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N-Heterocyclic carbene catalyzed direct carbonylation of dimethylamine[†]

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N-Heterocyclic carbene (NHC) catalyzed direct carbonylation of dimethylamine leading to the formation of DMF was successfully accomplished under metal-free conditions. The catalytic efficiency was investigated and the turnover numbers can reach as high as > 300. The possible mechanism was also proposed.

Dimethylformamide (DMF) is an important chemical raw material and solvent in industry and the lab, and has been widely used for pesticides and medicinal intermediates.¹ The most common process for the formation of DMF is based on the direct carbonylation of dimethylamine in the presence of catalysts, such as sodium methoxide,² KF/ZnO,³ metal carbonyls,⁴ tetramethylammonium methoxide,⁵ CuCl⁶ and so on. For commercial application, sodium methoxide is undoubtedly a superior catalyst. Although it has many advantages, accumulation of several kinds of inorganic sodium salts, such as HCOONa and NaHCO₃, that form in the presence of even small amounts of CO2 and H2O, can frequently cause the blockage of the pipeline after the reaction cycle and consequently a considerable amount of waste water will be produced.⁷ The alternative method for the production of DMF is active hydrogenation of CO₂ in the presence of dimethylamine catalyzed by homogeneous⁸ or heterogenous catalysts such as Pd(CO₃)(Ph₃P)₂,⁹ Cu/ZnO,¹⁰ RANEY[®] Ni,¹¹ supported Pt, Pd etc.¹² Although these methods are effective for the synthesis of DMF, most routes involved the use of expensive metal or metal complexes as the catalysts, and thus result in environmental concerns. Therefore, from these points of view, to find new metal-free and highly efficient catalyst is highly desirable.

NHCs have aroused considerable interest in the past two decades due to their wide applications in organic synthesis and organometallic chemistry.¹³ Since the pioneering work reported by Breslow and Wanzlick and the first stable crystal *N*-heterocyclic carbene isolated by Arduengo,¹⁴ NHCs have been used in a variety of catalytic chemical transformations. With respect to acting as organocatalysts, they have shown powerful catalytic performances and distinctive features in many organic reactions. Among several kinds of coupling reactions catalyzed by NHCs,¹³ the coupling reactions of the

carbene electron pair with other kinds of semi-carbene partners, for example CO, has not yet been fully investigated. It was reported that transient triplet carbene, but not singlet carbene, could react with CO to give ketenes easily maybe due to the electronic characterization difference of two types of carbenes.¹⁵ Lyashchuk first reported that 1,3-di-1-adamantylimidazol-2ylidene could couple with CO to give the ketene,¹⁶ but this was refuted by Arduengo one year later¹⁷ who demonstrated computationally a weakly bonded "van der Waals complex" intermediate rather than a chemically bonded species. Later, Bielawski¹⁸ and Betrand^{15b} reported that cyclic alkyl amino carbenes could react with CO to afford amino ketenes. More recently, Frenking gave a comprehensive theoretical study of carbonylation of CO with varied carbene structures.¹⁹ Based on these studies and with the interest to explore the application of NHCs, we wondered whether at increased pressure NHCs can activate CO. If this could be acheived, then the direct carbonylation of amines to synthesize formamide derivatives may be accomplished.

Initially, several imidazoline quaternary ammonium salts IPrHCl, SIAdHCl, IMesHCl and ICyHCl (Fig. 1) were prepared.²⁰ We supposed that in the presence of dimethylamine under pressure, HCl should be dissociated to form the carbene intermediate which may catalyze the direct carbonylation reaction. It is gratifying to find that a small amount of DMF was detected by GC-MS or isolated after distillation. For example, the reaction of 1 mol of dimethylamine, 2 mmol of SIAdHCl and 3 MPa of CO, at 130 °C for 4 h in an autoclave afforded DMF in 9% isolated yield (based on dimethylamine) after a simple distillation procedure (Table 1). The other carbene precusors gave slightly lower yields compared with that of SIAdHCl. With these results, we then



Fig. 1 Imidazoline quaternary ammonium salt catalysts.

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 Table 1
 Study of imidazoline quaternary ammonium salts on catalysis of dimethylamine to DMF^a

Entry	Catalyst	Yield (%)	
1	SIAdHCl	9	
2	IPrHCl	7	
3	IMesHCl	5.8	
4	ICyHCl	7	

^{*a*} Dimethylamine (1 mol), catalyst (2 mmol), methanol (200 mL), CO (3 MPa), 130 °C, 4 h; the reaction was carried in autoclave.

used the stable carbene directly to catalyze this reaction with the anticipation to improve the yield.

Based on the above results, two stable NHCs IPr and IMes were examined for this direct carbonylation reaction (Fig. 2). We were pleased to find that the catalytic effect of carbene was better than that of the corresponding precursors under the same reaction conditions (Table 2). With IPr as the catalyst, the isolated yield of DMF could be increased to 19.3% (entry 1). Compared with that of IPr, the catalytic activity of IMes was lower (entry 2). When the reaction time was prolonged to 36 h with IPr as the catalyst, the desired DMF can be obtained in 47.6% yield (entry 3). When the molar ratio of dimethylamine and catalyst was 500:1, increasing the CO pressure resulted in higher yield of DMF. Thus, 62.5% yield of DMF was obtained when 6 MPa of CO was applied (entry 4). Excellent yield (93.4%) was obtained when the molar ratio of dimethylamine and IPr catalyst was changed from 500:1 to 200:1 (entry 5). The recovered catalyst can be used repeatedly with reasonable activities (entries 6-7). Diethylamine as a substrate gave the carbonylation product in only 12.1% yield under the optimized conditions (entry 8). When dimethylamine was replaced by 33% aqueous methylamine solution, the desired N-methylformamide was obtained in 61% yield (entry 10). However, the use of the poorly nucleophilic aniline as a substrate did not give any desired product (entry 9). It is interesting to find that the use of water as a solvent can give DMF in 41.6% yield (entry 11), although toluene, ethanol, THF, DMF as the solvents did not afford any DMF. In the absence of any catalyst, DMF was only obtained in about 3% yield under 3 MPa of CO, 1 mol of dimethylamine at 130 °C for 24 h (entry 13). It is interesting to observe 14% yield of DMF when 4 mmol of PPh₃ was used as a catalyst (entry 12).

In order to elucidate the reaction mechanism, several experiments were performed. Under 3 MPa of CO, 130 °C for 24 h, 1 mmol of IPr as a catalyst, 200 mL of methanol as a solvent in stainless steel batch reactor, the mixture was checked by GC-MS and silver mirror reaction after cooling. According to the result of GC-MS and Tollens reagent, methyl formate can not be detected so that the ketene intermediate may be not formed, which is in accordance with the results of



Fig. 2 N-Heterocyclic carbene catalysts.

 Table 2
 NHC-catalyzed direct carbonylation of amines^a

Entry	Amine	Catalyst	Solvent	t/h	Yield $(\%)^b$	TON
1	(CH ₃) ₂ NH	IPr	MeOH	4	19.3	97
2	$(CH_3)_2NH$	IMes	MeOH	4	6.4	32
3	$(CH_3)_2NH$	IPr	MeOH	36	47.6	238
1 ^c	$(CH_3)_2NH$	IPr	MeOH	36	62.5	309
5^d	$(CH_3)_2NH$	IPr	MeOH	36	93.4	187
5 ^e	$(CH_3)_2NH$	IPr	MeOH	36	38.5	192
¹ 7	$(CH_3)_2NH$	IPr	MeOH	36	32.2	161
3	$(C_2H_5)_2NH$	IPr	MeOH	36	12.1	60
)	PhNH ₂	IPr	MeOH	36	_	
10	CH_3NH_2	IPr	H_2O	36	61	305
11	$(CH_3)_2NH$	IPr	H_2O	36	41.6	208
12^g	$(CH_3)_2NH$	PPh ₃	MeOH	24	14	17
13	$(CH_3)_2NH$		MeOH	24	3	

^{*a*} Standard conditions: amine (1 mol), carbon monoxide (3 MPa), catalyst (2 mmol), methanol (200 mL), 130 °C until otherwise noted. The reaction was carried in autoclave. ^{*b*} Isolated yield based on dialkylamine. ^{*c*} 6 MPa. ^{*d*} 5 mmol IPr. ^{*e*} Recovered catalyst from entry 5 was used. ^{*f*} Recovered catalyst from entry 6 was used. ^{*g*} 4 mmol PPh₃.



Fig. 3 Proposed catalytic mechanism.

Arduengo.¹⁷ Combined with the literature findings^{15–19} and aforementioned experimental results, a postulated mechanism is proposed in Fig. 3. First, carbon monoxide, dimethylamine and IPr are coupled to form the intermediate **A**, which releases one molecule of DMF and liberates IPr to complete this reaction. The driving force for the formation of **A** may be a weakly bonded "van der Waals complex".

In conclusion, an efficient NHC-catalyzed carbonylation of dimethylamine with carbon monoxide was successfully established notably with metal-free catalyst, which provided a new method for the synthesis of DMF. Further investigation including the mechanism, scope, and synthetic application of this system are in progress.

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Notes and references

† Reaction: The direct carbonylation of dimethylamine was carried out in a stainless steel batch reactor of 500 mL. 1 mol of dimethylamine gas was introduced into 150 mL of methanol at 0 °C. Then this solution was pressed into a batch reactor which contained the combined mixture of a known amount of catalyst and 50 mL of methanol. The reactor was heated to 130 °C with stirring speed about 900 rpm. Then CO was charged into the reactor until an indicated pressure was reached. After a certain time, the reactor was placed in ice-water and the gas was released. The reaction mixture was transferred into a three-necked flask. Methanol was evaporated and the mixture was distilled to give the purified product DMF. The quantitative and qualitative analysis of the reaction mixture was conducted using an Agilent GC-6890, MS-5973 instrument. Recovery process for catalyst: After distillation of DMF, black and semi-solid material was left over in the distillation flask. Water was added and the mixture was extracted by ethyl acetate three times. The combined organic phase

was washed with brine and dried over sodium sulfate. The solvent was evaporated and then dried in vacuum desiccator to give the recovered catalyst.

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