# **CHEMISTRY** A European Journal



## **Accepted Article**

**Title:** Reductive Coupling of CO2, Primary Amine and Aldehyde at Room Temperature: A Versatile Approach to Unsymmetrically N,N-Disubstituted Formamides

Authors: Zhimin Liu, Zhengang Ke, Leiduan Hao, Xiang Gao, Hongye Zhang, Yanfei Zhao, Bo Yu, Zhenzhen Yang, and Yu Chen

This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: Chem. Eur. J. 10.1002/chem.201701420

Link to VoR: http://dx.doi.org/10.1002/chem.201701420

Supported by ACES



## COMMUNICATION

#### WILEY-VCH

## Reductive Coupling of CO<sub>2</sub>, Primary Amine and Aldehyde at Room Temperature: A Versatile Approach to Unsymmetrically *N*,*N*-Disubstituted Formamides

Zhengang Ke,<sup>[a,b]</sup> Leiduan Hao,<sup>[a]</sup> Xiang Gao,<sup>[a,b]</sup> Hongye Zhang,<sup>[a]</sup> Yanfei Zhao,<sup>[a]</sup> Bo Yu,<sup>[a]</sup> Zhenzhen Yang,<sup>[a]</sup> Yu Chen,<sup>[a,b]</sup> and Zhimin Liu<sup>[a,b]\*</sup>

**Abstract:** Herein we present a simple, metal-free and versatile route to synthesize unsymmetrically *N*,*N*-disubstituted formamides (NNFAs) from CO<sub>2</sub>, primary amine and aldehyde promoted by ionic liquid (1-butyl-3-methylimidazolium chloride) at room temperature. This approach features wide scopes of amines and aldehydes, and various unsymmetrical NNFAs could be obtained in good to excellent yields. The ionic liquid can be reused at least five runs without obvious activity loss.

Unsymmetrically *N*,*N*-disubstituted formamides (NNFAs) are a kind of *N*-formamides with wide applications in organic and pharmaceutical synthesis, however, their synthesis is still challenging. To date many methods have been developed for synthesis of *N*-formamides, mainly based on the reactions of halohydrocarbons with formamides,<sup>[1]</sup> or on the reactions of imines/unsymmetrical secondary amines with formyl sources including formic acid,<sup>[2]</sup> formaldehyde,<sup>[3]</sup> methanol<sup>[4]</sup> and CO<sub>2</sub>/hydrogen<sup>[5]</sup>. Some of these methods could be applied in the synthesis of limited unsymmetrical NNFAs. Therefore, exploring simple, clean and versatile route to synthesis of unsymmetrical NNFAs with various *N*-substituents is highly desirable.

Carbon dioxide (CO<sub>2</sub>) is an abundant, easily available, nontoxic and renewable C1 building block, thus catalytic *N*formylation of amines with CO<sub>2</sub> provides clean route to the synthesis of *N*-formamides, which has been paid much attention in recent years.<sup>[6]</sup> Due to the thermodynamic stability and kinetic inertness of CO<sub>2</sub>, many efforts have been dedicated to the transformation of CO<sub>2</sub> under mild conditions.<sup>[7]</sup> Since the first report of *N*-formylation of amine and CO<sub>2</sub> with silanes as reducing reagents<sup>[5f]</sup>, many catalyst systems, such as *N*heterocyclic carbenes, carboxylates, metal complex, ionic liquids and frustrated Lewis pairs, using silanes as reducing reagents have been reported for the reductive *N*-formylation of amines with CO<sub>2</sub> under mild conditions.<sup>[6b,6c,8,9]</sup> However, the CO<sub>2</sub>involved direct synthesis of unsymmetrical NNFAs has not been reported yet in a literature survey.

Herein, we present a simple, metal-free and versatile route to synthesize unsymmetrical NNFAs via the direct threecomponent reductive coupling of  $CO_2$ , primary amine and aldehyde using phenylsilane (PhSiH<sub>3</sub>) as a reducing reagent promoted by the IL, 1-butyl-3-methylimidazolium chloride

[a] Z. Ke, Dr. L. Hao, X. Gao, Dr. H. Zhang, Dr. Y. Zhao, Dr. B. Yu, Dr. Z. Yang, Y. Chen, and Prof. Z. Liu Beijing National Laboratory for Molecular Sciences, Key Laboratory of Colloid, Interface and Thermodynamics, CAS Research/Education Center for Excellence in Molecular Sciences, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China.
[b] Z. Ke, X. Gao, Y. Chen, and Prof. Z. Liu

University of Chinese Academy of Sciences Beijing 100049, China.

Supporting information for this article is given via a link at the end of the document.

([BMIm]Cl), at ambient temperature (Scheme 1). This approach was tolerable to wide scopes of alkyl/aryl amines and alkyl/aryl aldehydes, and various unsymmetrical NNFAs could be produced in good to excellent yields via changing amines and aldehydes. More importantly, some unsymmetrical NNFAs with reductive substitutes could be obtained without the hydrogenation of the unsaturated bonds. The reaction mechanism exploration indicated that the direct coupling of amines and aldehydes formed imines in situ, which was further reductively N-formylated with CO2 in the presence of PhSiH3 catalyzed by the IL. This protocol was scalable, and the IL could be recycled five times without loss in activity. This solvent- and metal-free protocol may have promising applications in the commercial production of unsymmetrical NNFAs.



Scheme 1. One-step synthesis of unsymmetrical NNFAs through threecomponent coupling of primary amine, aldehyde and  $CO_2$ .

The preliminary three-component coupling reaction was performed using aniline, benzaldehyde and CO<sub>2</sub> to explore the suitable reaction conditions. Various imidazolium-based ILs were first examined for catalysing this reaction because they were proved to be effective for catalysing N-formylation of amines with CO2 previously.<sup>[9]</sup> As listed in Table 1, most of the tested ILs were effective for the reaction, among which [BMIm]CI exhibited the best performance, affording a product yield of 84% within 12 h at room temperature (Table 1, entry 1). The ILs with the same cation as [BMIm]Cl and different anions displayed the activity in order: [BMIm]Cl>[BMIm]NO<sub>3</sub>>[BMIm]Br, while [BMIm][BF<sub>4</sub>] and [BMIm][PF<sub>6</sub>] were ineffective for the reaction (Table 1, entries 1-5). 1-hexyl-3-methy-limidazoliumchloride ([HMIm]Cl) showed similar activity to [BMIm]Cl, with a product yield of 80% (Table 1, entries 1 and 6), suggesting that the alkyl substitute in the imidazolium ring had a little influence on the activity of the ILs with the Cl<sup>-</sup> anion, while the substitution with acidic group (e.g., -BSO<sub>3</sub>H) significantly impacted the activity of the IL (Table 1, entry 7). These results suggested that the cooperative effect from the cation and anion of the ILs was responsible for the activity of the ILs. The reaction could proceed with [BMIm]Cl even at atmospheric pressure, affording a product yield of 5%. Increasing the CO<sub>2</sub> pressure to 10 atm significantly improved the product yield to 84% (Table 1, entries 1,7,8). We investigated the influence of the amount of the used IL on the reaction. It was found that equimolar [BMIm]Cl was required for getting a satisfied product yield (Table 1, entries 1 and 10-12). In the case of small amount of IL (e.g., 0.2 equiv., entry 13) no product was detectable, implying that enough amount of the IL was indispensible. Examination of various silanes demonstrated that only PhSiH<sub>3</sub> was effective for this reaction under the experimental conditions (Table 1, entries 14-19). In addition, the amount of the used PhSiH<sub>3</sub> also influenced the reaction activity.

## COMMUNICATION

Table 1. Reaction conditions optimization         [a]							
Entr y	Catalyst/mmol	PCO <sub>2</sub> /atm	Solvent/mL	silane/mmol	Yield <sup>୲୭</sup> / %		
1	[BMIm]Cl/1	10	-	PhSiH <sub>3</sub> /2	84 (80 <sup>[c]</sup> )		
2	[BMIm]NO <sub>3</sub> /1	10	-	PhSiH₃/2	63 ´		
3	[BMIm]Br/1	10	-	PhSiH <sub>3</sub> /2	51		
4	[BMIm]BF₄/1	10	-	PhSiH₃/2	1		
5	[BMIm]PF <sub>6</sub> /1	10	-	PhSiH₃/2	0		
6	[HMIm]Cl/1	10	-	PhSiH₃/2	80		
7	[BSO₃HMIm]Cl /1	10	-	PhSiH₃/2	0		
8	[BMIm]Cl/1	1	-	PhSiH₃/2	5		
9	[BMIm]Cl/1	20	-	PhSiH <sub>3</sub> /2	85		
10	[BMIm]Cl/0.8	10	-	PhSiH <sub>3</sub> /2	76		
11	[BMIm]Cl/0.6	10	-	PhSiH₃/2	68		
12	[BMIm]Cl/0.4	10	-	PhSiH₃/2	29		
13	[BMIm]Cl/0.2	10	-	PhSiH₃/2	0		
14	[BMIm]Cl/1	10	-	Ph <sub>2</sub> SiH <sub>2</sub> /3	0		
15	[BMIm]Cl/1	10	-	Et <sub>2</sub> SiH <sub>2</sub> /3	0		
16	[BMIm]Cl/1	10	-	Et₃SiH/6	0		
17	[BMIm]Cl/1	10	-	CH <sub>3</sub> (EtO) <sub>2</sub> SiH /6	0		
18	[BMIm]Cl/1	10	-	(CH <sub>3</sub> ) <sub>2</sub> CISiH/6	0		
19	[BMIm]Cl/1	10	-	Et <sub>3</sub> SiH/6	0		
20	[BMIm]Cl/1	10	<i>n</i> -hexane	PhSiH₃/2	6		
21	[BMIm]Cl/1	10	acetone	PhSiH₃/2	0		
22	[BMIm]Cl/1	10	DMSO	PhSiH₃/2	38		
23	[BMIm]Cl/1	10	DMF	PhSiH₃/2	29		
24	[BMIm]Cl/1	10	THF	PhSiH₃/2	30		
25	[BMIm]Cl/1	10	1,4-dioxane	PhSiH <sub>3</sub> /2	17		
Poaction conditions: [a] aniling (1.0 mmol) bonzaldobydo (1.0 mmol) CO. (10							

Reaction conditions: [a] aniline (1.0 mmol), benzaldehyde (1.0 mmol),  $CO_2$  (10 atm), [BMIm]Cl (1.0 mmol), room temperature, 12 h. [b] The yield was determined by GC-FID, calibrated using *n*-dodecane as the internal standard. [c] Isolated yield.

The effect of solvents was investigated, and the results are listed in Table 1, entries 20-25. In sharp contrast, the solvents significantly influenced the product yields. Especially, using acetone as the solvent, the reductive formylation did not occur. In this work, the reaction was performed under the solvent-free conditions in most cases, thus the solvent effect was avoided. Based on the above results, the optimized reaction conditions were obtained as follows: 2 equiv. of PhSiH<sub>3</sub>, 1 equiv. of [BMIm]Cl together with 10 atm of CO<sub>2</sub> pressure, 30 °C.

Under the optimized conditions, the generality of the threecomponent coupling of primary amine, aldehyde and CO<sub>2</sub> was investigated. To get N-aryl-N-benzylformamides, aryl amines and aryl aldehydes were used as the substituent resources, and the coupling reaction was investigated under the optimized conditions (Table 2). To our delight, all the coupling reactions proceeded well, yielding the corresponding unsymmetrical NNFAs in good to excellent yields in most cases. For example, the coupling of CO<sub>2</sub> with aniline and benzaldehyde possessing electron-withdrawing groups (e.g., Cl, F) afforded improved product yields due to the substitution in the benzene rings of the aldehydes (Table 2, 1c-3c). Similar results were observed in the synthesis of 4c-6c and 7c-9c, and the isolated yields of 9c and 10c reached up to 92%. For the coupling of CO<sub>2</sub> with benzaldehyde and anilines, no matter what the substituents in benzene ring of anilines were electron-donoring or -withdrawing all the target products were obtained in enhanced yields (1c, 4c, 7c, 10c and 13c). Also, the coupling of CO<sub>2</sub> with 4fluorobenzaldehyde and anilines possessing electron-donoring groups gave rise to the products in very high yields. Notably, considerable yields of the products (e.g., 14c and 15c) were obtained when both anilines and benzaldehyde possessing electron-withdrawing groups in benzene rings were adopted.

The above results indicated that the protocol was highly efficient for the synthesis of *N*-aryl-*N*-benzyl disubstituted formamides.



Reaction conditions: [a] amine (1.0 mmol), aldehyde (1.0 mmol), PhSiH<sub>3</sub> (2.0 mmol), CO<sub>2</sub> (10 atm), [BMIm]CI (1.0 mmol), room temperature, 12 h. Yields of the isolated products. [b] The yield was determined by <sup>1</sup>H NMR, calibrated using 1,1,2,2,-tetrachloroethane as the internal standard.

Encouraged by the above results, we extended the scopes of the amines and aldehydes to aliphatic ones. Interestingly, all the three-component coupling reactions of CO2 with alkyl amines/aryl aldehydes, or aryl amines/alkyl aldehyde, or alkyl amine/alkyl aldehydes, took place successfully, affording the corresponding products in the yields of 70%-92% (18c-29c). For example, in the cases of n-hexylamine, n-pentylamine and cyclohexanecarboxaldehyde, the yields of corresponding products (28c and 29c) reached to 91% and 90%, respectively. Notably, compared to the aryl amines or aryl aldehydes, the aliphatic amines and aldehydes displayed relatively low reactivity, probably because aliphatic imines are relatively difficult to form and/or the electrophilic ability of aliphatic aldehydes are relatively weak relative to the aromatic aldehydes. Thus prolonged reaction time (e.g., 24h) was required for reaching high isolated yields of the products. The amines and aldehydes with reducible functional groups (e.g., -CN, -C=C-) were also examined. It was indicated that the reaction system was tolerable to the unsaturated chemical bonds, and the unsymmetrical NNFAs with reducible groups could be obtained in good yields (30c-36c). In addition, the reaction of 4nitrobenzaldehyde, aniline and CO<sub>2</sub> was also performed, and no target product was obtained. It was found that -NO2 was

## COMMUNICATION

unsaturated chemical bonds. <sup>[a]</sup>							
R <sup>1</sup> NH <sub>2</sub> CO <sub>2</sub>	+ R <sup>2</sup> CHO [BMIm]C	Cl (1.0 eqiv)					
R <sup>1</sup> =alkyl or aryl 10 atm	R <sup>2</sup> =alkyl or aryl <sup>30</sup> °0	C, 24h R <sup>1</sup>					
0 N_c-Hex 18c, 80%	О N_ с-Нех 19с, 88%	0 N_c-Hex 20c, 78%					
Meo N_c-Hex	0 n-Hex 22 <b>c</b> . 80%	n-Hex N Cl					
21c, 75%	0 <i>n</i> -Pen <sup>-N</sup>	n-Pen <sup>-N</sup>					
24c, 89%	25 <b>c</b> , 71%	26 <b>c</b> , 77%					
O N 30c, 64% <sup>[b]</sup>	0 N 31c, 70% <sup>[b]</sup>	N 0 N N 32c. 75% <sup>[b]</sup>					
0 NeO 33c, 79% <sup>[b]</sup>	0 N 34 <b>c</b> , 79% <sup>[b]</sup>	35 <b>c</b> , 82% <sup>[b]</sup>					
O N 36c, 76% <sup>[b]</sup>	amine (1.0 mmol) aldebug	te (1.0 mmol) PhSiH, (2.0					

#### Table 3. Synthesis of the unsymmetrical NNFAs with alkyl-substitution and/or

Reaction conditions: [a] amine (1.0 mmol), aldenyde (1.0 mmol), PhSH<sub>3</sub> (2.0 mmol), CO<sub>2</sub> (10 atm), [BMIm]CI (1.0 mmol), room temperature, 24 h. Yields of the isolated products. [b] The yield was determined by <sup>1</sup>H NMR, calibrated using 1,1,2,2,-tetrachloroethane as the internal standard.

reduced to  $-NH_2$  under the experimental conditions, resulting in the complicated products including *N*-phenylformamide, (*E*)-4-((phenylimino)methyl)aniline, *N*-(4-nitrobenzyl)aniline and *N*-(4-aminobenzyl)-*N*-phenylformamide.

The reusability of the IL was investigated, and it was indicated that the IL was reusable without obvious activity loss even reused for five times (Figure 1). In addition, the scalability of the protocol was examined by performing the reaction on the gram scale. Using 1.07 g of 4-methylaniline and corresponding amount of 4-fluorobenzaldehyde as starting materials, 2.14 g of *N*-(4-fluorobenzyl)-*N*-(*p*-tolyl)-formamide was obtained after 24 h, affording a satisfactory product yield of 88%. This indicated that the above protocol was practical and scalable, which may have promising application for the synthesis of the unsymmetrical NNFAs.

To reveal the mechanism of the *N*-formylation reaction, using aniline and benzaldehyde as the model substrates control experiments were performed. As known, amine could easily react with aldehyde to form imine.<sup>[10]</sup>



**Figure 1.** Recycling of [BMIm]Cl for the coupling of 4-methylaniline, benzaldehyde and CO<sub>2</sub>. Reaction conditions: 4-methylaniline (1.0 mmol), 4-fluorobenzaldehyde (1.0 mmol), PhSiH<sub>3</sub> (2.0 mmol), CO<sub>2</sub> (10 atm), [BMIm]Cl (1.0 mmol), room temperature, 12 h.

As expected, the reaction of aniline and benzaldehyde occurred rapidly at room temperature. formina benzylideneaniline in a yield of 99%. Thereafter, using benzylideneaniline as the starting material, the experiments as illustrated in Scheme 2 were carried out. The reaction of benzylideneaniline with CO<sub>2</sub> and PhSiH<sub>3</sub> proceeded very well in the presence of [BMIm]Cl, and the target product was obtained in a similar yield to that of 1c in Table 2 (Scheme 2a). Moreover, in this work it was demonstrated that benzylideneaniline could not be hydrogenated by PhSiH<sub>3</sub> to N-benzylaniline (Scheme 2b). The above results suggest that the formation of the unsymmetrical NNFA was realized via the formylation of the insitu generated imine with CO<sub>2</sub>/PhSiH<sub>3</sub>, rather than the Nformylation of secondary amine that could not be obtained under the experimental conditions. To explore the reaction mechanism of reductive N-formylation of benzylideneaniline with CO2 and PhSiH<sub>3</sub>, the reaction of PhSiH<sub>3</sub> (2 mmol) and CO<sub>2</sub> was carried out at room temperature, and the reaction solution was detected by <sup>1</sup>H NMR to determine the amounts of the formed formoxysilane and the residual PhSiH<sub>3</sub>. Subsequently, to the reaction solution desired amount of benzylideneaniline was added, and after 12h the reaction solution was examined again by <sup>1</sup>H NMR. As a result, N-benzyl-N-phenyl formamide was detected in a high yield (Figures S3), meanwhile it was found that PhSiH<sub>3</sub> involved the formation of benzylideneaniline (Scheme 2c). However, removing the IL through extraction with diethyl ether before the addition of benzylideneaniline into the solution, no N-benzyl-N-phenyl formamide was detected (Scheme 2d). This suggests that the IL catalyzed the reductive N-formylation of benzylideneaniline with formoxysilane and PhSiH<sub>3</sub>.

From the above experiments, it was indicated that the IL, [BMIm]Cl, play an important role in the reductive *N*-formylation of imine with  $CO_2$ /PhSiH<sub>3</sub>. As reported, the IL [BMIm]Cl has strong ability to form hydrogen-bond, and a hydrogen-bond network exists among the IL molecules.<sup>[11]</sup>

WILEY-VCH

OMMUNICATION

#### 10.1002/chem.201701420

#### WILEY-VCH



Scheme 2. Control experiments of benzylideneaniline with  $CO_2$  and/or  $PhSiH_3$  as well as the intermediate. Reaction conditions: [a] benzylideneaniline (1.0 mmol), PhSiH<sub>3</sub> (2.0 mmol),  $CO_2$  (10 atm), [BMIm]Cl (1.0 mmol), 30 °C, 12 h. [b] benzylideneaniline (1.0 mmol), PhSiH<sub>3</sub> (2.0 mmol), [BMIm]Cl (1.0 mmol), 30 °C, 12 h.

The mixing of PhSiH<sub>3</sub> or benzylideneaniline with the IL may destroy the original hydrogen-bond network of the IL and form a new one, which thus activates the Si-H of PhSiH<sub>3</sub> or the -N=CHof benzylideneaniline, facilitating them to convert further. To verify the role of [BMIm]CI in the reaction, the interaction between the IL and PhSiH<sub>3</sub> and that between the IL and benzylideneaniline were examined by <sup>1</sup>H NMR, <sup>13</sup>C NMR, <sup>1</sup>H-<sup>15</sup>N HMBC, <sup>35</sup>CI NMR and <sup>29</sup>Si NMR spectroscopy. It was indicated that the <sup>1</sup>H, <sup>13</sup>C, <sup>15</sup>N and <sup>35</sup>Cl NMR spectra of [BMIm]Cl changed as the IL mixed with phenylsilane or with benzylideneaniline, respectively (Figures S4, S5, S12). Especially, these changes became larger as the IL amount increased, suggesting that the between the IL and phenylsilane or interaction benzylideneaniline enhanced with the increase in the amount of the IL. This may explain the influence of the IL amount on the reaction. In the <sup>1</sup>H, and <sup>29</sup>Si NMR spectra of the [BMIm]Cl and PhSiH<sub>3</sub> mixture, the <sup>1</sup>H signal assigning to the Si-H shifted from 4.175 to 4.147 ppm as the IL amount increased to 1.0 equiv. (Figure S6), and the <sup>29</sup>Si signal assigning to the Si-H shifted downfield from -67.572 to -66.761 ppm (Figure S7), suggesting that the Si-H of PhSiH<sub>3</sub> was activated by the IL to some extent. The <sup>1</sup>H-<sup>15</sup>N spectra of the mixture gave more information (Figures S8,9). Obviously, the H atom of Si-H in PhSiH<sub>3</sub> was more electron-rich due to the interaction with the IL, which may facilitate the insertion of the electron-deficient CO2 into the Si-H to form formoxysilane intermediate. The NMR analysis on the mixture of the IL and benzylideneaniline (Figures S10-14) indicated that the electron cloud density of N atom in -N=CHincreased, and that of H atom decreased owing to the interaction with the IL, which may facilitate the C atom in -N=CH- to accept H from the activated PhSiH<sub>3</sub> in the reductive N-formylation of imines.

Based on the above results, a plausible reaction pathway was proposed as illustrated in Scheme 3. First, amine reacts with aldehyde to form imine rapidly, meanwhile [BMIm]Cl activates phenylsilane and the newly formed imine. Subsequently,  $CO_2$  inserts into the activated Si-H bond of PhSiH<sub>3</sub> to form the



Scheme 3. Plausible reaction mechanism of the unsymmetrical *N*-formylation reaction.

formoxysilane, which further reacts with the IL-activated imine accompanied with the reduction of the -C=N- bond, resulting in the final product.

In summary, a new, simple, metal-free and versatile route was presented for the synthesis of unsymmetrical NNFAs via a threecomponent reductive coupling of primary amine, aldehyde and CO<sub>2</sub> using phenylsilane promoted by [BMIm]Cl at room temperature. This approach allows wide substrate scope and excellent functional-group tolerance, producing various unsymmetrical NNFAs in good to excellent yields. It opens a new way to synthesis of unsymmetrical NNFAs, may have promising applications.

#### **Experimental Section**

All the formylation reactions were performed in a 16 mL high-pressure reactor with a Teflon inner container in batch operation mode. Typically, amine (1.0 mmol), aldehyde (1.0 mmol), [BMIm]Cl (1.0 mmol) and PhSiH<sub>3</sub> (2.0 mmol) were loaded into the reactor. After being sealed and flushed with CO<sub>2</sub> three times, the reactor was charged with CO<sub>2</sub> up to 1.0 MPa at room temperature. Subsequently, the reactor was moved into a water-bath of 30 °C and magnetically stirred for 12 h with a speed of 500 rpm. After reaction, excess CO<sub>2</sub> was vented, and the reaction mixture was extracted with 15 mL of diethyl ether for quantitative analysis by GC-FID. Then, the crude reaction mixture was concentrated by a rotary evaporator and purified by column chromatography using petroleum ether/EtOAc (100:1~5:1) to get the pure product. The corresponding formamide was identified by <sup>1</sup>H and <sup>13</sup>C NMR spectra.

#### Acknowledgements

This work was financially supported by the National Natural Science Foundation of China (Nos. 21533011, 21403252, 21503239, 21125314) and the Chinese Academy of Sciences (QYZDY-SSW-SLH013).

#### **Conflict of interest**

The authors declare no conflict of interest.

**Keywords:** reductive coupling • primary amine • aldehyde • Carbon dioxide • unsymmetrically *N*,*N*-disubstituted formamides

- a) F. Hermant, E. Urbańska, S. Seizilles de Mazancourt, T. Maubert, E. Nicolas, Y. Six, Organometallics 2014, 33, 5643-5653; b) K. Wimalasena, H. B. Wickman, M. P. D. Mahindaratne, *Eur. J. Org. Chem.* 2001, 2001, 3811-3817.
- a) A. Chandra Shekhar, A. Ravi Kumar, G. Sathaiah, V. Luke Paul, M. Sridhar, P. Shanthan Rao, *Tetrahedron Lett.* 2009, *50*, 7099-7101; b) I. Sorribes, K. Junge, M. Beller, *Chem. Eur. J.* 2014, *20*, 7878-7883; c)
   C. L. Allen, A. R. Chhatwal, J. M. J. Williams, *Chem. Commun.* 2012, *48*, 666-668; d) H. Lundberg, H. Adolfsson, *ACS Catal.* 2015, *5*, 3271-3277.
- [3] a) O. Saidi, M. J. Bamford, A. J. Blacker, J. Lynch, S. P. Marsden, P. Plucinski, R. J. Watson, J. M. J. Williams, *Tetrahedron Lett.* 2010, *51*, 5804-5806; b) M. H. S. Hamid, C. L. Allen, G. W. Lamb, A. C. Maxwell, H. C. Maytum, A. J. Watson, J. M. Williams, *J. Am. Chem. Soc.* 2009, *131*, 1766-1774; c) Z. Ke, Y. Zhang, X. Cui, F. Shi, *Green Chem.* 2016, *18*, 808-816; d) A. M. Whittaker, V. M. Dong, *Angew. Chem. Int. Ed.* 2015, *54*, 1312–1315.
- [4] a) J. Kothandaraman, S. Kar, R. Sen, A. Goeppert, G. A. Olah, G. K. S. Prakash, *J. Am. Chem. Soc.* 2017, *139*, 2549-2552; b) S. Chakraborty, U. Gellrich, Y. Diskin-Posner, G. Leitus, L. Avram, D. Milstein, *Angew. Chem. Int. Edit.* 2017, *56*, 4229-4233; c) B. Kang, S. H. Hong, *Adv.Synth. Catal.* 2015, *357*, 834-840.
- [5] a) K. Motokura, N. Takahashi, A. Miyaji, Y. Sakamoto, S. Yamaguchi, T. Baba, *Tetrahedron* 2014, *70*, 6951-6956; b) X. Cui, Y. Zhang, Y. Deng, F. Shi, *Chem. Commun.* 2014, *50*, 189-191; c) Q.-Y. Bi, J.-D. Lin, Y.-M. Liu, S.-H. Xie, H.-Y. He, Y. Cao, *Chem. Commun.* 2014, *50*, 9138-9140; d) L. Zhang, Z. Han, X. Zhao, Z. Wang, K. Ding, *Angew. Chem.* 2015, *127*, 6284-6287; *Angew. Chem. Int. Edit.* 2015, *54*, 6186-6189; e) C. Federsel, A. Boddien, R. Jackstell, R. Jennerjahn, P. J. Dyson, R. Scopelliti, G. Laurenczy, M. Beller, *Angew. Chem. Int. Edit.* 2010, *49*, 9777-9780; f) C. Das Neves Gomes, O. Jacquet, C. Villiers, P. Thuéry, M. Ephritikhine, T. Cantat, *Angew. Chem.* 2012, *124*, 191-194; *Angew. Chem. Int. Edit.* 2012, *51*, 187-190.
- a) S. Kumar, S. L. Jain, RSC Adv. 2014, 4, 64277-64279; b) A. Tiili, E.
   Blondiaux, X. Frogneux, T. Cantat, Green Chem. 2015, 17, 157-168; c)

H. Liu, Q. Mei, Q. Xu, J. Song, H. Liu, B. Han, Green Chem. 2017, 19, 196-201; d) J. Liu, C. Guo, Z. Zhang, T. Jiang, H. Liu, J. Song, H. Fan, B. Han, Chem. Commun. 2010, 46, 5770-5772; e) L. Zhang, Z. Han, X. Zhao, Z. Wang, K. Ding, Angew. Chem. Int. Edit. 2015, 54, 6186-6189; f) T. V. Nguyen, W. J. Yoo, S. Kobayashi, Angew. Chem. 2015, 127, 9341-9344; g) C. C. Chong, R. Kinjo, Angew. Chem. 2015, 127, 12284-12288; h) P. Ju, J. Chen, A. Chen, L. Chen, Y. Yu, ACS Sustain. Chem. Eng. 2017, 5, 2516-2528; i) C. Fang, C. Lu, M. Liu, Y. Zhu, Y. Fu, B.-L. Lin, ACS Catal. 2016, 6, 7876-7881.

- a) X. F. Liu, R. Ma, C. Qiao, H. Cao, L. N. He, *Chem.-Eur. J.* 2016, *22*, 16489-16493; b) H. Niu, L. Lu, R. Shi, C.-W. Chiang, A. Lei, *Chem. Commun.* 2017, *53*, 1148-1151; c) H. Lv, Q. Xing, C. Yue, Z. Lei, F. Li, *Chem. Commun.* 2016, *52*, 6545-6548; d) Y. Zhao, B. Yu, Z. Yang, H. Zhang, L. Hao, X. Gao, Z. Liu, *Angew. Chem. Int. Edit.* 2014, *53*, 5922-5925.
- [8] a) S. Zhang, Q. Mei, H. Liu, H. Liu, Z. Zhang, B. Han, *RSC Adv.* 2016, 6, 32370-32373; b) F. D. Bobbink, S. Das, P. J. Dyson, *Nat. Protocols* 2017, 12, 417-428; c) O. Jacquet, C. Das Neves Gomes, M. Ephritikhine, T. Cantat, *J. Am. Chem. Soc.* 2012, 134, 2934-2937; d) A.-L. Girard, N. Simon, M. Zanatta, S. Marmitt, P. Goncalves, J. Dupont *Green Chem.* 2014, 16, 2815-2825; e) B. Dong, L. Wang, S. Zhao, R. Ge, X. Song, Y. Wang, Y. Gao, *Chem. Commun.* 2016, 52, 7082-7085; f) S. Das, F. D. Bobbink, S. Bulut, M. Soudani, P. J. Dyson, *Chem. Commun.* 2016, 52, 2497-2500; g) A. Julian, V. Polo, E. Jaseer, F. J. Fernandez Alvarez, L. A. Oro, *ChemCatChem* 2015, 7, 3895-3902; h) M. Hulla, F. D. Bobbink, S. Das, P. J. Dyson, *ChemCatChem* 2016, 8, 3338-3342.
- [9] a) L. Hao, Y. Zhao, B. Yu, Z. Yang, H. Zhang, B. Han, X. Gao, Z. Liu, ACS Catal. 2015, 5, 4989-4993; b) J. Akbari, M. Hekmati, M. Sheykhan A. Heydari, Arkivoc 2009, 11, 123-129.
- a) D. Chusov, B. List, *Angew. Chem. Int. Edit.* 2014, *53*, 5199-5201; b)
   K. Beydoun, G. Ghattas, K. Thenert, J. Klankermayer, W. Leitner, *Angew. Chem. Int. Edit.* 2014, *53*, 11010-11014.
- [11] a) P. A. Hunt, C. R. Ashworth, R. P. Matthews, *Chem. Soc. Rev.* 2015, 44, 1257-1288; b) K. Fumino, V. Fossog, P. Stange, D. Paschek, R. Hempelmann, R. Ludwig, *Angew. Chem. Int. Edit.* 2015, 54, 2792-2795; c) M. C. Etter, *Acc. Chem. Res.* 1990, 23, 120-126.

### WILEY-VCH

## COMMUNICATION

#### **Entry for the Table of Contents**

## COMMUNICATION



A simple and versatile route is presented for the synthesis of unsymmetrically *N*,*N*-disubstituted formamides (NNFAs) via a three-component reductive coupling of CO<sub>2</sub>, amine and aldehyde under mild conditions, which could afford various unsymmetric NNFAs in good to excellent yields.

Zhengang Ke, Leiduan Hao, Xiang Gao, Hongye Zhang, Yanfei Zhao, Bo Yu, Zhenzhen Yang, Yu Chen, and Zhimin Liu

#### Page No. – Page No.

Reductive Coupling of CO<sub>2</sub>, Primary Amine and Aldehyde: A Versatile Approach to Unsymmetrically *N*,*N*-Disubstituted Formamides