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SYNTHETIC CONTROL LEADING TO CHIRAL COMPOUNDS

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Abstract—A highly diastereoselective cross aldol reaction is developed using divalent tin enolates formed from stannous trifluoromethanesulfonate and carbonyl compounds. The reaction is extended to a highly enantioselective cross aldol reaction employing chiral diamines derived from (*S*)-proline as ligands.

In recent years, biologically active compounds which possess both many labile functionalities and numerous chiral centers within the same molecule have attracted the attention of organic chemists as challenging synthetic targets. The complex structure and lability of these natural products have warranted the exploitation of highly selective reactions which necessarily proceed under mild conditions. Earlier works in these laboratories, such as "Oxidation–Reduction Condensations",[1] and "New Synthetic Reactions Using the Onium Salts of Azaarenes",[2] have demonstrated the feasibility of reactions to proceed under mild or essentially neutral conditions and subsequently we thus focused our attention on the development of highly selective reactions.

The concept of "Synthetic Control", i.e. utilization of metal chelates for inter- or intramolecular interactions leading to highly selective or entropically advantageous reactions, has proven to be a highly effective approach in synthetic reactions. For instance, metal enolate mediated aldol type reactions are known to provide very useful regio- and stereoselective C–C bond formations via intermolecular metal chelation.[3]

Over the past decade, we have explored the following two types of aldol reactions. Firstly, the titanium tetrachloride promoted aldol reaction, which realizes the use of silyl enol ethers as easily accessible, isolatable enolate precursors,[4] allows the use of carbonyl compound equivalents, such as ketals and acetals, as efficient acceptors for silyl enol ethers. The mildness of reaction conditions permits the presence of base sensitive functionalities which could not survive lithiated derivative mediated methods. Secondly, the vinyloxyborane mediated aldol reaction was found to proceed under very mild and essentially neutral conditions to afford aldols in excellent yields.[5] Moreover, the development of dialkylboryl trifluoromethanesulfonate (dialkylboryl triflate) gave rise to a versatile method for the generation of vinyloxyboranes from parent carbonyl compounds.[6] Owing to the high stereoselectivity of this reaction, it has found wide application in the stereoselective construction of acyclic precursors to natural products.[7]

Recently, during the course of our investigation of synthetic reactions promoted by divalent tin species, divalent tin enolates, generated from stannous trifluoromethanesulfonate and ketones, were found to react with aldehydes to afford aldol products with high *erythro*-stereoselectivity. This enolate also gave cross aldols between two different ketones.

Furthermore, a highly enantioselective version of this divalent tin promoted cross aldol reaction was developed employing chiral diamines derived from (*S*)-proline as ligands. We have already demonstrated that such chiral diamines, which are postulated to form rigid *cis*-fused 5-membered bicyclic structures by chelation to metal center, are effective ligands for highly enantioselective reactions.[8] Thus, based on similar assumptions, coordination of chiral diamine to metal center of the divalent tin enolate was presumed to lead to a highly enantioselective cross aldol reaction.

Recent progress of the diastereo- and enantioselective aldol reaction of divalent tin enolates is described herein.

RESULTS

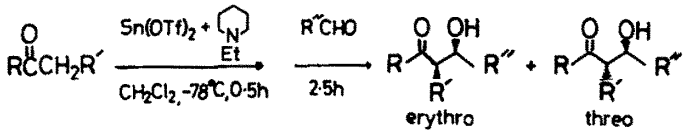
Stannous trifluoromethanesulfonate (triflate) promoted aldol reaction

It has been reported in the literature that stannous trifluoromethanesulfonate(triflate)[9] is readily prepared by heating anhydrous stannous chloride in excess trifluoromethanesulfonic acid. However, no example of its application in organic synthesis has been reported. We therefore, in an analogous procedure to that for the preparation of vinyloxyboranes, attempted to generate divalent tin enolates by treatment of stannous triflate with ketones in the presence of tertiary amine, and then to examine the reaction of the enolate with carbonyl compounds.

After the screening of various reaction conditions, it was clearly shown that in this reaction choice of base and solvent is crucial. And it was found that divalent tin enolates can be cleanly generated from stannous triflate and ketone in the presence of N-ethylpiperidine as a base in dichloromethane, and that the enolates react with various aldehydes under mild conditions to give aldol products with high *erythro*-stereoselectivity in good yields (Table 1).[10]

Furthermore, a convenient method for the stereoselective synthesis of *cis*-β-substituted-α,β-epoxyketone (**1**) was established by applying this stannous triflate mediated cross aldol reaction to the reaction between α-bromoketone and aldehydes. The preferentially formed adduct, *syn*-α-bromo-β-hydroxyketone (**2**), is converted to *cis*-α,β-epoxyketone (**1**) with minimum amount of isomerization to *trans* isomer via intramolecular S_N2 type

Table 1. Stannous triflate promoted aldol reaction between ketone and aldehyde



Entry	Ketone	Aldehyde	Yield(%)[a]	Erythro:Threo[b]
1	$C_6H_5COC_2H_5$	C_6H_5-CHO	71	>95: 5
2	$C_6H_5COC_2H_5$	i-C_3H_7CHO	80	91: 1
3	$C_6H_5COC_2H_5$	n-C_3H_7CHO	79	86:14
4	$C_2H_5COC_2H_5$	C_6H_5-CHO	77	87:13
5	$C_2H_5COC_2H_5$	i-C_3H_7-CHO	73	93: 7
6	$C_2H_5COC_2H_5$	n-C_3H_7-CHO	86	>91: 9[c]
7	i-$C_3H_7COC_2H_5$	C_6H_5-CHO	72	91: 9
8	cyclohexanone	C_6H_5-CHO	41	>95: 5

a) Isolated yield.
b) Aldol ratios determined by 90 MHz ^{1}H NMR or ^{13}C NMR.
c) Aldol ratio determined by 270 MHz ^{1}H NMR.

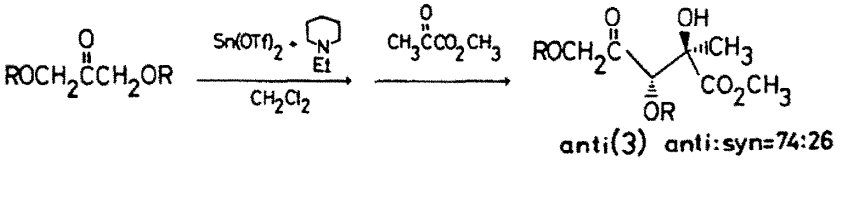
ring closure to oxirane by the action of potassium fluoride—dicyclohexyl-18-crown-6 on aldol (1) (Table 2).[11]

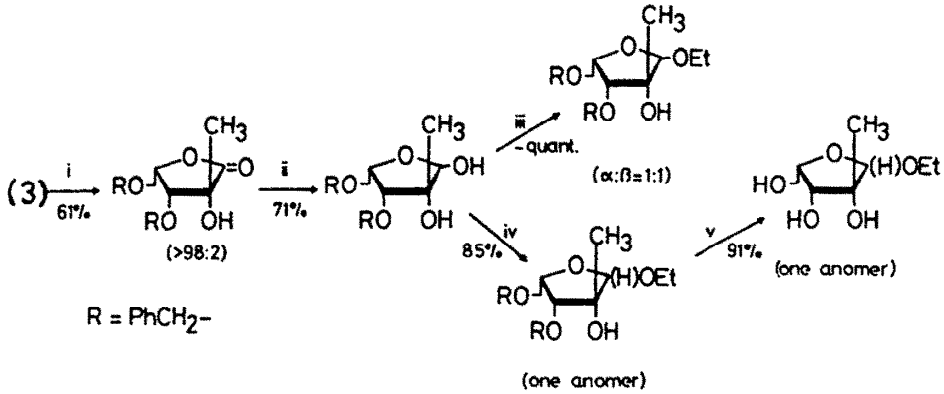
Interestingly, the present divalent tin enolate also displays enhanced reactivity toward ketones, and a facile method for the directed aldol reaction between two different ketones was realized by using divalent tin enolates prepared from stannous triflate and ketones. Examination of the diastereoselectivity in this reaction revealed that when an aromatic ketone is chosen as acceptor carbonyl compound, enhanced *threo*-selectivity is observed (Table 3).[12]

A branched-chain sugar, ethyl 2-C-methyl-DL-lyxofuranoside, was synthesized stereoselectively by application of this reaction, starting from 1,3-dihydroxy-2-propanone derivative and methyl pyruvate as shown in Scheme 1.[13]

Stannous triflate mediated aldol type reaction of 3-acylthiazolidine-2-thione

As well as β-hydroxy ketones, β-hydroxy carboxylic acid derivatives (ester, amide etc) and β-hydroxy aldehydes are useful synthetic intermediates for the construction of a variety of polyoxygenated natural

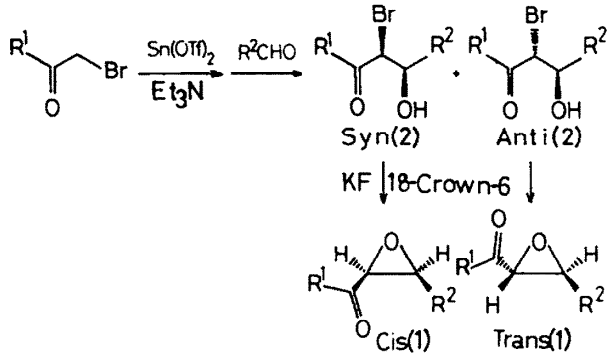




(i) Li(s-Bu)$_3$BH (ii) Dibal (iii) EtOH/H$^+$ (iv) KO^{t}Bu, excess EtI (v) H_2/5%Pd-C

Scheme 1.

Table 2. Synthesis of α,β-epoxyketone



Entry	α-Bromoketone	Aldehyde	Yield of α,β-Epoxyketones (%)[a,b]	Cis:Trans[e]
1	CH_3COCH_2Br	PhCHO	72	70:30[c]
2		$Ph(CH_2)_2CHO$	65	73:27[d]
3	$PhCOCH_2Br$	$Ph(CH_2)_2CHO$	80	66:34[c]
4		i-PrCHO	80	65:35[c]
5	$(CH_3)_3CCOCH_2Br$	PhCHO[f]	64	>95: 5[c]
6		$Ph(CH_2)_2CHO$[f]	48	>95: 5[c]
7		i-PrCHO[f]	47	>95: 5[c]

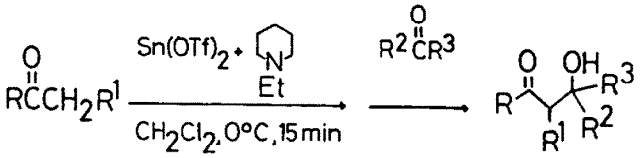
a) The reaction was carried out without purification of the intermediate aldol product.
b) Isolated yield based on α-bromoketones.
c) The diastereomer ratios were determined by 90 MHz ^1H NMR, by integration of the characteristic oxirane protons. Cis isomer has the coupling constant of about 5 Hz, and trans isomer has that of about 2 Hz.
d) The diastereomer ratio determined by HPLC.
e) These two isomers can be easily separated by silica-gel thin layer chromatography.
f) In this case, the reaction was carried out in dichloromethane. Compared with the reaction in tetrahydrofurane, higher yeild without loss of diastereoselectivity was obtained.

products. Our initial attempts to enolize various carbonyl compounds using stannous triflate have not yet met with success probably due to their low acidity of α-proton (ester, amide) of self-polymerization of the starting material (aldehyde). Thus, an equivalent of such carbonyl compounds was sought. 3-Acylthiazolidine-2-thione was chosen as an equivalent molecule since we have previously reported that 3-acylthiazolidine-2-thione can be cleanly converted to the corresponding aldehyde by reduction with diisobutylaluminum hydride.[14] Furthermore, transformations of 3-acylthiazolidine-2-thione have been widely studied, and it has been shown that a variety of carboxylic acid derivatives are readily accessible under mild reaction conditions.[15] As expected, divalent tin enolates could be formed from stannous triflate and 3-acylthiazolidine-2-thione, and the corresponding aldol type products (4) were obtained in excellent yields with high *erythro*-selectivity (Table 4). The adducts (4) were easily transformed into β-hydroxy aldehyde and β-hydroxy carboxylic acid derivatives (Scheme 2).[16]

Enantioselective cross aldol reaction via divalent tin enolates

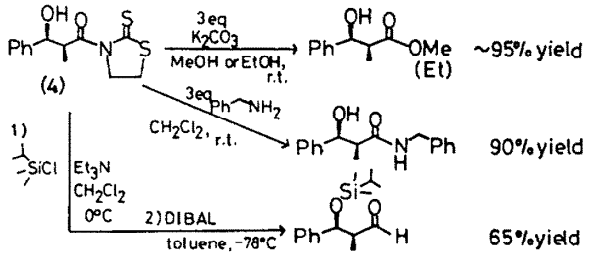
Recent development in the field of stereoselective aldol reactions has resulted in the exploitation of the asymmetric version of this reaction, and several successful methods have been reported using chiral carbonyl compounds as one of the component compounds[17] or by using chiral boron triflate as a generator of boron enolate.[18] However, the efficiency of these reactions is greatly diminished by the necessity of tedious procedures for the attachment and removal of the chiral sources. Thus, development of a highly enantioselective aldol reaction between two achiral carbonyl compounds utilizing chiral chelating agents is strongly desirable, though the influence of such chiral addends in the aldol reaction has not met with much success.[19]

Table 3. Cross aldol reaction between ketones



Entry	Enolized ketone R	Enolized ketone R^1	Acceptor ketone R^2	Acceptor ketone R^3	Reaction time (min)	Yield (%)[a]	Erythro:Threo
1	Ph	CH_3	$-(CH_2)_5-$		10	83	–
2			$-(CH_2)_5-$		10	75	–
3			Et	Et	60	80	–
4			Ph	CH_3	40	60	0:100[b]
5			$Ph(CH_2)_2$	CH_3	80	78	50: 50[b]
6	Ph	Et	$-(CH_2)_5-$		20	87	–
7			Ph	CH_3	35	41	0:100[b]
8	Ph	Cl	$-(CH_2)_5-$		15	87	–
9	Ph	i-Pr[e]	$-(CH_2)_5-$		2.5 h	48	–
10	Et	CH_3	Ph	CH_3	60	45	13: 87[b,c]
11	Ph	OC(O)Ph	$-(CH_2)_5-$		3	96	–
12			Ph	CH_3	55	85	30: 70[c,d]
13			Ph	CH_3 (−78°C)	5 h	48	>95: < 5

a) Isolated yield.
b) Diastereomeric ratio determined by ^{13}C NMR. Other isomer could not be detected.
c) Diastereomeric ratio determined by 90 MHz ^1H NMR.
d) Relative configuration assignment was not made.
e) Phenyl iso-propyl ketone.



Scheme 2.

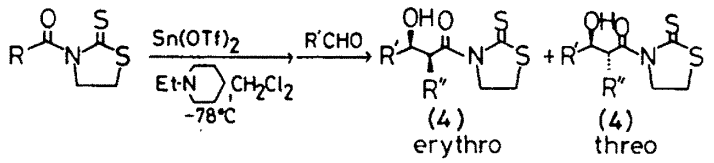
At this point, we considered the application of divalent tin enolates to a chiral chelate type asymmetric aldol reaction based on the consideration that suitable ligands should be able to coordinate to the divalent tin metal center, which has vacant d orbitals. Since we have demonstrated that chiral diamines are efficient ligands in certain asymmetric reactions, we directed our efforts to the examination of an enantioselective aldol reaction via divalent tin–chiral diamine complex, generated *in situ* from tin(II) enolate and chiral diamine derived from (*S*)-proline.

As a preliminry investigation the divalent tin enolate, formed from stannous triflate and propiophenone in dichloromethane in the presence of N-ethylpiperidine, was treated with diamine (**5**) and then with benzaldehyde at − 78°. Work-up of the reaction mixture afforded the cross-aldol product in 65% yield, and with optical purity of 60% based on NMR analysis of the corresponding MTPA ester. By conducting the reaction at − 95°, optical purity could be improved to 65%. Screening of the reaction conditions revealed that chiral diamine forms a 1:1 complex with the divalent tin enolate. We tentatively suggest formation of a rigid *cis*-fused 5-membered ring chelate in the transition state (Table 5).

Next, we systematically examined the effect of various chiral diamines and found that by use of diamine (**6**) as a ligand the corresponding aldol product was afforded in up to 80% ee (Table 6).

The enantioselectivity of the cross aldol reaction of

Table 4. The aldol type reaction of 3-acylthiazolidine-2-thione with aldehyde



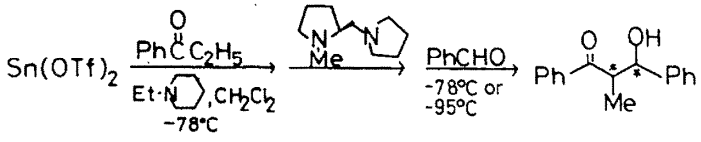
Entry	R in 1	Aldehyde	Yield(%)[a]	Erythro:Threo
1	CH_3	PhCHO	90	-
2		$PhCH_2CH_2CHO$	88	-
3		$(CH_3)_2CHCHO$	94	-
4	CH_3CH_2	PhCHO	94	97 : 3[b]
5		$PhCH_2CH_2CHO$	91	>97 : 3[c]
6		$(CH_3)_2CHCHO$	95	>97 : 3[c]
7	$PhCH_2CH_2$	PhCHO	88	>97 : 3[c]
8		$PhCH_2CH_2CHO$	95	>97 : 3[d]

a) Isolated yield.

b) The ratio was determined by separating each isomer. The stereochemistry of each compound was assigned by converting to the methyl ester.

c) Only one stereoisomer was detected from ^{13}C NMR spectrum. The stereochemisty was determined by converting to the corresponding methyl ester and comparison of ^{1}H or ^{13}C NMR spectrum with that of authentic sample.

Table 5. The effect of reaction conditions on optical purity



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

Entry	Reaction Conditions	Yield(%)	Erythro:Threo	Optical Purity(%)[a,b]
1	-78°C	66	6 : 1	60
2	-78°C, chiral diamine 0.5equiv.	74	6 : 1	30
3	-78°C, chiral diamine 2.0equiv.	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

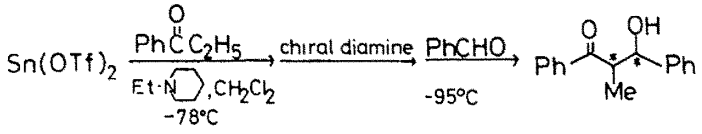
a) That of erythro isomer. Threo isomer shows almost the same degree of enantioselection.

b) Determined by ^{1}H and ^{19}F NMR measurement of its MTPA ester.

various aromatic ketones with both aromatic and aliphatic aldehydes was next studied, and, as shown in Table 8, 75–80% ee was achieved between aromatic ketones and aromatic aldehydes employing diamine (**6**) as a chiral ligand. In the case of aliphatic aldehydes, proper choice of the chiral ligand afforded the corresponding cross aldols in high optical purities (Table 7).[20]

To our surprise, the enantioselectivity achievable in the cross aldol reaction of aliphatic ketones with various aldehydes was rather low (up to 50% ee) when the above mentioned chiral diamines (**5**) to (**9**)

Table 6. The effect of employed chiral diamine on optical purity



Entry	Chiral Diamine	Yield(%)	Erythro:Threo	Optical Purity(%)[a)b)]
1	5	66	6 : 1	65
2	6	74	6 : 1	80
3	7	56	6 : 1	50
4	8	72	6 : 1	75
5	9	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.

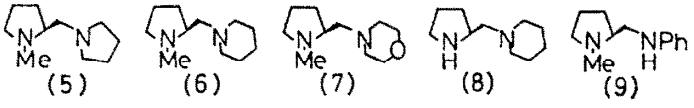
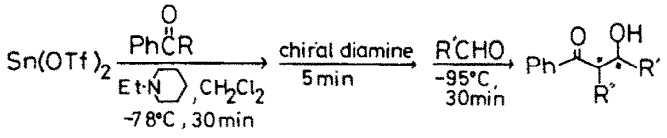


Table 7. Enantioselective cross aldol reaction between aromatic ketones and various aldehydes



Entry	Ketone	Aldehyde	Chiral Diamine	Yield(%)	Erythro:Threo	Optical Purity[a)] (%)
1	$PhCOCH_2CH_3$	PhCHO	6	74	6 : 1	80[b)]
2		p-Me-PhCHO	6	72	8 : 1	80[b)]
3		p-Cl-PhCHO	6	72	6 : 1	85[b)]
4		p-MeO-PhCHO	6	78	8 : 1	80[b)]
5	$PhCOCH_2CH_2CH_3$	PhCHO	6	72	5 : 1	75[b)]
6	$PhCOCH_3$	PhCHO	6	35[e)]	-	75[c)]
7	$PhCOCH_2CH_3$	$(CH_3)_2CHCHO$	9	69	>20 : 1	75[b)]
8		$(CH_3)_3CCHO$	6	57	erythro only	90[d)]
9		cyclo-$C_6H_{11}CHO$	6	67	4 : 1	80[b)]

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.

c) Determined by the optical rotation of the acetate of cross aldol product.

d) Determined by using chiral shift reagent $Eu(hfc)_3$.

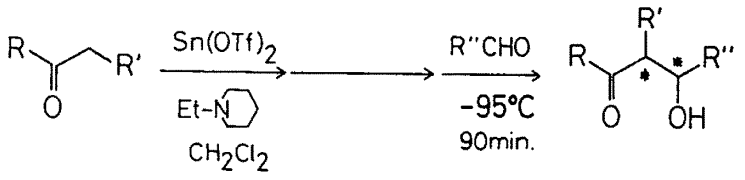
e) Self-coupled product of acetophenone was obtained in 64% yield.

were employed. Thus, we further examined a number of chiral sources and found that the tridentate ligand (**10**) was most effective for this reaction. And, as shown in Table 8, when *t*-butyl ethyl ketone was employed, 70–80% ee was realized with various aldehydes.

This asymmetric aldol reaction was next extended to the aldol type reaction of 3-acetylthiazolidine-2-thione with various achiral aldehydes via divalent tin enolate using chiral diamine (**6**) as a ligand. The corresponding aldol adduct (**11**) was obtained with high optical purity (Table 9).[21] As described in Section 2.3, the adduct (**11**) is easily converted to β-hydroxy aldehyde or β-hydroxy carboxylic acid derivatives, and thus this method constitutes a useful method for the preparation of a variety of optically active compounds.

It should be noted that this enantioselective aldol

Table 8. Enantioselective cross aldol reaction between aliphatic ketones and various aldehydes

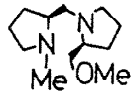


Entry	Ketone	Aldehyde	Chiral Diamine	Yield(%)	Erythro:Threo	Optical Purity(%) a)
1	$EtCOCH_2CH_3$	PhCHO	6	54	75 : 25	45 b)
2	$t\text{-}BuCOCH_2CH_3$	PhCHO	6	22	>95 : 5	53 b)
3		$PhCH_2CH_2CHO$	6	35	>95 : 5	53 c)
4	$EtCOCH_2CH_3$	PhCHO	10	60	75 : 25	55 b)
5		p-MeO-PhCHO	10	69	89 : 11	50 b)
6	$t\text{-}BuCOCH_2CH_3$	PhCHO	10	29	>95 : 5	80 b)
7		p-Cl-PhCHO	10	32	>95 : 5	80 b)
8		p-MeO-PhCHO	10	24	>95 : 5	77 b)
9		$PhCH_2CH_2CHO$	10	40	>95 : 5	70 c)

a) That of erythro isomer.

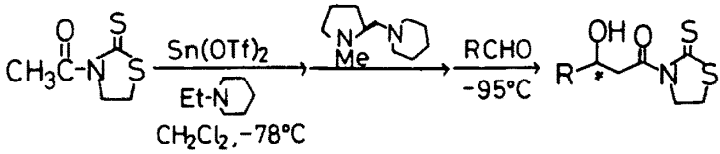
b) Determined by ^1H and ^{19}F NMR measurement of its MTPA ester.

c) Determined by using chiral shift reagent $Eu(hfc)_3$.



(10)

Table 9. Enantioselective aldol type reaction of 3-acetylthiazolidine-2-thione



Entry	Aldehyde	Yield(%)	$[\alpha]_D^{21}$ (c,C_6H_6)	Optical Purity(%) a)
1	PhCHO	79	-48.4°(1.1)	65 b)
2	$(CH_3)_2CHCHO$	63	-68.8°(0.8)	>90
3	$PhCH_2CH_2CHO$	76	-40.2°(1.4)	>90
4	cyclo-$C_6H_{11}CHO$	81	-61.5°(1.6)	88
5	C_2H_5CHO	70	-64.8°(1.0)	90
6	n-$C_5H_{11}CHO$	65	-51.6°(0.9)	90

a) Determined by the measurement of the ^1H NMR spectrum of the corresponding methyl ester using $Eu(hfc)_3$ as a chiral shift reagent. The $-OCH_3$ signal was completely separated.

b) In this case, the absolute configuration of the adduct was determined to be S by the optical rotation of the β-hydroxy carboxylic acid. In other cases, the absolute configurations were not rigorously established; however, judging from the similarity in the chemical shifts of $-OCH_3$ signals using the chiral shift reagent, other aldol products are thought to have the same absolute configuration.

reaction is a first example of forming cross aldols in high optical purity starting directly from simple achiral components utilizing the coordination of chiral diamine to the intermediate tin(II) enolates.

EXPERIMENTAL

Stannous trifluoromethanesulfonate

A modified procedure to that of Aubke *et al.* was employed: Thus, excess trifluoromethanesulfonic acid (40 g, 26.7 mmol) was added with vigorous stirring to anhyd. $SnCl_2$ (16 g, 8.4 mmol). Gaseous HCl was evolved in an exothermic reaction. To ensure complete reaction the mixture was heated at 80° for 48 hr. After removal of essentially all volatile products *in vacuo*, the resultant white solid was washed with minimal dry ether to remove the last traces of acid. After drying *in vacuo* with warming for several hr, the powdery, white solid of stannous trifluoromethanesulfonate obtained was used as such without further purification. Note: Preparation and all handling of $Sn(OSO_2CF_3)_2$ should be carried out under an inert atmosphere inthe strict absence of moisture.

Stannous triflate promoted aldol reaction between ketone and aldehyde (Table 1).

A typical reaction procedure is described for the reaction of 3-pentanone and n-butyraldehyde; to a suspension of stannous triflate (0.458 g, 1.1 mmol) and N-ethylpiperidine (0.138 g, 1.2 mmol) in 2 ml of dichloromethane was added dropwise 3-pentanone (0.086 g, 1.0 mmol) in 2 ml of CH_2Cl_2 at −78° under argon with stirring. At this point the suspension became a soln. After the mixture was stirred for 30 min, n-butyraldehyde (0.093 g, 1.3 mmol) in 2 ml of CH_2Cl_2 was added dropwise at this temp. The mixture was allowed to stand for 2.5 hr, then added to a vigorously stirred pH 7 phosphate buffer—CH_2Cl_2 mixture at 0°. After separation of the organic layers, the aqueous layer was extracted with CH_2Cl_2, three times, then the combined organic layers dried over Na_2SO_4. After concentration *in vacuo* the resultant oil was purified by flash column chromatography (hexane–Et_2O = 4:1) to yield 5-hydroxy-4-methyl-3-octanone (0.136 g, 86%, *erythro–threo* = >91:9). IR (neat) 3450, 1705 cm^{-1}; NMR (CCl_4) δ 0.88–1.56 (m, 13 H), 2.4–2.7 (m, 3 H), 3.6 (s, 1 H), 3.85 (m, 1 H), 2.70 MHz ^1H NMR ($CDCl_3$) δ 3.89 (m, J = 3 Hz, *erythro*) and 3.65 (m, J = 7 Hz, *threo*). All other aldol products (Table 1) gave identical spectral data with those reported in the literature.

Synthesis of α,β-epoxyketone (Table 2)

A typical reaction procedure is described for the reaction of bromoacetone and benzaldehyde; to a suspension of stannous triflate (355 mg, 0.85 mmol) and Et_3N (110 mg, 1.09 mmol) in 2 ml of THF was added dropwise bromoacetone (87 mg, 0.64 mmol) in 2 ml of THF at −78° under argon with stirring. After the mixture was stirred for 30 min, benzaldehyde (108 mg, 1.02 mmol) in 2 ml of THF was added dropwise and the mixture was stirred for another 30 min at this temp. The reaction was quenched with 10% aqueous citric acid soln and the organic materials were extracted with ether three times and dried over Na_2SO_4. After evaporation of the solvent, the resultant crude adduct in 2 ml of N,N-dimethylformamide was added dropwise to a suspension of KF (136 mg, 2.34 mmol) and dicyclohexyl-18-crown-6 (914 mg, 2.46 mmol) in 2 ml of N,N-dimethylformamide at room temp under argon with stirring. After the mixture was stirred for 12 hr, the reaction was quenched with pH 7 phosphate buffer soln and the organic materials were extracted with ether three times. The combined organic extracts were washed with brine and dried over Na_2SO_4. After evaporation of the solvent, the resultant oil was purified by silica-gel column chromatography (hexane–Et_2O = 8:1) to afford 3,4-epoxy-4-phenyl-2-butanone in 72% yield (*cis*:*trans* = 70:30) (Entry 1). IR (neat) 1715, 700 cm^{-1}; NMR ($CDCl_3$) δ for *cis* isomer, 1.77 (s, 3 H), 3.72 (d, J = 5 Hz, 1 H), 4.25 (d, J = 5 Hz, 1 H), 7.26 (s, 5 H), for *trans* isomer, 2.13 (s, 3 H), 3.42 (d, J = 2 Hz, 1 H), 3.93 (d, J = 2 Hz, 1 H), 7.26 (s, 5 H).

Other spectral data are presented:

3,4-*Epoxy*-6-*phenyl*-2-*hexanone* (Entry 2). IR (neat) 1710, 700 cm^{-1}; NMR ($CDCl_3$) δ for *cis* isomer 1.6–2.2 (m, 2 H), 2.03 (s, 3 H), 2.5–3.16 (m, 3 H), 3.28 (d, J = 4.5 Hz, 1 H), 7.14 (s, 5 H), for *trans* isomer 1.6–2.2 (m, 2 H), 1.87 (s, 3 H), 2.5–3.3 (m, 4 H), 7.14 (s, 5 H).

2,3-*Epoxy*-1,5-*diphenyl*-1-*pentanone* (Entry 3). IR (neat) 1690, 700 cm^{-1}; NMR ($CDCl_3$) δ for *cis* isomer 1.1–2.4 (m, 2 H), 2.4–3.5 (m, 3 H), 3.95 (d, J = 4.6 Hz, 1 H), 6.74–8.20 (m, 10 H), for *trans* isomer, 1.1–2.4 (m, 2 H), 2.4–3.5 (m, 3 H), 3.64 (d, J = 2.0 Hz, 1 H), 6.74–8.20 (m, 10 H).

2,3-*Epoxy*-4-*methyl*-1-*phenyl*-1-*pentanone* (Entry 4). IR (neat) 1690, 700 cm^{-1}; NMR ($CDCl_3$) δ for *cis* isomer 0.65–1.70 (m, 7 H), 2.7–3.0 (m, 1 h), 3.97 (d, J = 4.6 Hz, 1 H), 7.1–8.2 (m, 5 H), for *trans* isomer 0.65–1.60 (m, 7 H), 2.7–3.0 (m, 1 H), 3.73 (d, J = 2.0 Hz, 1 H), 7.1–8.2 (m, 5 H).

1,2-*Epoxy*-4,4-*dimethyl*-1-*phenyl*-3-*pentanone* (Entry 5). IR (neat) 1710, 700 cm^{-1}; NMR ($CDCl_3$) δ for *cis* isomer 0.92 (s, 9 H), 4.00 (d, J = 4.8 Hz, 1 H), 4.12 (d, J = 4.8 Hz, 1 H), 7.20 (s, 5 H), for *trans* isomer 1.16 (s, 9 H), 3.51 (d, J = 2.0 Hz, 1 H), 3.69 (d, J = 2.0 Hz, 1 H), 7.12 (s, 5 H).

4,5-*Epoxy*-2,2-*dimethyl*-7-*phenyl*-3-*heptanone* (Entry 6). IR (neat) 1710, 700 cm^{-1}; NMR ($CDCl_3$) δ for *cis* isomer 1.17 (s, 9 H), 1.5–2.3 (m, 2 H), 2.4–3.0 (m, 2 H), 3.21 (q, J = 4.6 Hz, 1 H), 3.87 (d, J = 4.6 Hz, 1 H), 7.11 (s, 9 H), for *trans* isomer 1.08 (s, 9 H), 1.75–2.05 (m, 2 H), 2.57–3.05 (m, 3 H), 3.32 (d, J = 1.8 Hz, 1 H), 7.10 (s, 5 H).

4,5-*Epoxy*-2,2,6-*trimethyl*-7-*phenyl*-3-*heptanone* (Entry 7). IR (neat) 1710 cm^{-1}; NMR ($CDCl_3$) δ for *cis* isomer 0.75–1.6 (m, 7 H), 1.17 (s, 9 H), 2.69 (dd, J = 2.4 Hz, 8 Hz, 1 H), 3.67 (d, J = 2.4 Hz, 1 H), for *trans* isomer 0.70–1.90 (m, 7 H), 1.17 (s, 9 H), 2.63 (dd, J = 2.0 Hz, 6.2 Hz, 1 H), 3.38 (d, J = 2.0 Hz, 1 H).

Cross aldol reaction between ketones (Table 3)

A typical reaction procedure is described for the reaction of propiophenone with acetophenone (Entry 4); to a suspension of stannous triflate (0.458 g, 1.1 mmol) and N-ethylpiperidine (0.138 g, 1.2 mmol) in 2 ml of CH_2Cl_2 was added dropwise propiophenone (0.134 g, 1.0 mmol) in 2 ml of CH_2Cl_2 at 0° under argon with stirring. After the mixture had been stirred for 15 min, acetophenone (0.156 g, 1.3 mmol) in 1 ml of CH_2Cl_2 was added dropwise at this temp. The mixture was allowed to stand for 1 hr, then pH 7 phosphate buffer added. After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2, three times, then the combined organic extracts dried over Na_2SO_4. After evaporation under reduced pressure, the resultant oil was purified by preparative TLC (hexane–Et_2O = 9:1) to yield crystalline *threo*-3-hydroxy-2-methyl-1,3-diphenyl-1-butanone (0.151 g, 60%). IR (neat) 3480, 1660 cm^{-1}; NMR (CCl_4) δ 1.35 (d, J = 7 Hz, 3 H), 1.45 (s, 3 H), 4.0 (q, J = 7 Hz, 1 H), 4.6 (s, 1 H), 7.0–7.6 (m, 8 H), 7.68–8.0 (m, 2 H).

Other spectral data are presented:

3-*Cyclohexyl*-3-*hydroxy*-2-*methyl*-1-*phenyl*-1-*propanone* (Entry 1). IR (neat) 3450, 1660 cm^{-1}; NMR ($CDCl_3$) δ 1.24 (d, J = 7 Hz, 3 H), 1.1–2.0 (br, 10 H), 3.5 (q, J = 7 Hz, 1 H), 3.72 (s, 1 H), 7.26–7.5 (m, 3 H), 7.72–7.95 (m, 2 H).

3-*Cyclopentyl*-3-*hydroxy*-2-*methyl*-1-*phenyl*-1-*propanone* (Entry 2). IR (heat) 3500, 1660 cm^{-1}; NMR (CCl_4) δ 1.24 (d, J = 7 Hz, 3 H), 1.3–2.0 (br, 8 H), 3.38 (q, J = 7 Hz, 1 H), 3.44 (s, 1 H), 7.3–7.54 (m, 3 H), 7.78–8.0 (m, 2 H).

3-*Ethyl*-3-*hydroxy*-2-*methyl*-1-*phenyl*-1-*pentanone* (Entry 3). IR (neat) 3450, 1660 cm^{-1}; NMR (CCl_4) δ 0.58–1.0 (m, 6 H), 1.5 (d, J = 7 Hz, 3 H), 3.48 (s, 1 H), 7.1–7.4 (m, 3 H), 7.6–7.9 (m, 2 H).

3-*Hydroxy*-2,3-*dimethyl*-1,5-*diphenyl*-1-*pentanone* (Entry 5). IR (neat) 3450, 1660 cm^{-1}; NMR (CCl_4) δ 1.1–1.4 (m, 6 H), 1.6–2.1 (m, 2 H), 2.55–2.9 (m, 2 H), 3.65 (q, J = 7 Hz, 1 H), 4.05 (s, 1 H), 7.0–7.55 (m, 8 H), 7.9–8.1 (m, 2 H).

3-*Cyclohexyl*-3-*hydroxy*-2-*ethyl*-1-*phenyl*-1-*propanone* (Entry 6). IR (neat) 3500, 1660 cm^{-1}, NMR (CCl_4) δ 0.76 (t, J = 7 Hz, 3 H), 1.0–1.94 (br, 12 H), 3.1–3.5 (m, 2 H), 7.2–7.4 (m, 3 H), 7.7–7.9 (m, 2 H).

Threo-3-*hydroxy*-2-*ethyl*-1,3-*dipehnyl*-1-*butanone* (Entry 7). IR (neat) 3450, 1660 cm^{-1}, NMR (CCl_4) δ 0.8 (t, J = 7 Hz, 3 H), 1.45 (s, 3 H), 1.6–2.0 (m, 2 H), 3.78 (dd, J = 6 Hz, 8 Hz, 1 H), 4.1 (s, 1 H), 6.8–7.65 (m, 10 H).

2-*Chloro*-3-*cyclohexyl*-3-*hydroxy*-1-*phenyl*-1-*propanone* (Entry 8). IR (neat) 3500, 1680 cm^{-1}, NMR (CCl_4) δ 1.1–2.2 (br, 10 H), 3.32 (br, s, 1 H), 4.86 (s, 1 H), 7.26–7.5 (m, 3 H), 7.78–7.96 (m, 2 H).

3-*Cyclohexyl*-3-*hydroxy*-2,2-*dimethyl*-1-*phenyl*-1-*propanone* (Entry 9). IR (neat) 3360, 1680 cm^{-1}; NMR (CCl_4) δ 1.1–2.4 (m, 17 H), 7.1–7.3 (m, 3 H), 7.8–8.2 (m, 2 H).

5-*Hydroxy*-4-*methyl*-5-*phenyl*-3-*hexanone* (Entry 10). IR (neat) 3450, 1690 cm^{-1}; NMR (CCl_4) δ for *threo* isomer 0.64 (t, J = 7 Hz, 3 H), 1.02 (d, J = 7 Hz, 3 H), 1.28 (s, 3 H), 1.75–2.2 (m, 2 H), 2.95 (*q*, J = 7 Hz, 1 H), 3.95 (br, 1 H), 7.0–7.3 (br, s, 5 H), for *erythro* isomer 0.78 (d, J = 7 Hz, 3 H), 1.0 (t, J = 7 Hz, 3 H, 1.36 (s, 3 H), 2.44 (q, J = 7 Hz, 2 H), 2.82 (q, J = 7 Hz, 1 H), 3.9 (br, 1 H), 7.1–7.5 (br, s, 5 H).

2-*Benzoyloxy*-3-*cyclohexyl*-3-*hydroxy*-1-*phenyl*-1-*propanone* (Entry 11). IR (neat) 3500, 1720, 1690 cm^{-1}; NMR ($CDCl_3$) δ 1.4–2.1 (m, 10 H), 2.8 (br, 1 H), 6.12 (s, 1 H), 7.35–7.8 (m, 6 H), 8.05–8.4 (m, 4 H).

2-*Benzoyloxy*-3-*hydroxy*-1,3-*diphenyl*-1-*butanone* (Entry 12). IR (neat) 3460, 1720, 1690 cm^{-1}; NMR ($CDCl_3$) δ 1.65 (s) and 1.78 (s, 3 H), 3.9 (br, 1 H), 6.25 (s) and 6.32 (s, 1 H), 7.0–8.2 (m, 15 H).

3-Acetylthiazolidine-2-thione was prepared from Ac_2O and thiazolidine-2-thione. 3-Propanoylthiazolidine-2-thione and 3-(3-phenylpropanoyl)thiazolidine-2-thione were prepared from the corresponding acyl chlorides and thiazolidine-2-thione according to the procedure described in ref. 14.

The aldol type reaction of 3-*acylthiazolidine*-2-*thione with aldehyde* (Table 4)

A general procedure is described for the cross aldol reaction between 3-propanoylthiazolidine-2-thione and benzaldehyde: To the CH_2Cl_2 suspension (2.0 ml) of stannous triflate (480 mg, 1.15 mmol) and N-ethylpiperidine (155 mg, 1.37 mmol) was added dropwise the CH_2Cl_2 soln (1.2 ml) of 3-propanoylthiazolidine-2-thione (163 mg, 0.93 mmol) at $-78°$. After further stirring at this temp for 15 min, a CH_2Cl_2 soln (1.2ml) of benzaldehyde (146 mg, 1.38 mmol) was added to the mixture, and the mixture was further stirred for 20 min. The reaction was quenched with pH 7 phosphate buffer soln and the white ppt was removed through Celite. The organic material was extracted with ether three times, the extracts were dried over Na_2SO_4, and evaporated *in vacuo*. The residual oil was purified by silica-gel column chromatography to afford 3-(3-hydroxy-2-methyl-3-phenylpropanoyl)-thiazolidine-2-thione in 94% yield (Entry 4). IR (neat) 3450, 1690 cm^{-1}, NMR ($CDCl_3$) δ 1.21 (d, J = 7 Hz, 3 H), 2.77–3.17 (m, 3 H), 4.00–4.25 (m, 2 H), 4.63–4.97 (m, 2 H), 7.33 (s, 5 H).

Other spectral data are presented:

3-(3-*Hydroxy*-3-*phenylpropanoyl*)*thiazolidine*-2-*thione* (Entry 1). IR (neat) 3400, 1680 cm^{-1}, NMR ($CDCl_3$) δ 3.13 (t, J = 7 Hz, 2 H), 3.35 (br, 1 H), 3.58 (d, J = 6 Hz, 2 H), 4.40 (t, J = 7 Hz, 2 H), 5.12 (t, J = 6 Hz, 1 H), 7.20 (s, 5 H).

3-(3-*Hydroxy*-5-*phenylpentanoyl*)*thiazolidine*-2-*thione* (Entry 2). IR (neat) 3420, 1690 cm^{-1}, NMRT ($CDCl_3$) δ 1.67–1.97 (m, 2 H), 2.60–2.87 (m, 2 H), 3.10 (br, 1 H), 3.17 (t, J = 7 Hz, 2 H), 3.30–3.43 (m, 2 H), 3.92–4.23 (m, 1 H), 4.47 (t, J = 7 Hz, 2 H), 7.20 (s, 5H).

3-(3-*Hydroxy*-4-*methylpentanoyl*)*thiazolidine*-2-*thione* (Entry 3). IR (neat) 3450, 1700 cm^{-1}, NMR ($CDCl_3$) δ 0.93–1.00 (d, J = 6 Hz, 6 H), 1.73 (m, 1 H), 3.00 (br, 1 H), 3.23–3.47 (m, 4 H), 3.77–4.00 (m, 1 H), 4.60 (t, J = 7 Hz, 2 H).

3-(3-*Hydroxy*-2-*methyl*-5-*phenylpentanoyl*)*thiazolidine*-2-*thione* (Entry 5). IR (neat) 3450, 1690 cm^{-1}, NMR ($CDCl_3$) δ 1.21 (d, J = 7 Hz, 3 H), 1.60–2.00 (m, 2 H), 2.47–2.90 (m, 2 H), 2.97 (br, 1 H), 3.13 (t, J = 7 Hz, 2 H), 3.87–4.10 (m, 1 H), 4.43 (t, J = 7 Hz, 2 H), 4.57 (dq, J = 3 Hz, 7 Hz, 1 H), 7.20 (s, 5 H).

3-(3-*Hydroxy*-2,4-*dimethylpentanoyl*)*thiazolidine*-2-*thione* (Entry 6). IR (neat) 3450, 1690 cm^{-1}, NMR ($CDCl_3$) δ 0.90 (d, J = 8 Hz, 8 H), 1.03 (d, J = 6 Hz, 3 H), 1.22 (d, J = 7 Hz, 3 H), 1.45–1.95 (m, 1 H), 2.95 (br, 1 H), 3.33 (dt, J = 2 Hz, 7 Hz, 2 H), 3.61 (dd, J = 4 Hz, 8 Hz, 1 H), 4.57 (t, J = 7 Hz, 2 H), 4.77 (dq, J = 4 Hz, 7 Hz, 1 H).

3-(2-*Benzyl*-3-*hydroxy*-3-*phenylpropanoyl*)*thiazolidine*-2-*thione* (Entry 7). IR (neat) 3470, 1680 cm^{-1}, NMR ($CDCl_3$) δ 2.33–3.20 (m, 4 H), 3.40 (br, 1 H), 3.87–4.07 (m, 2 H), 5.16–5.50 (m, 2 H), 7.00–7.57 (m, 10 H).

3-(2-*Benzyl*-3-*hydroxy*-5-*phenylpentanoyl*)*thiazolidine*-2-*tione* (Entry 8). IR (neat) 3450, 1690 cm^{-1}, NMR ($CDCl_3$) δ 1.17–2.17 (m, 2 H), 2.37–3.13 (m, 7 H), 3.93–4.17 (m, 3 H), 5.03–5.27 (m, 1 H), 7.23 (s, 10 H).

The structures of these compounds were further confirmed by converting to the corresponding methyl ester.

Derivations of the aldol adduct into ester, amide and aldehyde

Ester. To a MeOH soln (2 ml) of 3-(3-hydroxy-2-methyl-3-phenylpropanoyl)thiazolidine-2-thione (86 mg, 0.31 mmol) was added powdered K_2CO_3 (100 mg, 0.72 mmol) and the mixture was stirred for several min till the yellow color of the soln disappeared completely. A pH 7 phosphate buffer was added to the mixture and the organic materials were extracted with ether. The extracts were dried over Na_2SO_4 and then evaporated *in vacuo*. The crude product was purified by silica-gel TLC to afford the corresponding methyl ester (56 mg, 95%).

Amide. To CH_2Cl_2 soln (2 ml) of 3-(3-hydroxy-2-methyl-3-phenylpropanoyl)thiazolidine-2-thione (90 mg, 0.32 mmol) was added a CH_2Cl_2 soln of benzylamine (101 mg, 0.94 mmol) at room temp. The yellow color of the soln disappeared immediately, and pH 7 phosphate buffer soln was added. The organic materials were extracted with EtOAc and the extracts were dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by silica-gel TLC to afford the corresponding amide (77 mg, 90%).

Aldehyde. The OH function of the adduct was protected under the standard conditions (2 equiv isopropyldimethylsilyl chloride, 2 equiv Et_3N in CH_2Cl_2 at 0°, overnight) in 87% yield.

To a toluene soln (1.0 ml) of this protected compound (82 mg, 0.22 mmol) was added a toluene soln (0.80 ml, 1.83 ml/mmol) of DIBAL at $-78°$ and the mixture was further stirred for 10 min at this temp. The reaction was quenched with pH 7 phosphate buffer soln (0.2 ml) and Na_2SO_4 was added as a drying agent. After the removal of the ppts through Celite, the solvent was evaporated *in vacuo* and the residual oil was purified by silica-gel column chromatography to afford 3-isopropyldimethylsilyloxy-2-methyl-3-phenylpropanal in 75% yield.

Preparation of chiral diamine (6)

(S)-1-*Methyl*-2-[(*piperidin*-1-*yl*)*methyl*]*pyrrolidine*. To a CH_2Cl_2 soln (30 ml) of dicyclohexylcarbodiimide (7.10 g, 34 mmol) was added Boc-(*S*)-proline (7.30 g, 34 mmol) at 0° .15 min later, a CH_2Cl_2 soln (20 ml) of piperidine (3.20 g, 38 mmol) was slowly added to the mixture at 0° and the mixture was slowly warmed up to room temp and further stirred overnight. The solvent was evaporated *in vacuo* and EtOAc(100 ml) was added, and the ppt was removed by filtration. The organic layer was washed with 10% citric

acid soln, 4% $NaHCO_3$ soln and brine, and dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by silica-gel column chromatography to afford the corresponding amide (7.10 g, 74%).

A THF soln (20 ml) of the amide was slowly added to a THF suspension (20 ml) of $LiAlH_4$ (2.27 g, 60 mmol) at 0°, and the mixture was refluxed for 3.5 hr. Then, sat. Na_2SO_4 aq was added to the mixture at 0° and the organic materials were collected by decantation. The organic layer was dried over Na_2SO_4–K_2CO_3, and the solvent was removed by evaporation. The resultant oil was distilled to afford (**6**) (3.36 g, 73%), b.p. 126°/35 mm Hg, IR (neat) 2935, 2770, 1450 cm^{-1}, NMR ($CDCl_3$) δ 1.28–1.88 (m, 10 H), 1.88–2.50 (m, 8 H), 2.42 (s, 3 H), 2.92–3.15 (m, 1 H); $[\alpha]_D^{20}$ − 65.6° (*c* 0.56, EtOH).

Preparation of chiral diamine (**10**)

(2*S*,2′*S*)-2-*Methoxymethyl*-1-[(1-*methylpyrrolidin*-2-*yl*)*methyl*]*pyrrolidine*. To a THF (10 ml) suspension of KH (0.81 g, 20 mmol) was added a THF soln (40 ml) of (2*S*,2′*S*)-2-hydroxymethyl-1-[(1-methylpyrrolidin-2-yl)methyl]pyrrolidine[22] (3.75 g, 18.9 mmol) at room temp and the mixture was stirred for 1 hr at this temp. To this mixture was added a THF soln (20 ml) of MeI (2.68 g, 18.9 mmol) over 3 hr and the mixture was stirred overnight. The mixture was poured into sat. NaCl aq and the organic layer was extracted with ether. The extracts were dried over K_2CO_3 and then evaporated *in vacuo*. The resultant oil was distilled to afford **10** (2.59 g, 65%), b.p. 75°/0.6 mm Hg; IR (neat) 2950, 2770, 1450 cm^{-1}, NMR ($CDCl_3$) δ 1.0–2.7 (m, 14 H), 2.2 (s, 3 H), 2.7–3.4 (m, 4 H), 3.2 (s, 3 H); $[\alpha]_D^{20}$ − 156.3° (*c* 1.0, EtOH).

Enantioselective cross aldol reaction between ketone and aldehyde (Tables 7 and 8)

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 CH_2Cl_2 was added dropwise propiophenone (78 mg, 0.58 mmol) in 1.5 ml of CH_2Cl_2 at − 78° under argon. 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 CH_2Cl_2 was added dropwise, and the mixture was stirred for 5 min at this temp. Then the mixture was cooled to − 95°, and benzaldehyde (91 mg, 0.86 mmol) in 1.5 ml of CH_2Cl_2 was added dropwise. The mixture was further stirred for 30 min at the same temp, then quenched with pH 7 phosphate buffer. The organic layer was extracted with ether three times and the combined extracts were dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by silica-gel TLC to afford 3-hydroxy-2-methyl-1,3-diphenyl-1-propanone (103 mg, 75%). The optical purity of the product was determined by the measurement of ^1H and ^{19}F NMR spectra of the corresponding MTPA ester.

Enantioselective aldol type reaction of 3-*acetylthiazolidine*-2-*thione* (Table 9)

A typical procedure is described for the reaction of 3-acetyl-thiazolidine-2-thione and benzaldehyde using (*S*)-**6** as a chiral ligand; to a suspension of stannous triflate (253 mg, 0.61 mmol) and N-ethylpiperidine (80 mg, 0.71 mmol) in 1.5 ml of CH_2Cl_2 was added dropwise 3-acetylthiazolidine-2-thione (85 mg, 0.53 mmol) in 1.0 ml of CH_2Cl_2 at − 78° under argon. After the mixture was stirred for 15 min, (*S*)-1-methyl-2-[(piperidin-1-yl)methyl] pyrrolidine (124 mg, 0.77 mmol) in 1.0 ml of CH_2Cl_2 was added dropwise, and the mixture was stirred for 5 min at this temp. Then the mixture was cooled to − 95°, and benzaldehyde (96 mg, 0.91 mmol) in 1.0 ml of CH_2Cl_2 was added dropwise. The mixture was further stirred for 1 hr at this temp, then quenched with 0.2 N HCl. The organic layer was extracted with ether and the extracts were washed with brine, and dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by silica-gel column chromatography to afford the aldol product (112 mg, 79%). The optical purity of the product was determined by the ^1H NMR measurement of the corresponding methyl ester using $Eu(hfc)_3$ as a chiral shift reagent.

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