Recent Reviews:

Background:

- The reactivity of dialkylzinc reagents towards ketones and aldehydes is low; the rate of addition of Et₂Zn to benzaldehyde is negligible at room temperature.

- The addition of a catalytic amount of TMEDA will promote the addition of diethylzinc at room temperature to 4-benzoylbenzaldehyde in 93% yield.

\[
\begin{align*}
\text{Bz} & \quad + \quad \text{Et}_2\text{Zn} \quad \xrightarrow{5 \text{ mol } \% \text{ TMEDA}} \quad \text{BzOH} \\
& \text{toluene, } 23^\circ\text{C, } 14 \text{ h} \\
& 93\% 
\end{align*}
\]


- X-Ray structures of dimethylzinc and its adduct with 1,3,5-trimethylhexahydro-1,3,5-triazine show that upon bis-complexation, dimethylzinc shifts from a linear geometry to a tetrahedral geometry and that the carbon-zinc bond length increases from 1.95 Å to 1.98 Å. This is proposed to increase the nucleophilicity of the methyl groups, accelerating addition to carbonyl compounds.

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{Zn} \quad \text{CH}_3 \\
& \quad 180^\circ \\
& \quad 1.95 \text{ Å} \\
\text{Zn} & \quad \text{C} \\
& \quad 1.98 \text{ Å} \\
\end{align*}
\]


In 1984, Oguni and Omi found that a small amount of (S)-leucinol catalyzed the enantioselective addition (49% ee) of diethylzinc to benzaldehyde.

\[
\begin{align*}
\text{PhCHO} & \quad + \quad \text{(C}_2\text{H}_5)_2\text{Zn} \\
& \quad \xrightarrow{2 \text{ mol } \% \text{ (–)-DAIB}} \quad \text{PhCH}_3\text{OH} \\
& \quad \text{toluene, } 20^\circ\text{C, } 43 \text{ h} \\
& 96\% \text{ yield, } 49\% \text{ ee} 
\end{align*}
\]


- In 1986, Noyori et al. published the first highly selective procedure for the asymmetric addition of diethyl- and dimethylzinc to aldehydes employing (–)-3-exo-(dimethylamino)isoborneol (DAIB) as a chiral catalyst.

\[
\begin{align*}
\text{R} & \quad \text{H} \\
& \quad + \quad \text{R’}_2\text{Zn} \\
& \quad \xrightarrow{2 \text{ mol } \% \text{ (–)-DAIB}} \quad \text{R’R’} \\
& \quad \text{toluene, } 0^\circ\text{C} \\
\end{align*}
\]


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This observation is consistent with a mechanistic proposal involving two Zn atoms per aldehyde:

\[
\text{aldehyde : Et}_2\text{Zn : DAIB} \quad \text{% yield} \quad \text{% ee}
\]

\[
\begin{array}{ccc}
1 : 1 : 0 & 0 & - \\
1 : 1 : 1 & 1 & 0 \\
50 : 50 : 1 & 97 & 98
\end{array}
\]


• This observation is consistent with a mechanistic proposal involving two Zn atoms per aldehyde:

- A non-linear dependence of product ee on catalyst ee was observed. Heterochiral dimerization to form an unreactive species was invoked to account for in situ amplification of product ee:

- The stoichiometry of aldehyde, diethylzinc, and DAIB ligand determines reactivity: alkylation occurs only when the ratio of Et\(_2\)Zn : DAIB is greater than 1:


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Preparation of Organozinc Reagents:

- **Metallic Zinc Insertion:**
  - One of the early methods involves treatment of an alkyl iodide or bromide with zinc dust or an activated form of Zn, such as zinc-copper couple (Zn(Cu)). The method requires rather harsh conditions and is limited to low molecular weight dialkylzinc species due to the need to distill the products while avoiding competitive Wurtz coupling:
    
    \[
    \text{EtI} + \text{EtBr} \xrightarrow{\text{Zn-Cu neat, reflux}} \text{[EtZnI]} + \text{[EtZnBr]}
    \]
    
    Schlenk Equilibrium
    
    \[
    \text{EtZn} + \text{BrZn} \xrightarrow{200 \degree C, \text{distillation} <30 \text{mmHg}} \text{Et}_2\text{Zn}
    \]

- Methanesulfonic acid can be used to activate zinc metal:
  
  \[
  \text{Et}_2\text{O}_2\text{CBr} \xrightarrow{1.5 \text{M MgBr (5 mol%) in THF, 70\degree C}} \text{[Et}_2\text{O}_2\text{CZnBr]}
  \]
  
  \[
  \begin{align*}
  &\xrightarrow{1.0 \text{M ZnCl}_2 \text{in Et}_2\text{O}} 10.0 \text{kg} \text{Et}_2\text{O}_2\text{CBr}
  
  &\xrightarrow{2. \text{N HCl, 72\%}} 10.6 \text{kg} \text{Et}_2\text{O}_2\text{CF}
  \end{align*}
  \]

- **Transmetallation with a Zinc Salt:**
  - Substrates that are less readily prepared by direct reduction can be prepared by treatment of a Zinc(II) halide with two equivalents of alkyllithium or alkylmagnesium halide:
    
    \[
    \text{N}_2\text{N}_2\text{H}_2\text{H}_2\text{Cl}_2 \xrightarrow{1. n-BuLi, THF, –60 \degree C} \text{[N}_2\text{N}_2\text{H}_2\text{Li]} + \text{ZnCl}_2
    \]
    
    Unstable above –50\degree C
    
    \[
    \begin{align*}
    &\xrightarrow{\text{stable, ZnCl}_2 \text{ (5 mol%) in } \text{H}_2\text{O, 60\degree C}} \text{N}_2\text{N}_2\text{H}_2\text{Br}
    
    &\xrightarrow{\text{Br, 90\% in hexanes}} \text{[N}_2\text{N}_2\text{H}_2\text{Br]}
    \end{align*}
    \]

In many cases, lithium or magnesium halide byproducts must be removed to avoid salt complexation with chiral additives in subsequent enantioselective processes.

1.4-Dioxane forms insoluble complexes with magnesium halides and allows the synthesis of diorganozinc reagents that were not commercially available to subsequently be used in asymmetric additions to carbonyl compounds:

- \[
  \text{ZnCl}_2 \text{ (1.0 M in Et}_2\text{O) + MgBr (1.0 M in Et}_2\text{O) \rightarrow filtration} \] 


- \[
  \text{Zn(OCH}_3\text{)}_2 \text{ can also be used. The byproduct, CH}_3\text{OMgCl, precipitates from the reaction mixture and salt-free ethereal solutions of diorganozinc can be obtained after filtration or centrifugation:}
  \]


- \[
  \text{N,N,N,N-} \text{tetraethylethylenediamine (TEEDA) can be used to scavenge salts and the resulting in situ formed zinc reagents function in catalytic asymmetric addition reactions to aldehydes:}
  \]


Iodine-zinc exchange reactions have been used to prepare dialkylzinc species containing esters, nitriles, chlorides, sulfonamides, and boronic acids. CuI or UV light were found to accelerate the reaction. Removal of excess Et₂Zn and EtI was necessary to drive the reaction:


Substrate decomposition occurred in the absence of ZnEt₂.

Aryl and alkenyl iodides can undergo halogen-zinc exchange with i-Pr₂Zn. Li(acac)₂ activates the intermediate mixed diorganozinc as an ate complex and promotes the second exchange:


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Alkylzinc Addition to Aldehydes:

- A variety of chiral catalysts and ligands have been developed that promote the addition of dialkylzinc reagents to give enantiomERICALLY enriched secondary alcohols. Only a few representative ones are shown here:

1. ![Structure](image1.png)
2. ![Structure](image2.png)
3. ![Structure](image3.png)
4. ![Structure](image4.png)
5. ![Structure](image5.png)

- Ligand 1 extends the scope of the initial DAIB reaction to include aliphatic aldehydes:

\[
\text{PhCH}_3 + \text{Et}_2\text{Zn} \rightarrow \text{PhCH}_2\text{Et}
\]


- Chemoselective addition to aldehydes can be achieved in the presence of ketones:

\[
\text{Ph}_{\text{OCH}} + \text{n-BuLi} \rightarrow \text{PhCH}
\]


- Using 5 as a chiral additive, either enantiomer of the product can be obtained by changing the reaction conditions:

\[
\text{PhOH} + \text{Et}_2\text{Zn} \rightarrow \text{PhOH}
\]


- Unsymmetrical dialkyl zinc containing a trimethylsilylmethyl group as a non-transferable group can be prepared to avoid losing one equivalent of valuable alkyl zinc precursor:

\[
\text{Cl(CH}_2)_4\text{Zn} + \text{TMSCH}_2\text{Zn} \rightarrow \text{Cl(CH}_2)_4\text{Zn}(\text{CH}_2\text{TMS})
\]

**Alkenylzinc Addition to Aldehydes:**

- The first example of catalytic asymmetric vinylzinc additions to aldehydes was reported using a chiral diaminoalcohol ligand:


- Mixed organozinc reagents, formed via transmetallation of organoboron or organozirconium with dialkylzinc, can be used to form enantiomerically enriched allylic alcohols in the presence of a chiral amino alcohol catalyst:


**Dialkylzinc Reagents in Synthesis:**

- **Bu₂Cu(CN)Li₂**
  - THF, –60 → 0 ºC
  - 95%


- **(n-C₅H₁₁)₂Zn Ti(Oi-Pr)₄** (6 20 mol%)
  - toluene
  - –78 → –20 ºC
  - 88% yield, >98% ee

  (-)-Gloeosporone


- **(Br(CH₂)₅)₂Zn Ti(Oi-Pr)₄** (6 8 mol%)
  - toluene
  - –60 → –20 ºC
  - 69%, 92% ee

  Ginnol


- **(Cy)₂BH·S(CH₃)₂**
  - hexanes
  - –20 → 23 ºC
  - 60%, 82% de


- **Et₂Zn**
  - (–)-DAIB (1 mol%)
  - 60%, 82% de


- **Bu₂Zn**
  - toluene
  - –30 ºC
  - 83%, 97% ee

* Hydride migration from a boron ate complex provides access to enantiomerically enriched Z-allylic alcohols:

\[
\text{Cl} = \text{OTBDPS} \quad \rightarrow \quad \text{Cy/B = OTBDPS} \\
\text{Et}_2\text{Zn} \quad \text{TEEDA} \\
\text{MTBE} \quad -20 \rightarrow 23^\circ C \\
\text{t-BuLi} \quad -78 \rightarrow 23^\circ C
\]


* Tri-substituted Z-allylic alcohol can also be prepared:

\[
\text{Br} = \text{n-Bu} \\
\text{t-BuLi} \quad \text{Et}_2\text{O}, -78^\circ C \\
\text{ZnBr}_2, \text{Et}_2\text{O}, 0^\circ C \\
\text{TBAF}, \text{THF} \quad 0 \rightarrow 23^\circ C
\]


* Direct transmetallations from vinyl iodides provide alkenylzinc reagents not accessible through hydroboration or hydrozirconation:

\[
\text{H}_3\text{CO} \quad \text{I} \\
\text{Li(acac)}_2 \quad \text{(26 mol%)} \\
\text{NMP}, 0^\circ C
\]


Alkenylzinc Reagents in Synthesis:

\[
\text{TMS} = \text{CH}_3\text{I} \\
\text{Et}_2\text{Zn} \\
\text{Li(acac)}_2 \quad \text{(2.5 equiv)} \\
\text{Ph} \quad \text{OLiPh} \\
\text{TIPS} = \text{CH}_3\text{I} \\
\text{TMS} \quad \text{TIPS}
\]

Unlike dialkylzinc additions, diphenylzinc additions to aldehydes take place smoothly even without a catalyst. This background reaction has made it more difficult to develop enantioselective variants.

Arylzinc Addition to Aldehydes:


* Widely available aryl boronic acids and boroxines can be directly transformed into arylzinc reagents and undergo enantioselective arylation of aldehydes with excellent selectivity:

Widely available arylboronic acids and boroxines can be directly transformed into arylzinc reagents and undergo enantioselective arylation of aldehydes with excellent selectivity:

Mixed alkylalkynylzinc reagents can be prepared directly from terminal acetylenes and have been shown to undergo catalyzed 1,2-additions to aldehydes with good enantioselectivities.

R1 \[\text{Et}_2\text{Zn} \rightarrow \text{R}_1\text{ZnEt}\]

\[\text{R}_2\text{H} \rightarrow \text{R}_2\text{Zn} \rightarrow \text{R}_2\text{ZnEt}\]

The low yields in these reactions was attributed in part to competitive addition of ethyl groups to the aldehydes.
In 2000, Carreira et al. published an in situ preparation of alkylnylzinc reagents and their addition to aldehydes with excellent enantioselectivities and yields.

The reactions can be carried out without rigorous exclusion of oxygen or moisture using reagent-grade toluene (84–1000 ppm H₂O).

All reagents are stoichiometric or superstoichiometric.


It was shown that by raising the reaction temperature to 60 °C, the in situ zinc acetylide formation and addition reaction can be made catalytic in both zinc and chiral ligand.

The system is less effective for aromatic aldehydes because of a competitive Cannizzaro reaction.

A mannose-derived auxiliary was employed to promote diastereoselective alkynylzinc additions to nitrones. The nitrone auxiliary was prepared from mannose, acetone and N-hydroxylamine.

Hydroxylamines are readily reduced to free amines:

\[
\text{RCHO} + \text{Zn(OH)}_2 \rightarrow \text{RCH(OH)N}^+_{\text{C}}\text{X}\text{C}^* + \text{ZnCl}_2
\]

The oxazepanedione shown below, prepared in 3 steps from ephedrine and dimethyl malonate, undergoes condensation with aldehydes mediated by TiCl₄. Conjugate addition of zinc alkynylides followed by hydrolysis and decarboxylation give β-alkynyl acids in good yields and selectivities:

[Chem 115]


The use of ZnCl₂ homogenizes the reaction mixture and obviates the need for N,N-dimethylethanolamine:

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
<th>Overall yield (%)</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃</td>
<td>Ph</td>
<td>88</td>
<td>95:5</td>
</tr>
<tr>
<td>i-Pr</td>
<td>C(OH)Me₂</td>
<td>98</td>
<td>96:4</td>
</tr>
<tr>
<td>i-Bu</td>
<td>Ph</td>
<td>91</td>
<td>97:3</td>
</tr>
<tr>
<td>Ph</td>
<td>SiMe₃</td>
<td>88</td>
<td>95:5</td>
</tr>
</tbody>
</table>

[Organosilicon Reagents: Asymmetric Additions to Carbonyl Compounds]


Lowering the loading of Zn(OTf)₂ to 20 mol% resulted in lower selectivites and isolated yields.


A highly effective two-catalyst system was reported for the addition of zinc acetylide to aromatic aldehydes. The stereochemistry of BINOL determines the stereochemistry of the products, while the second ligand improves catalytic activity and enantioselectivity:


Alkynylzinc Reagents in Synthesis:

\[
\text{Ph-} = \text{H} + \text{H} \quad \text{CH}_3 \quad \text{OTBS} \quad \text{CO}_2\text{CH}_3 \quad \text{(-)-N-Me-ephe}
\]
\[
\text{Zn}(\text{OTf})_2, \text{Et}_3\text{N} \\
\text{toluene, } 23 ^\circ \text{C} \\
90\%, \text{dr} = 6 : 1
\]

\[
\text{BOMO}_n \quad \text{O} \quad \text{H} \quad \text{CH}\text{(OMe)}_2 \\
\text{(CH}_3\text{O)}_2\text{HC} \quad \text{10 steps}
\]

\[
\text{TBAF, DMF, THF} \\
\text{–78} \rightarrow \text{5} ^\circ \text{C, } 99\% \\
\text{single diastereomer}
\]

\[
\text{BOMO}_n \quad \text{O} \quad \text{Me} \quad \text{O} \\
\text{(CH}_3\text{O)}_2\text{H} \quad \text{7 steps}
\]

\[
\text{(-)-Salvinorin A}
\]

\[
\text{Me} \quad \text{OH} \\
\text{AcO}_n
\]

\[
\text{H}_3\text{CO}_2\text{C} \\
\text{H}_3\text{CO}_2\text{C}
\]

\[
\text{(-)-Tulearin C}
\]

Asymmetric Addition to Ketones:

- Ketones are less reactive than aldehydes and often give 1,2-addition products in lower yields because of competitive enolization or reduction of the carbonyl group.

- Using Ti(Oi-Pr)$_4$ as a Lewis acid, ligand 9 catalyzes the formation of tertiary alcohols with high selectivity:

\[
\text{Et}_2\text{Zn, Ti(Oi-Pr)$_4$}
\]

\[
\text{toluene, 23 °C}
\]


Salen ligand 10 and Schiff base ligand 11 were found to promote efficient addition of zinc acetylides to ketones:

\[
\begin{align*}
\text{Et}_2\text{Zn, Ti(Oi-Pr)$_4$} \\
\text{hexanes, 23 °C}
\end{align*}
\]

78%, 99% ee

\[
\begin{align*}
\text{Et}_2\text{Zn, Ti(Oi-Pr)$_4$} \\
\text{hexanes, –18 °C}
\end{align*}
\]

83%, 94% ee

- This method is only effective for aromatic ketones.


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