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# FULL PAPER

## Lewis Acid Catalyzed Reductive Amination of Aldehydes and Ketones with N,N-Dimethylformamide as Dimethyl Amino Source, Reductant and Solvent

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**Abstract:** A practical zinc acetate dihydrate catalyzed reductive amination of various carbonyl compounds with DMF as  $Me_2N$  source, reductant and solvent is developed. This reaction shows broad substrate scope, good functionality tolerance, avoids pressure-proof reactor and column chromatograph isolation operation in up to 98 %

yield, to make it an attractive method for the preparation of *N*,*N*-dimethyl tertiary amines.

**Keywords:** reductive amination; DMF; aldehydes; ketones; tertiary amines

#### Introduction

Amines are highly valuable compounds in organic synthesis, fine chemicals and pharmaceuticals.<sup>[1]</sup> Specifically, N,N-dimethyl tertiary amines have also been used as ligands/organocatalysts, modifiers for reversed phase chromatography and buffers in sequential analysis of proteins and peptides.<sup>[2]</sup> The pursuit for practical and efficient preparation of these amines has attracted great attention. Among them, reductive amination of carbonyl compounds in the presence of a suitable reductant is one of the most powerful methods, especially those by generating instable imines in situ to avoid the problematic imine isolation. In majority of the reductive aminations, heterogeneous stoichiometric boron hvdride reduction<sup>[3]</sup> and homogeneous catalytic (transfer) hydrogenation<sup>[4]</sup> dominate the scene. However, the use of a stoichiometric amount of boron hydrides generates copious waste and is associated with other shorting comings, such as the chemoselectivity of NaBH<sub>4</sub> for C=N to C=O bonds and the toxicity issues of NaBH<sub>3</sub>CN, <sup>[3, 5]</sup> two most widely used boron hydrides in reductive amination. In homogeneous catalytic system, the orgaometallic (transfer) hydrogenation generally requires noble metal catalysts and special ligands, and suffers from low chemoselectivity for C=C, C  $\equiv$  C, CN and nitro moities; <sup>[6, 7]</sup> while the organocatalytic transfer hydrogenation using Hantzsch esters <sup>[8]</sup> and organosilanes<sup>[9, 10]</sup> suffers low atom economy. Thus, there is still much room for improvement in view of the requirements of green chemistry.

On the other hand, N,N-dimethylformamide (DMF) is an excellent polar solvent wildly used in almost al. laboratories. More importantly, DMF can act as reactant to incorporate CO, HCO, Me<sub>2</sub>N, Me<sub>2</sub>NCO and "C" (to form CN) units into products. [11a, 11b] Beside, DMF has also been reported to be an effective ligand for various metals, such as Cu<sup>II</sup>, Ag<sup>I</sup>, Au<sup>III</sup> and Pd<sup>II</sup>, and DMF was able to further reduce\_ these metal complexes under suitable conditions. [11b, <sup>11c]</sup> These three aspects inspired us to envision a reductive amination of carbonyl compounds using readily available DMF as Me<sub>2</sub>N source, reductant and solvent. Actually, the reductive amination of carbonyl compounds with ammonium formate (HCO2<sup>-</sup>NH4<sup>+</sup>) as reactant is called as Leuckart-Wallach reaction, which was first discovered by Rudolf Leuckart in 1885. [12a-c] However, the classic Leuckart-Wallach reaction needed a high temperature around 240 °C. sealed reactor (autoclave), and long reaction period to obtain low to moderate yields, which remained essentially unchanged, until the introduction of microwave technology to provide much better yields in a shorter time, but still requiring a high temperature around 250 °C. <sup>[12d, 12e]</sup> Recently, the reductive amination of cyclohexanone with DMF/H<sub>2</sub>O was realized under a harsh condition of 225 °C and 30 bar in autoclave. [12f]

For the reductive amination of carbonyl compounds to prepare N,N-dimethyl tertiary amines, the Me<sub>2</sub>N source generally includes gaseous

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dimethylamine, dimethylamine solution (in water or alcohol) and dimethylamine hydrochloride, which causes operational difficulties such as dangerous gas manipulation, precise weighting and pressure-proof reactor. Thus, a reductive amination of carbonyl compounds with readily available DMF as Me<sub>2</sub>N source, reductant and solvent would fulfill the requirements of green chemistry to provide a practical and convenient method for the preparation of N,N-dimethyl tertiary amines. In this context, N,Ndialkyl formamides have been proved to act as dialkyl amine source using catalytic amount of MgCl<sub>2</sub> stoichiometric  $HCO_2H$ , and however, low conversions (15-65%) and low yields (22-50%) based on ketones were realized.<sup>[13]</sup> In order to decrease the reaction temperature, we speculated that the addition of a suitable Lewis acid was critical, because Lewis acid was able to accelerate the hydrolysis of DMF to produce dimethylamine and formic acid, at the same time, to promote the imine formation by increasing the electrophilic reactivity of carbonyl compounds to condense with dimethylamine.

#### **Results and Discussion**

We first chose 2-naphthaldehyde (1a) as the model substrate since it and its reductive amination product possess relative high boiling point to prevent the loss during workup and purification. With the above considerations in mind, the reaction of 2naphthaldehyde (1a) and DMF (2a, ACS reagent, used as purchased) both as reactant and solvent was examined, and no desired reductive amination product (3a) can be detected in the absence of Lewis acid catalyst (Table 1, entry 1). As our speculation, when the most widely used Lewis acid AlCl<sub>3</sub> or FeCl<sub>3</sub> was added as catalyst, the reductive amination afforded product (3a) in 88% and 61% yield, respectively (entries 2 and 3). Subsequent screening on Lewis acid catalyst revealed that this reductive amination can be effectively accelerated by most of Lewis acids tested such as the  $Co(OAc)_2$ ,  $Cu(OAc)_2 \cdot H_2O$ ,  $Zn(OAc)_2 \cdot 2H_2O$ , and  $SnCl_2 \cdot 2H_2O$ (entries 4-7, and many others listed in SI). Besides these metal containing Lewis acids, metal-free  $BF_3$ ·Et<sub>2</sub>O was also effective (entry 8), which can exclude the possibility that the organometallic species was involved in this reductive amination. However, Brønsted acid such as aqueous HCl and Brønsted base such as K<sub>2</sub>CO<sub>3</sub> were invalid (entries 9 and 10), which was consistent with our speculation that the Lewis acid catalyst played a dual role both in DMF hydrolysis and imine formation. Although many Lewis acids exemplified similar activity when the reductive amination was carried out at 150 °C for 24 h,  $Zn(OAc)_2 \cdot 2H_2O$  was chose for further study because its activity was roughly maintained at lower catalyst loading, lower reaction temperature and shorter reaction time (entries 11-13, see Tabel S1 of SI for details on compare between Zn(OAc)<sub>2</sub>·2H<sub>2</sub>O and other Lewis acids). Since the first step of this

transformation was the hydrolysis of DMF to produce dimethylamine and HCO<sub>2</sub>H, to find out how much H<sub>2</sub>O was required by this reductive amination, the control reaction using CaH<sub>2</sub> dried DMF and precisely weighted H<sub>2</sub>O was performed, which revealed that the addition of 5.5 equivalence of H<sub>2</sub>O resulted in a quantitative GC yield and a 97% isolated yield, while less or more water would produce lower the yields (see Table S4 of SI for detailed result for the influence of  $H_2O$ ). The subsequent control experiments revealed that both removing the Lewis acid or replacing it by HCO<sub>2</sub>H (generated by the hydrolysis of DMF) resulted in very low yields (entries 17 and 18), which further supported the critical role of Lewis acid to this reductive amination.

**Table 1**. Optimization of the reaction conditions. <sup>[a]</sup>

CHO +	DMF 2a	<b>LA</b> ( mol% ) H <sub>2</sub> O (equiv) 150 °C, 24 h	3a
entry	LA (m	ol%) H	20 vield

entry		LA (mol%)	$H_2O$	yield		
			(equiv)	(%) <sup>[b]</sup>		
	1			N.D.		
	2	AlCl <sub>3</sub> (10)		88	6	
	3	FeCl <sub>3</sub> (10)		61		
	4	Co(OAc) <sub>2</sub> (10)		90		
	5	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O (10)		88		
	6	Zn(OAc)2·2H2O (10)		91		
	7	SnCl <sub>2</sub> ·2H <sub>2</sub> O (10)		90		
	8	BF3·Et2O (10)		90	_	
	9	HCl (10)		< 2		
	10	K <sub>2</sub> CO <sub>3</sub> (10)		N.D.	(	
	11	Zn(OAc) <sub>2</sub> ·2H <sub>2</sub> O (5)		84		
	12 <sup>[c]</sup>	Zn(OAc)2·2H2O (10)		75		
	13 <sup>[d]</sup>	Zn(OAc) <sub>2</sub> ·2H <sub>2</sub> O (10)		70		
	14 <sup>[e]</sup>	Zn(OAc) <sub>2</sub> ·2H <sub>2</sub> O (10)	4	57	(	
	15 <sup>[e]</sup>	Zn(OAc)2·2H2O (10)	5.5	<b>99 (97)</b>		
	16 <sup>[e]</sup>	Zn(OAc) <sub>2</sub> ·2H <sub>2</sub> O (10)	7	80		
	17 <sup>[e]</sup>		5.5	5	C	
	18 <sup>[e]</sup>	HCO <sub>2</sub> H (10)	5.5	11		

<sup>[a]</sup> Conditions: **1a** (0.2 mmol), LA (Lewis acid, mol%), DMF (0.5 mL) and H<sub>2</sub>O (equiv) were reacted at 150 °C for 24 h under air atmosphere unless otherwise noted. N. D. = not detected.

<sup>[b]</sup> GC yield based on **1a** with mesitylene as an internal standard; isolated yield showed in brackets.

<sup>[c]</sup> Reacted for 12 h.

<sup>[d]</sup> Reacted at 130 °C.

<sup>[e]</sup> CaH<sub>2</sub> dried DMF and H<sub>2</sub>O under argon were added.

It's worth noting that this  $Zn(OAc)_2$  catalyzed reductive amination was very clean thus the workup for this reaction were very simple, no time consuming and costly column chromatograph was required. After the reaction, simple dilution the reaction mixture with brine, extraction with diethyl ether and evaporation of the solvent of organic layer could provide the product in 97% isolated yield with >98% purity (Table 1, entry 15). The easy workup procedure was especially important for the preparation of tertiary amines to avoid the possible loss due to adsorption to immobile phase, oxidation by air and adsorbing CO<sub>2</sub> during column chromatograph isolation. Under the optimized reaction conditions, a scale up experiment (10 mmol scales) was conducted to provide the reductive amination product (3a, 1.82 g) in a 98% isolated yield.

T	ahle	2	Substrate	scone	of	aromatic	aldeh	vdes	[a]
1.	anc	∠	Substrate	scope	UI.	aromatic	aluch	vucs.	



<sup>[a]</sup> Conditions: **1** (0.2 mmol),  $Zn(OAc)_2 \cdot 2H_2O$  (10 mol%, 0.02 mmol), DMF (0.5 mL) and  $H_2O$  (5.5 equiv) were reacted at 150 °C for 24 h under air atmosphere unless otherwise noted; isolated yield. <sup>[b]</sup> Reacted at 140 °C.

With the optimized reaction conditions in hand (Table 1, entry 14), we proceeded to investigate the generality of this  $Zn(OAc)_2$  catalyzed reductive amination of aromatic aldehydes with DMF. The substrate scope for the aromatic aldehyde moiety is listed in Table 2. Naphthaldehydes (**1a** and **1b**) and

aromatic aldehydes bearing electron-donating or withdrawing substituents (1c-1r) were successfully tolerated to afford the corresponding N,N-dimethyl tertiary amine (3a-3r) in good yields, such as methoxy (1c-1f), methyl (1g-1i), tert-butyl (1j), cyano (1k and 1l), chloro (1m-1o), bromo (1p and 1q) and trifluoromethyl (1r) groups. Among them, when substituents was located at ortho position of aldehydic carbonyl group such as ortho-methyl, chloro and bromo benzaldehydes (1i, 1o and 1q), which provided similar yields to the para-, metasubstituted counterparts, so no obvious steric hindrance effect for this reaction was found. To our delight, the cyano and bromo substitutents (1k, 1l, 1p and 1q) can be tolerated under the reductive condition, which would be beneficial for the further modification of these products considering the various transformations based on cyano group and arylbromides.

**Table 3.** Substrate scope of hetero-aromatic aldehydes, aliphatic aldehydes and ketones.<sup>[a]</sup>



<sup>[a]</sup> Conditions: **1** (0.2 mmol),  $Zn(OAc)_2 \cdot 2H_2O$  (10 mol%, 0.02 mmol), DMF (0.5 mL) and  $H_2O$  (5.5 equiv) were reacted at 150 °C for 24 h under air atmosphere unless otherwise noted; isolated yield. <sup>[b]</sup> Reacted for 48 h.

Encouraged by the exciting results obtained from this Zn(OAc)<sub>2</sub> catalyzed reductive amination of aromatic aldehydes with DMF, further application of the optimized reaction conditions to hetero-aromatic aldehydes, aliphatic aldehydes and ketones were carried out (Table 3). As expected, hetero-aromatic aldehydes such as pyridine-4-carbaldehyde (1s), thiophene-carbaldehydes (1t and 1u), aliphatic such as cinnamaldehyde (1v), aldehydes 3phenylpropanal (1w),2-phenylpropanal (1x).aliphatic ketones such as  $\beta$ -tetralone (1y), 2-indanone (1z) and 4-substituted cyclohexanone (1aa) were all successfully transformed into the corresponding tertiary amine in moderate to good yields. We are delighted that this reductive amination didn't affect the  $\alpha,\beta$ -conjugated C=C bond of cinnamaldehyde during the reductive conditions. It's worth noting that

almost all of the aromatic/aliphatic aldehydes and aliphatic ketones tested were able to react with DMF to provide the corresponding tertiary amine in high yield, and the purification was realized by simple extraction and condensation. The difference in yields was mostly caused by the loss during the condensation step to evaporate the solvent, so the simple aliphatic aldehyde such as *n*-butanal was not tested. Next, the reductive amination of aryl ketones such as acetophenone and 1-tetralone was also tried under the optimized condition; however, the reactions were much slower compared with aliphatic ketones. For acetophenone, only an 8 % yield was obtained, and for 1-tetralone, no desired product was detected at all, which might be caused by the more stable and less reactive characteristics of aryl ketones compared with aliphatic ketones.

hand, besides DMF, On the other N.Ndiethylformamide (2b), N-methylformamide (2c) and *N*-unsubstituted formamide (2d) were also suitable substrates for this  $Zn(OAc)_2$  catalyzed reductive amination (Scheme While N,N-1). the diethylformamide (2b) provided tertiary amine 3ab, the latter two substrates yielded the corresponding Ndi-substituted and mono-substituted formamide products 3ac and 3ad, respectively, which might be obtained from the reduction of the N-formyl-Nmethyl iminium (for 2c) and *N*-formyl imine (for 2d) intermediates by in situ generated formic acid.



Scheme 1. Substrate scope of formamides.

To gain more information on the reaction mechanism, several control experiments were

conducted. First, replacing the DMF by DMF-d<sup>7</sup>, the Zn(OAc)<sub>2</sub> catalyzed reductive amination of 2naphthaldehyde (1a) afforded the deuterated tertiary amine  $3a-d^7$ , which not only supports that the formic acid-d<sup>1</sup> obtained from the hydrolysis of DMF-d<sup>7</sup> serves as the reductant for this transformation, but also provided a convenient method for the synthesis of deuterium-labeled N,N-dimethyl tertiary amines considering the ready availability of DMF-d<sup>7</sup> due to its wide usage in NMR test as a deuterated solvent. (Scheme 2a). Second, the isotopic competing reaction of DMF and DMF-d<sup>7</sup> resulted product 3a and 3a' in a ratio of 1 : 1, revealing that the hydride transfer step is not rate-determining (Scheme 2b). Third, in the absence of  $Zn(OAc)_2 \cdot 2H_2O$  and with N-methyl pyrrolidinone (NMP) as solvent, the reductive amination of 2-naphthaldehyde (1a) by dimethyl amine in ethanol solution and aqueous formic acid was carefully conducted in a thick-wall glass tube (precaution on the gaseous dimethyl amine leak and glassware crack, see SI for details, Scheme 2c), successfully producing the tertiary amine product 3a in 98% yield, which further confirmed the role of DMF as a "pool" of dimethyl amine and formic acid to provide them in a slow and steady rate for the subsequent condensation and reduction step. The addition of water and Lewis acid could accelerate the hydrolysis of DMF.

On the basis of the mechanistic experiments described above and literature reports on reductive amination with formic acid as reductant, a mechanism for this  $Zn(OAc)_2$  catalyzed reductive amination of 2-naphthaldehyde (**1a**) with DMF is proposed in Scheme 3. First, catalyzed by  $Zn(OAc)_2$ , DMF is hydrolyzed to give dimethyl amine and formic acid in low concentration. Second, the  $Zn(OAc)_2$  further promotes the condensation of 2-naphthaldehyde and dimethyl amine to generate the iminium cation intermediate **I**, which is easily reduced by formic acid to provide the tertiary amine product **3a**.



Scheme 2. Mechanistic investigation on the multiple C-H bonds transformation.



Scheme 3. Proposed mechanism.

### Conclusion

We have developed an practical Zn(OAc)<sub>2</sub>-catalyzed reductive amination of various carbonyl compounds with DMF. This reaction utilized the most common and cheap  $Zn(OAc)_2 \cdot 2H_2O$  as catalyst, widely used DMF as a slow and steady source of Me<sub>2</sub>N and reductant to avoid pressure-proof reactor and operation. This reaction shows good functionality tolerance and broad substrate scope including aromatic/aliphatic aldehyde, aliphatic ketone, to react with N-di-substituted, mono-substituted and unsubstituted formamide, in up to 98% isolated yield. At the same time, the reaction is so clean that no column chromatograph is required and simple extractioncondensation procedure would provide the products in high purity. These distinguishing features makes this protocol an attractive strategy for the preparation of N,N-dimethyl tertiary amines, both in laboratory and chemical process.

### **Experimental Section**

# A general experimental procedure is described as follows:

An oven-dried reaction vessel was charged with 2naphthaldehyde (**1a**, 0.2 mmol, 1 equiv), zinc acetate dihydrate (0.02 mmol, 10 mol %), H<sub>2</sub>O (5.5 equiv), N,N-dimethylformamide (**2a**, 0.5 mL) under air. The vessel was sealed and heated at 150 °C (oil bath temperature) for 24 h. After cooling down, 10 mL brine was added in, followed by extractions with ether (3x10 mL). The organic layer was combined, washed with brine (2x10 mL), dried with anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give N,N-dimethyl-1-(naphthalen-2-yl)methanamine (**3a**, 35.9 mg) in 97% yield.

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The authors declare no competing financial interest.

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- 30 examples and up to 98% yield
- free of presure-proof autoclave manipulation
- free of column-chromatograph purification