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STEREOSELECTIVE SYNTHESIS OF CIS-α,β-EPOXYKETONES VIA DIVALENT TIN ENOLATE

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A convenient method for the stereoselective synthesis of cis-β-substituted-α,β-epoxyketone is established employing $Sn(OTf)_2$ mediated cross aldol reaction between α-bromoketone and aldehyde followed by successive treatment of the adduct with KF-dicyclohexyl-18-crown-6.

α,β-Epoxyketone is known as a versatile synthetic intermediate because of its multiple functionality and it is expected that stereoselective synthesis of these α,β-epoxyketones would furnish a new entry into the stereoselective construction of various polyoxygenated compounds.[1)]

Though the trans-β-substituted-α,β-epoxyketones are easily obtained by the hydrogen peroxide epoxidation of α,β-unsaturated ketones,[2)] the formation of cis-β-substituted-α,β-epoxyketones cannot be attained by the same procedure because the reaction is carried out under thermodynamic control. Therefore, a reported method for the synthesis of cis-epoxyketones needs multistep manipulations starting from cis-α,β-unsaturated ketones.[3)]

Recently, we reported a new aldol reaction using stannous trifluoromethanesulfonate.[4)] And the mildness of this reaction prompted us to examine the reaction of α-bromoketone with aldehyde to obtain α-bromo-β-hydroxyketone, which would then be converted to the α,β-epoxyketone. In this case, syn-α-bromo-β-hydroxyketone[5)] is expected to form cis-α,β-epoxyketone via intramolecular SN2 type closure of the oxirane ring.[6)]

In the first place, we examined the stereoselectivity of the aldol reaction between bromoacetone and benzaldehyde. According to the previously mentioned procedure, stannous triflate was treated with bromoacetone in the presence of N-ethylpiperidine at -78 °C in dichloromethane, followed by addition of benzaldehyde to afford the cross aldol products in 57% yield with the syn(1)-anti(2) ratio of about 1:1. With the aim of raising the syn-anti ratio, screenings of the reaction solvents and bases were performed. [Table I].

As shown in this table, the stereoselectivity of this reaction is widely dependent on the reaction solvent, and it was found that tetrahydrofuran is the best solvent realizing syn-anti ratio of 81:19. On the other hand, effect of the base is small, and rather higher selectivity was achieved by the employment of triethylamine.

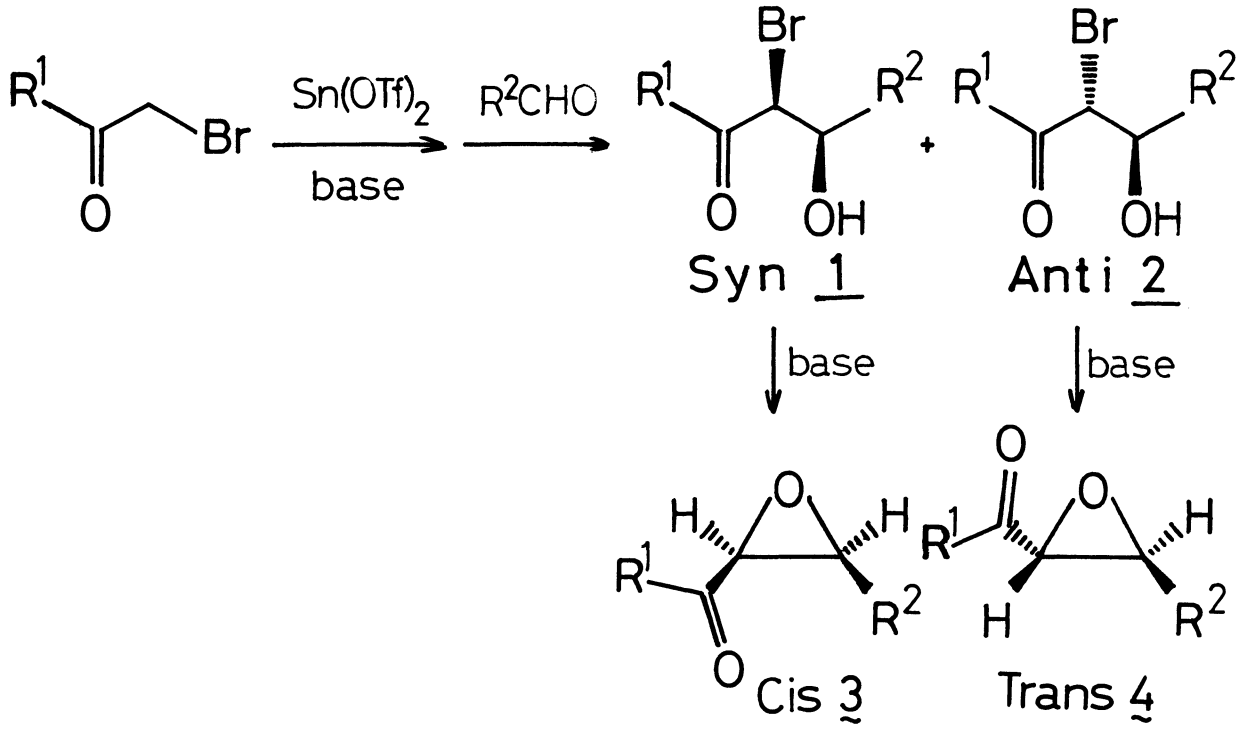

Table I. Solvent Effect on the Stereoselectivity of the Aldol Reaction[a)]

Entry	Solvent	Yield of Aldol (%)[b)]	Syn : Anti[c)]
1	CH_2Cl_2	57	1 : 1
2	THF	61	81 : 19
3	toluene	80	43 : 57
4	Et_2O	32	1 : 1

a) Reaction between bromoacetone and benzaldehyde. Enolization was carried out at -78 °C for 15 min employing N-ethylpiperidine as base, then aldehyde added and reaction run for 1 h. Molar ratio of $Sn(OTf)_2$: N-ethylpiperidine : bromoacetone : benzaldehyde = 1.1:1.2:1.0:1.1.

b) Isolated yield.

c) The diastereomer ratio was determined by 90 MHz ^1H NMR, by integration of the characteristic methyl protons. Syn isomer appears at δ 2.19 and anti isomer at δ 2.33.

Next, we examined the oxirane-formation step, and it was found that syn-α-bromo-β-hydroxyketone quite easily isomerized into thermodynamically stable anti-α-bromo-β-hydroxyketone[7)] and then cyclized to afford trans-α,β-epoxyketone. For example, when 81:19 mixture of (1) and (2) was treated with triethylamine, exclusive formation of trans-α,β-epoxyketone was observed in nearly quantitative yield. Then, we further examined various HBr captors and finally found that use of KF-dicyclohexyl-18-crown-6 affords the corresponding epoxyketone with minimum amount of isomerized product. [Table II].

Table II. Base Effect on the Oxirane Formation Step[a)f)]

Entry	Base	Cis : Trans[d)]
1	Et_3N[b)]	trans only
2	CsF[b)]	67 : 33
3	KF [b) e)]	trans only
4	KF/dicyclohexyl-18-crown-6[c)]	70 : 30

a) Reaction was carried out at 0 °C for 12 h using the adduct of bromoacetone and benzaldehyde (syn : anti=80 : 20).
b) Molar ratio of aldol adduct : base = 1 : 5.
c) Molar ratio of aldol adduct : base : crown ether = 1 : 4 : 4.
d) The diastereomer ratio was determined by 90 MHz ^{1}H NMR, by integration of the characteristic oxirane protons. Cis isomer has the coupling constant of 5 Hz (δ 3.72, 4.25), and trans isomer has that of 2 Hz (δ 3.42, 3.93).
e) It takes 3 days to complete the reaction.
f) Epoxyketone was obtained in almost quantitative yield in each case.

Having attained the best conditions for this reaction, we finally examined the stereoselectivity which could be achieved between various α-bromoketones and aldehydes, and found that in each case, cis-epoxyketone can be obtained in moderate to high stereoselectivity. [Table III].

Table III. Synthesis of α,β-Epoxyketones[a)]

Entry	α-Bromoketone	Aldehyde	Yield of α,β-Epoxyketones (%)[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-bromoketone. All samples gave satisfactory ^{1}H NMR and IR spectra.
c) The diastereomer ratios were determined by 90 MHz ^{1}H 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 tetrahydrofuran, higher yield without loss of diastereoselectivity was obtained.

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 triethylamine (110 mg, 1.09 mmol) in 2 ml of tetrahydrofuran was added dropwise bromoacetone (87 mg, 0.64 mmol) in 2 ml of tetrahydrofuran at -78 °C under argon atmosphere with stirring. After the mixture was stirred for 30 min, benzaldehyde (108 mg, 1.02 mmol) in 2 ml of tetrahydrofuran was added dropwise and the reaction mixture was stirred for another 30 min at this temperature. The reaction was quenched with 10% aqueous citric acid solution and the organic materials were extracted with ether three times and dried over anhydrous 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 potassium fluoride (136 mg, 2.34 mmol) and dicyclohexyl-18-crown-6 (914 mg, 2.46 mmol) in 2 ml of N,N-dimethylformamide at room temperature. under argon with stirring. After the mixture was stirred for 12 hours, the reaction was quenched with pH 7 phosphate buffer solution and the organic materials were extracted with ether three times. The combined organic extracts were washed with brine and dried over anhydrous 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 1,2-epoxy-1-phenyl-3-butanone in 72% yield (cis : trans = 70 : 30).

It is noted that various cis-epoxyketones can be easily obtained stereoselectively on treatment of α-bromo-β-hydroxyketones, formed by the stannous triflate mediated aldol reaction, with potassium fluoride-18-crown-6. Further studies directed towards the utilization of this reaction for synthesis of polyoxygenated natural products are now in progress.

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7) For example, syn-isomer partially isomerizes into anti-isomer on silica gel or when kept long at room temperature.

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