Manganese-Catalyzed Environmentally Benign Dehydrogenative Coupling of Alcohols and Amines to Form Aldimines and H₂: A Catalytic and Mechanistic Study

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S *Supporting Information*

ABSTRACT: The catalytic dehydrogenative coupling of alcohols and amines to form aldimines represents an environmentally benign methodology in organic chemistry. This has been accomplished in recent years mainly with precious-metal-based catalysts. We present the dehydrogenative coupling of alcohols and amines to form imines and H₂ that is catalyzed, for the first time, by a complex of the earth-abundant Mn. Detailed mechanistic study was carried out with the aid of NMR spectroscopy, intermediate isolation, and X-ray analysis.

Figure 1. Overview of the present work and the dearomatized Mn pincer **1** used in this study.

Imines and their derivatives are important synthesis intermediates because of their diverse reactivity and have been extensively utilized in the synthesis of dyes, fragrances, fungicides, pharmaceuticals, and agricultural chemicals.[1] Imines also serve as common ligands in coordination chemistry. Conventionally, imines are synthesized by the acid-catalyzed condensation of aldehydes or ketones with amines. Recently, versatile alternative methods have been reported, such as oxidation of secondary amines,[2] self-condensation of primary amines upon oxidation,[3] oxidative coupling of alcohols and amines,[4] hydroamination of alkynes with amines,[5] and the partial hydrogenation of nitriles followed by coupling with the amines.[6] Self-coupling of amines uses O₂ as an oxidant; the products are limited to symmetric imines.

Alternatively, direct acceptorless dehydrogenative coupling of alcohols and amines is one of the most promising, green synthesis pathways for the preparation of imines because alcohols are readily available by a variety of industrial processes and can be obtained renewably via fermentation or catalytic conversion of lignocellulosic biomass.[7] Only H₂ and water are produced as byproducts in this pathway (Figure 1). In 2010, we reported the first acceptorless dehydrogenative coupling of alcohols and amines to form imines selectively, catalyzed by a Ru pincer complex.[8] Since then, this field has progressed rapidly; several catalytic systems for such transformation have been developed, mainly with precious-metals-based catalysts.[9]

There is strong current interest in the replacement of noble metal catalysts by more economical, environmentally friendly catalysts based on earth-abundant metals.[10] Noteworthy progress has been made in the area of homogeneous earth-abundant-metal-based hydrogenation and dehydrogenation catalysis.[11]
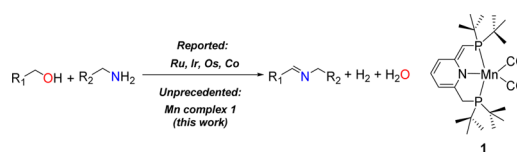
Recently, Feringa and Barta, as well as Kempe reported the alkylation of amines with alcohols by a borrowing hydrogen methodology utilizing an Fe catalyst based on cyclopentadienone ligands or a Co catalyst based on a triazine backbone[12] in which an imine intermediate is in situ hydrogenated to the corresponding amine. Several Fe-based catalysts for the hydrogenation and dehydrogenation of alkynes, ketones, aldehydes, esters, and alcohols were developed.[13] Substantial efforts were also made toward the development of Co catalysts for homogeneous hydrogenation and dehydrogenation reactions.[14] Recently, we reported the hydrogenation of nitriles and esters catalyzed by a homogeneous pincer Co complex.[15] In contrast to the development of several homogeneous catalysts based on Fe and Co, catalytic reactions based on Mn complexes are less developed.[16] To our knowledge, there are no literature reports on hydrogenation and dehydrogenation reactions catalyzed by Mn complexes, although Mn is one of the most earth-abundant transition metals, third only to Fe and Ti. We report the unprecedented dehydrogenative coupling of alcohols and amines catalyzed by a Mn PNP pincer complex, selectively yielding imines and H₂.

Dehydrogenative coupling of benzyl alcohol with benzylamine to give *N*-benzylidene-1-phenylmethanamine was chosen as a model system for initial studies. A dry toluene solution containing equimolar amounts of benzyl alcohol and benzylamine and a catalytic amount of **1**[17] (Figure 1) was heated at 135 °C (bath temperature) for the specified time (Table 1). The products were analyzed by GC-MS and NMR and identified by comparison with authentic samples. Heating a solution of benzyl alcohol (0.5 mmol) and benzylamine (0.5 mmol) with **1** (4 mol %) in a closed system under a N₂ atmosphere at 135 °C in toluene (2 mL) resulted in 76% conversion to *N*-benzylidene-1-phenylmethanamine after 30 h (Table 1, entry 1). Analysis of the gas phase by

Table 1. Optimization of Reaction Conditions for the Coupling of Benzyl Alcohol with Benzylamine Catalyzed by 1[a]
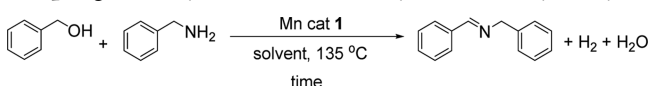
| entry	cat (mol %)	solvent	time (h)	conv. (%)[b]	yield of imine (%)[c]
1	4	toluene	30	76	76
2	4	benzene	36	85	82
3	3	benzene	48	90	89
4	2	benzene	48	62	62
5	3	benzene	60	92	92
6	3	benzene	60	94	94[d]
7	3	dioxane	60	<5	<5
8	3	THF	60	<5	<5
9	3	benzene	60	98	98 (86)[e]

[a]Reaction conditions: alcohol (0.5 mmol), amine (0.5 mmol), Mn cat, and solvent (2 mL) at 135 °C (bath temperature) in a closed system under N_2 atmosphere. [b]Based on the consumption of benzyl alcohol. [c]Yields were determined by ^{1}H NMR with respect to toluene or dioxane as an internal standard or by GC analysis; [d]Reaction was carried out under argon atmosphere in an open system; [e]Catalyst generated in situ from mer-[Mn(PNP^{tBu})(CO)$_3$]Br[17] and one equivalent of t-BuOK, see SI for details. Isolated yield in parentheses.

GC revealed the formation of H_2. No side products, such as amides or esters which were observed in small amounts when a Ru catalyst was used,[8] were observed here. Interestingly, no products resulting from hydrogenation of the imine double bond, such as dibenzylamine, were observed.

Carrying out the reaction in benzene (2 mL) for 36 h in a closed system resulted in 85% consumption of benzyl alcohol and 82% yield of *N*-benzylidene-1-phenylmethanamine, together with a small amount of unreacted aldehyde generated from the alcohol (Table 1, entry 2). Lowering the loading of **1** from 4 mol % to 3 or 2 mol % resulted in 89% and 62% yield of *N*-benzylidene-1-phenylmethanamine, respectively, after 48 h (Table 1, entries 3 and 4). However, extending the reaction time to 60 h while using 3 mol % of **1** resulted in 92% yield of the desired imine (Table 1, entry 5). We note that when the dehydrogenation reaction was carried out in an open system under an argon atmosphere 94% of *N*-benzylidene-1-phenylmethanamine was furnished which is comparable to the yield obtained in the closed system (Table 1, entries 5 and 6) indicating that the presence of H_2 does not have a significant effect on the reaction. Use of polar solvents has an adverse effect. With dioxane or THF as solvents, only <5% of *N*-benzylidene-1-phenylmethanamine was formed in both cases (Table 1, entries 7 and 8), with the rest being the starting compounds. The catalyst can be generated in situ from the air stable mer-[Mn(PNP^{tBu})(CO)$_3$]Br[17] and an equivalent of t-BuOK (Table 1, entry 9, and Supporting Information (SI)).

Under optimized conditions (Table 1, entry 5), we explored the substrate scope. A variety of substituted benzyl alcohols underwent efficient dehydrogenative coupling with amines containing either electron-donating or -withdrawing substituents (Table 2, see SI for more detailed table). Heating a solution of benzyl alcohol with cyclohexylamine or 2-phenylethylamine using **1** at 135 °C in benzene (2 mL) in a closed system resulted in exclusive formation of the corresponding imines in 93% and 95% yields, respectively (Table 2, entries 1 and 2). Use of amines bearing electron-donating substituents often resulted in higher yields than when amines with electron-withdrawing substituents were used, presumably because of higher nucleophilicity of the former. 4-Methoxybenzylamine and 4-fluorobenzylamine react

Table 2. Dehydrogenative Coupling of Various Alcohols and Amines Catalyzed by 1[a]
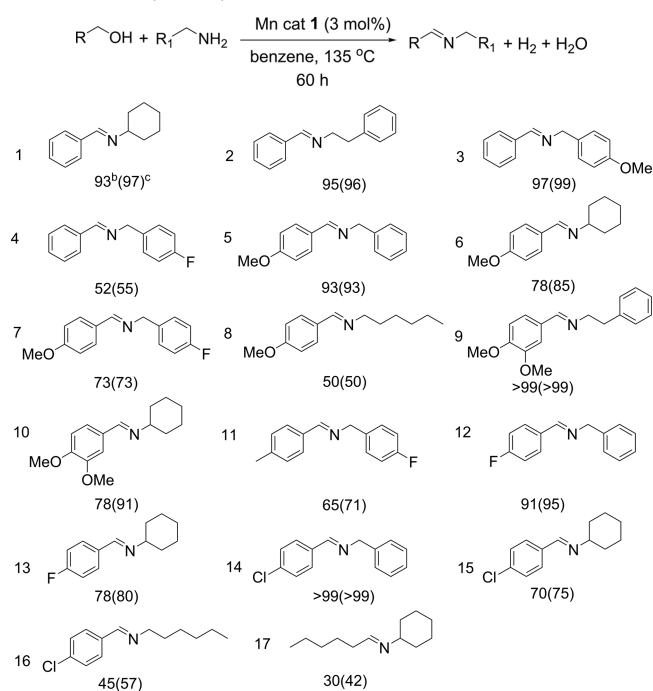
[a]Reaction conditions: alcohol (0.5 mmol), amine (0.5 mmol), Mn cat (3 mol %), and benzene (2 mL) at 135 °C (bath temperature) for 60 h in a closed system under N_2 atmosphere. [b]Yields were determined by ^{1}H NMR with respect to toluene or dioxane as an internal standard or by GC analysis. [c]Based on the consumption of alcohol.

with benzyl alcohol under similar reaction conditions to give 97% and 52% yield of the corresponding imines (Table 2, entries 3 and 4). Analysis of the reaction mixture in the latter case by ^{1}H NMR and GC-MS indicated the presence of the starting materials and a small amount of benzaldehyde. **1** also catalyzed effectively the reaction of 4-methoxybenzyl alcohol with benzylamine, cyclo-hexylamine, and 4-fluorobenzylamine to afford corresponding imines in 93%, 78%, and 73% yield, respectively (Table 2, entries 5−7). When hexylamine reacted with 4-methoxybenzyl alcohol, only 50% of the corresponding imine was formed under analogous reaction conditions (Table 2, entry 8). Extending the reaction time slightly increased the yield of the desired imine.

Reaction of 3,4-dimethoxybenzyl alcohol with 2-phenylethyl-amine or cyclohexylamine furnished the corresponding imines in 99% and 78% yield, respectively (Table 2, entries 9 and 10). 4-Methylbenzyl alcohol reacted with the 4-fluorobenzylamine to yield the corresponding imine in 65% yield and traces of aldehyde (Table 2, entry 11). Alcohols with an electron-withdrawing substituent at the para position also underwent the catalytic reaction. Reaction of 4-fluorobenzyl alcohol with benzylamine or cyclohexylamine using **1** produced 91% and 78% of the corresponding imines, respectively (Table 2, entries 12 and 13). The catalytic reaction of 4-chlorobenzyl alcohol with benzyl-amine and cyclohexylamine under analogous reaction conditions yielded 99% and 70% of the corresponding imines, respectively (Table 2, entries 14 and 15). However, the reaction with aliphatic amines under analogous reaction conditions proceeded slowly; reaction of 4-cholorobenzyl alcohol with hexylamine produced the imine in 45% yield (Table 2, entry 16). The lower yield of imine in case of hexylamine, compared to that of cyclohexylamine, can be attributed to the higher nucleophilicity of the latter.

Synthesis of aliphatic imines is intrinsically more challenging because of their relative instability. Aliphatic alcohols react with aliphatic amines to give the imine, albeit at a lower yield. 1-Hexanol reacted with cyclohexylamine to yield the corresponding imine in 30% yield (Table 2, entry 17). Extending the reaction time did not increase the yield of the desired imine appreciably.

Aiming at gaining insight regarding possible intermediates, the reaction of **1** with benzyl alcohol was monitored by $^{31}P\{^1H\}$NMR (Figure 2). **1** exhibits a set of two sharp doublets at δ 87.15 and 101.3 ppm ($^2J_{P-P}$ = 68.2 Hz) in the $^{31}P\{^1H\}$ NMR spectrum (Figure 2A). When dissolved in benzyl alcohol (270 equiv), a dramatic change in the $^{31}P\{^1H\}$ NMR spectrum was observed, with the appearance of a broad singlet at δ 104.5 ppm, suggesting a dynamic process (Figure 2B). This could be due to reversible formation of an alkoxo complex with concomitant aromatization of the pincer ligand, as observed previously in the case of a Ru pincer system.[18] To verify this, the alkoxo complex [Mn(PNP^{tBu})-(OCH$_2$Ph)(CO)$_2$] (**2**) was synthesized independently by addition of 3 equiv of benzyl alcohol to a saturated pentane solution of **1**. X-ray diffraction of crystals of **2**, obtained at −38 °C (Scheme 1 inset), revealed the activation of the O-H bond of the benzyl alcohol by **1**. Complex **2** exhibits a Mn(I) center in a distorted octahedral geometry, with the alkoxo moiety bound in an axial position (SI). The IR spectrum of **2** exhibits absorption bands at 1814 and 1891 cm^{-1} that are characteristic of an octahedral dicarbonyl compound in a cis arrangement. Previously, we demonstrated similar activation of X-H bonds (X = H, O, and N) by metal-ligand cooperation (MLC) using PNP- or PNN-based Ru pincer complexes under catalytic or stoichiometric conditions.[19]
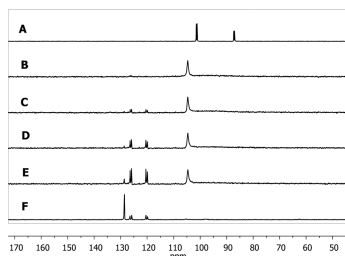

Figure 2. Selected part of $^{31}P\{^1H\}$ NMR spectra of **1** with benzyl alcohol at room temperature: (A) **1** in C$_6$D$_6$, (B) **1** in neat benzyl alcohol, (C) after 20 min of addition, (D) after 60 min of addition, (E) after 120 min of addition, and (F) complexes **4** and **5** independently dissolved in benzyl alcohol.

Continuing the NMR experiment, 20 min after adding benzyl alcohol to **1**, a new set of two sharp AB doublets appeared in solution at δ 120.2 and 126.2 ppm ($^2J_{P-P}$ = 106.4 Hz, Figure 2C), which we assign to the benzaldehyde adduct, [Mn(PNP^{tBu}-OCHPh)(CO)$_2$] (**4**, Scheme 1). Formation of **4** involves the dehydrogenation of benzyl alcohol to benzaldehyde by **1** followed by its electrophilic attack on the dearomatized ligand. Analogous alkoxo and aldehyde-addition complexes were observed in alcohol dehydrogenative coupling catalyzed by a PNP-Ru complex (Scheme 1).[18] In accord with our data, we believe that the mechanism of the Mn-catalyzed process follows a pathway similar to that of the PNP Ru-catalyzed reactions. The dehydrogenation of the alcohol likely proceeds through a (presumably concerted) bifunctional proton and hydride transfer, illustrated as transition state **3** (Scheme 1).[20] Formation of the aldehyde by direct β-H elimination of the alkoxy ligand of coordinatively saturated **2** (reversibly formed under the reaction

Scheme 1. Proposed Mechanism for Imine Formation[a]
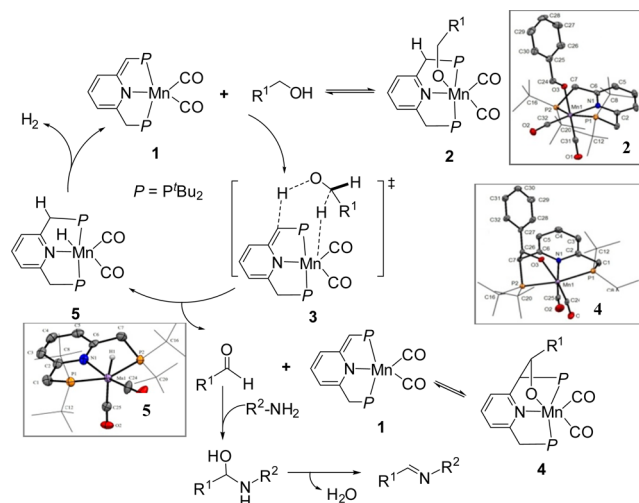
[a]The X-ray structures of complexes **2**, **4**, and **5** are shown in the insets (see SI for details).

conditions) is less likely. The identity of **4** was also verified by its independent synthesis. Treating a saturated THF solution of **1** with two equivalents of benzaldehyde, followed by exposure to pentane vapor, yielded after 72 h at 25 °C single crystals of **4**. The X-ray structure of **4** (Scheme 1 inset), indicates the product of aldehyde binding to the ligand framework with formation of Mn-O and C-O bonds. ^{31}P NMR of **4** in neat benzyl alcohol was found to be in accordance with the NMR experiment (Figure 2F). This eliminates the possibility of subsequent attack of alcohol on **4**.

Moreover, in continuation of the NMR experiment, after 60 min a new singlet at δ 128.7 ppm appeared (Figure 2D,E). This was identified as the hydride complex [Mn(PNP^{tBu})H(CO)$_2$] (**5**). Interestingly, when this reaction mixture was pressurized with H$_2$, an increase in intensity of the singlet at δ 128.7 ppm was observed, indicating formation of Mn-H complex **5**. Moreover, **5** was separately synthesized by treatment of **1** with H$_2$ in C$_6$D$_6$. ^1H NMR spectrum of **5** shows a hydride resonance at δ −4.19 ppm. The molecular structure of **5** is presented in Scheme 1 (inset), obtained from a single-crystal X-ray analysis. Dissolving it in neat benzyl alcohol verified assignment of the observed ^{31}P NMR signal in the NMR experiment (Figure 2F). **5** then undergoes dehydrogenation under the catalytic condition to regenerate active **1**, which then enters into the second catalytic cycle (Scheme 1). The released aldehyde reacts with an amine to yield an unstable hemiaminal, which releases a molecule of water to form the final imine product. Although few studies related to the mechanistic aspects of the Ru-catalyzed dehydrogenation of alcohols are reported, most of them are based on computational studies, except for few reports.[9h,18] This is a rare case of isolation and structural characterization of possible intermediates in catalytic dehydrogenation of alcohols.

In summary, an unprecedented dehydrogenative coupling of alcohols and amines to form imines catalyzed by a complex of earth-abundant Mn is reported. The catalytic reaction proceeds under neutral conditions with liberation of H$_2$. A variety of alcohols and amines were employed to furnish imines in good to excellent yields in an environmentally friendly method. A mechanistic study involving NMR spectroscopy, intermediate isolation, and X-ray crystallography sheds light on the catalytic mechanism.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b13519.

　　Experimental details. (PDF)
　　Crystallographic information files for **2**, **4**, and **5**. (CIF)

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A.M. and A.N. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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