Direct coupling of alcohols to form esters and amides with evolution of H$_2$ using in situ formed ruthenium catalysts

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A simple approach for the catalytic conversion of primary alcohols into their corresponding esters and amides, with evolution of H$_2$ gas using in situ formed ruthenium PNP- and PNN-pincer catalysts, is presented. The evaluation showed conversions for the esterification with turnover numbers as high as 4300, and $>$ 400 for the amidation.

Catalytic hydrogenation and dehydrogenation reactions play a major role in industrial processes as well as in academic research. In recent years especially progress in the catalytic acceptorless dehydrogenation of primary alcohols is remarkable. In most cases ruthenium hydride or iridium complexes were used for the transformation of primary alcohols into aldehydes.$^1$ Depending on the reaction conditions, tailor-made catalysts are also applicable for various tandem- or domino-reactions$^2$ revealing high selectivity. In this respect the formation of esters,$^3$ (aza)Wittig,$^4$ Aldol,$^3$ and Knoevenagel-products is known.$^4$ Most remarkably, in the presence of amines, amides$^5$ are easily accessible. For this purpose today’s most active catalyst is a ruthenium pincer complex [Ru(PNN)H(CO)] (1, PNN = [6-(di-tert-butylphosphino)methyl]pyridin-2-ylmethyl]-diethylamine; Fig. 1) with a cooperative dearomatised pyridine pincer-ligand backbone. It is active for the direct-synthesis of esters starting from primary alcohols as well as amides if amines are present as well.$^5$

In other attempts it has been shown that certain ruthenium pincer complexes are suitable to convert alcohols and amines into the corresponding coupled imines.$^6$ Moreover, it has been shown that certain ruthenium and iridium pincer complexes are highly active for the production of hydrogen gas from isopropanol, for the direct conversion of ethanol into ethyl acetate and for the hydrogenation of (chiral) esters ruthenium and osmium pincer complexes were successfully applied.$^7$ In the case of the osmium complexes, also selective hydrogenation of unsaturated fatty acid esters to the corresponding unsaturated alcohols was demonstrated, as well as the dehydrogenative coupling of aliphatic alcohols to form their esters. In general, ruthenium hydride complexes are often used for hydrogenation of a variety of compounds including ketones, aldehydes, alkenes and alkenes under hydrogen gas or under transfer hydrogenation conditions.$^4$ And today it is widely accepted that in most of these transformations metal dihydrogen complexes are key intermediates.$^8$

Based on previous results using the [Ru(PNN)H(CO)] catalyst 1 with a hemi-labile and cooperative pincer-backbone,$^3$ now the simple in situ formation of ruthenium dehydrogenation catalysts (Scheme 1) for the transformation of primary alcohols into esters with evolution of two equivalents of dihydrogen gas is presented (Table 1). As depicted in Scheme 1, the treatment of the readily available ruthenium precursor [Ru(COD)(2-methylallyl)$_2$] (2, COD = 1,5-cyclooctadiene) with either the hemi-labile PNN (3)

![Complex 1](image-url)

**Fig. 1** Complex 1 for the catalytic dehydrogenative coupling of primary alcohols to homoesters and amides.

**Scheme 1** Protocol for the in situ formed precatalysts 5 and 6.
or the stronger PNP (4) pincer ligand leads presumably to the in situ formation of the precatalysts [Ru(PNN)(2-methylallyl)]\textsubscript{5} and [Ru(PNP)(2-methylallyl)]\textsubscript{6}. This stays in agreement with previous findings, where the exchange of COD in [Ru(COD)-(2-methylallyl)]\textsubscript{2} with chelating phosphine ligands has been described by different research groups.\textsuperscript{9} Thus, for the initial catalytic experiments we focussed first on the stronger coordinating PNp-ligand 4.

Using a precatalyst loading of 1.0 mol\% , a variety of aliphatic alcohols (7 and 9–13) show moderate to high conversions into the corresponding esters. For example, the treatment of 1-hexanol with a mixture of 2 and PNP 4 (1.3 eq.), dissolved in toluene, gave >99\% conversion into the corresponding homoester within 15 h under reflux (entry 1). Using this protocol with other primary alcohols, moderate to good conversions and selectivities were obtained (Table 1, entries 3–6). Consistently, a lowering of the catalyst loading showed also decreasing conversions, i.e. 33\% ester was formed for the treatment of 1-hexanol with the 0.1 mol\% catalyst in 20 h (entry 2).

Encouraged by these results, consequently the PNN ligand 3 was tested, since its corresponding ruthenium complex 1 is known to show a superior activity for this kind of dehydrogenative couplings of primary alcohols.\textsuperscript{5} And indeed, the treatment of 7 with 2 and 3 (1.0 and 1.3 mol\% respectively) gave 97\% yield after 1 h using again toluene as a solvent (Table 1, entry 7). Lowering the catalyst loadings showed still very high conversion (98\% after 20 h, entry 8) with just 0.05 mol\% catalyst and still remarkable high conversions (86\% after 20 h, entry 9) were obtained with 0.02 mol\% catalyst. The conversion of 86\% with 0.02 mol\% of catalyst 5 is related to a turnover number (TON) of 4300 after 20 hours. Complex 1 gave otherwise a TON of ~1000 after six hours under similar conditions, and presumably with a higher substrate loading a similar high TON.\textsuperscript{5} However, the activity of the in situ formed species based on precatalyst 5 is remarkable in comparison to the one of complex 1. Other primary alcohols showed also moderate (68\%) to very high conversions (99\%) with catalyst loadings as low as 1.0 mol\% to 0.05 mol\% (Table 1; entries 10–14).

To further evaluate the potential of the protocol for the in situ formed catalytic systems, both systems were tested for the challenging dehydrogenative coupling of primary alcohols with primary amines (Table 2). This pioneering reaction has been published in 2007 using catalyst 1.\textsuperscript{5} And, indeed, treating a toluene solution with our in situ systems (2,3 or 2,4) results in the preferred formation of amides in the latter case (Table 2).

The addition of 100 eq. of 1-hexanol 7 and 100 eq. of 1-hexylamine 14 to a solution of Ru-2/PNP-4 in toluene resulted in a high substrate conversion, but relatively poor selectivity for the amide (amide: ester = 44:56; Table 2; entry 1). Using the system Ru-2/PNN-3 for these substrates instead, hexanoic acid hexylamide 15 is formed with high conversions (98\%) and much better selectivity (88\%, entry 2). A lowering of the catalyst concentration to a value of 0.2 mol\% still leads to the amide (82\%; TON = 410) with almost unchanged selectivity (83\%, entry 3). Similar results were obtained with 1-hexanol 7 and benzylamine 16 as substrates (conversion: 91\%, 86\% amide; entry 4). In comparison to previously reported in situ catalysts for the direct amidation of alcohols, we found here a quite active system which uses comparably low catalyst loadings without the need for the addition of base. Other direct amidation methods use higher metal precursor (2–10 mol\%) and ligand loadings (2–10 mol\%) and catalytic active species are only obtained in the presence of base (8–30 mol\%).\textsuperscript{59c}

Further experiments with 1-hexylamine 14 as the sole substrate support the previously proposed mechanism for this type of dehydrogenative coupling.\textsuperscript{2,5} Heating the amine in toluene in the presence of Ru-2/PNN-3 gave no products, neither the simple 1-hexylamine, nor one of the possible coupling products N-hexyl-hexanamidimine or dihexyl amine (coupling under ammonia loss). This result indicates that the
crucial reaction step is the formation of the aldehyde as the reactive intermediate,\textsuperscript{3,5} which then reacts with a primary amine (or primary alcohol) to give the hemi-amidate (or hemi-acetate) which is then dehydrogenated to the corresponding amide (or ester). The aldehyde intermediate was also identified by IR-techniques and trapped in an indirect Wittig-reaction in similar reactions.\textsuperscript{10} Moreover, it is known that ruthenium hydrides are capable of decarbonylating primary alcohols under mild conditions (room temperature),\textsuperscript{11a} or at elevated temperature.\textsuperscript{11b} This decarbonylation results in the formation of a ruthenium pincer complex carrying CO as a ligand. Such a complex might exhibit a similar reactivity as presented catalysts are sensitive to these functional groups in hydrocarbons.

**Conclusions**

In conclusion, the easy applicable conversion of primary alcohols into their corresponding esters using \textit{in situ} formed catalyst systems was demonstrated. Likewise, primary alcohols can be coupled with primary amines resulting in amide formation with high selectivity. This protocol allows use of a variety of substrates carrying OH\textendash{} and NH\textsubscript{2}\textendash{} functionalities as the presented catalysts are sensitive to these functional groups in hydrocarbons.

**Experimental section**

**General information**

All reactions were carried out in flame-dried glassware under argon. All alcohols and amines were obtained from Sigma Aldrich or Acros and dried or deoxygenated prior to use. [Ru(COD)(2-methylallyl)]\textsubscript{2} \textsuperscript{3} was used as received from Acros. Toluene was dried over magnesium antracene. GC analyses were performed on a HP GC-MS/GC-EI SSQ7000 or on a HP 6890 GC System/HP Mass Selective Detector 5973.

**General procedure for the direct esterification**

Experimental protocol for entry 1 (Table 1: esters): the reactions were performed under argon-flow in a dried 20 mL three-necked round bottom flask, equipped with a reflux condenser with an argon inlet/outlet, a second argon valve and a screw-capped adapter with a Teflon-coated septum. 10 mg of [Ru(COD)(2-methylallyl)]\textsubscript{2} \textsuperscript{2} were introduced followed by the addition of 1.3 equivalents of the PNP ligand \textsuperscript{4} (16 mg, 40.7 \mu mól). Then, 5 mL of toluene were added via a syringe and the mixture was stirred at 60 °C for 5 hours followed by addition of 100 equivalents of 1-hexanol \textsuperscript{7} (319 mg, 3.1 mmol) via a syringe through the Teflon-coated septum. Afterwards the reaction mixture was heated to 120 °C for 15 h. The sample was analysed by GC and GC-MS.

**General procedure for the direct amidation**

Experimental protocol for entry 2 (Table 2: amides): the reactions were performed under argon-flow in a dried 20 mL three-necked round bottom flask, equipped with a reflux condenser with an argon inlet/outlet, a second argon valve and a screw-capped adapter with a Teflon-coated septum. 20 mg of [Ru(COD)(2-methylallyl)]\textsubscript{2} \textsuperscript{2} (62.6 \mu mól) were introduced followed by the addition of 1.3 equivalents of the PNN \textsuperscript{3} (26 mg, 81.4 \mu mól). Then, 5 mL of toluene were added via a syringe and the mixture was stirred at 60 °C for 5 hours followed by addition of 100 equivalents of 1-hexanol \textsuperscript{7} (638 mg, 6.2 mmol) and 100 equivalents of 1-hexylamine \textsuperscript{14} (626 mg, 6.2 mmol) via a syringe through the Teflon-coated septum. Afterwards the reaction mixture was heated to 120 °C for 20 h. The sample was analysed by GC and GC-MS.

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**Notes and references**


