Catalytic Enantioselective Reformatsky Reactions

A Catalytic, Me₂Zn-Mediated, Enantioselective Reformatsky Reaction With Ketones


Catalytic Enantioselective Reformatsky Reaction with Aldehydes


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The Reformatsky Reaction

Discovered in 1887:

\[ \text{XZn} \stackrel{\text{Zn}}{\longrightarrow} \text{R}^1\text{OH} \]

\[ \alpha\text{-halo carbonyl} \]

Asymmetric Variants

\[ \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Ph} \]

1) Ni(acac)$_2$ (5 mol %) Et$_2$Zn (1.5 equiv) CH$_2$Cl$_2$, 0 °C

2) acetophenone (1equiv) –30 °C

84% yield


\[ \text{(S)-(+)2-phenylglycinol} \]

\[ \text{Ph} \quad \text{HN} \quad \text{OMEM} \]

\[ \text{Cl} \quad \text{Br} \quad \text{Ph} \quad \text{HN} \quad \text{OMEM} \]

\[ \text{Cl} \quad \text{Br} \quad \text{HN} \quad \text{OMEM} \quad \text{CO$_2$fBu} \]

\[ \text{H$_2$N} \quad \text{HN} \quad \text{OMEM} \quad \text{CO$_2$fBu} \]

>99% ee

Catalytic Asymmetric Reformatsky Reaction with Ketones

Previous Work:

\[
\text{Ar-}NH_2 + RCHO + \text{Br} \text{C} = \text{O} \quad \xrightarrow{\text{Me}_2\text{Zn (4 equiv) \ NiCl}_2(\text{PPh}_3)_2 (8 \text{ mol } \%)} \quad \text{epheedrine ligand (1.6 equiv) \ toluene}} \quad \text{up to 92\% ee}
\]


- Variety of ligands screened, only the salen ligand showed any reactivity
- ClMn(salen) determined to be optimal catalyst
- Size of nucleophile is important for enantioselectivity.

\[X = \text{OEt}, 95\% \text{ conversion, } 63\% \text{ ee}\]
\[X = \text{OPh}, 50\% \text{ conversion, } 16\% \text{ ee}\]
\[X = \text{OtBu}, 90\% \text{ conversion, racemic}\]
Additive and Scope of Enantioselective Reformatsky

ketone + \( \text{Me}_2\text{Zn} \) (2 equiv)\[ \text{ClMn(salen)} \) (20 mol %) \( \rightarrow \)
\( \text{4-phenylpyridine N-oxide} \) (25 mol %) \( \rightarrow \)
\( \text{Me}_2\text{Zn (2 equiv)} \) with \( \text{ClMn(salen)} \) (20 mol %) in the presence of 4-phenylpyridine N-oxide (25 mol %) yields the desired product with high enantiomeric purity.

- N-oxides have been shown to increase conversion and eliminate side products in the Mn(salen)-catalyzed epoxidation of olefins.
- Displaces chlorine to yield a more reactive complex


70% yield, 96% ee
45% yield, 86% ee
55% yield, 85% ee
70% yield, 57% ee
77% yield, 23% ee
40% yield, 21% ee
78% yield, 86% ee
A Leading Result

Can a catalytic, asymmetric Reformatsky reaction be applied to aldehydes?
**Enantioselective Reformatsky Reaction with Aldehydes**

PhCHO + I(2 equiv) + Me₂Zn (2 equiv) → Me₂Zn (2 equiv) BINOL cat. (10 mol %) → Et₂O, 25 °C, 24h

Increased conversion:

- More reactive Zn (Et₂Zn, iPr₂Zn) gave lower ee.
- NiCl₂(PPh₃)₂ and RhCl(PPh₃)₃ led to non-reproducible results.
- Exposure of Me₂Zn to air to form alkyl peroxides (RZnOOR)

<table>
<thead>
<tr>
<th>mol % cat. (SiX₃ = TBS)</th>
<th>ee (%)</th>
<th>Under atmosphere of air, there is evidence of a significant background rate.</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>70</td>
<td>Slow addition of the aldehyde component (over 10 min.) can limit the rate and provide the optimal selectivity.</td>
</tr>
<tr>
<td>30</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>74</td>
<td></td>
</tr>
</tbody>
</table>

Proposed Catalytic Cycle

- Combination of dialkylzinc and oxygen to generate alkyl radicals is well preceded.

- Diethyl succinate observed (by GC) in the case of slow addition of benzaldehyde.
Scope of Enantioselective Reformatsky

\[
\begin{align*}
&\text{RCHO} + \text{I-2-iodoacetate (2 equiv)} \\
&\xrightarrow{\text{Me}_2\text{Zn (8 equiv)}} \\
&\text{Et}_2\text{O, 25 °C, 1h}} \\
&\text{air} \\
\end{align*}
\]

72% yield, 84% ee

72% yield, 76% ee

75% yield, 54% ee

72% yield, 84% ee

72% yield, 76% ee

76% yield, 72% ee

56% yield, 7% ee

87% yield, 30% ee

70% yield, 50% ee

substituted benzaldehydes gave similar results
**BINOL-Catalyzed Reformatsky Reaction with Ketones**

\[
\text{Me}_2\text{Zn (8 equiv)} \quad \text{cat. } (\text{SiX}_3 = \text{TMS}) \quad (20 \text{ mol } \%) \\
\text{Et}_2\text{O, 25 °C, 1h} \\
\rightarrow \\
\begin{array}{c}
\text{R}^1\text{OH} \\
\text{R}^2
\end{array}
\]

- 85% yield, 80% ee
- 70% yield, 96% ee
- 65% yield, 90% ee
- 45% yield, 86% ee
- 80% yield, 85% ee
- 55% yield, 85% ee

- 89% yield, 50% ee
- 54% yield, 49% ee
- 72% yield, 48% ee
- 30% yield, 75% ee
- 40% yield, 82% ee

*ee and yields in blue from Cozzi, *ACIE*, 2006 (with ClMn(salen) catalyst)*