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ENANTIOSELECTIVE CROSS ALDOL REACTION VIA DIVALENT TIN ENOLATE

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Highly enantioselective cross aldol reaction between aromatic ketones and various aldehydes is achieved via divalent tin enolates employing chiral diamines derived from (S)-proline as ligands.

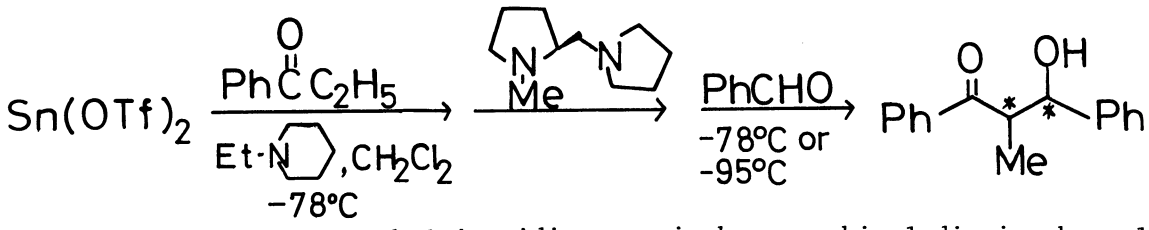
Aldol reaction is one of the most fundamental carbon-carbon bond forming reactions in organic synthesis, and recently, in connection with the total synthesis of numerous macrolide and ionophore antibiotics, extensive studies on the stereocontrol of this reaction have been carried out using various metal enolates.[1] And more recently, several results have also been reported in the field of asymmetric aldol reaction.[2-7] However, in these reactions, chiral carbonyl compounds[2-7] (that is, chiral auxiliary groups are attached to the ketone equivalent molecules) or oxazoline derivatives[7] are employed as one of the component compounds. Judging from the simplicity of the reaction, exploitation of asymmetric cross aldol reaction starting directly from simple ketone and aldehyde is strongly desired as a synthetic tool.[8]

In the previous paper, we reported a new aldol reaction via divalent tin enolates generated in situ from ketones and stannous trifluoromethanesulfonate (stannous triflate).[9] Based on the cosiderations that divalent tin, having vacant d orbitals, is able to accept a bidentate ligand, and that (S)-proline derived chiral diamines are efficient ligands in certain asymmetric reactions by virtue of forming a rigid five-five membered ring chelate in the transition state,[10] we have studied the enantioselective aldol reaction via divalent tin enolates using chiral diamines derived from (S)-proline as ligands.[11,12]

Now, we wish to report the first example of forming highly optically pure aldols formed from aromatic ketones and various aldehydes. In the first place, stannous triflate was treated with propiophenone in dichloromethane in the presence of N-ethylpiperidine as a base, and then (S)-1-methyl-2-[(pyrrolidin-1-yl)-methyl]pyrrolidine,[13] a chiral diamine, was added, and finally benzaldehyde was added to this reaction mixture. Usual work-up of this reaction mixture afforded the cross aldol product in 65% yield, and the optical purity of this product was shown to be about 60% based on NMR measurement after converting the aldol to its MTPA ester.[14]

Next, various reaction conditions were examined and the results are

summarized in Table I.



(Sn(OTf)$_2$:N-ethylpiperidine:propiophenone:chiral diamine:benzaldehyde =1.0:1.15:0.8:1.2:1.2)

Table I. The Effect of Reaction Conditions on Optical Purity.

Reaction Conditions	Yield(%)	Erythro:Threo	Optical Purity(%)[a)b)]
1. -78°C	66	6 : 1	60
2. -78°C, chiral diamine 0.5eq	74	6 : 1	30
3. -78°C, chiral diamine 2.0eq	61	6 : 1	60
4. benzaldehyde added at -95°C	66	6 : 1	65
5. warmed to room temperature after the addition of benzaldehyde	75	1 : 2	0

a) That of erythro isomer. Threo isomer shows almost the same degree of enantioselection.
b) Determined by ^{1}H and ^{19}F NMR measurement of its MTPA ester.

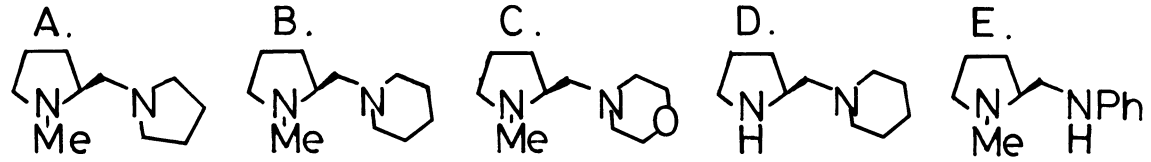
As shown in entry 2 and 3, chiral diamine forms a 1:1 complex with divalent tin enolate, and the optical purity of the product rose up to 65% when benzaldehyde was added at -95°C.

Having attained the best reaction conditions, we next examined various chiral diamines,[13] and found that in the case of the reaction of propiophenone and benzaldehyde, use of (S)-1-methyl-2-[(piperidin-1-yl)methyl]pyrrolidine as a ligand affords the corresponding aldol product in up to 80% e.e.

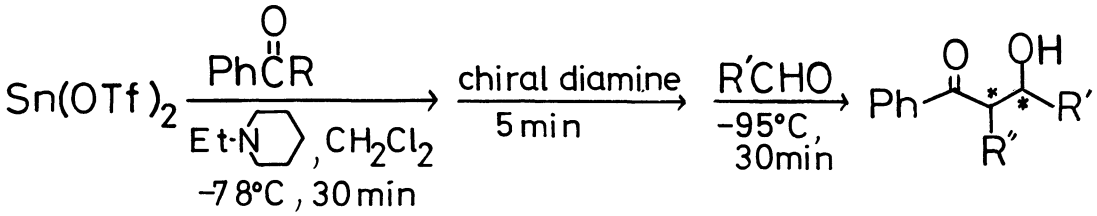
Table II. The Effect of Employed Chiral Diamine on Optical Purity.

Chiral Diamine	Yield(%)	Erythro:Threo	Optical Purity(%)[a)b)]
A	66	6 : 1	65
B	74	6 : 1	80
C	56	6 : 1	50
D	72	6 : 1	75
E	66	20 : 1	20

a) That of erythro isomer. Threo isomer shows almost the same degree of enantioselection.
b) Determined by ^{1}H and ^{19}F NMR measurement of its MTPA ester.



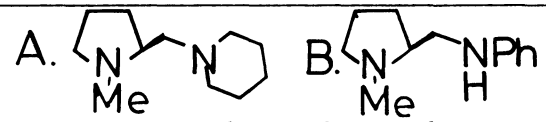
The enantioselectivity of the cross aldol reaction of various aromatic ketones with both aromatic and aliphatic aldehydes was studied and, as shown in Table III, 75 to 85% enantiomeric excess was achieved between aromatic ketones and aromatic aldehydes using (S)-1-methyl-2-[(piperidin-1-yl)methyl]-pyrrolidine as a chiral ligand. As for aliphatic aldehydes, proper choice of the chiral ligands afforded the corresponding cross aldols in high optical purity.



($Sn(OTf)_2$:N-ethylpiperidine:ketone:chiral diamine:aldehyde=1.0:1.15:0.8:1.2:1.2)

Table III. Enantioselective Cross Aldol Reaction between Aromatic Ketones and Various Aldehydes.

Ketone	Aldehyde	Chiral Diamine	Yield(%)[f]	Erythro:Threo	Optical Purity(%)[a]
$PhCOCH_2CH_3$	PhCHO	A	74	6 : 1	80[b]
	p-Me-PhCHO	A	72	8 : 1	80[b]
	p-Cl-PhCHO	A	72	6 : 1	85[b]
	p-MeO-PhCHO	A	78	8 : 1	80[b]
$PhCOCH_2CH_2CH_3$	PhCHO	A	72	5 : 1	75[b]
$PhCOCH_3$	PhCHO	A	35[e]	-	75[c]
$PhCOCH_2CH_3$	$(CH_3)_2CHCHO$	B	69	>20 : 1	75[b]
	$(CH_3)_3CCHO$	A	57	erythro only	90[d]
	cyclo-$C_6H_{11}CHO$	A	67	4 : 1	80[b]

Chiral Diamine 

a) That of erythro isomer. Threo isomer shows almost the same degree of enantioselection.
b) Determined by ^1H and ^{19}F NMR measurement of its MTPA ester.
c) Determined by optical rotation of the acetate of cross aldol product. See reference 3). Absolute configuration was shown to be (S).
d) Determined by using chiral shift reagent Eu(hfc).
e) Self-coupled product of acetophenone was obtained in 64% yield.
f) Satisfactory NMR and IR spectra were obtained for each compound.

A typical procedure is described for the reaction of propiophenone and benzaldehyde using (S)-1-methyl-2-[(piperidin-1-yl)methyl]pyrrolidine as a chiral ligand; to a suspension of stannous triflate (296 mg, 0.71 mmol) and N-ethylpiperidine (95 mg, 0.84 mmol) in 2 ml of dichloromethane was added dropwise propiophenone (78 mg, 0.58 mmol) in 1.5 ml of dichloromethane at -78°C under argon atmosphere. After the mixture was stirred for 30 min, (S)-1-methyl-2-[(piperidin-1-yl)methyl]pyrrolidine (158 mg, 0.87 mmol) in 1.5 ml of dichloromethane was added dropwise, and the mixture was stirred for 5 min at this temperature. Then the reaction mixture was cooled to -95°C, and benzaldehyde (91 mg, 0.86 mmol) in 1.5 ml of dichloromethane was added dropwise. The reaction mixture was further stirred

for 30 min at the same temperature, then quenched with pH7 phosphate buffer. The organic layer was extracted with ether three times and the combined extracts were dried over anhydrous Na_2SO_4. After evaporation of the solvent, the crude product was purified by silica gel thin layer chromatography to afford 3-hydroxy-2-methyl-1,3-diphenyl-1-propanone (103 mg, 74% yield).

It is noted that the present enantioselective aldol reaction is the first example of forming cross aldol in high optical purity starting directly from ketone and aldehyde utilizing the coordination of the chiral diamine to the intermediate tin (II) enolate. Further studies on this type of enantioselective aldol reaction including the combination of alkyl ketone and various aldehydes are now in progress.

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