Base-Metal Catalysis Hot Paper

International Edition: DOI: 10.1002/anie.201700681
German Edition: DOI: 10.1002/ange.201700681

Manganese-Catalyzed N-Formylation of Amines by Methanol Liberating H_2: A Catalytic and Mechanistic Study

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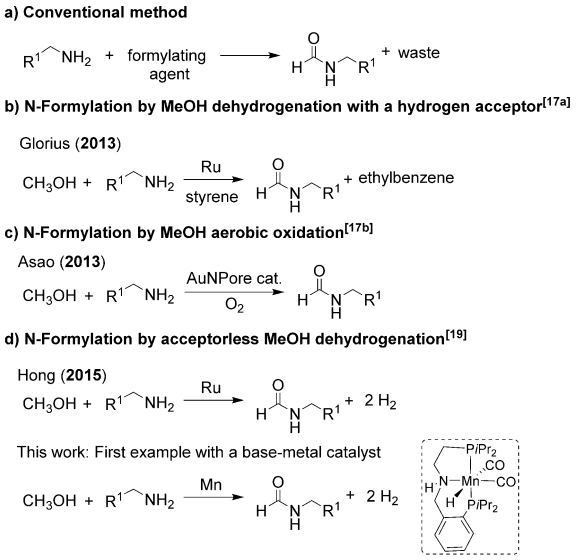
Abstract: *The first example of a base metal (manganese) catalyzed acceptorless dehydrogenative coupling of methanol and amines to form formamides is reported herein. The novel pincer complex (iPr-PN^{H}P)Mn(H)(CO)$_2$ catalyzes the reaction under mild conditions in the absence of any additives, bases, or hydrogen acceptors. Mechanistic insight based on the observation of an intermediate and DFT calculations is also provided.*

Formamides are valuable intermediates in the synthesis of pharmaceuticals, agrochemicals, dyes, and fragrances.[1] They also serve as industrial solvents,[2] and are useful reagents for the Vilsmeier–Haack reaction and in the synthesis of formamidines and isocyanates.[3,4] In addition, formyl moieties are important amine protecting groups in peptide synthesis.[5]

In general, an excess of the formylating reagent and the corresponding amine is required for the synthesis of formamides.[6] Several other methods have also been developed recently.[1c,7] However, most of them suffer from toxicity issues, expensive reagents, moisture sensitivity, poorly accessible starting materials, long reaction times, and the generation of copious waste.[8] In terms of sustainability, an attractive "green" route is the acceptorless dehydrogenative coupling (ADC) of methanol with amines; methanol is an abundant feedstock that can be obtained from renewable resources (biomass) and atmospheric CO_2.[9]

Acceptorless dehydrogenative couplings of alcohols to form C–C and C–N bonds have emerged as a powerful approach for various environmentally benign organic transformations.[10] However, catalytic dehydrogenation to the aldehyde is considerably more problematic for methanol ($\Delta H = 84\ kJ\,mol^{-1}$) than for higher alcohols, such as ethanol ($\Delta H = 68\ kJ\,mol^{-1}$),[11] and the generated formaldehyde is very unstable towards decomposition to CO and hydrogen, making dehydrogenative couplings using methanol challenging and less explored. There are only a few reports on methanol dehydrogenation.[12] In 2011, Krische and co-workers reported an iridium-catalyzed direct C–C bond coupling of 1,1-disubstituted allenes and methanol to form homoallylic neopentyl alcohols in which methanol dehydrogenation was considered to be a crucial step.[12a] The groups of Beller, Grützmacher, and Fujita as well as our own group reported on the aqueous-phase dehydrogenation of methanol to generate H_2 using pincer Ru and Ir catalysts.[13–16] An NHC/Ru complex catalyzed dehydrogenative coupling of methanol and amines to formamides with excess styrene as the hydrogen acceptor was described by Glorius and co-workers (Scheme 1 b).[17a]



Scheme 1. Synthetic strategies towards *N*-formamides.

Gold-catalyzed aerobic N-formylation using methanol was reported by the Asao group (Scheme 1 c).[17b] In addition, an ADC of *ortho*-aminobenzamides and methanol to quinazolinones in the presence of an Ir complex was reported by Li and co-workers.[18] Ru-catalyzed ADCs of methanol with amines to formamides were reported by Hong and Kanga (Scheme 1 d),[19a] and very recently by Prakash and co-workers for *N*,*N*′-dimethylethylenediamine.[19b] However, the aforementioned elegant transformations are all based on precious noble-metal catalysts.

Replacing expensive metal-based catalysts by earth-abundant base-metal complexes (Fe, Co, Ni, Mn) in homogeneous catalysis is of much interest nowadays.[20–23] In fact, considerable progress in catalysis by complexes of earth-abundant metals has been made for various (de)hydrogen-

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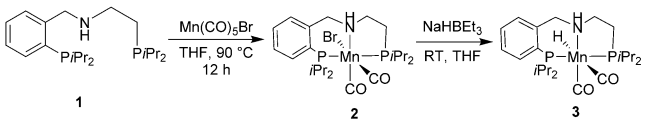
ation reactions, including the dehydrogenation of aqueous methanol to form H_2 and CO_2[23a] and dehydrogenative couplings of methanol to form methyl formate[23b] catalyzed by iron complexes. Substantial efforts have also been made towards the application of manganese[24–29] in (de)hydrogenation reactions; manganese is the third most abundant metal in the earth's crust after iron and titanium.

Subsequent to our report on the dehydrogenative coupling of alcohols and amines to give imines[24a] with a pincer Mn(PNP*t*Bu) catalyst, several other reports on Mn-catalyzed (de)hydrogenation reactions appeared. Recently, C-alkylations of ketones[25a] and N-alkylations of amines using alcohols[25b] based on so-called "borrowing hydrogen strategies" were reported by Beller and co-workers. The groups of Beller and Kempe independently developed ketone hydrogenation reactions catalyzed by Mn pincer complexes, including nitrile hydrogenation by Beller.[26] Very recently, Beller[27a] and co-workers and our group[27b] independently described the hydrogenation of esters to alcohols with Mn(PNP) pincer complexes as the catalysts.

To the best of our knowledge, the desirable ADC of methanol and amines to form formamides catalyzed by complexes of base metals has not been reported thus far. Herein, we report such a reaction, which gave formamides as the major products under mild conditions in the presence of a new Mn complex. Mechanistic insight based on the observation of an intermediate and DFT calculations is also provided.

Treatment of our previously reported *i*Pr-PN^{H}P ligand **1**[30] with $Mn(CO)_5Br$ (1 equiv) at 90 °C in THF led to the formation of the yellow Mn(*i*Pr-PN^{H}P)$(CO)_2$Br complex (**2**)



Scheme 2. Synthesis of the manganese(I) complexes.

in 86% yield (Scheme 2). Single crystals of **2** that were suitable for X-ray diffraction were obtained by slow diffusion of pentane into a saturated solution of the compound in toluene at −30 °C. The molecular structure exhibits an octahedral geometry with meridional coordination of the *i*Pr-PN^{H}P ligand (Figure 1; see also the Supporting Information).

The addition of $NaHBEt_3$ (1 equiv) to a solution of **2** in THF at room temperature furnished the monohydrido complex (*i*Pr-PN^{H}P)Mn(H)$(CO)_2$ (**3**) in 88% yield (Scheme 2). The ^{1}H NMR spectrum of **3** displays a triplet at $\delta = -5.5$ ppm (t, $^2J_{PH} = 60$ Hz, Mn−H), which corresponds to the hydride ligand. The IR stretching bands at 1805 and 1879 cm^{-1} in a 1:1 ratio correspond to the orthogonal carbonyl ligands of **3**.

Complex **3** catalyzes the dehydrogenative coupling of methanol and amines. Thus the reaction of piperidine (0.5 mmol) and **3** (2 mol%) in MeOH (1 mL) at 110 °C in a closed system resulted in the formation of *N*-formylpiperidine in 86% yield after 12 h (Table 1, entry 1). It is noteworthy that this reaction proceeds in the absence of a hydrogen acceptor. GC analysis of the gases in the headspace indicated the formation of H_2. A small amount of *N*-methylpiperidine (13%) was also observed, which results from reductive amination of the formaldehyde intermediate with the amine in a borrowing hydrogen process.[31] However, when the reaction was carried out in an open system at reflux, *N*-formylpiperidine was formed in only 35% yield after 24 h, which might be due to the lower temperature, along with the formation of an unidentified product; as expected, N-methylation of piperidine was not observed (see the Supporting Information, Table S1, entry 3).

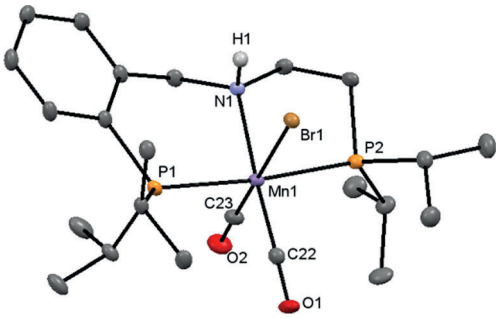
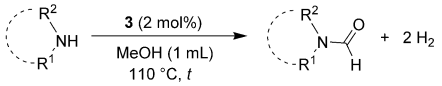


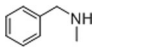
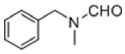
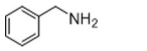
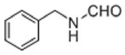
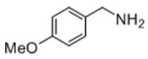
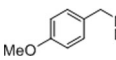
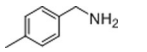
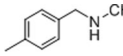
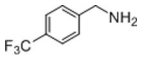
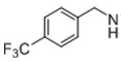
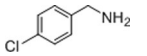
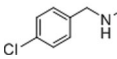
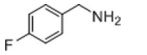
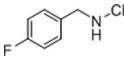
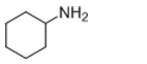
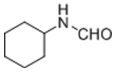
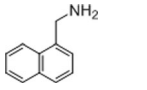
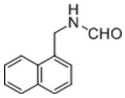
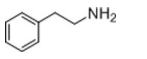
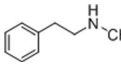
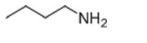
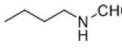
Figure 1. Molecular structure of **2**.[33] Thermal ellipsoids set at 50% probability. Selected hydrogen atoms omitted for clarity. For bond lengths, angles, and experimental details, see the Supporting Information.

Next, the scope of this unprecedented base-metal-catalyzed ADC of methanol was probed with different amines. As shown in Table 1, the cyclic secondary amines pyrrolidine and morpholine were converted into the corresponding formamides in moderate to good yields (entries 2 and 3). The reaction of *N*-methylbenzylamine with methanol afforded *N*-benzyl-*N*-methylformamide in 78% yield (entry 4). Exploring the scope further, dehydrogenative reactions of methanol with various substituted primary benzylamines were studied. The reaction of methanol with benzylamine, 4-methoxybenzylamine, and 4-methylbenzylamine afforded the corresponding formamides in good yields (67–74%, entries 5–7). Reactions of methanol with benzylic amines bearing electron-withdrawing groups in the *para* position (*p*-CF_3, *p*-Cl, *p*-F) afforded the corresponding formamides in moderate yields (entries 8–10). The reaction of primary amines is not limited to benzylamines. The reaction of methanol and cyclohexylamine furnished *N*-cyclohexylformamide in 66% yield (entry 11). Similarly, *N*-(2-phenylethyl)formamide and
N-butylformamide were obtained in 53 and 64% yield, respectively, upon heating methanol and the corresponding amines (entries 13 and 14). 1-Naphthylmethylamine was formylated in 62% yield after 15 h (entry 12).

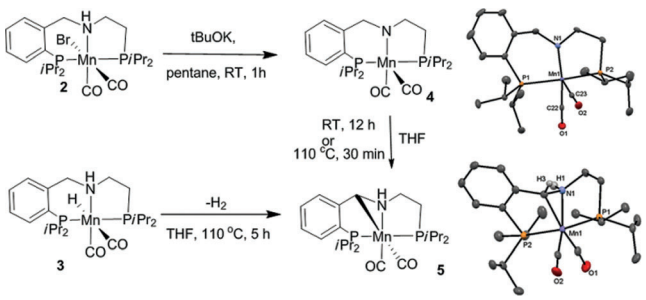
To gain insight into the mechanism of the manganese-catalyzed ADC of methanol and amines, the amine complex **2** was reacted with *t*BuOK (1.2 equiv) in pentane at room temperature. Deep red crystals of the amido species **4** were obtained (Scheme 3; for full characterization, see the Supporting Information), and its structure was confirmed by X-ray diffraction (Scheme 3; see also the Supporting Infor-

Table 1: Acceptorless dehydrogenative formylation of amines with methanol and catalyst **3**.[a]



Entry[a]	Amine	Product	t [h]	Conv. [%][b]	Yield [%][b]
1			12 12 12	99 99 99	86 72[c] 78[d]
2			14	97	61
3			24	99	50
4			15	99	78
5			14	99	70
6			12	99	67
7			18	99	74
8			12	83	71
9			12	99	56
10			14	99	57
11			12	93	66
12			15	99	62
13			24	99	53
14			15	97	64

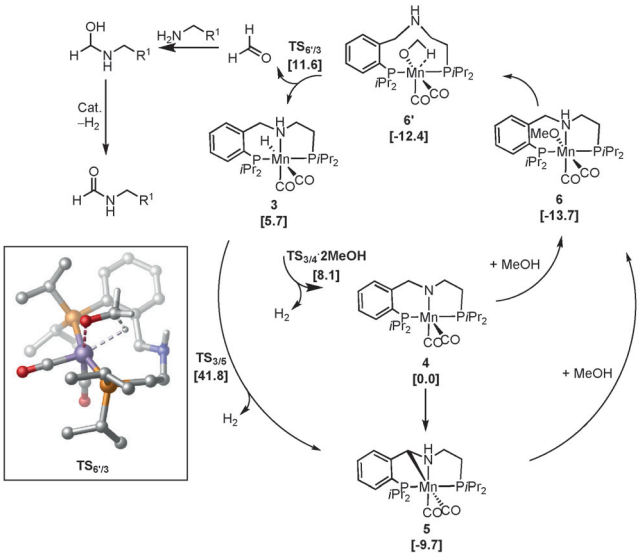
[a] Reaction conditions: Amine (0.5 mmol), MeOH (1 mL), **3** (0.01 mmol), heated in a 100 mL closed Fischer–Porter tube at 110 °C. [b] Yields and conversions determined by GC or NMR analysis using toluene or *meta*-xylene as the internal standard. The conversions are based on amine consumption. [c] Complex **4** as the catalyst. [d] Complex **5** as the catalyst. Differences in yield and conversion indicate the formation of the N-methylated amine and also an unidentified side product.



Scheme 3. Reactivity of complexes **2** and **3**.

mation).[33] Employing the freshly prepared amido complex **4** (2 mol%) as a catalyst in the dehydrogenative coupling of methanol and piperidine at 110 °C yielded 72% of *N*-formylpiperidine after 12 h (Table 1, entry 1, second row). However, **4** turned out to be unstable at room temperature (stable at −30 °C for several hours), and was transformed into the thermodynamically more stable light yellow metalated complex **5** (Scheme 3) at room temperature in less than 12 h or upon heating at 110 °C for 30 min. Thus intramolecular C–H activation took place, involving cooperation between the metal center and the amido ligand of **4**. Heating complex **3** at 110 °C in THF also resulted in the formation of **5** (Scheme 3). Its structure was confirmed by X-ray diffraction[33] and detailed NMR spectroscopic studies (see the Supporting Information). Complex **5** also catalyzed the dehydrogenative coupling reaction, providing *N*-formylpiperidine in 78% yield after 12 h (Table 1, entry 1, third row).

Significantly, treatment of **4** with methanol (2 equiv) in C_6D_6 at room temperature resulted in instant formation of a new complex that exhibited broad resonances in the ^{1}H NMR spectrum and two broad ^{31}P{^{1}H} NMR signals at $\delta = 55$ and 85 ppm. Upon conducting the experiment in [D_8]toluene with methanol (1 equiv), the ^{31}P NMR spectrum at −30 °C exhibited two sharp doublets at $\delta = 57.1$ ($^2J_{PP} = 142$ Hz) and 88.7 ppm ($^2J_{PP} = 142$ Hz), attributable to methoxy complex **6** (Scheme 4). A sharp signal at $\delta =$ 3.9 ppm in the ^{1}H NMR spectrum (−30 °C) was assigned to a proton of the methoxy ligand. Another sharp minor resonance at $\delta = 3.1$ ppm, overlapping with other resonances, was due to free methanol. Irradiation of the signal at $\delta =$ 3.9 ppm (1D NOE study at −30 °C) led to an NOE enhancement of the resonances at $\delta = 3.1$ ppm, indicating exchange with free methanol. ^{2}H NMR spectroscopy of the



Scheme 4. Plausible mechanism for the acceptorless dehydrogenative coupling of methanol and amines. $\Delta G_{vib+rot}$ values calculated at the SMD(MeOH)-TPSS-D3BJ/def2-TZVPP//BP86-D3/def2-SV(P) level of theory are given in square brackets. The transition state $\mathbf{TS_{6'/3}}$ is shown in the inset.

reaction of amido complex **4** with CD_3OD (1 equiv) at −30 °C revealed signals at $\delta = 3.9$ and 3.1 ppm (see the Supporting Information) for the coordinated methoxy ligand and free methanol. The N−D signal was not detected, likely because of overlap with CD_3O signals. These results represent a rare direct observation of an alkoxy intermediate in O−H activation by an amido-amine metal–ligand cooperation (MLC).[28] However, **6** turned out to be unstable, and removal of the solvent regenerated amido complex **4** along with a small amount of free ligand and an unidentified product with $^{31}P\{^1H\}$ NMR resonances at $\delta = 71$ and 96 ppm. Complex **5** required excess methanol and longer reaction times (3 h) to form methoxy complex **6** at room temperature (see the Supporting Information). In addition, when complex **5** was heated in methanol at 100 °C, partial formation of hydrido complex **3** was observed after 30 min, and after 1 h, it was converted into methoxy complex **6**.

With these experimental results in hand, we became interested in elucidating whether the benzylic CH group is involved in H_2 liberation in the actual catalytic transformation. Therefore, DFT calculations at the SMD(MeOH)-TPSS-D3BJ/def2-TZVPP//BP86-D3/def2-SV(P) level of theory were carried out (Scheme 4). In agreement with the experimental results, **5** was predicted to be thermodynamically more stable than **4** by 9.7 kcal mol^{-1}. The reaction of **4** or **5** with methanol gives rise to methoxy complex **6**. Hydrogen abstraction from the methoxy ligand by β-hydride elimination requires dissociation of the NH group and the formation of the agostic intermediate **6′**.[32] Formaldehyde and the hydrido complex **3** are generated by this β-hydride elimination with a barrier of 11.6 kcal mol^{-1} with respect to **4** and free methanol. H_2 liberation from **3**, involving two methanol molecules as a proton shuttle, requires only a low activation energy (8.1 kcal mol^{-1} with respect to **4**). In contrast, the transition state for H_2 liberation involving the benzylic CH group was found to be higher in energy (41.8 kcal mol^{-1} with respect to **4**). According to these computations, this transition state cannot be stabilized by additional methanol molecules, most likely owing to the fact that the benzylic CH group is not capable of forming hydrogen bonds to the methanol molecules. The formed formaldehyde reacts with the amine to generate a hemiaminal, which liberates hydrogen in another catalytic cycle to give the formamide (Scheme 4).

In conclusion, we have demonstrated that *N*-formylamines can be formed by acceptorless dehydrogenative couplings of methanol and amines that were catalyzed by a base-metal (manganese) catalyst for the first time. The reaction proceeds without any additives using the pincer catalyst (*i*Pr-PN^{H}P)Mn(H)(CO)$_2$ (**3**) under homogeneous conditions. A plausible mechanism is provided that is based on the rare direct observation of an intermediate that is formed by O−H bond activation of methanol by metal–ligand cooperation.

Acknowledgements

This research was supported by the Israel Science Foundation, the MINERVA Foundation, and the Kimmel Center for Molecular Design. D.M. holds the Israel Matz Professorial Chair of Organic Chemistry. S.C. thanks the Swiss Friends of the Weizmann Institute of Science Committee for a generous postdoctoral fellowship.

Conflict of interest

The authors declare no conflict of interest.

Keywords: dehydrogenation · formylation · manganese · methanol · pincer complexes

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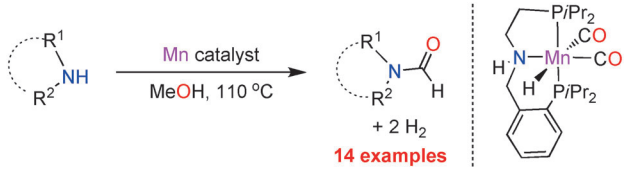
[33] CCDC 1528327 (**2**), 1528328 (**5**), and 1528329 (**4**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

Manuscript received: January 19, 2017
Final Article published: ■■ ■■, ■■■■

Communications

Base-Metal Catalysis

S. Chakraborty, U. Gellrich, Y. Diskin-Posner, G. Leitus, L. Avram, D. Milstein* _____ ■■■■–■■■■



Manganese-Catalyzed N-Formylation of Amines by Methanol Liberating H_2: A Catalytic and Mechanistic Study

Back to basics: An acceptorless dehydrogenative coupling of methanol and amines to form formamides that is catalyzed by a well-defined manganese pincer complex (see scheme) is reported. Mechanistic insight based on the observation of an intermediate and density functional calculations is also provided.