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An efficient catalytic method for hydrophosphination of heterocumulenes with diethylzinc as precatalyst without a solvent†

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Commercially available compound $ZnEt_2$ acts as an efficient precatalyst for the solvent-free hydrophosphinations of heterocumulenes using Ph_2PH as reagent. As far as we knew, this has been not reported in group 12 metal catalyzing reactions. A suggested mechanism of this reaction is explored, and the intermediate $[\{Ph_2PC(N^iPr)_2\}ZnEt]_2$ is obtained and characterized by a single-crystal X-ray structural analysis.

Introduction

As group 12 metal, zinc has Lewis acidity similar to those main group metals, which makes it widely used in various catalytic reactions, especially enantioselective transformations.[1–4] As the earth-abundant first-row transition metal, zinc has high availability, low prices and low toxicity when compared with most of the traditional transition metals. Therefore, sustainable development awareness and the increasing risk of environmental pollution has motivated researchers to exploring the application of zinc complexes. Diethylzinc, with an accessible price is one of the simplest zinc complexes, which was firstly synthesized by E. Frankland in 1848 and structural defined by J. Bacsa *et al.* in 2011.[5,6] In recent years, $ZnEt_2$ has been extensively used in asymmetric addition of aldehydes and ketones,[7–10] Mannich reactions,[11,12] aldol reactions,[13,14] Henry reactions,[15,16] *etc.* However, $ZnEt_2$ being used in the reaction without auxiliary ligands are rare.[17]

Organophosphorus compounds are becoming significant in modern industrial chemistry and academics as they are widely used in the organic modification of materials,[18] syntheses of pesticides[19] and catalysts,[20] and design of pharmaceuticals.[21] The synthesis of organophosphorus compounds has become a hot research area.[22–25] Heterocumulenes with R–N=C=E (E = O, S, N–R) skeletons, containing a chain of two double bonds, are commercially available and widely used in the syntheses of phosphaguanidines, phosphaureas, and phosphathioureas. These organophosphorus compounds are widely used as stabilizing ligands for various metal compounds.[26–29] Hydrophosphination and Hydrophosphorylation, the addition of P–H or P(O)–H bonds to unsaturated substrates is a particularly attractive approach since its 100% atom economical yield. So far, many transition metal-catalyzed reactions have been reported, such as the addition of phosphine oxide to C=C and C≡C bonds.[30–36] Furthermore, a number of metal catalysts have been investigated and reported involving organic alkali metal compounds,[37] heavier group 2 complexes,[38] Rare-Earth-metal complexes,[39–41] and late transition metal compounds[42,43] to promote the addition of the phosphines P–H to carbodiimides, isocyanates, and isothiocyanates.

Previously, our group reported on $LAlH_2$ (L = HC(CMeNAr)$_2$, Ar = 2,6-Et$_2$C$_6$H$_3$) (**1**, Fig. 1) catalyzed hydrogenation of carbodiimides using alkyne and pinacolborane.[44] Inspired by those results, we have planned to carry out aluminum-catalyzed hydrophosphination of heterocumulenes. Recently, M. Itazaki *et al.* reported the catalyst-free hydrophosphination of isocyanates and isothiocyanates with diphenylphosphine under neat conditions, which limited to a range of small aromatic isocyanates and isothiocyanates.[45] In particular, cyclohexyl isocyanate and adamantylisocyanate exhibited no reactivity under
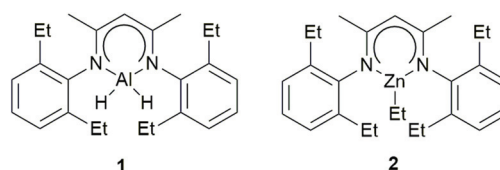
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Fig. 1 The structures of aluminum hydride (**1**) and zinc ethyl (**2**).

the same conditions. Furthermore, they demonstrated the negative effect of solvents on hydrophosphination. Therefore, we limited the scope of our study to the catalysis of aliphatic and large aromatic heterocumulenes under solvent-free conditions. However, aluminum compounds failed to act as catalysts as expected. So we shifted **1** to the zinc compound LZnEt (**2**, Fig. 1),[46] which has a similar structure to **1**, and successfully catalyzed the reaction of Ph$_2$PH with *N,N'*-diisopropyl carbodiimide (DIC). Then we shifted our research direction to zinc-catalyzed hydrophosphination of heterocumulenes, and its reaction mechanism.

Herein, we report on the unprecedented example of ZnEt$_2$ without auxiliary ligands used as a catalyst for catalytic hydrophosphination of aliphatic and large aromatic heterocumulenes, producing phospha-guanidines, phosphaureas and phosphathioureas with moderate conditions and high efficiency.

Results and discussion

At first, we examined the catalytic performance of different metallic compounds including LAlH$_2$ (L = HC(CMeNAr)$_2$, Ar = 2,6-Et$_2$C$_6$H$_3$) **1**, LZnEt **2**, AlMe$_3$ **3**, HAl(^{i}Bu)$_2$ **4**, CuCl$_2$ **5**, ZnCl$_2$ **6**, Zn(OAc)$_2$ **7**, and ZnEt$_2$ **8** for the hydrophosphination of DIC with Ph$_2$PH in a 1:1 molar ratio at 60 °C under neat conditions (Table 1, entries 1–8). In the presence of 5 mol% of organoaluminum compounds **1**, **3**, **4**, and Lewis acid **5** no reactions were observed to yield any products after 24 h. The results indicated that organoaluminum compounds and CuCl$_2$ did not contribute to the hydrophosphination of carbodiimide (Table 1, entries 1–4). Then we attempted to use Inorganic and organic zinc compounds **2**, **6**, **7**, and **8** as pre-catalysts, under the same condition. We found, that the desired P–H addition product ^{i}PrN=C(PPh$_2$)(NH^{i}Pr) **9a** was generated, and the cata-

lytic performance of inorganic zinc compounds was significantly inferior to that of organic zinc compounds (entries 5–8). Besides, reactions catalyzed by organozinc compounds reached a yield of 99% in 5 min (entries 7 and 8). Therefore, we thought that the high temperature might not be necessary to reach a level like that in the case of rare earth metals.[39,41] Indeed, we showed that this reaction proceeds at room temperature (entries 9 and 10). Moreover, the reaction of DIC with Ph$_2$PH proceeds at room temperature without solvent. After 5 min, the reaction catalyzed by **8** was substantially completed (entry 9), while the reaction catalyzed by **2** was only converted to 73% within 12 h (entry 10). Decreasing the catalyst loading to 3 mol%, the reaction afforded the product only in a yield of 52% within 15 min (entry 11). Hence, 5 mol% of catalyst **8** at ambient temperature in neat condition was chosen to be the optimum reaction condition for the hydrophosphination of heterocumulenes.

In order to see the scope and limitation of ZnEt$_2$-catalyzed hydrophosphination of heterocumulenes, we examined reactions with several heterocumulenes under the optimized conditions in hand. It was found that Ph$_2$PH worked well with *N,N'*-dicyclohexylcarbodiimide, and similarly to isopropyl *N,N'*-diisopropylcarbodiimide, producing the corresponding final product CyN=C(PPh$_2$)(NHCy) **9b** in almost quantitative yields in 5 min (Table 2, entry 1). In the past, no successful reaction of *N,N'*-di-*tert*-butylcarbodiimide with Ph$_2$PH was ever

Table 1 Optimization of the reaction conditions[a]

Entry	Catayst (mol%)	T [°C]	Time	Yield[b]
1	**1** (5%)	60	24 h	0%
2	**3** (5%)	60	24 h	0%
3	**4** (5%)	60	24 h	0%
4	**5** (5%)	60	24 h	0%
5	**6** (5%)	60	24 h	75%
6	**7** (5%)	60	24 h	87%
7	**2** (5%)	60	5 min	>99%
8	**8** (5%)	60	5 min	>99%
9	**8** (5%)	25	5 min	>99%
10	**2** (5%)	25	12 h	73%
11	**8** (3%)	25	15 min	52%

[a] Reactions carried out using 1.0 mmol of DIC, 1.0 mmol of Ph$_2$PH in 10 mL Schlenk flask without solvent under nitrogen atmosphere. [b] Yield determined by ^{31}P NMR.

Table 2 Hydrophosphination of heterocumulenes catalyzed by **8**[a]

R—N=C=E   +   R'$_2$PH   →   (5 mol% **8**, neat, r.t.)

E = N-R, O, S
R = ^{i}Pr, Cy, ^{t}Bu, 2,6-diisopropylphenyl
R' = Ph, Cy

Entry	R/E/R'	RNCE/ R'$_2$PH	Time	Yield	I:II[c]
1	Cy/N–Cy/Ph	1:1	5 min	99%	100:0
2[b]	^{t}Bu/N–^{t}Bu/Ph	1:1	24 h	0%	0:0
3	^{i}Pr/O/Ph	1:1	2 min	99%	100:0
4	Cy/O/Ph	1:1	2 min	99%	100:0
5	^{t}Bu/O/Ph	1:1	1 h	44%	100:0
6	^{i}Pr/S/Ph	1:1	2 h	98%	100:0
7	Cy/S/Ph	1:1	2 h	97%	100:0
8	^{t}Bu/S/Ph	1:1	24 h	62%	100:0
9[b]	2,6-^{i}Pr$_2$C$_6$H$_3$/N– 2,6-^{i}Pr$_2$C$_6$H$_3$/Ph	1:1	24 h	0%	0:0
10	2,6-^{i}Pr$_2$C$_6$H$_3$/O/Ph	1:1	15 min	99%	100:0
11	2,6-^{i}Pr$_2$C$_6$H$_3$/S/Ph	1:1	24 h	69%	27:73
12	2,6-^{i}Pr$_2$C$_6$H$_3$/S/Ph	2:1	24 h	76%	38:62
13	2,6-^{i}Pr$_2$C$_6$H$_3$/S/Ph	3:1	24 h	84%	83:17
14[b]	^{i}Pr/N–^{i}Pr/Cy	1:1	24 h	0%	0:0
15[b]	^{i}Pr/O/Cy	1:1	24 h	0%	0:0
16[b]	^{i}Pr/S/Cy	1:1	24 h	0%	0:0

[a] Conditions: 1.0 mmol of RNCE, 1.0 R'$_2$PH, 5 mol% catalyst **8** are charged in a screw-capped vial under nitrogen atmosphere, and the reaction mixture is carried out at room temperature. Chemical yields determined using ^{31}P NMR spectroscopy. [b] Reaction condition: 60 °C. [c] Ratio of single insertion to double insertion products.

reported, owing to the steric blocking.[38,41] Similarly, we also failed to catalyze this reaction (Table 2, entry 2). It turned out that the bulky hindrance of the substrate has a significant impact on the reaction. Then, the hydrophosphination also worked well with the aliphatic isocyanates as isopropyl and cyclohexyl isocyanates were converted to $Ph_2PC(O)NH(^iPr)$ **9c** and $Ph_2PC(O)NHCy$ **9d** in 2 min (Table 2, entries 3 and 4). The hydrophosphination of aliphatic isocyanates was also affected by steric hindrance, as *tert*-butyl isocyanate was converted to $Ph_2PC(O)NH(^tBu)$ **9e** in only 44% within 1 hour (Table 2, entry 5). Again, it is found that the increase in steric demands of the isothiocyanate *N*-substituents also affects the yield of the hydrophosphination, producing the corresponding product of *tert*-butyl **9h** in a yield of 62% at 60 °C in 24 hours. The corresponding products of isopropyl **9f** and cyclohexyl **9g** groups are formed in good to quantitative yields within 2 hours (entries 6–8). The influence on the hydrophosphination of heterocumulenes performance might be attributable to the electron-withdrawing ability of E (E = N–R, O, S) which favors the attack of Ph_2P^-. Furthermore, the reactions of large aromatic heterocumulenes and Ph_2PH might be due to a completely different phenomenon. *N,N′*-(2,6-Diisopropylphenyl)carbodiimide failed to obtain the corresponding product in 24 hours, even though heating to 60 °C (entry 9). This may be explained, that the steric effect of diisopropylphenyl is greater than the electron-donating effect. 2,6-Diisopropylphenyl isocyanate was almost totally reduced to the single insertion product $Ph_2PC(O)NH$ $(2,6-^iPr_2C_6H_3)$ **9i** within 15 min (entry 10). This demonstrates that $ZnEt_2$-catalyzed hydrophosphination of isocyanates has similar addition selectivity to copper-catalyzed reactions.[43] What is surprising is that 2,6-diisopropylphenyl isothiocyanate only obtained products in a 69% yield. The single insertion product $Ph_2PC(O)NH(2,6-^iPr_2C_6H_3)$ **9j** and the double insertion product $Ph_2PC(O)N(2,6-^iPr_2C_6H_3)C(O)NH(2,6-^iPr_2C_6H_3)$ **9k** was observed in a ratio of 27:73 (entry 11). To investigate the addition selectivity of this reaction, the ratio of $2,6-^iPr_2C_6H_3/S/$ Ph_2PH was changed from 1:1 to 2:1 and 3:1. More surprisingly, the reaction results were different from the previously investigated regularity, in which the proportion of double insertion product decreased, while the ratios of $^iPr_2C_6H_3/S$ increased (entries 12 and 13). Finally, we explored the influences of hydrophosphination reagents on the reaction, using Cy_2PH as a reactant with carbodiimide, isocyanate, and isothiocyanate. However, no corresponding products were obtained (entries 14–16). It might be explained by the reduced acidity of the hydrophosphination reagent, which is consistent with the findings of M. R. Crimmin *et al.*[38]

To investigate the mechanism of these reactions, we carried out the reaction of **8** with one equivalent of Ph_2PH at room temperature. It resulted in a zinc compound of composition $EtZnPPh_2$ **A**, which was first synthesized in 1965.[47,48] On the basis of reaction previously reported in the literature,[49] the reaction of **8** with DIC yielded $[\{EtC(N^iPr)_2\}ZnEt]_2$ **A′** for 70 h at 90 °C. Thus, it was reasonable to presume that Ph_2PH was the first to react with $ZnEt_2$ at the beginning of the reaction, and generated the active species. Then, the stoichiometric reaction

of compound **9a** with one equivalent of **4** in diethylether was carried out, to explore the step2 intermediate in this process. It resulted in the zinc compound $[\{Ph_2PC(N^iPr)_2\}ZnEt]_2$ **C**, which was characterized by single-crystal X-ray diffraction analysis (Fig. 2). Formation of compound **C** maybe helpful in binary polymerization of $\{Ph_2PC(N^iPr)_2\}ZnEt$ **B**, which is consistent with previously published literature.[17,37,39] Unfortunately, our attempts to isolate **B** *via* various synthetic routes have not been successful. Besides, we carried out the stoichiometric reaction of compound **C** with one equivalent of DIC, in which the emergence of a new doublet resonance (N–H) at δ 3.41 ppm and δ 3.39 ppm in the ^{1}H NMR spectrum proved compound **C** was an effective intermediate product.

According to those results discussed and previous research, the proposed catalytic cycle is shown in Scheme 1. The first step is deprotonation of Ph_2PH, which generates the intermediate **A** and starts the cycle. The second step of the catalytic
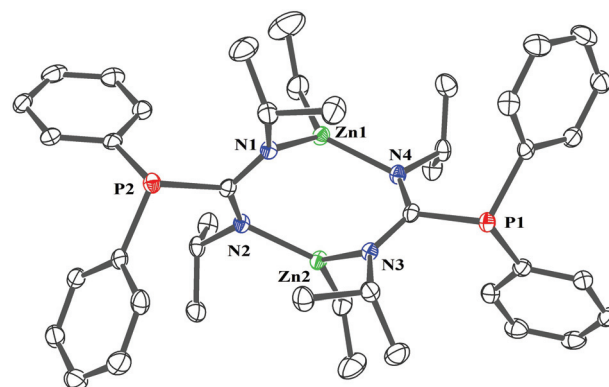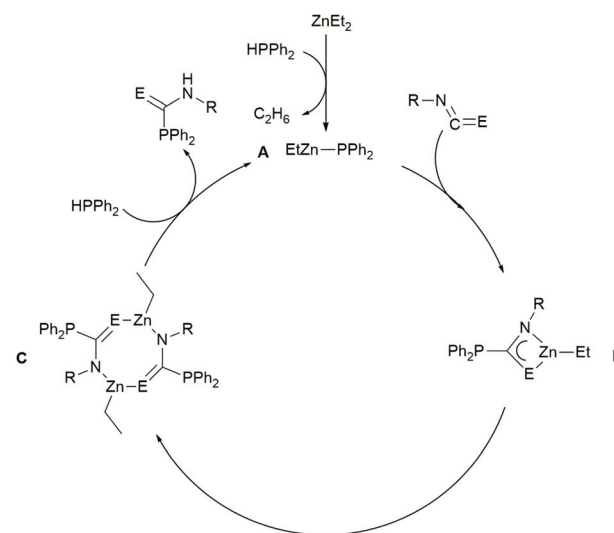

Fig. 2 X-ray single-crystal structure of **C**. Thermal ellipsoids are set at 50% probability level. All hydrogen atoms are omitted for clarity.

Scheme 1 The proposed mechanism of hydrophosphination of heteroalkenes catalyzed by **8**.

cycle is the insertion of the heteroalkenes into a Zn–PPh$_2$ bond, which produces the intermediate **B**. The last step *via* protonolysis of Ph$_2$PH with **C**, formed by dimerization of **B**, to yield the hydrophosphination product and regenerate the active species.

Conclusions

In conclusion, the highly efficient and 100% atom-productive catalytic hydrophosphination of heteroalkenes has been elucidated by using the low-cost and commercially available zinc compound ZnEt$_2$. This is the first time that group 12 organometallic compound as catalysts for these reactions, and is a green and highly selective method to afford phospha-guanidines, phosphaureas and phosphathioureas. Under ambient temperature in neat condition, the electronic effect and steric hindrance of ligands on catalytic reactions were discussed, and several unreported hydrophosphinations were synthesized. Finally, a reliable mechanism for the catalytic cycle has been proposed by carrying out a series of stoichiometric reactions, and a constant intermediate product [{Ph$_2$PC(N^{i}Pr)$_2$}ZnEt]$_2$ has been synthesized. These results indicate ZnEt$_2$-catalyzed hydrophosphinations of heterocumulenes are environmentally sustainable.

Conflicts of interest

There are no conflicts to declare.

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