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The effect of coordination on the reaction of *N*-tosyl imines with diethylzinc

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Abstract—The effect of coordination on the reaction of *N*-tosyl imines and diethylzinc was studied in detail. It showed that there was strong coordination between *N*-tosyl imine and diethylzinc. Due to this coordination, *N*-tosyl imines could be reduced directly through the β-H transferring mechanism by diethylzinc in nonpolar solvents to afford the corresponding secondary amines in excellent yields at mild conditions. The coordination of diethylzinc and *N*-tosyl imine was hindered by reacting in polar solvents or adding TMEDA to the reaction, it afforded ethylating product partially or exclusively.

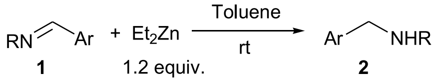
1. Introduction

The reduction of imines to amines is an important transformation in organic chemistry. Most of the methods involve borohydride reagents or transition metal hydrogenation catalysts;[1] Few general methods employing main group Lewis acid catalysts have appeared.[2] Imines also could be reduced by Grignard reagents bearing β-H. Thies et al. have observed that *N*-benzylidene-*N*-butylimine could be partially reduced to amines by *i*-PrMgI during the addition reaction.[3] Davis et al. have also found that *N*-sulfinylimine could be slightly reduced to amines by *n*-BuMgCl during the addition reaction.[4] Crowe et al. have even reported that, in the presence of a catalytic amount of Cp_2TiCl_2, *n*-BuMgCl could be used as the reductive reagent in the reduction of imine.[5]

Diethylzinc has been widely applied in organic synthesis, such as addition to aldehydes,[6] ketones[7] and imines,[1a] radical addition as chain-transfer agent[2b,8] and catalytic enantioselective reduction of ketones as the precatalyst.[9]

Though diethylzinc could reduce benzaldehyde to afford benzyl alcohol as the byproduct in the addition reaction to benzaldehyde,[10] there are also a few reports about the reduction of imines by diethylzinc during the enantioselective addition to the imines.[11]

Table 1. Reduction of imines by diethylzinc in toluene



Entry	Ar	R	Time (h)	Yield[a] of **2** (%)
1	**1a**, Ph	Ts	1	**2a**, 98
2	**1b**, 4-$MeOC_6H_4$		1	**2b**, 96
3	**1c**, 2-$MeOC_6H_4$		1	**2c**, quant.
4	**1d**, 4-MeC_6H_4		2	**2d**, 71
5	**1e**, 4-ClC_6H_4		1	**2e**, 98
6	**1f**, 1-$C_{10}H_7$		5	**2f**, 70
7	**1g**, Ph	Ms	1	**2g**, 86
8	**1h**, Ph	$P(O)Ph_2$	24	—
9	**1i**, Ph	Ph	24	—
10	**1j**, Ph	2-$MeOC_6H_4$	24	—

[a] Isolated yield.

Various imines were allowed to react with diethylzinc in toluene at rt, the results were summarized in Table 1. All *N*-tosyl imines afforded the corresponding reduction products with good to excellent yields exclusively (entry 1–7, Table 1) while there was no reductive or addition reaction product under the same conditions in the case of *N*-aryl aldimines and *N*-phosphinylimine (entry 8–10, Table 1). For *N*-phosphinylimine had the similar structure to *N*-tosyl imine, it was possible due to the bond length differences between *N*-tosyl-imine and *N*-phosphinylimine.

The effect of solvents on the reaction of *N*-tosyl imine and diethylzinc was studied. The results were shown in Table 2. It turned out that solvents had strong effect on the reaction.

Keywords: *N*-Tosyl imines; Diethylzinc; Reduction; Ethylation; Solvent effect; Coordination.

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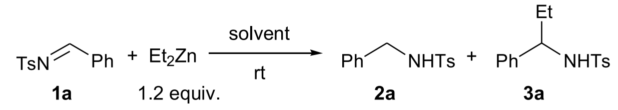
Table 2. Effect of the solvents



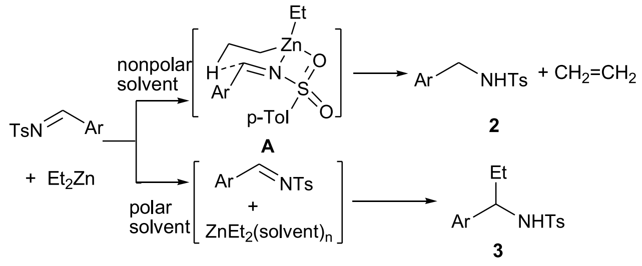
Entry	Solvent	Time (h)	**2a**[a] (%)	**3a**[a](%)
1	Hexane	3	92	—
2	Toluene	1	98	—
3	THF	6	27	40
4	Et_2O	6	65	14
5	CH_3CN	6	51	18
6	CH_2Cl_2	6	85	14

[a] Isolated yield.

It was found that *N*-tosyl imine **1a** could be readily reduced by diethylzinc at very mild conditions in nonpolar solvents (entry 1–2, Table 2). Though the *N*-tosyl imine **1a** and the corresponding reduction product **2a** were almost insoluble in hexane, the reduction reaction still proceeded smoothly (entry 1, Table 2). The reaction phenomenon in toluene was especially interesting. Those *N*-tosyl imines could not be dissolved in toluene completely under the reaction conditions (entry 1–7, Table 1). After diethylzinc was added into the mixture, the turbid mixture became clear. About 30 min later, white precipitates came out in company with a releasing gas which was trapped by liquid N_2 and proved to be ethylene by GC–MS.

But in polar solvents, ethylating product was also found in the reaction along with reduction product (entry 3–6, Table 2).

According to the reaction phenomenon and results, we proposed the reaction of *N*-tosyl imines and diethylzinc in different solvents may proceed as Scheme 1.

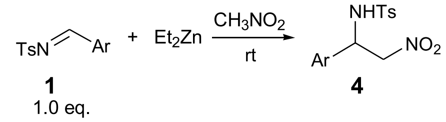


Scheme 1.

In nonpolar solvent diethylzinc and the *N*-tosyl imine brought out a zinc specie with the presumed structure **A**, then the β-hydrogen atom of the ethyl group was transferred to the C=N double bond with release of ethylene, therefore the reduction product **2** was formed. The product **2** was obtained exclusively in toluene and hexane.

On the contrary, the polar solvent such as THF, which could coordinate predominately with diethylzinc and activate diethylzinc in some extent, led to the addition reaction. As a result, the addition product **3** became the main product (entry 3, Table 2). When weaker coordination solvent such as Et_2O was used, it was still predominated by the reduction reaction was still the (entry 4, Table 2).

Table 3. Nitro-Mannich reaction in CH_3NO_2



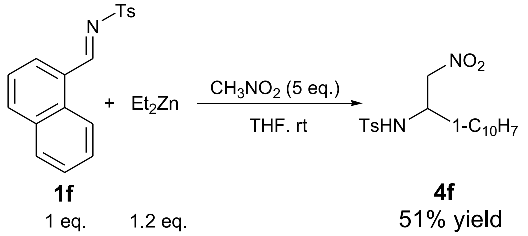
Entry	Ar	Amount of Et_2Zn (equiv)	Time (h)	Yield[a] of 4 (%)
1	**1a**, Ph	1.2	6	**4a**, 73
2		0.5	18	**4a**, 62
3		0.2	24	**4a**, 25
4	**1b**, 4-$MeOC_6H_4$	1.2	6	**4b**, 86
5	**1c**, 2-$MeOC_6H_4$		6	**4c**, 59
6	**1d**, 4-MeC_6H_4		6	**4d**, 79
7	**1e**, 4-ClC_6H_4		6	**4e**, 75
9	**1f**, 1-$C_{10}H_7$		12	**4f**, 50[b]

[a] Isolated yield.

[b] 47% Reduction product **2f** was isolated.

The coordination between *N*-tosyl imine and diethylzinc was shown more obviously in nitro-Mannich reaction when CH_3NO_2 was used as the reaction solvent (Table 3). In those reaction, it was found that dialkylzinc could only promote but not catalyze the nitro-Mannich reaction either in CH_3NO_2 (entry 1–3, Table 3) or in other solvents such as toluene, hexane, CH_2Cl_2, Et_2O and THF, while even Et_3N (20 mol%) could catalyze the nitro-Mannich reaction of *N*-tosyl imine with a yield of 74%.[12]

Interestingly, when imine **1f** and diethylzinc were reacted in CH_3NO_2, the product ratio between **4f** (nitro-Mannich adduct) and **2f** (reduction product) was almost 1:1 (entry 9, Table 3). We thought it might be caused by the steric effect, which suppressed the nitro-Mannich reaction. If a stronger coordination ligand was added to break the coordination between imine **1f** and diethylzinc, it would reduce the amount of reduction product. Indeed, when this reaction was taken place in THF, no reduction product was detected other than 51% nitro-Mannich addition product **4f** (Scheme 2). These were all in accordance with the β-H transferring mechanism also.



Scheme 2.

This could be confirmed by the results of another steric hindered imine **1k** (Scheme 3). Similar to the imine **1f**, it took much longer time, 12 h, for imine **1k** to be reduced in toluene than other imines **1a–1e** and the reduction product **2k** was also isolated with 15% yield when imine **1k** and diethylzinc was reacted in CH_3NO_2. Unlike imine **1a**, the reduction product **2k** was the major one when it was reacted in THF.

The coordination effects could be proven by following experiments more clearly. Diethylzinc with an equiv of