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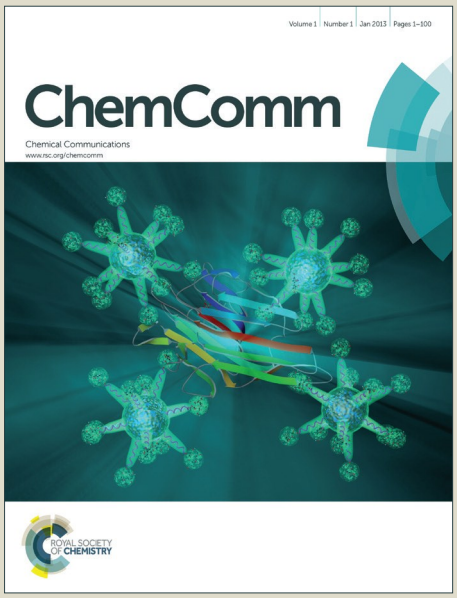

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Solvent-promoted Catalyst-free *N*-Formylation of Amines Using Carbon Dioxide under Ambient Conditions

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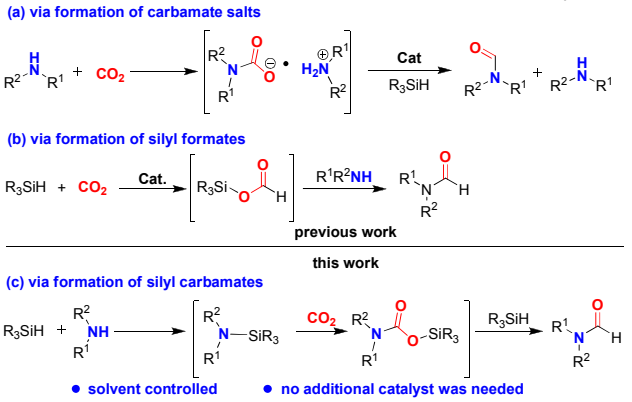
An unprecedented catalyst-free formylation of amines with CO_2 and hydrosilanes was developed. Solvent plays a vital role in promoting the interaction of amines with hydrosilanes and subsequent CO_2 insertion, thus facilitates the simultaneous activation of N-H and Si-H bonds. Based on relevant mechanistic studies, a plausible mechanism involving silyl carbamates intermediate is proposed.

The CO_2-involved chemical synthesis has been and continues to be a very active research area because CO_2 is an abundant, renewable, cheap and green C1 resource.[1] Among the CO_2-involved chemical syntheses documented, the *N*-formylation reaction of amines with CO_2 and hydrosilanes is a promising pathway for the production of formamides, which have been widely applied as solvents and key intermediates in organic synthesis and industry.[2,3] However, due to the inherent stability and kinetic inertness of CO_2, its conversion under mild conditions, especially at room temperature and atmospheric pressure is a big challenge. Hence, chemists are committed to developing more efficient catalytic methods for this reaction. Among the methods developed, metal-based catalysts including Rh[4], Pd[5], Cu[6], Fe[7], Ni[8], Zn[9], have been widely employed. Recently, metal-free catalytic systems such as *N*-heterocyclic carbenes (NHCs)[10], ionic liquids (ILs)[11], organic bases[12] ect. have also been developed as a green alternative. Depending on the activation modes, these catalytic methods are mainly classified into two types: (1) reaction of activated CO_2 with amines to form the carbamate salts, followed by their reduction with R_3SiH (Scheme 1, a).[9a,12] (2) activation of Si-H bond accompanied by CO_2 insertion to form silyl formates, which could act as a "formyl synthon" to react with amines (Scheme 1, b).[4,7d,8,11b] In these cases, an additional catalyst was needed and generally only one component of the amine/silane system was activated.



Scheme 1. Formylation of amines with CO_2 and hydrosilanes.

Mostly, the formylation of amines follows the catalytic mode of Scheme 1b. Recently, Cantat and co-workers developed NHCs-catalyzed *N*-formylation of amines using CO_2 and hydrosilanes.[10] In this transformation, the nucleophilicity and basicity of NHC played a crucial role. One possible mechanism involves the activation of Si-H bond through Lewis acid-base NHC-Si interaction.[13] As we know, amines could also act as a nucleophile and Lewis base by donating a pair of electrons. Inspired by this property, it is speculated that whether we can realize the activation mode of NHCs by using the amine substrate. One potential problem is that the basicity or nucleophilicity of amines is not strong enough to activate Si-H bond. As is reported, the nucleophilicity and basicity of

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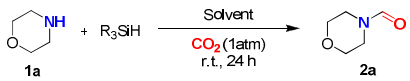
amines could be tuned by solvation and polarization in different solvents.[14] In view of this, we envisioned it's possible that by utilizing appropriate solvent, the nucleophilicity and basicity of amine could be tuned strong enough to activate organosilanes *via* Lewis acid-base N-Si interaction, which is similar to the Lewis acid-base NHC-Si interaction. Thus, amines would probably be able to induce their formylation with CO_2 and hydrosilanes without using any additional catalysts (Scheme 1, c). In this reaction system, amines and hydrosilanes were activated simultaneously, which makes subsequent insertion of CO_2 more favorable.

In our initial experiment, the formylation of morpholine(**1a**) with atmospheric pressure of CO_2 and phenylsilane as a model reaction was performed in various solvents and the results are listed in Table 1. The reaction could hardly proceed in non-polar solvents, such as n-hexane, benzene and toluene (Table 1, entries 1 to 3). Then we screened different polar solvents. Weakly polar solvents such as THF, 1,4-dioxane and $CHCl_3$ were also not suitable for this reaction (entries 4 to 6). When CH_3CN was used, **2a** was obtained in 12% yield (entry 7). To our delight, a quantitative yield of **2a** was achieved in 24 h at room temperature when highly polar aprotic solvents, such as DMSO or DMF was used (entries 8 and 9). This can probably be rationalized by the good solubility of CO_2 in DMSO or DMF and the appropriate basicity/nucleophilicity of amines in highly polar aprotic solvents. Meanwhile, some other factors such as the solvents' acidity/basicity are not negligible either. In a word, the solvent has comprehensive effect on the activity of the present formylation reaction. Furthermore, we investigated the effect of DMSO/THF mixed solvent. The results indicated that the product yield increases with increasing proportion of DMSO in the mixed solvent (Table S1 in the ESI, entries 10 to 14). We were also pleased to find that this reaction also proceeded successfully using Et_3SiH or $(EtO)_3SiH$ as the reductant, providing the desired product in almost quantitative yields (entries 10 and 11).

Table 1 Optimization of reaction conditions.[a]



Entry	Solvent	Hydrosilane	Yield (%)[b]
1	n-Hexane	$PhSiH_3$	n.r.
2	Benzene	$PhSiH_3$	n.r.
3	Toluene	$PhSiH_3$	trace
4	THF	$PhSiH_3$	trace
5	1,4-dioxane	$PhSiH_3$	trace
6	$CHCl_3$	$PhSiH_3$	n.r.
7	CH_3CN	$PhSiH_3$	12
8	DMF	$PhSiH_3$	>99
9	DMSO	$PhSiH_3$	>99
10[c]	DMSO	Et_3SiH	>99
11[d]	DMSO	$(EtO)_3SiH$	>99

[a] Reaction conditions: morpholine (0.5 mmol), R_3SiH (0.75 mmol), CO_2 (1 atm), solvent (2 mL), room temperature, 24 h. [b] The yield was determined by GC, calibrated using n-hexadecane as the internal standard. [c] Et_3SiH (2.25 mmol). [d] $(EtO)_3SiH$ (2.25 mmol).

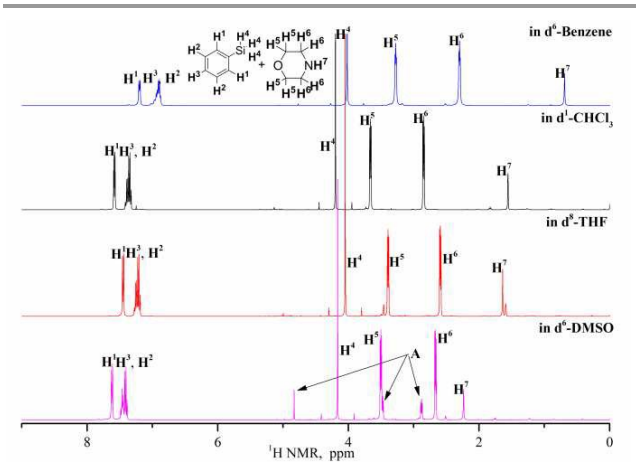


Figure 1. ^1H NMR spectra for the mixture of morpholine and phenylsilane in different solvents (**A** is corresponding to intermediate **A** in Scheme 2).

In order to clarify the special role of solvents, we investigated the mixture of morpholine and phenylsilane in different deuterated solvents. After stirring for four hours, the resulted mixtures were characterized by NMR. As shown in Figure 1, in non-to-weakly polar solvents such as d^6-benzene, $CDCl_3$ and d^8-THF, only signals for morpholine and phenylsilane were observed. In contrast, for the mixture in highly polar d^6-DMSO, new signals appeared, which were assigned to a new species **A** resulted from the interaction of morpholine and phenylsilane (Scheme 2). These results indicated that one reason for the outstanding efficiency of DMSO in this formylation may be its ability in promoting the interaction of amine and hydrosilane. This interaction facilitated the simultaneous activation of N-H and Si-H bonds, which might make it more favorable for CO_2 insertion. We speculated that the interaction of amine with hydrosilane is mainly influenced by the polarity of solvent, which tuned the basicity/nucleophilicity of amine through solvation and polarization. To confirm this, the solutions of morpholine in different deuterated solvents ($CDCl_3$, d^6-benzene, CD_3CN and d^6-DMSO) were examined by ^1H NMR analysis (Figure S1 in the supporting information). From the ^1H NMR spectra, it's found that the ^1H signals of N-H proton in morpholine appeared in a range of 1.05 to 2.28 ppm, following the order: d^6-DMSO (2.28 ppm) > CD_3CN (1.78 ppm) > $CDCl_3$ (1.71 ppm) > d^6-benzene (1.05 ppm), which is in agreement with the polarity order of these solvents. To some content, this result proved the influence of solvents polarity on the properties of amine, which was in accordance with the experimental results in Table 1.

With the optimized conditions in hand, we further investigated the scope of this formylation with various amines (Table 2). Primary or secondary aliphatic amines with different substituents were subjected to *N*-formylations and provide the corresponding formamides **2b** and **2c** quantitatively. Steric hindered amantadine could also undergo formylation smoothly, giving **2d** in nearly quantitative yield. Annular secondary amine such as tetrahydroisoquinoline was also acitve for this reaction, giving **2e** in 89% yield. For

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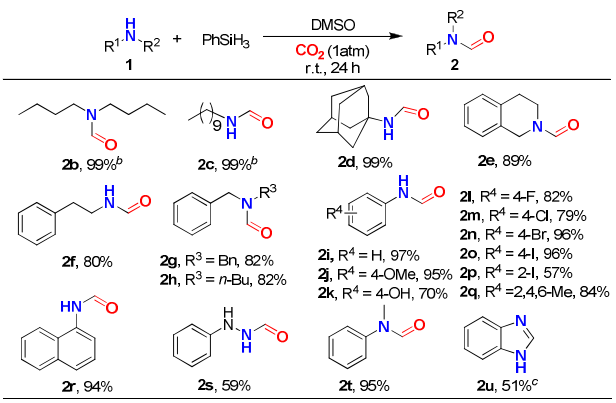
phenylethylamine and different *N*-alkyl substituted benzylamine, the formylation proceeded smoothly to provide the desired products **2f** to **2h** in 80-82% yields. Delightfully, weakly nucleophilic aromatic amines were also suitable for this formylation. For example, the reaction of aniline provided **2i** in 97% yield. Both electron-donating (-OMe, -OH) and weakly electron-withdrawing (-F, -Cl) substituents on the benzene ring were well tolerated, providing **2j** to **2m** in 70-95% yields. Unfortunately, strongly electron-withdrawing substituents (-NO_2, -CN) on the benzene ring were not tolerated, with the substrates recovered quantitatively. Notably, for the reaction of bifunctionalized *p*-hydroxyaniline, *N*-formylation product **2k** was solely obtained, while no *O*-formylation product was observed, which demonstrated the good chemoselectivity of the present reaction system. Moreover, anilines substituted with active halogen groups (-Br, -I) furnished the corresponding halogen-substituted formamides in excellent yields (**2n** and **2o**), thus providing the potential for further functionalization. Compared with the result of 4-iodoaniline (**2o**, 96% yield), yield of the reaction with 2-iodoaniline (**2p**, 57% yield) was lower, which may be attributed to the steric hindrance and the electron-withdrawing inductive effect of iodine substituent. The steric hindered 2,4,6-trimethyl aniline worked efficiently toward this formylation to afford **2q** in 84% yield. Naphthylamine was also conveniently converted into the corresponding formamides **2r** in 94% yield. In addition, the current formylation reaction was regioselective for phenylhydrazine where two N-H bonds could be formylated, only one product generated from formylation of the less sterically hindered N-H bond was obtained (**2s**). *N*-methyl aniline was also compatible with the standard reaction conditions, providing **2t** in 95% yield. When *o*-phenylenediamine was used, benzimidazole (**2u**) was obtained in 51% yield as the final product, which may be generated through intramolecular nucleophilic cyclization/dehydration of the formylated intermediate. Notably, good chemoselectivity was achieved for the formylation of primary amines, in which only mono-formylated product was isolated and no double-formylated product was observed. In contrast, the double-formylated product was hard to be suppressed in some catalytic systems.[7a,10c,11b]

Table 2 Formylation of various amines with CO_2 and phenylsilane.[a]



[a] Reaction conditions: amine (0.5 mmol), $PhSiH_3$ (0.75 mmol), DMSO (2 mL), room temperature, 24 h, isolated yield. [b] The yield was determined by GC. [c] 60 °C.

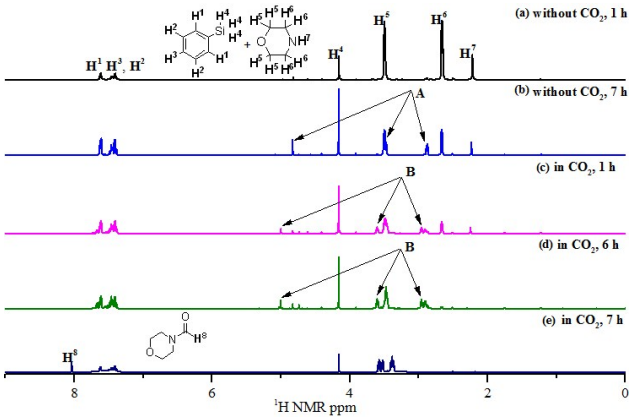


Figure 2. ^{1}H NMR chemical shift of the reaction system at different time. We shaked the reaction mixture in the first six hours to reduce the reaction rate and during the period of 6-7 h in CO_2 the reaction mixture was stirred to accelerate the transformation rate. (**A** and **B** are corresponding to the intermediates **A** , **B** in Scheme 2)

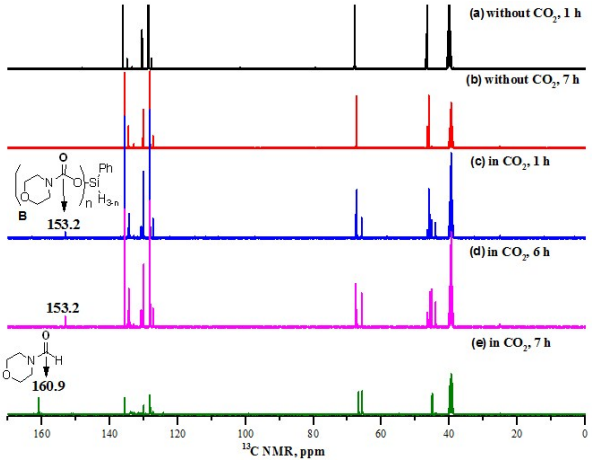


Figure 3. ^{13}C NMR chemical shifts of the reaction system at different time. We shaked the reaction mixture in the first six hours to reduce the reaction rate and during the period of 6-7 h in CO_2 the reaction mixture was stirred to accelerate the transformation rate. (A and B are corresponding to the intermediates **A** , **B** in Scheme 2)

Clarifying the mechanism of a novel reaction system is very important from the viewpoint of its scientific interest and application in designing other synthetic strategies. Initially, *in situ* NMR (^{1}H and ^{13}C) analyses in d^6-DMSO were conducted to investigate the reaction of morpholine with phenylsilane in the absence of CO_2. As shown in Figure 2a-2b, new ^{1}H NMR signals appeared after shaking the NMR tube for 7 hours. These new signals were assigned to a new species **A** resulted from the cross coupling of amine with hydrosilane. Subsequently, CO_2 was inflated and continued to shake the NMR tube. After 1 hour, a second batch of new peaks appeared (Figure 2c) and became obviously stronger after 6 hours (Figure 2d). Meanwhile, the signals corresponding to **A** decreased a lot. At the same time, the formation of new intermediate **B** was further approved by the appearance of a new ^{13}C NMR signal appeared at δ 153.2 ppm (Figure 3c and 3d), which could be

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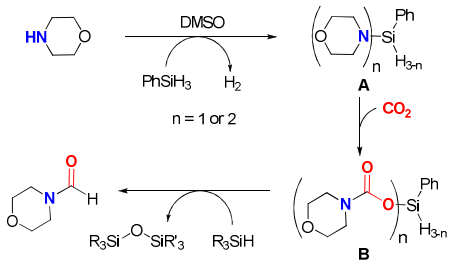
assigned to the carbonyl carbon of silyl carbamates **B** (Figure 3).[15] These results strongly indicate that **B** was formed through insertion of CO_2 into the Si-N species **A** and this process is faster than the formation of **A**. With shaking time prolonged, the signals corresponding to substrate decreased and that of **B** increased gradually. Finally, the signals for amide product appeared and that for amine substrate disappeared almostly (Figure 2e and Figure 3e). The formation of **A** and **B** was also confirmed by *in situ* ^{29}Si NMR analysis (Figure S2 in the ESI).



Scheme 2. Proposed mechanism for *N*-formylation of amines with CO_2 and hydrosilanes.

Based on the investigations above, a possible reaction pathway was proposed in Scheme 2. Firstly, the nucleophilicity and basicity of morpholine are tuned by solvation and polarization in highly polar DMSO, which promotes the cross-coupling of morpholine with phenylsilane to form intermediate **A**. At the same time, hydrogen gas is released, which was observed as soon as the mixture of phenylsilane and morpholine was added into anhydrous DMSO. Subsequently, insertion of CO_2 into N-Si bond of **A** generates the silyl carbamate **B**. Finally, **B** underwent hydrosilylation with a second hydrosilane to provide the amide product.

In conclusion, we have developed a catalyst-free system for the formylation of amines with atmospheric pressure of CO_2 at room temperature, affording the corresponding formamides in excellent yield and selectivity. Solvent plays a key role in this reaction by promoting the Lewis acid-base interaction between amines and silanes and thus facilitates the generation of **A** with a new N-Si bond formation. A reaction pathway, including formation of silyl carbamate which is then reduced to formamide by hydrosilanes, was proposed based on relevant mechanistic studies.

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Notes and references

1 (a) W. Wang, S. P. Wang, X. B. Ma and J. L. Gong, *Chem. Soc. Rev.*, 2011, **40**, 3703; (b) J. F. Shi, Y. J. Jiang, Z. Y. Jiang, X. Y. Wang, X. L. Wang, S. H. Zhang, P. P. Han and C. Yang, *Chem. Soc. Rev.*, 2015, **44**, 5981; (c) Y. W. Li, S. H. Chana and Q. Sun, *Nanoscale*, 2015, **7**, 8663; (d) K. Huang, C.-L. Sun and Z.-J. Shi, *Chem. Soc. Rev.*, 2011, **40**, 2435; (e) T. Sakakura, J.-C. Choi and H. Yasuda, *Chem. Rev.* 2007, **107**, 2365; (f) M. Aresta, A. Dibenedetto and A. Angelini, *Chem. Rev.* 2014, **114**, 1709.

2 A. Tlili, E. Blondiaux, X. Frogneux and T. Cantat, *Green Chem.*, 2015, **17**, 157.

3 (a) K. C. Waterman, W. B. Arikpo, M. B. Fergione, T. W. Graul, B. A. Johnson, B. C. Macdonald, M. C. Roy and R. J. Timpano, *J. Pharm. Sci.*, 2008, **97**, 1499; (b) W.-P. Mai, H.-H. Wang, Z.-C. Li, J.-W. Yuan, Y.-M. Xiao, L.-R. Yang, P. Mao and L.-B. Qu, *Chem. Commun.*, 2012, **48**, 10117; (c) S. T. Ding and N. Jiao, *J. Am. Chem. Soc.*, 2011, **133**, 12374.

4 For selected examples of Rh-catalyzed *N*-formylation with CO_2, see: (a) T. V. Q. Nguyen, W.-J. Yoo and S. Kobayashi, *Angew. Chem. Int. Ed.*, 2015, **54**, 9209; (b) S. Itagaki, K. Yamaguchi and N. Mizuno, *J. Mol. Catal. A-Chem.*, 2013, **366**, 347.

5 For select example of Pd-catalyzed *N*-formylation with CO_2, see: X. J. Cui, Y. Zhang, Y. Q. Deng and F. Shi, *Chem. Commun.*, 2014, **50**, 189.

6 For select examples of Cu-catalyzed *N*-formylation with CO_2, see: (a) K. Motokura, N. Takahashi, D. Kashiwame, S. Yamaguchi, A. Miyaji and T. Baba, *Catal. Sci. Technol.*, 2013, **3**, 2392; (b) K. Motokura, D. Kashiwame, N. Takahashi, A. Miyaji and T. Baba, *Chem. Eur. J.*, 2013, **19**, 10030; (c) R. Shintani and K. Nozaki, *Organometallics*, 2013, **32**, 2459; (d) K. Motokura, N. Takahashi, A. Miyaji, Y. Sakamoto, S. Yamaguchi and T. Baba, *Tetrahedron*, 2014, **70**, 6951; (e) M. Nasrollahzadeh, S. M. Sajadi and A. Hatamifard, *J. Colloid. Interf. Sci.*, 2015, **460**, 146.

7 For select examples of Fe-catalyzed *N*-formylation with CO_2, see: (a) X. Frogneux, O. Jacquet and T. Cantat, *Catal. Sci. Technol.*, 2014, **4**, 1529; (b) C. Federsel, A. Boddien, R. Jackstell, R. Jennerjahn, P. J. Dyson, R. Scopelliti, G. Laurenczy and M. Beller, *Angew. Chem. Int. Ed.* 2010, **49**, 9777; (c) M. Kooti, E. Nasiri, *J. Mol. Catal. A-Chem.*, 2015, **406**, 168; (d) G. H. Jin, C. G. Werncke, Y. Escudié, S. Sabo-Etienne and S. Bontemps, *J. Am. Chem. Soc.* 2015, **137**, 9563.

8 For select example of Ni-catalyzed *N*-formylation with CO_2, see: L. González-Sebastián, M. Flores-Alamo and J. J. García, *Organometallics*, 2013, **32**, 7186.

9 For select examples of Zn-catalyzed *N*-formylation with CO_2, see: (a) Z.-Z. Yang, B. Yu, H. Y. Zhang, Y. F. Zhao, G. P. Ji and Z. M. Liu, *RSC Adv.*, 2015, **5**, 19613; (b) O. Jacquet, X. Frogneux, C. Das Neves Gomes and T. Cantat, *Chem. Sci.*, 2013, **4**, 2127.

10 For select examples of NHC-catalyzed *N*-formylation with CO_2, see: (a) O. Jacquet, C. Das Neves Gomes, M. Ephritikhine, and T. Cantat, *ChemCatChem,* 2013, **5**, 117; (b) Q. H. Zhou and Y. X. Li, *J. Am. Chem. Soc.*, 2015, **137**, 10182; (c) O. Jacquet, C. Das Neves Gomes, M. Ephritikhine and T. Cantat, *J. Am. Chem. Soc.*, 2012, **134**, 2934.

11 For select examples of ILs-catalyzed *N*-formylation with CO_2, see: (a) X. Gao, B. Yu, Z. Z. Yang, Y. F. Zhao, H. Y. Zhang, L. D. Hao, B. X. Han and Z. M. Liu, *ACS Catal.*, 2015, **5**, 6648; (b) L. D. Hao, Y. F. Zhao, B. Yu, Z. Z. Yang, H. Y. Zhang, B. X. Han, X. Gao and Z. M. Liu, *ACS Catal.*, 2015, **5**, 4989.

12 For select examples of organic base-catalyzed *N*-formylation with CO_2, see: C. Das Neves Gomes, O. Jacquet, C. Villiers, P. Thuéry, M. Ephritikhine and T. Cantat, *Angew. Chem. Int. Ed.*, 2012, **51**, 187.

13 (a) M. J. Fuchter, *Chem. Eur. J.*, 2010, **16**, 12286; (b) S. N. Riduan, Y. G. Zhang and J. Y. Ying, *Angew. Chem. Int. Ed.* 2009, **48**, 3322.

14 (a) D. H. Aue, H. M. Webb, M. T. Bowers, *J. Am. Chem. Soc.*, 1976, **98**, 318; (b) A. J. Parker, *Electrochim. Acta*, 1976, **21**, 671; (c) A. Streitwieser, et al., "Introduction to Org. Chem. ", 2nd ed., Macmillan Publishing Co., Inc. New York, 1981, 725.(d) C. Reichardt, *Chem. Rev.,* 1994, **94**, 2319.

15 S. Tanaka, T. Yamamura, S. Nakane, M. Kitamura, *Chem. Commun.*, 2015, **51**, 13110.