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Chiral diethylzinc complexes with diamine ligands: synthesis, crystal structure and enantioselective solvent-free alkylation

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Abstract

In search for conglomerates of stereochemically labile organometallic reagents, three new complexes between diethylzinc and diamine ligands have been synthesized and structurally characterized by single-crystal X-ray diffraction methods. Ligands include *N*,*N*,*N′*,*N′*-tetraethylethylenediamine (teeda), *N*-isopropyl-*N*,*N′*,*N′*-trimethylethylenediamine (itmeda), and (−)-sparteine (spa). Diethylzinc forms monomeric complexes, exhibiting a distorted tetrahedral coordination geometry around zinc in all three complexes, viz. [ZnEt$_2$(teeda)] (**1**), [ZnEt$_2$(itmeda)] (**2**), and [ZnEt$_2$(spa)] (**3**). Both **1** and **2** are stereochemically labile and exhibit chiral complexes, displaying different types of conformational chirality, but they form racemic crystals. By using the chiral crystals of **3** in a nucleophilic addition to benzaldehyde in the absence of solvent at low temperature, an increase in ee from approximately 8 to 10% was obtained (compared to the same reaction in solution). It thus seems feasible, not only to retain the enantioselectivity obtained in solution, but perhaps even to increase the ee by using solventless reactions.

Keywords: Conglomerate; Diethylzinc; *N*-chirogenic; Solid-state reaction; Solvent-free reaction

1. Introduction

Enantioselectivity in asymmetric synthesis can be introduced in different ways, e.g., by using chiral organometallic reagents, such as organozinc complexes [1], organolithium complexes [2], or Grignards reagents [3], and there are two major methods to obtain an optically active organometallic reagent. The first method utilizes coordination of a chiral neutral ligand (e.g., solvent) to the metal center [4–9], while the other method involves modification of the organometallic reagent by protic chiral auxiliaries such as alcohols or amines, giving organometallic alkoxides or amides, respectively [10–13]. Such ligands, neutral or anionic, are usually stereochemically inert in solution, i.e., they have a chirogenic center that does not undergo rapid inversion at the reaction temperature. One drawback with the standard methods is that both enantiomers of the reagent (and consequently, the product) may not be easily accessible. A solution to this problem could be to use auxiliaries or reagents that enantiomerize in solution but retain their optical activity in the solid state. *N*,*N*,*N′*,*N′*-tetramethylethylenediamine, (tmeda) is an achiral ligand that crystallizes as a conformationally chiral complex with ZnEt$_2$ [14]. Depending on the orientation of the ethyl ligands around zinc in such complexes, the molecule can be either achiral (A) or chiral (B) (see Scheme 1). There is, of course, no optical activity in a solution of such a complex, since the ethyl groups are free to change conformation, but in the solid state it would be possible to observe optical activity (provided that a conglomer-

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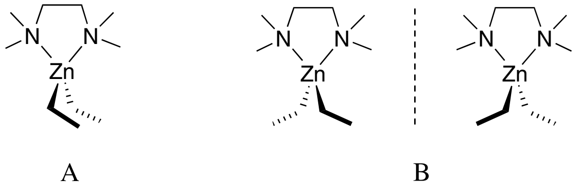
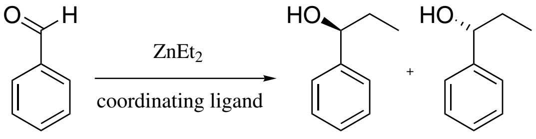


Scheme 1.



Scheme 2.

ate is formed on crystallization) using for example solid-state CD spectroscopy [15].

When a racemic solution of chiral metal complexes crystallizes, it normally forms racemic crystals which contain the enantiomers in a 1:1 ratio down to the unit cell level. But in 5–10% of the cases [16], a conglomerate is formed where the enantiomers are separated in different crystals, i.e., each crystal is enantiopure. The total composition of the sample is usually still racemic, since equal amounts of the enantiomorphic crystals are formed. However, if a stereochemically labile complex, which racemizes in solution but is optically active in the solid state, crystallizes as a conglomerate, the result may be exclusive formation of one of the enantiomers by total spontaneous resolution. This rare phenomenon arises when a stereochemically labile complex crystallizes (induced either by seeding with one of the enantiomers or by slow primary nucleation) via secondary nucleation and results in a theoretical yield and enantiomeric excess (ee) of 100%. Total spontaneous resolution can be utilized in absolute asymmetric synthesis where enantioenriched compounds are prepared from achiral (or racemic) starting materials in the absence of optically active catalysts or reagents [17–22]. The [$ZnEt_2$(tmeda)] [14] reagent is conformationally chiral, but it crystallizes in centrosymmetric *C*2/*c*, i.e., both conformers are present in the same crystal and racemic crystals are formed, which cannot undergo total spontaneous resolution. Therefore, in this work we set out to prepare a stereolabile complex between diethylzinc and another bidentate *N*,*N*-ligand. The commercially available *N*,*N*,*N*′,*N*′-tetraethylethylenediamine (teeda) ligand is closely related to the tmeda ligand, and might consequently form a similar (conformationally chiral) complex, which could crystallize as a conglomerate. Such a complex, which is stereochemically labile in solution, but can be optically active in the solid state, can be utilised as a reagent in, for example, alkyl transfer reactions to aldehydes. The reaction of organometallic compounds with carbonyl substrates is one of the most fundamental reactions in synthetic organic chemistry. Monomeric dialkylzinc complexes possessing a sp-hybridized linear geometry are nearly inert to carbonyl compounds, since the alkyl–metal bond is rather nonpolar. However, addition of a ligand generates a bent C–Zn–C coordination geometry, which facilitates alkyl transfer reactions. For example, 1-phenyl-1-propanol can be synthesized from benzaldehyde in an alkyl transfer reaction with diethylzinc and a catalytic amount of ligand, e.g., the teeda ligand (Scheme 2).

If conformationally chiral complexes that are stereochemically labile in solution are to be used as reagents, a solid-state alkylation is necessary so that optical activity is maintained. In order to compare the enantioselectivity of the solid-state reaction with the ee produced by an analogous solution reaction, it is necessary to choose a ligand (responsible for the enantioselectivity of the reaction) that is stereochemically inert in solution. The teeda ligand is obviously not suitable for this purpose. Instead, our intention was to use the commercially available (−)-sparteine as a chiral ligand in the alkyl transfer reaction of diethylzinc with benzaldehyde. It is advantageous to use a ligand that does not give a high ee in solution, since it may be difficult to completely rule out that some of the solid-state reaction actually proceeds in solution. A comparative study between the enantioselectivity in the solid-state and in solution has, to the best of our knowledge, not been attempted before [23].

2. Experimental

2.1. Materials

All manipulations with diethylzinc complexes were carried out under nitrogen, using standard Schlenk techniques. Diethylzinc (Aldrich, 1.0 M in hexane) was used as received, while (−)-sparteine and *N*,*N*,*N*′,*N*′-tetraethylethylenediamine (teeda) was distilled from CaH_2 and stored over 4 Å molecular sieves prior to use.

2.2. Synthesis of N-isopropyl-N,N′,N′trimethylethylenediamine (itmeda)

The synthesis followed earlier published procedures [24]. Toluene (100 ml), *N*,*N*-dimethylethylenediamine (20 ml, 0.18 mol) and acetone (30 ml, 0.40 mol) were refluxed for 12 h using a Dean–Stark trap. Evaporation in vacuo yielded a yellow oil. Ethanol (100 ml) and $NaBH_4$ (6.90 g, 0.18 mol) were added in small portions and the solution was stirred for 2 h. The reaction was quenched with water (70 ml) and the remainder was extracted with CH_2Cl_2 (3 × 100 ml). The combined organic phase was dried over $MgSO_4$. Evaporation in vacuo yielded a bright