

Catalytic Enantioselective Reformatsky Reactions

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

Cozzi, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2951-2954.

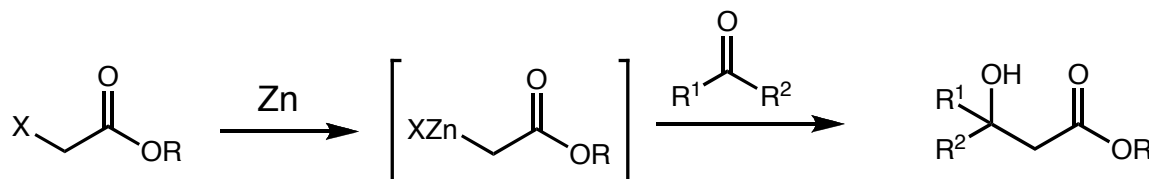
Catalytic Enantioselective Reformatsky Reaction with Aldehydes

Fernández-Ibáñez, M. A.; Maciá, B.; Minnaard, A. J.; Feringa, B. L.
Angew. Chem., Int. Ed. **2008**, *47*, 1317-1319.

Brooks Maki
Scheidt Group Meeting
April 15, 2008

The Reformatsky Reaction

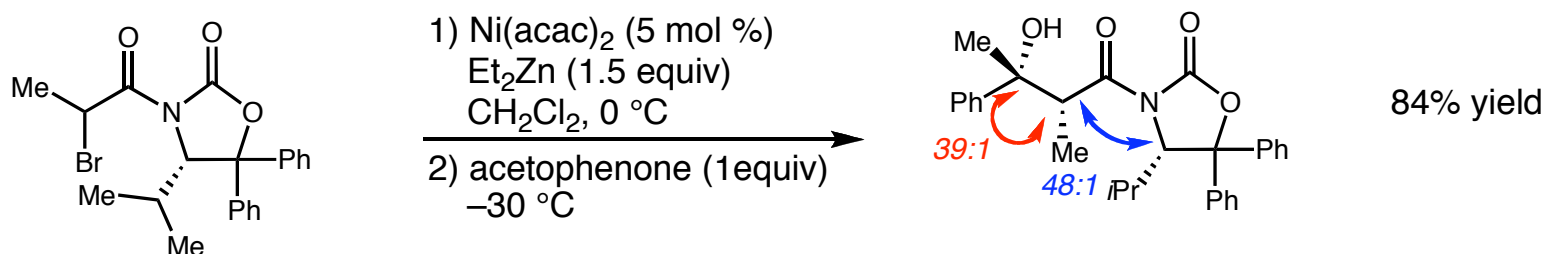
Discovered in 1887:



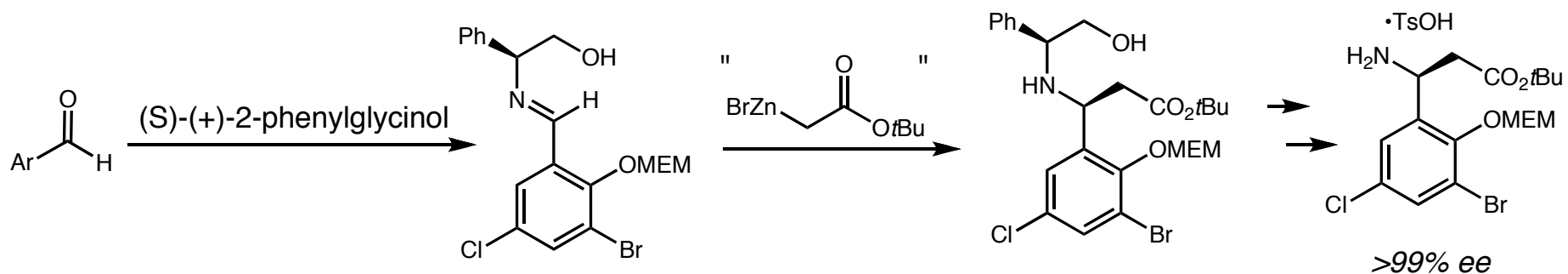
α -halo carbonyl

- Aldol/Enolate equivalent
- Excellent functional group compatibility
- Can be done with R_2Zn (with another metal such as Rh or Ni)

Asymmetric Variants



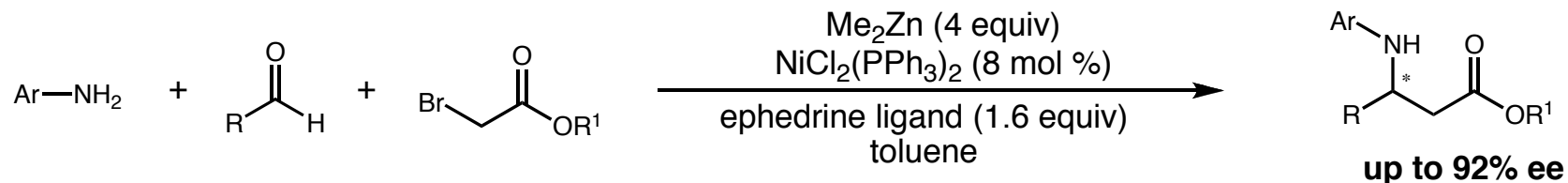
Yang, T.-K.; et al. *Tetrahedron: Asymmetry* **2007**, *18*, 949-962.



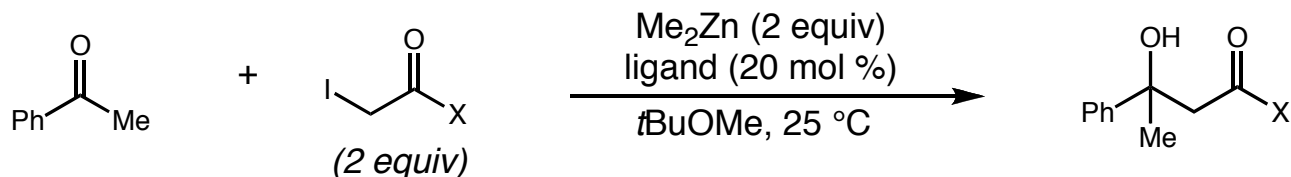
Clark, J. D.; et al. *Org. Proc. Res. Dev.* **2004**, *8*, 51-61.

Catalytic Asymmetric Reformatsky Reaction with Ketones

Previous Work:

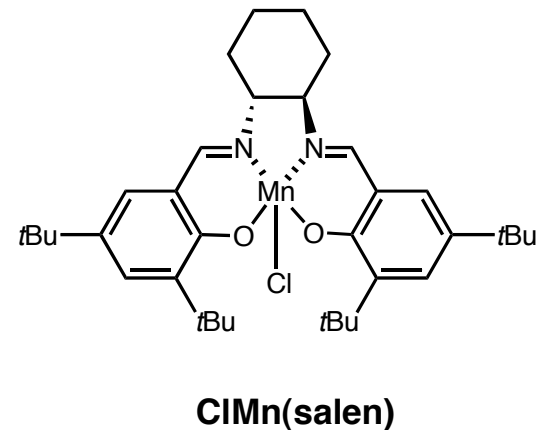


Cozzi, et al. *Angew. Chem. Int. Ed.* **2005**, *44*, 3600-3603.

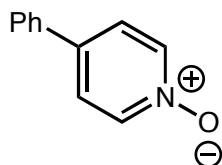
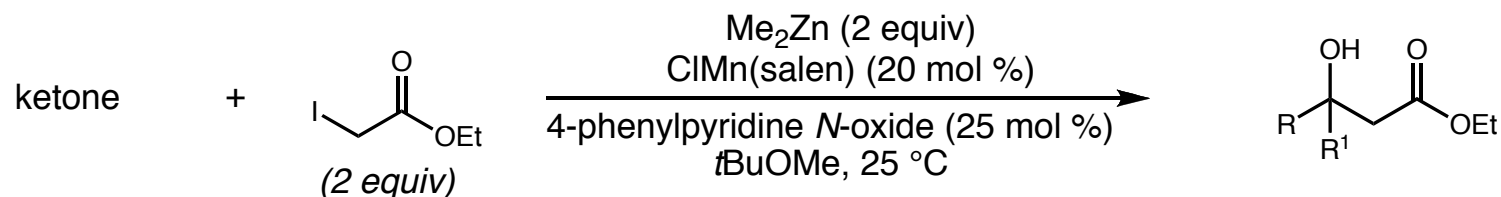


- Variety of ligands screened, only the salen ligand showed any reactivity
- $\text{ClMn}(\text{salen})$ determined to be optimal catalyst
- Size of nucleophile is important for enantioselectivity.

X = OEt, 95% conversion, 63% ee
X = OPh, 50% conversion, 16% ee
X = OtBu, 90% conversion, racemic



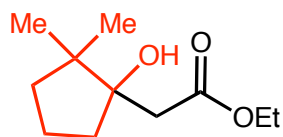
Additive and Scope of Enantioselective Reformatsky



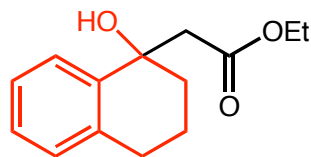
4-phenylpyridine *N*-oxide

- *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

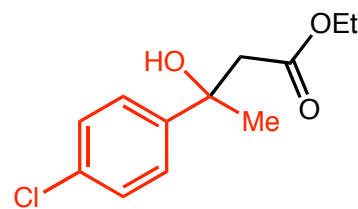
Skarzewski, et al. *J. Mol. Catal. A* **1995** 103, L63-L68.



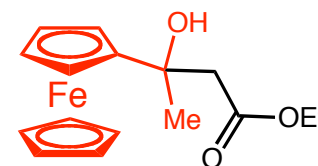
70% yield, 96% ee



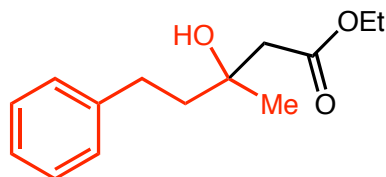
45% yield, 86% ee



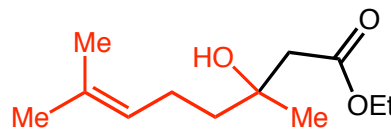
55% yield, 85% ee



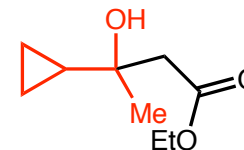
70% yield, 57% ee



77% yield, 23% ee

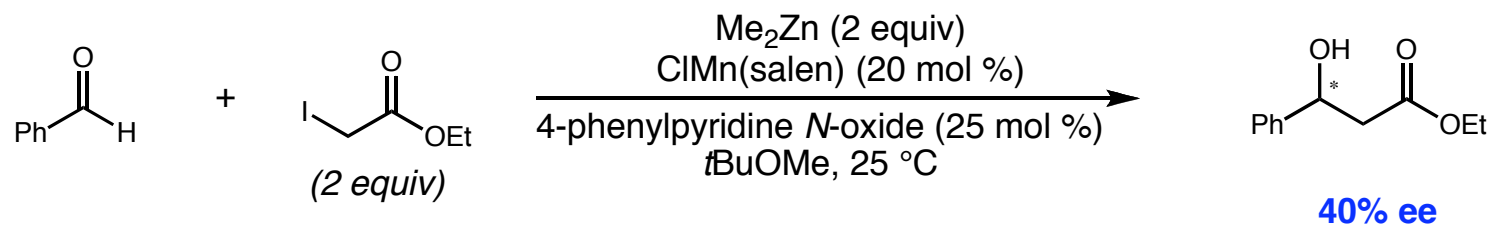


40% yield, 21% ee



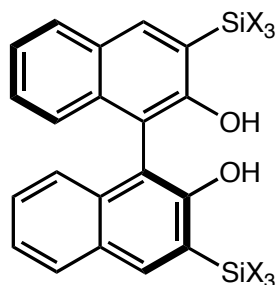
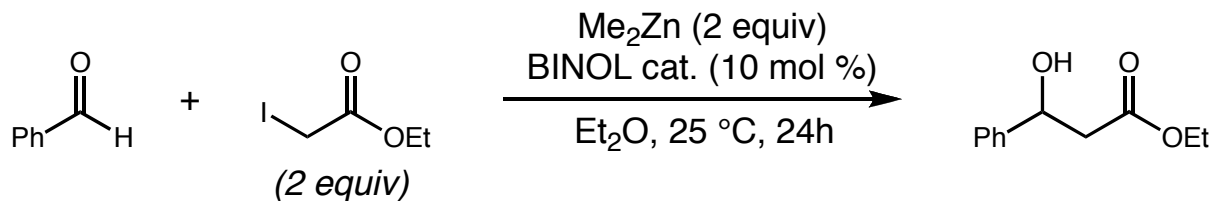
78% yield, 86% ee

A Leading Result



Can a catalytic, asymmetric Reformatsky reaction be applied to aldehydes?

Enantioselective Reformatsky Reaction with Aldehydes



$\text{SiX}_3 = \text{TMS}, 62\% \text{ ee}$
 $= \text{TBS}, 68\% \text{ ee}$
 $= \text{TIPS}, 69\% \text{ ee}$

• conversion low (<20%) for each

Increased conversion:

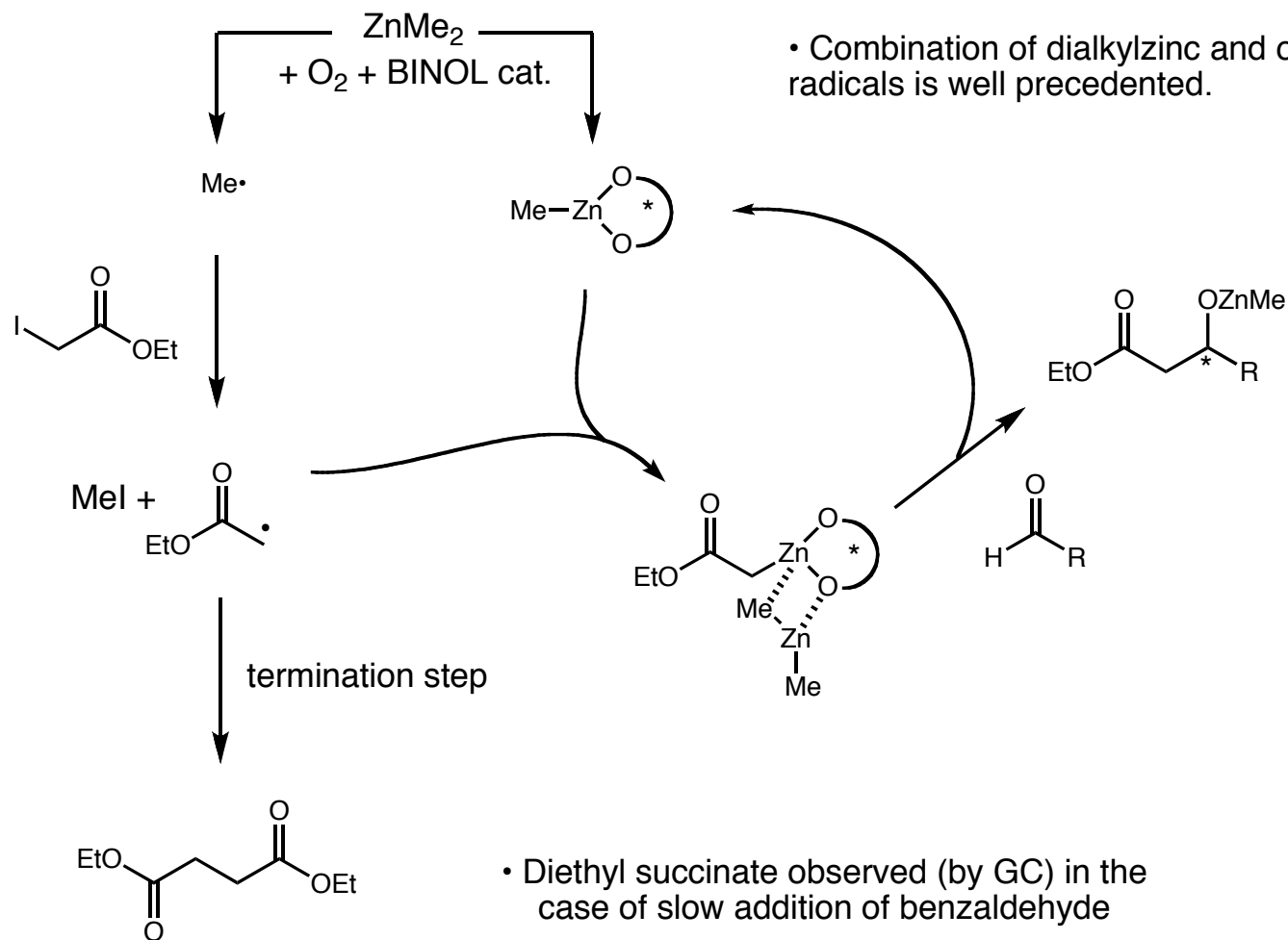
- More reactive Zn (Et_2Zn , $i\text{Pr}_2\text{Zn}$) gave lower ee.
- $\text{NiCl}_2(\text{PPh}_3)_2$ and $\text{RhCl}(\text{PPh}_3)_3$ led to non-reproducible results
- Exposure of Me_2Zn to air to form alkyl peroxides (RZnOOR)

mol % cat. ($\text{SiX}_3 = \text{TBS}$)	ee (%)
10	58
20	70
30	80
50	74

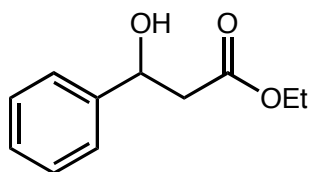
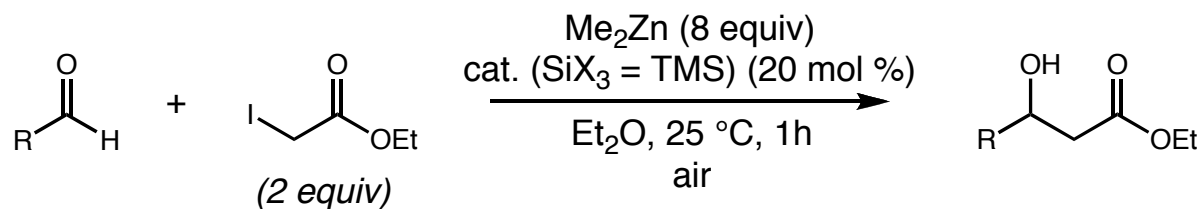
Under atmosphere of air, there is evidence of a significant background rate.

Slow addition of the aldehyde component (over 10 min.) can limit the rate and provide the optimal selectivity.

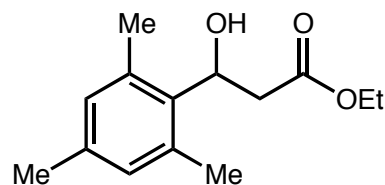
Proposed Catalytic Cycle



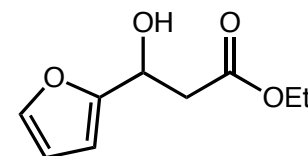
Scope of Enantioselective Reformatsky



72% yield, 84% ee

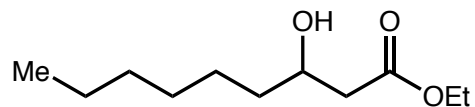


72% yield, 76% ee

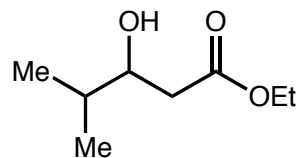


75% yield, 54% ee

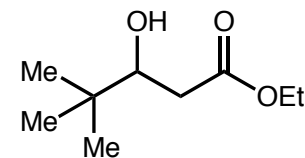
substituted benzaldehydes gave similar results



56% yield, 7% ee

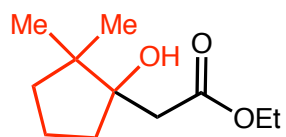
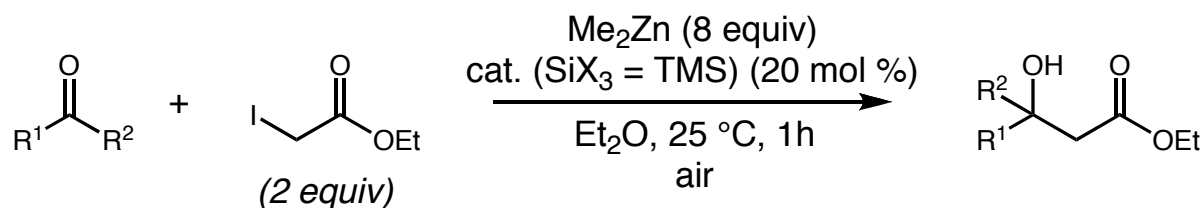


87% yield, 30% ee

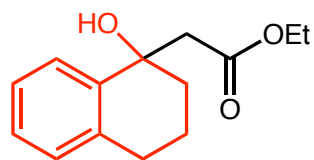


70% yield, 50% ee

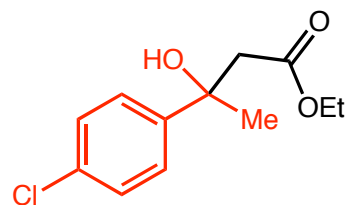
BINOL-Catalyzed Reformatsky Reaction with Ketones



85% yield, 80% ee
70% yield, 96% ee

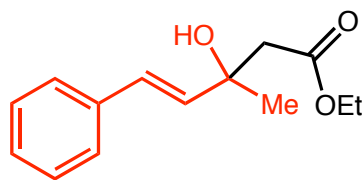


65% yield, 90% ee
45% yield, 86% ee

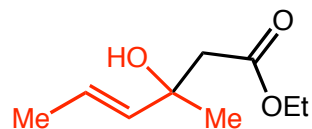


80% yield, 85% ee
55% yield, 85% ee

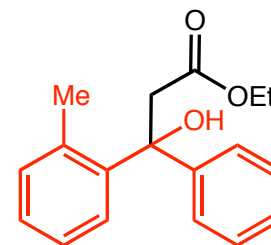
• ee and yields in blue from Cozzi, *ACIE*, 2006 (with CIMn(salen) catalyst)



89% yield, 50% ee
54% yield, 49% ee



72% yield, 48% ee
30% yield, 75% ee



40% yield, 82% ee