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In Situ Generated Cobalt Catalyst for the Dehydrogenative Coupling of Alcohols and Amines into Imines

Fabrizio Bottaro and Robert Madsen^{*,[a]}

Abstract: An in situ formed cobalt catalyst is developed from cobalt(II)bromide, bis[2-(diisopropylphosphino)-4-methylphenyl]amine and zinc metal. The catalyst mediates the acceptorless dehydrogenative coupling of alcohols and amines into imines with the release of hydrogen gas and the transformation is applied to the synthesis of a variety of imines from different alcohols and amines. The mechanism is investigated with labelled substrates and based on the results a cobalt(I) PNP complex is believed to be the catalytically active species which abstracts hydrogen gas from the alcohol through a metal ligand bifunctional pathway.

Introduction

The use of Earth-abundant metals for homogeneous catalysis has experienced a significant revival in recent years since they constitute inexpensive alternatives to the more common precious metal catalysts from the platinum group metals. This development is seen for a number of transformations including cross coupling reactions,^[1] C-H activations^[2] and reactions with hydrogen gas.^[3] In the latter category, the acceptorless dehydrogenation of alcohols comprises an important transformation where hydrogen gas is liberated from an alcohol without the use of a stoichiometric oxidant. The resulting aldehyde or ketone can then undergo a variety of subsequent transformations in the same vessel such as aldol condensations, formation of heterocycles, and reactions with oxygen and nitrogen nucleophiles where an additional dehydrogenation is sometimes involved.^[3] The most widely used non-precious metal catalysts for these transformations have been complexes based on manganese, iron, cobalt and nickel^[3] while copper,^[4] zinc^[5] and molybdenum^[6] catalysts have also been employed in special cases.

The first homogeneous cobalt catalyst for the dehydrogenation of alcohols was presented in 2013 where PNP pincer complex **1** was shown to catalyze the dehydrogenative coupling of alcohols and amines to form imines (Figure 1).^[7] By using slightly different conditions the dehydrogenation with complex **1** has also been used to form secondary amines, heterocycles and alkylated ketones.^[8] Furthermore, the complex has been utilized to catalyze the transfer hydrogenation of ketones and imines with isopropanol.^[9] These discoveries

sparked an interest in cobalt pincer complexes for dehydrogenative reactions with alcohols.^[10] PNP pincer complex **2** was subsequently shown to mediate the coupling of primary alcohols with aromatic amines, esters, amides and secondary alcohols in transformations where only water is formed as a byproduct.^[11] PCP pincer complex **3** also catalyzed the alkylation of aromatic amines with primary alcohols^[12] while PNN pincer complex **4** catalyzed the dehydrogenative formation of both pyrroles and benzimidazoles.^[13] Very recently, similar NNN and SNS pincer cobalt(II) complexes have been used for the synthesis of amines, imines and heterocycles.^[14] In addition, a cobalt(II) complex with a PPPN tetradentate tripodal ligand has been employed for the synthesis of ketones and esters from alcohols^[15] while $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ in the presence of PPh_3 has been shown to mediate secondary amine formation from alcohols and primary amines.^[16] Conversely, several related cobalt complexes have been shown to catalyze the hydrogenation of aldehydes, ketones, imines, nitriles and alkenes.^[17] In all the reported transformations with the release of hydrogen gas, the reactions were performed with a presynthesized cobalt complex. Since some of these cobalt complexes are not easily prepared, it prompted us to look for a more convenient in situ formed catalyst setup.

Figure 1. Examples of cobalt pincer complexes for alcohol dehydrogenation.

Herein, we describe the first in situ generated cobalt catalyst system for liberating hydrogen gas from alcohols and the protocol has been employed for the synthesis of imines from alcohols and amines. The mechanism has been studied with labelled substrates and the in situ formed complex is believed to catalyze the dehydrogenation by an outer-sphere hydrogen transfer pathway.

Results and Discussion

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Initially, we attempted to synthesize complex **1** which is prepared in 3 steps from CoCl_2 .^[18] However, in our hands it proved completely impossible to produce this complex by standard Schlenk techniques in the absence of a glove box. Thus, we decided to switch to a different approach and investigate more easily available in situ formed catalysts. Benzyl alcohol and cyclohexylamine were selected as the substrates for these exploratory investigations. Experimental mechanistic studies with complex **1** had suggested a cobalt(I) – cobalt(III) catalytic cycle where the starting cobalt(II) compound is reduced to the lower oxidation state by the alcohol.^[19] This indicates that a reducing agent may be necessary when using a cobalt(II) halide as the cobalt source.

Thus, the substrates were first treated with CoBr_2 , PNP^{Cy} ligand **5** (Figure 2) and acid-activated zinc metal, which afforded 20% yield of the imine **8** in refluxing toluene (Table 1, entry 1). An improvement was observed when the ligand was changed to PNP^{Pr} ligand **6**, but full conversion of the alcohol and the amine was still not achieved. A lower yield was observed with CoCl_2 as the cobalt source while essentially no conversion was detected with mono- and bidentate phosphine ligands (see Table S1 in the Supporting Information). However, by changing the solvent to refluxing mesitylene full conversion of the substrates was accomplished and the yield of the Schiff base improved to 69% (entry 3). The reaction was not affected by adjusting the loading of CoBr_2 to 5% and the amount of Zn to 10% (entry 4). A lower yield was achieved with a 5% loading of the ligand (entry 5) which may be due to a competing complexation to Zn(II) while 5% of Zn gave almost no conversion (entry 6). No reaction occurred in the absence of Zn or with ZnBr_2 instead of the metal indicating that zinc serves as a reducing agent for cobalt and that the alcohol is unable to perform this reduction under these conditions. Manganese metal and NaHBET_3 were also investigated as reducing agents, but in both cases lower yields of the imine was obtained (entry 7 and 8).

Figure 2. Ligands for the dehydrogenative transformation.

To further improve the yield several additives were included in the investigation. The strong base KOtBu and molecular sieves are both common additives in these dehydrogenative transformations, but in this case they did not further promote the reaction (entry 9 and 10). The strong desiccants LiBr and CaO , on the other hand, led to small improvements in the yield of **8** (entry 11 and 12). We have previously used the nitride salts Ca_3N_2 and Mg_3N_2 in these water-releasing reactions and they may serve a dual role as both bases and desiccants.^[20] In the present reaction Ca_3N_2 also improved the yield slightly (entry 13), but a more notable influence was observed with Mg_3N_2 . With 10% of this salt the imine yield improved to 87% (entry 14) while 5% of Mg_3N_2 gave 83% yield of the Schiff base (entry 15).

Repeating the latter experiment with 5% of ligand **6** lowered the yield to 57% (entry 16) which again shows the need for a 10% ligand loading. Accordingly, Mg_3N_2 was selected as the additive for the dehydrogenative transformation and the optimized conditions consisted of CoBr_2 (5%), ligand **6** (10%), Zn (10%) and Mg_3N_2 (10%) in refluxing mesitylene. Equimolar amounts of the alcohol and the amine were used since a slight excess of the amine did not give better results. *N*-Benzyl cyclohexylamine was obtained as a byproduct in entry 7 while in the remaining cases only 0 – 2% of this secondary amine could be detected. No other byproducts were observed and in the absence of cyclohexylamine only a small amount (7%) of benzaldehyde was formed.

Table 1. Optimization of cobalt-catalyzed dehydrogenation.^[a]

$\text{Ph-CH}_2\text{-OH} + \text{H}_2\text{N-Cy} \xrightarrow[\text{mesitylene, 164 } ^\circ\text{C, 24 h}]{\text{5\% CoBr}_2, \text{ 10\% 6, Reducing agent, Additive}} \text{Ph-CH=N-Cy}$ 8			
Entry	Reducing agent	Additive	Yield [%] ^[b]
1 ^[c]	100% Zn	-	20
2 ^[d]	100% Zn	-	35
3 ^[e]	100% Zn	-	69
4	10% Zn	-	69
5 ^[f]	10% Zn	-	50
6	5% Zn	-	<5
7	20% Mn	-	45 ^[g]
8	10% NaHBET_3	-	22
9	10% Zn	10% KOtBu	68
10	10% Zn	4 Å MS (100 mg)	56
11	10% Zn	10% LiBr	72
12	10% Zn	10% CaO	78
13	10% Zn	20% Ca_3N_2	73
14 ^[h]	10% Zn	10% Mg_3N_2	87
15 ^[h]	10% Zn	5% Mg_3N_2	83
16 ^[f, h]	10% Zn	5% Mg_3N_2	57

[a] Reaction conditions: BnOH (1 mmol), CyNH_2 (1.2 mmol), CoBr_2 (0.05 mmol), **6** (0.1 mmol), reducing agent, additive, mesitylene (3 mL), reflux, 24 h. [b] Determined by GC. [c] With CoBr_2 (0.1 mmol) and **5** (0.1 mmol) in toluene. [d] With CoBr_2 (0.1 mmol) and **6** (0.1 mmol) in toluene. [e] With CoBr_2 (0.1 mmol). [f] With **6** (0.05 mmol). [g] 10% of BnNHCy was also formed. [h] With CyNH_2 (1 mmol).

The optimized conditions were then applied to a number of alcohols and amines to investigate the substrate scope and limitations of the method (Table 2). First various alcohols were

subjected to cyclohexylamine and the products were isolated by flash chromatography. This afforded 75% yield of the parent *N*-benzylidenecyclohexylamine (**8**) while the corresponding *p*-methyl compound **9** was isolated in 69% yield. The four *p*-halo-substituted benzyl alcohols gave rise to imines **10** – **13** in 57 – 82% yield with no sign of any competing dehalogenation. *p*-Methoxy- and *p*-methylthiobenzyl alcohol afforded imines **14** and **15** in 67 and 63% yield, respectively, while the *p*-(trifluoromethyl) and *p*-(trifluoromethoxy) analogues **16** and **17** were isolated in 70 and 58% yield. Ortho substituents were also accommodated as seen for *o*-methyl and *o*-methoxy compounds **18** and **19**, which were obtained in 69 – 71% yield. 2-Naphthalenemethanol gave imine **20** in 71% yield while the more hindered 1-naphthalenemethanol afforded the product **21** in 53% yield. *p*-Nitrobenzyl alcohol furnished the Schiff base **22** in only 40% yield which may be due to some competing reduction of the nitro group. *p*-Hydroxybenzyl alcohol and hexan-1-ol, on the other hand, did not react with cyclohexylamine in the dehydrogenative transformation (results not shown).

Table 2. Imine formation from different alcohols and amines.^[a]

[a] Reaction conditions: Alcohol (1 mmol), amine (1.0 mmol), CoBr₂ (0.05 mmol), **6** (0.1 mmol), Zn (0.1 mmol), Mg₃N₂ (0.1 mmol), mesitylene (3 mL), reflux, 24 h (isolated yields). [b] *cis*-But-2-ene-1,4-diol (10 mmol), CyNH₂ (10 mmol), CoBr₂ (0.5 mmol), **6** (1 mmol), Zn (1 mmol), Mg₃N₂ (1 mmol), mesitylene (15 mL), reflux, 72 h.

Next, benzyl alcohol was submitted to the reaction with different primary amines (Table 2). The chiral amine (*R*)-1-(1-naphthyl)ethylamine gave rise to imine **23** in 75% yield with no sign of a competing racemization. 1-Adamantylamine afforded imine **24** in a similar 70% yield while a lower yield of 53% was obtained for **25** in the reaction with benzylamine. The less nucleophilic *p*-anisidine and the more hindered benzhydrylamine only furnished 36 – 41% yield of the corresponding imines **26** and **27** with some starting material remaining, while almost no conversion occurred with tritylamine and aniline (results not shown). This indicates that the nucleophilicity of the amine is important in the transformation for converting the aldehyde into the imine. As mentioned above, only little conversion of benzyl alcohol into benzaldehyde occurred in the absence of the amine. Thus, the imine formation seems to be an important driving force for the overall transformation by effectively removing the aldehyde from the mixture. The analogous secondary amine from a concomitant reduction of the imine functionality was the only byproduct that sometimes could be detected in trace amounts from the reactions in Table 2.

A pyrrole could also be prepared as shown for the formation of 1-cyclohexylpyrrole (**28**) from *cis*-but-2-ene-1,4-diol and cyclohexylamine. The reaction was performed on 10 mmol scale with a longer reaction time to give **28** in 55% isolated yield. Similar yields have been reported in the same transformation with other catalysts.^[20a]

The evolution of hydrogen gas was verified by repeating the optimized experiment in Table 1, entry 14 in a closed system with two connected Schlenk tubes where the second tube contained diphenylacetylene and Pd/C in methanol.^[6] After 24 h and full conversion into the imine in the first tube, GC analysis of the second tube showed reduction of diphenylacetylene into bibenzyl, which validates the dehydrogenative pathway of the transformation. The reaction between benzyl alcohol and cyclohexylamine under the optimized conditions was also repeated with 0.1 mL of mercury added from the beginning. This experiment showed no significant decrease in the yield, which supports the fact that a homogeneous cobalt catalyst is responsible for the transformation and not cobalt nanoparticles.

The mechanism for the dehydrogenation has previously been studied in detail with complex **1** where three key experimental observations were made.^[19] First, a PNP cobalt(III) hydride complex was isolated from C–H insertion with acetophenone and shown to be catalytically active.^[19] Second, deuterium-labelled 1-phenylethanol underwent isotope

scrambling at the benzylic position indicating a reversible dehydrogenation with a cobalt dihydride species.^[19] Third, the corresponding N-methyl PNP complex reacted with a similar activity as complex **1** suggesting no involvement from the N–H proton in **1** in the catalytic cycle.^[19] These observations led to the proposal of a cobalt(I) – cobalt(III) catalytic cycle where the alcohol first undergoes oxidative addition to the cobalt(I) complex to form a cobalt(III) alkoxide. Subsequent β -hydride elimination gives rise to a cobalt(III) dihydride which eliminates hydrogen gas to regenerate the cobalt(I) complex.^[19] The pathway has also been calculated by density functional theory (DFT) and seems feasible especially when considering the uncertainties of the computational methods.^[21]

To gain information about the mechanism of the present system several experiments were performed with labelled compounds. When PhCD₂OH was used in the reaction with cyclohexylamine, the product was exclusively PhCD=NCy with no isotope scrambling at the benzylic position. This indicates that the dehydrogenation is irreversible or a cobalt monohydride species is formed. The kinetic isotope effect was measured with PhCD₂OH and PhCH₂OH and found to be 1.8 showing that hydride abstraction is a slow step in the transformation. A Hammett study was carried out with four *para*-substituted benzyl alcohols (X = OMe, Me, F, and H) which were allowed to compete with the parent benzyl alcohol in the reaction with cyclohexylamine.^[22] Their relative reactivities (k_X/k_H) were determined and used to construct a Hammett plot from the equation $\lg(k_X/k_H) = \rho \cdot \sigma$ (Figure 3). The best correlation was found with the σ^+ values^[23] giving rise to a straight line with a ρ value of -0.09 . This small negative value shows that a partial positive charge is formed at the benzylic position in the transition state of the rate-limiting step, which is consistent with a hydride abstraction from the alcohol. No correlation was found with σ^- values^[24] and benzylic radicals are therefore not involved in the reaction. This was also confirmed by repeating the reaction in Table 1, entry 14 in the presence of the radical scavengers cyclohexa-1,4-diene and 2,4-diphenyl-4-methylpent-1-ene which in both cases had relatively little influence on the yield of the product.

Figure 3. Hammett plot for the reaction with *para*-substituted benzyl alcohols.

The corresponding N-methyl PNP ligand **7** (Figure 2) was also prepared and included in the study. It furnished essentially the same yield of imine **8** under the optimized conditions as when the reaction was performed with ligand **6**. However, when the reaction mixture afterwards was analyzed by LCMS, no trace of ligand **7** (or its phosphine oxide) could be detected. Instead, the phosphine oxide of the demethylated ligand **6** was observed indicating that the N-methyl group is removed under the reaction conditions. In fact, it is known with nickel, palladium and platinum complexes that these N-methyl bis(*ortho*-phosphinoaryl)amines readily undergo N-methyl cleavage upon complexation with the metal halides.^[25] As a result, the successful imination with ligand **7** does not provide any information about the involvement of the amino group in the catalytic cycle.

Very recently, the hydrogenation of acetophenone catalyzed by a cobalt(I) hydride complex with ligand **5** was investigated by DFT.^[26] Various pathways were included in the study and the lowest barrier was found for an outer-sphere metal ligand bifunctional mechanism.^[26] This is a monohydride pathway and involves participation from the amino group in the ligand. The present experimental study with ligand **6** has indicated a lower valent cobalt complex as the catalytically active species and that both a monohydride route and the involvement of the amino group are possible. Therefore, we consider the most likely scenario for the dehydrogenation to involve formation of cobalt(II) PNP complex **29-Br**, which upon reduction with zinc generates the amido complex **30** (Figure 4). The corresponding chloride complex **29-Cl** has previously been prepared from the lithium salt of **6** and CoCl₂ and characterized by ¹H NMR.^[27] When we treated ligand **6** with CoCl₂ and Mg₃N₂ in benzene-*d*₆, compound **29-Cl** was still obtained according to ¹H NMR indicating that elimination of HCl occurs easily with the base.^[28] The same experiment with CoBr₂, **6** and Mg₃N₂ afforded a similar ¹H NMR spectrum believed to be that of complex **29-Br**. Compound **29-Cl** has previously been reduced with *tert*-butyl lithium to complex **30** although the latter has not been detected, but instead characterized as the [(PNP)Co]₂(μ_2 -N₂) complex.^[27] Under our reaction conditions, we believe zinc is responsible for the reduction of cobalt(II) complex **29-Br** to the corresponding cobalt(I) species **30**.

The catalytic cycle then involves reaction with the alcohol through an outer-sphere hydrogen transfer to give cobalt(I) monohydride **31** from which hydrogen gas is eliminated to regenerate **30**. It should be noted that cobalt stays in oxidation state I during the catalytic cycle and the pathway does not involve the previously proposed oxidative addition of the alcohol,^[19] which is not a common step for the first-row transition metals. The same bifunctional pathway has been identified in DFT calculations of alcohol dehydrogenations catalyzed by manganese, rhenium, iron and iridium PNP complexes.^[29]

Figure 4. Proposed mechanism for cobalt-catalyzed dehydrogenation.

Conclusions

In summary, we have described an in situ formed cobalt catalyst system for releasing hydrogen gas from alcohols. The combination of CoBr_2 , ligand **6**, Zn and Mg_3N_2 allows for the acceptorless synthesis of imines from alcohols and amines. The new protocol can be carried out with a standard laboratory setup and circumvents the difficult synthesis of organocobalt complexes. Contrary to the previously proposed pathway, the mechanism is believed to involve a catalytic cycle with cobalt(I) species and an outer-sphere hydrogen transfer from the alcohol.

Experimental Section

General Information: All commercially available reagents were purchased from Sigma-Aldrich or Strem Chemicals and were used as received. Mesitylene was reagent grade, stored over activated 4 Å molecular sieves for 24 to 48 h and degassed through 3 freeze-pump-thaw cycles under an atmosphere of nitrogen. Gas chromatography was performed on a Shimadzu GCMS-QP2010S instrument fitted with an Equity 5, 30 m $\times$ 0.25 mm $\times$ 0.25 μm column. Helium was used as the carrier gas and ionization was performed by electron impact (70 eV). Flash column chromatography separations were performed on silica gel 60 (40 – 63 μm). NMR spectra were recorded on a Bruker Ascend 400 and a Bruker Avance 800 spectrometer. Chemical shifts were measured relative to the signals of residual CHCl_3 ($\delta_{\text{H}} = 7.26$ ppm) and CDCl_3 ($\delta_{\text{C}} = 77.16$ ppm). LCMS analysis was carried out on a Waters ACQUITY UPLC system with a PDA and SQD2 electrospray detector and a Thermo Accucore C18 2.6 μm , 2.1 $\times$ 50 mm column.

General Procedure: An oven-dried Schlenk tube (24 $\times$ 150 mm) was charged with CoBr_2 (11 mg, 0.05 mmol), acid-activated Zn dust (7 mg, 0.10 mmol), Mg_3N_2 (10 mg, 0.10 mmol), ligand **6** (43 mg, 0.10 mmol) and

a stir bar. The tube was inserted into a Radleys carousel, vacuum was applied and the tube was filled with nitrogen (repeated 3 times). Degassed mesitylene (3 mL) was added with a syringe through the septum and the reaction vessel was heated to 164 $^{\circ}\text{C}$ with stirring. The alcohol (1.0 mmol) and the amine (1.0 mmol) were added with a syringe and the reaction was stirred for 24 h under a flow of nitrogen. The mixture was then concentrated under reduced pressure and the residue purified by silica gel flash chromatography eluting with 98/2 hexane/ Et_3N (the column was first treated with pure Et_3N).

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Keywords: Alcohols • Cobalt • Dehydrogenation • Imines • Homogeneous catalysis

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F. Bottaro, R. Madsen*

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**In Situ Generated Cobalt Catalyst for
the Dehydrogenative Coupling of
Alcohols and Amines into Imines**

Convenient cobalt: A cobalt catalyst is formed in situ from CoBr_2 , a PNP ligand and Zn and shown to mediate the synthesis of imines from alcohols and amines with the release of hydrogen gas. The catalytically active species is believed to be a cobalt(I) complex, which removes hydrogen gas from the alcohol by a metal ligand bifunctional mechanism.