

Addition of Diethylzinc to Imines Promoted by Lewis Acid

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Abstract: *The alkylation of imines by using diethylzinc reagent in the presence of Lewis acid afforded secondary amines in high yield.* © 1998 Elsevier Science Ltd. All rights reserved.

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The addition of dialkylzinc reagents to aldehydes¹ and ketones² in the presence of a promoter is well documented, and widely used in organic synthesis. However, imines are unreactive to dialkylzinc even in the presence of a stoichiometric amount of an amino alcohol as a promoter at elevated temperature and it is not surprising that the same reaction fails to provide amines because of low reactivity of imines towards nucleophilic attack. Recently, some strategies have been developed in order to raise the reactivity of imines and to realize the transformation of imines to amines. Katritzky³ reported that diethylzinc was reacted with N-(amidobenzyl) benzotriazoles (masked N-acetyl imines) to afford the corresponding amides. Soon afterwards, Soai⁴ and Tanner⁵ found that dialkylzinc reagents were added to N-(diphenylphosphinoyl) imines in the presence of catalytic or stoichiometric amounts of chiral β -amino alcohols with high enantioselectivities. Ukaji⁶ used a nitron as an activated imine and allowed it to react with dialkylzinc to afford the corresponding alkylated amines. All of these methodologies realized the addition reaction in their own systems but no general solution to the dialkylzinc addition to imines was provided. Also, all substrates they used are aldimines derived from aromatic aldehydes. Although the Lewis acid activation method has been used in imine chemistry⁷, only a few reports have appeared in the literature to employ this kind of activation method to the reaction of dialkylzinc with imines⁸. We have previously reported that imines were activated in allylation and aziridination reactions simply through the reaction of imines with chlorotrimethylsilane⁹. Now we would like to disclose that

this activation procedure can also be employed for the alkylation of imines by using diethylzinc¹⁰. In the presence of chlorotrimethylsilane, reaction of imines with diethylzinc gave rise to the corresponding amines in high yield (eq. 1. Table 1)

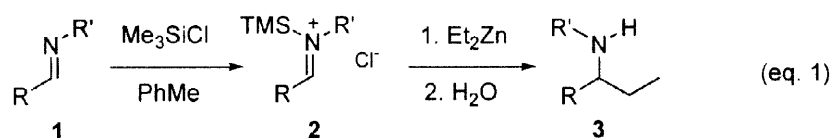
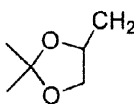


Table 1. The addition of diethylzinc to imines activated by TMSCl^a.

Entry	R	R'	Yield(%) ^b
1	Ph	Ph	81
2	Ph	p-ClC ₆ H ₄	78
3	p-ClC ₆ H ₄	Ph	96
4	o-CF ₃ C ₆ H ₄	Ph	94
5	p-CH ₃ OC ₆ H ₄	Ph	67 (89 ^c)
6	C ₁₀ H ₇	Ph	78
7	(CH ₃) ₂ CHCH ₂	p-ClC ₆ H ₄	60 (83 ^c)
8	CH ₃ (CH ₂) ₈	Ph	41
9		Ph	75 ^d
10	Ph	Bn	29

^a Imine:Me₃SiCl:Et₂Zn = 1:1:2 and run at room temperature. ^b Isolated yield, all new compounds give satisfactory analysis results. ^c Run at refluxed PhMe. ^d ZnCl₂ was used instead of TMSCl, *syn* : *anti* ratio is 3 : >97 determined by 300 MHz ¹H-NMR.

From Table 1 it can be found that all reactions proceeded smoothly for N-aryl aldimines and furnished amines in good to excellent yields, while the R group in aldimines **1** could be either aromatic and aliphatic. Higher yields are obtained when aromatic aldimines with electron-withdrawing groups are employed (Entries 3 and 4) compared to that with electron-donating groups (Entry 5). The reaction with enolizable aliphatic aldimines also takes place successfully to afford the desired products (Entries 7,8). It is worthwhile to note that BF₃·OEt₂ and ZnCl₂ are also efficient Lewis acids to promote this reaction but Ti(O-*i*Pr)₄ gives products in

lower yields. For chiral phenylacetone-D-glyceraldimine, the de's of the addition product is 3 : >97 when ZnCl_2 is used (Entry 9) while it lowers to only 57 : 43 when Me_3SiCl and $\text{BF}_3\cdot\text{OEt}_2$ are used as promoter. The property of solvent does not effect the yield of reaction. Either polar or non-polar solvents, such as CH_2Cl_2 , THF, CH_3CN and PhMe, are suitable for this reaction. On the other hand, a temperature effect was observed. Reactions run at higher temperature provide better yields (Entries 5 and 7).

In conclusion, a simple and efficient alkylation of aldimines with diethylzinc reagent in the presence of Lewis acid is developed. No amino alcohol promoter is needed, which is necessary in the dialkylzinc addition to carbonyl compounds^{1,2}. Because of the tolerance of dialkylzinc reagents^{10,11}, this procedure provides a general way to secondary amines. The investigation of the asymmetric version of this reaction is under way.

General procedure: To a solution of aldimine **1** in dry toluene (5 mL) was added chlorotrimethylsilane (1 mmol) at 0 °C. The mixture was stirred for 15 min at this temperature. Diethylzinc (1 M in hexane, 2mL) was added and then the resulting solution was allowed warm to room temperature. The stirring was continued and the reaction was monitored by TLC. After completion, the reaction was quenched with saturated aq. NH_4Cl (15 mL). The mixture was extracted with dichloromethane (3 X 30 mL), the organic phase was combined and dried with MgSO_4 . The solvent was removed under reduced pressure and the residue was purified by preparative TLC to provide the required amine.

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