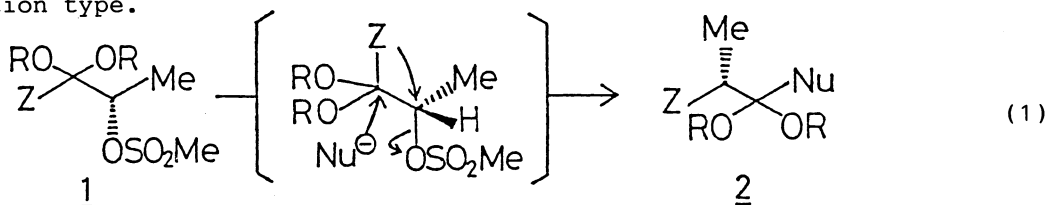


SUBSTITUTION-TYPE 1,2-REARRANGEMENT BY USING ORGANOALUMINUM REAGENTS.
SYNTHESIS OF CHIRAL α -ARYL(OR ALKENYL)KETONE ACETALS¹⁾

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Title compounds were synthesized *via* novel stereospecific 1,2-rearrangement of an aryl (or alkenyl) group accompanied by introduction of an alkyl or alkynyl group by using organoaluminum reagents.

Recently we have reported the synthesis of optically pure α -substituted aldehyde acetals (2, Eq. 1: Nu=hydride), synthetic equivalents of aldehydes, *via* reductive rearrangement by using the combination of DIBAL and Et₃Al as the activator (pull effect).²⁾ Other driving force is the push effect of the electron pairs of the oxygen atom of acetal oriented antiperiplanar to the migrating group and the attacking hydride. This rearrangement reaction is completed by introduction of hydride into the carbon bearing the migrating group, hence it is regarded as the substitution type.



If carbanion serves as a nucleophile in the same manner, introduction of a carbon chain will be realized to give title compounds (2, Eq. 1: Nu=alkyl or alkynyl). Organoaluminum reagents were chosen, as they are expected to be effective both as the activator of sulfonyloxy group and as the origin of alkyl or alkynyl groups.³⁾ At first introduction of an alkyl group was examined (Eq. 2). Sulfonyloxyketone acetal (1)⁴⁾ was treated with 3.3 equiv. of Me₃Al⁵⁾ in dichloromethane to give desired ketone acetal (3), dimethylated ether (4), and deprotected ketone (5) (Table 1, entry 1). It will be deduced to the strong Lewis acidity of the trialkyl aluminum reagent. To suppress these side reactions, following two solutions were tried. One was the exchange of solvent into toluene, because it is expected that an increase in association of the reagent in toluene will decrease its acidity. In fact, formation of the by-products became trace, but the reactivity of reagents also decreased too (entries 2,3). The other way was the conversion of a half of reagent into the ate complex, for the sake of the above effect and increasing the nucleophilicity of the reagents. Furthermore, as the alkyl group will be supplied from the ate complex which has a large nucleophilicity, the free Lewis acid is recovered and more than 1.5 equiv. of Lewis acid to the unre-

acted substrate always exists in the reaction system. Although it was needed to raise the reaction temperature, formation of by-products reduced to trace amount as expected. A typical procedure was as follows: Under an argon atmosphere, BuLi (1.5 equiv., 0.8 M hexane solution) was added to a solution of Me₃Al (3 equiv., 1 M in hexane) at -42 °C. After 30 min, a solution of 1 (1 equiv.) in toluene was added, and then the temperature was gradually raised to 0 °C. After stirring for 2 h, an excess pyridine was added. The reaction mixture was quenched by an aqueous NaHCO₃ and extracted with diethyl ether. The organic layer was concentrated and purified by preparative silica-gel TLC (hexane-diethyl ether)⁶⁾ to give (S)-ketone acetal (3) in 89% yield. The results for other compounds are shown in Table 1. Alkenyl groups similarly migrated to afford geometrically pure 3.^{7,8)}

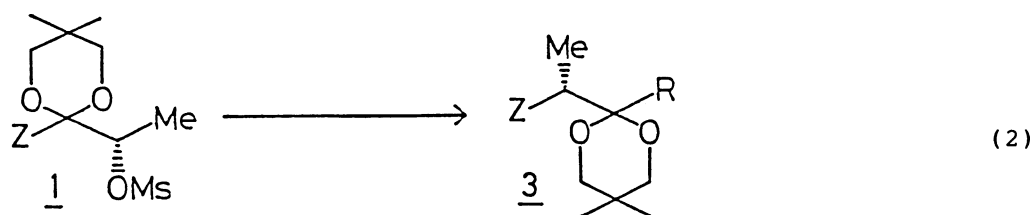


Table 1. Introduction of an alkyl group

Entry	Z	R	Reagent/equiv.	Temp/°C	Time/h	Yield%	[α] _D ^c /° (t/°C, c, in CHCl ₃)
1	MeO-C ₆ H ₄ -	Me	Me ₃ Al(3.3)	-70→-50	8	39 ^{a, c)}	
2	"	"	" (3.0)	-70→-40	10	27 ^{b, c)}	
3	"	"	" (3.0)	-40→-35	3	14 ^{b, c)}	
4	"	"	Me ₃ Al(3.0)-BuLi(1.5)	0	2	89 ^{b)}	+ 4.0 (25, 0.66)
5	"	Et	Et ₃ Al(3.0)-" (1.5)	-20→-10	5	90 ^{b)}	+22.6 (27, 0.66)
6	"	Bu	Bu ₃ Al(4.6)-" (2.3)	-15→	0 15	84 ^{b)}	+13.0 (27, 0.71)
7	Ph-	Me	Me ₃ Al(3.0)-" (1.5)	-25→	0 3	80 ^{b)}	+12.4 (18, 0.58)
8	"	Bu	Bu ₃ Al(3.0)-" (1.5)	-18→-15	3	92 ^{b)}	+15.2 (22, 0.46)
9	Ph-	Me	Me ₃ Al(3.0)-" (1.5)	-10→	0 2	94 ^{b)}	-19.3 (20, 0.49)

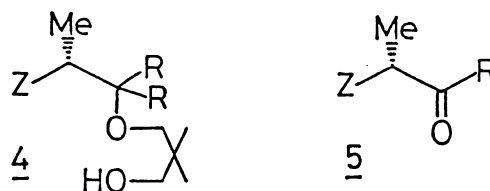
a) In toluene. b) In CH₂Cl₂.

c) Yields of by-products

entry 1: 4; 11% 5; 14%.

2: 4; trace 5; trace 1; 49%.

3: 4; 19% 5; 66%.



The effect of the structure of the substrates are summarized in Table 2. Taking into consideration the reaction temperature and time, the migratory aptitude is enhanced by migrating group in the order (Z)-alkenyl > (E)-alkenyl > p-methoxyphenyl > phenyl (entries 1,2,3,6), and by acetal groups in the order dimethyl > trimethylene > 2,2-dimethyltrimethylene (entries 3,4,5). These results might be deduced to the substituent effect of migrating groups and the steric crowding of the molecule.⁹⁾

Table 2. Migratory aptitude in introduction of a methyl group

Entry	Z	R	Temp/°C	Time/h	Yield/%	$[\alpha]_D^{20}$ (t/°C, c, in CHCl ₃)
1	Ph-CH=CH-		-25→ 0	3	80	+15.2 (22, 0.46)
2	Ph-CH=CH-	"	-10→ 0	2	94	-19.3 (20, 0.49)
3	MeO-C ₆ H ₄ -	"	0	2	89	+ 4.0 (25, 0.66)
4	"		-42→-20	4	81	+ 1.9 (26, 0.75)
5	"	Me	-45→-32	7	92	-36.5 (27, 1.11)
6	C ₆ H ₅ -		0	19	67	+ 6.1 (23, 0.69)

The enantiomeric excess of 3 was determined to be over 99% by ¹H-NMR measurement of deprotected ketone (5) (Fig. 1).^{10,11} The absolute configuration of 3 was determined to be S form from the sign of specific rotation of ketone (5); $[\alpha]_D^{32} = +256^\circ$ (c0.59, dioxane).¹²

Next, introduction of an alkynyl group was examined (Eq. 3).¹³ Treatment of 1 by the combination of diethyl hexynyl aluminum and its ate complex mainly resulted in introduction of an ethyl group to give 3 (Table 3, entry 1). Because of push effect of electron from the alkynyl group, alkynyl aluminum is weaker acid than alkyl aluminum. Therefore, reactions using alkynyl aluminum and dialkynyl aluminum³⁾ were examined in the similar manner. As the results in Table 3 show, the use of dialkynyl aluminum in toluene was the best to give desired acetal (6). Different from the case of the ate complex, the attack of alkynyl group was the main reaction. Furthermore, it is considered that the selectivity of the attacking group was influenced by the rate of migration using alkyl alkynyl aluminum (entries 2,4).

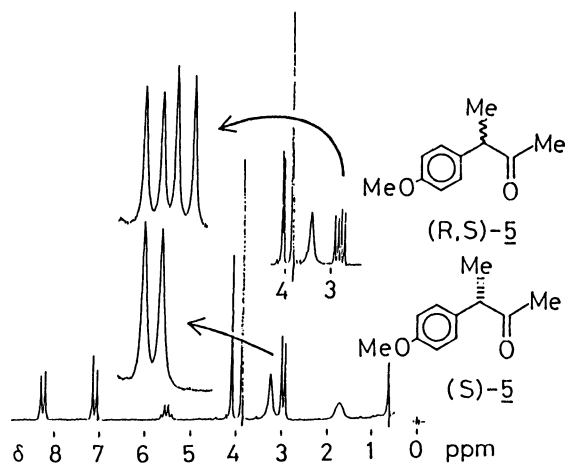


Fig. 1. Determination of e.e.

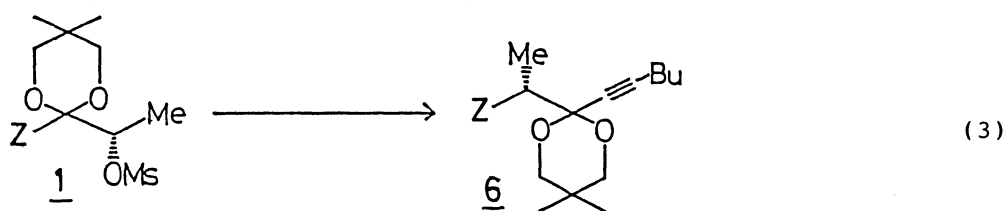


Table 3. Introduction of an alkynyl group

Entry	Z	Reagent/equiv.	Temp/°C	Time/h	Yield%	$[\alpha]_D^{20}$ (t/°C, c, in CHCl ₃)
1	MeO-C ₆ H ₄	Et ₂ Al-C≡C-Bu(3.0)-BuLi(1.5)	-20	0 3 ^{a)}	4(76 ^{c)}	—
2	"	Et ₂ Al-C≡C-Bu(3.0)	-15	0 20 ^{b)}	81(17 ^{d)}	+10.0 (24, 0.96)
3	"	EtAl(C≡C-Bu) ₂ (3.0)	-40	-20 1.5 ^{a)} -20 9	81(15 ^{d)}	"
4	Ph [^] ^	Et ₂ Al-C≡C-Bu(3.0)	-42	-10 22 ^{b)}	40(51 ^{c)}	—
5	"	EtAl(C≡C-Bu) ₂ (3.0)	-40	0 1.5 ^{b)} 0 25	68(15 ^{e)}	+62.9 (23, 0.45)
6	"	"	-20	0 4 ^{a)}	84	"

a) In toluene. b) In CH₂Cl₂. c) Yield of 3 (introduction of an ethyl group).

d) Yield of 4 (introduction of two alkynyl groups). e) Recovery of substrate (1).

References

- 1) This work was presented at the 50th National Meeting of Chemical Society of Japan, April 2, 1985, Abstract II, 1023.
- 2) Y. Honda, M. Sakai, and G. Tsuchihashi, *Chem. Lett.*, **1985**, 1153.
- 3) Substitution-type Claisen rearrangement promoted by organoaluminum reagents was reported; K. Takai, I. Mori, K. Oshima, and H. Nozaki, *Bull. Chem. Soc. Jpn.*, **57**, 446 (1984).
- 4) The starting compounds (1) were synthesized by the reported procedure^{2,6)} from (S)-O-(1-ethoxyethyl)-N,N-dimethyl lactamide.
- 5) It has been previously found that more than two equiv. of Lewis acid is needed to activate the sulfonyloxy group.²⁾
- 6) Ketone dimethyl acetal (3) was purified by preparative silica-gel TLC containing 5 wt% of Na₂CO₃.
- 7) Synthetic procedure for the alkenyl derivatives has been reported; Y. Honda, A. Ori, and G. Tsuchihashi, *Chem. Lett.*, **1986**, 13.
- 8) Determined by HPLC measurement by using Zorbax-Sil (4.6 mm x 25 cm, Du Pont); hexane/ethyl acetate=98/2 (v/v), flow rate 0.3 ml/min, $k'_Z=2.54$, $\alpha=k'_E/k'_Z=1.07$.
- 9) By the study using the Dreiding stereomodel, (Z)-alkenyl group is revealed to be located in extremely crowded circumstance, and this is considered to result its easy migration.
- 10) Ketone acetal (3) was hydrolyzed by treatment with 0.01 M HCl in acetone to give ketone (5) quantitatively.
- 11) The difference in chemical shift for the proton on C-4 of (R)-5 and (S)-5 was about 0.14 ppm in the presence of 0.35 equiv. of Eu(TFC)₃ in CCl₄. The doublet in the higher field due to (R)-5 was not detected in the reaction product.
- 12) Optically active (S)-(+)-5; $[\alpha]_D^{20} = +218^\circ$ (c1.50, dioxane), has been synthesized from (S)-2-(p-methoxyphenyl)-propionic acid: D. J. Collins and J. J. Hobbs, *Aust. J. Chem.*, **23**, 119 (1970).
- 13) A trial to introduce an alkenyl group by using diisobutyl alkenyl aluminum, which was prepared from DIBAL and alkyne, resulted in the reductive rearrangement to give the aldehyde acetal (2) quantitatively.

(Received November 22, 1985)