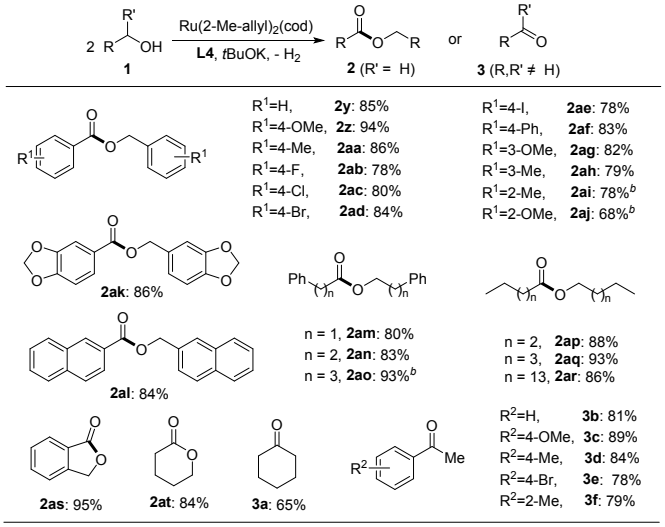
Table 2. Dehydrogenative cross-coupling of alcohols.[a]



[a]Reaction conditions: **1** (0.3 mmol), **1'** (4.5 mmol), **L4** (2.0 mol%), [Ru] (1 mol%), K_2CO_3 (20 mol%), *n*-heptane (2 mL), 120 °C for 16 h; isolated yields. [b]GC yields. [c]0.3 mmol of **1'** was used.

Furthermore, Ru-catalyzed dehydrogenation alcohols for preparation of esters or ketones was also investigated (Table 3). The reactions of benzyl alcohol type substrates with electron-donating or electron-withdrawing groups gave ester products in good to excellent yields (68-94%, **2y**-**2al**; Table 3). Other tested aliphatic alcohols were transformed into the corresponding esters in good yields (80-93%, **2am**-**ar**; Table 3). It is noteworthy that other alcohols including diols and secondary alcohols could also be successfully dehydrogenated into the desired lactones in excellent yields (95%, **2as**; 84%, **2at**), and ketone products in good yields, respectively (65-89%, **3a-f**; Table 3).

Table 3. Ru-catalyzed dehydrogenative preparation of esters and ketones.[a]



[a]Reaction conditions: **1** (0.3 mmol), **L4** (2 mol%), [Ru] (2 mol%), *t*BuOK (10 mol%), *n*-heptane (2 mL), 100 °C for 16 h; isolated yields. [b]GC yields.

NMR spectroscopic experiments were carried out using $[RuCl_2(p\text{-cymene})]_2$ and ligand **L4** in *d*-toluene. Firstly, the interaction of ligand's phosphine oxide moiety with alcohol molecules was observed using ^{31}P NMR. Free ligand **L4** exhibited two singlet signals at 31.4 and -15.2 ppm (Figure 1a). Upon adding 30 equiv. of benzyl alcohol, the phosphorous signal of phosphine oxide moved downfield to 37.5 ppm while the phosphine signal remains unchanged (Figure 1b). This is clear evidence for phosphine oxide/alcohol interaction *via* hydrogen bonding.[18]

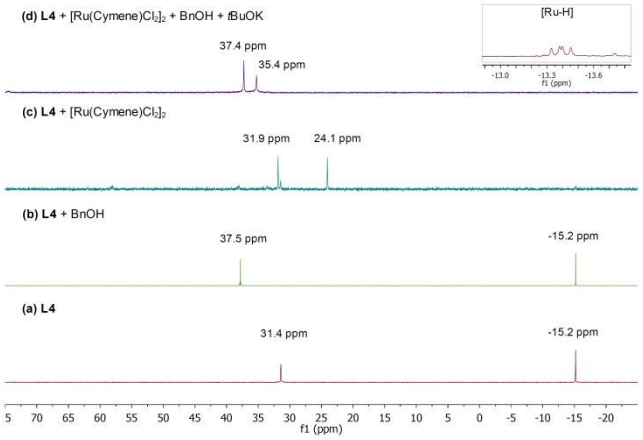


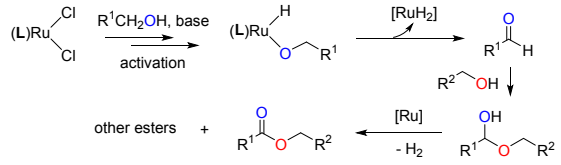
Figure 1. ^{31}P NMR spectra in *d*-toluene. (a) Ligand **L4**; (b) **L4** and benzyl alcohol; (c) After complexation of **L4** with $[RuCl_2(p\text{-cymene})]_2$; (d) Reaction mixture, and Ru-H in the insert.

Upon complexation of **L4** with Ru-precursor at 80 °C for 30 min, Ru-P coordination was observed while P=O moiety remained free from metal coordination (δ ^{31}P: 31.9, 24.1 ppm; Figure 1c). The dehydrogenation reaction of benzyl alcohol using *in situ* NMR showed that phosphine oxide is not coordinated to ruthenium

metal center, while the hydrogen bonding between phosphine oxides and benzyl alcohol is persistent. Specifically, addition of *t*BuOK (2 equiv. to Ru) and BnOH (3.5 equiv.) followed by heating at 90 °C for 2 h, new signals were detected (δ ^{31}P: 37.4, 35.4 ppm; Figure 1d). This suggests that hydrogen bonding is sustained during the reaction and presumably plays promoting and discriminating role for alcohol substrates in cross-coupling dehydrogenations.

During ^{1}H NMR studies, significant amounts of Ru-H hydride species were detected (δ ^{1}H: -13.38 ppm; insert in Figure 1d). This signal corresponds to the formation of active hydride species (eg. Ru[**L4**]H(OBn)) responsible for the slow generation of benzaldehyde *via* β-hydride elimination.

Scheme 3. Proposed reaction pathway.



Consistently, trace amounts of benzaldehyde were detected by GC-MS and observed during monitoring the reaction by *in situ* ^{1}H NMR (10.50 ppm). We further carried out controlled experiments showing considerable reactivity for ester product formation by using aldehydes and alcohols as starting materials. Hence, we propose that dehydrogenation of alcohols to aldehydes *via* Ru[**L4**]H(OBn) is a slow step while the formation of ester products is through further dehydrogenation of hemiacetal intermediates (Scheme 3).

Conclusions

In conclusion, we have discovered that phosphine-phosphine oxide ligands can be synthesized *via* a novel intramolecular oxygen-transfer alkylation procedure. Preliminary mechanistic studies imply that the hydrogen bonding between phosphine oxide moiety and alcohol substrates plays an important role for the challenging selective cross-coupling dehydrogenations. Further use of phosphine oxide in ligand design for other types of selective transformations is currently pursued.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful for the financial supports from the Program for Innovative Research Team of the Ministry of Education, the Program for Liaoning Innovative Research Team in University, and NSFC (21633013, 21101109, 21602228).

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DOI: 10.1039/C8CC10315A

TOC

Aldehyde effect was discovered and utilized for ligand design in the dehydrogenation reactions using PN(H)P pincer ligands.