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ASYMMETRIC INDUCTION BY CHIRAL HETEROCYCLIC COMPOUNDS: REACTION OF CHIRAL N-METHYL-4-PHENYL-1,3-OXAZOLIDINES WITH ORGANOMETALLIC REAGENTS

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Abstract —— The reaction of (2S,4R)-2-alkyl-N-methyl-4-phenyl-1,3-oxazolidines (1a-c) with Grignard reagent gave (1R,1'R)-form compounds (2a-c) as the major product. On the contrary, the reaction of 1a-c with organotitanium reagent gave (1S,1'R)-form compounds (3a-c) as the major product. This stereoselectivity is a remarkable characteristic of the reaction of 1,3-oxazolidines with organometallic reagents.

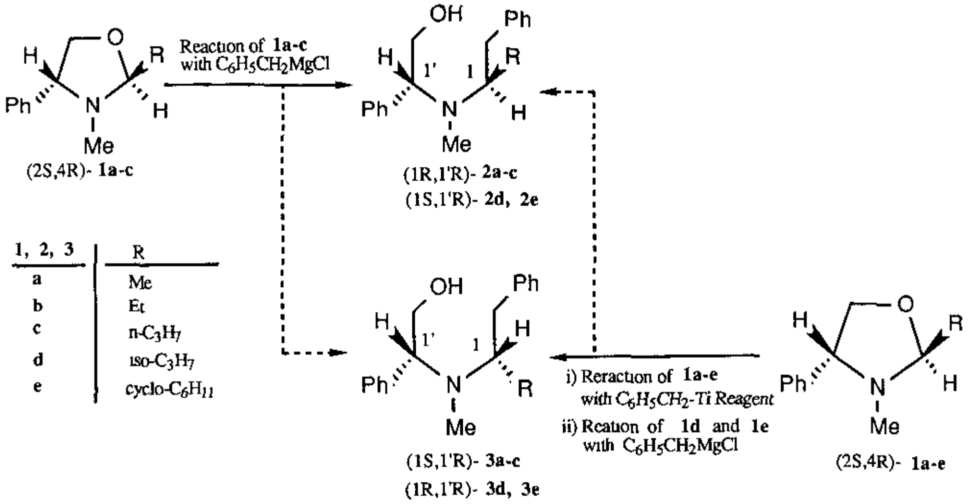
The preparation of chiral N-methyl-1,3-oxazolidines is easily achieved by the condensation of chiral N-methylethanolamines with various aldehydes, and the reaction of these compounds with Grignard reagents gave chiral amines having a newly created chiral center by cleavage of the 1,3-oxazolidine ring.[1,2] We wish to describe herein a stereoselective reaction of the chiral N-methyl-4-phenyl-1,3-oxazolidines with Grignard and organotitanium reagents.

The reaction of the (2S,4R)-2-alkyl-N-methyl-4-phenyl-1,3-oxazolidines (1a-e) with benzylmagnesium chloride in ether at room temperature afforded diastereomeric mixtures of (1R,1'R)- and (1S,1'R)-1-alkyl-N-2'-hydroxy-1'-phenylethyl-N-methyl-2-phenylethylamines (2a-e and 3a-e).[2]

On the other hand, the reaction of (2S,4R)-1a-c with benzyltitanium triisopropoxide in ether or tetrahydrofuran (THF) afforded the diastereomeric mixtures of (1R,1'R)- and (1S,1'R)-products (2a-c and 3a-c). A typical experimental procedure was as follows: Benzylmagnesium chloride (8 mM in 8 ml of THF) was slowly added dropwise to a stirred solution of chlorotitanium triisopropoxide (8 mM) in THF

(10 ml) at 0°C under a nitrogen atmosphere and the stirring was continued for 1-2 h. The resulting mixture was added dropwise to a stirred solution of 1a-c (2 mM) in THF (5 ml), and the stirring was continued at 30-40°C under a nitrogen atmosphere for 15~20 h. After treatment with a small amount of water, the resulting white precipitate was filtered off, and the organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel with CH_2Cl_2: MeOH (97:3) to give a diastereomeric mixture (2a-c and 3a-c) as a colorless oil.

Scheme 1



Further, the reaction of 1a, 1d, and 1e with dibenzyltitanium diisopropoxide gave also the diastereomeric mixtures of (1S,1'R)- and (1R,1'R)-compounds (2a, 2d, 2e; and 3a, 3d, 3e). On the other hand, the reaction of 1a with organotitanium ate-complex, i.e., chloromagnesium tetrakis(isopropanolato)benzyltitanate, gave the diastereomeric mixture of 2a and 3a.

The structures and the absolute configurations of these compounds were confirmed by comparing the proton nuclear magnetic resonance (^{1}H-nmr) spectra of 2a, 2b, 2d, 2e, 3a, 3b, 3d and 3e with related compounds described in a previous paper.[2] The structures of new compounds (1c, 2c, and 3c) were confirmed by ^{1}H-nmr and mass spectral analyses.[3] The ratio of two diastereomeric mixtures in each case was estimated by the comparison of the peak height of the ^{1}H-nmr spectra.

These experimental results are summarized in Table I.

Table I Reaction of (2S,4R)-2-Alkyl-N-methyl-4-phenyl-1,3-oxazolidines (1a-e) with Organometallic Reagents

Substrates R	Reagents	(equivalents)	Conditions °C	 h	Products Yield[a] (%)	 Ratio of 2 : 3
CH_3	$C_6H_5CH_2MgCl$	(3)	20	3	86	80 : 20[b]
C_2H_5	"	(3)	20	3	87	75 : 25[b]
n-C_3H_7	"	(2)	10	4	82	68 : 32
iso-C_3H_7	"	(3)	20	4	85	39 : 61[b]
cyclo-C_6H_{11}	"	(3)	20	4	88	25 : 75[b]
CH_3	$C_6H_5CH_2Ti(O\text{-}i\text{-}C_3H_7)_3$	(3)	40	15	83	8 : 92
C_2H_5	"	(3)	40	15	71	26 : 74
n-C_3H_7	"	(3)	30	20	63	37 : 63
CH_3	$(C_6H_5CH_2)_2Ti(O\text{-}i\text{-}C_3H_7)_2$	(2)	20	12	60	35 : 65
iso-C_3H_7	"	(3)	20	12	60	30 : 70
cyclo-C_6H_{11}	"	(3)	20	12	60	32 : 68
CH_3	$C_6H_5CH_2Ti^-(O\text{-}i\text{-}C_3H_7)_4 \cdot Mg^+Cl$	(3)	40	15	80	15 : 85
CH_3	$TiCl_4$ + $C_6H_5CH_2MgCl$	(4)	20	5	55	60 : 40

a) The yields are for isolated products.

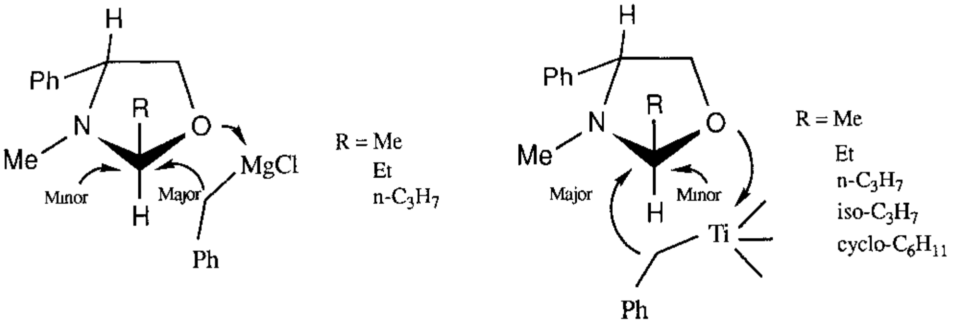
b) Cited from our previous paper (Ref. 2).

The major products (2a-c) for the reaction of (2S,4R)-1a-c with Grignard reagent were identified with the minor products obtained from the reaction of (2S,4R)-1a-c with organotitanium reagent, whereas the minor products (3a-c) obtained from the reaction with Grignard reagent were identified with the major products of the reaction with organotitanium reagent. On the other hand, the major products (3d and 3e) for the reaction of (2S,4R)-1d and 1e with Grignard reagent were identified with the major products obtained from the reaction of organotitanium reagents as shown in Scheme 1.

Previously, we had reported that the reaction of 1d and 1e with Grignard reagent results in cleavage of the 1,3-oxazolidine ring by attack of the organometallic species.[2] Then, the reaction of 1a with Grignard reagent in the presence of titanium tetrachloride was attempted since it was considered that the titanium reagent as a Lewis acid would cleave the 1,3-oxazolidine ring, followed by attack of the Grignard reagent to form the intermediate immonium salt. However, it affored 2a as the major product contrary to expectations.

Yamamoto et al.[4] reported that the attack of organotitanium reagent occurs from behind the cleaved carbon-oxygen bond of 1,3-dioxanes. Then, it was also considered in the case of 1,3-oxazolidines that the organotitanium reagent attacks the carbon atom at the 2-position of the ring from the backside of the carbon-oxygen bond, while the Grignard reagent attacks from the cleaved side of the carbon-oxygen bond as shown Scheme 2.

Scheme 2



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2) H.Takahashi, Y.Chida, K.Higashiyama, and H.Onishi, Chem. Pharm. Bull., 1985, 33, 4662.

3) The ^{1}H-nmr spectra were obtained with a JEOL JNM-FX100 and/or JNM-GX400 spectrometers. The mass spectra were recorded with a JEOL JMS-D300 spectrometer.

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