



## Metalation Reactions Hot Paper

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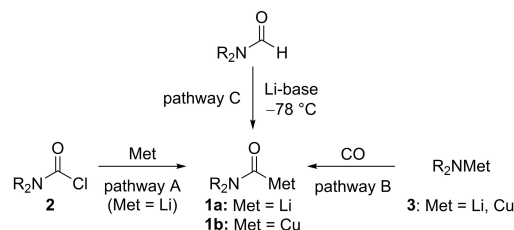
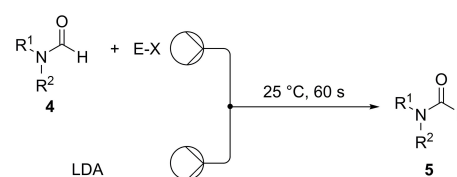
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## Preparation of Functionalized Amides Using Dicarbamoylzincs

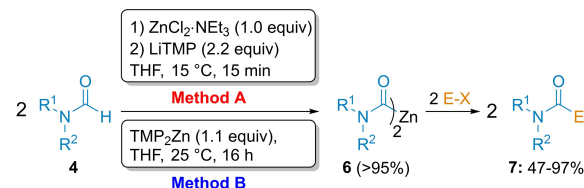
Dimitrije Djukanovic, Maximilian A. Ganiek, Kohei Nishi, Konstantin Karaghiosoff, Kazushi Mashima, and Paul Knochel\*

**Abstract:** We report a new convenient preparation of dicarbamoylzincs of type  $(R^1R^2NCO)_2Zn$  by the treatment of  $ZnCl_2$  and formamides  $R^1R^2NCHO$  with LiTMP in THF (15 °C, 15 min) or by the reaction of formamides  $R^1R^2NCHO$  with  $TMP_2Zn$  (25 °C, 16 h). This second method tolerates sensitive groups such as an ester, ketone or nitro function. Reaction of these dicarbamoylzincs with allylic, benzylic, aryl, alkenyl bromides, acid chlorides, aldehydes or enones provided various poly-functionalized amides in 47–97 % yields.  $^{13}C$  NMR characterization of these new carbamoylzinc derivatives is reported.

Reagents displaying an umpolung of reactivity have attracted much attention.<sup>[1]</sup> Especially, acyl anion equivalents have found many synthetic applications.<sup>[2]</sup> Also, related carbamoyl organometallics of type **1** have been prepared either by reduction of the corresponding carbamoyl chloride **2** by lithium metal (pathway A),<sup>[3]</sup> by the insertion of CO to copper or lithium amides of type **3** (pathway B)<sup>[4]</sup> or by the metalation of various formamides **4** with lithium bases such as LDA or *t*-BuLi at low temperature (Scheme 1).<sup>[5,6]</sup> Recently, Reeves used carbamoyllithiums prepared in toluene by lithiation with LDA for the addition to *N*-sulfonyl imines producing  $\alpha$ -amino acids.<sup>[7]</sup> All these methods suffer from drawbacks such as a limited functional group compatibility, the use of a toxic gas or cryogenic reaction temperatures. Recently, we have reported that lithium amides like LiTMP (TMP = 2,2,6,6-tetramethylpiperidyl)

 Previous work in batch:<sup>[3–5]</sup>

 Previous work in continuous flow:<sup>[10]</sup>


This work:



Scheme 1. Preparations of carbamoylmatal reagents.

were compatible with metallic salts such as  $ZnCl_2 \cdot 2LiCl$ ,  $MgCl_2$  and  $CuCN \cdot 2LiCl$  at low temperature.<sup>[8]</sup> The stability of such Lewis pairs, which may be considered as frustrated Lewis pairs,<sup>[9]</sup> allowed in situ trapping metalations of various arenes and heteroarenes.<sup>[8]</sup> This in situ protocol was expanded by generating carbamoyllithiums of type **1a** in the presence of various electrophiles in continuous flow.<sup>[10]</sup> The Barbier procedure was essential for the success of the reaction conducted in continuous flow and allowed to prepare a wide range of products of type **5**. Although this reaction represented a synthetic advance, it did not allow the performance of cross-couplings with aryl and heteroaryl halides and required a flow apparatus. Catalytic aminocarbonylation protocols<sup>[11]</sup> involve usually highly toxic CO gas, an amine and an aryl halide. Those performed in the absence of CO gas are scarce.<sup>[6e, f, 12]</sup> Herein, we have reported the synthesis of a new room temperature stable dicarbamoylzinc species **6** (stable at least 16 h at 25 °C)<sup>[13]</sup> using two complementary methods (Method A and B) and their reactions with a range of electrophiles such as allylic and benzylic bromides, aldehydes, acid chlorides, enones and heteroaryl or alkenyl bromides producing functionalized amides of type **7**.

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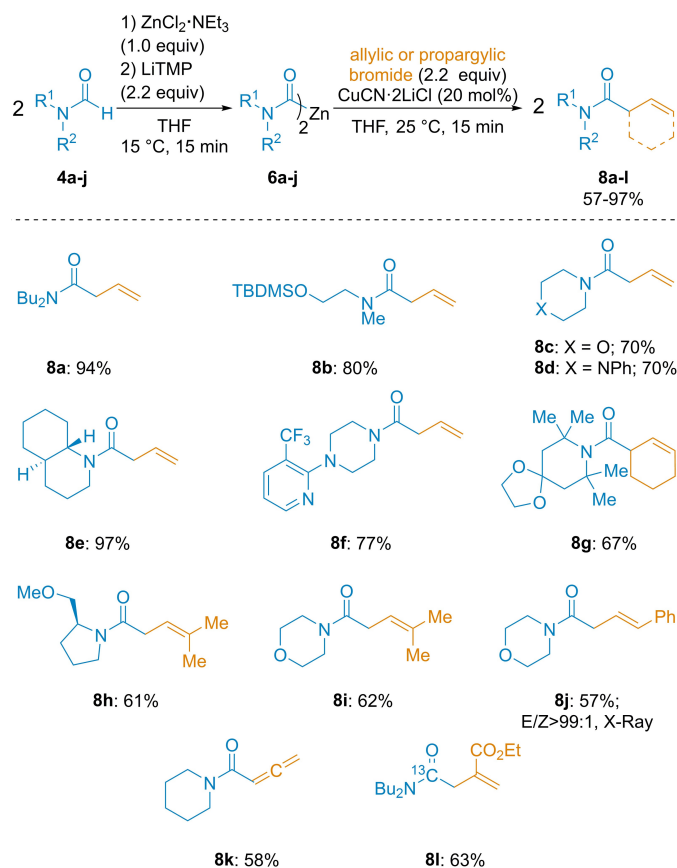
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Thus, in preliminary experiments we have treated a THF mixture of formamides of type **4** (1.0 equiv) and ZnCl<sub>2</sub> (0.5 equiv) in the presence (or absence) of Et<sub>3</sub>N (0.5 equiv)<sup>[14]</sup> with various lithium amide bases such as LDA, Cy<sub>2</sub>NLi (Cy = cyclohexyl)<sup>[15]</sup> and LiTMP in order to prepare the dicarbamoylzinc species **6** at temperatures between 0–25 °C for 15 min. The conversion to the zinc reagent **6** was evaluated by performing copper-catalyzed allylations with allyl bromide on reaction aliquots.<sup>[16]</sup> These experiments showed that LiTMP (2.2 equiv; 0.5 M in THF) was the best base for achieving this lithiation (performed in the presence of ZnCl<sub>2</sub>) providing the dicarbamoylzinc **6**.<sup>[17]</sup>

With these conditions in hand, we have examined the reaction scope. Thus, *N,N*-dibutylformamide (**4a**) was converted to the dicarbamoylzinc **6a** (LiTMP, 2.2 equiv; ZnCl<sub>2</sub>·NEt<sub>3</sub>, 1.0 equiv; 15 °C, 15 min). We have isolated, after a copper-catalyzed allylation with allyl bromide, the expected amide **8a** in 94 % isolated yield (both carbamoyl moieties were reacting). Various formamides (**4b–4h**) were zincated by this procedure leading to **6b–j**, which provided the desired allylated products **8b–8j** in 57–97 % yield (Scheme 2). Interestingly, although copper-zinc cuprates of type RCu(CN)ZnX<sup>[18]</sup> gave usually S<sub>N</sub>2'-substitution allylation products, we have observed the formation of only S<sub>N</sub>2-substitution allylation products using prenyl bromide (**8h**



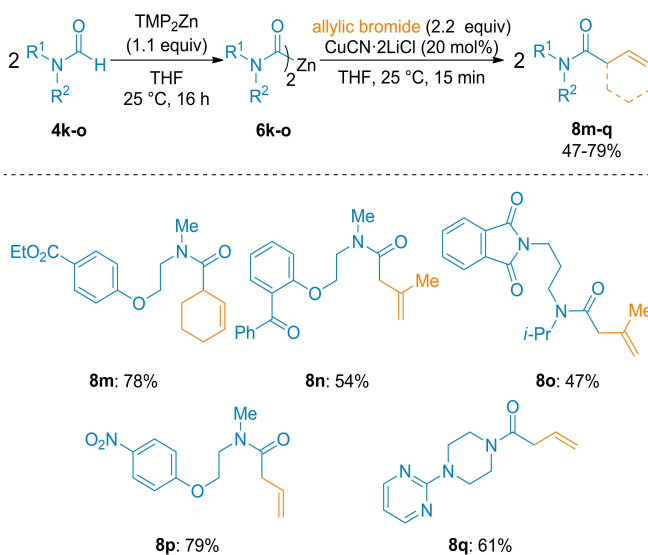
**Scheme 2.** Allylation of dicarbamoylzincs of type **6** with allylic and propargylic bromides providing polyfunctional amides of type **8**. The indicated yields refer to analytically pure isolated product.

and **8i**; 61–62 % yield) or cinammyl bromide (**8j**; 57 % yield, S<sub>N</sub>2/S<sub>N</sub>2' > 9:1).<sup>[19]</sup> This unusual regioselectivity may be due to the carbonyl group coordination to the copper center resulting in a different Zn/Cu-cluster. In contrast, with propargyl bromide, we have obtained only the S<sub>N</sub>2' product, i.e. the allenic amide **8k** (58 % yield). Interestingly, we have also used this method for the preparation of <sup>13</sup>C-labeled amide **8l** from Bu<sub>2</sub>N<sup>13</sup>CHO.<sup>[20]</sup>

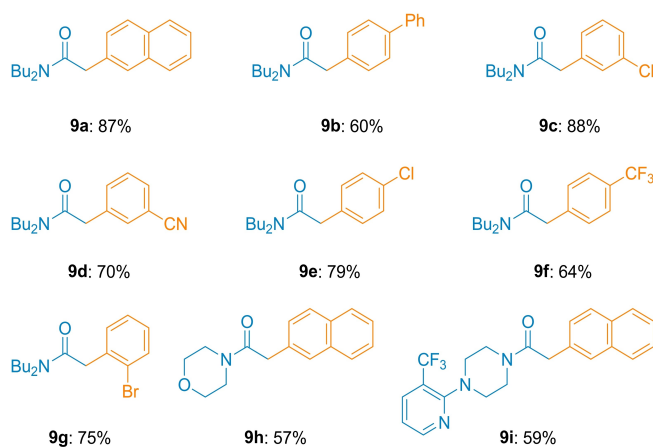
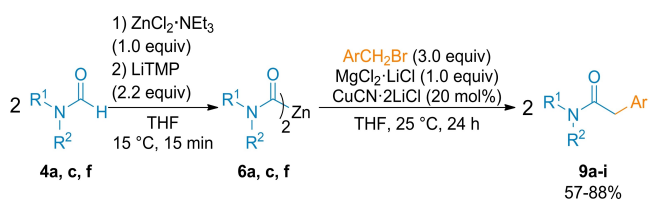
In order to tolerate more sensitive groups such as an ester, ketone or a nitro function, we have directly treated several formamides (**4k–o**) with TMP<sub>2</sub>Zn<sup>[21]</sup> in THF at 25 °C for 16 h (Method B) affording the desired zinc reagents **6k–o** which after allylation gave the desired polyfunctional products **8m–q** containing an ester, a ketone, an imide and a nitro group (Scheme 3).

Dicarbamoylzincs of type **6** also underwent smooth benzylations with various benzylic bromides in the presence of MgCl<sub>2</sub>·LiCl (1.0 equiv) affording polyfunctional arylacetamide derivatives (**9a–9i**) in 57–88 % yield (Scheme 4). In the absence of MgCl<sub>2</sub>·LiCl, a homo-coupling product of benzylic bromide (1,2-diarylethane) was observed. The positive effect of MgCl<sub>2</sub> was also mandatory for performing addition reactions to aldehydes.<sup>[22]</sup> Thus, the reaction of **6a** and **6e** with benzaldehydes in the presence of MgCl<sub>2</sub>·LiCl (1.0 equiv) gave the expected α-hydroxyamides (**10a,b**) in 57–74 % yield (Scheme 5).<sup>[23]</sup>

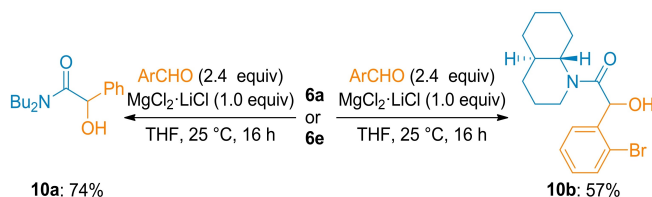
Acylation with various acid chlorides were performed in the absence of any catalyst and a complete acylation of various dicarbamoylzinc reagents of type **6** with acid chlorides at 25 °C, 16 h resulting in the formation of α-ketoamides (**11a–11d**) in 54–84 % yield (Scheme 6). In the reaction of **6a** with diphenylphosphinic chloride *N,N*-dibutyl-1-(diphenylphosphoryl)formamide **11e** was produced in 70 % yield.



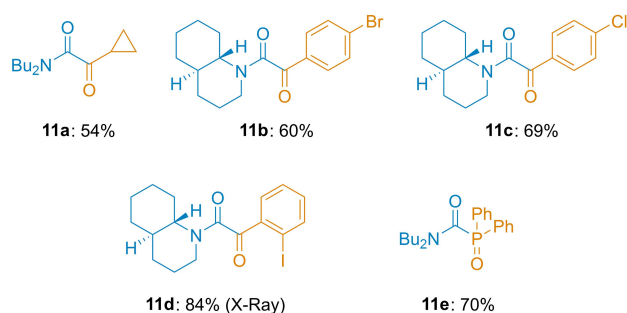
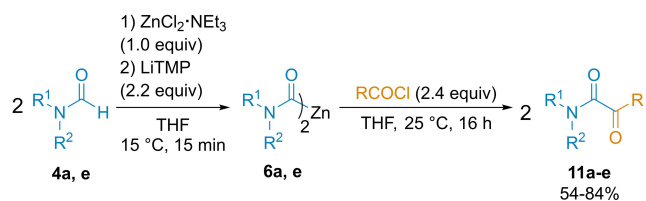
**Scheme 3.** Allylation of dicarbamoylzincs of type **6** with allylic bromides providing polyfunctional amides of type **8**. The indicated yields refer to analytically pure isolated product.



**Scheme 4.** Cu-catalyzed benzylation of dicarbamoylzincs **6** with benzylic bromides. The indicated yields refer to analytically pure isolated product.



**Scheme 5.** Mg-mediated hydroxyalkylation of dicarbamoylzincs **6** with aldehydes. The indicated yields refer to analytically pure isolated product.



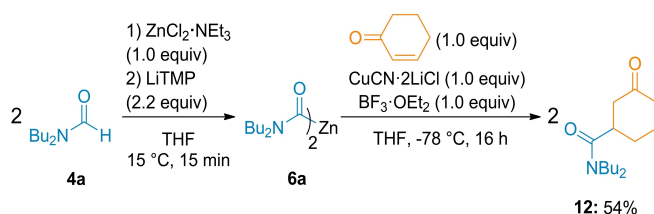
**Scheme 6.** Acylation of dicarbamoylzincs **6** with acid chlorides. The indicated yields refer to analytically pure isolated product.

Interestingly, a 1,4-addition was achieved starting with 2-cyclohexen-1-one and amide **4a**. Thus, the corresponding zinc reagent **6a** was cooled to  $-78^\circ\text{C}$  and treated with  $\text{CuCN} \cdot 2\text{LiCl}$  (1.0 equiv) for 0.5 h followed by  $\text{BF}_3 \cdot \text{OEt}_2$  (1.0 equiv)<sup>[24]</sup> and cyclohexenone (1.0 equiv) to give after 16 h at  $-78^\circ\text{C}$  the Michael adduct **12** in 54% isolated yield (Scheme 7).

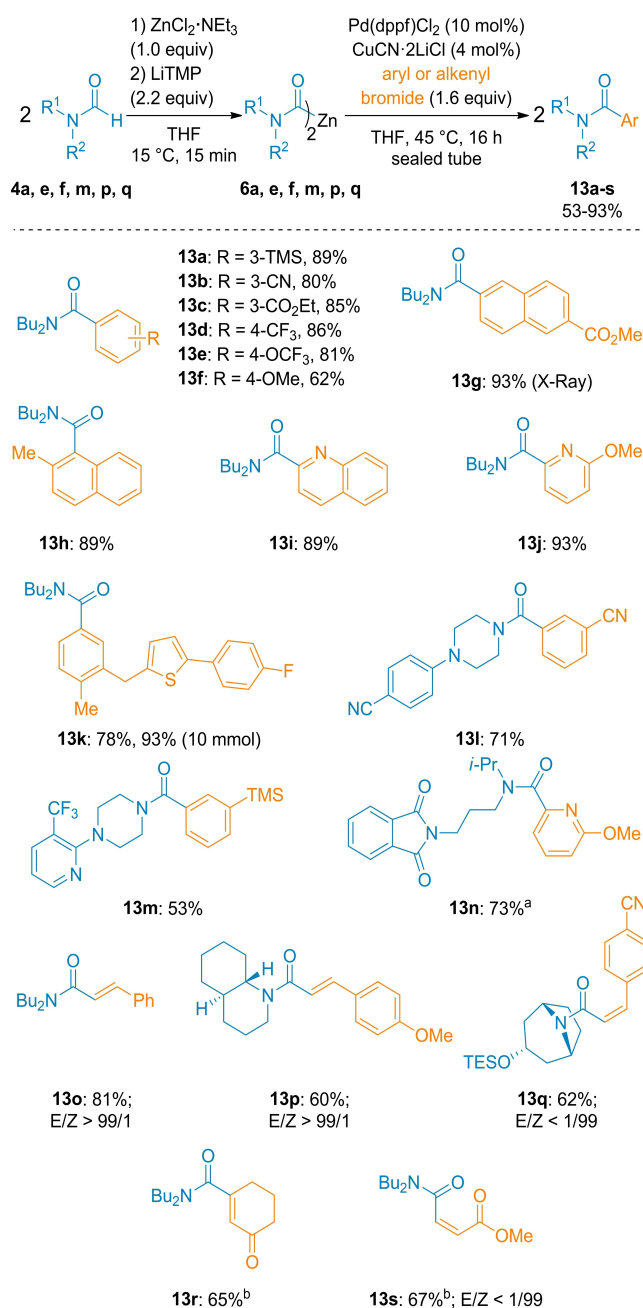
We have examined cross-coupling reactions with various functionalized aryl bromides and noticed that a dual-catalysis<sup>[25]</sup> involving a copper catalyst (4 mol%  $\text{CuCN} \cdot 2\text{LiCl}$ ) and a palladium catalyst (10 mol%  $\text{Pd}(\text{dppf})\text{Cl}_2$ ) ( $\text{dppf} = 1,1'$ -bis(diphenylphosphino)ferrocene) was required. Using only  $\text{Pd}(\text{dppf})\text{Cl}_2$  or a  $\text{CuCN} \cdot 2\text{LiCl}$  gave almost no product. In a typical experiment, we have prepared **6a** from *N,N*-dibutylformamide (2.0 equiv) with the usual procedure (Method A). Addition of 10 mol%  $\text{Pd}(\text{dppf})\text{Cl}_2$ , aryl/alkenyl bromide and 4 mol%  $\text{CuCN} \cdot 2\text{LiCl}$  gave after heating the reaction mixture for 16 h at  $45^\circ\text{C}$  in a sealed tube the desired cross-coupling products **13a–13q** in 53–93% isolated yield (Scheme 8). Scale-up of this procedure has been demonstrated in the preparation of **13k** (10 mmol scale; Scheme 8) with reduction of catalyst loading (2 mol%  $\text{Pd}(\text{dppf})\text{Cl}_2$ , 0.8 mol%  $\text{CuCN} \cdot 2\text{LiCl}$ ).

A  $^{13}\text{C}$  NMR-characterisation of *N,N*-dibutylcarbamoylzinc reagent was done. Thus, the  $^{13}\text{C}$  NMR spectra of the reaction mixture obtained by treating **4a**/ $\text{ZnCl}_2$  mixture with LiTMP showed a new characteristic carbonyl signal ( $\delta = 219.4$  ppm), together with a broad signal around  $\delta = 225$  ppm (Figure 1a). To confirm the assignment of these resonances, we have prepared dicarbamoylzinc **6a** by an alternative method. Thus, treatment of  $\text{Bu}_2\text{NLi}$  at  $-78^\circ\text{C}$  with CO gas led to *N,N*-dibutylcarbamoyllithium<sup>[4d,e]</sup> (1.0 equiv) which was transmetalated under CO atmosphere with  $\text{ZnCl}_2$  (0.5 equiv) to give the dicarbamoylzinc reagent **6a**. Indeed, an identical  $^{13}\text{C}$  NMR signal with a chemical shift for the carbonyl group  $\delta = 219.4$  ppm (Figure 1b) was observed. Also, by using 0.3 equiv of  $\text{ZnCl}_2$  we obtained the zincate **14a** (Figure 1c). Finally,  $\text{TMP}_2\text{Zn} \cdot 2\text{LiCl}$  as a metalation reagent afforded spectroscopically pure diorganozinc reagent **6a** (Figure 1d).

In summary, we have reported a new convenient in situ lithiation with LiTMP of various formamides **4** in the presence of  $\text{ZnCl}_2$  providing new dicarbamoylzincs **6** which underwent allylations, benzylations, arylations, alkenylations, acylations, hydroxyalkylations and 1,4-additions providing polyfunctional amides in good yields (Method A).

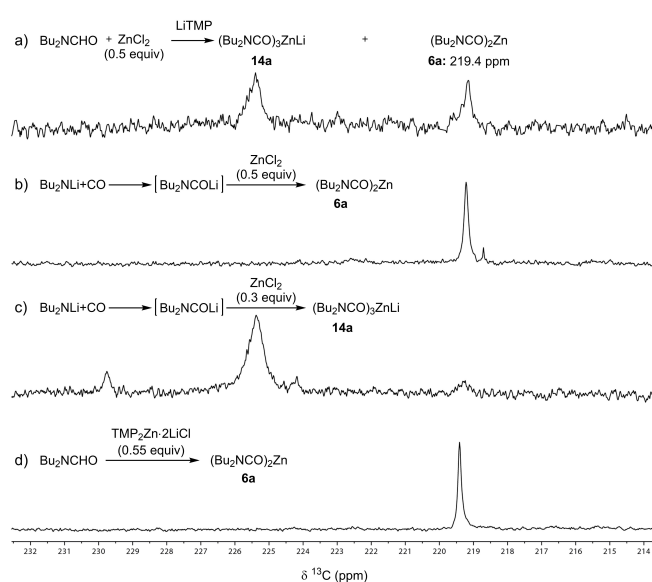


**Scheme 7.** Cu-mediated 1,4-addition of **6a** to 2-cyclohexen-1-one in the presence of  $\text{BF}_3 \cdot \text{OEt}_2$ . The indicated yields refer to analytically pure isolated product.



**Scheme 8.** Pd- and Cu-dual catalyzed cross-couplings of dicarbamoylzincs **6** with aryl and alkenyl bromides. The indicated yields refer to analytically pure isolated product. [a] Metalation performed with  $\text{TMP}_2\text{Zn} \cdot 2\text{MgCl}_2 \cdot 2\text{LiCl}$ . [b] Reaction performed from alkenyl iodides using  $\text{CuCN} \cdot 2\text{LiCl}$  (1.0 equiv) without [Pd] catalyst.

Alternatively, we have also demonstrated that the reaction of polyfunctional formamides with  $\text{TMP}_2\text{Zn}$  provides dicarbamoylzincs containing sensitive functions such as ester, ketone or nitro (Method B). <sup>13</sup>C NMR investigations confirmed the formation of  $(\text{R}_2\text{NCO})_2\text{Zn}$  and related aggregate  $(\text{R}_2\text{NCO})_3\text{ZnLi}$  under these reaction conditions.



**Figure 1.** <sup>13</sup>C NMR spectra of dicarbamoylzinc **6a** and lithium tricarbamoylzincate **14a** generated via different methods.

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## Conflict of Interest

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

**Keywords:** Amides • Carbamoyl • Lithium • Metalation • Zinc

- [1] T. A. Hase, *Umposed Synthons*, Wiley, New York, **1987**.
- [2] a) D. Seebach, *Synthesis* **1969**, *1*, 17; b) D. Seebach, *Synthesis* **1977**, *6*, 357; c) D. Seebach, *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239; *Angew. Chem.* **1979**, *91*, 259; d) W. A. Eger, R. L. Grange, H. Schill, R. Goumont, T. Clark, C. M. Williams, *Eur. J. Org. Chem.* **2011**, 2548.
- [3] a) D. J. Ramón, M. Yus, *Tetrahedron Lett.* **1993**, *34*, 7115; b) D. J. Ramón, M. Yus, *Tetrahedron* **1996**, *52*, 13739; c) For a flow procedure on Li insertion in carbamoyl chlorides see: A. Nagaki, Y. Takahashi, J.-I. Yoshida, *Angew. Chem. Int. Ed.* **2016**, *55*, 5327; *Angew. Chem.* **2016**, *128*, 5413.
- [4] a) V. Rautenstrauch, M. Joyeux, *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 83; *Angew. Chem.* **1979**, *91*, 72; b) V. Rautenstrauch, M. Joyeux, *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 85; *Angew. Chem.* **1979**, *91*, 73; c) T. Tsuda, M. Miwa, T. Saegusa, *J. Org.*

- Chem.* **1979**, *44*, 3734; d) T. Mizuno, I. Nishiguchi, T. Okushi, T. Hirashima, *Tetrahedron Lett.* **1991**, *32*, 6867; e) T. Mizuno, I. Nishiguchi, T. Hirashima, *Tetrahedron Lett.* **1993**, *49*, 2403.
- [5] a) B. Bánhidai, U. Schöllkopf, *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 836; *Angew. Chem.* **1973**, *85*, 860; b) D. Enders, D. Seebach, *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 1014; *Angew. Chem.* **1973**, *85*, 1104; c) R. R. Fraser, P. R. Hubert, *Can. J. Chem.* **1974**, *52*, 185; d) U. Schöllkopf, H. Beckhaus, *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 293; *Angew. Chem.* **1976**, *88*, 296; e) D. Seebach, W. Lubosch, D. Enders, *Chem. Ber.* **1976**, *109*, 1309; f) A. S. Fletcher, K. Smith, K. Swaminathan, *J. Chem. Soc. Perkin Trans. 1* **1977**, 1881; g) D. Enders, H. Lotter, *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 795; *Angew. Chem.* **1981**, *93*, 831.
- [6] The reports of other carbamoyl organometallics see: a) Y. Yoshida, S. Asano, S. Inoue, *Chem. Lett.* **1984**, *13*, 1073; b) C. M. Lindsay, D. A. Widdowson, *J. Chem. Soc. Perkin Trans. 1* **1988**, 569; c) T. Hiiri, T. Mogami, N. Kambe, S.-I. Fujiwara, N. Sonoda, *Synth. Commun.* **1990**, *20*, 703; d) R. F. Cunico, *Tetrahedron Lett.* **2001**, *42*, 2931; e) R. F. Cunico, B. C. Maity, *Org. Lett.* **2002**, *4*, 4357; f) R. F. Cunico, B. C. Maity, *Org. Lett.* **2003**, *5*, 4947; g) R. F. Cunico, J. Chen, *Synth. Commun.* **2003**, *33*, 1963; h) J. Chen, R. F. Cunico, *J. Org. Chem.* **2004**, *69*, 5509; i) R. F. Cunico, A. R. Motta, *Org. Lett.* **2005**, *7*, 771; j) R. F. Cunico, R. K. Pandey, *J. Org. Chem.* **2005**, *70*, 9048; k) R. F. Cunico, A. R. Motta, *J. Organomet. Chem.* **2006**, *691*, 3109; l) N. Kambe, T. Inoue, T. Takeda, S.-I. Fujiwara, N. Sonoda, *J. Am. Chem. Soc.* **2006**, *128*, 12650; m) W. Ren, M. Yamane, *J. Org. Chem.* **2010**, *75*, 3017; n) Y. Yao, W. Tong, J. Chen, *Mendeleev Commun.* **2014**, *24*, 176.
- [7] a) J. T. Reeves, Z. Tan, M. A. Herbage, Z. S. Han, M. A. Marsini, Z. Li, G. Li, Y. Xu, K. R. Fandrick, N. C. Gonnella, S. Campbell, S. Ma, N. Grinberg, H. Lee, B. Z. Lu, C. H. Senanayake, *J. Am. Chem. Soc.* **2013**, *135*, 5565; b) J. T. Reeves, C. Lorenc, K. Camara, Z. Li, H. Lee, C. A. Busacca, C. H. Senanayake, *J. Org. Chem.* **2014**, *79*, 5895; c) C. W. Seifert, S. Pindi, G. Li, *J. Org. Chem.* **2015**, *80*, 447; d) M. J. Kerner, C. A. Kuttruff, M. Chevliakov, F. G. Buono, D. A. Gao, M. Krawiec, C. A. Busacca, C. H. Senanayake, P. Wipf, J. T. Reeves, *Org. Lett.* **2021**, *23*, 4396.
- [8] a) A. Frischmuth, M. Fernandez, N. M. Barl, F. Achraimer, H. Zipse, G. Berionni, H. Mayr, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2014**, *53*, 7928; *Angew. Chem.* **2014**, *126*, 8062; b) M. R. Becker, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 12501; *Angew. Chem.* **2015**, *127*, 12681.
- [9] D. W. Stephan, G. Erker, *Angew. Chem. Int. Ed.* **2015**, *54*, 6400; *Angew. Chem.* **2015**, *127*, 6498.
- [10] M. A. Ganiek, M. R. Becker, G. Berionni, H. Zipse, P. Knochel, *Chem. Eur. J.* **2017**, *23*, 10280.
- [11] a) A. Brennfürer, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2009**, *48*, 4114; *Angew. Chem.* **2009**, *121*, 4176; b) X. Fang, R. Jackstell, M. Beller, *Angew. Chem. Int. Ed.* **2013**, *52*, 14089; *Angew. Chem.* **2013**, *125*, 14339; c) X. Fang, H. Li, R. Jackstell, M. Beller, *J. Am. Chem. Soc.* **2014**, *136*, 16039; d) J. Liu, H. Li, A. Spannenberg, R. Franke, R. Jackstell, M. Beller, *Angew. Chem. Int. Ed.* **2016**, *55*, 13544; *Angew. Chem.* **2016**, *128*, 13742; e) J.-B. Peng, X.-F. Wu, *Angew. Chem. Int. Ed.* **2018**, *57*, 1152; *Angew. Chem.* **2018**, *130*, 1166; f) F. Zhao, H.-J. Ai, X.-F. Wu, *Angew. Chem. Int. Ed.* **2022**, *61*, e202200062; *Angew. Chem.* **2022**, *134*, e202200062.
- [12] a) K. Hosoi, K. Nozaki, T. Hiyama, *Org. Lett.* **2002**, *4*, 2849; b) N. Pastori, C. Greco, A. Clerici, C. Punta, O. Porta, *Org. Lett.* **2010**, *12*, 3898.
- [13] The stability of carbamoylzinc was evaluated by performing Cu-catalyzed allylations with allyl bromide in different time intervals. For full data please see Supporting Information page 7.
- [14] The addition of Et<sub>3</sub>N was performed in order to solubilize ZnCl<sub>2</sub>. However, we have verified that its presence or absence did not influence the formation of **6** as well as the subsequent trapping reactions with electrophiles.
- [15] a) M. R. Becker, M. A. Ganiek, P. Knochel, *Chem. Sci.* **2015**, *6*, 6649; b) M. R. Becker, P. Knochel, *Org. Lett.* **2016**, *18*, 1462.
- [16] See Supporting Information pages 6–10 for full optimization data and a typical procedure.
- [17] We have excluded that TMP<sub>2</sub>Zn (generated from LiTMP with ZnCl<sub>2</sub>) was the metalating species since the addition of TMP<sub>2</sub>Zn to formamides **4** did not afford comparable amount of Cu-catalyzed allylation product within the short reaction time of 15 min.
- [18] a) P. Knochel, R. D. Singer, *Chem. Rev.* **1993**, *93*, 2117; b) P. Knochel, M. J. Rozema, C. E. Tucker in *Organocopper Reagents: A Practical Approach* (Ed.: R. J. K. Taylor), Oxford University Press, Oxford, **1994**, p. 85; c) P. Knochel, N. Millot, A. L. Rodriguez, C. E. Tucker, *Org. React.* **2004**, *58*, 417; d) J. Skotnitzki, L. Spessert, P. Knochel, *Angew. Chem. Int. Ed.* **2019**, *58*, 1509; *Angew. Chem.* **2019**, *131*, 1523.
- [19] Deposition Numbers 2164155 (for **4m**), 2164152 (for **4p**), 2164153 (for **8j**), 2164154 (for **11d**) und 2164156 (for **13g**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service. See Supporting Information pages 134–154 for full crystallographic data.
- [20] J. Z. Ho, C. S. Elmore, M. A. Wallace, D. Yao, M. P. Braun, D. C. Dean, D. G. Melillo, C. Chen, *Helv. Chim. Acta* **2005**, *88*, 1040.
- [21] a) S. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685; *Angew. Chem.* **2007**, *119*, 7829; b) A. Kremsmair, A. Hess, B. Heinz, P. Knochel, *Chem. Eur. J.* **2022**, *28*, e202103269.
- [22] a) A. Metzger, S. Bernhardt, G. Manolikakes, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 4665; *Angew. Chem.* **2010**, *122*, 4769. For the effect of ZnCl<sub>2</sub> in addition reactions of Grignard reagents see: b) M. Hatano, S. Suzuki, K. Ishihara, *J. Am. Chem. Soc.* **2006**, *128*, 9998; c) M. Hatano, O. Ito, S. Suzuki, K. Ishihara, *J. Org. Chem.* **2010**, *75*, 5008.
- [23] Very slow additions to aldehydes in the absence of MgCl<sub>2</sub>·LiCl were observed.
- [24] a) Y. Yamamoto, *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 947; *Angew. Chem.* **1986**, *98*, 945; b) M. C. P. Yeh, P. Knochel, L. E. Santa, *Tetrahedron Lett.* **1988**, *29*, 3887.
- [25] a) A. E. Allen, D. W. C. MacMillan, *Chem. Sci.* **2012**, *3*, 633; b) F. Romiti, J. del Pozo, P. H. S. Paioti, S. A. Gonsales, X. Li, F. W. W. Hartrampf, A. H. Hoveyda, *J. Am. Chem. Soc.* **2019**, *141*, 17952; c) U. B. Kim, D. J. Jung, H. J. Jeon, K. Rathwell, S. Lee, *Chem. Rev.* **2020**, *120*, 13382.

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