in a small amount of C_6H_6 and subjected to the preparative separation on silica gel thin-layer[11] with n-C_6H_{14}–$(CH_3)_2CO$ (2: 3) as developing solvent. The major fraction due to I was scraped, extracted with $CHCl_3$–EtOH (1: 1) and centrifuged to remove the silica gel. The supernatant solution was concentrated to dryness *in vacuo* and the residue was recrystallized from n-C_6H_{14}–C_6H_6 (9: 1) to colorless needles(I), mp 138°. Yield approximately 26 mg in each case of the decomposition experiments. No depression of mp was observed on admixture with the authentic sample of *cis*-4-cyclohexene-1,2-dicarboximide.[6] The infrared, nuclear magnetic resonance and mass spectra were entirely identical with those of the authentic sample. Mass Spectrum *m/e*: 151.065 (M^+, Calcd. for $C_8H_9O_2N$ 151.063), 123 (M^+—CO), 108 (M^+—CONH).

11) 0.5 mm layer of Silica gel GF_{254}, activated at 110° for 1 hour.

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A Stereoselective Synthesis of α-Chloro-α-phenylacetamide by the Reaction of optically Active Schiff Base with Dichlorocarbene

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Optically active N-benzylidene-*R*(+)- and *S*(−)-α-methylbenzylamines (**1b,c**) were allowed to react with dichlorocarbene to give optically active α-methylbenzylamine-α-chloro-α-phenylacetamides (**3b,c**), and the ratio of diastereomers was R–R: S–R=73: 27 and S–S: R–S=79: 21, respectively.

Keywords——stereoselective synthesis; α-chloro-α-phenylacetamide; optically active Schiff base; dichlorocarbene; ^{1}H–NMR

Fields and Sandri[2] reported that the addition of dichlorocarbene to the carbon-nitrogen double bond of N-benzylideneaniline gave 1,3-diphenyl-1,2-dichloroaziridine, followed by facile conversion to α-chloro-α-phenylacetamide by rearrangement under hydrolysis conditions. Several similar aziridine formations have been also recorded.[3–6] The mechanism of these reactions was proposed by Brooks and co-workers to proceed through the formation of the intermediate carbonium ion.[7]

We tried to apply these reactions to the stereoselective synthesis of α-chloro-α-phenylacetamides (**3**) using the optically active Schiff bases (**1b, c**). The Schiff bases (**1b, c**), N-benzylidene-*R*(+)-α-methylbenzylamine (**1b**) and N-benzylidene-*S*(−)-α-methylbenzylamine (**1c**), were prepared by the reaction of the corresponding optically active amine with benzaldehyde in benzene. Prior to the reactions with **1b** and **1c**, dichlorocarbene, generated *in situ* from sodium methoxide and chloroform, was allowed to react with N-benzylidenebenzylamine (**1a**) in anhydrous n-hexane to give N-benzyl-α-chloro-α-phenylacetamide (**3a**) in a 37% yield. Furthermore, in order to examine the racemization of the optically active Schiff base during the reaction, hydrolysis of **1c** with 6N hydrochloric acid was attempted, but the specific rotation

1) Location: *5–1, Oe-hon-machi, Kumamoto, 862, Japan.*
2) E.K. Fields and J.M. Sandri, *Chemical Industry* (London), **1959**, 1216.
3) J.A. Deyrup and R.B. Greenwald, *Tetrahedron Letters*, **1965**, 321.
4) J.A. Deyrup and R.B. Greenwald, *J. Am. Chem. Soc.*, **87**, 4538 (1965).
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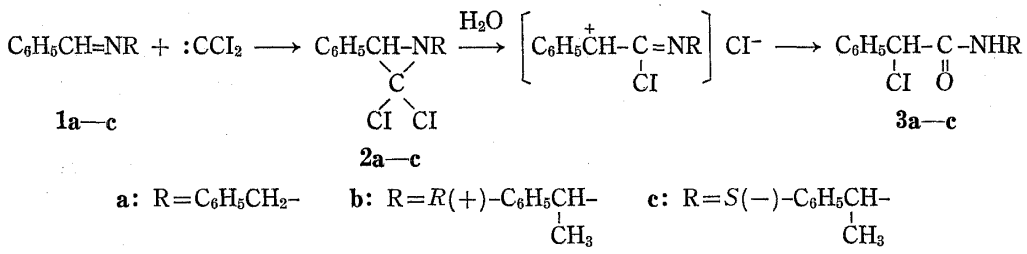

Chart 1

of the formed optically active α-methylbenzylamine showed little racemization. The reactions with **1b** and **1c** were carried out under the similar reaction conditions, without isolation of the intermediately formed dichloroaziridine (**2**), and the resulting optically active diastereomers (**3b, c**) were obtained in a 29—37% yield. The specific rotations of **3b** and **3c** showed $[\alpha]_D^{15}$ (EtOH)+101.4° and $[\alpha]_D^{15}$ (EtOH)−102.8°, respectively, in a crude product, and $[\alpha]_D^{15}$ (EtOH)+154.6° and $[\alpha]_D^{15}$ (EtOH)−157.1° in a pure state after recrystallization from ethanol until they did not show further change of the specific rotation. The configuration of the α-carbon atom in **3b** and **3c** obtained, which was asymmetrically induced by the adjacent optically active amino group, was decided by the comparison of the specific rotation of the authentic samples synthesized by the alternative route. The authentic sample, N-*S*-α-methylbenzyl-*S*-α-chloro-α-phenylacetamide (**4a**), was prepared by the reaction of *S*(−)-α-methylbenzylamine with *S*(+)-α-chloro-α-phenylacetylchloride (**5a**), which was synthesized through diazotation and chlorination of *S*(+)-phenylglycine.[8]

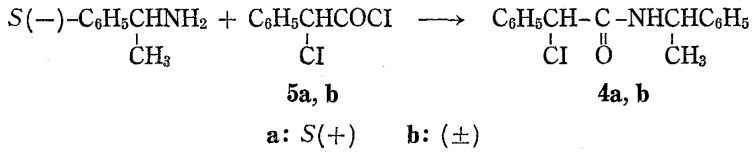

Chart 2

The specific rotation of **3c** in the pure state after recrystallization showed the same value as that of **4a** and, therefore, the configuration and the direction of α-chloro-α-phenylacetyl moiety of **3c** was clearly proved to be *S*(+). To the contrary, it is reasonable to conclude that **3b** involves *R*(−) configuration.

The specific rotations of these diastereomers (**3a—c** and **4a—b**) obtained are listed in Table I.

Table I. N-Alkyl-α-chloro-α-phenylacetamide (**3b—c** and **4a—b**)

	Configuration of α-chloro-α-phenylacetyl moiety	$[\alpha]_D^{15}$ (*c*, EtOH)[a]	Ratio of diastereomer[b]	$[\alpha]_D^{15}$ (*c*, EtOH)[c]
3b	*R*(−)	+101.4° (*c*=1.1)	R-R : S-R =73:27	+154.6° (*c*=0.6)
3c	*S*(+)	−102.8° (*c*=1.1)	S-S : R-S =79:21	−157.1° (*c*=0.6)
4a	*S*(+)	—	S-S : R-S =100:0	−153.5° (*c*=1.3)
4b	(±)	−89.4° (*c*=1.6)	S-S : R-S =50:50	—

a) These specific rotations were given by measuring the corresponding crude products.
b) The ratio of diastereomers were calculated from integration of ^{1}H-NMR spectra.
c) These specific rotations were given by measuring the compounds purified until they did not show further change.

The ratio of the diastereomers in the crude products of **3b** and **3c** was also determined by ^{1}H-nuclear magnetic resonance (NMR) spectrum. The α-chloromethine proton of *S*-α-

8) S.C.J. Fu, S.M. Birnbaum, and J.P. Greenstein, *J. Am. Chem. Soc.*, **76**, 6054 (1965).

methylbenzyl-α-chloro-α-phenylacetamide (**4b**), prepared from *S*(−)-α-methylbenzylamine and (±)-α-chloro-α-phenylacetylchloride (**5b**), exhibited two singlets at 5.25 and 5.30 ppm in equal integration, as shown in Figure 1. These two singlets were also observed in the ^{1}H–NMR spectra of the crude products of **3b** and **3c**, though the integration was, of course, in unequal. By the calculation of the integration, the ratio of the diastereomers in the crude products of **3b** and **3c** was determined to be R–R: S–R=73: 27 and S–S: R–S=79: 21, respectively.

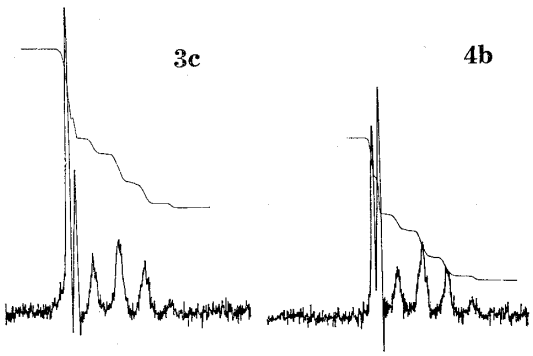

Fig. 1. NMR Spectra of α-Chloromethine Shift in **3c** and **4b**

Experimental

The specific rotations were measured by JASCO DIP-4 Polarimeter using 10 mm cell. ^{1}H–NMR spectra were taken with JNMC-60H at 60 MHz in $CDCl_3$. Infrared(IR) spectra were obtained on JASCO IRA-1 spectrophotometer.

N-Benzylidenebenzylamine (1a—c)——A solution of benzaldehyde (10.6 g, 100 mmol) in benzene (10 ml) was gradually added into a solution of amine (100 mmol) in benzene (30 ml) under cooling with ice-water. The reaction mixture was dried over anhydrous Na_2SO_4 (10 g) overnight at room temperature. After removal of the solvent, the residue was distilled under reduced pressure. The compounds (**1a—c**) obtained are listed in Table II.

Table II. N-Benzylidenebenzylamine (**1a—c**)

	bp (mmHg)	$[\alpha]_D^{15}$ (*c*, EtOH)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
1a	134° (1.5)	—	$C_{14}H_{13}N$	86.11	6.71	7.17	86.46	6.51	6.93
1b[a]	143° (4.0)	−72.4° (*c*=2.6)	$C_{15}H_{15}N$	86.08	7.22	6.69	85.69	7.04	6.57
1c[b]	126° (1.5)	+69.4° (*c*=2.5)	$C_{15}H_{15}N$	86.08	7.22	6.69	85.90	7.38	6.91

a) *R*(+)-$C_6H_5\underset{\displaystyle CH_3}{\underset{|}{C}}HNH_2$, $[\alpha]_D^{15}$ +40.0° (*c*=3.1, benzene)
b) *S*(−)-$C_6H_5\underset{\displaystyle CH_3}{\underset{|}{C}}HNH_2$, $[\alpha]_D^{15}$ −42.2° (*c*=5.7, benzene)

Examination of Racemization of N-Benzylidene-*S*(−)-α-methylbenzylamine (1c)——N-benzylidene-*S*(−)-α-methylbenzylamine (**1c**) (1.5 g, 7.2 mmol) was hydrolyzed with 6N HCl (20 ml) for 6 hr. The solution was extracted with ether (10 ml) to remove the formed aldehyde. The aqueous solution was made to alkaline with 10N NaOH, and then extracted with ether (15 ml). The extract was washed with H_2O (10 ml) twice, and dried over anhydrous Na_2SO_4. After removal of ether, the residue was distilled under reduced pressure to give *S*(−)-α-methylbenzylamine (0.6 g, 69%): bp 83—84° (20 mmHg), $[\alpha]_D^{15}$ −42.0° (*c*=6.8, benzene).

N-Alkyl-α-chloro-α-phenylacetamides (3a—c)——A mixture of N-benzylidenebenzylamine (**1a—c**) (10 mmol), NaOMe (2.2 g, 40 mmol), and dry *n*-hexane (20 ml) was stirred with cooling for 4 hr. Chloroform (4.8 g, 40 mmol) was gradually added with stirring to the mixture, stirring was continued overnight at room temperature, and ether (20 ml) was added. The precipitated NaCl was filtered off. The filtrate was evaporated to dryness under reduced pressure. The residue was chromatographed on silica-gel and eluted with *n*-hexane–chloroform. The fraction containing the compound (**3a—c**) was evaporated to dryness under reduced pressure. Their configurations, physical data, ^{1}H–NMR and IR spectra, and elemental analyses are shown in Table I and Table III.

N-*S*-α-Methylbenzyl-*S*-α-chloro-α-phenylacetamide (4a) from *S*-phenylglycine

***S*(+)-α-Chloro-α-phenylacetic Acid**——This compound was prepared by adding $NaNO_2$ (11.0 g, 160 mmol) to a solution of *S*(+)-phenylglycine (15.1 g, 100 mmol) in 6N HCl (125 ml) at −5——2° according to the method of Greenstein.[8] The yield was 5.5 g (36%): bp 125—126° (3 mmHg), mp 46—47° after recrystal-

Table III. N-Alkyl-α-chloro-α-phenylacetamide (**3a**—**c** and **4a**—**b**)

	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	N	IR ν_{max}^{KBr} cm^{-1}	^{1}H-NMR spectra (δ) in $CDCl_3$
3a	95— 96	37	$C_{15}H_{14}ONCl$	69.37 (69.25)	5.43 (5.57)	5.39 (5.05)	3310(NH) 1640(C=O)	7.28 (arom, s, 5H), 7.20 (arom, s, 5H), 7.05 (NH, broad, 1H), 5.33 (CH, s, 1H), 4.43 (CH_2, d, 2H)
3b	139—140	33	$C_{16}H_{16}ONCl$	70.20 (70.53)	5.89 (5.81)	5.12 (4.92)	3280(NH) 1640(C=O)	7.24 (arom, s, 5H), 7.19 (arom, s, 5H), 6.90 (NH, broad, 1H), 5.29 and 5.25 (CH, s, 1H), 5.05 (CH, t, 1H), 1.51 (CH_3, d, 3H)
3c	143—144	29	$C_{16}H_{16}ONCl$	70.20 (69.97)	5.89 (5.60)	5.12 (4.94)	3280(NH) 1640(C=O)	7.28 (arom, s, 5H), 7.23 (arom, s, 5H), 6.90 (NH, broad, 1H), 5.30 and 5.26 (CH, s, 1H), 5.07 (CH, t, 1H), 1.51 (CH_3, d, 3H)
4a	143—144	75	$C_{16}H_{16}ONCl$	70.20 (70.17)	5.89 (5.49)	5.12 (4.92)	3280(NH) 1640(C=O)	7.21 (arom, s, 5H), 7.19 (arom, s, 5H), 7.10 (NH, broad, 1H), 5.30 (CH, s, 1H), 5.08 (CH, t, 1H), 1.52 (CH_3, d, 3H)
4b	111—112	78	$C_{16}H_{16}ONCl$	70.20 (70.18)	5.89 (5.74)	5.12 (4.90)	3280(NH) 1640(C=O)	7.38 (arom, s, 5H), 7.31 (arom, s, 5H), 7.01 (NH, broad, 1H), 5.30 and 5.25 (CH, s, 1H), 5.04 (CH, t, 1H), 1.43 (CH_3, d, 3H)

lization from dry benzene. IR ν_{max}^{film} cm^{-1}: 1720 (C=O). $[\alpha]_D^{15}$ +12.7° (c=3.7, dry benzene). *Anal.* Calcd. for $C_8H_7O_2Cl$: C, 56.33; H, 4.13. Found: C, 56.57; H, 4.14.

***S*(+)-α-Chloro-α-phenylacetylchloride (5a)**——This compound was prepared by treating *S*(+)-α-chloro-α-phenylacetic acid (4.0 g, 23 mmol) with $SOCl_2$ (3.0 g, 25 mmol) at −10°.[7] The yield was 2.3 g (53%): bp 114° (21 mmHg). IR ν_{max}^{film} cm^{-1}: 1805 (C=O).

N-*S*-α-Methylbenzyl-*S*-α-chloro-α-phenylacetamide (4a)——A solution of *S*(−)-α-methylbenzylamine (1.3 g, 10.8 mmol) in dry benzene (10 ml) was added drop by drop, into a solution of **5a** (1.0 g, 5.4 mmol) in dry benzene (10 ml) under cooling with ice-water. The reaction mixture was stirred for 4 hr at room temperature and filtered to remove the precipitated amine hydrochloride. The filtrate was washed with 1N HCl (10 ml) and with water (10 ml), respectively twice, and then dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was recrystallized from EtOH to afford **4a** (1.1 g, 75%): mp 131—132°. $[\alpha]_D^{15}$ −153.5° (c=1.3, EtOH).

N-*S*-α-Methylbenzyl-α-chloro-α-phenylacetamide (4b)——This compound was prepared by the method described in **4a** from (±)-α-chloro-α-phenylacetylchloride (**5b**) (1.1 g, 5.8 mmol) and *S*(−)-α-methylbenzylamine (1.4 g, 11.6 mmol) to give **4b** (1.2 g, 78%): mp 111—112°. $[\alpha]_D^{15}$ −89.4° (c=1.6, EtOH). The specific rotation was measured after evaporated to dryness and then drying over NaOH.