An Improved Asymmetric Reformatsky Reaction Mediated by (-)-N,N-Dimethylaminoisoborneol

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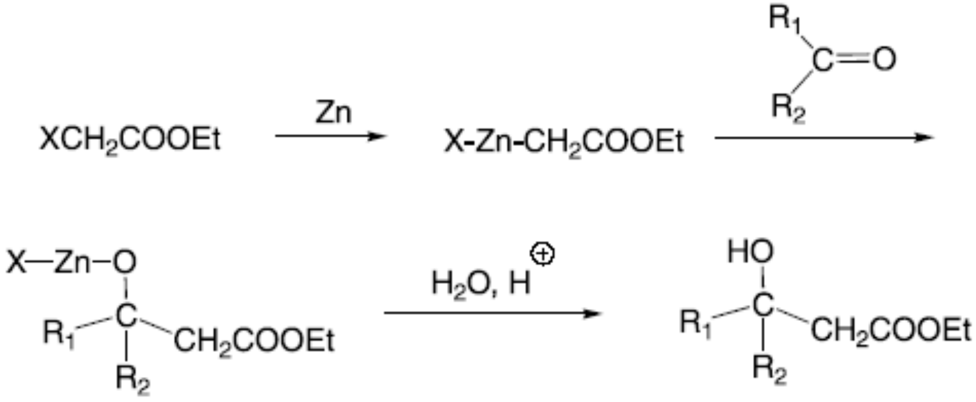
Outline

- **Background**
- **Features and Mechanism**
- **Extensions to the Reformatsky Reaction**
- **Improved Asymmetric Reformatsky Reaction**
- **Conclusions and Next Directions**

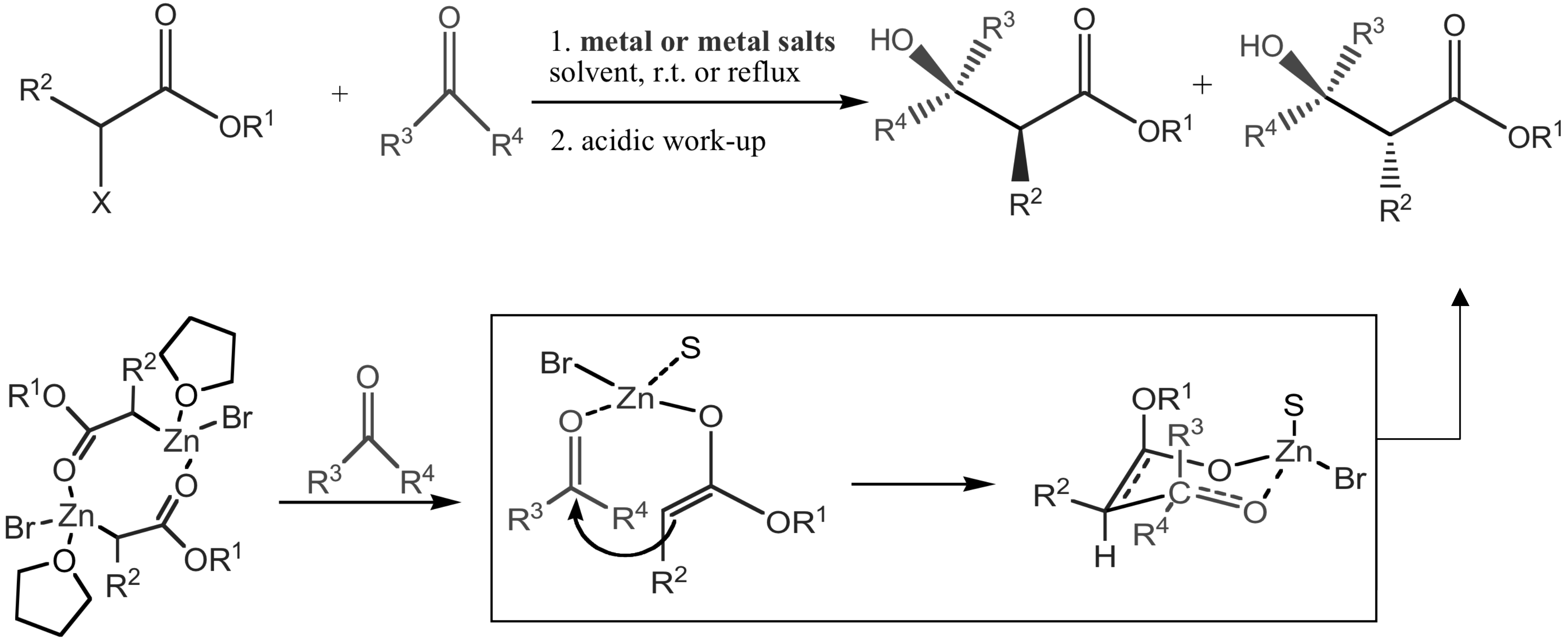
Reformatsky Reaction

- Discovered by S. Reformatsky in 1887
- The classical reformatsky involved a zinc-induced reaction between an α-halo ester and an aldehyde or ketone.



"Reformatsky reactions are defined as those resulting from metal insertions into carbon-halogen bonds activated by carbonyl, carbonyl derived or carbonyl related groups in vicinal or vinylogous positions with practically all kinds of electrophiles."

Mechanism


O
R2
OR1
X
+
O
R3
R4
1. metal or metal salts
solvent, r.t. or reflux
2. acidic work-up
HO
R3
O
R4
OR1
R2
+
HO
R3
O
R4
OR1
R2
R1O
R2
Zn
Br
O
O
Br
Zn
O
R2
OR1
O
R3
R4
Br
Zn
S
O
O
R3
R4
OR1
R2
OR1
R3
S
O
Zn
Br
R2
C
O
H
R4

Key Features

Features:

- **One Pot Synthesis**
- **Carried out in ether solvents or ether/polar solvent mixtures (CH_3CN, DMF, DMSO, HMPA)**
- **Mild conditions**
- **high stereoselectivity**
- **Use of activated metal reagents or low-valent metal salts**
  - **Activated Metals:**
    - Zn, Li, Mg, Cd, Ba, In, Ge, Ni, Co, Ce
  - **Metal Salts:**
    - $CrCl_2$, $SmCl_2$, $TiCl_2$

Synthetic Utility:

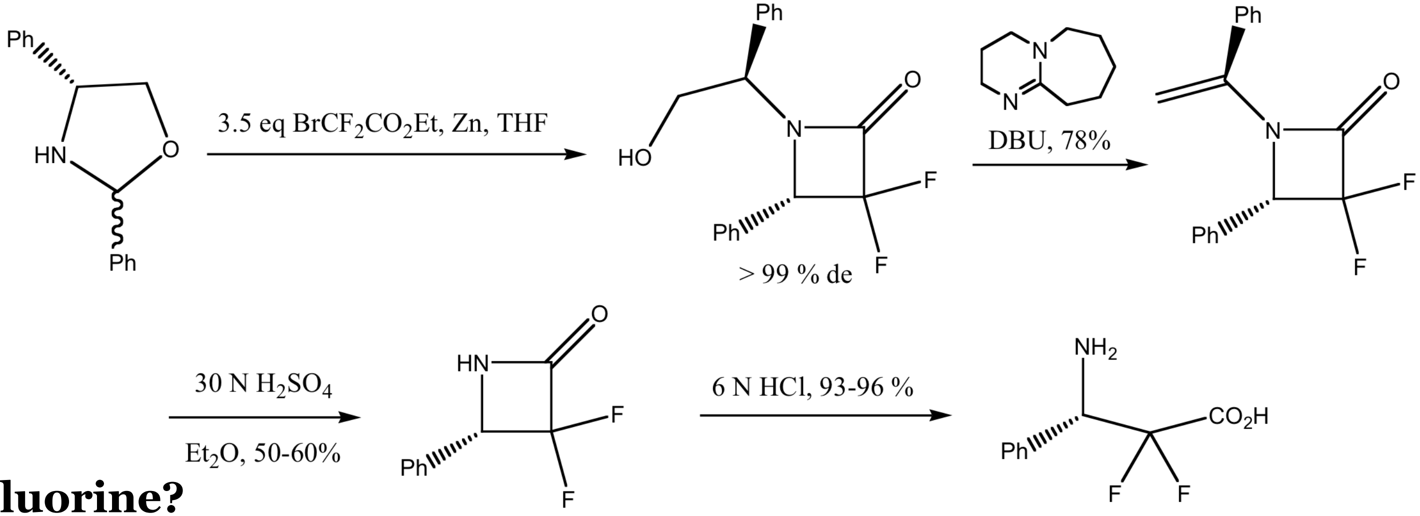
β-hydroxyesters are valuable precursors in natural products synthesis and pharmaceuticals

Advantages over the Classic Aldol:

- Mild/Neutral Conditions
- Works for sterically crowded ketones
- Ester enolate can be formed in presence of highly enolizable aldehyde and ketone functionalities
- Intra- and Inter- molecular reactions feasible
- Variety of Electrophiles can be used

The Reformatsky using Chiral Auxiliaries

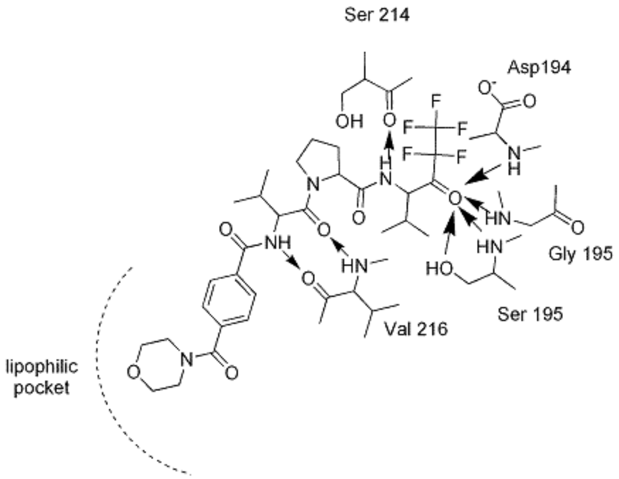
- Diastereoselective formation of Fluroazetidones via a reformatsky-type reaction of Ethyl Bromodifluoroacetate with Chiral 1,3-Oxazolidines



Why Fluorine?

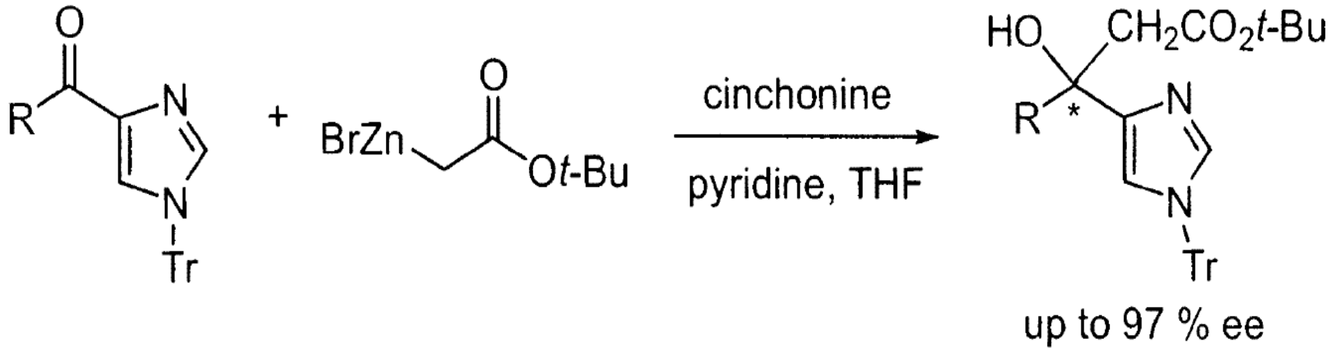
- **Small VDW radius and electronegativity has significant effect on physical and chemical properties of molecules**
- ***gem*-difluoro amino acids and derivatives are valuable tools for the inhibition of metabolic processes**

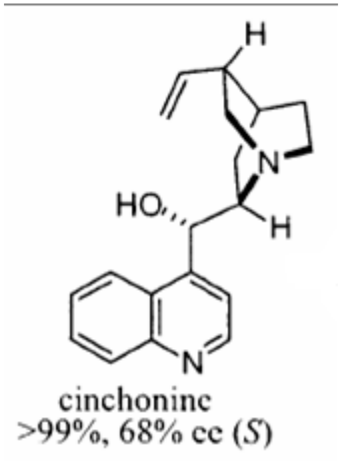
•Difluoroazetidin-2-ones exhibit specific properties as inhibitors of Leucocyte Elastase



The Reformatsky using Chiral Ligands

- Achieved highly enantioselective Reformatsky reaction of Ketones using cinchona alkaloids as chiral ligands



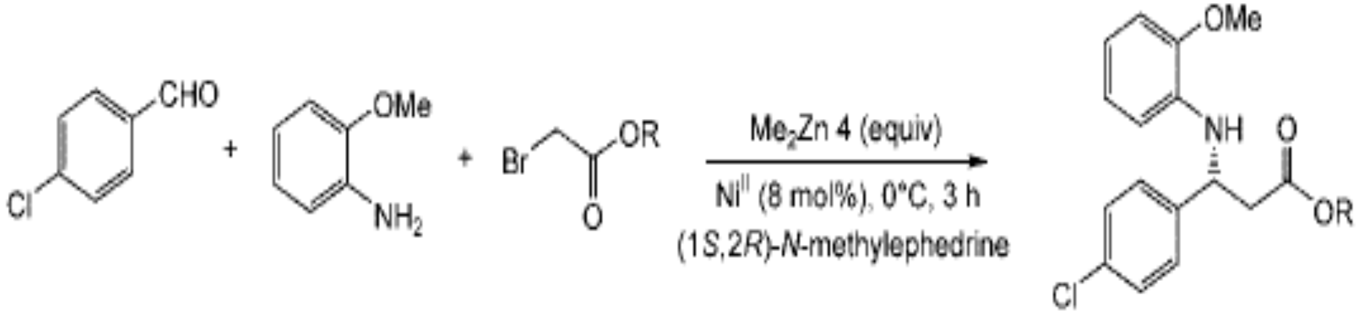


cinchonine
>99%, 68% ee (*S*)

- **Chelation with the sp²-nitrogen adjacent to the reactive carbonyl controlled the facial selectivity to give the chiral alcohol**

An Efficient Route to β-amino Esters

- Enantioselective one-pot imino-Reformatsky reaction of 4-chlorobenzaldehyde with 2-methoxy-aniline and bromoacetates



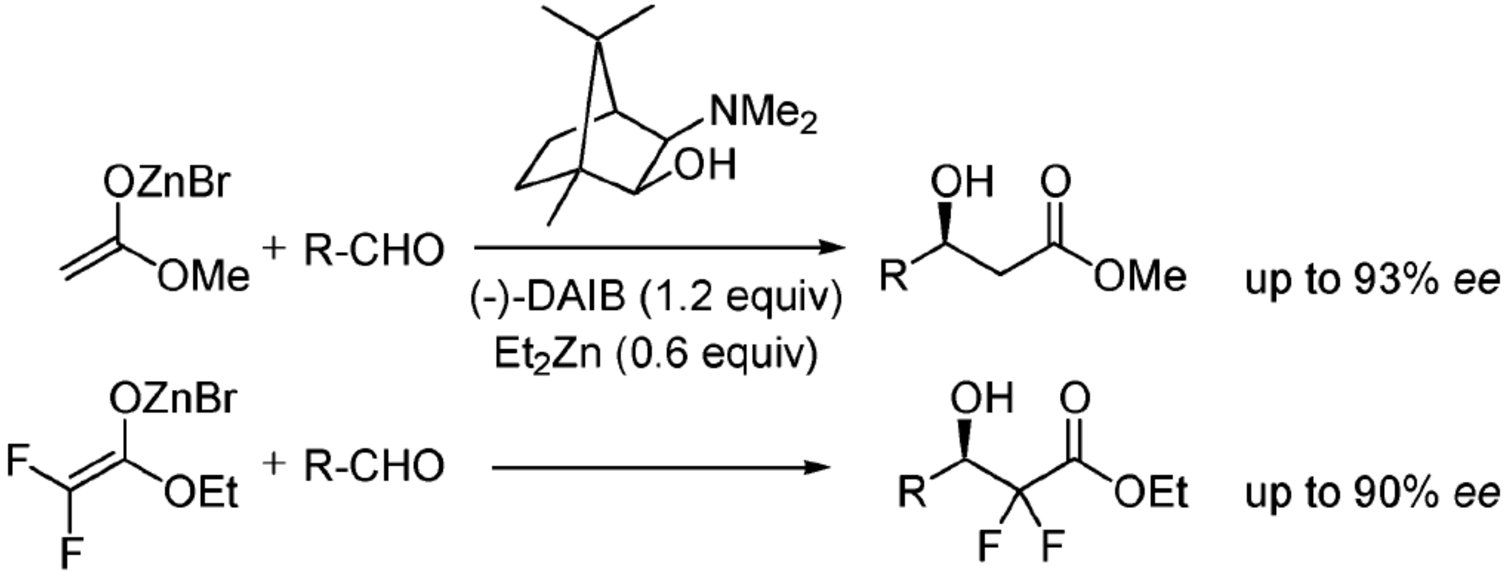
Key Features

- one-pot synthesis
- catalytic
- enantioselective
- highly efficient, practical
- ligand can be recovered
- Gave β-amino esters in good yield

Development of an Improved Asymmetric Reformatsky

Problem: The direct Reformatsky reaction via insertion of activated zinc into α-bromoacetates lack generality and have low enantioselectivities

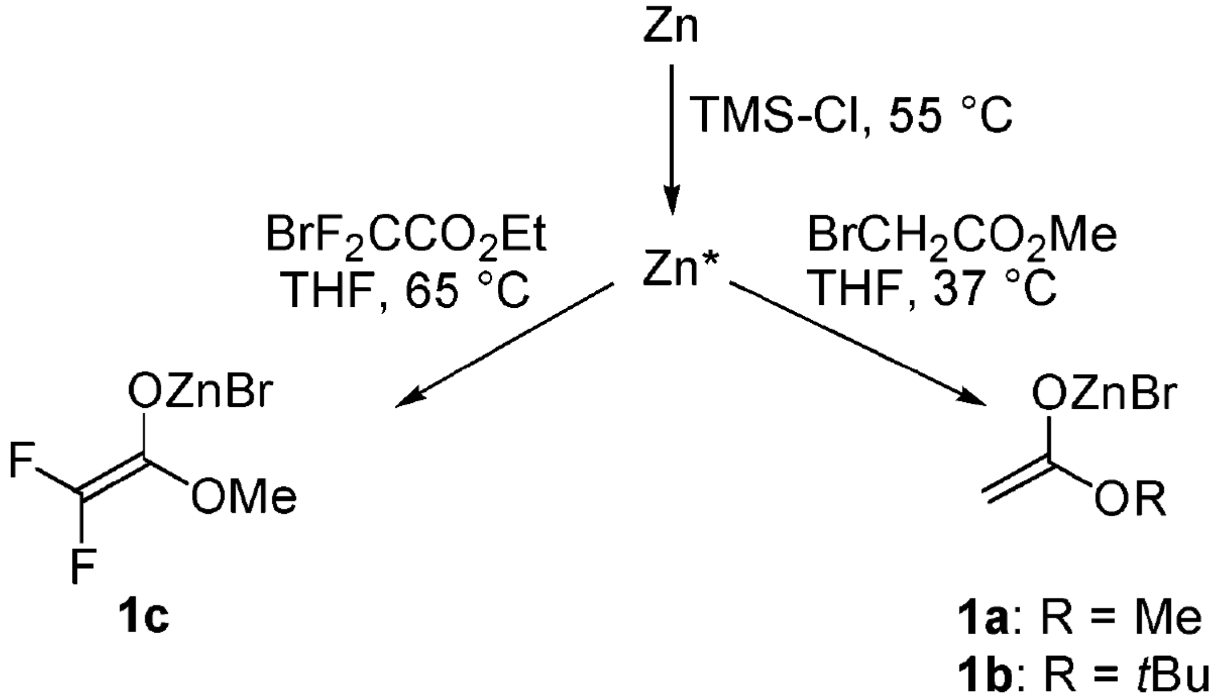
Solution: Utilization of (-) DAIB as a ligand achieved good enantioselective additions of Reformatsky Reagents into aliphatic and aromatic aldehydes.



Synthesis of Reformatsky Reagents

- **Reformatsky reagents prepared via direct zinc insertion into bromoacetic esters**

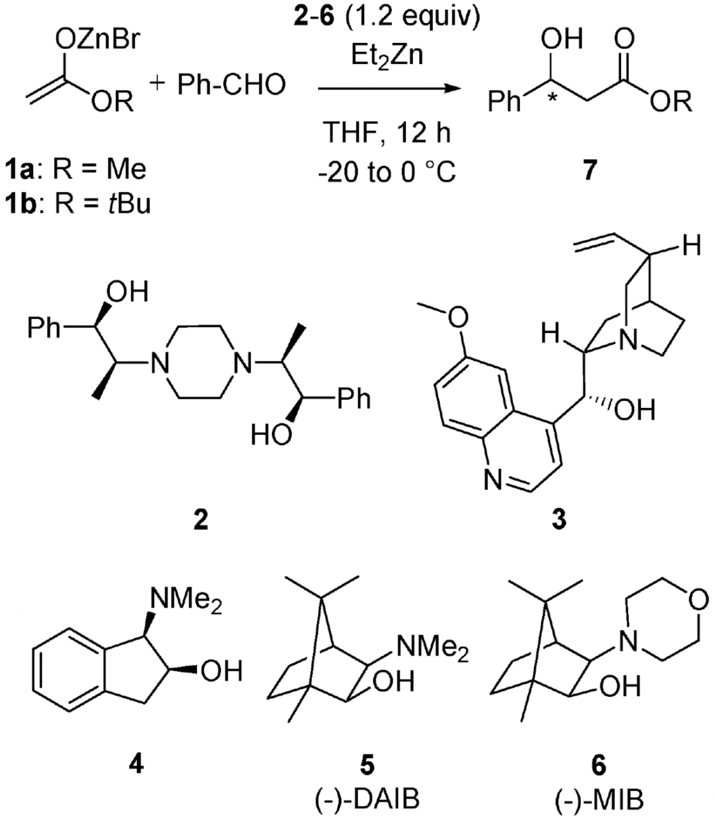
Scheme 1. Preparation of Reformatsky Reagents **1a−c**



Tested Various Chiral Ligands

- **Examined amino alcohols that give high asymmetric inductions as chiral ligands for the addition of diethylzinc into aldehydes**

Table 1. Reformatsky Reaction with Various Chiral Amino Alcohols



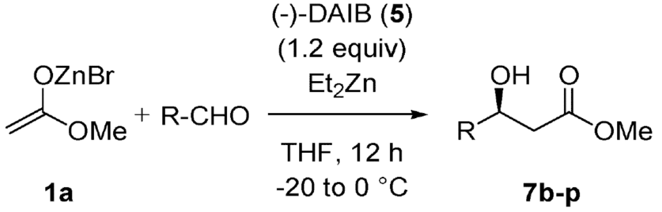
entry	amino alcohol	R	yield (%)	ee[d] (%)
1	**2**	Me	99[b]	61
2	**3**	Me	99[b]	9
3	**4**	Me	99[b]	26
4	**5**	Me	75[c]	86
5	**5**	*t*Bu	84[b]	78
6	**6**	Me	93[b]	72

[a] All reactions were performed on a 0.5 mmol scale using amino alcohol (1.2 equiv, 0.6 equiv in case of **2**), Et_2Zn (0.7 equiv), and Reformatsky reagent (1.1 equiv). [b] Conversion determined by GC analysis with tetradecane as internal standard. [c] Isolated yield. [d] Determined by GC analysis (Chiraldex CB).

**** BuLi and MeMgCl used as deprotonating agents led to racemic mixtures or very poor ee**

Examined Substrate Scope

Table 2. Reformatsky Reaction with (−)-DAIB and Various Aldehydes[a]



entry	R	product	conv (%)	yield[b] (%)	ee[c,d] (%)
1	4-bromophenyl	**7b**	79	87	81
2	2-bromophenyl	**7c**	71	91	78
3	4-chlorophenyl	**7d**	85	65	80
4	4-cyanophenyl	**7e**	89	88	72
5	4-isopropylphenyl	**7f**	63	90	88
6	4-methylthiophenyl[e]	**7g**	57	93	93
7	3-benzothienyl	**7h**	62	94	90
8	2-thienyl	**7i**	86	85	92
9	3-thienyl	**7j**	88	87	93
10	2-furyl	**7k**	99	86	84
11	neopentyl	**7l**	77	83	92
12	*n*-pentyl	**7m**	64	88	78
13	2,2-dimethyl-2-methoxyethyl	**7n**	61	85	74
14	benzyloxymethyl	**7o**	79	87	66
15	2-phenylvinyl	**7p**	48	92	71

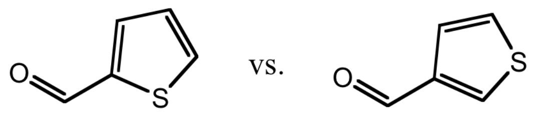
[a] See Table 1. [b] Isolated yield based on conversion. [c] Determined by chiral GC (Chiraldex CB) or chiral HPLC (Chiralcel OD-H). [d] The absolute stereochemistry (*S*) was assigned by comparison of the optical rotation with literature data.[4e,13] [e] For a procedure, see ref 17.

4-methylthiophenyl Derivative = intermediate in Synthesis of Duloxetine, Inhibitor of Serotonin and Norephedrine uptake carriers

- **Electron Rich vs Poor**
  - **e- rich increase ee, lower % conversion**
- **Sulfur containing**
  - **ee enhanced regardless of position on substrate**
- **Aliphatic aldehydes**
  - **more hindered substrates, greater increase in ee**

Substrate Scope for Fluorinated Reagent

- **Observed that electron poor aldehydes had an increase in ee with the fluorinated reagent**
- **Position of the sulfur atom has significant effect on ee**



- **Also selective for Sterically hindered, aliphatic aldehydes**

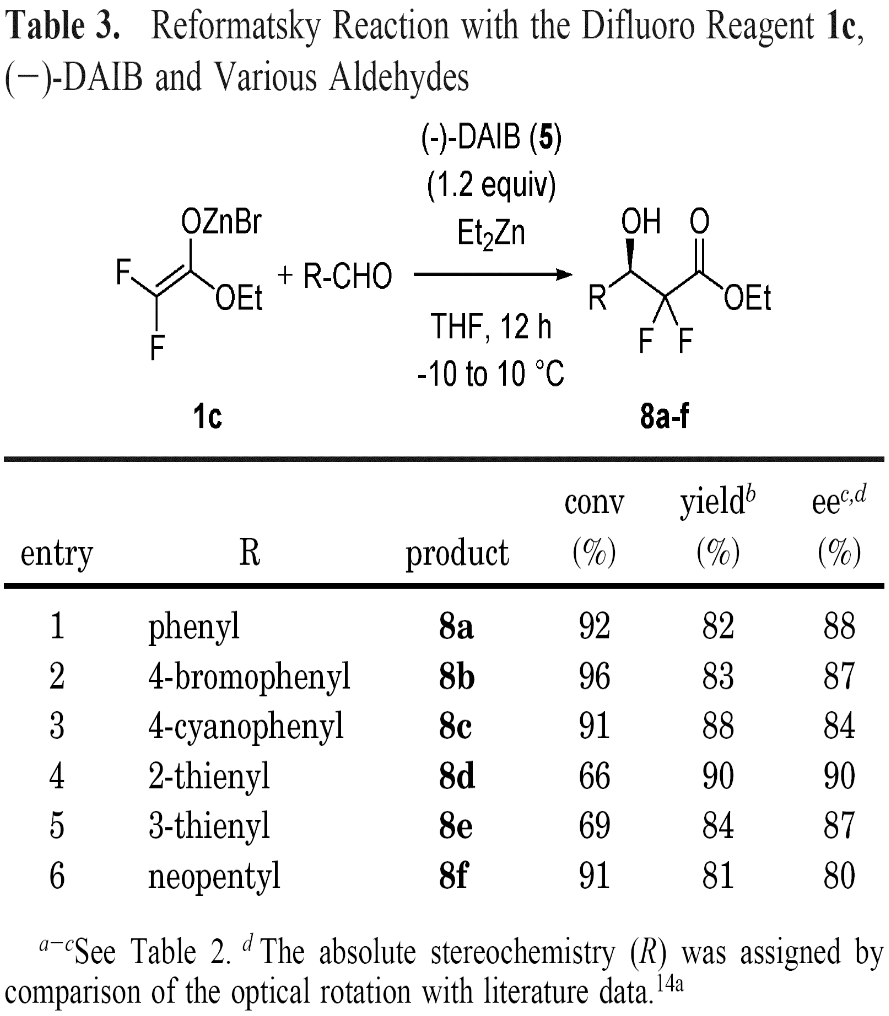


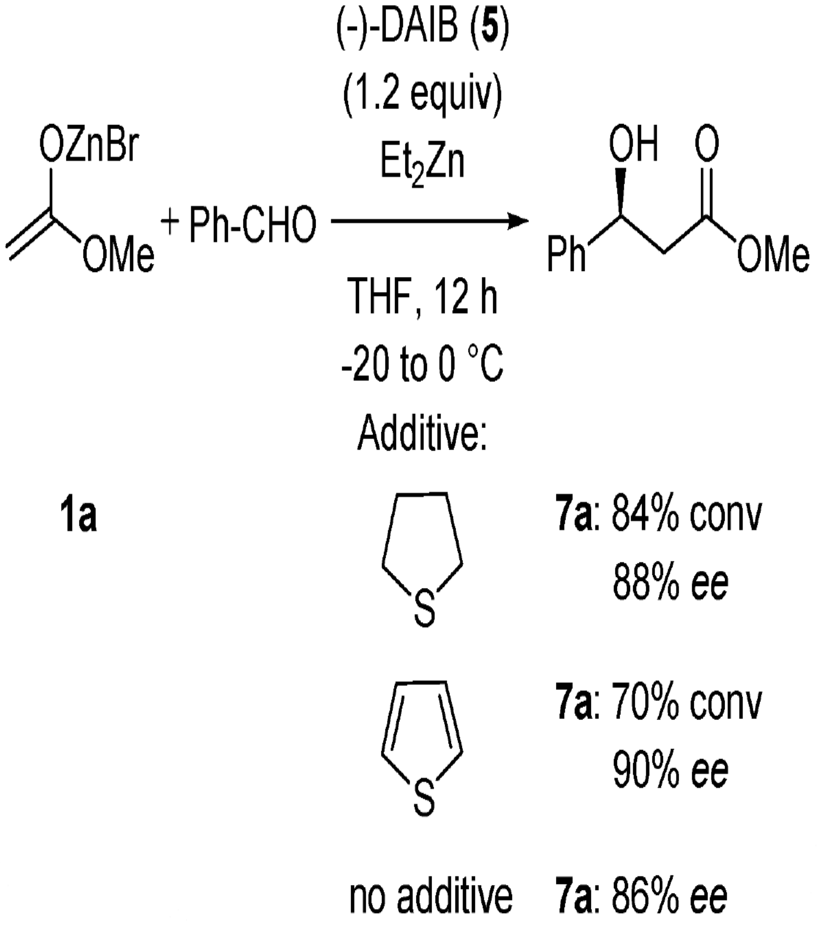
Table 3. Reformatsky Reaction with the Difluoro Reagent **1c**, (−)-DAIB and Various Aldehydes

entry	R	product	conv (%)	yield^{b} (%)	ee^{c,d} (%)
1	phenyl	**8a**	92	82	88
2	4-bromophenyl	**8b**	96	83	87
3	4-cyanophenyl	**8c**	91	88	84
4	2-thienyl	**8d**	66	90	90
5	3-thienyl	**8e**	69	84	87
6	neopentyl	**8f**	91	81	80

[a−c] See Table 2. [d] The absolute stereochemistry (*R*) was assigned by comparison of the optical rotation with literature data.[14a]

Effects of Sulfur Additives

Scheme 2. Reformatsky Reaction Using Sulfur Additives



- **Sulfur containing compounds used as additives showed an increase in the enantioselectivity**

Conclusions

- **(-) DAIB is an excellent ligand for the enantioselective addition of the Reformatsky Reagent in to various aldehydes**
- **High enantioselectivities were obtained for thiophene aldehydes or sterically hindered aliphatic aldehydes**
- **Addition of the difluoro zinc reagent also proceeded with high enantioselectivity**
- **The presence of sulfur additives had a significant impact on the selectivity of these reactions**

Next Directions

- **Investigate the role of sulfur on the selectivity of these reactions and its involvement with regards to the mechanism for the reaction**
- **Explore the effects of sulfur additives in fluoro-derived substrates**
- **Can this ligand be used in catalytic application?**
- **Explore the benefit of using different metals or metal salts other than Zn**

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Thank you!