CHAPTER-2

Present work on organozinc compounds
Introduction

As discussed in the 1st chapter, organozinc reagents are important organometallics in asymmetric synthesis. Amongst these, dialkylzincs have proved to be excellent nucleophiles in asymmetric addition to carbonyl compounds mainly because of well established methods and use of simple ligands. However, lack of wide commercial availability, high cost and their pyrophoric nature demands an easy \textit{in situ} preparation of these reagents. Significant efforts have been made by various research groups to circumvent these difficulties, which includes preparation of diorganozincs by boron-zinc\textsuperscript{3} or iodine-zinc\textsuperscript{4} exchange and transmetallation of alkyl lithium or Grignard reagents with zinc salts.\textsuperscript{5} One of the major drawbacks in the case of \textit{in situ} preparation of diorganozinc reagents from alkyl lithium or Grignard reagent and ZnX\textsubscript{2}, is the formation of lithium and magnesium salts which affect enantioselectivity.\textsuperscript{5c,e} To overcome this difficulty, additional tasks like centrifugation / filtration\textsuperscript{5a-c} or the use of complexing agent like TMEDA have been explored.\textsuperscript{5d,e} Therefore search for other alternatives is desirable. We have been interested in the reagents of type RZnX\textsuperscript{6} (X = Cl, Br, I) which are easily accessible and represent the best choice in this context. Organozinc halides have been used as nucleophiles in few asymmetric reactions like catalytic enantioselective 1,4-addition\textsuperscript{7} and asymmetric Negishi coupling.\textsuperscript{8} Only few examples of the use of organozine halides in catalytic enantioselective addition to aldehyde are known.\textsuperscript{9} Similar to organozinc halides, triorganozincate reagents are also less explored in asymmetric synthesis.\textsuperscript{10-13} Development of new methods for their application in asymmetric synthesis would lead these reagents as a valuable organometallics.

The present chapter describes the preparation of RZnX (X = Cl, Br, I, OAc) and the corresponding organozincates and their applications in enantioselective alkylation of aldehyde. It has been divided into three sections.

**Section 2A:** Preparation of alkylzinc halides and alkylzinc acetates

**Section 2B:** Enantioselective addition of RZnX to benzaldehyde

**Section 2C:** Organozincates and their enantioselective addition to benzaldehyde
Section 2A

Preparation of alkylzinc halides and alkylzinc acetates

1. Preparation of RZnX by oxidative insertion

It is evident from the literature that the oxidative insertion of zinc into organic halides is the most studied reaction. The oxidative insertion is most general and attractive protocol for the preparation of organozinc halides. After the discovery of first oxidative addition of zinc into a carbon-halogen bond in 1849 by Frankland, numerous procedures have been developed for the activation of zinc to achieve efficient conversion. The heterogeneous reaction conditions and the nature of zinc often pose a problem of reproducibility in the oxidative insertion. After longer expose to air, the surface of metallic zinc gets coated with a layer of zinc oxide that creates the difficulty in initiating the insertion reaction. Therefore the oxide layer must be removed before the zinc metal gets engaged in insertion process with organic halide. The most common initial step for the activation of zinc metal involves washing of the commercial zinc with aqueous HCl. Further activation can be done by making alloys with Cu, Ag, Hg. Another methods for in situ activation of zinc metal includes treatment of the zinc metal with activators such as 1,2-dibromoethane, TMSCl, Bromine, Iodine, DIBALH and ultrasound irriadiation.

The rate of oxidative insertion of zinc depends on various factors such as, nature of organic moiety in the substrate, the halide, method for activation of zinc and reaction parameters such as temperature, concentration and the solvent. Apart from the preparation of organozinc halides using highly reactive Rieke Zinc, which is tedious, there are very few methods for the preparation of alkylzinc bromides from commercial zinc and unactivated alkyl bromides. The two reliable methods known in the literature require use of polar solvents like N,N-dimethyl acetamide or use of 1,2-dibromoethane as activator. However DMA is not suitable for large scale preparation, whereas 1,2-dibromoethane has limitations due to its carcinogenic toxicity. Our aim was to develop a easier preparative method for alkylzinc halides in solvent like tetrahydrofuran which is more convenient and easy to handle.

We examined various additives / activators for the preparation of alkylzinc bromides by oxidative insertion and the results obtained are discussed below.
Results and discussion

The efficiency of oxidative insertion into carbon-halogen bond can be increased in number of ways like activation of zinc and use of additives which can form soluble complex with zinc reagent to give freshly active metallic surface for further reaction.

We examined various additives / activators for the reaction of primary alkyl bromides with zinc dust in THF at 50 to 55 °C (Table 1). Initially we have reacted zinc dust with RBr (R = Et, *n*-Bu) using catalytic amount of zinc activators like MeI, Br₂, and HCl (in Et₂O). Most of the zinc was unreacted in all the cases (Table 1, entries 1–3). Similar kind of results were obtained in the case of radical initiator such as CuI, CeCl₃ and InCl₃ (entries 4–6). The examination of iodide salts such as LiI and TBAI, which can convert alkyl bromide into more reactive iodide, also failed to give the zinc reagent (entries 7 and 8). We also examined the complexing agents like TBAB and ethane-1,2-dimethyl thioether in stoichiometric amount. But in both the cases most of the zinc was unreacted (entries 9 and 10).
Table 1. Reaction of alkyl bromides with zinc

\[
\text{RBr} + \text{Zn} \xrightarrow{\text{THF} \ 50-55 \ ^\circ\text{C}} \ \text{RZnBr}
\]

\(\text{R} = \text{Et}, \ n-\text{Bu}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>RBr</th>
<th>Additives (equiv)</th>
<th>Time (h)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtBr</td>
<td>MeI (0.1)</td>
<td>24</td>
<td>Most of the zinc was unreacted</td>
</tr>
<tr>
<td>2</td>
<td>BuBr</td>
<td>Br(_2) (0.2)</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>BuBr</td>
<td>HCl in Et(_2)O (0.2)</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>EtBr</td>
<td>CuI (0.05)</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>EtBr</td>
<td>CeCl(_3) (0.1)</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>EtBr</td>
<td>InCl(_3) (0.1)</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>EtBr</td>
<td>LiI (0.1)</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>EtBr</td>
<td>TBAI (0.1)</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>BuBr</td>
<td>Bu(_4)NBr (1.0)</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>BuBr</td>
<td>MeSCH(_2)CH(_2)SMe (1.0)</td>
<td>24</td>
<td></td>
</tr>
</tbody>
</table>

We therefore decided to investigate the reaction systematically using \(n\)-BuX \((X = \text{Cl, Br, I})\). Without the use of any additive, more than 95\% zinc was consumed in the reaction of butyl iodide (1.1 equiv) with zinc dust (1 equiv) in THF at 50–55 °C in 24 h (Table 2, entry 1). However iodometric titration\(^2^9\) revealed yield of 60\%. When 1.1 equivalent of LiCl was used, the rate of the reaction was dramatically increased and the reaction was completed in only 2 h under similar reaction conditions (entry 2). However, butyl bromide was found to be unreactive under these reaction conditions (entry 3). We then employed activators like TMSCl, 1,2-dibromoethane and iodine in catalytic amount. Most of the zinc was unreacted in all the cases (entries 4–6). Use of catalytic amount of TMSCl in combination with stoichiometric LiCl gave only 8\% yield of the butylzinc bromide after 48 h (entry 7), whereas 1,2-dibromoethane did not initiate the reaction (entry 8). Interestingly, in the presence of 5 mol\% I\(_2\) and 1.1 equivalents of LiCl, butylzinc bromide was obtained in 65\% yield (entry 9). The reaction was completed in 18 h with high reproducibility. The presence of both LiCl and iodine is necessary for the complete conversion
Encouraged by these results, we examined other activators such as LiI and TBAI. Comparable results were obtained in both the

\[ \text{BuX} + \text{Zn} \xrightarrow{50-55 \degree C} \text{RZnX} \]

<table>
<thead>
<tr>
<th>Entry</th>
<th>BuX</th>
<th>Solvent</th>
<th>Additives</th>
<th>Time (h)</th>
<th>Yield a (%)</th>
<th>Zn consumed (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BuI</td>
<td>THF</td>
<td>none</td>
<td>24</td>
<td>60</td>
<td>&gt;95</td>
</tr>
<tr>
<td>2</td>
<td>BuI</td>
<td>THF</td>
<td>1.1 equiv. LiCl</td>
<td>2</td>
<td>70</td>
<td>quantitative</td>
</tr>
<tr>
<td>3</td>
<td>BuBr</td>
<td>THF</td>
<td>1.1 equiv. LiCl</td>
<td>48</td>
<td>–</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>BuBr</td>
<td>THF</td>
<td>10 mol% TMSCl</td>
<td>48</td>
<td>–</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>BuBr</td>
<td>THF</td>
<td>10 mol% (CH(_2)Br(_2))</td>
<td>48</td>
<td>–</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>BuBr</td>
<td>THF</td>
<td>5 mol% I(_2)</td>
<td>48</td>
<td>–</td>
<td>28</td>
</tr>
<tr>
<td>7</td>
<td>BuBr</td>
<td>THF</td>
<td>1.1 equiv. LiCl, 5 mol% TMSCl</td>
<td>48</td>
<td>8</td>
<td>24</td>
</tr>
<tr>
<td>8</td>
<td>BuBr</td>
<td>THF</td>
<td>1.1 equiv. LiCl, 10 mol% I(_2), 5 mol% TMSCl</td>
<td>48</td>
<td>–</td>
<td>26</td>
</tr>
<tr>
<td>9</td>
<td>BuBr</td>
<td>THF</td>
<td>1.1 equiv. LiCl, 10 mol% TBAI</td>
<td>18</td>
<td>65</td>
<td>quantitative</td>
</tr>
<tr>
<td>10</td>
<td>BuBr</td>
<td>THF</td>
<td>1.1 equiv. LiCl, 5 mol% LiI, 10 mol% TMSCl</td>
<td>24</td>
<td>62</td>
<td>quantitative</td>
</tr>
<tr>
<td>11</td>
<td>BuBr</td>
<td>THF</td>
<td>1.1 equiv. LiCl, 10 mol% LiCl, 5 mol% TBAI</td>
<td>26</td>
<td>62</td>
<td>quantitative</td>
</tr>
<tr>
<td>12</td>
<td>BuBr</td>
<td>THF</td>
<td>1.1 equiv. LiCl, 2 mol% I(_2), 5 mol% TMSCl</td>
<td>48</td>
<td>52</td>
<td>&gt;95</td>
</tr>
<tr>
<td>13</td>
<td>BuBr</td>
<td>THF</td>
<td>1.1 equiv. LiCl, 5 mol% LiI, 5 mol% TMSCl</td>
<td>48</td>
<td>48</td>
<td>&gt;95</td>
</tr>
<tr>
<td>14</td>
<td>BuCl</td>
<td>THF</td>
<td>1.1 equiv. LiCl, 5 mol% I(_2), 5 mol% TMSCl</td>
<td>48</td>
<td>–</td>
<td>25</td>
</tr>
<tr>
<td>15</td>
<td>BuCl</td>
<td>EtOAc</td>
<td>1.1 equiv. LiCl, 5 mol% I(_2), 5 mol% TMSCl</td>
<td>48</td>
<td>–</td>
<td>24</td>
</tr>
<tr>
<td>16</td>
<td>BuCl</td>
<td>DMA</td>
<td>5 mol% I(_2), 5 mol% TMSCl</td>
<td>48</td>
<td>–</td>
<td>31</td>
</tr>
</tbody>
</table>

*Yields were determined by iodometric titration.*
cases with slight longer reaction time (entries 10 and 11). We also studied the effect of iodine loading on the reaction rate. When iodine loading was reduced to 2 mol %, the reaction proceeds much slowly (entry 12). Similar results were observed in the case of LiI (entry 13). Next, less reactive butyl chloride was subjected to the oxidative insertion in the presence of LiCl and catalytic amount of iodine and TMSCl. However most of the zinc was unreacted even after 48 h (entry 14). Use of polar solvents such as EtOAc and DMA also did not help (entries 15 and 16).

The mechanism of zinc insertion is well studied by Rieke et al. In the course of our study, GC-MS analysis of the hydrolyzed reaction mixture (entries 9, 10 and 11, Table 2) showed the formation of a small amount of butyl iodide. On the basis of these results, we proposed the possible mechanism as shown in scheme 1. The formation of butyl iodide could be explained by the nucleophilic displacement of bromide of BuBr by I$^-$ generated from the reaction of zinc and I$_2$. This more reactive butyl iodide reacts with zinc in the presence of LiCl to form the complex A. The complex A exchanges the iodide with butyl bromide to give complex B and BuI is recycled back in the insertion process.

Scheme 1. Proposed mechanism for the oxidative insertion

Since iodides provided good results, we further examined these reaction conditions for the preparation of various alkylzinc bromides. Under optimized reaction conditions, various alkyl bromides were reacted with zinc dust (Table 3). Thus, the reaction of ethyl bromide with zinc dust (1.5 equiv) in the presence of LiCl (1.1 equiv) and 5 mol% iodine provided EtZnBr·LiCl in 75% yield (entry 1). Other
Table 3. Preparation of RZnX (X = Br, Cl) using LiCl and catalytic I₂

\[
RX + Zn + LiCl \xrightarrow{5 \text{ mol\% I}_2} \text{RZnX} \cdot \text{LiCl} \\
\text{THF, 50-55 °C}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>RX</th>
<th>Time (h)</th>
<th>Yielda (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ethyl bromide</td>
<td>14</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>\textit{n}-Butyl bromide</td>
<td>18</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>\textit{n}-Hexyl bromide</td>
<td>20</td>
<td>74</td>
</tr>
<tr>
<td>4</td>
<td>\textit{n}-Octyl bromide</td>
<td>24</td>
<td>72</td>
</tr>
<tr>
<td>5</td>
<td>Ethyl-4-bromo-butyrate</td>
<td>10</td>
<td>73</td>
</tr>
<tr>
<td>6</td>
<td>\textit{iso}-Butyl bromide</td>
<td>48</td>
<td>42</td>
</tr>
<tr>
<td>7</td>
<td>\textit{iso}-Propyl bromide</td>
<td>48</td>
<td>25</td>
</tr>
<tr>
<td>8</td>
<td>\textit{tert}-Butyl bromide</td>
<td>24</td>
<td>40</td>
</tr>
<tr>
<td>9</td>
<td>Allyl chloride</td>
<td>10</td>
<td>68</td>
</tr>
<tr>
<td>10</td>
<td>Benzyl chloride</td>
<td>5</td>
<td>75</td>
</tr>
</tbody>
</table>

a Yields were determined by iodometric titration.

Bromides like \textit{n}-butyl, \textit{n}-hexyl and \textit{n}-octyl bromide were also converted to the corresponding zinc reagent in good yield (entries 2–4). Functionalized alkyl bromide like ethyl 4-bromo-butyrate provided corresponding zinc reagent in 73% yield (entry 5). Due to the steric bulk around bromide, the reaction of \textit{iso}-butyl and \textit{iso}-propyl bromide was slow and incomplete after 48 h (entries 6 and 7). In the case of \textit{tert}-butyl bromide only 40% yield of the product was obtained although zinc was used quantitatively. To find out the reason for this abnormal result, we performed the above reaction without LiCl under similar reaction conditions (eq 1). In this case,

\[
t-\text{BuBr} + Zn \xrightarrow{5 \text{ mol\% I}_2, \text{ THF}} t-\text{BuZnBr} \\
\text{50-55 °C, 24 h}
\]
iodometric titration of the reaction mixture did not show the presence of zinc reagent although 84% zinc was reacted. The GC-MS analysis of reaction mixture showed two major peaks at (m/z 168) and (m/z 226) which corresponds to the probable structures of 1 and 2 respectively (Figure 1). The above results clearly indicates that LiCl stabilizes the zinc reagent by forming the complex $t$-BuZnBr$\cdot$LiCl and also explain the reason for low yield.

![Figure 1](image)

At this stage, the mechanism for the formation of 1 and 2 is not clear. However, it can be explained by assuming the formation of tert-butyl radical (I) (Scheme 2), which can decompose to give 2-methyl-1-propene (II). The intermediate II can generate radical at allylic positions (path-a) and consequent coupling with I gives hydrocarbon 1. The formation of 2 can be explained by generation of radical III by coupling of I with II at vinylic position (path-b), which on homocoupling gives hydrocarbon 2.

![Scheme 2](image)

Scheme 2. Proposed mechanism for the formation of hydrocarbon 1 and 2

Allyl chloride and benzyl chloride were also reacted under the above optimized conditions. Corresponding zinc reagents were obtained in good yield (Table 3, entries 9 and 10).
To confirm the formation of the above described reagents, some of these were reacted with carbonyl electrophiles. Thus, the reaction of BuZnBr-LiCl with benzoyl chloride in the presence of CuCN·2LiCl\textsuperscript{20d} provided 1-phenyl-1-pentanone (3) in 86% isolated yield (eq 2). Also the treatment of benzylzinc chloride with benzaldehyde gave expected product 4 in good yield (eq 3).

\[
\begin{align*}
\text{PhCOCl} + \text{BuZnBr-LiCl} & \xrightarrow{\text{CuCN·2LiCl}} \text{Bu} & \text{PhCO} & \text{3} \\
& \text{THF} & -10 \text{ to } 0 \text{ °C, 6 h} & \text{86% yield}
\end{align*}
\]

\[
\begin{align*}
\text{PhCH}_2\text{ZnCl} + \text{PhCHO} & \xrightarrow{\text{THF}} \text{PhCH} & \text{OH} & \text{Ph} & \text{4} \\
& \text{0 °C to RT, 6 h} & \text{85% yield}
\end{align*}
\]

2. Preparation of RZnX by transmetallation or ligand exchange

Organozinc halides also can be prepared by transmetallation\textsuperscript{31,32} that is, reaction of RLi or RMgX with zinc halide. We have prepared EtZnCl-Mg(Br)Cl (5) by stoichiometric reaction of RMgBr (R = alkyl) with ZnCl\textsubscript{2} (eq 4). To study the ligand effect in RZnX, we extended this method for the preparation of RZnOAc. Thus, the reaction of EtMgBr with Zn(OAc)\textsubscript{2} gave EtZnOAc-Mg(OAc)Br (6) with more than 95% yield (eq 5). The yield was determined by iodometric titration. Using this method, there is always formation of magnesium salts in stoichiometric amount.

\[
\begin{align*}
\text{EtMgBr} + \text{ZnCl}_2 & \xrightarrow{\text{THF}} \text{EtZnCl·Mg(Br)Cl} & \text{5} \\
& \text{0 to 25 °C, 1 h} & \\
\text{EtMgBr} + \text{Zn(OAc)}_2 & \xrightarrow{\text{THF}} \text{EtZnOAc·Mg(OAc)Br} & \text{6} \\
& \text{0 to 25 °C, 1 h} & \\
\text{Et}_2\text{Zn} + \text{ZnCl}_2 & \xrightarrow{\text{THF:hexane}} \text{2 EtZnCl} & \text{7} \\
& \text{25 °C, 1 h} & \\
\text{Et}_2\text{Zn} + \text{Zn(OAc)}_2 & \xrightarrow{\text{THF:hexane}} \text{2 EtZnOAc} & \text{8} \\
& \text{25 °C, 1 h} & 
\end{align*}
\]
along with zinc reagent. To study the magnesium / lithium salt effect on the reactivity of RZnX, we also prepared salt-free alkylzinc halides. The salt-free RZnX (X = Cl, Br, I, OAc) can be prepared by reaction of R₂Zn and ZnX₂, the so called “ligand exchange.”³³ Thus ethylzinc chloride (7) and ethylzinc acetate (8) were obtained by the reaction of diethylzinc with ZnCl₂³³c and Zn(OAc)₂³³d respectively (eq 6 and 7) according to the literature procedures. All these reagents can be stored for several days as a THF solution under inert atmosphere.
Section 2B

Enantioselective addition of RZnX to benzaldehyde

Enantioselective addition of diorganozinc reagents to carbonyl compounds emerged as one of the powerful tools for the preparation of optically active alcohols. Introduction of chiral heteroatom containing ligands to the zinc complex allows facial differentiation in the addition of the alkyl group to carbonyl substrate. After the first report of Oguni and Omi\textsuperscript{34} and pioneering work of Noyori and Soai, numbers of ligand accelerated methods have been developed for the catalytic enantioselective addition of dialkylzinc reagents to aldehyde. A majority of the catalyst for this reaction were based on chiral $\beta$-amino alcohols.\textsuperscript{1} Our interest in this field led us to study the reagent of type RZnX (X = Cl, Br, I, OCOR') which have been rarely studied. High covalent character and less Lewis acidity of zinc centre are responsible for the poor reactivity of these reagents. The reactivity of these reagents towards carbonyl substrates can be enhanced by, (i) substrate activation with Lewis acid (Figure 2a), (ii) Reagent activation with Lewis base catalyst (Figure 2b). Lewis acid coordinates with carbonyl oxygen resulting in increased electrophilicity of carbonyl carbon. Organozinc halides (RZnX) have bent structure and differ fundamentally from diorganozinc compounds (RZnR) which occur as monomers with sp-hybridized linear geometry.\textsuperscript{35a} Due to the presence of electronegative atom, accepter character of zinc in RZnX is enhanced. This leads to association of molecules and hence such compounds are always exists as dimers or higher associates.\textsuperscript{35b} Addition of nitrogen/oxygen containing ligand can break this unreactive oligomeric association and provide reactive organozinc halides monomeric species.

![Figure 2](image-url)
We presumed that a bidentate chelating agent can coordinate with zinc centre and forms tetrahedral complex\textsuperscript{33a,36} (Figure 2c), resulting in enhanced metal-alkyl bond polarity and hence increased nucleophilicity of the alkyl group. We have done a systematic study on the reactivity of alkylzinc halides towards aldehyde by examining various catalysts / chelating agent derived from N-Me ephedrine and simple diols. These results are discussed below.

**Results and discussion**

For our present study, we chose simple chiral ligands (9–14) as shown in figure 3.

![Chemical structures](attachment:image.png)

**Figure 3**

**Preparation of catalysts**

Several catalysts 15–24 (Figure 4) were prepared by the treatment of chiral ligand with organometallic reagent. The change in the metal center (aluminum, titanium, zinc, magnesium, lithium) provides change in Lewis acidities and also the coordinating ability of nitrogen/oxygen atoms.
Figure 4

Aluminum alkoxide 15 was prepared by the reaction of (−)-13 with Et₂AlCl (Scheme 3).

Scheme 3. Preparation of catalyst 15

N-Me ephedrine derived alkoxides 16 and 17 were prepared by treatment of (−)-9 with BuLi/EtMgBr (Scheme 4).

Scheme 4. Preparation of catalyst 16 and 17
Catalysts 18 and 19 were prepared by the treatment of (−)-10 with diethylzinc and Ti(OiPr)$_4$ respectively (Scheme 5).

Scheme 5. Preparation of catalyst 18 and 19

Magnesium-dialkoxides 21, 23 and 24 were prepared by the treatment of corresponding diols (12, 13 and 14) with 2 equivalent of EtMgBr (Scheme 6).

Scheme 6. Preparation of magnesium-dialkoxides

Lithium-dialkoxides 20 and 22 were prepared by the treatment of $n$-BuLi with corresponding diols (−)-12 and (−)-13 respectively (Scheme 7).

Scheme 7. Preparation of lithium-dialkoxides

We then evaluated these catalysts for the addition of RZnX to benzaldehyde. Alkylzinc halides (RZnX) are known to be weakly active nucleophiles. Initially we examined the reactivity of salt free RZnX 7 and 8 (prepared by ligand exchange method, $R = Et$, $X = Cl$, OAc) with benzaldehyde in the presence of various
catalysts/chelating agent (Table 4). Without any additive, both the reagents 7 and 8 do not react with benzaldehyde (Table 4, entry 1). Similar kind of reactivity was observed in the case of catalytic amount of Lewis acid catalyst 15 (entry 2). We then examined N-Me ephedrine derived bifunctional catalysts 16 and 18. These catalysts can play a dual role by acting as Lewis acids to activate the carbonyl substrate and also as Lewis base to activate the zinc reagent\textsuperscript{38} (Figure 5). However the strategy did not prove fruitful (entries 3 and 4).

![Figure 5](image)

We decided to examine next bidentate chelating agents. First we used chelating agent like N-Me morpholine. But these reagents did not reacted with benzaldehyde in the presence of catalytic or stoichiometric amount of N-Me morpholine (entries 5 and 6). We then employed metal dialkoxides\textsuperscript{39} 20 and 23 which are stronger chelating agent. Only starting material was recovered in both the cases (entries 7 and 8). When the reaction of EtZnCl 7 was carried out in the presence of one equivalent of MgCl\textsubscript{2}, alkylated product (25) was obtained in 31% yield along with the formation of propiophenone (26) and benzyl alcohol (27) (entry 9). Origin of byproducts can be explained by Oppenauer oxidation\textsuperscript{40} of intermediate zinc-alkoxide I (Scheme 8). The zinc reagent 8 also gave similar kind of results in the presence of Mg(OAc)Br (entry 10). However other Lewis acids such as ZnCl\textsubscript{2} and LiCl failed to provide the alkylated product (entries 11 and 12).
Table 4. Addition of EtZnX (X = Cl, OAc) to benzaldehyde

\[ \text{EtZnX} + \text{PhCHO} \rightarrow \text{Ph} \text{OZnX} \quad \text{(I)} \]

Scheme 8. Proposed mechanism for the formation of byproducts 26 and 27
Above results suggest that the reaction is not a Lewis catalyzed one. Instead, MgX$_2$ in stoichiometric amount forms addition complex$^{32f}$ (Figure 6), which is responsible for the reaction.

![Figure 6](image)

$S$ = solvent molecule

We also examined reactivity of RZnX-LiX (prepared by insertion method) in the presence of various catalysts (Scheme 9). Only trace amount of expected product was observed in all the cases.

![Scheme 9](image)

**Scheme 9.** Reaction of RZnX-LiCl with benzaldehyde

Since MgX$_2$ has role on the reactivity of RZnX, we next examined the reactivity of the zinc reagents 5 and 6 in which stoichiometric amount of MgX$_2$ is present. In our initial experiment, the reaction of reagent 5 with PhCHO without any additive gave only 11% 1-phenyl-1-propanol (25) in 4 h at 25 $^\circ$C (Table 5, entry 1). This suggested that the effect of MgX$_2$ is not very pronounced.
Table 5. Addition of EtZnCl⋅Mg(Br)Cl to benzaldehyde

\[
\text{EtZnCl} \cdot \text{Mg(Br)Cl} + \text{PhCHO} \xrightarrow{\text{catalyst (10 mol\%)}} \text{THF} \rightarrow \text{PhCHOCH}_{2}\text{CH}_3, \text{PhCH}_2\text{OH and unreacted PhCHO.}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield a (%)</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>0 to 25</td>
<td>4</td>
<td>11</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>0 to 25</td>
<td>16</td>
<td>63</td>
<td>&lt;1</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>0</td>
<td>8</td>
<td>66</td>
<td>&lt;1</td>
</tr>
<tr>
<td>4</td>
<td>21</td>
<td>0</td>
<td>8</td>
<td>62</td>
<td>&lt;1</td>
</tr>
<tr>
<td>5</td>
<td>23</td>
<td>0</td>
<td>8</td>
<td>64</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

\(^{a}\) Isolated yields; remaining was PhCOCH\(_2\)CH\(_3\), PhCH\(_2\)OH and unreacted PhCHO.

We therefore proceeded to evaluate various dicordinate ligands for the reaction. These were, chiral chelating agent like \((2R,3S)-(-)-4\)-methyl-2,3-diphenyl morpholine (11) and lithium/magnesium dialkoxides 20, 21 and 23. One equivalent of 1,4-dioxane was added to reduce the Lewis acidic effect of Mg(Br)Cl. Although good yields were obtained, negligible enantioselectivity was realized in all the cases.

One of the difficulties in handling the zinc halides is their hygroscopic nature. We decided to use zinc acetate which is non-hygroscopic and can be a good alternative to zinc halides. The zinc reagent EtZnOAc⋅Mg(OAc)Br (6), prepared by the transmetallation of EtMgBr with zinc acetate, was reacted with benzaldehyde without any additive. It revealed reactivity pattern similar to that of reagent 5. In the presence of chiral chelating agent 11, expected product 25 was obtained in 18% yield as a racemate (Table 6, entry 2). Interestingly, the reaction of 6 in the presence of lithium-dialkoxide 22 provided 31% yield with 13% ee (entry 3). The corresponding magnesium-dialkoxide 23 furnished 34% yield with 28% ee (entry 4). Our attempts to isolate the reagent 6 were unsuccessful. To verify the formation of EtZnOAc from EtMgBr and Zn(OAc)\(_2\), salt free zinc reagent 8 was reacted with benzaldehyde in the presence of stoichiometric amount of Mg(OAc)Br (prepared by stoichiometric reaction of EtMgBr with AcOH) (eq 8).
These results obtained were comparable to the results with the reagent 6. Also the comparison of reactivity difference between the reagent 8 (Table 4, entry 8) and reagent 6 (Table 6, entry 4) revealed that the presence of MgX$_2$ was crucial. One of the reasons for moderate selectivity was attributed to MgX$_2$-promoted background reaction.$^{41}$ To overcome this problem, we added complexing agents like 1,4-dioxane or TMEDA. However, this modification proved inconsequential (entries 5 and 6). By changing the solvent from THF to methyl tert-butyl ether (MTBE), enantioselectivity increased to 50% (entry 7). Enantiomeric excess was determined by chiral HPLC. When the reaction was carried out at room temperature, the product was isolated in 60% yield but the enantioselectivity was dropped to 39% (entry 8). Similar results were obtained when diethyl ether was used as the solvent (entry 9). Other magnesium-dialkoxides 21 and 24 proved inferior to 23 (entries 10 and 11).
**Table 6.** Enantioselective addition of EtZnOAc·Mg(OAc)Br to benzaldehyde

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
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<tr>
<td>1</td>
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<td>THF</td>
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<td>4</td>
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<td>2</td>
<td>11</td>
<td>THF</td>
<td>0</td>
<td>8</td>
<td>18</td>
<td>-</td>
</tr>
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<td>8</td>
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<td>13</td>
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<tr>
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<td>8</td>
<td>34</td>
<td>28</td>
</tr>
<tr>
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<td>23</td>
<td>THF</td>
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<td>8</td>
<td>37</td>
<td>18</td>
</tr>
<tr>
<td>6</td>
<td>23</td>
<td>THF</td>
<td>0</td>
<td>8</td>
<td>22</td>
<td>21</td>
</tr>
<tr>
<td>7</td>
<td>23</td>
<td>MTBE</td>
<td>0</td>
<td>8</td>
<td>44</td>
<td>50</td>
</tr>
<tr>
<td>8</td>
<td>23</td>
<td>MTBE</td>
<td>25</td>
<td>24</td>
<td>60</td>
<td>39</td>
</tr>
<tr>
<td>9</td>
<td>23</td>
<td>Et₂O</td>
<td>25</td>
<td>24</td>
<td>54</td>
<td>38</td>
</tr>
<tr>
<td>10</td>
<td>21</td>
<td>MTBE</td>
<td>25</td>
<td>24</td>
<td>45</td>
<td>&lt;5</td>
</tr>
<tr>
<td>11</td>
<td>24</td>
<td>MTBE</td>
<td>25</td>
<td>24</td>
<td>49</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

- The reactions were carried out at 0.4-0.5 molar concentrations. b Isolated yields of the desired product. c Determined by comparison of optical rotation with known literature value or chiral GC / HPLC analysis. d One equivalent of 1,4-dioxane was added. e One equivalent of TMEDA was added.

Heterogeneous reaction mixtures result during the use of solvents other than THF. After extensive optimization, it was found that by adding the Grignard reagent to a suspension of zinc acetate and (−)-13 in THF, homogenous solution was obtained at 0 °C. This reagent was then reacted with benzaldehyde to obtain 30% yield of the product with 40% ee (Table 7, entry 1). We also studied the effect of stoichiometry of Grignard reagent with respect to zinc acetate. It was found that the rate of the reaction as well as enantioselectivity varied with the change in stoichiometry. Best results were obtained when the ratio was 1:1 (entries 1, 2 and 3). In the case of 1.2 equivalent EtMgBr (Table 7, entry 3), the excess Grignard reagent can generate diethylzinc by reacting with preformed EtZnOAc. This hypothesis was supported by addition of commercial diethylzinc to benzaldehyde, which gave...
comparable results (eq 9). In terms of halide effect in RMgX, bromide and iodide were found to be better than chloride (entries 4, 5 and 6). We also examined other Grignard reagents under these conditions. n-Butyl and iso-butyl magnesium bromide provided 13% and 16% enantioselectivity respectively (entries 5 and 7). In the case of t-BuMgCl, no reaction took place at all.

Table 7. Enantioselective addition of various RZnOAc-Mg(OAc)X to benzaldehyde

<table>
<thead>
<tr>
<th>Entry</th>
<th>RMgX</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtMgBr</td>
<td>0</td>
<td>8</td>
<td>25</td>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>2&lt;sup&gt;d&lt;/sup&gt;</td>
<td>EtMgBr</td>
<td>0</td>
<td>24</td>
<td>25</td>
<td>18</td>
<td>36</td>
</tr>
<tr>
<td>3&lt;sup&gt;e&lt;/sup&gt;</td>
<td>EtMgBr</td>
<td>0</td>
<td>4</td>
<td>25</td>
<td>60</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>BuMgCl</td>
<td>0</td>
<td>8</td>
<td>28</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>BuMgBr</td>
<td>0</td>
<td>4</td>
<td>28</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>6&lt;sup&gt;f&lt;/sup&gt;</td>
<td>BuMgI</td>
<td>0</td>
<td>4</td>
<td>28</td>
<td>41</td>
<td>50</td>
</tr>
<tr>
<td>7</td>
<td>i-BuMgBr</td>
<td>0</td>
<td>8</td>
<td>29</td>
<td>5</td>
<td>16</td>
</tr>
<tr>
<td>8</td>
<td>t-BuMgCl</td>
<td>0–25</td>
<td>24</td>
<td>-</td>
<td>g</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup> The stoichiometric ratio of RMgX:Zn(OAc)<sub>2</sub>:(−)-13:PhCHO was 1.7:1.5:0.1:1.0 respectively unless otherwise noted. <sup>b</sup> Isolated yields of the desired product. <sup>c</sup> ee Was determined by chiral GC or HPLC analysis. <sup>d</sup> 0.8 equiv. EtMgBr was added with respect to Zn(OAc)<sub>2</sub>. <sup>e</sup> 1.2 equiv. EtMgBr was added with respect to Zn(OAc)<sub>2</sub>. <sup>f</sup> The reaction was carried out in THF:Et<sub>2</sub>O. <sup>g</sup> The starting material was recovered.

$$\text{PhCHO, THF} \quad \text{(-)-13} \quad \text{PhCHO, THF} \quad \text{PhCHO, THF}$$

$$\text{RMgX} + \text{Zn(OAc)}_2 \rightarrow \text{PhCHO, THF}$$

$$\begin{array}{cccccc}
\text{Entry} & \text{RMgX} & \text{Temp. (°C)} & \text{Time (h)} & \text{Product} & \text{Yield}\text{ (%)} & \text{ee}\text{ (%)} \\
1 & \text{EtMgBr} & 0 & 8 & 25 & 30 & 40 \\
2<sup>d</sup> & \text{EtMgBr} & 0 & 24 & 25 & 18 & 36 \\
3<sup>e</sup> & \text{EtMgBr} & 0 & 4 & 25 & 60 & 8 \\
4 & \text{BuMgCl} & 0 & 8 & 28 & 5 & 0 \\
5 & \text{BuMgBr} & 0 & 4 & 28 & 17 & 13 \\
6<sup>f</sup> & \text{BuMgI} & 0 & 4 & 28 & 41 & 50 \\
7 & \text{i-BuMgBr} & 0 & 8 & 29 & 5 & 16 \\
8 & \text{t-BuMgCl} & 0–25 & 24 & - & g & - \\
\end{array}$$

\[ \text{76% yield, 14% ee} \]
Mechanism:

The difference in the selectivity showed by ligand (−)-13 compared to other diols was attributed to the rigid backbone and the steric bulk due to phenyl rings present in the molecule. At this stage a precise model which explains the outcome of stereoselectivity using reagent 6 is not clear. However we presume that the oxygen atoms of the metal alkoxide 23, EtZnOAc, BrMg(OAc), and PhCHO bind as depicted in figure 7a. The resulting cyclic transition state could be responsible for stereoselection. This would also explain the lack of enantioselectivity with the reagent 5, which proceeds through MgX₂-catalyzed acyclic pathway (Figure 7b).

**Figure 7.** Proposed mechanism for enantioselective alkylation
Section 2C

Organozincates and their enantioselective addition to benzaldehyde

Addition of organo-zinc reagents to various organic electrophiles has become one of the common methods to construct carbon-carbon bond. The preparation of dialkylzincs\(^2,31\) and organozincates\(^{6a,32f,42}\) is well documented in the literature. Diorganozinc reagents have \(sp\)-hybridized linear geometry (Figure 8a). Pure dialkylzinc reagents react sluggishly with aldehydes and ketones. However, their reactivity can be enhanced by incorporation by a third substituent like alkyl or heteroatom containing ligand on zinc centre (Figure 8b). Richey \textit{et al.}\(^{42f}\) reported that the treatment of alkali metal alkoxide with diethylzinc produces triorganozincates species \((R_3ZnOR)M\), which reacts rapidly with aldehyde and ketones. We envisaged that introduction of two chiral alkoxides would form chiral-zincate species (Figure 8c) which can react enantioselectively with aldehyde. In this context, optically active diols would be ideal ligands.

![Figure 8](image)

We have prepared various chiral-zincates using optically active diols. The present section deals with the results obtained in this study.

**Results and discussion**

In our initial study, we examined the reactivity pattern of alkylzincates prepared from \(\text{ZnX}_2\) and \(\text{RMgX}\). In the present work, alkylzinc reagents were prepared by the reaction of \(\text{ZnX}_2\) (\(X = \text{Cl}, \text{OAc}\)) with \(n\) equivalent of \(\text{EtMgBr}\) (\(n = 2\) and 3) (eq 10, 11 and 12).
The reaction of $\text{Et}_2\text{Zn} \cdot 2\text{Mg}(\text{X})\text{Br}$ ($\text{X} = \text{Cl}, \text{OAc}$) with 0.9 equivalent benzaldehyde proceeds quantitatively in 1 h at 0 °C (Table 8, entries 1 and 2). This indicates the presence of magnesium salt ($\text{Mg}(\text{X})\text{Br}$ ($\text{X} = \text{Cl}, \text{OAc}$)) increases the reactivity of diethylzinc reagent. In addition to this, we observed that there is a dramatic decrease in reactivity when $\text{Mg}(\text{X})\text{Br}$ is replaced by less Lewis acidic $\text{Mg}(\text{OAc})_2$. It was done by the reaction of $\text{Zn}(\text{OAc})_2$ with two equivalents of $\text{EtMgBr}$ in the presence of excess NaOAc (Scheme 10). The treatment of in situ formed reagent with benzaldehyde provided only 49% yield of the product.

Scheme 10

Next, the reagent prepared from two equivalents of $\text{EtMgBr}$ with $\text{ZnCl}_2/\text{Zn}(\text{OAc})_2$ was reacted with 1.9 equivalent benzaldehyde. After 1 h GC analysis revealed formation of 73% product in both the cases (entries 3 and 4). These results indicate that more than one equivalent of alkyl group gets transferred, which can be explained by scheme 11. When the mixture of $\text{ZnX}_2$ ($\text{X} = \text{Cl}, \text{OAc}$) and 2$\text{EtMgBr}$ was equilibrated for longer time (16 h) at room temperature, approximately 50% yield of the product was obtained in both the cases (entries 5 and 6). This difference in the reactivity can be attributed to the formation of ate complexes $\text{I}$ and $\text{II}$ depicted in eq 13 and 14 respectively. After longer stirring ate complex decomposes to give $\text{Et}_2\text{Zn}$, which can transfer only one alkyl group.
\[
\text{2 EtMgBr} + \text{ZnCl}_2 \xrightarrow{\text{THF, 0 \degree C}} \text{Et}_2\text{Zn} + 2\text{Mg(Br)Cl} \quad (13)
\]

\[
\text{2 EtMgBr + Zn(OAc)}_2 \xrightarrow{\text{THF, 0 \degree C}} \text{Et}_2\text{Zn} + 2\text{Mg(OAc)Br} \quad (14)
\]

\[
\text{3 EtMgBr} + \text{ZnX}_2 \xrightarrow{\text{THF, 0 \degree C}} \text{Et}_2\text{Zn} + 2\text{Mg(X)Br} \quad (15)
\]

\[
\text{X = Cl, OAc}
\]

**Table 8. Addition of ethylzincates to benzaldehyde**

<table>
<thead>
<tr>
<th>Entry</th>
<th>(n) EtMgBr + ZnX₂</th>
<th>[Temp ((^{\circ})C), Time (h)](^a)</th>
<th>PhCHO (equiv.)</th>
<th>Product(^b) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 EtMgBr + ZnCl₂</td>
<td>0–25, 1 h</td>
<td>0.9</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>2 EtMgBr + Zn(OAc)₂</td>
<td>0–25, 1 h</td>
<td>0.9</td>
<td>quantitative</td>
</tr>
<tr>
<td>3</td>
<td>2 EtMgBr + ZnCl₂</td>
<td>0, 0.5</td>
<td>1.9</td>
<td>73</td>
</tr>
<tr>
<td>4</td>
<td>2 EtMgBr + Zn(OAc)₂</td>
<td>0, 0.5</td>
<td>1.9</td>
<td>73</td>
</tr>
<tr>
<td>5</td>
<td>2 EtMgBr + ZnCl₂</td>
<td>0–25, 16 h</td>
<td>1.9</td>
<td>58</td>
</tr>
<tr>
<td>6</td>
<td>2 EtMgBr + Zn(OAc)₂</td>
<td>0–25, 16 h</td>
<td>1.9</td>
<td>48</td>
</tr>
<tr>
<td>7</td>
<td>3 EtMgBr + ZnCl₂</td>
<td>0, 0.5</td>
<td>2.9</td>
<td>78</td>
</tr>
<tr>
<td>8</td>
<td>3 EtMgBr + Zn(OAc)₂</td>
<td>0, 0.5</td>
<td>2.9</td>
<td>86</td>
</tr>
</tbody>
</table>

\(^a\) The mixture of EtMgBr and ZnX₂ was stirred at mentioned temperature and time before the addition of aldehyde. \(^b\)Yields by GC analysis; remaining propiophenone benzyl alcohol and unreacted benzaldehyde.

We also studied the reactivity of trialkylzincates with benzaldehyde. In the present study, the triethylzincate III was prepared by reacting ZnX₄ (X = Cl, OAc)
with three equivalents of EtMgBr at 0 °C (eq 15). The reaction of III with 2.9 equivalent PhCHO gave 78% and 86% yield of the product in case of ZnCl₂ and Zn(OAc)₂ respectively. These results indicate that more than two equivalents of alkyl group can transfer in both cases. The possible explanation for the above results can be that the ate complex III first reacts with one equivalent of PhCHO via a six-membered TS-1 (Scheme 11) to give the expected product and Et₂Zn. The resulting ate complex I / II further react with 2nd equivalent of PhCHO via TS-2 and gives product and EtZnX, (X = Cl or OAc). Finally EtZnX then reacts with 3rd equivalent of PhCHO in the presence of Mg(X)Br via TS-3. From the above results it can be concluded that the zincate species generated from ZnX₂ and RMgBr can transfer all the three alkyl groups to benzaldehyde. Based upon these findings we planned to prepare optically active triorganozincates to achieve enantioselective version.

Scheme 11. Possible mechanism for the transfer of all three alkyl group.
Enantioselective addition of organozincates to benzaldehyde

We anticipated that simple $C_2$-symmetric chiral diols$^{43}$ would serve as non transferrable ligand and effective chiral inducer for this transformation. We chose simple chiral diols such as ($-$)-12, ($-$)-13 and (+)-14 as chiral source. Diols are known$^{39f}$ to form alkoxide 30 when reacted with diethylzinc at 80 °C (Scheme 12, path-a). Alkoxide 30 also can be prepared from sodium/magnesium dialkoxide and ZnCl$_2$ (path-b and path-c respectively). The alkoxide 30 on treatment with stoichiometric Grignard reagent would give chiral zincate complex-IV, which can react with aldehyde enantioselectively.

![Scheme 12](image)

In our initial study, zincate complex prepared from diol ($-$)-13 via path-b (or path-c) on reaction with benzaldehyde gave desired product in low enantioselectivity (Scheme 13). Increased enantioselectivity was realized when the chiral zincate-complex was prepared using path-a. Therefore we prepared chiral zinc-alkoxides 30a, 30b and 30c (Figure 9) by heating the equimolar quantity of diethylzinc and corresponding diols at 80 °C according to path-a in scheme 12.
We then examined these *in situ* generated zinc-alkoxides (30a-c) in enantioselective addition to benzaldehyde under different reaction conditions (Table 9). First we examined the zinc-alkoxide 30a. One equivalent of EtMgBr was added to a suspension of 30a in toluene at 0 °C. The resulting zincate complex was then treated with benzaldehyde at 0 °C (Condition A). The product was isolated in 66% yield with 24% ee (Table 9, entry 1). Low enantioselectivity was observed when addition sequence of Grignard reagent and aldehyde was reversed (Condition B) (entry 2). The enantioselectivity was increased substantially (to 50%) when the addition was done simultaneously (Condition C) (entry 3). Lowering the temperature from 0 to −78 °C diminished the enantioselectivity (entry 4). Less solubility of 30a at low temperature promotes the direct addition of Grignard regent to aldehyde, which could be the reason for lower enantioselectivity. The use of EtMgBr-LiCl (a structurally different Grignard reagent) did not help (entry 5). Poor enantioselectivity was realized in the case of zinc-alkoxides 30b and 30c (entries 6 and 7).
Table 9. Enantioselective addition of chiral-zincates to benzaldehyde

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkoxide&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Condition&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Temp (°C), Time (h)</th>
<th>Yield&lt;sup&gt;c&lt;/sup&gt; (%)</th>
<th>ee&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30a</td>
<td>A</td>
<td>0</td>
<td>2</td>
<td>66</td>
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<tr>
<td>2</td>
<td>30a</td>
<td>B</td>
<td>0</td>
<td>2</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>30a</td>
<td>C</td>
<td>0</td>
<td>2</td>
<td>59</td>
</tr>
<tr>
<td>4</td>
<td>30a</td>
<td>C</td>
<td>−78 to 0</td>
<td>2</td>
<td>64</td>
</tr>
<tr>
<td>5&lt;sup&gt;e&lt;/sup&gt;</td>
<td>30a</td>
<td>C</td>
<td>0</td>
<td>2</td>
<td>67</td>
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</tr>
<tr>
<td>7</td>
<td>30c</td>
<td>C</td>
<td>0</td>
<td>2</td>
<td>69</td>
</tr>
</tbody>
</table>

<sup>a</sup> The ratio of zinc-alkoxide:RMgX:PhCHO was 1:1:1 respectively.  
<sup>b</sup> Condition A: Grignard reagent was added to zinc-alkoxide and after 15 minutes benzaldehyde was added; Condition B: Benzaldehyde was added before the addition of Grignard reagent; Condition C: Grignard reagent and aldehyde were added simultaneously.  
<sup>c</sup> Isolated yields of the desired product.  
<sup>d</sup> Determined by comparison of optical rotation with known literature value.  
<sup>e</sup>EtMgBr-LiCl complex was added instead of EtMgBr.
Conclusions

- We have found a simple procedure for the preparation of alkylzinc bromides in THF by the use of LiCl as additive and I₂ as activator. Using optimized conditions, various alkylzinc bromides were prepared in good yields. We have also prepared successfully alkylzinc acetates by transmetallation method.

- Salt-free RZnX exhibit poor reactivity towards benzaldehyde. Moderate enantioselectivity was achieved in the case of TADDOL-magnesium dialkoxide using RZnOAc as alkylating agent.

- We have also observed that ate complex formed by the reaction of ZnX₂ and RMgX can transfer all alkyl groups to benzaldehyde. Moderate enantioselectivity was realized in the case of TADDOL-zincate.
Experimental Section

General

All the solvents and reagents were purified and dried according to procedures given in D. D. Perrin’s purification of Laboratory chemicals.\textsuperscript{45} Zinc dust (325 mesh) was purchased from Sisco Research Laboratories, India. Diethylzinc was purchased from Sigma-Aldrich chemical company. Benzaldehyde was freshly distilled before use. THF was freshly distilled over sodium benzophenone ketyl. Anhydrous zinc acetate was obtained by heating Zn(OAc)$_2$.2H$_2$O at 90 °C for 4 h under the reduced pressure. All the reactions were performed in oven dried (120 °C) glasswares under an argon atmosphere. Ligand 10 was prepared by reacting (1\textsubscript{R},2\textsubscript{S})-(-)-norephedrine and \textit{p}-toluenesulfonyl chloride following literature procedure.\textsuperscript{46a} Diol 13 was prepared according to the literature procedure.\textsuperscript{46b} GC analysis was carried out using HP-5 (30m x 0.25 m x 0.25 μ) column.

Preparation of organozinc halides by oxidative insertion using LiCl as additive and I$_2$ as catalyst.

The following procedure for preparation of \textit{n}-BuZnBr-LiCl is representative (entry 2 in table-3).

To a 25 mL two-necked round bottom flask equipped with a stir bar and a reflux condenser was added zinc dust (0.490 g, 7.5 mmol) and LiCl (0.233 g, 5.5 mmol). The mixture was heated at 150 °C for 1 h under high vacuum and cooled to room temperature under argon. Anhydrous THF (5 mL) and I$_2$ (0.063 g, 0.25 mmol) were introduced in the flask and the mixture was stirred at room temperature for 15 minutes (red color of I$_2$ disappears completely). \textit{n}-Butyl bromide (0.53 mL, 5 mmol) was then added and the reaction mixture was stirred at 50–55 °C for 18 h. The flask was cooled to room temperature and mixture was allowed to settle for 1 h. The yield of the zinc reagent was determined by iodometric titration.

**Iodometric titration:**

One mL of supernatant aliquot from the reaction mixture was transferred to 10 mL round bottom flask under argon atmosphere. To this, I$_2$ (0.5 M solution in benzene or THF) was added dropwise at 0 °C until solution becomes brown. The
amount of I$_2$ consumed corresponds to one equivalent of alkylzinc halide.$^{29}$

Calculation for total volume indicated 74% yield of the $n$-butylzinc bromide.

**Reaction of butylzinc bromide with benzyloxy chloride**

A 50 ml two neck round bottom flask was charged $n$-BuZnBr⋅LiCl (6 mmol, 8.1 mL of 0.74 M solution in THF) and cooled to −10 °C. CuCN⋅2LiCl (6 mmol, 6 mL of 1 M solution in THF) was added to the solution. The resulting faint green colored solution was stirred for 15 minutes. Then benzoxy chloride (0.58 mL, 5 mmol) was added dropwise over 5 minutes and the reaction mixture was allowed to warm to 0 °C and stirred for 6 h. The reaction mixture was quenched cautiously by 2 mL saturated aqueous NH$_4$Cl, acidified with 1N HCl and extracted with diethyl ether (3 x 20 mL). The combined extract was washed with brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by “flash chromatography” on silica gel (230-400 mesh) using ethyl acetate: petroleum ether as the eluent to obtain 3 as oily liquid.

![Butylzinc Bromide](image)

**Yield** : 0.70 g (86%)

**IR (neat)** : 3063, 2958, 1681, 1450 cm$^{-1}$

**$^1$H NMR (CDCl$_3$)** :

- δ 0.96 (t, $J = 7.20$ Hz, 3H), 1.31−1.52 (m, 2H),
- 1.64−1.83 (m, 2H), 2.97 (t, $J = 7.58$ Hz, 2H),
- 7.38−7.62 (m, 3H, ArH), 7.90−8.04 (m, 2H, ArH)

**Reaction of benzylzinc chloride with benzaaldheyde**

The same procedure (described for $n$-BuZnBr⋅LiCl) was followed for the preparation of PhCH$_2$ZnCl⋅LiCl.

A 25 ml two neck round bottom flask was charged with PhCH$_2$ZnCl⋅LiCl (6 mmol, 8 mL of 0.75 M solution in THF) and the solution was cooled to 0 °C. Benzaldehyde (0.5 mL, 5 mmol) was added dropwise over 5 minutes and the reaction mixture was allowed to warm to room temperature and stirred for 6 h. The mixture
was then quenched cautiously by 1 mL MeOH at 0 °C. Saturated aqueous NH₄Cl (20 mL) was added and the mixture was extracted with ethyl acetate (3 x 20 mL). The combined extract was washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The crude compound was purified by “flash chromatography” on silica gel using ethyl acetate: petroleum ether as the eluent to obtain 4 as a white solid.

![Image of compound 4]

Yield: 0.84 g (85%)
Melting point: 64–66 °C (Lit. 67–67.5 °C)
IR (CHCl₃): 3599, 3016, 2920, 1454 cm⁻¹
¹H NMR (CDCl₃): δ 1.95 (d, J = 2.9 Hz, 1H, OH), 2.95–3.06 (m, 2H), 4.84–4.96 (m, 1H), 7.15–7.43 (m, 10H, ArH)

Preparation of (2R,3S)-(−)-4-methyl-2,3-diphenylmorpholine (11)

A 10 mL round bottom flask was charged with (2R,3S)-(−)-2,3-diphenylmorpholine (0.239 g, 1 mmol), formic acid (2 mL) and formaldehyde (2 mL). The reaction mixture was then refluxed for 1.5 h and cooled to room temperature. Unreacted formic acid and formaldehyde were removed on rotary evaporator. The residue was treated with 10 mL water followed by 5 mL of 2N aqueous NaOH and extracted with DCM (3 x 10 mL). The combined extract was washed with water (10 mL) followed by brine, dried over Na₂SO₄ and concentrated under reduced pressure. The crude compound was treated with HCl in MeOH. The resulting hydrochloride was washed with ether, and basified using aqueous NaOH to obtain 11 as a white solid.

![Image of compound 11]
Yield : 0.232 g (92%)

TLC data : Rf (EtOAc): 0.46

Melting point : 54–56 °C

$[\alpha]_D^{25}$ : $-126.4$ (c 1.06, CHCl₃)

IR (CHCl₃) : 3018, 2860, 1492, 1450 cm⁻¹

$^1$H NMR (CDCl₃) : δ 2.16 (s, 3H), 2.47 (brd, $J = 11.28$ Hz, 1H), 2.95 (td, $J = 12.11$ Hz and 3.85 Hz, 1H), 3.9 (d, $J = 3.02$ Hz, 1H), 4.05 (td, $J = 11.55$ Hz and 3.30 Hz, 1H), 4.31 (brdd, $J = 11.28$ Hz and 3.3 Hz, 1H), 5.10 (d, $J = 3.02$ Hz, 1H), 7.0–7.37 (m, 10H, ArH)

$^{13}$C NMR (CDCl₃) : δ 139.4, 134.2, 131.2, 127.6, 127.2, 126.9, 126.5, 125.8, 81.2, 68.1, 67.6, 47.6, 43.1

Analysis for C₁₇H₁₉NO

Calculated (%) : C, 80.60; H, 7.56; N, 5.53

Found (%) : C, 80.20; H, 7.62; N, 5.12

Preparation of EtZnCl·Mg(Br)Cl (5)

In a 25 mL two neck round bottom flask, anhydrous zinc chloride (0.654 g, 4.8 mmol) was dissolved in anhydrous THF (3.4 mL). The solution was cooled to 0 °C, treated with EtMgBr (4.8 mmol, 6.15 mL of 0.78 M solution in THF) dropwise over 10 minutes. The resulting solution was stirred at 0 °C for 1 h. Ice bath was then removed and reaction mixture was stirred for 1 h at room temperature to provide 0.5 M solution (by iodometric titration) of 5.

Preparation of EtZnOAc·Mg(OAc)Br (6)

To the suspension of anhydrous Zn(OAc)₂ (2.75 g, 15 mmol) in anhydrous THF (13.3 mL) was added EtMgBr (15 mmol, 16.66 mL of 0.9 M solution in THF) dropwise at 0 °C over 10 minutes. Zinc acetate was dissolved within 10–15 min. and solution became clear. Resulting solution was stirred at 0 °C for 1 h and then at room temperature for 1 h to obtain 0.5 M solution (by iodometric titration) of 6.
Preparation of reagent (7) and (8)

To a solution of ZnCl$_2$ (or Zn(OAc)$_2$) (5 mmol) in 16.5 mL THF was added diethylzinc (5 mmol, 3.44 mL of 1.45 M solution in hexane) dropwise at room temperature over 5 minutes. The resulting clear solution was then stirred for 1 h to obtain 0.5 M solution (by iodometric titration) of 7 or 8.

General procedure for the preparation of magnesium-dialkoxides (21, 23 and 24)

In a 10 mL round bottom flask containing magnetic stir bar and rubber septum, the diol ((−)-12 or (−)-13 or (+)-14) (0.4 mmol) was dissolved in 2 mL anhydrous THF. The solution was cooled to 0 °C and treated with EtMgBr (0.8 mmol, 0.84 mL of 0.95 M solution in THF). After 15 minutes ice bath was removed and the mixture was stirred at room temperature for 15 minutes. The resulting solution of magnesium-dialkoxides (21, 23 and 24 respectively) was used as it is for alkylation step.

General procedure for the preparation of lithium-dialkoxides (20 and 22)

In a 10 mL round bottom flask containing magnetic stir bar and rubber septum, the diol ((−)-12 or (−)-13) (0.22 mmol) was dissolved in 1.5 mL anhydrous THF. The solution was cooled to 0 °C and treated with $n$-BuLi (0.44 mmol, 0.27 mL of 1.6 M solution in cyclohexane). After 15 minutes ice bath was removed and stirring was continued at room temperature for 15 minutes to obtain lithium-dialkoxides 20 and 22 respectively.

Magnesium-dialkoxide catalyzed addition of EtZnCl·Mg(Br)Cl (5) to benzaldehyde

The following procedure for the addition of EtZnCl·Mg(Br)Cl to benzaldehyde catalyzed by 23 is representative (entry 5 in table-5).

To a 50 mL two necked round bottom flask was added EtZnCl·Mg(Br)Cl (5) (4.8 mmol, 9.6 mL of 0.5 M solution in THF) followed by 1,4-dioxane (0.41 mL, 4.8 mmol) at 0 °C. After 15 minutes, the catalyst 23 (0.4 mmol, solution in THF) was added. The resulting heterogeneous reaction mixture was stirred for next 10 minutes and was treated with benzaldehyde (0.4 mL, 4 mmol). After 8 h at 0 °C, the mixture was cautiously quenched with MeOH (1 mL), diluted with EtOAc (20 mL), washed
with saturated NH₄Cl solution and dried over anhydrous Na₂SO₄. Evaporation of the solvent followed by Kugelrohr distillation (150 °C, 0 torr) provided the product contaminated with benzyl alcohol and unreacted benzaldehyde. The crude compound was then purified by flash chromatography on silica gel (230-400 mesh) using ethyl acetate: petroleum ether as the eluent to obtain 25 as an oil.

Yield : 0.348 g (64%)

$\left[\alpha\right]_{D}^{25}$ : 0

ee : 0

$^1$H NMR (CDCl₃) : 0.91 (t, $J = 7.45$ Hz, 3H), 1.68–1.90 (m, 3H, CH₂ and OH), 4.59 (t, $J = 6.57$ Hz, 1H), 7.22–7.37 (m, 5 H, ArH).

Addition of EtZnOAc·Mg(OAc)Br (6) to benzaldehyde catalyzed by magnesium-dialkoxide (23)

The following procedure for the addition of EtZnOAc·Mg(OAc)Br to benzaldehyde catalyzed by 23 is representative (entry 7 in table-6). The catalyst 23 was prepared in MTBE by following the same procedure as described for THF.

To the catalyst 23 (0.2 mmol) in MTBE was added EtZnOAc·Mg(OAc)Br (2.4 mmol, 0.5 M solution in MTBE) at 0 °C under argon atmosphere. The heterogeneous reaction mixture was stirred vigorously for next 5 minutes and treated with benzaldehyde (0.2 mL, 2 mmol). After 8 h at 0 °C the reaction was cautiously quenched with MeOH (1 mL). Usual work-up and purification provided desired product (S)-25.

Yield : 0.12 g (44%)

$\left[\alpha\right]_{D}^{25}$ : –25.5 (c 5.0, CHCl₃) [lit.⁴⁹a –46.7 (c 5.1, CHCl₃)]

ee : 50% (by HPLC)
**HPLC**

Chiralcel OD-H column, \(i\)-PrOH: \(n\)-Hexane (2:98), flow rate 0.5 mL/min., detection at 254 nm., \(t_R = 24.375\) min, \(t_R = 31.333\) min.

**One pot procedure for enantioselective addition of RZnOAc·Mg(OAc)Br to benzaldehyde**

The following procedure for the addition of RZnOAc·Mg(OAc)Br to benzaldehyde is representative (Table-7).

In a 50 mL two neck round bottom flask anhydrous Zn(OAc)\(_2\) (1.1 g, 6 mmol) and \((-\)-)\(-13\) (0.186 g, 0.4 mmol) were suspended in anhydrous THF (5 mL). The mixture was cooled to 0 °C and treated dropwise with RMgBr (6.8 mmol, 6.8 mL of 1 M solution in THF) under argon atmosphere. The reaction mixture was stirred for next 1 h resulting in a clear solution. Benzaldehyde (0.4 mL, 4 mmol) was then added and the mixture was stirred for the time indicated in table-7. The reaction was cautiously quenched with MeOH (1 mL). Usual work-up and purification provided pure alcohol.

**\((S)\)-1-phenylpropan-1-ol (25)\**

<table>
<thead>
<tr>
<th>Yield</th>
<th>0.163 g (30%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>([\alpha]_{D}^{25})</td>
<td>(-19.3) ((c) 5.18, CHCl(_3)) [lit.(^{49a}) (-46.7) ((c) 5.1, CHCl(_3))]</td>
</tr>
<tr>
<td>ee</td>
<td>40% (by chiral GC)</td>
</tr>
</tbody>
</table>

**Chiral GC**

CP-Cyclodextrin-B-2,3,6-M-19 capillary column, at 100 °C (1 min.), 20 deg./min., 110 °C (40 min.), 20 deg/min, 230 deg (5 min.) \(t_R = 33.261\) min, \(t_R = 34.370\) min.

**\((S)\)-1-phenylpentan-1-ol (28)\**
Yield: 0.11 g (17%)

$[\alpha]_D^{26}$: $-5.0$ (c 3.2, C$_6$H$_6$) [lit.$^{49b}$ $-39.9$ (c 3.08, C$_6$H$_6$)]

ee: 13% (by HPLC)

HPLC: Chiralcel OD-H column, $i$-PrOH:$n$-Hexane (10:90), flow rate 0.5 mL/min., detection at 254 nm., $t_R = 12.350$ min, $t_R = 13.200$ min.

$^1$H NMR (CDCl$_3$): 0.88 (t, $J = 6.69$ Hz, 3H), 1.16−1.45 (m, 4H), 1.65−1.85 (m, 3H, CH$_2$ and OH), 4.61−4.71 (m, 1H), 7.22−7.40 (m, 5 H, ArH).

(S)-3-methyl-1-phenylbutan-1-ol (29)

Yield: 0.032 g (5%)

$[\alpha]_D^{28}$: $-8.33$ (c 3.2, n-heptane) [lit.$^{49c}$ $-32.3$ (c 16.7, n-heptane)]

ee: 16% (by chiral GC)

Chiral GC: C$_r$-Cyclodextrin-B-2,3,6-M-19 capillary column, at 122 °C (50 min.), 20 deg./min., 230 °C (1 min.), $t_R = 36.519$ min., $t_R = 37.742$ min.

$^1$H NMR (CDCl$_3$): $\delta$ 0.95 (d, $J = 6.06$ Hz, 6H), 1.44−1.56 (m, 1H), 1.65−1.85 (m, 3H, CH$_2$ and OH), 4.68−4.81 (m, 1H), 7.27−7.38 (m, 5 H, ArH).

Addition of diethylzinc to benzaldehyde catalyzed by 23 (as described in eq 9)

To a solution of diethylzinc (3.6 mmol, 2.48 mL of 1.45 M solution in hexane) was added 0.3 mmol of catalyst 23 (solution in THF) followed by benzaldehyde (0.3 mL, 3 mmol) at 0 °C. After 2 h at 0 °C TLC indicated...
benzaldehyde was consumed completely. Thereafter the reaction mixture was quenched with 1 mL MeOH. Usual work-up and purification provided desired product (S)-25.

Yield : 0.31 g (76%)

$[\alpha]^{25}_D$ : $-6.66$ (c 5.4, CHCl$_3$) [lit.$^{49a} - 46.7$ (c 5.1, CHCl$_3$)]

ee : 14%

**Addition of ethylzinc reagents prepared from ZnX$_2$ and n EtMgBr (entries 3–6 in table-8)**

The following procedure for the addition of ethylzinc reagent (prepared from two equivalent of EtMgBr and ZnX$_2$) to benzaldehyde is representative.

A solution of ZnCl$_2$ (or Zn(OAc)$_2$) (1 mmol) in 1 mL THF was cooled to 0 °C. EtMgBr (2 mmol, 2.44 mL of 0.82 M solution in THF) was then added dropwise over 5 minutes. The reaction mixture was then stirred at mentioned temperature and time indicated in table-8 (entries 3–6). The mixture was then treated with PhCHO (0.19 mL, 1.9 mmol) at 0 °C. After 1 h the reaction mixture was analyzed by GC.

**Addition of triethylzincates to benzaldehyde (entries 7 and 8 in table-8)**

A solution of ZnCl$_2$ (or Zn(OAc)$_2$) (2 mmol) in 2 mL THF was cooled to 0 °C and treated with EtMgBr (6 mmol, 6 mL of 1 M solution in THF) dropwise over 10 minutes. The reaction mixture was stirred at 0 °C for 30 minutes. PhCHO (0.58 mL, 5.8 mmol) was then added and after 1 h the reaction mixture was analyzed by GC.

**General procedure for the preparation of zinc-alkoxides (30a-c)**

To a 50 mL two neck round bottom flask with a stir bar and a reflux condenser was added the diol ((−)-13 or (−)-12 or (+)-14) (3 mmol) in 5 mL anhydrous toluene. The mixture was heated at 80 °C to dissolve the diol completely and diethylzinc (3 mmol, 2.06 mL of 1.45 M solution in hexane) was added dropwise at the same temperature. Immediate evolution of ethane was observed. The reaction mixture was stirred at 80 °C for 0.5 h. A viscous solution of zinc alkoxide (30a or 30b or 30c respectively) was obtained, which was utilized as such for alkylation step.
Addition of chiral-zincate catalyzed by zinc-alkoxide (30a-c)

The following procedure for the addition of chiral-zincate to benzaldehyde using zinc alkoxide 30a is representative (Condition C, entry 3 in table-9).

The suspension of zinc-alkoxide 30a (3 mmol) was cooled to 0 °C and treated with EtMgBr (3 mmol, 3 mL of 1 M solution in THF) and benzaldehyde (3 mmol, 0.3 mL in 2 mL toluene) simultaneously over 10 minutes. As addition proceeds, zinc-alkoxide dissolves completely and solution becomes clear. Reaction mixture was stirred for 2 h at 0 °C and cautiously quenched by 1 mL MeOH. Usual work-up and purification provided the desired product (S)-25.

<table>
<thead>
<tr>
<th>Yield</th>
<th>: 0.24 g (59%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$[\alpha]_D^{25}$</td>
<td>: $-23.15$ (c 4.96, CHCl₃) [lit.$^{49a}$ – 46.7 (c 5.1, CHCl₃)]</td>
</tr>
<tr>
<td>ee</td>
<td>: 50%</td>
</tr>
</tbody>
</table>
References


48. Preparation of (2R, 3S)-(−)-2,3-diphenylmorpholine is described in Chapter-3, Section-A.

NMR Spectra and Chiral HPLC / GC Chromatogram
$^1$H-NMR of compound 3 (CDCl$_3$, 200MHz)

$^1$H-NMR of compound 4 (CDCl$_3$, 200MHz)
$^1$H-NMR of compound 11 (CDCl$_3$, 200MHz)

$^{13}$C-NMR of compound 11 (CDCl$_3$, 50.32MHz)
DEPT NMR of compound 11

\[
\begin{array}{c}
\text{Ph} \\
\text{N} \\
\text{Me} \\
\text{OH}
\end{array}
\]

1H-NMR of compound 25 (CDCl₃, 200MHz)

\[
\begin{array}{c}
\text{Ph} \\
\text{OH}
\end{array}
\]
$^1$H-NMR of compound 28 (CDCl$_3$, 200MHz)

$^1$H-NMR of compound 29 (CDCl$_3$, 200MHz)
Determination of enantiomeric excess for RZnOAc-Mg(OAc)Br addition product

\[
\text{(±)-25}
\]

50% ee, Chiralcel OD-H column; \(i\)-PrOH:\(n\)-Hexane (2:98); 0.5 mL/min.; 254 nm. Retention time: \(t_R = 24.375\) min, \(t_R = 31.333\) min.
13% ee, Chiralcel OD-H column; \(i\)-PrOH:\(n\)-Hexane (10:90); 0.5 mL/min.; 254 nm. Retention time: \(t_R = 12.35\) min, \(t_R = 13.20\) min.
16% ee; GC analysis (CP-Cyclodextrin-B-2,3,6-M-19 capillary column), at 122 °C (50 min.), 20 deg./min., 230 °C (1 min.), Retention time: $t_R = 36.519$ min., $t_R = 37.742$ min.