ORGANIC LETTERS

2013
Vol. 15, No. 3
650–653

Cobalt-Catalyzed Acceptorless Alcohol Dehydrogenation: Synthesis of Imines from Alcohols and Amines

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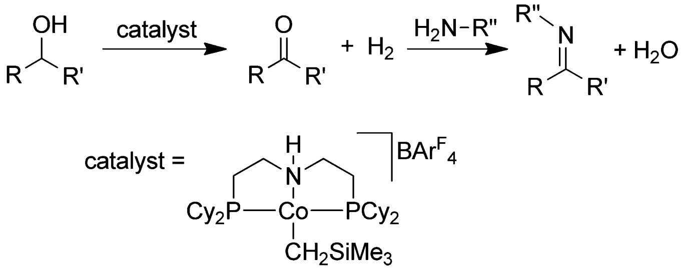
Received December 19, 2012

ABSTRACT



A cobalt catalyst has been developed for the acceptorless dehydrogenation of alcohols and applied to synthesize imines from alcohols and amines. Deuterium labeling studies suggest that the reaction proceeds by an initial reversible alcohol dehydrogenation step involving a cobalt hydride intermediate.

The acceptorless dehydrogenation of alcohols is an efficient and atom-economical method to convert alcohols into carbonyl compounds and other derivatives.[1,2] Alcohol dehydrogenation has applications in hydrogen storage and production, as a selective and low-temperature route to generate hydrogen from biomass-derived alcohols and carbohydrates.[3] It also has synthetic applications, including the oxidant-free synthesis of carbonyl compounds,[4] and tandem coupling reactions involving C–N and C–C bond formation[5,6] for the synthesis of imines[7] and amides[8] and the β-functionalization of alcohols.[9] Despite the importance of this transformation, examples of homogeneous catalysts for the acceptorless dehydrogenation of alcohols have thus far been limited to precious metals, especially Ru,[10] Rh,[11] and Ir.[12] The development of nonprecious metal catalysts would be a significant advance from the perspective of cost, abundance, and sustainable chemistry.

Herein, we report an earth-abundant metal cobalt catalyst for the acceptorless dehydrogenation of alcohols and

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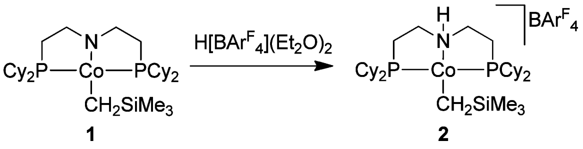
10.1021/ol303479f

its application to the synthesis of imines from alcohols and amines. For the imine formation reaction, the cobalt catalyst displays comparable activity to previously reported Ru catalysts[7a,b] and is effective for a range of benzylic and aliphatic alcohols and amines. No additional additives are necessary, highlighting the potential of cobalt as an alternative to precious-metal ruthenium, iridium, and osmium catalysts.

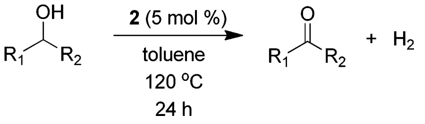
Recently, we reported that the cationic cobalt(II) alkyl complex $[(PNHP^{Cy})Co(CH_2SiMe_3)]BAr^F_4$ (**2**) is a precatalyst for the hydrogenation of alkenes, aldehydes, ketones, and imines.[13] Given the high activities observed for catalytic hydrogenation, we hypothesized that precatalyst **2** might also possess some activity for the dehydrogenation of alcohols. Complex **2** was generated *in situ* from the reaction of the neutral cobalt alkyl complex $(PNP^{Cy})Co(CH_2SiMe_3)$ (**1**) with $H[BAr^F_4]\cdot(Et_2O)_2$ (BAr^F_4 = $B(3,5\text{-}(CF_3)_2C_6H_3)_4$)[14] as previously described (Scheme 1).[13] We found that when a toluene solution of 1-phenylethanol was heated to reflux with **2** (5 mol %), acetophenone was formed in 90% isolated yield after 24 h, revealing that the cobalt catalyst is indeed capable of efficient alcohol dehydrogenation (Table 1, entry 1).

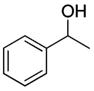
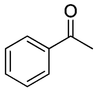
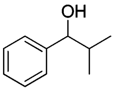
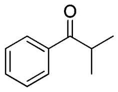
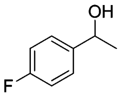
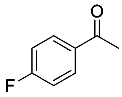
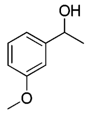
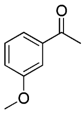
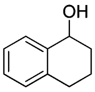
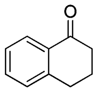
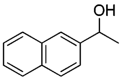
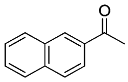
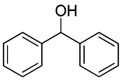
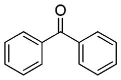
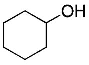
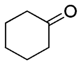
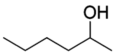
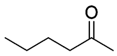
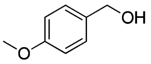
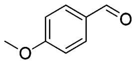
Scheme 1. Cobalt Complexes **1** and **2**



Cobalt catalyst **2** (5 mol %) was then tested for the acceptorless dehydrogenation of several different alcohols; the results are shown in Table 1. Dehydrogenation of secondary benzylic alcohols, including α-isopropylbenzylalcohol, tetrahydro-1-naphthol, and diphenylmethanol, proceeded readily within 24 h in refluxing toluene, affording the corresponding ketones in high isolated yields (65−95%, entries 2−7). Dehydrogenation of the secondary aliphatic alcohols 2-hexanol and cyclohexanol was also observed under the same conditions, affording 2-hexanone and cyclohexanone in 64% and 56% GC yields, respectively. The cobalt catalyst was less effective for the acceptorless dehydrogenation of the primary alcohol 4-methoxybenzyl alcohol, affording 4-methoxybenzaldehyde in only 24% yield.

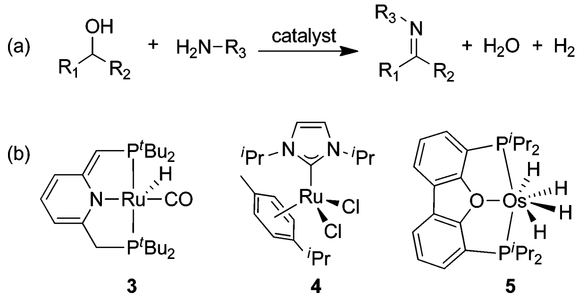
Table 1. Acceptorless Dehydrogenation of Selected Alcohols Using Cobalt Catalyst **2**[a]



entry	substrate	product	isolated yield [%]
1			90
2			81
3[b]			65
4			95
5			92
6			70
7			94
8			56[d]
9[b,c]			64[d]
10			24

[a] Conditions: Substrate (0.5 mmol), 5 mol % catalyst (5 mol % complex **1** and 5 mol % $H[BAr^F_4]\cdot(Et_2O)_2$) in toluene (2 mL) in a 100 mL reaction vessel, 120 °C. [b] 42 h. [c] Reaction run in THF. [d] Determined by GC.

Scheme 2. (a) Dehydrogenative Coupling of Alcohols and Amines To Form Imines; (b) Previously Reported Catalysts for the Imine Formation Reaction[7]



We then explored the application of the cobalt catalyst to the synthesis of imines via the dehydrogenative coupling of alcohol and amine reagents (Scheme 2a). This environmentally friendly approach to imine synthesis has advantages in terms of overall atom economy, producing water and hydrogen as the only reaction byproducts. Few prior examples of the direct synthesis of imines from

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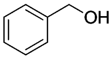
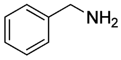
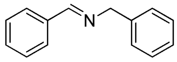
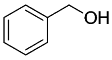
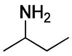
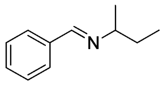
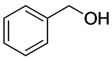
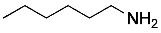
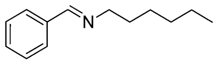
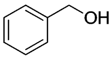
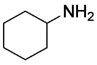
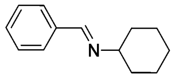
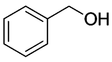
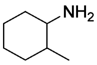
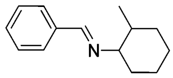
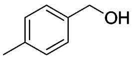
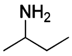
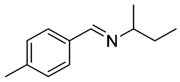
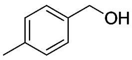
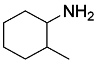
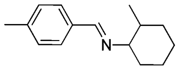
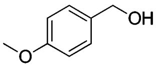
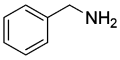
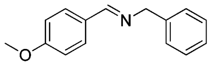
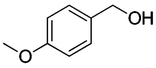
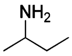
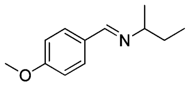
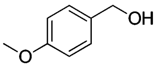
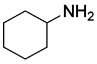
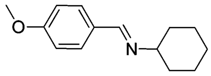
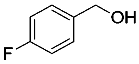
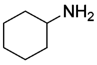
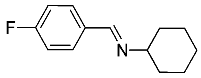
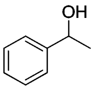
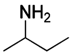
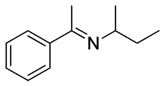
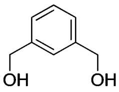
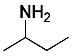
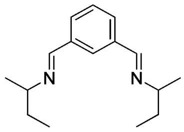
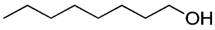
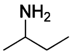
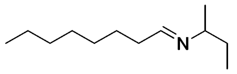
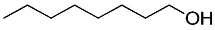
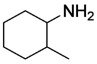
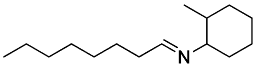
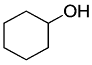
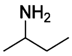
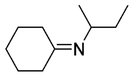
(12) Ir: (a) Morales-Morales, D.; Redón, R.; Wang, Z.; Lee, D. W.; Yung, C.; Magnuson, K.; Jensen, C. M. *Can. J. Chem.* **2001**, *79*, 823–829. (b) Musa, S.; Shaposhnikov, I.; Cohen, S.; Gelman, D. *Angew. Chem., Int. Ed.* **2011**, *50*, 3533–3537. (c) Mena, I.; Casado, M. A.; Polo, V.; Garcia-Orduña, P.; Lahoz, F. J.; Oro, L. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 8259–8263.

(13) Zhang, G.; Scott, B. L.; Hanson, S. K. *Angew. Chem., Int. Ed.* **2012**, *51*, 12102–12106.

(14) Brookhart, M.; Grant, B.; Volpe, A. F. *Organometallics* **1992**, *11*, 3920–3922.

Table 2. Cobalt-Catalyzed Synthesis of Imines from Alcohols and Amines[a]

entry	substrate A	substrate B	time (h)	product	GC yield % (isolated yield)
1[b]			27		80 (73) imine 15 amine
2			52		96 (85) imine <2 amine
3			48		88 (75) imine 12 amine
4			45		93 (83) imine 4 amine
5			50		99 (90) imine
6			50		94 (84) imine
7			50		96 (85) imine
8			52		93 (80) imine
9			45		98 (88) imine
10			50		81 (70) imine
11			52		74 (61) imine
12[d]			48		64 imine
13[c,d]			48		95 (85) imine
14[c,d]			48		70 imine 6 amine
15[c,d]			50		71 imine 3 amine
16[c,d]			48		56 imine 6 ketone

[a] Conditions: Substrate A (1.0 mmol), substrate B (1.1 mmol, except for *sec*-butylamine, 5.0 mmol), 1 mol % catalyst (1 mol % complex **1** and 1 mol % $H[BAr^F_4]\cdot(Et_2O)_2$), toluene (2 mL), 120 °C. [b] 0.2 mol % catalyst (0.2 mol % complex **1** and 0.2 mol % $H[BAr^F_4]\cdot(Et_2O)_2$). [c] 2 mol % catalyst was used (2 mol % complex **1** and 2 mol % $H[BAr^F_4]\cdot(Et_2O)_2$). [d] Reactions run in THF (2 mL).

alcohols and amines via dehydrogenation have been reported.[7] Milstein and co-workers first developed the ruthenium pincer catalyst **3** (Scheme 2b) for the dehydrogenative coupling of alcohols and amines to generate imines,[7a] and additional examples of ruthenium and osmium catalysts have been uncovered recently (**4** and **5**, Scheme 2b).[7b,c]

The imine formation reaction was tested by heating benzyl alcohol in the presence of benzylamine with cobalt precatalyst **2** (2 mol %) in toluene at 120 °C. After 24 h, GC-MS analysis of the reaction revealed complete conversion of the starting material, affording a mixture of the imine *N*-benzylidenebenzylamine (51%) and dibenzylamine (49%). When a lower catalyst load was used (0.2 mol %), 95% conversion was observed after 27 h and the selectivity for the imine increased to 80%. The cationic cobalt precatalyst proved to be essential for the imine formation reaction.

When the neutral cobalt alkyl complex **1** (2 mol %) was tested as a catalyst, only a very low yield of the imine product (7%) was obtained after 24 h (toluene, 120 °C). In the absence of a cobalt catalyst, no product formation was observed in a control reaction with benzyl alcohol and benzyl amine.

Further experiments explored the substrate scope of the imine formation reaction. Using benzyl alcohol as the substrate, a number of different amines were tested using cobalt precatalyst **2** (1 mol %, generated *in situ* from **1** and $H[BAr^F{}_4]\cdot(Et_2O)_2$) in refluxing toluene solvent (Table 2, entries 1−5). For a variety of primary amines, high yields (73−90% isolated yields) of the imine products were obtained within about 48 h. GC-MS analysis of the reaction mixture revealed that, in addition to the imine product and unreacted starting material, in some cases the corresponding amines were formed as byproducts in low yield (generally ≤10%; see Table 2 where noted for details).

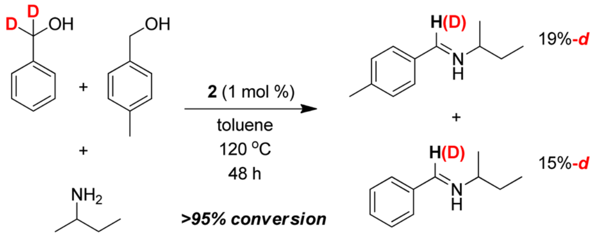
The impact of varying the substituents on the benzyl alcohol coupling partner was also assessed. The imine formation reaction proceeded in high yields with either electron donating (4-methyl, 4-methoxy) or electron withdrawing (4-fluoro) substituents on the benzyl alcohol (entries 6−11). The secondary alcohol 1-phenylethanol reacted readily with *sec*-butylamine in THF solvent, affording the corresponding ketimine in good yield (64%, entry 12), along with unreacted starting material (36%). For the disubstituted benzyl alcohol 1,3-benzene-dimethanol, the di-imine product was obtained in high yield (entry 13).

The synthesis of aliphatic imines is considered more challenging than benzylimines, as the aliphatic imine products are typically more readily hydrolyzed.[7] Furthermore, previous reports of amine alkylation reveal that aliphatic alcohols are often less reactive substrates than benzylic alcohols.[15] Using cobalt catalyst **2**, the dehydrogenative coupling reaction was tested with aliphatic alcohols in THF, affording aliphatic imines in moderate yields (Table 2, entries 14−16). For the reaction of the secondary aliphatic alcohol cyclohexanol with *sec*-butylamine, the imine product was obtained in 56% yield, along with cyclohexanone (6%) (entry 16). Notably, no formation of amide or ester products was detected. Amide and ester byproducts have been observed in previous imine formation reactions catalyzed by Ru complexes **3** and **4** (Scheme 2b).[8,16] For related Ru catalysts of PNN pincer ligands, amides are produced as the major products upon the dehydrogenative coupling of alcohols and amines.[8a]

Previous examples of the synthesis of imines from alcohols and amines have been proposed to proceed by a pathway involving initial alcohol dehydrogenation, generating an aldehyde or ketone intermediate which then undergoes Schiff base condensation with the amine to generate the imine product and water.[7] However, while alcohol dehydrogenation is a well-known reaction for homogeneous ruthenium complexes,[10] there is little precedent for cobalt catalysts. To gain further insight into possible mechanisms of the cobalt catalyst several additional experiments were performed.

To confirm the production of hydrogen gas, the cobalt-catalyzed imine formation reaction between benzyl alcohol and *sec*-butylamine was performed, and then the headspace gas was collected and used to successfully hydrogenate an olefin in a separate flask. Consistent with a pathway involving initial alcohol dehydrogenation, no coupling reaction was observed when the reaction was tested with *tert*-butanol. A deuterium labeling study was carried out by testing the reaction of a 1:1 mixture of 4-methylbenzyl alcohol and α,α-d_2-benzyl alcohol with *sec*-butylamine (5 equiv). The reagents were heated with cobalt precatalyst **2** in toluene at 120 °C for 48 h. *N*-4-Methylbenzylidene-*sec*-butylamine and *N*-benzylidene-*sec*-butylamine were observed as reaction products (Scheme 3). H/D scrambling was detected in both of the imine products, suggesting that the initial alcohol dehydrogenation step is reversible and implicating a cobalt hydride species as a catalytic intermediate.

Scheme 3. Deuterium Labeling Study of the Imine Formation Reaction



Further supporting the proposal of reversible dehydrogenation, cobalt complex **2** was heated at 120 °C with a 1:1 mixture of α,α-d_2-benzyl alcohol and 4-methoxybenzaldehyde for 24 h, and then the 4-methoxybenzaldehyde was recovered and isolated from the reaction mixture. Deuterium incorporation (58%) into the aldehyde position of 4-methoxybenzaldehyde was detected by ^1H NMR spectroscopy.

In summary, the cobalt catalyst described here is a promising example of a homogeneous earth-abundant metal catalyst for the acceptorless dehydrogenation of alcohols. The catalytic dehydrogenation reaction has been successfully applied to the synthesis of imines from alcohols and amines. Deuterium labeling studies indicate that the imine formation reaction proceeds by an initial reversible alcohol dehydrogenation step involving a cobalt hydride intermediate. These findings have significant implications for future catalyst development, highlighting the broader potential of cobalt for mimicking the reactivity of precious metal catalysts.

Acknowledgment. This work was funded by Los Alamos National Laboratory LDRD Early Career Award (2011-0537ER) and Director's Post-Doctoral Fellowship (G.Z.).

Supporting Information Available. Experimental details and spectroscopic data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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