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Highly Efficient Ruthenium-Catalyzed N-Formylation of Amines with H_2 and CO_2**

*Lei Zhang, Zhaobin Han, Xiaoyu Zhao, Zheng Wang, and Kuiling Ding**

Abstract: *A highly efficient catalyst system based on ruthenium-pincer-type complexes has been discovered for N-formylation of various amines with CO_2 and H_2, thus affording the corresponding formamides with excellent productivity (turnover numbers of up to 1 940 000 in a single batch) and selectivity. Using a simple catalyst recycling protocol, the catalyst was reused for 12 runs in N,N-dimethylformamide production without significant loss of activity, thus demonstrating the potential for practical utilization of this cost-effective process. A one-pot two-step procedure for hydrogenation of CO_2 to methanol via the intermediacy of formamide formation has also been developed.*

Formamides are a class of chemicals with widespread applications in industry as solvents and raw materials for syntheses.[1] For example, *N,N*-dimethylformamide (DMF), an industrial solvent with huge annual global market volume, has also served as an extremely versatile multipurpose reagent in numerous synthetic processes.[2] Among the methods developed for the production of various formamides, the most general approach is the N-formylation of amines with formic acid or formate in the presence of a catalyst.[3] Industrially, DMF is produced by a $NaOCH_3$-catalyzed reaction of dimethylamine with toxic CO in methanol.[4] An alternative green route for the N-formylation of amines is the use of cheap, abundant, and safe CO_2 along with H_2 as a formylating reagent, and development of this technology has attracted long-term interest from both academia and industry.[5] In 1970 Haynes reported the first homogeneous catalyst for the preparation of DMF from CO_2, H_2, and dimethylamine with a turnover number (TON) up to 1200.[6] An elegant procedure for DMF synthesis was reported by Noyori and co-workers in 1994, and TONs of up to 370 000 were achieved at 100 °C with 80 atm H_2 in supercritical CO_2 (130 atm) using $[RuCl_2\{P(CH_3)_3\}_4]$ as the catalyst.[7] Extension to bulkier dialkylamines was less successful, and resulted in lower activity (TON < 820). Baiker et al. improved the efficiency by using the bidentade Ru/phosphine complex $[RuCl_2(dppe)_2]$ [dppe = (1,2-bis(diphenylphosphino)ethane)] as the catalyst, and a TON of up to 740 000 was attained at 100 °C with 130 atm of CO_2 and 85 atm of H_2.[8] Since 2010, Beller et al. have reported the development of catalytic systems based on complexes of nonprecious metals such as Fe^{II} and Co^{II}, complexes which also demonstrated high activities in the hydrogenation of CO_2 for the production of DMF (TON of up to 5100).[9] At the same time of these studies, recent progress was made on the hydrogenative transformation of CO_2 into formic acid[10] or methanol,[11] as well as reductive functionalization of CO_2 to produce methylated amine derivatives[5,12] in the context of chemical utilization of CO_2.[13] Despite these remarkable achievements, however, the attractive N-formylation of amines by CO_2 hydrogenation has not yet found industrial application, and is presumably hampered by major drawbacks in catalyst recycling and energy consumption. Herein, we report a highly efficient and recyclable ruthenium catalyst, based on a pincer-type complex, for N-formylation of various amines with H_2 and CO_2, to afford the corresponding formamides with TONs of up to 1 940 000 under relatively mild reaction conditions. A one-pot two-step procedure for the hydrogenation of CO_2 to methanol via the intermediacy of formamide formation has also been accomplished using morpholine as an example.[14]

We envisioned that the transition-metal complexes **1a–l** (Figure 1), with their robust nature and well-defined pincer-type structures,[15] might be worthwhile candidates for the catalysis of N-formylation reactions. Some of the complexes have been shown to be excellent catalysts for the hydrogenation of various carboxylic and carbonic acid derivatives.[16,17] Encouraged by these facts, we initiated the study with N-formylation of morpholine (**2a**) as the model reaction and the Ru/PNP pincer complex **1b** as the catalyst. A preliminary survey of various reaction parameters, including temperature, CO_2/H_2 partial pressures, and solvent was performed under a catalyst loading of 0.1 mol% in the presence of 0.1 mol% *t*BuOK, and the results are summarized in Table S2 (see the Supporting Information). These data indicated that the reaction was best performed in THF at 120 °C under a CO_2/H_2 partial pressure of 35/35 atm/atm, to afford *N*-formylmorpholine (**3a**) in good yield (75%). Further attempts to improve this N-formylation reaction were made by screening the catalytic activity of ruthenium(II) or iridium(III) complexes of a variety of tridentate PNP, PNN, NNN, and SNS ligands (**1a–l**; Figure 1). The results are shown in Table 1. At a molar ratio of **2a**/catalyst/*t*BuOK = 1000:1:1, all the catalysts **1a–l** were found to be active for morpholine N-formylation, but a significant variation in catalytic activity was observed depending on the type of the supporting ligand

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[*] Dr. L. Zhang, Dr. Z. Han, X. Zhao, Dr. Z. Wang, Prof. Dr. K. Ding
State Key Laboratory of Organometallic Chemistry
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
345 Lingling Road, Shanghai 200032 (P.R. China)
E-mail: kding@mail.sioc.ac.cn

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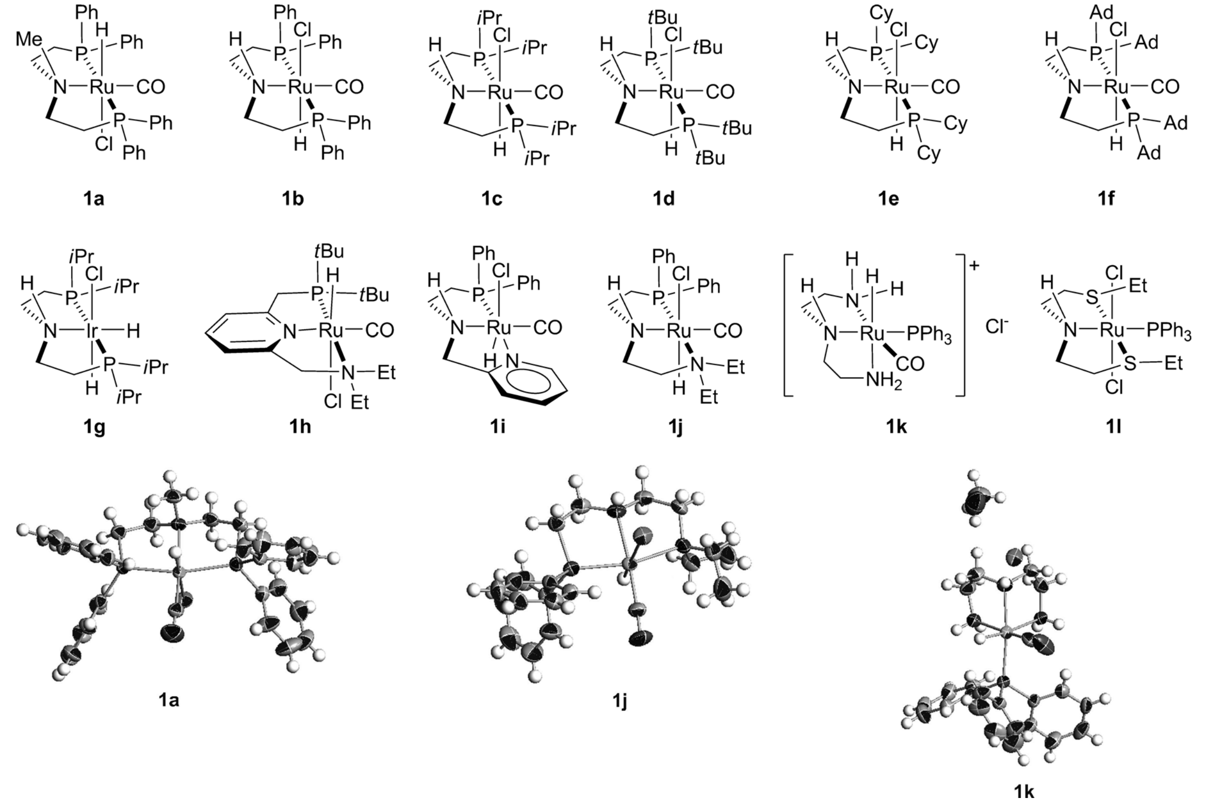
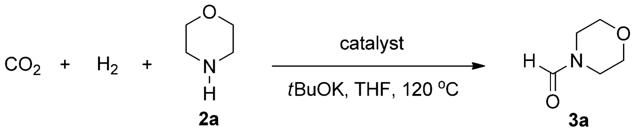


Figure 1. The catalysts employed in the catalysis of N-formylation of morpholine and X-ray crystal structures of catalysts **1a** (left), **1j** (middle), and **1k** (right). C gray, H white, Ru turquoise, P violet, N blue, O red, C green.

(entries 1–12). While the ruthenium hydride complexes of PNP (**1a**–**f**) or PNN ligands (**1h**–**j**), and the Ir/PNP complex **1g** exhibited comparably better catalytic activities in the reaction (TONs ranging from 360 to 790; entries 1–10), the ruthenium hydride NNN complex **1k** and Ru/SNS complex **1l** were remarkably less reactive (TONs of 80 and 20, respectively; entries 11 and 12), probably as a result of the different electronic nature of their donating atoms. It is also noteworthy that although all these complexes were known or found to adopt a pseudo-octahedral coordination geometry, our X-ray diffractional studies revealed that the tridentate NNN ligand is bound in a *fac*-ligation mode to the ruthenium hydride moiety in **1k** (Figure 1, right), which is structurally quite different from both the Ru/PNP complex **1a** and Ru/PNN complex **1j**, both of which bind in a *mer*-mode (Figure 1, left and middle). Such a subtle difference in coordination geometry would lead to a different microenvrionment around the active metal sites, and hence might also contribute to the observed difference in activity among the series. Since the strong basic nature of morpholine might be effectively utilized for the catalyst activation, we further examined the **1a**-catalyzed reaction in the absence of any external additive (entry 13). Under the otherwise identical reaction conditions, it turned out that no significant difference was observed for the **1a**-catalyzed reactions with or without use of *t*BuOK (entries 13 versus 1). Therefore, subsequent reactions were conducted without use of any basic additive. Further attempts to reduce the catalyst loadings for the reaction afforded very exciting results, as the TON values were found to increase dramatically from 720 to 61 000, along with gradual lowering of **1a** loading from 0.1 to 0.001 mol% (entries 13–17). It has been widely recognized that for CO_2 hydrogenation to formic acid, the presence of a base (such as NEt_3) is required to shift the unfavorable thermodynamic equilibrium of the CO_2 hydrogenation. Presumably, the presence of a large concentration of amine enhances the reaction by substantially shifting the equilibrium towards formic acid salt formation, and/or facilitates the subsequent amidation reaction owing to the presence of excess free nucleophilic amine. Clearly, the relative amount of the amine base (morpholine) is a limiting factor which is crucial to the whole transformation. Indeed, further lowering the loading of **1a** to the ppm level (0.00004–0.0001 mol%, entries 18–20) resulted in an extremely high catalytic turnover number (up to 1 940 000; entry 19), albeit at a cost of prolonged reaction time. The excellent productivity of **1a** also attests to its robust nature in the reaction, and allows long-lasting activity which survives prolonged heating in the vessel.

By using a catalyst loading of 0.01 mol% of **1a**, an array of primary and secondary amines (**2a**–**q**) were examined in the N-formylation under the reaction conditions specified in entry 15 of Table 1, with the exception that the reaction time was prolonged to 16 hours. As shown in Table 2, the N-formylation reaction proceeded smoothly in each case, to selectively afford the corresponding formamides **3a**–**q** in good to excellent yields. It is remarkable that functional groups such as methoxy, pyridyl, hydroxy are well tolerated, and both the open-chain or cyclic amines are amenable to the

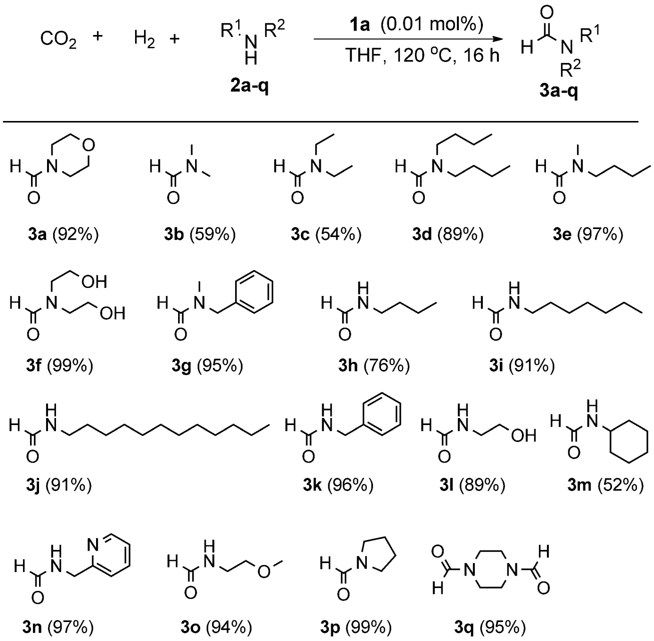
Table 1: Catalyst screening for the N-formylation of morpholine.[a]



Entry	Cat (mol %)	t [h]	Yield [%][b]	TON
1	**1a** (0.1)	2	79	790
2	**1b** (0.1)	2	75	750
3	**1c** (0.1)	2	69	690
4	**1d** (0.1)	2	78	780
5	**1e** (0.1)	2	72	720
6	**1f** (0.1)	2	68	680
7	**1g** (0.1)	2	72	720
8	**1h** (0.1)	2	64	640
9	**1i** (0.1)	2	35	350
10	**1j** (0.1)	2	36	360
11	**1k** (0.1)	2	8	80
12	**1l** (0.1)	2	2	20
13[c]	**1a** (0.1)	2	72	720
14[c,d]	**1a** (0.01)	2	92	9200
15[c,d]	**1a** (0.005)	2	99	19800
16[c,d]	**1a** (0.0025)	2	69	27600
17[c,d]	**1a** (0.001)	2	61	61000
18[c,e]	**1a** (0.0001)	48	97[h]	970000
19[c,f]	**1a** (0.00005)	96	97[h]	1940000
20[c,g]	**1a** (0.00004)	157	74[h]	1850000

[a] Reaction conditions: morpholine (10 mmol), $P_{CO_2} = P_{H_2} = 35$ atm, cat (0.1 mol %), tBuOK (0.1 mol %), THF (2 mL), 120 °C. [b] Yield of **3a** was determined by GC. [c] Reactions were performed in the absence of tBuOK. [d] Morpholine (20 mmol). [e] Morpholine (100 mmol), THF (10 mL). [f] Morpholine (200 mmol), THF (10 mL). [g] Morpholine (500 mmol), THF (20 mL). [h] Yield of isolated **3a**. THF = tetrahydrofuran.

Table 2: **1a**-catalyzed *N*-formylation of amines with H_2 and CO_2.[a,b]

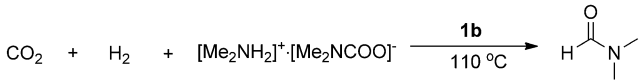


[a] Conditions: amine **2a–q** (20 mmol), **1a** (0.01 mol %), $P_{CO_2} = P_{H_2} = 35$ atm, THF (2 mL), 120 °C, 16 h. [b] Yield of isolated product.

procedure, thus giving the corresponding formamides in synthetically satisfactory yields.

Given the paramount importance of DMF, we have also further optimized the reaction conditions for N-formylation of dimethlyamine.The results are summarized in Tables S3 and S4 (see the Supporting Information), and demonstrated that with the catalyst **1b** at a loading of 0.000093 mol %, a TON value of up to 599000 was achieved under a set of reaction conditions almost identical to those discussed above for formylation of morpholine. As a valuable attribute of the robust structure, **1b** turned out to be readily recycled for at least 12 rounds in the preparation of DMF using our protocol (Table 3). The recycling runs were performed at a **1b** loading of 0.002 mol % (S/C = 50000), and after each specified reaction time period (5–7 h) DMF was vacuum distilled from the reaction mixture, and the residue containing the catalyst was simply transferred back into the reactor for next run, without special precautions to air. As shown in Table 3, **1b** was reused for 12 runs without significant loss in activity (TONs ranging from 22400 to 37000), thus demonstrating a high potential for further practical application in DMF manufacturing.

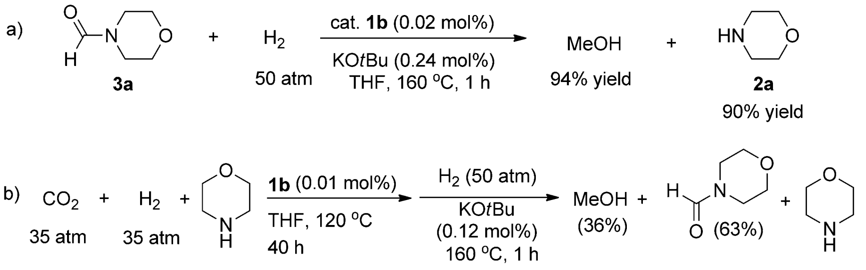
Table 3: Recycling of the catalyst **1b** in the preparation of DMF.[a]



Run	t [h]	Yield [%][b]	TON
1	5.5	71	37000
2	5.0	44	25000
3	5.0	67	33300
4	5.0	55	27920
5	5.0	45	22400
6	5.0	52	25900
7	5.0	47	24300
8	7.0	58	29740
9	6.0	63	33680
10	6.0	59	30000
11	5.0	51	26750
12	5.0	56	28870

[a] Reaction conditions: dimethylammonium dimethylcarbamate (35 g), $P_{CO_2} = P_{H_2} = 35$ atm, cat **1b** (0.002 mol %), DMF (5 mL), 120 °C. [b] Yield of isolated DMF.

Further hydrogenation of the resulting formamides has also been accomplished using **1b** under 50 atm of H_2 at an elevated temperature (160 °C). In this case, a substoichiometric amount of tBuOK was used as the additive, and the formamide **3a** was smoothly hydrogenated to methanol (94 % GC yield) and morpholine by C–N bond cleavage (Scheme 1 a). A one-pot sequential N-formylation and hydrogenation of the resulting formamide was also possible, as exemplified in the case illustrated in Scheme 1 b. Herein morpholine was first transformed into the N-formylated product by a **1b**-catalyzed reaction with CO_2 and H_2, and the resulting **3a** was then hydrogenatively cleaved into methanol, under slightly modified reaction conditions, in a single autoclave without intermediate isolation. Although



Scheme 1. a) Catalytic hydrogenation of the formamide **3a**. b) One-pot two-step transformation of CO_2 to methanol.

a moderate yield of methanol was attained in this case, the results indicated the feasibility of hydrogenation of CO_2 to methanol via a formamide intermediate.

In conclusion, we have developed a highly efficient ruthenium-catalyzed N-formylation of various primary and secondary amines with H_2 and CO_2, thus affoding the corresponding formamides in excellent yield and selectivity under relatively mild reaction conditions. In a single batch operation TONs of up to 1940000 and 599000 have been achieved for the N-formylation of morpholine and dimethylamine, respectively. Most interestingly, **1b** was readily reused in DMF production for 12 runs without significant loss of activity, thus substantially enhancing the cost-effectiveness of the protocol, and suggesting a promising future for technical development. Finally, a one-pot two-step procedure for the hydrogenation of CO_2 to methanol via the intermediacy of formamide formation has also been demonstrated with morpholine as an example. Further studies to unveil the mechanistic relationship of the formylation and subsequent hydrogenation are ongoing in this lab.

Keywords: amines · hydrogenation · ligand effects · ruthenium · synthetic methods

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