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Direct Conversion of Alcohols to Acetals and H_2 Catalyzed by an Acridine-Based Ruthenium Pincer Complex

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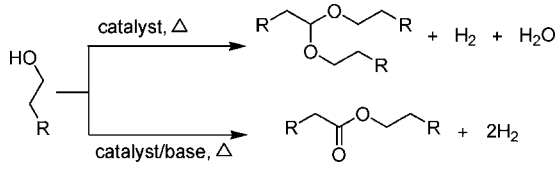
Acetals, aldehydes, and esters are important industrial products and serve as useful intermediates for the introduction of other functional groups.[1] Although an assortment of methods have been exploited for the synthesis of acetals,[2] most of them are based on acid-catalyzed reactions and require an aldehyde or ketone as a reactant. The selective oxidation of primary alcohols to aldehydes is still a challenging procedure.[3] Most of the existing acetalization reactions use toxic and corrosive reagents and involve halogenated solvents and additives. While they are widely applicable for the synthesis of dimethyl and diethyl acetals,[2] practical methods for the preparation of acetals from alcohols larger than C_3−OH are needed. Direct catalytic transformations of alcohols to acetals are of interest, as they could circumvent the need for aldehydes or aldehyde derivatives. However, there is only one report[4] of such a reaction, with 24 turnovers.

We previously reported the selective dehydrogenative coupling of primary alcohols to esters and H_2 catalyzed by the *dearomatized* complex RuH(CO)(PNN*) [PNN* = deprotonated PNN; PNN= (2-(di-*tert*-butylphosphinomethyl)-6-diethylaminomethyl)pyridine] under neutral conditions.[5a,b] The aromatic complexes RuHCl(CO)(PNN) and RuHCl(CO)(PNP) [PNP = 2,6-bis(di-*tert*-butylphosphinomethyl)pyridine] catalyzed the reaction upon addition of base but failed to react with alcohols in neutral media. The mechanistic basis for these reactions, and for the related catalytic ester hydrogenation to alcohols,[5c] was discussed.[5]

We recently reported the novel acridine-based ruthenium pincer complex RuHCl(CO)(A-^{i}Pr-PNP) (**1**) [A-^{i}Pr-PNP = 4,5-bis-(diisopropylphosphinomethyl)acridine], which catalyzed the selective coupling of alcohols with ammonia to yield primary amines.[6] We now report that complex **1** catalyzes the conversion of primary alcohols to acetals under neutral conditions and to esters in the presence of a base, as illustrated in Scheme 1.

Scheme 1. Catalytic Conversion of Alcohols to Acetals and Esters



The structure of complex **1**, determined by X-ray diffraction, reveals a distorted octahedral geometry around the ruthenium center (Figure 1), with an unusually long Ru−N bond [2.479 Å, compared with 2.103 Å in RuHCl(CO)(PNN)[5a]] and the CO ligand coordinated trans to the acridinyl nitrogen atom. Upon complexation, the acridine ligand becomes bent at the middle aryl ring to adopt a boat-shaped structure with a dihedral angle of 167.6°.[7] This diminished aromaticity upon coordination likely persists in solution, as indicated by the ^{1}H NMR spectrum of **1**, which exhibits the C9*H* proton of the acridine ring at 8.15 ppm, an upfield shift of 0.46 ppm relative to C9*H* of uncomplexed A-^{i}Pr-PNP (8.61 ppm).

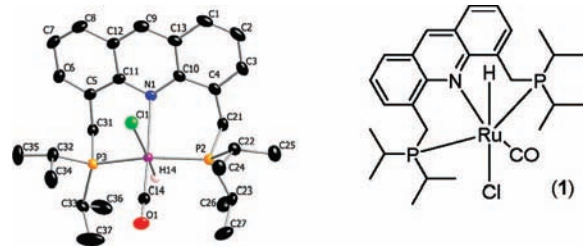


Figure 1. Structure of complex **1** (50% probability level). Hydrogen atoms (except hydride) have been omitted for clarity. Selected bond distances (Å) and angles (deg): Ru1−N1, 2.479(2); Ru1−P2, 2.3134(7); Ru1−C1, 1.797(3); C(9)−C(12), 1.381(4); C(9)−C(13), 1.381(4); P2−Ru−P3, 155.90(2); N1−Ru1−C14, 167.19(9).

The air-stable complex **1** catalyzes the dehydrogenative transformation of alcohols to acetals under neutral conditions. Thus, refluxing a 0.1 mol % solution of complex **1** in neat 1-hexanol (157 °C) under a flow of argon for 48 h resulted in 97.7% conversion of the alcohol to 52.4% 1,1-bis(hexyloxy)hexane (a hexyl acetal), 10.8% hexyl hexanoate, and 1% 1-hexanal (Table 1, entry 1). GC−MS analysis of this reaction mixture revealed the presence of an *E*,*Z* mixture of 1-hexyloxy-1-hexene enol ethers, which corresponded to the rest of the converted hexanol. When the reaction mixture was heated at 157 °C for 72 h, 92% conversion

Table 1. Direct Transformation of Primary Alcohols to Acetals and Esters Catalyzed by RuHCl(A-^{i}Pr-PNP)(CO)[a]

						yield (%)[b]	
entry	KOH equiv	alcohol	temp (°C)	time (h)	conv (%)	acetal	ester
1	0	1-hexanol	157	48	97.7	52.4	10.8
2	0	1-hexanol	157[c]	72	92.0	81.5	9.5
3	1	1-hexanol	157	26	86.0	1	92
4	1	1-hexanol	157	40	92.0	0.6	93
5	0	ethanol	78	115	0	0	0
6	0	1-pentanol	137	72	93.8	92	0.9
7	1	1-pentanol	137	60	96.8	1.3	78.3
8	0	1-hexanol[d]	157	120	82.9	71.5	11.5
9	1	1-hexanol[d]	157	80	93.4	6.4	82.3
10	0	$PhCH_2OH$[e]	168	72	100	0	99.5

[a] In the reaction, 0.01 mmol of catalyst and 10 mmol of alcohol were refluxed neat under an Ar flow. For ester formation, 0.01 mmol of KOH was added [b] Yields are based on the conversion of alcohols. When the sum of the values is less than 100%, other products were observed in small amounts. Aldehydes were present in all reaction mixtures in amounts ranging from 0.5 to 8.8% [c] Oil bath temperature. [d] 50 mmol of 1-hexanol was used. [e] Mesitylene (2 mL) was added, and the solution was refluxed.

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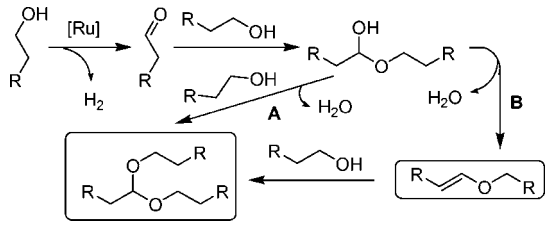
Scheme 2. Proposed Pathways for Acetalization



of 1-hexanol was observed; the acetal was obtained in 81.5% yield, and the ester yield was 9.5% (Table 1, entry 2). The enol ether products disappeared, suggesting that they are intermediates in acetal formation. 1,1-Bis(hexyloxy)hexane is a food-flavoring substance.[8] Significantly, in the presence of 1 equiv of base relative to Ru, complex **1** exhibited different catalytic activity, acting as a dehydrogenative esterification catalyst. Thus, refluxing a 0.1 mol % solution of **1** with 0.1 mol % KOH in neat 1-hexanol for 26 h resulted in 86% conversion of 1-hexanol to provide 92% hexyl hexanoate and traces of hexyl acetal (1%) and 1-hexanal (2.6%) (Table 1, entry 3). Prolonging the reflux to 40 h under the same conditions resulted in 92% conversion of 1-hexanol (entry 4). When a lower alcohol such as ethanol was subjected to catalysis in the absence of base under reflux (bp 78 °C), no products were observed (entry 5), indicating the necessity of a higher temperature. 1-Butanol (bp 118 °C) also failed to react; however when it was refluxed together with 1-hexanol, cross-products were obtained, and the condensation proceeded unselectively. Similarly, reaction of benzyl alcohol with 1-hexanol was not selective. When 1-pentanol was subjected to the catalysis for 72 h, 92% acetal (920 turnovers) and 0.9% pentyl pentanoate were obtained (entry 6). As with 1-hexanol, 1-pentanol in the presence of KOH yielded predominantly the ester pentyl pentanoate (entry 7).

When the process was scaled up, reaction of 50 mmol of 1-hexanol with 0.01 mmol of complex **1** resulted in a 71.5% yield (3575 turnovers) of hexyl acetal under neutral conditions after 120 h, and in the presence of 1 equiv of KOH relative to Ru, a yield of 82.9% (4145 turnovers) of hexyl hexanoate was obtained after 80 h (entries 9 and 10). Apparently, dehydrogenative esterification of hexanol proceeds faster than acetal formation.

Interestingly, irrespective of the absence of base, benzyl alcohol provided benzyl benzoate (99.5%) when refluxed in mesitylene solution with 0.01 mmol of complex **1** (entry 10). No acetal was observed, although benzaldehyde dibenzylacetal is stable and easily formed upon acid-catalyzed reaction of benzaldehyde with benzyl alcohol.[9]

Addition of 1 equiv (relative to Ru) of HCl to the complex **1** (0.1 mol%)-catalyzed reaction of 1-hexanol did not increase the yield of acetal. In a separate experiment, when 2 mmol of 1-hexanal and 4 mmol of 1-hexanol were heated at 157 °C in a closed system in the presence of a catalytic amount of HCl, no hexyl acetal was formed. These experiments tend to rule out an acid-catalyzed mechanism in the formation of higher acetals.

Although further studies are required to elucidate the mechanism, we envisage dehydrogenation of the primary alcohol to the aldehyde followed by hemiacetal[4,5,10] formation. Subsequent water elimination may take place to provide enol ether intermediates (route B, Scheme 2), which upon addition of alcohols to the C=C bond yield the acetal. This mechanism, rather than the traditional acid-catalyzed direct substitution of the hydroxy group of the hemiacetal by an alcohol molecule (route A, Scheme 2), is supported by the observation of enol ether intermediates. In addition, the hemiacetal formed from benzaldehyde and benzyl alcohol, which cannot form an enol ether, does not form an acetal (Table 1, entry 10) but rather undergoes dehydrogenation to the ester. Addition of alcohols to enol ethers to form acetals is known.[11] When a base is added, a Ru(0) intermediate formed by deprotonation of **1** may be the actual catalyst involved in ester formation, which likely proceeds by dehydrogenation of a hemiacetal intermediate[5] rather than by a Tischenko disproportionation[12] of an aldehyde intermediate. Thus, refluxing 200 equiv of benzaldehyde with **1** in mesitylene for 24 h produced no benzyl benzoate, while under the same conditions, **1** catalyzed the reaction of 200 equiv each of benzaldehyde and benzyl alcohol to give benzyl benzoate in 93% yield.

It is not clear at this stage why the acridine-based complex **1** catalyzes acetal formation in the absence of base, when no reaction was observed under the same conditions with the pyridine-based complexes (see above). Perhaps the much longer Ru−N bond and bent middle acridine ring result in "hemilability" of the acridine moiety, affording a potential vacant site and a localized "internal base". Alcohol coordination followed by deprotonation by the adjacent acridinyl nitrogen can lead after β-H elimination to a hemiacetal (via aldehyde), which undergoes dehydration.

In conclusion, **1** efficiently catalyzes the direct dehydrogenation of alcohols to acetals and H_2 in neutral media. This reaction is unprecedented, except for a report with low catalytic activity.[4] In the presence of a base, **1** predominantly catalyzes the formation of esters. Mechanistic studies are underway.

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Supporting Information Available: Experimental procedures and X-ray data for complex **1** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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