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Mn-Catalyzed Selective Double and Mono *N*-Formylation and *N*-Methylation of Amines Using CO_2

Zijun Huang,[a,d] Xiaolin Jiang,[a,b] Shaofang Zhou,[a] Peiju Yang,[a] Chen-Xia Du,[c] and Yuehui Li*[a]

Abstract: Functionalization of amines using CO_2 is of fundamental importance considering the abundance of amines and CO_2. In this context, the catalytic formylation or methylation of amines have been developed and represent convenient and successful protocols for selective CO_2 utilization as C1 building block. Here, we present new advances in this area and report the first example of selective catalytic double *N*-formylation of aryl amines by using a di-nuclear Mn-complex in the presence of phenylsilane. This robust system also allows for selective formylation and methylation of amines under various conditions.

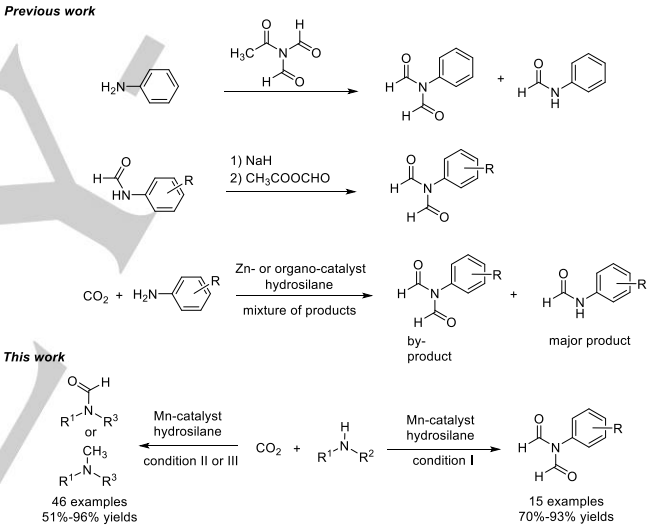
Introduction

Catalytic utilization of CO_2 as C1 building block in the functionalization of N-H bond is of fundamental importance for developing sustainable chemical transformations. Recent progress in this area includes formylation, methylation as well as urea/urethane formation are based on innovative discoveries of organometallic and organo-catalysts.[1]

Complementary to known formylation reactions, double *N*-formylation of primary amines provides bis-formylated amine products (*N*,*N*-diformylamines), which constitutes useful intermediates for drug discovery.[2] *N*,*N*-diformylamines preparation is under developed with scarce reports limited to the use of *N*,*N*-diformylacetamide or acetic-formic anhydride as the source of formyl group (Scheme 1). However, these methods have drawbacks of using harsh conditions and tedious synthetic procedures.[3]

Alternatively, double *N*-formylation of primary amines to *N*,*N*-diformylamines has been reported as side reactions when using CO_2 as carbon source for the reductive formylation of N-H bonds. Specifically, mixtures of mono- and bis-formylated amines were obtained in the presence of various catalysts, including Zn complexes,[4] *N*-heterocyclic carbenes,[5] glycine betaine,[6] γ-valerolactone[7] and metal–organic frameworks[8]. The selective double *N*-formylation method to the best of our knowledge is yet to be developed. Hence, the discovery of novel catalysts to transform abundant CO_2 for this purpose is highly desirable.

Herein, we report the first efficient example of selective double *N*-formylation of primary arylamines using newly discovered dinuclear Mn-complexes. The desired *N*,*N*-diformylanilines were obtained in good to excellent yields. Furthermore, selective formylation or methylation of amines could be achieved by tuning the reaction parameters. These results demonstrate the important application potential of this methodology for the versatile reductive modification of amines using CO_2 (Scheme 1).



Scheme 1. Formylation/methylation of amines.

Results and Discussion

Double *N*-formylation

In continuation of our interest in catalytic utilization of CO_2,[9] we have undertaken a study to develop double *N*-formylation methods for amine functionalization. For this purpose, double formylation reactions were carried out via an *in-situ* catalyst formation by using ligands and metal precursors combination under various reaction conditions.

Initially, we used *p*-methoxy-aniline as model substrate and screened various transition metal precursors. We observed that the reactivity is clearly affected. We found that only $Mn_2(CO)_{10}$ has higher catalytic activity with conversion of 23% (entry 5, Table 1), while other metal precursors were mostly inactive. Then, we proceeded by introducing different ligands (**L1** - **L8** and PPh_3) to $Mn_2(CO)_{10}$ and varied conversion results were observed (Table 1). We found that Mn-catalyzed reactions with ligands **L1**, **L4**, **L5**, **L6** and **L8,** gave improved conversions to doubly formylated product

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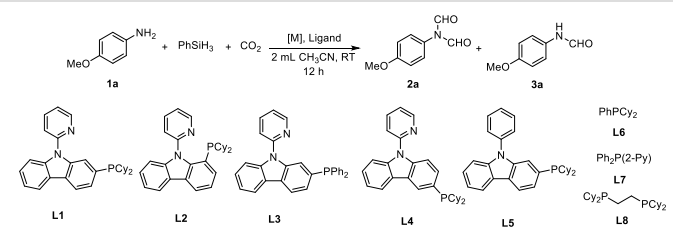
Supporting information for this article is given via a link at the end of the document. CCDC 1890807 contains the supplementary crystallographic data for this paper.

(entries 7,10, 11, 13 and 15, Table 1). Mn-catalyzed reaction in the presence of **L1** afforded best conversion giving product **2a** (double formylation of amine) in 42% yield along with product **3a** (single formylation of amine) in 56% yield in 12 hours. To our delight, enhanced catalytic reactivity and better yields were achieved upon longer reaction time providing product **2a** in 61% (entry 16, Table 1). Furthermore, the reaction was improved greatly in the presence of 4 equiv. of phenylsilane giving product **2a** in 90% yield (entry 17, Table 1). Lastly, we found that increasing CO_2 pressure to 15 bar afforded product **2a** in slightly higher yield (93%; entry 18, Table 1).

Table 1. Catalytic double formylation of *p*-methoxy-aniline[a]



Entry	[M] (mol%)	Ligand/ (mol%)	Conv.[b] (%)	Yield [b] (%)	
				2a	**3a**
1	-	-	<1	ND	Trace
2	$Fe_3(CO)_{12}$/0.5	-	<1	ND	Trace
3	Ni(cod)/1	-	<1	ND	Trace
4	$Co_2(CO)_8$/0.5	-	<1	ND	Trace
5	$Mn_2(CO)_{10}$/0.5	-	23	ND	22
6	-	**L1**/2	70	ND	58
7	$Mn_2(CO)_{10}$/0.5	**L1**/2	>99	42	56
8	$Mn_2(CO)_{10}$/0.5	**L2**/2	56	ND	55
9	$Mn_2(CO)_{10}$/0.5	**L3**/2	42	ND	40
10	$Mn_2(CO)_{10}$/0.5	**L4**/2	>99	37	62
11	$Mn_2(CO)_{10}$/0.5	**L5**/2	>99	29	69
12	$Mn_2(CO)_{10}$/0.5	PPh_3/2	15	ND	14
13	$Mn_2(CO)_{10}$/0.5	**L6**/2	>99	25	69
14	$Mn_2(CO)_{10}$/0.5	**L7**/2	19	ND	16
15	$Mn_2(CO)_{10}$/0.5	**L8**/1	>99	26	72
16[c]	$Mn_2(CO)$10/0.5	**L1**/2	>99	61	35
17[c, d]	$Mn_2(CO)_{10}$/0.5	**L1**/2	>99	90	8
18[c, d, e]	$Mn_2(CO)_{10}$/0.5	**L1**/2	>99	93	4

[a] Reaction conditions: **1a** (0.5 mmol), CO_2 (10 bar), $PhSiH_3$ (1.0 mmol). [b] Conversion and yield determined by GC using *n*-dodecane as the internal standard. [c] 24 h. [d] $PhSiH_3$ (2.0 mmol). [e] 15 bar CO_2. RT = room temperature. ND = no detection. PPh_3 = triphenylphosphine.

In order to understand the coordination mode of **L1** with Mn metal center, single crystals of $Mn_2(CO)_8$(**L1**)$_2$ were prepared from mixture of $Mn_2(CO)_{10}$ and **L1** in CH_3CN at room temperature and the structure elucidated by single X-ray diffraction method (Figure 1). On crystals bulk analysis, the simulated XRD pattern from single crystal structure and the experimental XRD data of the crystallized powder were in total agreement. Analysis of the single-crystal X-ray diffraction structure revealed that $Mn_2(CO)_8$(**L1**)$_2$ crystallizes in $P3_121$ space group. The symmetrical unit of $Mn_2(CO)_8$(**L1**)$_2$ consists of two Mn center and two molecules of **L1**. $Mn_2(CO)_8$(**L1**)$_2$ complex was deliberately synthesized as pre-formed catalyst and tested in the formylation reaction. The reaction of *p*-methoxy-aniline (**1a**) and CO_2 with phenylsilane in the presence of 0.5 mol% of $Mn_2(CO)_8$(**L1**)$_2$ afforded formylation of amine to give **3a** in 77% yield and bis-formylated product **2a** was not detected by GC indicating this complex is related with the formation of active species. Presumably, mononuclear Mn-complex might be responsible for the high reactivity of double *N*-formylation. Moreover, the presence of Lewis base pyridine moiety in **L1** is important for the crucial cleavage of Mn-Mn bond (Table S3 in the Supporting Information).

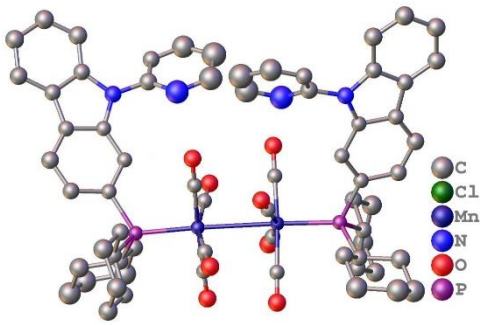


Figure 1. ORTEP diagram of $Mn_2(CO)_8$(**L1**)$_2$. All hydrogen atoms have been omitted for clarity.

Under the optimized reaction conditions, we firstly carried out reactions of a variety of substituted arylamines **1** in the presence of $Mn_2(CO)_{10}$ and **L1** with phenylsilane and carbon dioxide affording the bis-formylated product as shown in Table 2. Electron-rich group substituted arylamines proceeded smoothly furnishing the corresponding products **2a** - **2f** and **2k** - **2n** in excellent yields. The reactions of arylamines bearing electron-withdrawing groups such as Cl and Br could also be transformed to bis-formylatied products in good yields. It is noteworthy that the reaction of 4-fluoroaniline **1g** and 4-iodoaniline **1j** gave the desired products **2g** and **2j** in slightly lower yields as 74% and 70%, respectively. The reaction of naphthalen-1-amine **1o** also afforded the corresponding bis-formylated product **2o** in good yield.

Subsequently, we further conducted the *N*-formylation of amines by reducing CO_2 pressure (Table 3; detailed reaction conditions optimization described in Table S1 in the Supporting Information). Various substituted primary arylamines (**1a** - **1m**) exhibited good activity and afforded the cooresponding products in excellent yields. Meanwhile, reactions with secondary arylamines bearing either electron-rich (**1p** - **1r**; **1u** - **1w**) or electron-withdrawing groups (**1s, 1t)** gave *N*-formylated products in good yields.

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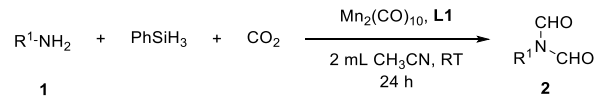
Table 2. Double formylation reactions of aryl amines.



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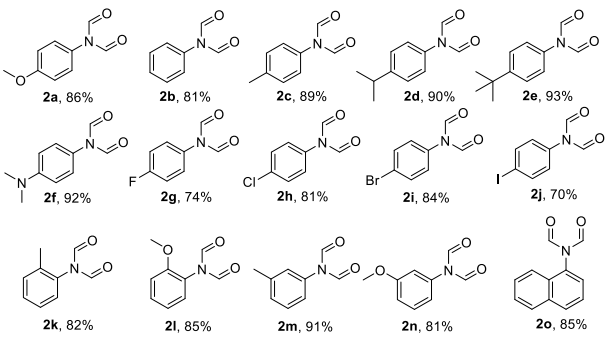
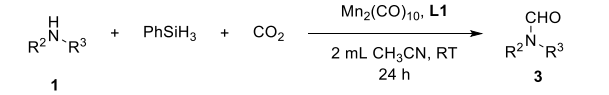


[a] Reaction conditions: $Mn_2(CO)_{10}$ (0.5 mol%), **L1** (2 mol%),**1** (0.5 mmol), CO_2 (15 bar), $PhSiH_3$ (2.0 mmol), CH_3CN (2.0 mL), room temperature, 24 h. Isolated yields. [b] Yield determined by GC using *n*-dodecane as the internal standard.

Table 3. Substrate scope for *N*-formylation of amines using CO_2[a]



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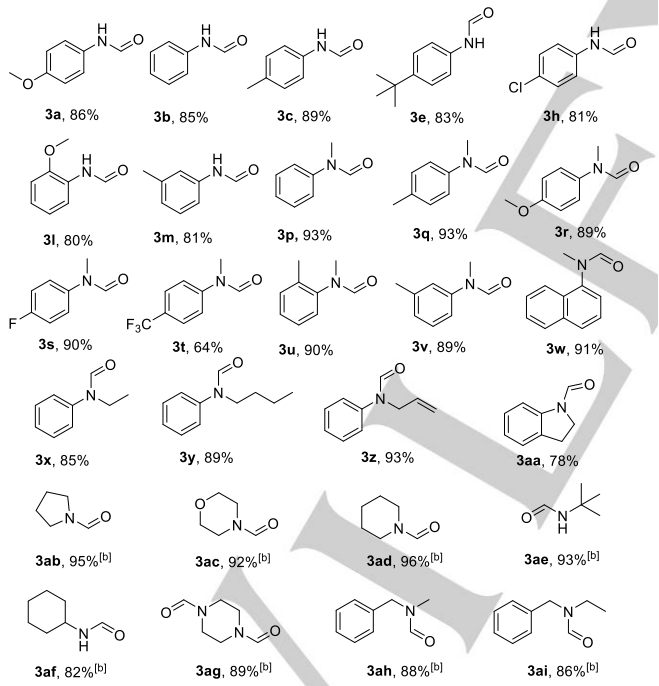
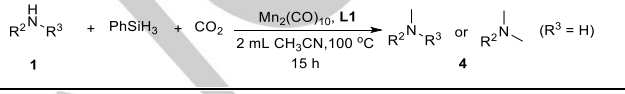


[a] Reaction conditions: $Mn_2(CO)_{10}$ (0.5 mol%), **L1** (2 mol%),**1** (0.5 mmol), CO_2 (1 bar), $PhSiH_3$ (1.0 mmol), CH_3CN (2.0 mL), room temperature, 12 h. Isolated yields are shown. [b] Yield determined by GC using *n*-dodecane as the internal standard.

However, we observed significant decrease in the yield to 64% due to the strong electron-withdrawing effect when *N*-methyl-4-(trifluoromethyl) aniline (**1t**) was used. In order to evaluate the effect of *N*-alkyl substituents on the reaction of arylamines, ethyl, *n*-butyl, and allyl substituted arylamines substrates were used. The reactions of **1x**, **1y** and **1z** with phenylsilane and carbon dioxide were performed and the corresponding products **3x**, **3y** and **3z** were isolated in 85%, 89% and 93% yields respectively. Noteworthy to mention that indoline (**1aa**) could also be utilized as substrate to produce formamide **3aa** in 78% yield. Furthermore, in order to examine the generality of this procedure, we tested aliphatic, heterocyclic and benzilc amines and they were all well tolerated. Specifically, pyrrolidine (**1ab**), morpholine (**1ac**), piperidine (**1ad**), 2-methylpropan-2-amine (**1ae**), hexylamime (**1af**), piperazine (**1ag**), *N*-methylbenzylamine (**1ah**) and *N*-ethylbenzylamine (**1ai**) were all *N*-fomylated with excellent yields (82-96% yields; Table 3).

Table 4. Substrate scope for *N*-methylation of amines using CO_2[a]



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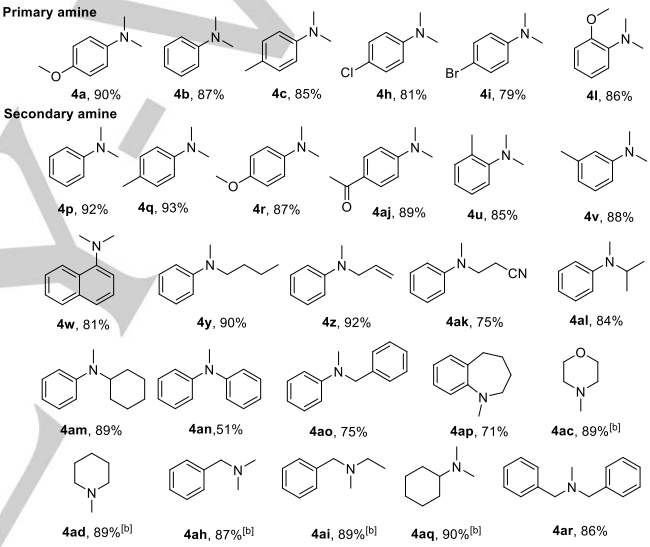


[a] Reaction conditions: $Mn_2(CO)_{10}$ (0.5 mol%), **L1** (2 mol%),1 (0.5 mmol), CO_2 (1 bar), $PhSiH_3$ (1.5 mmol), CH_3CN (2.0 mL), 100 °C, 15 h. Isolated yields. [b] Yield determined by GC using *n*-dodecane as the internal standard.

Finally, *N*-methylation of amines was also achieved when using higher amounts of phenylsilane under low pressure (1 bar) at elevated temperature under low pressure (1 bar). (Table 4; conditions optimization depicted in Table S2 in the Supporting Information). Bis-*N*-methylated products (**4a** - **4c** and **4h**, **4i**, **4l**) were obtained in good to excellent yields (79% - 90%) with substituted primary arylamines substrates. Secondary amines having aryl substituents (**1p** - **1r**,**1u** - **1w**, **1y**, **1z**, **1aj**, **1ak** - **1ap**) were also well tolerated and afforded the corresponding *N*-methylated products (**4**) in moderate to excellent yields (71% - 92%). Howerer, the reaction with sterically hindered amine (**1an**) afforded *N*-methylated amines in lower yield (51%). Meanwhile, aliphatic amine morpholine **1ac** was successfully transformed to the corresponding methylated product in good yield (89%). Similarely, piperidine **1ad** was also methylated to afforded *N*-methylpiperidine in 89% yield. Secondary amines bearing benzylic substitutent **1ah**, **1ai**, and **1ar** were converted to methylated products in comparable yields (86% - 89%). Moreover,

N-methylcyclohexylamine (**1aq)** was also transformed to the corresponding dimethylhexylamine in 90% yield.

Furthermore, preliminary kinetic studies were performed to gain mechanistic understanding for this bis-formylation reaction as depicted in Figure 2. Firstly, primary amine **1a** was converted completely into *N*-formylated product **3a** within four hours. Interestingly, during this period bis-formylated product **2a** was not detected by GC. Subsequently, bis-formylated product **2a** started to be formed at a slightly lower reaction rate, with the consumption

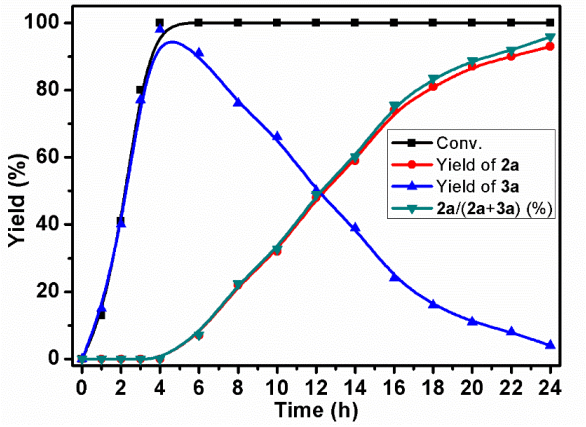
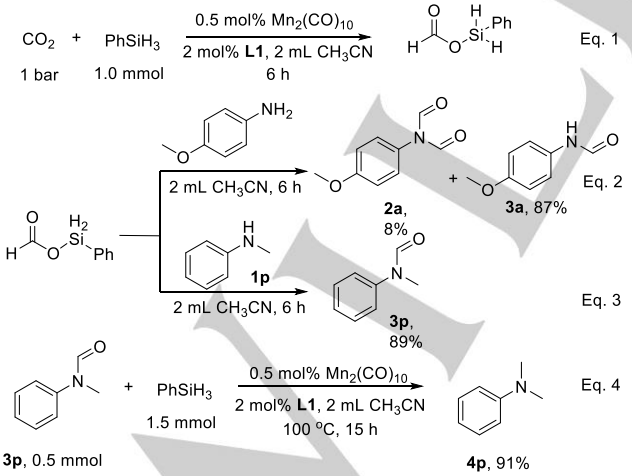


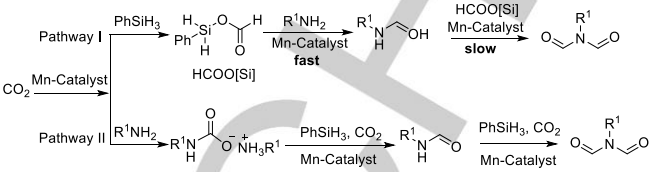
Figure 2. Reaction profiles for the bis-formylated of amines using CO_2. Reaction conditions: $Mn_2(CO)_{10}$ (0.5 mol%), **L1** (2 mol%),**1a** (0.5 mmol), CO_2 (15 bar), $PhSiH_3$ (2.0 mmol), CH_3CN (2.0 mL), room temperature, yield determined by GC using *n*-dodecane as the internal standard.

of **3a**. This behaviour implies that primary amine substrates are not favored for di-formylation reaction. Di-formylated product would only start forming once the substrate is completely consumed in the initial mono-formylation step. This imperative tuning effect by substrate is suggested to be responsible for the highly selective mono and di-formylation reactions using Mn-catalysts.



Scheme 2. Control experiments

To gain further insight, we performed control experiments using phenylsilane and CO_2 at room temperature. The possible reaction intermediate silyl formate was prepared through the reaction of CO_2 with phenylsilane in the presence of Mn-catalyst (Eq.1, Scheme 2). Then, the *in-situ* formed silyl formate was exposed to *p*-methoxy-aniline (**1a**), giving bis-formylated product (**2a**) in 8% yield and afforded *N*-(4-methoxyphenyl)formamide (**3a**) in higher yield (87%), while comparable yield of 89% was obtained for the reaction of *N*-methylaniline (Eq.2, Eq.3, Scheme 2). These control experiments indicate that silyl formate is the active formylation reagent in this transformation.



Scheme 3. Proposed reaction pathways for Double N-Formylation

Recent studies[4,6,7,10,11] indicate that *N*-formylation of amines might involve two main steps: 1) hydrosilylation of CO_2 to form silyl formates for the formation of formylated intermediates, and 2) reduction of formamides to produce the methylated product. Consistently, *N*-formyl-*N*-methylaniline **3p** could be formed smoothly as indicated in the reaction profile of amine **1p**. In addition, **3p** is rapidly consumed within six hours (Figure S6 in Supporting Information). Specifically, when **3p** reacts with $PhSiH_3$ under heating conditions, 91% yield of **4p** was obtained (Eq. 4, Scheme 2).

On the basis of the above experimental results and recent experimental evidence on CO_2 reduction,[12,13] a possible mechanism for this Mn-catalyzed reductive functionalization of CO_2 in the presence of amine is proposed in Scheme 3. Our findings imply that under the pressurized condition, diformylation reaction is more favoured to obtain the desired *N*,*N*-diformylamine product, although through mono-formylated intermediate with silyl formate as the formylation reagent (pathway I). Meanwhile, the reaction pathway II involves the formation of carbamate salt intermediate first, followed by the Mn-catalyzed reduction to give the mono-formylation product.

Conclusions

In summary, we have demonstrated the first catalytic double *N*-formylation of aryl amines using CO_2 in the presence of hydrosilanes. Specifically, under mild conditions, good to excellent yields of the desired imide type *N*,*N*-diformylated products were obtained. Furthermore, the same catalyst was found to be efficient for both formylation and methylation of aliphatic and aryl amines. Kenitic studies provided insights into the reaction mechanism with the activity and selectivity is tuned by reaction parameters.

Acknowledgements

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Keywords: double formylation, CO_2 utilization, manganese, amine, homogeneous catalysis

[1] a) M. Aresta, A. Dibenedetto, A. Angelini, *Chem. Rev.* **2014**, *114*, 1709-1742; b) Y. Li, X. Cui, K. Dong, K. Junge, M. Beller, *ACS Catal*. **2017**, *7*, 1077-1086; c) Q. Liu, L. Wu, R. Jackstell, M. Beller, *Nat. Commun.* **2015**, *6*, 5933; d) Y. Lu, Z.-H. Gao, X.-Y. Chen, J. Guo, Z. Liu, Y. Dang, S. Ye, Z.-X. Wang, *Chem. Sci.* **2017**, *8*, 7637; e) X.-F. Liu, X.-Y. Li, C. Qiao, H.-C. Fu, L.-N. He, *Angew. Chem. Int. Ed.* **2017**, *56*, 7425; f) F. J. Fernández-Alvarez, L. A. Oro, *ChemCatChem* **2018**, *10*, 4783; g) X.-F. Liu, X.-Y. Li, C. Qiao, L.-N. He, *Synlett* **2018**, *29*, 548; h) Y. Zhang, X. Dai, H. Wang, F. Shi, *Acta Phys. -Chim. Sin.* **2018**, 34, 845; i) R. A. Pramuditaa, K. Motokura, *Green Chem.* **2018**, *20*, 4834; j) R. H. Lam, C. M. A. McQueen, I. Pernik, R. T. McBurney, A. F. Hill, B. A. Messerle, *Green Chem.* **2019**, *21*, 538.

[2] a) M. Harfenist, C. T. Joyner, P. D. Mize, H. L. White, J. Med. Chem. **1994**, *37*, 2086-2089; b) Patent EP1541558A1, Shionogi Co. Ltd. 2003.

[3] a) E. Allenstein, V. Beyl, W. Eitel, *Chem. Ber.* **1969**, *102*, 4089; b) L. M. Yagupolskii, K. I. Petko, A. N. Retchitsky, I. I. Maletina, *J. Fluorine Chem.* **1996**, *76*, 95-98.

[4] R. Luo, X. Lin, Y. Chen, W. Zhang, X. Zhou, H. Ji, *ChemSusChem* **2017**, *10*, 1224-1232.

[5] a) O. Jacquet, C. D. N. Gomes, M. Ephritikhine, T. Cantat, *J. Am. Chem. Soc*. **2012**, *134*, 2934-2937; b) H. Lv, W. Wang, F. Li, *Chem. Eur. J.* **2018**, *24*, 16588- 16594.

[6] C. Xie, J. Song, H. Wu, B. Zhou, C. Wu, B. Han, *ACS Sustainable Chem. Eng.* **2017**, *5*, 7086-7092.

[7] J. Song, B. Zhou, H. Liu, C. Xie, Q. Meng, Z. Zhang, B. Han, *Green Chem.* **2016**, *18*, 3956-3961.

[8] H. Alamgholiloo, S. Rostamnia, A. Hassankhani, R. Banaeia, *Synlett* **2018**, *29*, 1593-1596.

[9] a) Z. Xin, J. Zhang, K. Sordakis, M. Beller, C.-X. Du, G. Laurenczy, Y. Li, *ChemSusChem* **2018**, *11*, 2077-2082; b) H. Wang, Y. Dong, C. Zheng, C. A. Sandoval, M. Makha, Y. Li, *Chem* **2018**, *4*, 2883-2893.

[10] a) C. C. Chong, R. Kinjo, *Angew. Chem., Int. Ed.* **2015**, *54*, 12116 -12120; b) L. Hao, Y. Zhao, B. Yu, Z. Yang, H. Zhang, B. Han, X. Gao, Z. Liu, *ACS Catal.* **2015**, *5*, 4989-4993; c) T. V. Nguyen, W. J. Yoo, S. Kobayashi, *Angew. Chem., Int. Ed.* **2015**, *54*, 9209-9212; d) G. Jin, C. G. Werncke, Y. Escudie, S. Sabo-Etienne, S. Bontemps, *J. Am. Chem. Soc.* **2015**, *137*, 9563-9566; e) C. Fang, C. Lu, B.-L. Lin, et al., *ACS Catal.* **2016**, *6*, 7876–7881.

[11] A. Julian, V. Polo, E. A. Jaseer, F. J. Ferna´ ndez-Alvarez, L. A. Oro,´ *ChemCatChem* **2015**, *7*, 3895-3902.

[12] a) H. Niu, L. Lu, R. Shi, C.-W. Chiang, A. Lei, *Chem. Commun.* **2017**, *53*, 1148-1151; b) X.-D. Li, S.-M. Xia, K.-H. Chen, X.-F. Liu, H.-R. Li, L.-N. He, *Green Chem.* **2018**, ***20***, 4853-4858; c) M.Hulla, G. Laurenczy, P.J. Dyson, *ACS Catal.* **2018**, *8*, 10619-10630.

[13] a) J. A. Garduño J. J. García, *ACS Catal.* **2019**, *9,* 392−401; b) Z. Mao, B. T. Gregg, A. R. Cutler, *J. Am. Chem. Soc.* **1995**, *117*, 10139-10140; c) B.T.Gregg, A. R. Cutler, *Organometallics* **1994**,*13*, 1039-1043.

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Layout 2:

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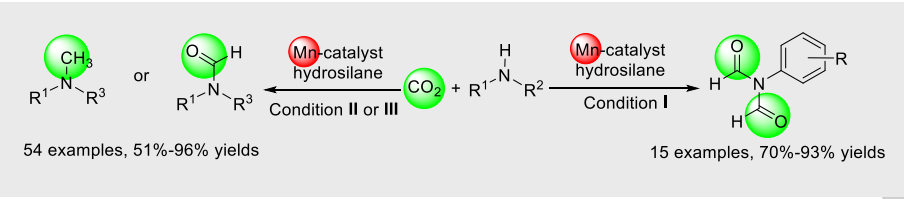

Bis-formylated product! We have demonstrated the first example of selective catalytic double N-formylation of aryl amines by using a di-nuclear Mn-complex in the presence of phenylsilane. Furthermore, this robust system also allows for selective formylation and methylation of amines under various conditions.

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Mn-Catalyzed Selective Double and Mono *N*-Formylation and *N*-Methylation of Amines Using CO_2