Catalytic Enantioselective Reformatsky Reaction of Alkyl Iodoacetate with Aldehydes Catalyzed by Chiral Schiff Base

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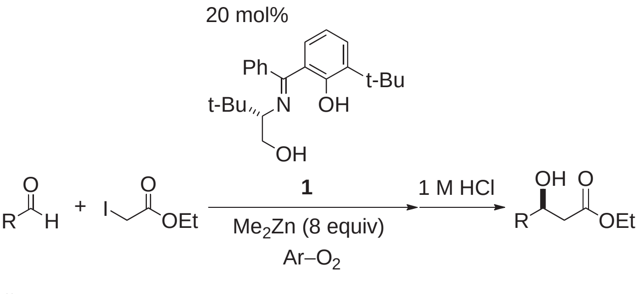
The catalytic enantioselective Reformatsky reaction with aldehydes catalyzed by chiral Schiff base **1** in the presence of Me_2Zn under Ar–O_2 atmosphere was achieved (up to 72% ee). This process provides a potential method for the synthesis of chiral β-hydroxy esters in high enantiomeric excess.

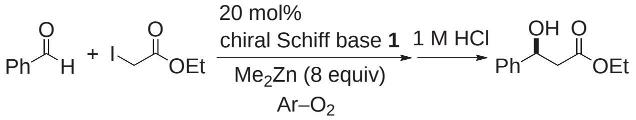
The first practical catalytic enantioselective Reformatsky reaction with ketones was reported by Cozzi in 2006.[1a] He reported the reaction of unsymmetric ketones with ethyl iodoacetate using ClMn(salen) catalyst. After that report, Feringa and his co-workers reported the catalytic enantioselective Reformatsky reaction of ketones with ethyl iodoacetate using chiral binaphthol derivatives.[1b] In 2008, the same researchers also reported the enantioselective Reformatsky reaction with aldehydes.[2] Cozzi also reported the enantioselective imino-Reformatsky reaction using *N*-methylephedrine as the chiral ligand.[3,4] All of these methods are mediated by Me_2Zn (2–8 equiv) in an ethereal solvent, such as Et_2O, *t*-BuOMe, and Et_2O/THF.

We have reported chiral Schiff base-catalyzed asymmetric reactions, such as enantioselective trimethylsilylcyanation of aldehydes,[5] asymmetric alkylation of aldehydes,[6] enantioselective addition of diketene to aldehydes,[7] and enantioselective 1,4-addition of enones.[8] Chiral Schiff base ligands have the following characteristic features. (i) They show high enantioselective recognition. (ii) The introduction of substituents to a Schiff base framework is easy, therefore, they have high tuning potential for a variety of reactions and substrates. (iii) In the case of ketoimine Schiff bases, handling is particularly easy and the ligand can be recovered after hydrolysis. Herein, we report the catalytic enantioselective Reformatsky reaction with aldehydes catalyzed by chiral Schiff base **1** in the presence of Me_2Zn under Ar–O_2 atmosphere (Scheme 1).[9]



Scheme 1. Catalytic enantioselective Reformatsky reaction with aldehydes catalyzed by chiral Schiff base **1**.

Table 1. Enantioselective Reformatsky reaction in various solvents[a]



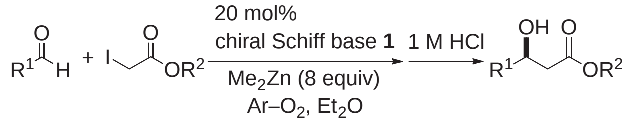
Entry	Solvent	Temp/°C	Time/h	Yield/%[b]	% ee[c]
1	Et_2O	25	1	98	68 (S)
2	Et_2O	0	3	99	60 (S)
3	THF	30	24	33	46 (S)
4	*t*-BuOMe	30	3	99	57 (S)
5	CH_2Cl_2	30	3	93	62 (S)
6	Toluene	30	3	60	52 (S)

[a]All reactions were carried out using 2 equiv of ethyl iodoacetate. PhCHO was added slowly for 20 min. [b]Isolated yield after Kugelrohr distillation. [c]HPLC analysis (CHIRALCEL OD-H).

Though Cozzi and Feringa carried out the reaction in ethereal solvent using 2 M Me_2Zn toluene solution, we examined the reaction using neat Me_2Zn to investigate the solvent effect strictly (Table 1). Using THF as a solvent, the reactivity decreased. These reactions were carried out at room temperature (25–30 °C). The reactions at 0 °C did not increase the enantioselectivity or caused some decrease of the enantioselectivity.[10]

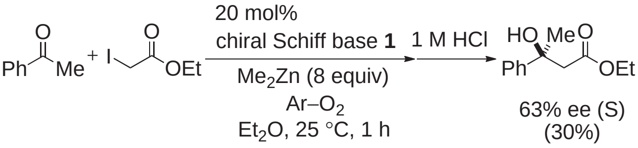
Then, we examined the enantioselective Reformatsky reaction of various aldehydes with ethyl iodoacetate using chiral Schiff base **1**. All reactions were carried out in Et_2O at room temperature under Ar–O_2 atmosphere using Me_2Zn. The obtained results are summarized in Table 2. Most aromatic aldehydes we examined were converted to corresponding chiral β-hydroxy esters in high yield (83–94%) and enantiomeric excess (61–72% ee). In the case of hetero aromatic and α,β-unsaturated aldehydes, the enantioselectivities were moderate.

Table 2. Enantioselective Reformatsky reaction of various aldehydes with alkyl iodoacetate[a]



Entry	R^1	R^2	Temp/°C	Time/h	Yield/%[b]	% ee[c,d]
1	4-$MeOC_6H_4$	Et	27	1	87	72 (S)
2	4-MeC_6H_4	Et	23	1	94	61 (S)
3	4-ClC_6H_4	Et	23	1	83	68 (S)
4	4-BrC_6H_4	Et	26	1	86	68 (S)
5	2-Thienyl	Et	25	8	83	58 (S)[e]
6	(*E*)-$C_6H_5CH{=}CH$	Et	25	1	88	30 (S)
7	Ph	*t*-Bu	30	24	99	56 (S)

[a]All reactions were carried out using 2 equiv of ethyl iodoacetate. [b]Isolated yield after Kugelrohr distillation. [c]HPLC analysis (CHIRALCEL OD-H or CHIRALPAK AS, see Supporting Information). [d]All absolute configurations were determined by the comparison of the optical rotation values with those of reported ones unless otherwise noted. [e]Absolute configuration was estimated by the order of retention time of HPLC.



Scheme 2. Catalytic enantioselective Reformatsky reaction with acetophenone catalyzed by chiral Schiff base **1**.

The reaction of benzaldehyde with *tert*-butyl iodoacetate using the same chiral Schiff base **1** was performed under the same reaction conditions (Table 2, Entry 7). The product was obtained in 99% yield with 56% ee (S). In comparison with the reaction of ethyl iodoacetate, it took longer to complete the reaction in the case of the reaction of *tert*-butyl iodoacetate.

Next, we examined the reaction of acetophenone with ethyl iodoacetate using chiral Schiff base **1** to give the product in 63% ee (S) (30% yield) (Scheme 2). The reactions of other unsymmetric ketones are now in progress.

As for the reaction mechanism, Cozzi and Feringa proposed radical mechanisms. Actually, to obtain high yield, air (molecular oxygen) was used in Feringa's system,[1b,2a] and 4-phenylpyridine *N*-oxide, *tert*-butyl hydroperoxide and air were used in Cozzi's system.[1a,2b,3] These authors suggested the generation of methyl radical species by addition of the above oxidants, because without the oxidants the yield of the product was very low (10–20% yield even for 24 h, rt). However, in our case, the product was actually obtained in 40% yield and 64% ee (S) in the absence of oxygen (for 1 h, 25 °C). We suppose that oxygen accelerates the reaction, but is not essential to promote the reaction, and that a reaction pathway other than a radical mechanism initiated by oxygen may also exist.

In summary, the catalytic enantioselective Reformatsky reaction of aldehydes catalyzed by chiral Schiff base **1** in the presence of Me_2Zn under Ar–O_2 atmosphere was reported (up to 72% ee). The chiral β-hydroxy esters were obtained directly from carbonyl compounds with high enantiomeric excess.[11]

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This paper is dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday.

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9 We examined a variety of chiral Schiff bases we reported in ref. 5 and 6. Among those, chiral Schiff base **1** was the best choice. Especially, the existence of a *tert*-butyl group at the ortho position of a phenolic hydroxy group is essential to obtain high ee. For example, the Schiff base only absent a *tert*-butyl group at the ortho position of phenolic hydroxy group **1** (Other substituents are completely the same) gave only 22% ee (S) in 95% yield.
10 **General procedure for catalytic enantioselective Reformatsky reaction**: Dimethylzinc (0.28 mL, 4.0 mmol) was added to a solution of chiral Schiff base **1** (35.4 mg, 0.1 mmol) and ethyl iodoacetate (118.4 µL, 1.0 mmol) in solvent (6 mL) at room temperature under argon atmosphere. After exchange of argon to oxygen diluted with argon, the solution of aldehyde (0.5 mmol) in solvent (2 mL) was added slowly. The reaction mixture was stirred under argon and oxygen atmosphere. After confirmation of the completion of the reaction by TLC analysis, the mixture was quenched by addition of *i*-PrOH (5 mL) then 1 M HCl (20 mL). After extraction with diethyl ether (20 mL × 3) and evaporation, the obtained residue was columned on silica gel (eluent; hexane:ethyl acetate = 5:1), the following Kugelrohr distillation afforded the product. Enantiomeric excess (ee) was determined by HPLC analysis (CHIRALCEL OD-H or CHIRALPAK AS, see Supporting Information).
11 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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