Diethylzinc: A Simple and Efficient Catalyst for the Swift Hydroamination at Room Temperature

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Abstract: Diethylzinc and dimethylanilinium tetrakis(pentafluorophenyl)borate were found to catalyze hydroaminations at room temperature in high efficiency and very short reaction times. The reactivity of the proposed cationic zinc species, which is assumed to catalyze the reaction, strongly depends on the coordinative abilities of the counterion.

Keywords: amines; catalysis; heterocycles; hydroamination; zinc

The importance of nitrogen-containing compounds like amines, enamines and imines has caused many efforts to develop efficient methods for their synthesis. Hydroaminations of alkenes and alkynes represent the most atom efficient processes in this respect. Consequently the development of catalytic additions of amines to C,C bonds has received much attention.^[1-17] Numerous metals were applied in the hydroamination of alkenes and alkynes such as lithium,^[1] group 4 metals,^[2] the lanthanides,^[3,4,5] group 3 metals,^[6] the platinum metals,^[7] calcium,^[8] copper,^[9] silver^[10] and gold.^[11] The scope of catalytic hydroamination has been reviewed recently.^[12,13] Except for Zn these metals are either expensive or lack tolerance towards functional groups. The cheap metal Zn is somewhat outstanding for it is non-toxic nature and the fact that it tolerates many functional groups. Zn has already been applied to the hydroamination of aminoolefins as the aminotroponiminate complex (ATIs).^[14] The ATI-Zn catalysts turned out to be relatively robust towards moisture and air compared to dialkylzinc compounds. Ligand-free Zn catalysts have also been reported for the hydroamination of alkynes^[15] and in a

single case for a olefin^[16] but they needed elevated temperatures.

We herein present the ZnEt₂-catalyzed hydroamination of aminoolefins and aminoalkynes which was carried out at room temperature for most of the given examples. We already reported the increased reactivity of Zn catalysts by adding [PhNHMe₂][B(C₆F₅)₄] (**1**) as activator.^[17] This effect was even more dramatic for ZnEt₂, because it did not lead to any hydroamination at room temperature whereas the addition of **1** allows the reaction to proceed rapidly (Scheme 1).



Scheme 1. Demonstration of the activation of $ZnEt_2$ by 2.

Thus, substrate 2 was cyclized within 35 min (Table 2, entry 1). In order to investigate the role of the activator we checked other Brønsted acids. Substrate 2 was chosen as a test system for it was shown to undergo hydroamination easily. We started our screening with the non-fluorinated analogues of 1: [PhNHMe₂] [BPh₄] (Table 1, entry 4) and [Et₃NH][BPh₄] (Table 1, entry 3). In both cases, neither at room temperature nor at 80 °C, could 2 be cyclized. We also observed that [Et₃NH][BPh₄] did not dissolve during the reaction whereas [PhNHMe₂][BPh₄] dissolved instantly upon the addition of ZnEt₂. Similar solubility behav-



Entry	Activator ^[c]	Temperature [°C]	Conversion [%]/Time	
1	$[NH_4][BF_4]$	80		
2	[PhNHMe ₂][BF ₄]	80	0%/2 d	
3	[Et ₃ NH][BPh ₄]	80	0%/2 d	
4	[PhNHMe ₂][BPh ₄]	80	0%/2 d	
5	[PhNHMe ₂][OTf]	80	30%/21 d	
6	HOTf	80	8%/21 d	
7	$[PhNHMe_2][Al(hFiP)_4]^{[a]}$	r.t.	25%/5 d	
8	$[PhNHMe_2][Al(pFtB)_4]^{[b]}$	r.t.	>99%/45 min	
9	$[PhNHMe_2][B(C_6F_5)_4]$	r.t.	>99%/35 min	

Table 1. Screening of different activators in the ZnEt₂-catalyzed hydroamination of 2.

^[a] hF*i*P: hexafluoroisopropyl alcohol.

^[b] pFtB: perfluoro-*tert*-butyl alcohol.

^[c] Experiments were carried out with 2.5 mol% of each ZnEt₂ and activator in 0.5 mL C₆D₆ in a flame-sealed NMR tube.

iour occurred for $[NH_4][BF_4]$ (Table 1, entry 1) and $[PhNHMe_2][BF_4]$ (Table 1, entry 2). The ammonia salt did not dissolve whereas the anilinium salt was brought into solution spontaneously by adding ZnEt₂. Neither salt led to the desired hydroamination of **2**. Triflic acid and the corresponding anilinium salt showed good solubility and led to slow hydroamination at 80 °C (Table 1, entries 5 and 6). The reactivity of the Zn catalyst seemed to correlate with the coordination behaviour of the anion. In order to underline this suggestion we searched for a less coordinating anion than the triflate anion.

Krossing et al. designed different WCAs (weakly coordinating anions) based on aluminium showing high thermal and chemical stability.^[18] We synthesized an analogue to **1** based on Krossing's synthesis of $[(Et_2O)_2H][Al(pFtB)_4]$.^[19] [PhNHMe₂][Al(pFtB)₄] (**3**) showed similar reactivity as **1** towards hydroamination. Both **1** and **3** are claimed to carry the least coordinating anions in our series.^[20]] Therefore it is obvious that the reactivity of the Zn catalyst increases as the coordination strength of the activator's counterion decreases.

The commercially available activator **1** showed the best results so far and so further experiments were carried out with this compound. We also tested if an excess of 1 could improve the reaction times but even two equivalents related to the employed ZnEt₂ did not show higher conversion rates. Use of only a "substoichiometric" amount of activator led to prolonged reaction times. We observed the release of ethane. The disappearance of the ethyl group can be observed by ¹H NMR spectroscopy during the reaction. Therefore we assume the formation of a cationic zinc species. This hydroamination can proceed through two mechanistic pathways: 1) Lewis-acid catalysis with activation of the C,C multiple bond or 2) activation of the amine to a metalloamide which then undergoes olefin insertion.[13b,21]

As 1 displays a Brønsted acid which are known to catalyze the hydroamination of, for example, aminoolefins^[22] or norbornenes, we tested 1 without $ZnEt_2$ towards the hydroamination of 2. However, at room temperature the reaction proceeded very slowly so that even with 10 mol% of 1 the conversion did not exceed 5% after 24 h (90% conversion after 8 days). It is perfectly obvious that the combination of $ZnEt_2$ and 1 is much more reactive towards hydroamination than the single components.

Initial experiments showed successful hydroamination of primary and secondary amines. In order to test functional groups (heterocycles) we focused on secondary amines. The results of the hydroamination of different aminoolefins are shown in Table 2. The short reaction times reflect the high reactivity of our catalytic system that nevertheless tolerates different functional groups such as furans (Table 2, entry 4), thiophenes (Table 2, entry 5), sulfonamides (Table 2, entry 6) and silvl ethers (Table 2, entries 7 and 8). A catalyst loading of 2.5 mol% was sufficient and the temperature could be kept at room temperature in most of the cases. Hydrazine-olefins did not lead to hydroamination at room temperature but cyclized swiftly at 80°C within 3 h (Table 2, entry 10). To the best of our knowledge, this is the first Zn catalyst that cyclizes an aminoolefin that does not carry a digeminal substitution (Thorpe-Ingold effect)^[23] although high temperatures and long reaction times are necessary (Table 2, entry 11). This also reflects the hightemperature and long-term stability of our catalyst. For the isolation of the products the absence of ligands which might be difficult to separate is a big advantage. Thus only the filtration over a small pad of silica and removal of the solvent and volatiles was necessary to work up the reaction.

We were also interested if aminoalkynes could be cyclized with the new catalytic system. 5-Hexynylamine (4) was subjected to 2.5 mol% of each $ZnEt_2$ and 1. Within 30 h at 80 °C 4 was converted to an en-

Entry ^[a]	Substrate	Product	Temperature [°C]	Time ^[b]	Yield [%] ^[c]
1	H N~Ph	N-Ph	r.t.	35 min	95
2	Ph Ph H N Ph	Ph Ph Ph	r.t.	80 min	94
3	Me Me H	Me Me Ph	r.t.	5.5 h	89
4	Ph Ph H O	Ph N O	r.t.	11 h	93
5	H. s	√√N_√S	r.t.	27 h	98
6	H		r.t.	18 h	99
7			r.t.	30 min	98
8			r.t.	40 min	94
9	N H H	Me	r.t.	2 h	98
10	Ph Ph H N N	Ph N-N	80	3 h	99
11	North State	\sum N \sim	180	21 d	90

Table 2	Results	for the	hydroa	mination	of differen	t aminoolefins.
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^[a] Experiments were carried out with 2.5 mol% of each $ZnEt_2$ and $[PhNHMe_2][B(C_6F_5)_4]$ and 0.43 mmol of substrate in 0.5 mL of C_6D_6 in a flame-sealed NMR tube.

^[b] Elapsed time until full conversion.

^[c] Isolated yield.



Scheme 2. Hydroamination of a primary aminoalkyne and subsequent reduction.

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alkynes could be applied.

amine which readily tautomerized to an imine

(Scheme 2). To isolate the corresponding volatile

amine the imine was reduced and converted to the ammonium salt by adding concentrated HCl. After

drying at high vacuum 5 could be isolated as a colourless solid in quantitive yield. Also secondary amino-

Thus substrate 6 underwent hydroamination at 80 °C and furnished the corresponding enamine within

50 h (Scheme 3). The enamine was hydrolyzed in



Scheme 3. Hydroamination of a secondary aminoalkyne and subsequent hydrolysis.

DCM upon the addition of silica. After stirring over night and filtration the corresponding keto amine **7** was isolated as yellowish oil in 90% yield.

In conclusion, we report a highly efficient catalyst for the hydroamination of aminoolefins and aminoalkynes. All parts of the catalytic system are commercially available and, due to the fact that expensive ligands are not needed, our system is not costly. The reactivity of the catalyst strongly depends on the coordination capability of the anion of the employed activator. The reactivity may be increased even further by less coordinating WCAs. To the best of our knowledge $ZnEt_2/[PhNHMe_2][B(C_6F_5)_4]$ displays the highest reactivity of all Zn system for the hydroamination of aminoolefins so far.

Experimental Section

General Procedure for the Zinc-Catalyzed Hydroamination

To a solution of substrate (0.43 mmol) in 0.5 mL C_6D_6 were added 11 µL of a 1 M solution of ZnEt₂ in hexane (11 µmol, 2.5 mol%) and 9 mg of [PhNMe₂H][B(C_6F_5)₄] (11 µmol, 2.5 mol%) under a nitrogen atmosphere. A dried NMR tube was charged with the resulting solution and flame sealed under vacuum. The reaction progress was monitored by ¹H NMR for the stated time. When the reaction was judged to be completed or did not show any further progress the crude reaction mixture was filtered over a small pad of silica, which was rinsed with MTBE. After removal of the solvent and volatiles, the product was obtained in good purity.

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