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Review

Enantioselective dialkylzinc-mediated alkynylation, arylation and alkenylation of carbonyl groups

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ABSTRACT

Enantiopure diarylmethanols, propargylic and allylic alcohols are important building blocks for the synthesis of a *plethora* of natural products and pharmaceutically relevant compounds. Among several methods employed for their synthesis, the enantioselective addition of diorganozinc compounds to carbonyl compounds in the presence of appropriate ligands becomes increasingly significant. In this comprehensive review, methods based on the use of readily available diethyl- and dimethylzinc for the formation of more complex compounds are compared and discussed. Available data on the mechanisms and transition states of reactions are presented.

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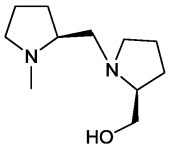
1. Introduction

Enantioselective alkynylation, alkenylation and arylation reactions are now a well established tool in the arsenal of a contemporary organic chemist. At first glance, excellent results obtained so far indicate that synthetic chemistry cannot add much to this. However, many of these results were reported for model compounds, *e.g.* phenylacetylene and, though they add to our knowledge about this chemistry, they are of little value for the practical applications in the synthesis. This review focuses on the dialkylzinc-mediated, enantioselective addition to aldehydes and ketones leading to allylic alcohols, propargylic alcohols and diarylmethanols since the first publications on each topic appeared in print. Several reviews on these topics were published [1–14], many of which being personal accounts. Numerous ligands were applied for both alkynylation and arylation or alkenylation; therefore, a review dealing with all these topics seems to be justified. The main goal of this review is to summarise the results obtained in this area, indicating existing and new challenges, and problems which still remain to be solved. The author attempted to write this review as comprehensively as possible. However, in order to make it more compact and easier to read, many schemes presenting detailed information about substrates, yields and enantioselectivities were placed in supplementary materials. These schemes are numbered separately; however, the numbering of ligands and compounds is consecutive both in the review and supplementary materials in order to facilitate the simultaneous reading of both parts.

The addition of organometallic reagents to carbonyl groups is one of the most common methods for the formation of carbon–carbon bonds. Performing the organometallic additions in a chiral environment leads to the chiral secondary and tertiary alcohols, which are of great synthetic importance. The most popular and most readily available organometallic reagents are Grignard reagents. Unfortunately, their addition to aldehydes and ketones is difficult to control due to their high reactivity. Recent reports show new prospects for such catalytic, enantioselective reactions [15–22], but so far more efficient methods have been based on organozinc compounds. The addition of dialkylzincs to carbonyl compounds is a very slow process in the absence of the catalyst. The situation changes in the presence of an appropriate ligand, usually β-amino alcohol. The first efficient diethylzinc addition to benzaldehyde giving 1-phenylpropanol in the presence of L-proline-derived β-amino alcohol **L1** was reported by Mukaiyama et al. [23].



L1

This reaction proceeded with a good chemical yield (78%), but no asymmetric induction was observed. Several years later Oguni and Omi reported the synthesis of 1-phenylpropanol catalysed by (*S*)-leucinol with 49% ee [24]. The breakthrough was made by Noyori, who used DAIB (3-*exo*-dimethylaminoisoborneol) **L2** as a very efficient ligand for the addition of diethylzinc to benzaldehyde. For the first time 1-phenylpropanol was obtained in 99% ee and 98% yield [25]. Since then, hundreds of reports have been published, and the addition of dialkylzinc to carbonyl compounds has been reviewed thoroughly [26–28,5,29,30,8].

It has been shown that after coordinating to an amino alcohol ligand, the linear structure of dialkylzinc is converted to approximately tetrahedral. The carbon–zinc bond becomes longer, which results in a lower bond energy and a higher nucleophilicity of the alkyl group [31,32]. The mechanism of the addition and the stereochemical model proposed by Noyori [26] and others [33–35] (Scheme 1) is still widely accepted. It is important to stress that 2 equiv. of dialkylzinc are required for this reaction, since compound **I** does not react with aldehyde; the addition of the second dialkylzinc molecule forming **II** is necessary for an alkyl transfer to the carbonyl group. The enantioselectivity of the reaction depends on the presence or absence of steric repulsions between zinc's alkyl group and the aryl moiety of an aldehyde (**III** or **IV**, respectively).

In 1989 Yoshioka, Ohno and Kobayashi showed the effectiveness of bis(sulphonamides) as ligands in the dialkylzinc addition to aldehydes in the presence of titanium tetraisopropoxide [36]. They used a series of diaminocyclohexane-derived sulphonamides and the best results were obtained for triflic acid derivative **L3** (Scheme 2).

The originally postulated mechanism of the reaction of (bis)sulphonamides in the presence of $Ti(OiPr)_4$ suggests an exchange reaction leading to complex **VII** [36]. Walsh proved that **L3** does not react with even a 5-fold excess of $Ti(OiPr)_4$ [37,38], and the active complex **VII** is formed through (bis)sulphonamide zinc species, as proposed earlier by Denmark [39].

The pool of ligands used for reactions performed in the presence of titanium tetraisopropoxide was soon extended to chiral *N*-sulphonamido alcohols [40], as well as TADDOLs [41], BINOLs [42–44] and their derivatives [45,46]. All these classes of compounds found broad use as ligands, and as Professor Seebach described it [41], the dialkylzinc addition "[became] a sport in organic synthesis, generating a number of unusual achievements."

The diol- and sulphonamide-catalysed additions of dialkylzinc to aldehydes in the absence of titanium tetraisopropoxide proceed with low enantioselectivities and rates; therefore, the mechanisms of titanium-promoted reactions were investigated thoroughly by research groups of Seebach [46], Walsh [47–50], Yus [51] and Gau [52], giving deep insight into the reaction's pathway. Seebach and Walsh concentrated on TADDOLs and BINOLs, respectively, while Yus and Gau studied the addition in the presence of β-hydroxy sulphonamides. The mechanism of titanium-promoted reactions, which emerged from very carefully designed studies of Walsh and Gau, is very similar for diols (such as TADDOLs and BINOLs) and β-hydroxy sulphonamides; its slightly simplified version is shown in Scheme 3.

The dimeric complex **VIII** is created initially but it has no catalytic activity and, in the presence of the excess of titanium tetraisopropoxide, is transformed into binuclear L^*Ti_2 complex **IX**. The role of the dialkylzinc reagent is to transfer the alkyl group to titanium and to form complex **X**. Dialkylzinc is incapable of delivering the alkyl group to **IX**, however it reacts with $Ti(OiPr)_4$, giving alkyltitanium compound $R'Ti(OiPr)_3$, which transfers R′ to **IX**, yielding complex **X**. The more Lewis acidic titanium atom coordinates aldehyde, while the other one delivers the alkyl group to the carbonyl moiety. The addition proceeds with simultaneous transfer of the aryl aldehyde oxygen to adjacent titanium atom. The excess of $Ti(OiPr)_4$ now reacts with **XII**, thus forming alkoxide of the newly formed chiral alcohol and regenerating complex **VIII** or **IX**. The alkoxide is incapable of interacting with chiral complexes; therefore, the possibility of the background autoinduction reaction altering the enantioselectivity of the process is minimised [49].

The addition reactions preformed in the absence or presence of a Lewis acid, most often $Ti(OiPr)_4$, are usually catalysed by different groups of ligands and have a different mechanisms. Therefore, these reactions are discussed in separate chapters of this review.

Due to their high functional group tolerance, diorganozincs are excellent reagents for organic synthesis. To make them useful, easy access to diorganozinc other than the simplest dimethyl- and diethylzinc that are commercially available is required. While there are several methods for the synthesis of such compounds, the