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PREPARATION AND REACTION OF FUNCTIONALIZED ORGANOINDIUM REAGENTS

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CONTENTS

PREFACE

The studies presented in this thesis have been carried out under the direction of Professor KAWAI Masao and Professor BUTSUGAN Yasuo at the Department of Applied Chemistry of Nagoya Institute of Technology during 1994-1999. The author was very happy to spend his course along with the worldwide development of indium chemistry.

The author wishes to express his grateful gratitude to Professor BUTSUGAN Yasuo and Professor KAWAI Masao for their continuous encouragement and patient advice throughout the work. The author also wishes to express his sincere thanks to Associate Professor ARAKI Shuki for his valuable advice and stimulating discussion during the course of this work. Furthermore, the author is sincerely grateful to Dr. YAMAMURA Hatsuo for his helpful discussion and comments. The author is also indebted to Messrs. IKEDA Takahiro, SHIMIZU Hidetaka, INOUE Shin'ichirou, KAMEI Toshiya and KINOSHITA Kenji for their active collaborations. Valuable discussion with the author's colleagues are gratefully acknowledged.

Finally the author thanks his parents for their affectionate encouragement throughout the work.

HIRASHITA Tsunehisa

March 1999

INTRODUCTION

In the previous decade, the chemistry of indium has attracted the interest of chemists to an increasing extent.

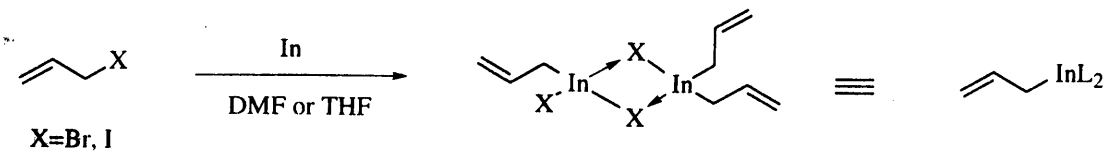
History of Organoindium Reagents in Organic Synthesis.

In contrast to the well known chemistry of B, Al and Tl in organic synthesis, very little attention had been paid to indium. In 1940, Gilman first introduced organoindium compound for chemical transformation in which triphenylindium reacted with benzaldehyde to give the corresponding alcohol in moderate yield.[1] However any advantage was not found compared to other general organometals such as organolithium and Grignard reagents. This low reactivity of organoindium compound might have prevented further investigation from synthetic view.

In 1975, Rieke reported that activated indium was prepared by the reduction of indium trichloride with potassium in xylene.[2] The reaction of ethyl α-bromoacetate with aldehyde in the presence of this activated indium afforded the corresponding β-hydroxy acetate in high yield. In 1988, Araki et al. discovered that allylindium reagents are easily prepared from allyl halides with commercially available indium and have enough reactivity for carbon-carbon bond formation with satisfactory selectivity. After this report has been published, considerable amount of studies on the synthetic uses of allylindium reagents were reported. In these years, allylindium reagents have been developed for use in water.

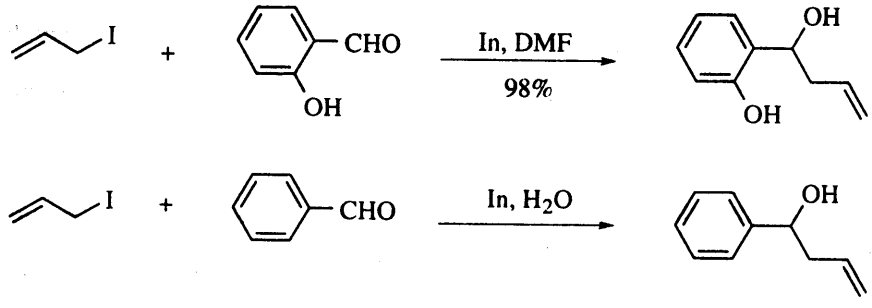
Allylation of carbonyl compounds.

The reaction of metallic indium with allyl halides or phosphates in polar solvent such as DMF and THF gave allylindium sesquihalides (Scheme 1). It is known that two-thirds of the allyl groups on the allylindium sesquihalide are transferred to the carbonyl compounds.



Scheme 1

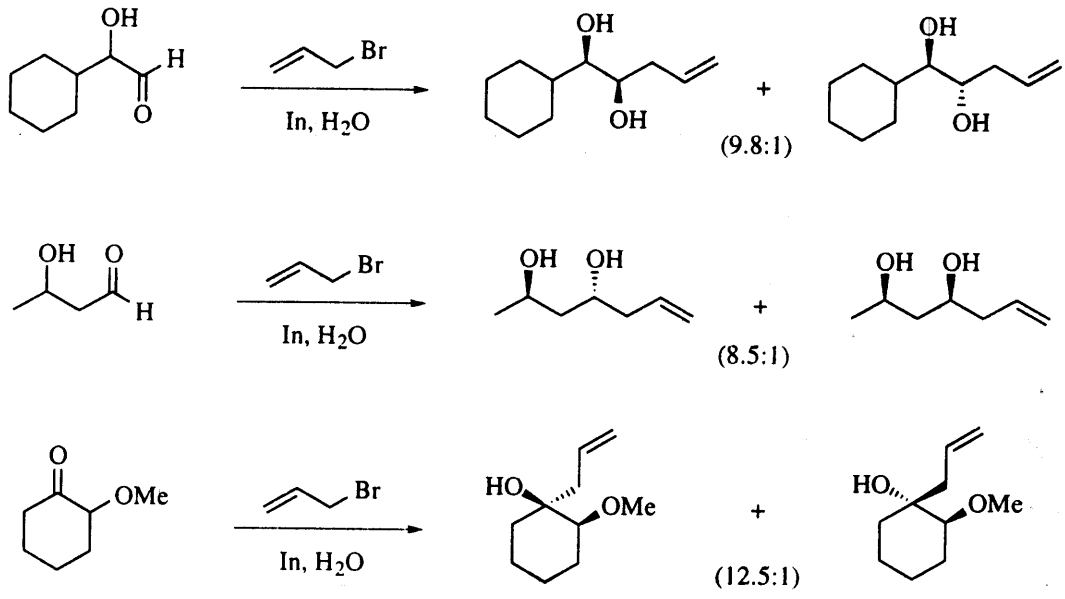
The reaction of allylindium with salicylaldehyde gives the corresponding homoallyic alcohol with no decrease of the yield compared to other ordinary carbonyl compounds such as benzaldehyde. These results showed that allylindium reagents could be compatible with activated proton. Moreover allylation can be carried out in aqueous media (Scheme 2).[4]



Scheme 2

Allylation of carbonyl compounds possessing adjacent hetero atom.

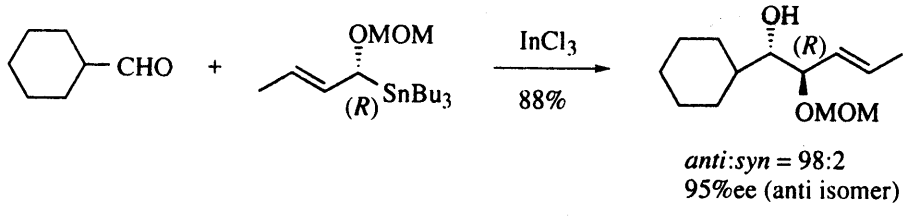
Paquette and his co-worker reported that carbonyl compounds bearing adjacent hetero atom underwent allylation in chelation mode in both aqueous and organic conditions (Scheme 3).[5] The chelation/non-chelation ratio is very high in the case where free hydroxy group was involved. Free hydroxy group played an important role in chelation of indium to determine the stereoselectivity as well as to accelerate allylation.



Scheme 3

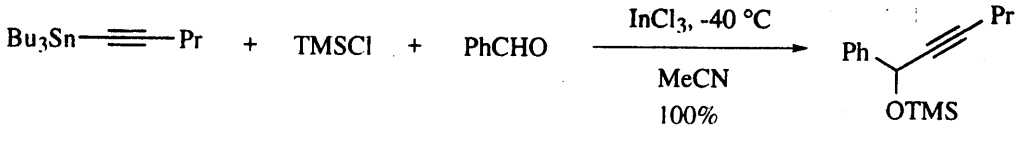
Transmetalation from allyltin compounds.

In 1993, Marshall and his co-workers reported that the reaction of allyltin with aldehyde in the presence of $InCl_3$.[6] The treatment of indium trichloride provided threo diol in the coupling reaction of chiral allyltin with aldehyde (Scheme 4).



Scheme 4

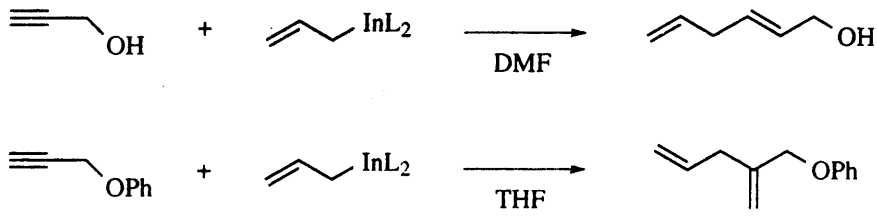
Indium trichloride also promoted the addition of alkynyltins to aldehydes (Scheme 5).[6g]



Scheme 5

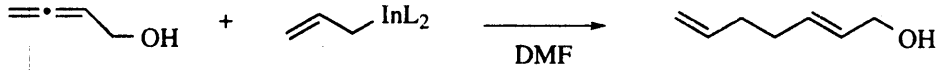
Allylindation of alkyne and allenol.

Allylindation of alkynes afford 1,4-dienes. Araki first reported that allylindation of alkynols proceeded in DMF.[7] Unactivated simple alkyne underwent smooth allylindation to give 1,4-diene by using THF as solvent instead of DMF.[8] The regioselectivity of allylindation depends on the structure of alkenes. Thus alkenes bearing hydroxy group near carbon-carbon triple bond gave inner alkene, while simple alkene or protected alkynol gave outer alkene (Scheme 6).



Scheme 6

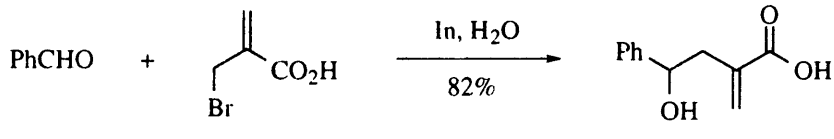
Allenols underwent allylindation to afford 1,5-dienes in high yield (Scheme 7).[9]



Scheme 7

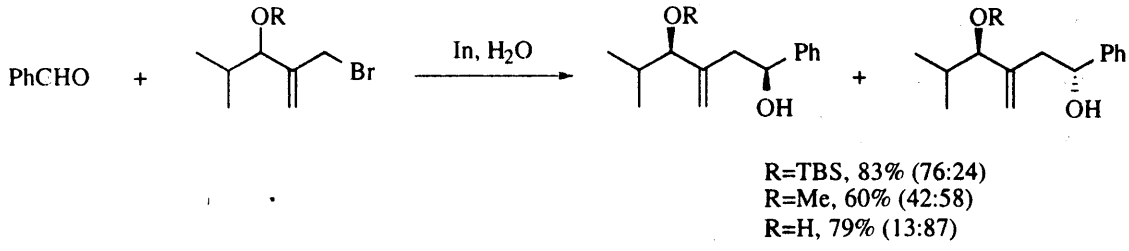
Preparation and reaction of functionalized allylindium reagents.

Some applications of functionalized allylindium reagent were reported. Allylindium possessing carboxyl group on the β-position reacted with aldehyde in water to give the corresponding homoallylic alcohol (Scheme 8).[10]



Scheme 8

The stereoselectivity of the coupling reactions of oxygen-substituted allylic bromide with aldehydes was reported (Scheme 9).[5f,11] The couplings involving hydroxy bromide and aldehyde proceeded with high levels of 1,4-asymmetric introduction.



R=TBS, 83% (76:24)
R=Me, 60% (42:58)
R=H, 79% (13:87)

Scheme 9

In Chapter 1 are described the preparation and reaction of α-halo organoindium reagents. Reaction of organoindium reagents derived from *gem*-dihalides with metallic indium with electrophile was investigated. In Chapter 2 are described the reaction of dihalopropene with indium and the coupling with resulting reagents with carbonyl compounds. 1,3-Dichloropropene gave γ-chloroallylindium reagents exclusively, giving oxiranes upon the coupling with aldehydes. In the case of 1,3-dibromopropene the results were complicated; both oxiranes and homoallylic alcohols were obtained. 3-Bromo-1-iodopropene afforded homoallylic alcohol exclusively. In Chapter 3 are described the preparation and reaction of dieneylindium and enynylindium reagents, which reacted with aldehydes at the γ-position selectively. In Chapter 4 are described the allylindation of cyclopropene derivatives. The hydroxymethyl substituent on the cyclopropenes exert significant effects based on the intramolecular chelation and controlled the stereochemical outcome of the coupling products. In Chapter 5 are described the preparation and reaction of γ-alkoxy or trimethylsilyl substituted allylindium reagents, which were prepared by the treatment of the corresponding allylic lithium compounds with $InCl_3$. The reaction of γ-alkoxyallylindium reagents with aldehydes gave the corresponding mono-protected diols. In the case of benzaldehyde high syn-selectivity was observed. α,γ-Disubstituted allylindium reagents were also investigated.

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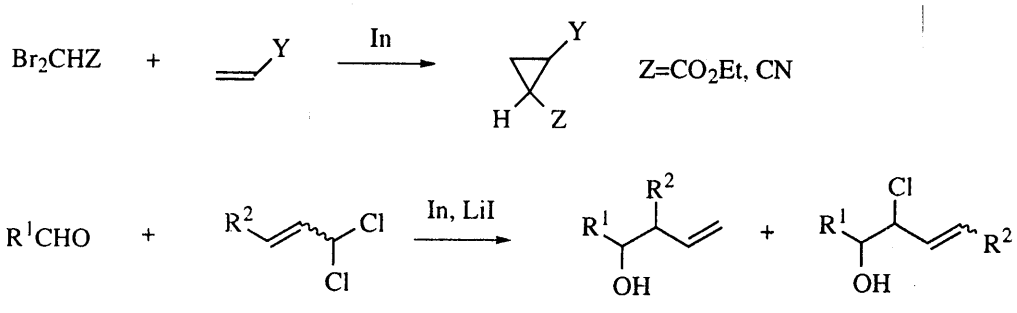
CHAPTER 1

Reaction of a-Halo Organoindium Reagentswith Carbonyl Compounds and Electron-deficient Alkenes

Summary

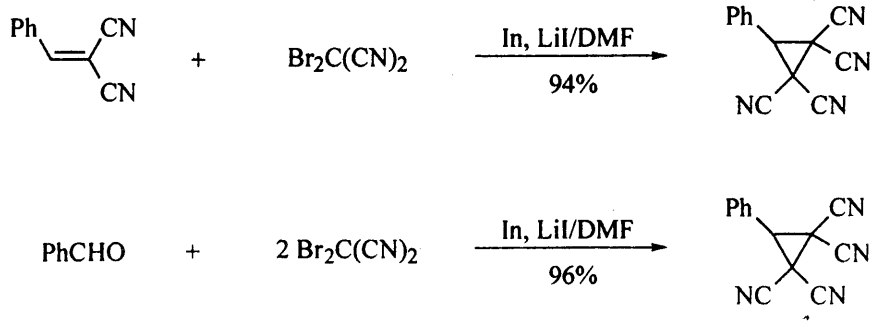
A variety of α-halo organoindium reagents were prepared *in situ* from the reaction of *gem*-dihalo compounds with indium metal, and their reactions with carbonyl compounds and electron-deficient alkenes were examined. The reactions of simple 1,1-diiodoalkanes with indium metal gave no defined products but benzal iodide gave stilbene in a moderate yield. α-Halo organoindium reagents drived from α,α-dibromo carbonyl compounds gave oxiranes and cyclopropanes upon the reactions with aldehydes and alkenes, respectively. 3,3-Dichloropropenes reacted with aldehydes in the presence of indium metal to give the corresponding chlorohydrins and/or homoallylalcohols, depending on the structures of both the dichloropropenes and aldehydes employed.



INTRODUCTION

α-Halo organometallic compounds are an interesting family of organometallic reagents. They are generally referred to as metal carbenoids and used as precursors to carbenes.[1] Organoalkaline metals[2] and organomercuries[3] possessing halogen atom at the α-carbon are such examples. In some cases, on the other hand, they behave as α-halo carbanionic species and, by the reaction with electrophiles, they are used for various organic transformations; of which the typical examples are olefination, epoxidation, and cyclopropanation. To date, a variety of α-halo organometallic compounds have hitherto been synthesized and extensively studied in organic synthesis. Simmons-Smith cyclopropanation based on zinc carbenoids is a well-known example of the versatile reactions of such metal carbenoid reagents.

Indium-mediated reactions have recently emerged as a useful tool in organic synthesis.[4] Araki and his co-worker have previously reported that the organoindium compounds derived from dibromo-substituted active methylene compounds, such as dibromomalononitrile, and indium metal reacted with alkenes and carbonyl compounds to give cyclopropanes and oxiranes, depending on the nature of the reagents and substrates (Scheme 1).[5]



Scheme 1

The most plausible intermediates of these reactions are considered to be α-halo organoindium reagents. This chapter describes further reactions of *gem*-dihalo compounds with indium metal in the presence or absence of carbon electrophiles.

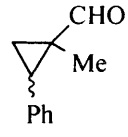
RESULTS

a. 1,1-Diiodoalkanes.

The reaction of 1,1-diiodoalkanes such as diiodomethane, 1,1-diiodooctane, and 1,1-diiodo-2,2-dimethylpropane with indium powder in *N*,*N*-dimethylformamide (DMF) was sluggish at room temperature. At higher temperature (>100 ℃) indium metal was consumed, but the reactions gave, after hydrolysis, only intractable polymeric materials. Even in the presence of electrophiles (aldehydes, acid chlorides, and electron-deficient alkenes), no products could be characterized. In THF, indium was consumed promptly in the case of diiodomethane at rt. However, in the presence of electrophole, no cross coupling product was obtained. Similary, the reaction of dibromodifluoromethane or iodoform with indium gave no cross-coupling product. Though the consumption of indium was observed, any cross coupling product could not be detected.

b. Benzal iodide.

Benzal iodide was heated with indium in DMF at 60 ℃ for 1 h. Aqueous work-up of the reaction mixture gave (*E*)- and (*Z*)-stilbene in 36% yield, together with benzaldehyde (17% yield) and benzoic acid (18%). The stilbene could be formed via indium-mediated deiodinative dimerization of benzal iodide, whereas the latter two are considered to be formed from the benzal iodide via hydrolysis and the subsequent autoxidation, respectively. The same reaction was examined in the presence of various kinds of electrophiles, but no cross-coupling was observed. Only with methacrolein, a low yield (7%) of cyclopropane **1** could be isolated.



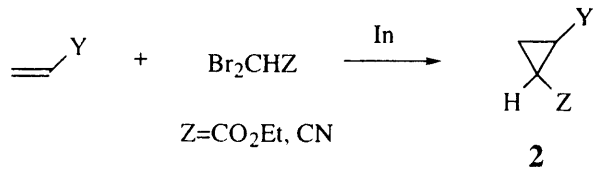
1

c. α,α-Dibromo ester, nitrile, and ketone.

The organoindium reagents derived from ethyl dibromoacetate and dibromoacetonitrile readily reacted with electron-deficient alkenes giving the corresponding cyclopropane **2** (Table 1). The yields are generally lower than those of the previously reported dibromo-substituted

active methylene cases.[5] The resulting cyclopropanes were mixtures of *cis*- and *trans*-stereoisomers, indicating that the addition of the organoindium reagents is not stereoselective.

Table 1. Indium-mediated Reaction of Ethyl Dibromoacetate and Dibromoacetonitrile with Electron-deficient Alkenes



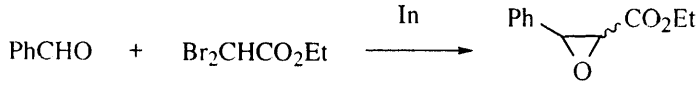
Z=CO_2Et, CN

2

Dibromo compound	Alkene	Product	Yield/%	*cis* : *trans*
Br_2CHCO_2Et	$PhCH=C(CN)_2$	**2a**	69	49 : 51
	$EtCH=CH(CN)CO_2Et$	**2b**	65	57 : 43
Br_2CHCN	$PhCH=C(CN)_2$	**2c**	60	17 : 83
	$EtCH=CH(CN)CO_2Et$	**2d**	42	44 : 56
	$CH_2=CHCO_2Et$	**2e**	15	---[a]

[a] Not determined.

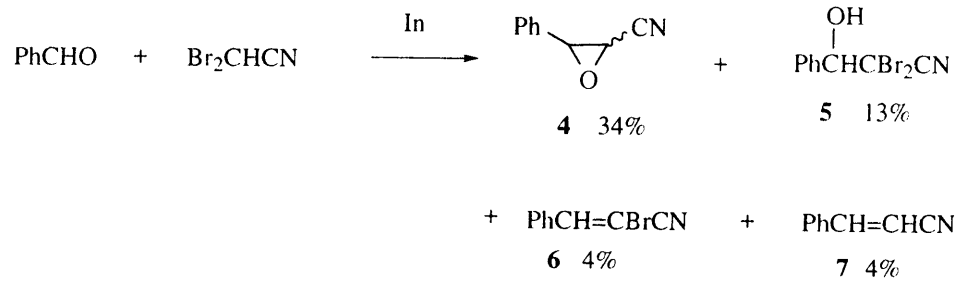
Ethyl dibromoacetate reacted with benzaldehhyde in the presence of indium metal to give a high yield of oxirane **3** (Scheme 2).



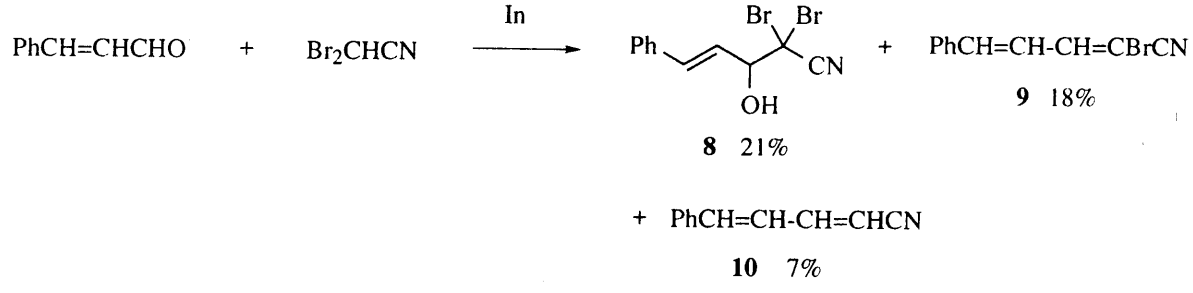
3 81%

Scheme 2

On the other hand, the reaction of the α-bromoorganoindium reagent, derived from dibromoacetonitrile, with carbonyl compounds is rather complicated; benzaldehyde gave a low yield (34%) of oxirane **4**, together with bromohydrin **5**, 2-bromocinnamonitrile (**6**), and cinnamonitrile (**7**) (Scheme 3). The reaction with cinnamaldehyde gave bromohydrin **8** and dienes **9** and **10**. The dibromo alcohols **5** and **8** are considered to be formed via a condensation of the conjugate base of dibromoacetonitrile with the aldehydes (Scheme 4).[6]

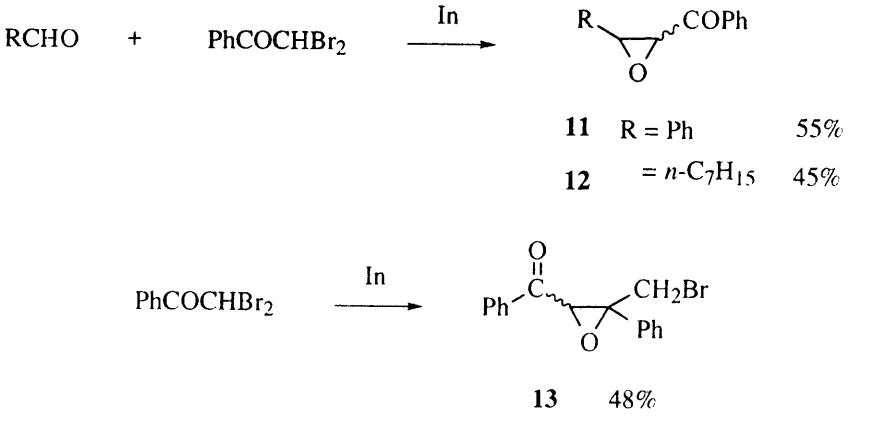


Scheme 3



Scheme 4

Upon treatment with indium powder, α-dibromoacetophenone reacted with benzaldehyde and octanal to give the corresponding oxiranes **11** and **12** in moderate yields (Scheme 3). Without aldehydes, the dibromide was dimerized to give epoxy ketone **13** in 48% yield. Interestingly, the dibromomethyl group of α,α-dibromoacetophenone was converted to a bromomethyl group in **13** during this reaction. The reaction mechanism is discussed later.

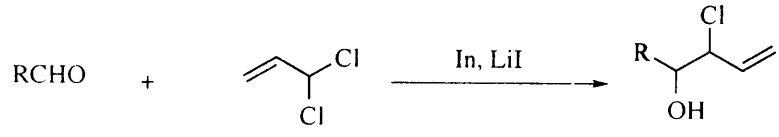


Scheme 5

d. 3,3-Dichloropropene.

Indium-mediated reaction of 3,3-dichloropropene with aldehydes in the presence of lithium iodide gave chlorohydrin **14** exclusively (Table 2). The products were mixtures of *syn*- and *anti*-stereoisomers. The stereochemical assignment was easily achieved by converting the chlorohydrin **14** to the corresponding oxirane which was analyzed by ^{1}H NMR analysis. This protocol provide a convenient route to substituted vinyloxiranes which are generally difficult to prepare.[7]

Table 2. Indium-mediated Reaction of 3,3-Dichloropropene with Aldehydes



14

Aldehyde	product	Yield/%	*syn* : *anti*
PhCHO	**14a**	93	78 : 22
4-MeOC$_6$H$_4$CHO	**14b**	72	84 : 16
PhCH=CHCHO	**14c**	55	59 : 41
Me(CH$_2$)$_2$CH=CHCHO	**14d**	42	65 : 35
Me(CH$_2$)$_6$CHO	**14e**	71	54 : 46

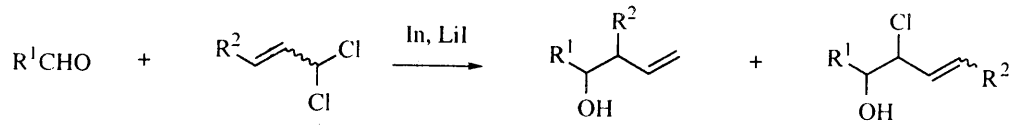
e. 1-Substituted 3,3-dichloropropenes.

3,3-Dichloro-1-phenylpropene reacted with aldehydes, in the presence of indium and lithium iodide, to give homoallylalcohol **15** as the major product together with small amounts of chlorohydrin **16** (Table 3).

Interestingly, the ratio homoallylalcohol/chlorohydrin depends largely on the aldehydes employed; with increase the bulkiness of the aldehydes, the ratio increases; and octanal, benzaldehyde, and 2-hexenal gave the corresponding homoallylalcohols exclusively. Other 1-substituted 3,3-dichloropropenes gave similar results, though the yields are lower and the reac-

tions required higher temperature (100-120 ℃). In the reaction of 3,3-dichloro-1,1-diphenylpropene with formalin, the corresponding homoallylic alcohol **15k** was obtained. It should be emphasized here that both the chlorine atoms in the starting 3,3-dichloropropenes are lost in homoallylalcohol **15**.

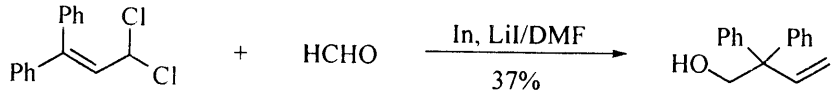
Table 3. Indium-mediated Reaction of 1-Substituted 3,3-Dichloropropene with Aldehydes



15 **16**

entry	R^1	R^2	Yield/%		entry	R^1	R^2	Yield/%	
			15	**16**				**15**	**16**
a	H	Ph	28	50	f	$Me(CH_2)_2CH=CH$	Ph	41	0
b	Et	Ph	69	10	g	Ph	Me	29	0
c	*n*-Pr	Ph	82	15	h	Ph	*n*-Pr	10	0
d	n-C_7H_{15}	Ph	50	0	i	n-C_7H_{15}	Me	27	0
e	Ph	Ph	75	0	j	n-C_7H_{15}	*n*-Pr	13	0

The reaction of 3,3-dichloro-1,1-diphenylpropene with formaldehyde gave the corresponding homoallylic alcohol exclusively (Scheme 6). With Benzaldehyde, no reaction proceeded.

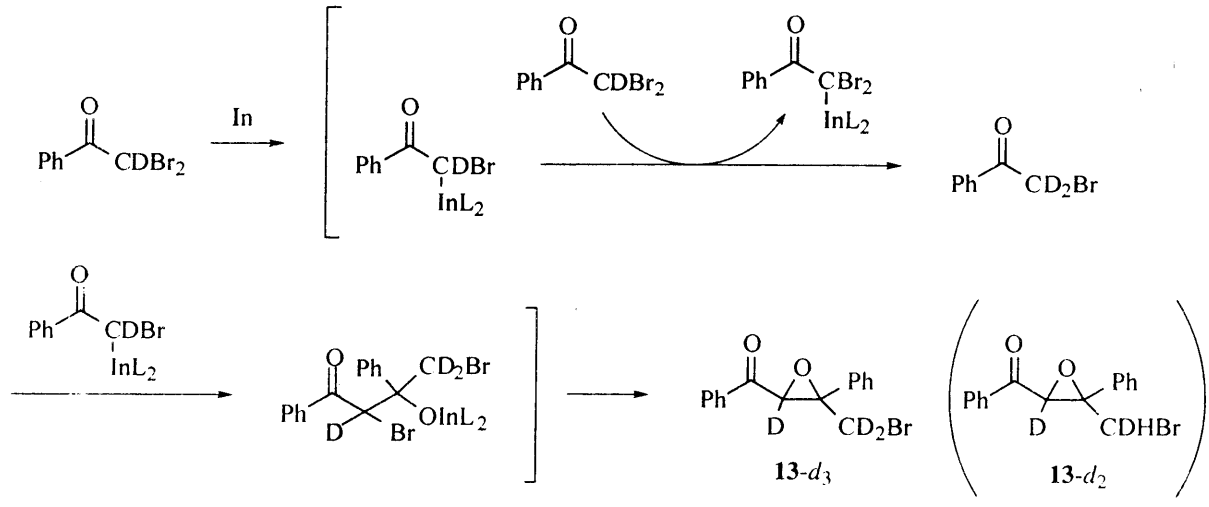


Scheme 6

DISCUSSION

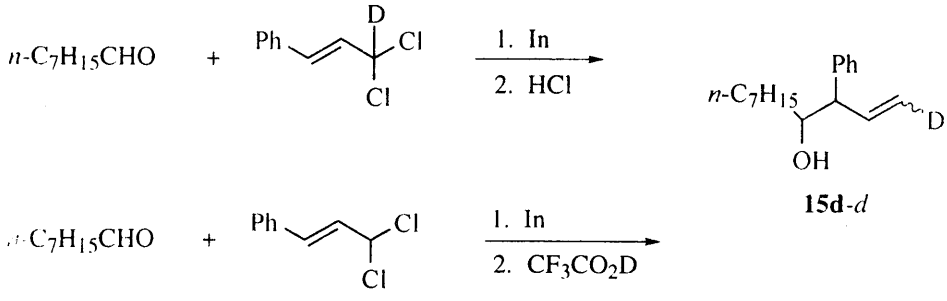
The α-haloorganoindium reagents derived from *gem*-dihalides and indium metal showed diverse reactivity toward electrophiles depending on the structures of the reagents. The presence of activating groups on the α–carbon, in particular electron-withdrawing substituents, increases the nucleophilicity of the indium carbenoids giving higher yields of coupling products with carbon electrophiles. Thus, the reactivity of the α-haloindium reagents derived from dibromoacetate, dibromoacetonitrile, and α,α-dibromoacetophenone is lower than that from dibromo-substituted active methylene compounds, generally giving lower yields of the corresponding cyclopropanes and oxiranes by the reaction with electron-deficient alkenes and carbonyl compounds, respectively. Benzal iodide scarecely reacted with such electrophiles, and simple 1,1-dihaloalkanes were failed to give any defined products.

Indium-mediated self-condensation of α,α-dibromoacetophenone gave rise to **13** which bears a bromomethyl group in place of the original dibromomethyl group. One of possible mechanisms for the formation of **13** could be a dimerization of the α-bromoorganoindium reagent, α-bromo-α-indioacetophenone. However, quenching the reaction with trifluoroacetic acid-*d* resulted in no deuterium-incorporation; thus excluding the possibility of this process. Then, we prepared α,α-dibromo-α-deuterioacetophenone and subjected to the same reaction. When quenched with diluted HCl, the product was a mixture of **13**-d_2 (64%) and **13**-d_3 (36%) based on MS and ^{1}H NMR spectroscopy. The formation of **13**-d_3 is reasonably explained by Scheme 7: *e.g.*, initially produced α-bromo- α-indioacetophenone abstracts the acidic α-D of the starting α,α-dibromo-α-deuterio-acetophenone to produce phenacyl bromide- α, α-d_2, which coupled with the indium carbnoid to furnish **13**-d_3.[8]



Scheme 7

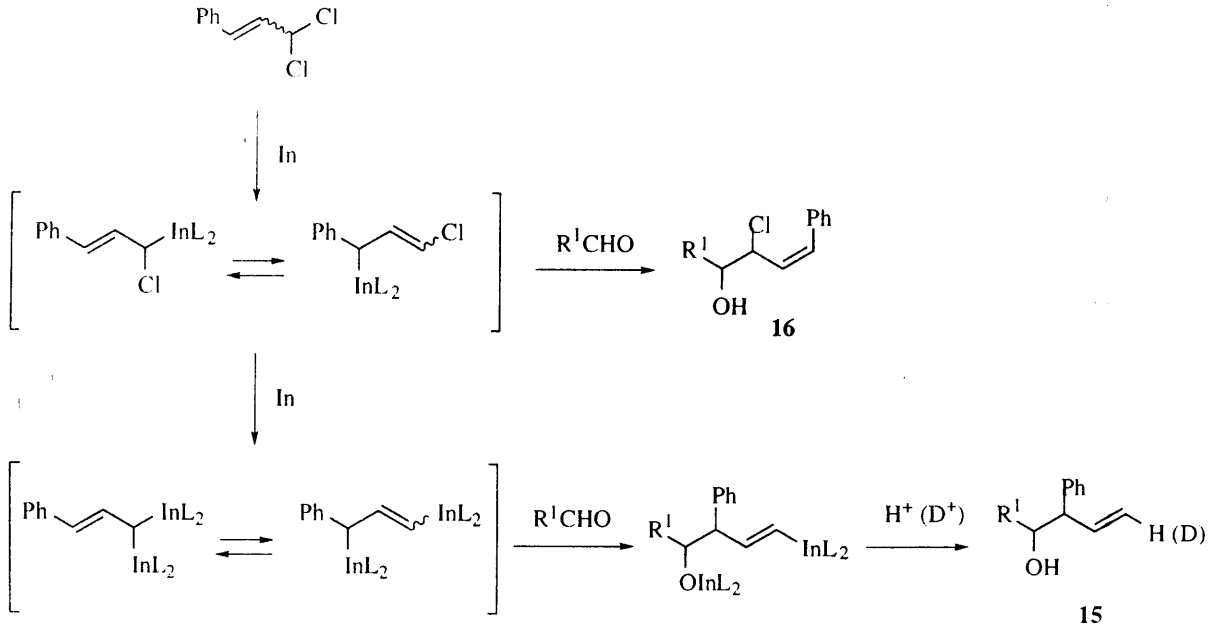
The reaction of 1-substituted 3,3-dichloropropene with aldehydes gave homoallylalcohol **15** preferentially or, in some cases, exclusively. In order to rationalize the reaction mechanism, the reaction of 3,3-dichloro-3-deuterio-1-phenylpropene with octanal was examined (Scheme 8). The coupling reaction was carried out in a usual manner and the reaction was quenched with diluted. HCl. The product **15d**-*d* (*E*:*Z* = 2.5:1) was obtained in 50% yield without loss of D. When the reaction of non-deuterated 3,3-dichloro-1-phenylpropene with octanal was quenched with trifluoroacetic acid-*d*, the same compound **15d**-*d* with 70% D was produced.



Scheme 8

Based on these results, a plausible reaction sequence for the reaction of 1-substituted 3,3-dichloropropenes is illustrated in Scheme 8, which includes *gem*-bisindium species as a key intermediate. Reactive aldehydes such as formaldehyde readily react with allylic monoindium intermediate to give chlorohydrin **16**, whereas higher aldehydes react preferentially with more nucleophilic *gem*-bisindium reagent to furnish homoallyllic alcohol **15**. Re-

cently, a variety of *gem*-bismetallic reagents are described in literature and atttract much attention;[9] however, this is the first example of allylic *gem*-bisindium compounds.



Scheme 9

EXPERIMENTAL SECTION

General. IR spectra were recorded on a JASCO IRA-102 spectrophotometer. ^{1}H NMR spectra were obtained for solutions in $CDCl_3$ on a Hitachi R-90 spectrometer (90 MHz) or a Varian XL-200 spectrometer (200 MHz) with Me_4Si as internal standard; *J*-values are given in Hz. ^{13}C NMR spectra were measured for solutions in $CDCl_3$ with a Varian XL-200 spectrometer (50 MHz). Mass spectra were measured on a Hitachi M-2000 spectrometer at 70 eV. Elemental analyses were done at the Elemental Analysis Center of Kyoto University. All reactions were carried out under argon. Indium powder (99.99%), stabilized by 0.5% MgO, was obtained from Nacalai Tesque Co. Ltd. The following materials were synthesized according to the published methods: benzal iodide,[10] 1,1-diiodo-2,2-dimethylpropane,[11] 1,1-diiodooctane,[12] dibromoacetonitrile,[13] ethyl dibromoacetate,[14] 1,1-dibromoacetophenone,[15] 3,3-dichloropropene,[16] and 3,3-dichloro-1-phenylpropene.[17]

Reaction of benzal iodide with indium. Benzal iodide (340 mg, 1.0 mmol) and indium powder (115 mg, 1.0 mmol) were stirred in DMF (3.0 mL) at 60 ℃ for 1 h. The reaction mixture was cooled to room temperature and poured into water. The products were extracted with diethyl ether. The extracts were washed with brine and dried (Na_2SO_4). After the solvent was removed under reduced pressure, the residue was column chromatographed (silica gel; dichloromethane:hexane = 1:1) to give stilbene (*E*/*Z* mixture) (32 mg, 36%), benzaldehyde (18 mg, 17%), and benzoic acid (22 mg, 18%).

Indium-induced reaction of benzal iodide with methacrolein. A mixture of indium powder (115 mg, 1.0 mmol), benzal iodide (350 mg, 1.0 mmol), and methacrolein (83 μL, 1.0 mmol) in DMF (3.0 mL) was heated with stirring at 105 ℃ for 4 h. The reaction mixture was worked up as above to give stilbene (25 mg, 28%), benzaldehyde (16 mg, 15%), and 1-methyl-2-phenylcyclopropanecarboxyaldehyde (**1**)[18] (*cis*:*trans* = 13:87) (11 mg, 7%). The *cis*/*trans* ratio was determined based on the ^{1}H NMR.

Indium-mediated reaction of ethyl dibromoacetate and dibromoacetonitrile with electron-deficient alkenes. The following reaction of ethyl dibromoacetate with

benzylidenemalononitrile represents the general procedure. A mixture of ethyl dibromoacetate (490 mg, 2.0 mmol), benzylidenemalononitrile (150 mg, 1.0 mmol), and indium powder (230 g, 2.0 mmol) in DMF (3.0 mL) was ultrasonicated for 2.5 h at room temperature. Usual aqueous work-up and column chromatography on silica gel (dichloromethane:hexane = 4:1) gave ethyl 1,1-dicyano-2-phenylcyclopropanecarboxylate (**2a**) (*cis*:*trans* = 51:49) (170 mg, 69%). Separation of the *cis*- and *trans*-isomers was achieved by careful column chromatography. Other reactions were similarly carried out and the results are summarized in Table 1.

Ethyl 1,1-dicyano-2-phenylcyclopropanecarboxylate (2a).[19] *cis*-Isomer: colourless needles; mp 75-78 ℃ ; *Rf* 0.51 (silica gel; dichloromethane:hexane = 4:1); IR (melt, cm^{-1}): 3065, 2995, 2256 (CN), 1744 (C=O), 1502, 1450, 1410, 1396, 1374, 1354, 1294, 1202, 1098, 1030, 972, 840, 740, 700; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.20 (t, *J* = 7.1 Hz, 3H, Me), 3.10 (d, *J* = 10.5 Hz, 1H, C*H*CO_2Et), 3.59 (d, *J* = 10.5 Hz, 1H, C*H*Ph), 4.20 (q, *J* = 7.1 Hz, 2H, CH_2), 7.20-7.40 (m, 5H, Ph); MS: *m/z* (rel. intensity) 195 (M^+-OEt, 9), 168 (M^+-CO_2Et, 100). *trans*-Isomer: colourless crystals; mp 68-70 ℃ (*lit.*[19] mp 68-69 ℃); *Rf* 0.63 (silica gel; dichloromethane:hexane = 4:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.38 (t, *J* = 7.1 Hz, 3H, Me), 3.14 (d, *J* = 8.1 Hz, 1H, C*H*CO_2Et), 3.69 (d, *J* = 8.1 Hz, 1H, C*H*Ph), 4.37 (q, *J* = 7.1 Hz, 2H, CH_2), 7.25-7.38 (m, 2H, Ph), 7.40-7.50 (m, 3H, Ph).

Diethyl 1-cyano-3-ethyl-1,2-cyclopropanedicarboxylate (2b). *cis*-Isomer: IR (neat, cm^{-1}): 2985, 2246 (CN), 1736 (C=O), 1464, 1380, 1316, 1292, 1250, 1188, 1094, 1030, 848; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.09 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 1.31 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.35 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.79-2.03 (m, 2H, CH_2CH_3), 2.11 (m, 1H, CH), 2.71 (d, *J* = 9.6 Hz, 1H, C*H*CO_2Et), 4.25 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 4.29 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$); MS: *m/z* (rel. intensity) 240 (M^++1, 1), 194 (M^+-OEt, 30), 166 (M^+-CO_2Et, 85), 138 (100). *trans*-Isomer: IR (neat, cm^{-1}): 2995, 2950, 2250 (CN), 1742 (C=O), 1462, 1444, 1372, 1302, 1292, 1260, 1186, 1400, 1038, 1020; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.15 (t, *J* = 7.4 Hz, 3H, CH_2CH_3), 1.26 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.33 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.56-1.83 (m, 2H, CH_2CH_3),

2.30-2.42 (m, 2H, CH ×2), 4.17 (q, J = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 4.26 (dq, J = 7.1, 2.1 Hz, 2H, $CO_2CH_2CH_3$); MS: *m/z* (rel. intensity) 240 (M^++1, 2), 194 (M^+-OEt, 42), 166 (M^+-CO_2Et, 95), 138 (100). Anal. (*cis/trans* mixture): calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.07; H, 7.04; N, 5.78.

3-Phenyl-1,1,2-cyclopropanetricarbonitrile (2c). *cis*-Isomer: colourless crystals; mp 156 ℃ (dec); IR (neat, cm^{-1}): 3050, 3025, 2256 (CN), 1604, 1502, 1450, 1342, 1276, 1094, 1014, 832, 768, 738, 698, 664, 658; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.13 (d, J = 9.6 Hz, 1H, CHCN), 3.57 (d, J = 9.6 Hz, 1H, CH), 7.51 (s, 5H, Ph); MS: *m/z* (rel. intensity) 193 (M^+, 100). Anal: calcd for $C_{12}H_7N_3$: C, 74.60; H, 3.65; N, 21.75. Found: C, 74.90; H, 3.55; N, 21.99. *trans*-Isomer: pale yellow oil; bp 170 ℃ / 3 Torr; IR (neat, cm^{-1}): 3045, 2256 (CN), 1602, 1586, 1506, 1450, 1404, 1208, 1086, 1002, 912, 784, 746, 698, 660; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.08 (d, J = 7.6 Hz, 1H, CHCN), 3.70 (d, J = 7.6 Hz, 1H, CH), 7.32 (m, 2H, Ph), 7.45 (m, 3H, Ph); MS: *m/z* (rel. intensity) 193 (M^+, 100). Anal: calcd for $C_{12}H_7N_3$: C, 74.60; H, 3.65; N, 21.75. Found: C, 74.57; H, 3.44; N, 21.81.

Ethyl 1,2-dicyano-3-ethylcyclopropanecarboxylate (2d). *cis*-Isomer: colourless oil; IR (neat, cm^{-1}): 2980, 2945, 2050 (CN), 1744 (C=O), 1466, 1370, 1296, 1252, 1188, 1100, 1018, 858, 732; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.21 (t, J = 7.3 Hz, 3H, CH_2CH_3), 1.38 (t, J = 7.3 Hz, 3H, $CO_2CH_2CH_3$), 1.80-1.96 (m, 2H, CH_2CH_3), 2.14 (m, 1H, CH), 2.65 (d, J = 9.0 Hz, 1H, CHCN), 4.33 (q, J = 7.3 Hz, 2H, $CO_2CH_2CH_3$); MS: *m/z* (rel. intensity) 164 (M^+-CO, 23), 123 (100), 119 (M^+-CO_2Et, 83). Anal: calcd for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.57. Found: C, 61.80; H, 6.25; N, 14.43. *trans*-Isomer: colourless oil; IR (neat, cm^{-1}): 2980, 2945, 2252 (CN), 1748 (C=O), 1466, 1362, 1320, 1308, 1288, 1256, 1188, 1100, 1004, 856, 732; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.17 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.39 (t, J = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.61-1.87 (m, 2H, CH_2CH_3), 2.21 (d, J = 7.4 Hz, 1H, CHCN), 2.42 (q, J = 7.4 Hz, 1H, CH), 4.39 (q, J = 7.4 Hz, 2H, $CO_2CH_2CH_3$); MS: *m/z* (rel. intensity) 193 (M^+, 100), 164 (M^+-CO, 62), 123 (98), 119 (M^+-CO_2Et, 100).

Anal: calcd for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.57. Found: C, 61.94; H, 6.29; N, 14.56.

Ethyl 2-cyanocyclopropanecarboxylate (2e).[20] ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.32 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.70-3.00 (m, 4H, CH ×4), 4.28 (q, J = 7.2 Hz, 2H, $CO_2CH_2CH_3$).

Indium-mediated reaction of ethyl dibromoacetate with benzaldehyde. A mixture of ethyl dibromoacetate (490 mg, 2.0 mmol), benzaldehyde (100 μL, 1.0 mmol), and indium powder (230 mg, 2.0 mmol) in DMF (3.0 mL) was ultrasonicated for 2 h at room temperature. Usual aqueous work-up and column chromatography on silica gel (dichloromethane:hexane = 4:1) gave 2-ethoxycarbonyl-3-phenyloxirane (**3**)[21] (*cis*:*trans* = 55:45) (160 mg, 81%). The *cis*/*trans* ratio was determined based on the ^{1}H NMR analysis.

Indium-mediated reaction of dibromoacetonitrile with benzaldehyde. This reaction was similarly carried out as above and the following products were isolated; 2-cyano-3-phenyloxirane (**4**)[22] (*cis*:*trans* = 67:33) (34%, yield), 2,2-dibromo-3-hydroxy-3-phenylpropanenitrile (**5**) (13%), 2-bromo-3-phenylpropenenitrile (**6**) (4%), and 3-phenylpropenenitrile (**7**) (4%).

2,2-Dibromo-3-hydroxy-3-phenylpropanenitrile (5). IR (neat, cm^{-1}) 3465, 2250(CN), 1498, 1454, 1194, 1050, 1028, 772, 752, 712, 700; ^{1}H NMR (90 MHz, $CDCl_3$): δ 3.26 (s, 1H, OH), 5.13 (s, 1H, CH), 7.33-7.69 (m, 5H, Ph); MS: *m/z* (rel. intensity) 201/199/197 (Br_2CHCN, 17), 107 (PhCHOH, 100); Anal: calcd for $C_9H_7Br_2NO$: C, 35.45; H, 2.31. Found: C, 35.46; H, 2.48.

2-Bromo-3-phenylpropenenitrile (6).[23] IR (neat, cm^{-1}): 2210 (CN), 1596, 1574, 1498, 1448, 1204, 996, 916, 760, 730, 688; ^{1}H NMR (90 MHz, $CDCl_3$): δ 7.33-7.52 (m, 2H, Ph), 7.56 (s, 1H, =CH), 7.60-7.76 (m, 3H, Ph); MS: *m/z* (rel. intensity) 209/207 (M^+, 100).

Indium-mediated reaction of dibromoacetonitrile with cinnamaldehyde. This reaction was similarly carried out as above and the following products were isolated; 2,2-

dibromo-3-hydroxy-5-phenyl-4-pentenenitrile (**8**) (21% yield), 2-bromo-5-phenyl-2,4-pentadienenirile (**9**) (18%), and 5-phenyl-2,4-pentadienenitrile (**10**) (7%).

2,2-Dibromo-3-hydroxy-5-phenyl-4-pentenenitrile (8). IR (neat, cm^{-1}): 3450, 3030, 2240 (CN), 1648 (C=C), 1496, 1448, 1398, 1290, 1122, 1040, 968, 752, 692; ^1H NMR (90 MHz, $CDCl_3$): δ 2.97 (s, 1H, OH), 4.70 (d, *J* = 6.0 Hz, 1H, C*H*OH), 6.33 (dd, *J* = 15.6, 6.0 Hz, 1H, PhCH=C*H*), 6.97 (d, *J* = 15.6 Hz, 1H, PhC*H*=CH), 7.38-7.57 (m, 5H, Ph); MS: *m/z* (rel. intensity) 333/331/329 (M^+, 28), 133 (M^+-CBr_2CN, 100); Anal: calcd for $C_{11}H_9Br_2NO$: C, 39.79; H, 3.04. Found: C, 40.06; H, 3.04.

2-Bromo-5-phenyl-2,4-pentadienenitrile (9).[24] ^1H NMR (90 MHz, $CDCl_3$): δ 6.8-7.4 (m, 8H, Ph and =CH ×3); MS: *m/z* (rel. intensity) 235/233 (M^+, 75), 154 (M^+-Br, 100).

Indium-mediated reaction of α,α-dibromoacetophenone with benzaldehyde. A mixture of α,α-dibromoacetophenone (280 mg, 1.0 mmol), benzaldehyde (100 μL, 1.0 mmol), and indium powder (230 mg, 2.0 mmol) in DMF (3.0 mL) was ultrasonicated for 3 h at room temperature. Usual aqueous work-up and column chromatography on silica gel (dichloromethane:hexane = 5:4) gave 2-benzoyl-3-phenyloxirane (**11**)[25] (*cis*:*trans* = 88:12) (130 mg, 55%). The *cis*/*trans* ratio was determined based on the ^1H NMR analysis. The reaction with octanal was similarly carried out and 2-benzoyl-3-heptyloxirane (**12**) (*cis*:*trans* = 91:9) was obtained in 45% yield.

2-Benzoyl-3-heptyloxirane (12). IR (neat, cm^{-1}): 2935, 2855, 1688 (C=O), 1598, 1578, 1448, 1418, 1374, 1224, 960, 798; MS: *m/z* (rel. intensity) 246 (M^+, 3), 105 (PhCO, 100); ^1H NMR (200 MHz, $CDCl_3$) for *cis*-isomer: δ 0.84 (t, *J* = 6.9 Hz, 3H, Me), 1.13-1.54 (m, 12H, CH_2), 3.43 (dt, *J* = 5.8, 4.8 Hz, 1H, CH), 4.29 (d, *J* = 4.8 Hz, 1H, PhCOC*H*), 7.46-7.69 (m, 3H, Ph), 7.99-8.08 (m, 2H, Ph); the PhCOC*H* signal of the *trans*-isomer appeared at δ 4.03 (d, *J* = 1.9 Hz); HRMS: calcd for $C_{16}H_{22}O_2$: 246.1615, found: 246.1620.

Indium-mediated coupling of α,α-dibromoacetophenone. A mixture of α,α-dibromoacetophenone (280 mg, 1.0 mmol) and indium powder (115 mg, 1.0 mmol) in DMF (3.0 mL) was ultrasonicated for 3 h at room temperature. Usual aqueous work-up and column chromatography on silica gel (dichloromethane:hexane = 2:1) gave *cis*-2-bromomethyl-2-phenyl-3-benzoyloxirane (*cis*-**13**) (5.0 mg, 3%), *trans*-2-bromomethyl-2-phenyl-3-benzoyloxirane (*trans*-**13**) (71 mg, 45%), α,α-dibromoacetophenone (9%), and α-bromoacetophenone (4%).

cis-*2-Bromomethyl-2-phenyl-3-benzoyloxirane* (cis-*13*). Pale yellow oil (*lit.*[26] mp 133-134 ℃); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.70 (d, *J* = 11.7 Hz, 1H, CHBr), 3.84 (d, *J* = 11.7 Hz, 1H, CHBr), 4.44 (s, 1H, CH), 7.32-7.68 (m, 8H, Ph), 7.85 - 8.10 (m, 2H, Ph).

trans-*2-Bromomethyl-2-phenyl-3-benzoyloxirane* (trans-*13*). Colorless needles; mp 160-162 ℃ (*lit.*[26] mp 159-160 ℃); ^{1}H NMR (200 MHz): δ 3.86 (d, *J* = 11.2 Hz, 1H, CHBr), 3.99 (d, *J* = 11.2 Hz, 1H, CHBr), 4.63 (s, 1H, CH), 7.18-7.63 (m, 8H, Ph), 7.86-7.94 (m, 2H, Ph).

Experiments with deuterium-labeled α,α-dibromoacetophenone. α,α-Dibromo-α-deuterioacetophenone was obtained by stirring α,α-dibromoacetophenone (280 mg, 1.0 mmol) with sodium carbonate (320 mg, 3.0 mmol) in acetonitrile (3.0 mL) containing D_2O (0.60 mL) (overnight, room temperature). Purification by column chromatography (silica gel, dichloromethane) gave the product (96% D) in 97% yield. Reaction of the deuterium-labelled compound with indium metal was carried out and the deuterium-content of the product was determined by MS and ^{1}H NMR spectroscopy.

Indium-mediated reaction of 3,3-dichloropropene with aldehydes. The following reaction with benzaldehyde represents the general procedure. A mixture of indium powder (230 mg, 2.0 mmol), lithium iodide (540 mg, 4.0 mmol), 3,3-dichloropropene (220 mg, 2.0 mmol), and benzaldehyde (100 μL, 1.0 mmol) in DMF (6.0 mL) was ultrasonicated

for 3 h at room temperature. Usual aqueous work-up and column chromatography on silica gel (dichloromethane) gave 2-chloro-1-phenyl-1-buten-1-ol (**14a**)[27] (0.17 g, 93%). ^{1}H NMR analysis revealed that the product was a mixture of the diastereomers (78:22). Reactions with other aldehydes were similarly carried out. The results are summarized in Table 2.

2-Chloro-1-(p-methoxyphenyl)-3-buten-1-ol (14b). IR (neat, cm^{-1}): 3450, 2950. 1676, 1604, 1510, 1453, 1300, 1244, 1176, 1030, 930, 830, 780, 730; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.52 and 2.79 (each d, *J* = 3.5, 3.3 Hz, 1H, OH), 3.80 (s, 3 H, OMe), 4.52 (bt, *J* = 7.8 Hz, 1H, CHCl), 4.68 (dd, *J* = 7.7, 3.3 Hz, 0.84H, C*H*OH), 4.89 (dd, *J* = 4.9, 3.5 Hz 0.16H, C*H*OH), 5.09-5.35 (m, 2H, =CH_2), 5.69-5.87 (m, 1H, =CH-), 6.88 (d, *J* = 8.4 Hz, 2H, Ar), 7.26 (d, *J* = 8.4 Hz, 2H, Ar); MS: *m/z* (rel. intensity) 212 (M^+, 5), 137 (100); Anal: calcd for $C_{11}H_{13}ClO_2$: C, 62.12; H, 6.16. Found: C, 61.82; H, 6.16.

4-Chloro-1-phenyl-1,5-hexadien-3-ol (14c). IR (neat, cm^{-1}): 3400, 3025, 1662, 1492, 1442, 1020, 962, 928, 740, 692; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.32 and 2.42 (each d, *J* = 5.0 Hz, 1H, OH), 4.37-4.58 (m, 2H, CHCl and C*H*OH), 5.31 (d, *J* = 10.0 Hz, 1H, *cis* HC=CH_2), 5.42 (d, *J* = 16.0 Hz, 1H, *trans* HC=CH_2), 5.99 (m, 1H, -CH=), 6.24 (dd, *J* = 16.0, 5.6 Hz 1H, PhCH=C*H*-), 6.70 and 6.72 (each d, *J* = 16.0 Hz, 1H, PhC*H*=CH), 7.21-7.44 (m, 5H, Ph); MS: *m/z* (rel. intensity) 209 (M^+, 0.5), 133 (100); Anal: calcd for $C_{12}H_{13}ClO$: C, 69.07; H, 6.28. Found: C, 69.37; H, 6.48.

3-Chloro-1,5-nonadien-4-ol (14d). IR (neat, cm^{-1}): 3455, 3005, 1694, 1464, 1438, 1388, 980, 936; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.90 and 0.94 (each t, *J* = 7.2 Hz, total 3H, Me), 1.32-1.64 (m, 2H, CH_2), 1.97-2.12 (m, 2H, CH_2), 2.29 (d, *J* = 5.3 Hz, 1H, OH), 4.11-4.47 (m, 2H, CHCl and C*H*OH), 5.22-6.00 (m, 5H, =CH_2 and =CH ×3); MS: *m/z* (rel. intensity) 157 (M^+-H_2O, 17), 57 (100); Anal: calcd for $C_9H_{15}ClO$: C, 61.89; H, 8.66. Found: C, 62.00; H, 8.87.

3-Chloro-1-undecen-4-ol (14e). IR (neat, cm^{-1}): 3400, 2930, 1640, 1460, 1420, 1370, 1120, 1060, 980, 922, 750, 720; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.3 Hz,

3H, Me), 1.16-1.63 (m, 12H, CH_2), 2.09 and 2.12 (each d, J = 4.9, 6.1 Hz, total 1H, OH), 3.59-3.73 (m, 0.5H, CHCl), 3.73-3.85 (m, 0.5H, CHCl), 4.28-4.43 (m, 1H, C*H*OH), 5.24-5.40 (m, 2H, $=CH_2$), 5.86-6.06 (m, 1H, -CH=); MS: *m/z* (rel. intensity) 169 (M^+-Cl, 1), 69 (100); Anal: calcd for $C_{11}H_{21}ClO$: C, 64.53; H, 10.34. Found: C, 64.25; H, 10.60.

Indium-mediated reactions of 1-substituted 3,3-dichloropropene with aldehydes. These reactions were done in a way similar to the 3,3-dichloropropene case described above, except that the reaction temperature in entries *g* to *j* in Table 3 was 100-120 ℃. The results are summarized in Table 3.

2-Phenyl-3-buten-ol (15a).[28] IR (neat, cm^{-1}): 3375, 2930, 1638, 1598, 1494, 1448, 1052, 1022, 916, 754, 698; ^1H NMR (200 MHz, $CDCl_3$): δ 1.54 (bs, 1H, OH), 3.54 (dt, J = 7.7, 7.1 Hz, 1H, PhCH), 3.83 (d, J = 7.1 Hz, 1H, CH_2), 5.20 (dd, J = 16.8, 1.4 Hz, 1H, *trans* HC=CH_2), 5.22 (dd, J = 10.7, 1.4 Hz, 1H, *cis* HC=CH_2), 6.02 (ddd, J = 16.8, 10.7, 7.7 Hz, 1H, C*H*=CH_2), 7.19-7.62 (m, 5H, Ph).

4-Phenyl-5-hexen-3-ol (15b).[29] IR (neat, cm^{-1}): 3440, 2960, 1638, 1598, 1492, 1450, 1108, 970, 916, 758, 698; ^1H NMR (200 MHz, $CDCl_3$): δ 0.93 and 1.00 (each t, J = 7.3 Hz, total 3H, Me), 1.20-1.54 (m, 2H, CH_2), 1.80 (d, J = 4.0 Hz, 1H, OH), 3.22-3.37 (m, 1H, PhC*H*), 3.68-3.86 (m, 1H, C*H*OH), 5.21 (dd, J = 17.2, 1.7 Hz, 1H, *trans* HC=CH_2), 5.23 (dd, J = 9.8, 1.7 Hz, 1H, *cis* HC=CH_2), 5.97-6.22 (m, 1H, HC=C), 7.16-7.40 (m, 5H, Ph).

3-Phenyl-hepten-4-ol (15c).[30] IR (neat, cm^{-1}): 3300, 2950, 1638, 1600, 1494, 1450, 1120, 740, 700; ^1H NMR (200 MHz, $CDCl_3$): δ 0.78-0.98 (m, 3H, Me), 1.16-1.65 (m, 4H, CH_2 ×2), 1.78 (d, J = 2.5 Hz, 1H, OH), 3.20-3.35 (m, 1H, PhC*H*), 3.73-3.96 (m, 1H, C*H*OH), 5.04-5.26 (m, 2H, CH=CH_2), 5.86-6.22 (m, 1H, C*H*=CH_2), 7.13 - 7.42 (m, 5H, Ph).

3-Phenyl-1-undecen-4-ol (15d).[31] IR (neat, cm^{-1}): 3420, 2926, 2856, 1636, 1600, 1494, 1452, 1068, 992, 914, 756, 700; ^1H NMR (200 MHz, $CDCl_3$): δ 0.86 (t, J = 6.6

Hz, 3H, Me), 1.10-1.50 (m, 12H, CH_2), 1.78 (d, J = 4.2 Hz, 1H, OH), 3.42 (dd, J = 7.2, 8.4 Hz, 1H, C*H*Ph), 3.72-3.87 (m, 1H, C*H*OH), 5.20 (d, J = 16.2 Hz, 1H, *trans* HC=CH_2), 5.22 (d, J = 10.2 Hz, 1H, *cis* HC=CH_2), 6.15 (m, 1H, =CH-), 7.16-7.40 (m, Ph, 5H), MS: *m/z* (rel. intensity) 152 (18), 129 (0.5), 118 (100).

1,2-Diphenyl-3-buten-1-ol (15e).[32] IR (neat, cm^{-1}): 3420, 3035, 1630, 1600, 1494, 1448, 1384, 1294, 1184, 1016, 914, 846, 754, 694; ^1H NMR (200 MHz, $CDCl_3$): δ 2.06 (d, J = 2.5 Hz, 0.1H, OH), 2.30 (d, J = 2.5 Hz, 0.9H, OH), 3.55 (bt, J = 8.2 Hz, 1H, C*H*Ph), 4.85 (dd, J = 7.7, 2.5 Hz, 1H, C*H*OH), 5.22 (d, J = 18.2 Hz, 1H, *trans* =CH_2), 5.26 (d, J = 9.5 Hz, 1H, *cis* =CH_2), 6.16-6.35 (m, 1H, =CH-), 7.00-7.20 (m, 10H, Ph ×2); MS: *m/z* (rel. intensity) 115 (100).

3-Phenyl-1,5-nonadien-4-ol (15f). IR (neat, cm^{-1}): 3410, 2955, 2926, 1664, 1628, 1598, 1492, 1450, 1378, 1298, 1016, 964, 912, 752, 698; ^1H NMR (200 MHz, $CDCl_3$): δ 0.76 and 0.88 (each t, J = 7.5 Hz, total 3H, Me), 1.17-1.43 (m, 2H), 1.75 (s, 1H, OH), 1.80-2.06 (m, 2H, CH_2), 3.35 and 3.39 (each t, J = 8.4 Hz, 1H, C*H*Ph), 4.20-4.37 (m, 1H, C*H*OH), 5.02-5.77 (m, 4H, =CH_2 and =CH- ×2), 6.13-6.24 (m, 1H, =CH-), 7.16-7.41 (m, 5H, Ph); Anal: calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.15; H, 9.38.

2-Methyl-1-phenyl-3-buten-1-ol (15g).[33] IR (neat, cm^{-1}): 3400, 2950, 1700, 1638, 1600, 1490, 1444, 1368, 1190, 1016, 904, 784, 758, 696; ^1H NMR (200 MHz, $CDCl_3$): δ 0.87 (d, J = 6.8 Hz, 1.5 H, Me), 1.01 (d, J = 6.8 Hz, 1.5H, Me), 1.95 (bs, 0.5H, OH), 2.15 (bs, 0.5H, OH), 2.40-2.64 (m, 1H, C*H*Me), 4.36 (d, J = 7.9 Hz, 0.5H, C*H*OH), 4.62 (d, J = 5.5 Hz, 0.5H, C*H*OH), 5.00-5.25 (m, 2H, =CH_2), 5.67-5.91 (m, 1H, -CH=), 7.20-7.40 (m, 5H, Ph).

1-Phenyl-2-propyl-3-buten-1-ol (15h).[34] IR (neat, cm^{-1}): 3390, 2950, 1638, 1490, 1446, 1416, 1376, 1190, 1022, 990, 758, 796; ^1H NMR (200 MHz, $CDCl_3$): δ 0.78 and 0.87 (each t, J = 6.0 Hz, total 3H, Me), 1.03-1.59 (m, 4H, CH_2 ×2), 2.07 (bs, 1H, OH),

2.22-2.50 (m, 1H, CHPr), 4.39 (d, J = 7.9 Hz, 0.6H, C*H*OH), 4.61 (d, J = 5.8 Hz, 0.4H, C*H*OH), 4.96-5.29 (m, 2H, =CH_2), 5.42-5.68 (m, 1H, -CH=), 7.21-7.40 (m, 5H, Ph).

3-Methyl-1-undecen-4-ol (15i).[35] IR (neat, cm^{-1}): 3350, 2920, 1638, 1450, 1372, 992, 908, 720; ^{1}H NMR (200 MHz): δ 0.88 (bt, J = 7.6 Hz, 3H, Me), 1.01 (d, J = 2.0 Hz, 1.5H, Me), 1.05 (d, J = 2.0 Hz, 1.5H, Me), 1.18-1.62 (m, 13H, CH_2 ×6 and OH), 2.16-2.30 (m, 1H, C*H*Me), 3.37-3.51 (m, 1H, C*H*OH), 5.03-5.15 (m, 2H, =CH_2), 5.68-5.89 (m, 1H, -CH=).

3-Propyl-1-undecen-4-ol (15j). IR (neat, cm^{-1}): 3350, 2920, 1710, 1638, 1450, 1418, 1376, 1040, 996, 904, 794; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.86-0.92 (m, 6H, Me x2), 1.10-1.60 (m, 16H, CH_2 ×8), 1.70 (bs, 1H, OH), 1.94-2.18 (m, 1H, C*H*Pr), 3.39-3.52 (m, 1H, C*H*OH), 5.01-5.20 (m, 2H, =CH_2), 5.51-5.73 (m, 1H, -CH=); Anal: calcd for C_{14} H_{28}O: C, 79.18; H, 13.29. Found: C, 79.26; H, 13.51.

2-Chloro-4-phenyl-3-buten-1-ol (16a). IR (neat, cm^{-1}): 3350, 3090, 3040, 2940, 2875, 1624, 2598, 1492, 1448, 1180, 1054, 1020, 730, 696; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.49 (bs, 1 H, OH), 3.86 (d, J = 6.4 Hz, 2H, CH_2), 4.16 (dt, J = 9.3, 6.4 Hz, 1H, CHCl), 6.05 (dd, J = 9.3, 7.2 Hz, 1H, PhCH=C*H*), 6.24 (d, J = 7.2 Hz, 1H, PhC*H*=CH), 7.20-7.44 (m, 5H, Ph); Anal: calcd for $C_{10}H_{11}ClO$: C, 65.76; H, 6.07. Found: C, 65.69; H, 5.87.

4-Chloro-6-phenyl-5-hexen-3-ol (16b). IR (neat, cm^{-1}): 3430, 2960, 1684, 1622, 1598, 1490, 1448, 1316, 1118, 1028, 968, 860, 736, 694; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.98 (t, J = 7.4 Hz, 3H, Me), 1.37-1.60 (m, 2H, CH_2), 1.58 (bs, 1H, OH), 3.80 (dt, J = 7.4, 5.1 Hz, 1H, C*H*OH), 3.90-4.06 (m, 1H, CHCl), 6.19-6.30 (m, 2H, CH=CH), 7.19-7.46 (m, 5H, Ph); Anal: calcd for $C_{12}H_{15}ClO$: C, 68.41; H, 7.18. Found: C, 68.66; H, 6.97.

3-Chloro-1-phenyl-1-hepten-4-ol (16c). IR (neat, cm^{-1}): 3460, 2960, 1672, 1624, 1492, 1450, 1120, 970, 742, 696; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.91 (t, J = 7.1 Hz,

3H, Me), 1.42 (m, 4H, CH_2 ×2), 1.58 (bs, 1H, OH), 3.83-4.04 (m, 2H, CHCl and CHOH), 6.20-6.29 (m, 2H, CH=CH), 7.19-7.62 (m, 5H, Ph); Anal: calcd for $C_{13}H_{17}ClO$: C, 69.48; H, 7.62. Found: C, 69.50; H, 7.64.

Experiments with deuterium-labeled 1-phenyl-3,3-dichloropropene. 1-Phenyl-α-dichloro-3-deuteriopropene was synthesized from cinnamaldehyde-*d* prepared from pyridinium dichromate oxidation of cinnamyl alcohol-d_2, which in turn obtained by $LiAlD_4$ reduction of ethyl cinnamate. Reaction with the deuterium-labeled compound was carried out and the deuterium-contents of the products were determined by MS and ^1H NMR spectroscopy.

Preparation of 1,1-diphenyl-3,3-dichloropropene. To a mixture of thionyl chloride (2.6 mL, 36 mL) and HMPA (4 drops) β-phenylcinnnamaldehyde (1.0 g, 4.8 mmol) was added at 0 ℃ and stirred for 4.5 h at rt. The reaction mixture was poured into crashed ice and extracted with ether and washed with water, brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was subjected to Kugelrohr distillation at 180 ℃ under 4 Torr to give 3,3-dichloro-1,1-diphenylprpene (729 mg, 62%) as colorless oil.

1,1-Diphenyl-3,3-dichloropropene. IR (neat, cm^{-1}): 1660, 1496, 1442, 1356, 1278, 1098, 868, 762, 700; ^1H NMR (200 MHz, $CDCl_3$): δ 6.17 (d, J = 10.1 Hz, 1H), 6.41 (d, J = 10.1 Hz, 1H), 7.20-7.82 (m, 10H); Anal: calcd for C_{15} $H_{12}Cl_2$: C, 69.84; H, 4.40. Found: C, 69.60; H, 4.54.

Reaction of 3,3-dichloro-1,1-diphenylprpene with formaldehyde. A mixture of indium (115 mg, 1.0 mmol), anhydrous lithium iodide (270 mg, 2.0 mmol), 3,3-dichloro-1,1-diphenylprpene (132 mg, 0.5 mmol) and formalin (38 μL, 0.5 mmol) in DMF (3 mL) was stirred for 3 h at 50 ℃. The reaction mixture was quenched with diluted hydrochloric acid and the product was extracted with ether. The ether layer was washed with water, brine and dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was purified by column chromatography on silica gel (elusion with dichloromethane:hexane = 1:1) to give 2,2-diphenyl-3-butene-1-ol (**15k**) (41 mg, 37%).

2,2-Diphenyl-3-butene-1-ol (15k). IR (neat, cm^{-1}): 3425, 3060, 1596, 1490, 1440, 1240, 1050, 920, 756, 698; ^1H NMR (200 MHz, $CDCl_3$): δ 1.48 (t, J = 6.6 Hz, 1H, OH), 4.27 (d, J = 6.6 Hz, 2H, CH_2), 4.92 (dd, J = 17.6, 1.0 Hz, 1H, *trans* $=CH_2$), 5.39 (dd, J = 1.0 Hz, 1H, *cis* $=CH_2$), 6.48 (dd, J = 17.6, 10.7 Hz, 1H, -CH=), 7.15-7.38 (m, 10H, Ph); Anal: calcd for $C_{16}H_{16}O$: C, 85.68; H, 7.19. Found: C, 85.54; H, 7.23.

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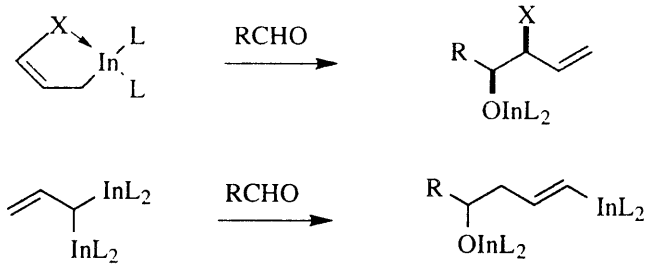
CHAPTER 2

Indium-mediated Reaction of 1,3-Dihalopropenes with Carbonyl Compounds. Generation of Novel 3,3-Diindiopropene

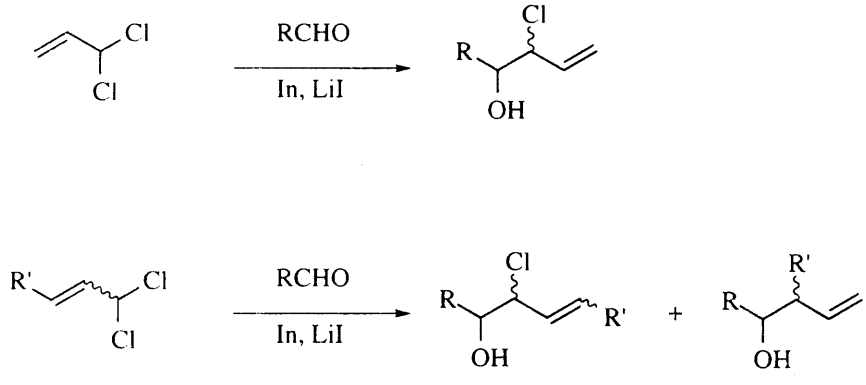
Summary

Indium-mediated reaction of 1,3-dichloropropene with aldehyde gave *syn*-chlorohydrin predominantly. A similar reaction of 1,3-dibromopropene gave vinyloxirane and homoallyl alcohol; the former is formed from γ-bromoallylindium via the corresponding bromohydrin, and the latter is considered to be derived from a unique allylic diindium reagent, 3,3-diindiopropene. 3-Bromo-1-iodopropene gave the homoallylic alcohol exclusively.



INTRODUCTION

The previous chapter reported that the indium-mediated reaction of 3,3-dichloropropene with carbonyl compounds gives the corresponding chlorohydrins, whereas 1-substituted 3,3-dichloropropenes give homoallylic alcohols exclusively or predominantly (Scheme 1). In the latter reaction, an allylic diindium species was postulated as the intermediate leading to the homoallylic alcohols. Recently, an indium-mediated reaction of 1,3-dibromopropene with aldehydes in an aqueous medium was described.[1] Here an independent results on the indium-mediated reactions with 1,3-dichloro- and 1,3-dibromopropenes in organic solvents was described. The latter proceed *via* a different reaction pathway from that in water, consequently giving different products.



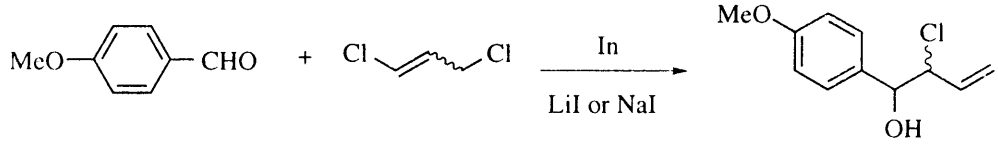
Scheme 1

RESULTS AND DISCUSSION

Reaction with 1,3-dichloropropene.

In the presence of lithium iodide or sodium iodide, indium was found to mediate readily the coupling of 1,3-dichloropropene (**1**) with aldehyde, and chlorohydrin **2** was obtained as the sole product. Without the iodide salts, no reaction occurred. Table 1 summarizes the results with *p*-anisaldehyde in various solvents. With increasing the solvent polarity, the diastereoselectivity (*syn/anti* ratio) increased.

Table 1. Reaction of *p*-Anisaldehyde with 1,3-Dichloropropene in Various Solvents [a]

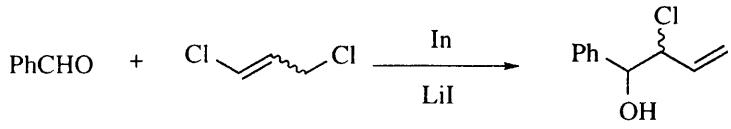


1 **2a**

Entry	Solvent	Additive	Yield/%	*syn:anti*
1	CH_2Cl_2	LiI	0	---
2	acetone	NaI	58	69:31
3	*t*-BuOH	LiI	56	71:29
4	THF	LiI	67	73:27
5	DMF	LiI	75	75:25
6	THF/H_2O (3:1)	LiI	93	81:19
7	MeOH	LiI	58	82:18
8	MeOH/H_2O (1:1)	LiI	45	90:10
9	H_2O[b]	LiI	26	80:20

a All reactions carried out with *p*-anisaldehyde (1 mmol), 1,3-dichloropropene (2 mmol), lithium (or sodium) iodide (2 mmol), and indium (1 mmol) at room temperature for 3 h. b Reaction time 15 h.

Table 2. Reaction of Benzaldehyde with 1,3-Dichloropropenea

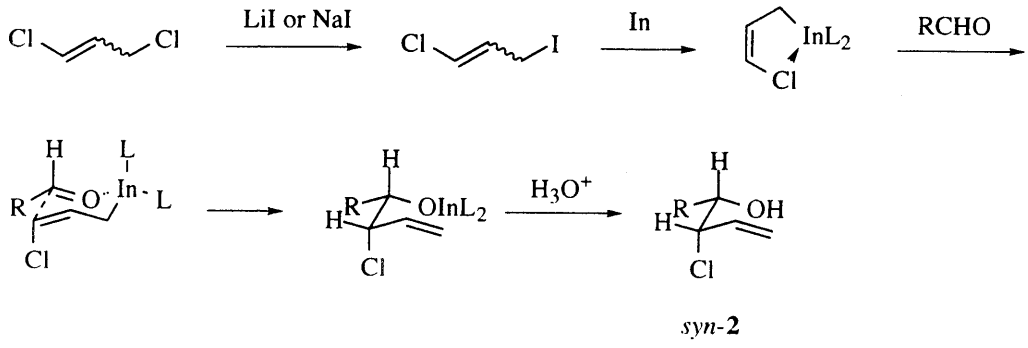


2b

entry	Solvent	Temp./℃	Yield/%	*syn*:*anti*
1	THF	0	88	79:21
2	THF	-78	59	81:19
3	MeOH	0	31	85:15
4	DMF	0	52	84:16
5	DMF	-60 to -30	83	92: 8

a All reactions carried out with benzaldehyde (1 mmol), 1,3-dichloropropene (2 mmol), lithium iodide (2 mmol), and indium (1 mmol) for 2 h.

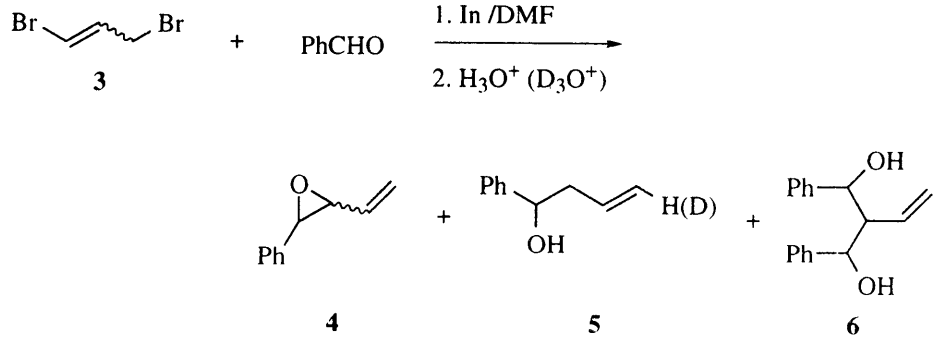
The effect of reaction temperature on diastereoselectivity was examined in the reaction with benzaldehyde (Table 2), which shows that temperature did not affect significantly the diastereoselectivity. It is noted that, in contrast to the above reactions, the reactions of γ-alkyl substituted allylindium reagents, such as cinnamyllindium reagents, with carbonyl compounds give *anti*-adducts predominantly.[2] The *syn*-selectivity observed in the present reaction may be explained by the fact that the intermediate γ-chloroallylindium reagent has a *Z*-configuration with an intramolecular chelation of the chlorine atom to the indium. Although the starting 1,3-dichloropropene was an *E*/*Z*-mixture (*E*/*Z* = 68/32), *E*/*Z*-isomerization is possible during the oxidative addition of indium.[3] A chair-like cyclic transition state in which the chlorine atom adopts an axial-position furnishes the *syn*-adduct **2** (Scheme 2).



Scheme 2

Reaction with 1,3-dibromopropene.

The indium-mediated reaction of 1,3-dibromopropene (**3**) with benzaldehyde was examined in DMF by changing reaction conditions (Scheme 3). These results was summarized in Table 3.



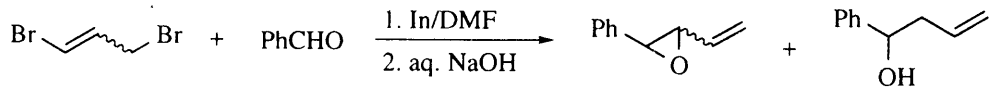
3 **4** **5** **6**

Scheme 3

When the reaction was conducted in a Barbier-type manner (1,3-dibromopropene, benzaldehyde, and indium all mixed together at the same time), the products were vinyloxirane **4** (56% yield) and homoallyl alcohol **5** (12%). Recently, the same reaction in water was reported and *gem*-bisallylation adduct **6** was obtained as the major product.[1] However, the formation of compound **6** was only modest (< 5%) in our reaction in DMF. A similar reaction with excess indium in a Grignard-type manner (preformation of the organoindium reagent from 1,3-dibromopropene and indium followed by the addition of benzaldehyde) gave an increased proportion of **5** (**4**: 19%, **5**: 41% yield), though prolonging the reaction time of 1,3-dibromopropene with indium did not change the ratio **4** : **5**. When the reaction

was quenched with DCl/D_2O, (*E*)-**3**-*d* (74% *d*) was obtained, whereas no deuterium was incorporated in **4**.

Table 3. Indium-mediated Reaction of 1,3-Dibromopropene with Benzaldehyde



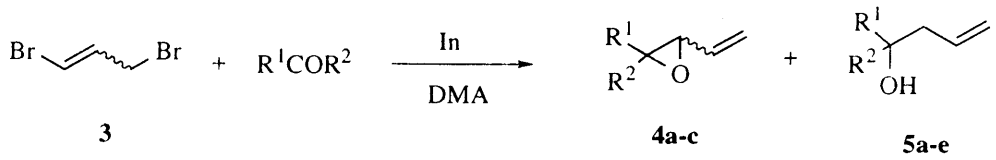
3 **4a** **5a**

Entry	Conditions				Yield (%)	Ratio
	Preparation	Reaction	**4a** (*cis*:*trans*)	**5a**	**4a+5a**	**4a/5a**
1[a]	-	0 ℃, 3 h	56 (86:14)	12	68	82:18
2[b]	0 ℃, 0.5 h	0 ℃, 1 h	23 (84:16)	44	67	34:66
3[b]	0 ℃, 1 h	0 ℃, 3 h	19 (83:17)	41	60	33:66
4[b]	0 ℃, 3 h	0 ℃, 1 h	17 (83:17)	30	47	36:64

a The reaction was carried out with **3** (1.0 mmol), benzaldehyde (3.4 mmol) and indium (1.0 mmol) in DMF (2 mL). b The reactions were carried out with **3** (1.0 mmol), benzaldehyde (3.4 mmol) and indium (5.0 mmol) in DMF (2 mL).

Next, this reaction was examined by changing the solvent and the ratio of the reactants indium/**3**/benzaldehyde (Table 4). *N*,*N*-Dimethylacetamide (DMA) was found to give better results than DMF. Only **4a** and **5a** were obtained and **6** did not form in DMA. As a small amount of bromohydrin was detected in the products, the reaction was quenched with diluted aqueous sodium hydroxide to convert the bromohydrin to **4a**. The product ratio **4a/5a** was found to be affected apparently by the ratio of indium/**3** used. Although increasing the indium ratio increased the ratio of **5a** (entries 1-3), the use of an excess of indium did not increase further the ratio of **5a** (entry 4). When the reaction was carried out in a Barbier-type manner (entries 5-7), a similar change of the ratio **4a/5a** was observed. The stereoselectivity of **4a** and the ratio **4a/5a** were not affected by the reaction temperature (entry 8). This reaction did not occur in THF. Coupling with other carbonyl compounds was carried out under similar conditions (entries 9-12). The reactions with *p*-

Table 4. Indium-mediated Reaction of 1,3-Dibromopropene with Carbonyl Compounds [a]



3 4a-c 5a-e

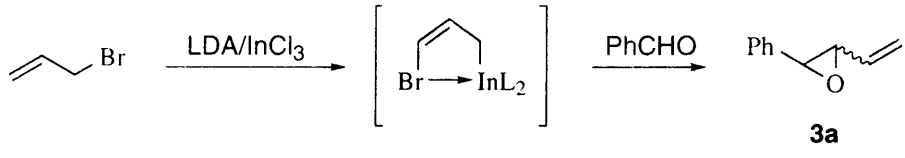
Entry	R^1COR^2		Ratio[b]	Method[c]	Yield (%)		Ratio
	R^1	R^2			**4** (*cis/trans*)	**5**	**4/5**
1	Ph	H	1:2:1	A	**4a** 56 (90:10)	**5a** 30	74:26
2	Ph	H	1:1:1	A	**4a** 30 (87:13)	**5a** 28	52:48
3	Ph	H	2:2:1	A	**4a** 45 (94:6)	**5a** 31	59:41
4	Ph	H	4:2:1	A	**4a** 44 (94:6)	**5a** 39	53:47
5	Ph	H	1:2:1	B	**4a** 66 (93:7)	**5a** 20	77:23
6	Ph	H	2:2:1	B	**4a** 38 (96:4)	**5a** 42	48:52
7	Ph	H	4:2:1	B	**4a** 21 (97:3)	**5a** 46	31:69
8[d]	Ph	H	2:2:1	A	**4a** 45 (92:8)	**5a** 28	62:38
9[e]	*p*-$O_2NC_6H_4$	H	2:2:1	A	**4b** 35 (88:12)	**5b** 60	37:63
10[e]	*n*-C_7H_{15}	H	2:2:1	A	**4c** 25 (70:30)	**5c** 75	25:75
11[e]	(*E*)-PhCH=CH	H	2:2:1	A	0	**5d** 60	0:100
12[e]	Ph	Me	2:2:1	A	0	**5e** 40	0:100

[a] The reactions were carried out in DMA at 0 ℃ for 2 h unless otherwise noted. [b] Indium/**3**/R^1COR^2. [c] Method A: Indium and 1,3-dibromopropene were stirred for 1 h before the addition of a carbonyl compound. Method B: Indium, 1,3-dibromopropene, and a carbonyl compound were mixed all together. [d] At -50 ℃. [e] At rt.

nitrobenzaldehyde and octanal gave the corresponding homoallylic alcohols **5b** and **5c** in higher yields and higher selectivities compared with the benzaldehyde case. High *cis*-selectivity was observed for oxiranes **4a** and **4b** from the aromatic aldehydes, whereas the *cis*-selectivity for the aliphatic aldehyde was lower. The coupling with cinnamaldehyde and

acetophenone yielded homoallylic alcohols **5d** and **5e** exclusively. Sterically demanding pivalaldehyde did not give the coupling products.

Preparation of γ-bromoallylindium reagents. Although γ-bromoallylindium was not obtained exclusively from the reaction of **3**, it could alternatively be prepared by the deprotonation of allyl bromide with LDA followed by transmetallation with indium trichloride. The γ-bromoallylindium thus prepared reacted with benzaldehyde to give **4a** exclusively in 72% (*cis/trans* = 83:17) (Scheme 4). It is known that allylic indium sesquibromides bearing alkyl- or aryl-substitutent(s) on the γ-carbon react with aldehydes to give *anti*-homoallylic alcohols unless the γ-substitutent is not sterically demanding.[2,4] On the contrary, the reaction of the allylindium reagents bearing chlorine or bromine at the γ-position gives *syn*-chlorohydrin or *cis*-oxirane stereoselectively. The chlorine or bromine atom on the allylindium is expected to coordinate intramolecularly to indium forming a chelated five-membered ring. Consequently, (*Z*)-γ-chloro- and bromoallylindium are considered to be more stable than the corresponding (*E*)-geometrical isomers.

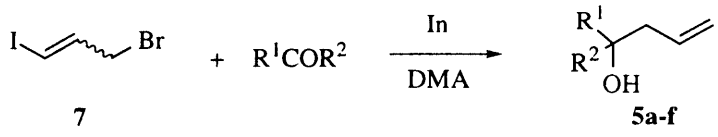


3a

Scheme 4

Indium-mediated reaction of 3-bromo-1-iodopropene with carbonyl compounds. The reaction of 3-bromo-1-iodopropene (**7**) and indium powder proceeded smoothly in DMA at room temperature. The resulting indium reagent was subjected to the reaction with benzaldehyde to give homoallylic alcohol **5a** exclusively (Table 5, entries 1-4). No halohydrin or vinyloxirane **4a** was formed. When this reaction was quenched with di-

Table 5. Indium-mediated Reaction of 3-Bromo-1-iodopropene with Carbonyl Compounds[a]



7 **5a-f**

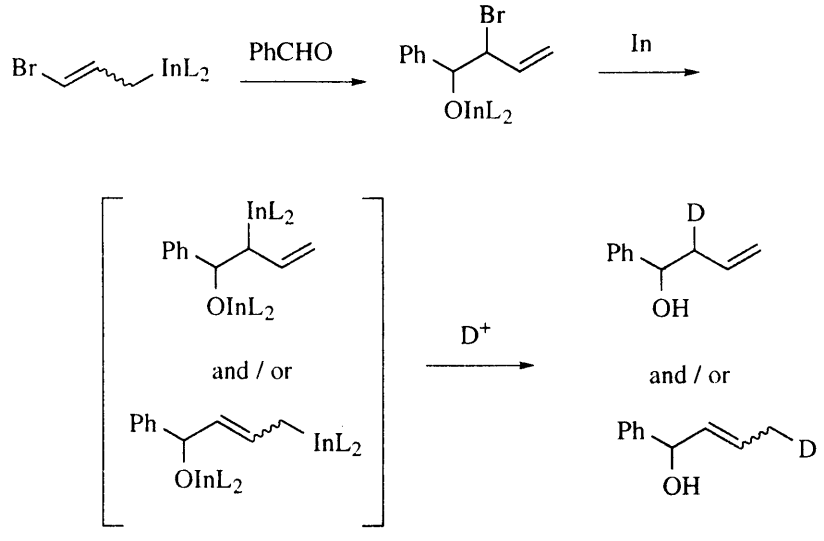
Entry	R^1COR^2		Ratio[b]	Solvent	Product	Yield (%)
	R^1	R^2				
1[c]	Ph	H	2:2:1	DMA	**5a**-*d*	77 (80%-*d*)
2	Ph	H	3:2:1	DMA	**5a**	85
3	Ph	H	4:2:1	DMA	**5a**	84
4	Ph	H	2:1:1	DMA	**5a**	89
5	Ph	H	2:1:1	THF	**5a**	31
6[d]	Ph	H	2:2:1	H_2O:THF[e]	**5a**	90
7	*n*-C_7H_{15}	H	2:2:1	DMA	**5c**	70
8	(*E*)-PhCH=CH	H	2:2:1	DMA	**5d**	68
9	Ph	Me	2:2:1	DMA	**5e**	71
10	4-*t*-butylcyclohexanone		2:2:1	DMA	**5f**	81[f]

[a] All reactions were carried out as described in Experimental Section. [b] Indium/**7**/aldehyde. [c] Quenched with diluted DCl. [d] This reaction was carried out overnight at rt. [e] H_2O/THF = 1:1. [f] Axial/equatorial alcohol=81:19

luted DCl, deuterium was incorporated at the terminal (*E*)-vinyl position of **5a** (80%-*d*) (entry 1), as was observed in a 1,3-dibromopropene case. Attempts to trap this vinylindium reagent with chlorotrimethylstannane and iodine were failed. Although the reaction of **7** with indium metal was sluggish in THF and hence the yield of **5a** was low (entry 5), it proceeded smoothly in an aqueous medium to give **5a** in high yield (entry 6). Coupling with other carbonyl compounds was carried out under similar conditions (entries 7-10). The reactions with acetophenone and 4-*t*-butylcyclohexanone gave the corresponding homoallylic alcohols **5e** and **5f** in good yields (entries 9 and 10), whereas no reaction pro-

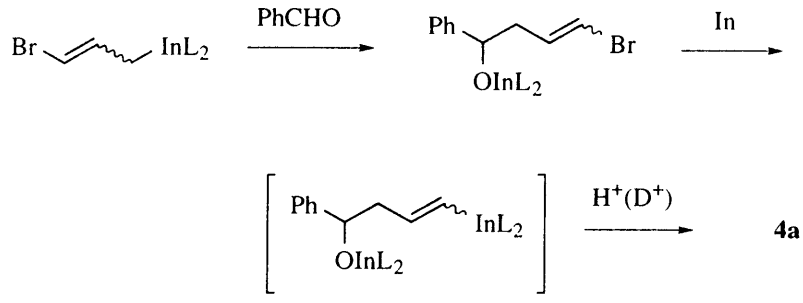
ceeded with sterically demanding ketones such as diisopropyl ketone and camphor. In the case of 4-*t*-butylcyclohexanone, the ratio of the product axial/equatorial alcohol (81:19) was almost coincident with that (82:18) of the reaction with allylindium sesquiiodide.[3]

Mechanistic considerations. In order to explain the formation of homoallylic alcohol **5** in the reactions of **3** and **7**, we proposed the intermediacy of the allylic diindium intermediate. Another mechanism involving a transformation of the initially formed bromohydrin indium salt to allylic indium species is unlikely (Scheme 5).



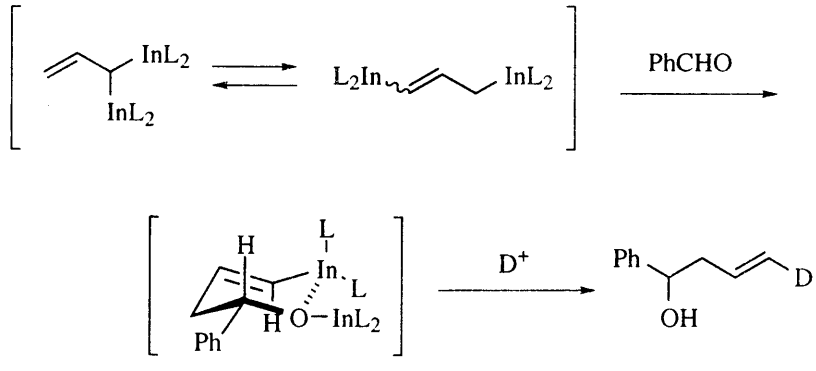
Scheme 5

This tandem reaction should give homoallylic alcohol with D on the internal carbon and/or allylic alcohol with D at the terminal carbon upon quenching with DCl. If γ-bromoallylindium could react with benzaldehyde at the α-position, homoallylic alcohol containing bromine at the olefinic terminal carbon would be formed (Scheme 6).



Scheme 6

If the bromine atom is replaced by indium, the resulting vinylindium species would lead to **4a**. However, under the conditions employed here, an oxidative addition of indium to a carbon-halogen bond takes place only for activated halides such as allyl halides and benzyl halides. Therefore, this mechanism involving the conversion of vinylic bromide to vinylindium is difficult to explain the formation of **4a**. Based on the observation that the increase of the amount of indium increases the ratio **4/3**, we conclude that the allylic diindium reagent is the most probable intermediate. The *E*-geometry of the D atom in compound **4a**-*d* can be reasonably explained by a six-membered coordination of the alkoxide oxygen to the vinylic indium atom (Scheme 7).

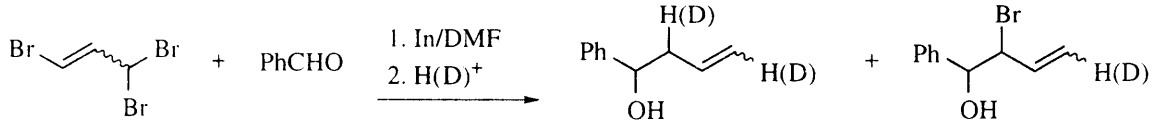


Scheme 7

The difficulty encountered in the displacement of the indium atom with electrophiles such as chlorostannane and iodine may come from this intramolecular coordination. The coordination of the alkoxide oxygen to the vinylic indium in the homoallylic alkoxide would prevent the attack of the electrophiles as was observed in a vinylzinc case.[5]

It was reported that **3** reacts with two molecules of aldehyde in the presence of indium metal in aqueous media to give diol **6**.[1] Although the indium-mediated reaction of **3** with aldehydes proceeds in both organic and aqueous media, the reaction courses and intermediates have thus been found not to be same. Furthermore, we have demonstrated that the ratio of diindium/γ-haloallylindium increases by changing the halogen of dihalopropene from Cl to Br and I, and the unique allylic diindium reagent can be prepared exclusively starting with **7**. γ-Haloallylindium compounds are considered to be in equilibrium with α-haloallylindium, and α-iodoallylindium is converted to the allylic *gem*-diindium reagent most readily. Even in aqueous media, compound **7** gave **5** in high yield and **6** was not formed at all.

1,3,3-Tribromopropene . The indium-mediated reaction of 1,3,3-tribromopropene (**8**) with benzaldehyde gave the corresponding homoallylic alcohol **5a** and bromohydrin **9**. When this reaction was quenched with 1 N DCl, deuterium was introduced both the homoallylic alcohol and bromohydrin (Scheme 8).



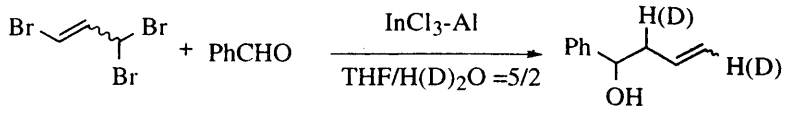
8 **5a**-d_2: 16%, *E*/*Z*=2/1 **9**: 15%

Scheme 8

This reaction could carry out in the presence of $InCl_3$-Al in aqueous THF giving the homoallylic alcohol exclusively (Table 6). Again deuterium incorporation in **5a** was observed when this reaction carried out in THF-D_2O media.

In order to explain this reaction mechanism, we propose two types of reaction course; one is step-by-step mechanism and the other is involved in triindium compound. Thus 1,3,3-tribromopropene reacted with indium to produce α,γ-dibromo substituted allylic in-

Table 6. Indium-mediated Reaction of 1,3,3-Tribromopropene with benzaldehyde [a]

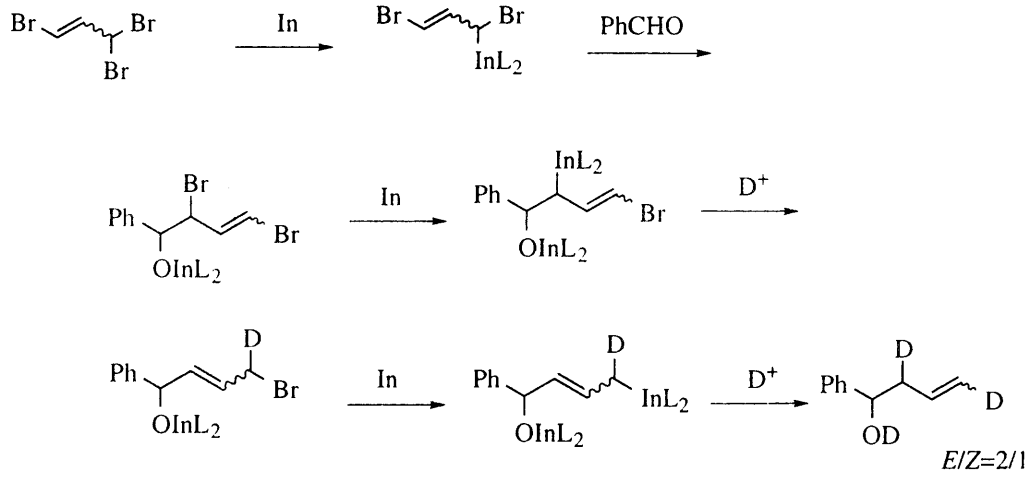


8 **5a** *E/Z*=2/1

PhCHO (mmol)	$InCl_3$ (mmol)	Yield (%)
0.8	0	0
1.5	0.03	15
0.25	0.5	38

a All reaction were carried out with **8** (0.5 mmol) at rt overnight

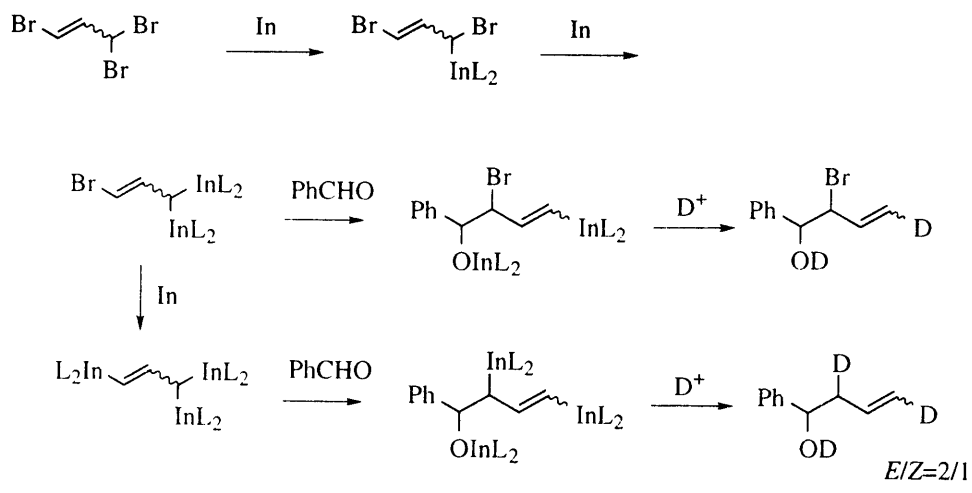
dium reagent, which reacted with benzaldehyde to give bromohydrin indium alkoxide. Subsequently, this bromohydrin further reacted with indium to give new allylindium reagent, and it was quenched with D_2O to afford new allyl bromide. Finally the bromide reacted with indium to give allylindium followed by displacement of indium by deuterium to furnish [2,4-D_2] homoallylic alcohol (Scheme 9).



Scheme 9

The other path involved in allylic triindium reagent is considered as follows (Scheme 10). First 1,3,3-tribromopropene reacts with indium to afford α,γ-dibromo substituted al-

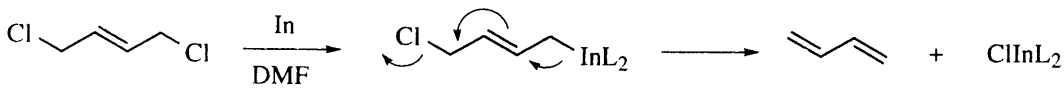
lylic indium reagent and further react with indium to give α or γ-bromo substituted allylic di-indium reagent. Finally this diindium was received the third oxidative addition of indium to furnish allylic triindium reagent.



Scheme 10

Although it has not been clear what is the intermediate in this reaction, 1,3,3-tribromopropene could act as allylic triindium compound under the influence of indium. In the present case, only one of C-Br bond changed to C-C bond, and the rest were converted to C-H bonds.

1,4-Dichloro-2-butene. The reaction of 1,4-dichloro-2-butene with indium proceeded smoothly in presence of lithium iodide in DMF. However when electrophile such as benzaldehyde was co–exsisted in the reaction mixture, no cress-coupling product was obtained. Presumably it is due to the β-elimination of γ-chloromehyl allylindium reagents (Scheme 11). γ-Chloromethyl substituted allylindim was regared as a vinylogue of β-chloroethylindium.



Scheme 11

EXPERIMENTAL SECTION

1,3-Dichloropropene and 1,3-dibromopropene are purchased from Tokyo kasei Co Led. and Aldrich Chemical and used without farther purification.

Reaction of 1,3-dichloropropene with* p-*anisaldehyde.

p-Anisaldehyde (120 μL, 1.0 mmol), 1,3-dichloropropene (230 μL, 2.0 mmol), indium powder (110 mg, 1.0 mmol), and lithium iodide (270 mg, 2.0 mmol) were stirred in DMF (3.0 mL) at room temperature. The reaction was quenched with diluted hydrochloric acid and extracted with ether. The ether layer was washed with water, brine and dried over anhydrous sodium sulfate. After being removed the solvent under reduced pressure the residue was purified by column chromatograph on silica gel (elusion with dichloromethane) to give 2-chloro-1-(4-methoxyphenyl)-3-buten-1-ol (75% yield). The spectroscopic data was listed in Chapter 1.

Reaction of 1,3-dibromopropene with benzaldehyde.

Barbier-type reaction: Benzaldehyde (350 μL, 3.4 mmol), 1,3-dibromopropene (0.10 mL, 1.0 mmol), and indium powder (115 mg, 1.0 mmol) were stirred in DMF (2 mL) at 0 ℃ for 3 h. After being quenched with aqueous sodium hydroxide (1 N, 2 mL), the products were extracted with ether. Column chromatographic separation gave **4** (*cis*:*trans*=86:14, 56% yield), **5** (12%), and **6** (5%).

Grignard-type reaction: 1,3-Dibromopropene (100 μL, 1.0 mmol) and indium powder (58 mg, 5.0 mmol) were stirred in DMF (2 mL) at 0 ℃ for 1 h. To the resulting organoindium reagent was added benzaldehyde (350 μL, 3.4 mmol), and the mixture was further stirred at 0 ℃ for 3 h. Column chromatography gave **4** (*cis*:*trans*=83:17, 19% yield) and **5** (41%). Compound **4** was not found in this reaction. A prolonged reaction time (3 h) of 1,3-dibromopropene with indium did not change the ratio **4:5**.

Reaction of 1,3-dibromopropene (3) with carbonyl compounds. The following reaction with benzaldehyde (Table 4, Entry 6) represents the general procedure.

A mixture of indium powder (115 mg, 1.0 mmol), 1,3-dibromopropene (**3**) (100 μL, 1.0 mmol), and benzaldehyde (51 μL, 0.50 mmol) was stirred in DMA (2 mL) at 0 ℃ for 2 h. The reaction mixture was quenched with 0.5 N sodium hydroxide. The product was extracted with diethyl ether. The extracts were washed with brine and dried over Na_2SO_4. After the solvent was removed under reduced pressure, the residue was purified by column chromatography on silica gel (elution with dichloromethane:hexane = 1:1) to give 2-phenyl-3-vinyloxirane (**4a**)[6] (28 mg, 38%) and 1-phenylbut-3-en-1-ol (**5a**)[7] (31 mg, 42%).

Products **4b**,[8] **4c**,[6] **5b**,[7] **5c**,[9] **5d**,[9] **5e**,[9] and **5f**[9] are known compounds. The *cis/trans* ratio of oxiranes **4a-c** was determined based on ^{1}H NMR.[10]

Reaction of γ-bromoallylindium derived from allyl bromide (Scheme 3).

To freshly distilled diisopropylamine (0.5 mL, 2.9 mmol) in THF (5 mL), *n*-BuLi (1.6 M in hexane, 1.8 mL, 2.9 mmol) was added dropwise at 0 ℃. The resulting pale yellow solution was stirred at 0 ℃ for 0.5 h. To a mixture of indium trichloride (222 mg, 1.0 mmol) and allyl bromide (250 μL, 3.0 mmol) in THF (4 mL) was added the freshly prepared LDA dropwise at -78 ℃. The suspension was stirred at -78 ℃ for 0.5 h, and then benzaldehyde (154 μL, 1.5 mmol) was added. The mixture was gradually warmed to room temperature during 2 h, and quenched with saturated aqueous ammonium chloride. The product was extracted with ether, washed with water, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica gel (elution with EtOAc:hexane = 1:9) to give **4a** (160 mg, 72%). The *cis/trans* ratio was 83:17 based on ^{1}H NMR analysis.

Preparation of 3-bromo-1-iodopropen. [11] A mixture of sodium iodide (19 g, 125 mmol) and ethyl propiolate (2.0 mL, 19 mmol) was heated in glacial acetic acid (XX mL) at 70 ℃ overnight. The reaction mixture was extracted with ether and the extract was washed with 3 N sodium oxide, brine and dried over anhydrous sodium sulfate. Solvent was removed under reduced pressure. The residue was distillated at 100 ℃ under 4 mmHg to give ethyl 3-iodopropenoate (4.4 g, 100%).

Ethyl 3-iodopropenoate; ^{1}H NMR (200 MHz, $CDCl_3$) 1.30 (t, J = 7.1 Hz, 3H), 4.23 (q, J = 7.1 Hz, 2H), 6.88 (d, J = 9.0 Hz, 1H), 7.43 (d, J = 9.0 Hz, 1H).

To a solution of ethyl 3-iodopropenoate (4.4 g, 19 mmol) in dry dichlorometane DIBAL (0.95 M in hexane, 38 mL) was added at 0 ℃. The reaction mixture was quenched with a mixture of hexane:methanol = 9:1 (10 mL) and diluted hydrochloric acid was added. The product was extracted with ether and the extract was washed with water and brine. The ether layer was dried over anhydrous sodium sulfate and concentrated under the reduced pressure. 1-Iodoprop-1-en-3-ol was obtained (2.5 g, 74%) as colorless oil.

1-Iodoprop-1-en-3-ol:[11] IR (neat, cm^{-1}) 1596, 1426, 1296, 1200, 946, 720; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.00 (d, J = 6.8 Hz, 2H, CH_2), 6.28-6.66 (m, 2H, CH=CH).

To a solution of 1-iodoprop-1-en-3-ol (2.5 g, 14 mmol) in ether (20 mL) phosphorous tribromide (1.5 mL) was added at 0 ℃ and sited for 15 min. The reaction mixture was quenched with diluted hydrochloric acid and extracted with ether. This ether layer was washed with water and dried over anhydrous sodium sulfate. After evaporation of the solvent 3-bromo-1-iodopropene (2.3 g, 70%) was obtained and submitted to reactions without farther purification.

Reaction of 3-bromo-1-iodopropene (7) with carbonyl compounds. The following reaction (Table 2, Entry 1) represents the general procedure.

Indium powder (158 mg, 1.4 mmol) and 3-bromo-1-iodopropene (**7**) (141 μL, 1.4 mmol) were stirred in DMA (2 mL) at 0 ℃ for 1 h. Benzaldehyde (71 μL, 0.70 mmol) was added and the mixture was stirred for another 1 h. The reaction was quenched with 1 M DCl in D_2O. The product was extracted with diethyl ether. The extracts were washed with brine and dried over Na_2SO_4. After the solvent was removed under reduced pressure, the residue was purified by column chromatography on silica gel (elution with dichloromethane) to give **5a**-*d* (79 mg, 77%). The deuterium content was confirmed to be 80% by ^{1}H NMR and MS.

(E)-[4-D]-1-phenylbut-3-en-1-ol (5a-d). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.85-1.95 (bs, 1H), 2.47-2.56 (m, 2H), 4.70-4.78 (m, 1H), 5.16 (dt, *J* = 17.0, 2.8 Hz, 1H), 5.73-5.91 (m, 1H), 7.14-7.38 (m, 5H).

Preparation of 1,3,3-tribromopropene [12] A mixture of 1-bromopropene (5.0 mL, 29 mmol), *N*-bromosuccinimide (21.6 g, 122 mmol) and AIBN (0.2 g, 1.2 mmol) was refluxed in CCl_4 for 3days. After being evaporated the solvent , the residue was distillated by Kugelrohr (bp_{30}110 ℃) to give 1,3,3-tribromopropene (3.8 g, 23%) was obtained as colorless oil. (lit.[12] bp_{16}88-92 ℃)

1,3,3-Tribromopropene (E/Z = 1:1). ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.10 (d, *J* = 8.2 Hz) and 6.12 (d, *J* = 7.1 Hz, total 1H), 6.49 (d, *J* = 9.9 Hz, *cis*) and 6.58 (d, *J* = 13.5 Hz, *trans*, total 1H), 6.69 (dd, *J* = 13.5, 8.2 Hz) and 6.80 (dd, *J* = 9.9, 7.1 Hz, total 1H).

Indium-promoted reaction of 1,3,3-tribromopropene with benzaldehyde (in DMF).

To the suspension of indium (115 mg, 1.0 mmol) in DMF (3 mL) 1,3,3-tribromopropene was added in 0 ℃ and stirred for 2 h. Benzaldehyde (51 μL, 0.50 mmol) was added and stirred for another 2 h. The reaction mixture was quenched with diluted hydrochloric acid and extracted with ether. The ether layer was washed with water, brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (elusion with dichloromethane) to give homoallylic alcohol (14 mg, 19%) and bromohydrin (29 mg, 17%).

When this reaction was quenched with DCl, the incorporation of deuterium was observed in both homoallyic alcohol (16%) and bromohydrin (15%) by ^{1}H NMR analysis.

[2 or 4-D$_1$]-2-bromo-1-phenylbut-3-en-1-ol[13] (*syn*/*anti* = 70:30). ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.60 (d, *J* = 3.3 Hz, *anti* OH) and 2.77 (d, *J* = 3.6 Hz, *syn* OH, total 1H), 4.68-4.79 (m, 1.68H, CHBr), 4.98-5.20 (m, 1.46H, C*H*OH), 5.88–6.01 (m, 1H), 7.30-7.40 (m, 5H, Ph).

[2,4-D_2]-1-phenylbut-3-en-1-ol (5a-d_2) (*ca. E*:*Z* = 2:1). ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.05 (s, 1H, OH), 4.74 (d, *J* = 7.1 Hz, 1H), 5.13 (dd, *J* = 9.1, 1.0 Hz) and 5.15 (dd, *J* = 17.2, 1.4 Hz, total 1H), 5.75–5.90 (m, 1H), 7.20–7.40 (m, 5H).

Indium-promoted reaction of 1,3,3-tribromopropene with benzaldehyde (in aqueous THF). A mixture of indium trichloride (11 mg, 0.03 mmol), 1,3,3-tribromopropene (140 mg, 0.5 mmol), benzaldehyde (150 μL, 1.5 mmol) and aluminum powder (214 mg, 1.6 mmol) in THF (2.5 mL) and water (1.0 mL) was stirred overnight at rt. The reaction mixture was quenched with diluted hydrochloric acid and extracted with ether and washed with water, brine, then dried over anhydrous sodium sulfate. After the solvent was removed under reduced pressure, the residue was purified by column chromatography on silica gel (elution with dichloromethane:) to give homoallylic alcohol 5a (33 mg, 15%).

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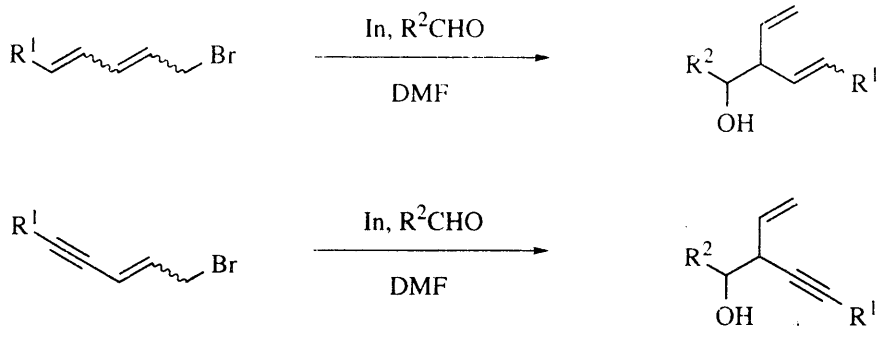
CHAPTER 3

High γ-Selectivity in the Coupling of Penta-2,4-dienyl- and Pent-2-en-4-ynylindium Reagents with Aldehydes

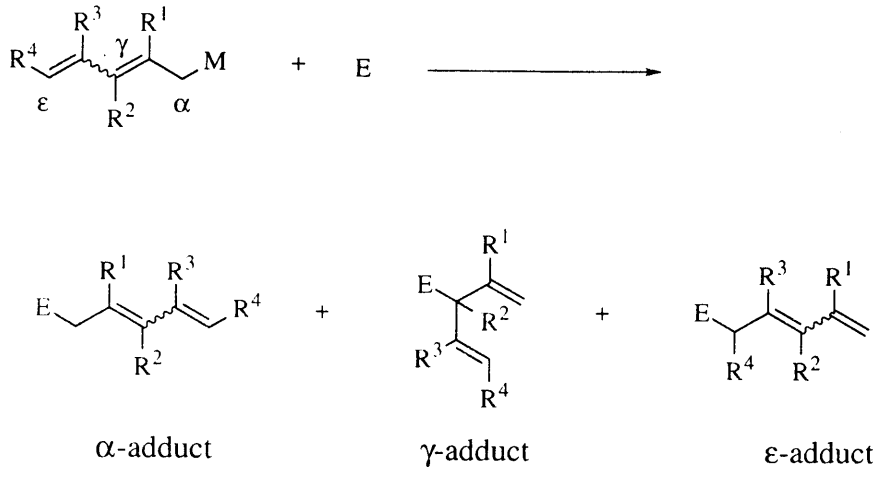
Summary

A variety of penta-2,4-dienyl- and pent-2-en-4-ynylindium reagents have been prepared *in situ* from the reaction of the corresponding allylic bromides with indium metal, and their reactions with carbonyl compounds have been examined. The reaction with aldehydes gives the corresponding homoallylic alcohols in high yields. The coupling occurs regioselectively at the g-position of these indium reagents. No a- and e-coupling products are formed.



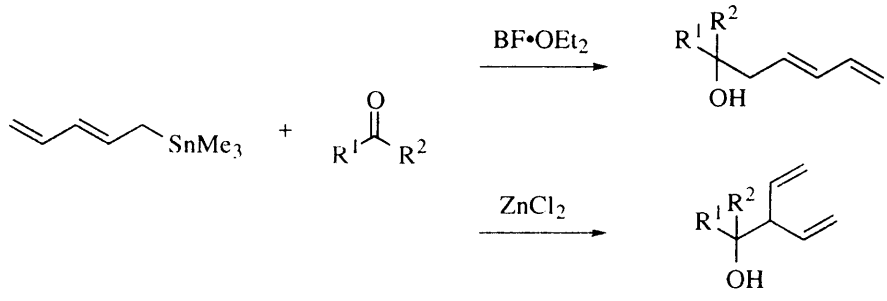
Introduction

Regioselective coupling of penta-2,4-dienylmetal reagents with electrophiles is a useful method in organic synthesis. When the coupling occurs at the terminal α- and/or ε-carbon(s) in a penta-2,4-dienylmetal, a conjugated penta-1,3-diene is formed, whereas at the internal γ-carbon a non-conjugated penta-1,4-diene is obtained (Scheme 1).



Scheme 1

A variety of penta-2,4-dienylmetal species have hitherto been studied, of which stannane and silane reagents have attracted much attention. Pentadienylstannanes and -silanes are known to react with carbonyl compounds in the presence of Lewis acids giving homoallyl alcohols.[1] Lewis acids play an important role to determine the regioselectivity. For example, in the presence of strong Lewis acids such as boron trifluoride etherate and aluminium chloride, pentadienylstannanes react at their terminal ε-carbon. In contrast, the pentadienylation occurs regioselectively at the γ-position when zinc chloride with a lower Lewis acidity was used (Scheme 2).[2]



Scheme 2

Although the metallic tin- and zinc-mediated reactions of pentadienyl bromides with carbonyl compounds have also been described to proceed selectively at the γ-position,[3] no detailed study has been reported.

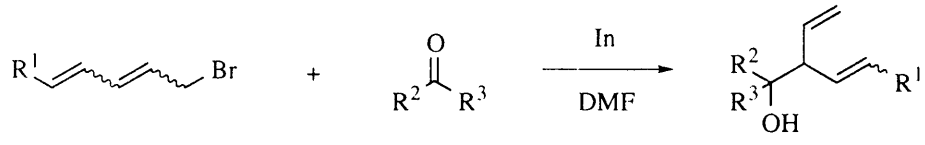
In order to control the regioselectivity of the reaction of pentadienylmetal with carbonyl compounds, we have focused on indium metal and undertaken the preparation and reactions of pentadienylindium reagents. Indium-mediated reactions have recently emerged as a useful tool in organic synthesis.[4] Allylindium reagents show high γ-selectivity in the allylation of a variety of carbonyl compounds, and some applications of allylindium reagents to natural product synthesis in aqueous media have been reported.[5] It has also been demonstrated that indium trichloride promotes the reaction of allylstannane with aldehydes to afford γ-adducts.[6] Recently, the reaction of pentadienylstannane with aldehyde promoted by indium trichloride was reported.[7] In these cases, indium trichloride is considered not to act as a Lewis acid for the activation of carbonyl compounds, but to form an allylic indium species via transmetalation from allylic stannane reagents.[6,7]

In this paper, we describe the preparation of penta-2,4-dienyl- and pent-2-en-4-ynylindium reagents, which are higher homologues of allylindium with an extended conjugated double bond or triple bond, and their regioselective coupling with carbonyl compounds.

Results and Discussion

Penta-2,4-dienylindium reagents were readily prepared from indium powder and the corresponding allylic bromides in N,N-dimethylformamide (DMF) at ambient temperature. Penta-2,4-dienylindium prepared in situ from penta-2,4-dienyl bromide (E:Z=90:10) reacted with benzaldehyde regioselctivity at the γ-position to give the coupling product quantitatively (Table 1, entry 1).

Table 1 Reaction of pentadienylindium reagents with carbonyl compounds



Entry	R^1	R^2	R^3	Conditionsa	Yield(%)[b]
1	H	Ph	H	A	97
2	Me	H	H	A	56 (32:68)[c]
3	Me	Ph	H	A	76[d]
4	Me	Ph	H	B	23[d]
5	Me	*n*-C_7H_{15}	H	A	89d
6	Me	*c*-C_6H_{11}	H	A	72 (68:20:12)[e]
7	Me	(*E*)-PhCH=CH	H	A	100d
8	Ph	Ph	H	A	85 (54:46)[f]
9	Me	*t*-Bu	H	C	0
10	Me	Ph	Me	A	0

a A: in DMF, 0 ℃, 3 h; B: in water, room temperature, overnight; C: in DMF, room temperature, overnight. b Isolated yieldc *E*:*Z* ratio. d Mixture of isomers. Diastereomeric ratio was not determined. e Diastereomeric ratio determined by ^{13}C NMR analysis. f Diastereomeric ratio determined by ^{1}H NMR analysis.

The indium-mediated reaction of hexa-2,4-dienyl bromide with aldehydes also gave the corresponding homoallylic alcohols in good yields (entries 2 - 7). Again, the γ-regioselectivity was perfectly achieved. The coupling product with formaldehyde was a mixture of geometrical isomers (*E*:*Z* = 32:68) (entry 2). 5-Phenylpenta-2,4-dienylindium also provided the γ-selectively coupled homoallyl alcohol (entry 8).

One of the characteristics of allylindium reagents is the variety of usable solvents. Allylation with allylindium can be carried out effectively in water,[5,8] but the indium-mediated reaction of hexa-2,4-dienyl bromide with benzaldehyde in water was sluggish to give the homoallyl alcohol in a poor yield and unreacted benzaldehyde was recovered (entry 4). The regio- and diastereoselectivity were almost coincident to those in DMF. From the reaction of a ketone or bulky aldehyde like pivaraldehyde, no cross-coupling product was obtained (entries 9 and 10). Addition of a Lewis acid is an effective method for the activation of carbonyl compounds. However, the addition of boron trifluoride etherate to the reaction of hexa-2,4-dienylindium and octanal resulted in only decrease of the yield, and the regio- and diastereoselectivities were not changed.

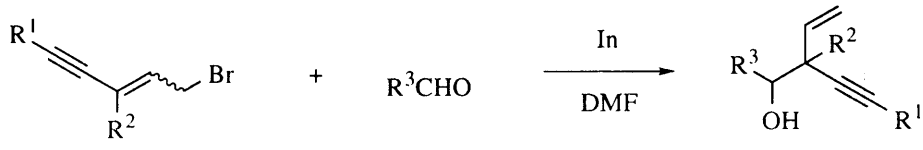
In principle, the γ-coupling reaction of hexadienylindium with aldehydes will give four diastereoisomers: pairs of *syn*/*anti* diastereomers and *E*/*Z* isomers. The homoallylic alcohol obtained in entry 6 was revealed by ^{13}C NMR analysis to be a mixture of three isomers in the ratio of 68:20:12. In the other cases, the homoallylic alcohols obtained are also considered to be mixtures of three or four possible isomers; however, the ratios were not determined.

It has been reported that both (*E*)- and (*Z*)-cinnamyl bromides give almost coincident diastereoselectivities with high *anti*-selectivity (>90%) in the reaction with aldehyde.[9] This fact suggests that the *E*,*Z*-isomerization occurs during the oxidative addition of indium to cinnamyl bromide, or that the *E*,*Z*-isomerization of cinnamylindium is faster than the coupling reaction. The reaction of (*E*,*E*)-5-phenylpenta-2,4-dienyl bromide gave a diastereoselectivity of 54:46,

bromide, or that the *E,Z*-isomerization of cinnamylindium is faster than the coupling reaction. The reaction of (*E,E*)-5-phenylpenta-2,4-dienyl bromide gave a diastereoselectivity of 54:46, whereas the *E*-geometry of the C^4 double bond was completely retained during the reaction (entry 8). If the transition state is assumed to be a six-membered cyclic type, the (*E,E*)-dienyl bromide, and even the (*Z,E*)-isomer, are expected to afford the *anti*-adduct as in the cinnamyl case. The observed low diastereoselectivity may be owing to the small energy difference between the two transition states leading to the *syn*- and *anti*-products.

The indium-mediated reaction of pent-2-en-4-ynyl bromides with aldehydes also proceeded smoothly (Table 2).

Table 2 Reaction of enynylindium reagents with aldehydes[a]



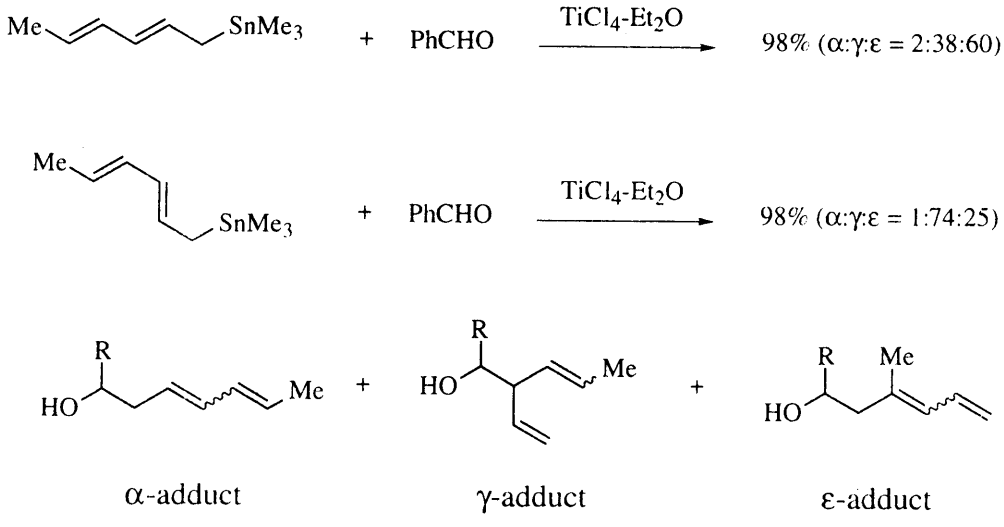
Entry	R^1	R^2	R^3	Yield(%)[b]
1	Ph	H	Ph	89 (67:33)
2	H	Me	Ph	30 (61:39)
3	H	Me	*n*-C_7H_{15}	36 (70:30)
4	H	Me	H	25
5	H	Me	*c*-C_6H_{11}	0

[a] All reactions were carried out in DMF at 0 ℃ for 3 h.

[b] Isolated yield. Numbers in parentheses show diastereomeric ratio by ^{1}H NMR analysis.

methyl group at the γ-position of the enynylindium reagent diminished the reactivity, giving lower yields of the products (entries 2-4). Sterically bulky cyclohexylcarboxyaldehyde did not react at all with this enynylindium (entry 5).

In summary, the indium-mediated reactions of penta-2,4-dienyl bromides and pent-2-en-4-ynyl bromides with aldehydes have been found to give the corresponding homoallylic alcohols with complete γ-selectivity. Because allylic indium reagents have strong Lewis acidity, the coupling reaction with carbonyl compounds is considered to proceed via a coordination to the carbonyl oxygen, forming a six-membered transition state. This is the source of the high γ-regioselectivity of these reactions. The poor diastereoselectivity may be attributable to the distorted six-membered ring, because the indium atom is too bulky to form a rigid six-membered ring in the transition state. It has also been demonstrated that the geometry of the starting dienyl bromides is not important to the regioselectivity of the reaction of pentadienylindium reagents. This is in sharp contrast to the cases of dienylstannane reagents, in which the regioselectivity largely depends on the geometry of the reagents (Scheme 3).[10]



Scheme 3

The present indium-prompted Barbier-type reactions are synthetically superior to the existing stannane- and silane-based ones, because of their high regioselectivity and experimental simplicity; there is no need to handle hazardous chemicals such as organometallics and Lewis acids.

EXPERIMENTAL SECTION

General

All dienyl bromides and enynyl bromides were prepared from the reaction of the correspon ing alcohols with phosphorous tribromide in ether, and used without further purification. Pent 2,4-dien-1-ol,[11] hexa-2,4-dien-1-ol,[12] 5-phenylpenta-2,4-dien-1-ol,[13] and 5-phenylpent-2-en-4-y 1-ol[14] were prepared according to the literature methods.

Preparation of 5-phenylpenta-2,4-dien-1-ol and 5-phenylpent-2-en-4-yn-1-c

To a suspension of sodium hydride dispersion (60%) in dry THF (10 mL) triethyl phosp noacetate (1.0 mL, 530 mmol) was added and stirred for 1 h at rt. Phenylpropargylaldehyde (6(µL, 4.9 mmol) was added and stirred for 1 h. The reaction mixture was quenched with water a the organic layer was separated, washed with water, brine and concentrated under reduced pressu The residue was subjected to Kugelrohr distillation (160 °C, 4 torr) giving ethyl 5-phenylpent-2-e 4-ynoate (305 mg, 31%).

Ethyl 5-phenylpent-2-en-4-ynoate: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.31 (t, J = 7.1 H 3H, CH_3), 4.24 (q, J = 7.1 Hz, 2H, CH_2), 6.31 (d, J = 15.8 Hz, 1H, C.tplbond.CC*H*=), 6.99 (J = 15.8 Hz 1H, =$CHCO_2Et$), 7.34-7.38 (m, 3H, *m*, *p*-Ph), 7.46-7.51 (m, 2H, *o*-Ph); IR (nea cm^{-1}) 2935, 2200, 1712, 1618, 1440, 1364, 1306, 1250, 1078, 958, 858, 756, 686.

To a solution of ethyl 5-phenylpent-2-en-4-ynoate (305 mg, 1.53 mmol) in dry hexane (mL) DIBAL (0.95 M, 4 mL) was added in -78 °C and stirred for 3.5 h at this temperature. Th reaction mixture was quenched with saturated ammonium chloride and added hydrochloric aci The product was extracted with ether and washed with water, brine and dried over anhydrous s dium sulfates. After the solvent was evaporated, 5-phenylpent-2-en-4-yn-1-ol (246 mg, 74% was obtained as colourless oil.

5-Phenylpent-2-en-4-yn-1-ol; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.28 (t, J = 5.6 Hz, 2H

=C*H*CH_2OH), 7.27-7.34 (m, 3H, *m*, *p*-Ph), 7.38-7.48 (m, 2H, *o*-Ph).

Similarly, the reaction of cinnamaldehyde gave 5-phenylpent-2-en-4-yn-1-ol (18%).

5-Phenylpent-2-en-4-yn-1-ol ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.26 (m, 2H, CH_2OH), 5.97 (dt, J = 15.1, 5.8 Hz, 1H, C^2H), 6.46 (dd, J = 15.1, 10.2 Hz, 1H, C^3H), 6.56 (d, J = 15.7 Hz, 1H, C^5H), 6.78 (dd, J = 15.7, 10.2 Hz, 1H, C^4H), 7.25-7.50 (m, 5H, Ph).

Reactions of dienyl and enynylindium reagents with aldehydes. Typical Procedure

A mixture of penta-2,4-dienyl bromide (*E/Z* mixture) (0.12 g, 1.0 mmol), indium powder (57 mg, 0.50 mmol) and benzaldehyde (51 μL, 0.50 mmol) was stirred in DMF (2.0 cm3) at 0 ℃ for 3 h. The reaction mixture was quenched with dilute hydrochloric acid. The product was extracted with diethyl ether. The extracts were washed with brine and dried (Na_2SO_4). After the solvent was removed under reduced pressure, the residue was column chromatographed (silica gel; dichloromethane) to give 2-ethenyl-1-phenylbut-3-en-1-ol (72 mg, 76%). Other reactions were similarly carried out and the results are summarised in Tables 1 and 2.

2-Ethenyl-1-phenylbut-3-en-1-ol.[15] ^{1}H NMR (200 MHz, $CDCl_3$): 7.17-7.44 (m, 5H, Ph), 5.58-5.97 (m, 2H, C*H*=CH_2), 4.88-5.32 (m, 4H, CH=C*H*$_2$), 4.60 (dd, J = 7.1, 3.2 Hz, 1H, C*H*OH), 3.05-3.17 (m, 1H, CH), 2.17 (d, J = 3.2 Hz, 1H, OH); IR (neat, cm^{-1}): 3430, 3080, 3030, 2980, 2876, 1630, 1600, 1490, 1450, 1410, 1380, 1290, 1190, 1150, 1080, 1030, 996, 910, 830, 760, 716, 696.

2-Ethenylpent-3-en-1-ol. ^{1}H NMR (200 MHz, $CDCl_3$): 5.05-5.85 (m, 5H, olefinic), 3.49-3.55 (m, 2H, C*H*$_2$OH), 3.32 (br. quint, J = 7.5, CH, *Z* isomer) and 2.92 (br. quint, J = 7.3 Hz, CH, *E* isomer) (total 1H), 1.65 - 1.73 (m, 3H, Me), 1.48 (br.t, J = 6.7 Hz, 1H, OH); IR (neat, cm^{-1}): 3360, 2920, 1638, 1444, 1418, 1378, 1050, 992, 962, 918, 720.

2-Ethenyl-1-phenylpent-3-en-1-ol.[15,16] ^{1}H NMR (200 MHz, $CDCl_3$): Major iso-

mer7.41-7.12 (m, 5H, Ph), 4.85-5.92 (m, 5H, olefinic), 4.45-4.55 (m, 1H, C*H*OH), 3.03 (q, J = 6.8 Hz, 1H, CH), 2.29 (d, J = 2.8 Hz, 1H, OH), 1.60 (dd, J = 5.7, 1.1 Hz, 3H, Me). Peaks of minor isomers were also observed: 3.38 (m, CH), 2.32 (br. d, J = 2.8 Hz, OH), 1.73 (dd, J = 6.3, 0.8 Hz, Me), 1.36 (dd, J = 6.6, 1.6 Hz, Me); IR (neat, cm^{-1}): 3450, 3100, 3050, 3000, 2950, 2900, 1640, 1600, 1500, 1436, 1380, 1190, 1080, 1040, 1000, 970, 920, 840, 760, 702.

4-Ethenyldodec-2-en-5-ol. ^{1}H NMR (200 MHz, $CDCl_3$): 5.02-5.90 (m, 5H, olefinic), 3.48 (br. s, 1H, C*H*OH), 2.65-3.22 (m, 1H, C*H*CH=), 1.60-1.78 (m, 3H, =CHCH_3), 1.50 (m, 1H, OH), 1.27 (s, 12H, CH_2), 0.88 (t, J = 6.0 Hz, 3H, CH_2CH_3). IR (neat, cm^{-1}): 3350, 3050, 3000, 2940, 2910, 2840, 1700, 1630, 1450, 1370, 1116, 1060, 986, 960, 906; Anal. Found: C, 79.86; H, 12.34. $C_{14}H_{26}O$ Calc.: C, 79.94; H, 12.46%.

1-Cyclohexyl-2-ethenylpent-3-en-1-ol. ^{1}H NMR: 5.00-5.94 (m, 5H, olefinic), 3.18-3.28 (m, C*H*OH and C*H*CH=) and 2.90 (q, J = 7.2 Hz C*H*CH=) (total 2H), 0.95-1.85 (m, 15H, Me, c-C_6H_{11}, and OH); ^{13}C NMR (olefinic carbon): diastereomer 1: 137.7, 130.9, 126.2, 116.1; diastereomer 2: 139.0, 127.8, 127.6, 115.0; diastereomer 3: 137.8, 129.4, 124.5, 115.7; IR (neat, cm^{-1}): 3400, 3070, 3020, 2930, 2850, 1630, 1444, 1410, 1390, 1370, 1240, 1304, 1260, 1200, 1180, 1140, 1080, 1060, 1036, 960, 940, 904, 894, 864, 838, 760, 720; Anal. Found: C, 80.56; H, 11.65. $C_{13}H_{22}O$ Calc.: C, 80.36; H, 11.41%.

4-Ethenyl-1-phenylhepta-1,5-dien-3-ol. ^{1}H NMR (200 MHz, $CDCl_3$): Major isomer 7.16-7.50 (m, 5H, Ph), 6.61 (dd, J = 16.0, 1.3 Hz, 1H, PhC*H*=CH), 6.22 (dd, J = 16.0, 6.2 Hz, 1H, PhCH=C*H*), 5.06-5.97 (m, 5H, olefinic), 4.17-4.26 (m, 1H, C*H*OH), 2.96 (q, J = 5.0 Hz, 1H, C*H*OH), 1.88 (d, J = 5.0 Hz, 1H, OH), 1.71 (dd, J = 6.0, 1.0 Hz, 3H, Me). Peaks of minor isomers were also observed: 3.25-3.40 (m, CH), 1.92 (d, J = 3.6 Hz, OH), 1.65 (dd, J = 6.8, 1.7 Hz, Me), 1.74 (dd, J = 7.4, 1.3 Hz, Me); IR (neat, cm^{-1}) 3400, 3075, 3020, 2970, 2900, 2875, 1660, 1630, 1594, 1574, 1490, 1444, 1370, 1200, 1150, 1060, 1020, 990, 960, 910, 830, 744, 690; Anal. Found: C, 83.78; H, 8.59. $C_{15}H_{18}O$ Calc.: C, 84.07; H, 8.47%.

2-Ethenyl-1,4-diphenylbut-3-en-1-ol.[17] ^{1}H NMR (200 MHz, $CDCl_3$): 7.1-7.4 (m, 10H, Ph), 6.49 (d, J = 16.0 Hz, =C*H*Ph, minor isomer) and 6.33 (dd, J = 16.0, 1.0 Hz, =C*H*Ph, major isomer) (total 1H), 6.29 (dd, J = 16.0, 8.2 Hz, C*H*=CHPh, minor isomer) and 6.07 (dd, J = 16.0, 7.4 Hz, C*H*=CHPh, major isomer) (total 1H), 5.92 (ddd, J = 17.0, 10.0, 8.5 Hz, C*H*=CH_2, major isomer) and 5.77 (ddd, J = 17.0, 11.0, 7.1 Hz, C*H*=CH_2, minor isomer) (total 1H), 5.17-5.28 (m, CH=CH_2) and 5.00-5.10 (m, CH=CH_2) (total 2H), 4.46 and 4.67 (each d, J = 6.9 Hz, 1H, C*H*OH), 3.20-3.31 (m, 1H, C*H*CH(Ph)OH), 2.28 (s, 1H, OH); IR (neat, cm^{-1}): 3400, 3005, 1628, 1592, 1488, 1442, 1380, 1296, 1080, 1038, 910, 740, 682.

2-Ethenyl-1,4-diphenylbut-3-yn-1-ol. ^{1}H NMR (200 MHz, $CDCl_3$): 7.25-7.50 (m, 10H, Ph), 5.91 (ddd, J = 17.0, 10, 6.8 Hz, C*H*=CH_2, minor isomer) and 5.72 (ddd, J = 17.0, 10.0, 5.5 Hz, C*H*=CH_2, major isomer) (total 1H), 5.48 (dt, J = 17, 1.6 Hz, (*E*)-CH=CH_2, major isomer) and 5.46 (dt, J = 17.0, 1.6 Hz, *E*-CH=CH_2, minor isomer) (total 1H), 5.24 (dt, J = 10.0, 1.6 Hz, *Z*-CH=CH_2, major isomer) and 5.30 (dt, J = 10.0, 1.6 Hz, (*Z*)-CH=CH_2, minor isomer) (total 1H), 4.74 (dd, J = 6.2, 3.9 Hz, C*H*OH, major isomer) and 4.86 (dd, J = 6.4, 3.6 Hz, C*H*OH, minor isomer) (total 1H), 3.63-3.72 (m, 1H, CH(OH)C*H*), 2.59 (d, J = 3.9 Hz, OH, major isomer) and 2.38 (d, J = 3.6 Hz, OH, minor isomer) (total 1H); IR (neat, cm^{-1}): 3450, 3045, 1640, 1598, 1490, 1452, 1400, 1042, 920, 756, 688; Anal. Found: C, 83.78; H, 8.59. $C_{15}H_{18}O$ Calc.: C, 84.07; H, 8.47%.

2-Ethynyl-2-methyl-1-phenylbut-3-en-1-ol. ^{1}H NMR (200 MHz, $CDCl_3$): 7.22-7.50 (m, 5H, Ph), 5.77 (dd, J = 17.0, 10.0 Hz, C*H*=CH_2, major isomer) and 5.72 (dd, J = 17.0, 10.0 Hz, C*H*=CH_2, minor isomer) (total 1H), 5.56 (dd, J = 17.0, 1.7 Hz, (*E*)-CH=CH_2, major isomer) and 5.37 (dd, J = 17.0, 1.4 Hz, *E*-CH=CH_2, minor isomer) (total 1H), 5.26 (dd, J = 10.0, 1.7 Hz, (*Z*)-CH=CH_2, major isomer) and 5.17 (dd, J = 10.0, 1.4 Hz, *Z*-CH=CH_2, minor isomer) (total 1H), 4.53 (d, J = 3.3 Hz, C*H*OH, major isomer) and 4.63 (d, J = 4.1 Hz, C*H*OH, minor isomer) (total 1H), 2.43 and 2.46 (each s, total 1H, OH), 2.44 (s, 1H, CH), 1.32 (s, Me, minor

isomer) and 1.20 (s, Me, major isomer) (total 3H); IR (neat, cm^{-1}): 3450, 3300, 3080, 2860, 1634 1490, 1450, 1400, 1364, 1240, 1190, 1130, 1080, 1040, 1020, 990, 920, 820, 780, 720, 700 Anal. Found: C, 83.90; H, 7.67 $C_{13}H_{14}O$ Calc.: C, 83.83; H,7.58%.

3-Ethynyl-3-methylundec-1-en-4-ol. ^{1}H NMR (200 MHz, $CDCl_3$): 5.78 (dd, J = 17.0, 11.0 Hz, C*H*=CH_2, minor isomer) and 5.73 (dd, J = 17.0, 10.0 Hz, C*H*=CH_2, major isomer) (total 1H), 5.48 (dd, J = 17.0, 1.5 Hz, (*E*)-CH=CH_2, minor isomer) and 5.44 (dd, J = 17, 1.5 Hz, (*E*)-CH=CH_2, major isomer) (total 1H), 5.22 (dd, J = 11.0, 1.5 Hz, (*Z*)-CH=CH_2, minor isomer) and 5.17 (dd, J = 10.0, 1.5 Hz, (*Z*)-CH=CH_2, major isomer) (total 1H), 3.29-3.45 (m, 1H, C*H*OH), 2.35 (s, 1H, CH), 1.78 (d, J = 4.9 Hz, OH, minor isomer) and 1.61 (d, J = 3.1 Hz, 1H, OH, major isomer) (total 1H), 1.36 (s, Me, minor isomer) and 1.30 (s, Me, major isomer) (total 3H), 1.27 (m, 12H, CH_2), 0.88 (t, J = 6.5 Hz, 3H, Me); IR (neat, cm^{-1}): 3450, 3300, 2925, 2105, 1638, 1558, 1404, 1378, 1260, 1064, 996, 964, 920; Anal. Found: C, 80.47; H, 11.59. $C_{14}H_{24}O$ Calc.: C, 80.71; H; 11.61%.

2-Ethynyl-2-methylbut-3-en-1-ol. ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.73 (dd, J = 17.0, 10.0 Hz, 1H, C*H*=CH_2), 5.48 (dd, J = 17.0, 1.5 Hz, 1H, (*E*)-CH=CH_2), 5.23 (dd, J = 10.0, 1.5 Hz, 1H, (*Z*)-CH=CH_2), 3.50 (s, 2H, CH_2OH), 2.36 (s, 1H, CH), 1.77 (br. s, 1H, OH), 1.32 (s, 3H, Me); IR (neat, cm^{-1}): 3400, 3300, 2890, 2110, 1640, 1450, 1406, 1306, 1268, 1048, 998, 922; Anal. Found: C, 75.67; H, 9.24. $C_7H_{10}O$ Calc.: C, 76.33; H, 9.15%.

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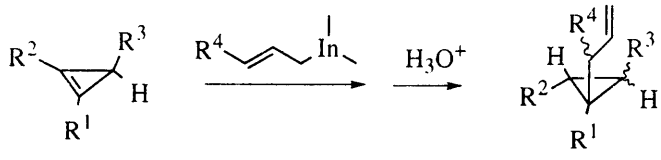
CHAPTER 4

Stereodivergent Allylindation of Cyclopropenes. Remarkable Stereodirection and Acceleration by Neighbouring Carboxyl and Hydroxyl Groups

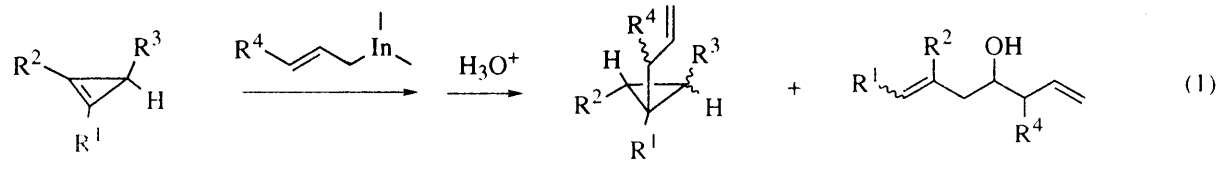
Summary

Stereodivergent allylindation of cyclopropene derivatives has been realised regio- and stereoselectively. The coupling occurs exclusively at the γ-carbon of allylic indium reagents and the more substituted carbon of the cyclopropene double bond. The carboxyl and hydroxymethyl groups on the cyclopropene C^3-carbon exert significant effects in *cis*-direction and acceleration of the allylindation based on the intramolecular chelation, whereas the ester group directs a *trans*-addition owing to the steric interaction with incoming allylindium reagents.



Introduction

Carbometalation of unsaturated compounds has long been the subject of great concern. [1] Of a variety of main group metals as well as transition metals, indium has recently received increasing interest as a versatile metal for carbometalation. Regioselective carboindation was first reported on alkynes with allylindium reagents. [2] Allenes were also found to undergo a clean regio- and stereoselective allylindation. [3] Thus, it has been shown that the carbon-carbon multiple bonds with enhanced s character, such as those of alkynes and allenes, undergo a smooth allylindation, whereas ordinary carbon-carbon double bonds are inert. Here we disclose that the first allylindation of cyclopropenes, [4] which possess an s character rich double bond ($sp^{1.19}$), [5] proceeds regio- and stereoselectively, where proximal carboxyl as well as hydroxyl groups exert significant effects in *cis*-direction and acceleration of the addition of allylindium reagents based on the intramolecular chelation.



(1)

	R^1	R^2	R^3
1a	*n*-C_6H_{13}	H	CH_2OH
b	*n*-C_6H_{13}	H	CO_2H
c	*n*-C_6H_{13}	H	CH_2OAc
d	*n*-C_6H_{13}	H	CO_2Et
e	Me	Me	CH_2OH
f	Et	Et	CH_2OH

	R^1	R^2	R^3	R^4
2	*n*-C_6H_{13}	H	CH_2OH	H
3	*n*-C_6H_{13}	H	CH_2OH	Me
4	*n*-C_6H_{13}	H	CH_2OH	Ph
5	*n*-C_6H_{13}	H	CO_2H	H
6	*n*-C_6H_{13}	H	CH_2OAc	H
7	*n*-C_6H_{13}	H	CO_2Et	H
8	Me	Me	CH_2OH	H
9	Me	Me	CH_2OH	Me
10	Et	Et	CH_2OH	H

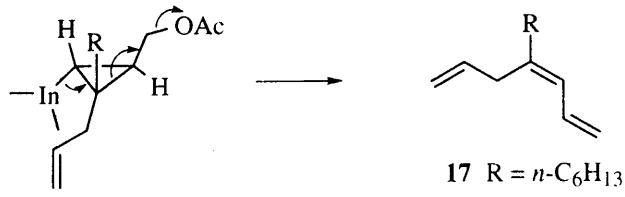
	R^1	R^2	R^4
11	H	*n*-C_6H_{13}	Me
12	H	*n*-C_6H_{13}	Ph
13	Me	Me	H
14	Me	Me	Me
15	Et	Et	H
16	Et	Et	Ph

Results and discussion

3-(Hydroxymethyl)-1-hexylcyclopropene (**1a**) gave the allylindation product in high yields (Table, entries 1-4) (eq. 1). The reaction proceeded both in organic and aqueous media, but the yield and the selectivity in THF were higher than those in DMF and in water. γ-Substituted allylic indium reagents reacted at the γ-carbon (entries 5 and 6). The regio- and stereoselectivities of the present allylindation are high: the allylic group was introduced exclusively to the substituted carbon of the cyclopropene double bond, and the allylindium reagents added preferentially from the *cis* face of the hydroxymethyl group (confirmed by Lanthanide-induced-shift experiments on the products), though the *cis*-selectivity decreased in DMF and in water. Surprisingly, the corresponding carboxylic acid **1b**, though less reactive than **1a**, also underwent the clean allylindation at elevated temperature with high regio- and stereoselectivities (entries 7 and 8).

The complete regioselectivity (allylation of the substituted carbon of cyclopropene) was again attained with the acetate **1c** (entries 9-11). Quenching the reaction with trifluoroacetic acid-*d* resulted in **6**-*d*, in which the deuterium atom was introduced exclusively *syn* to the allyl group, thus confirming a *syn*-addition mode of the allylindium derivative. Interestingly, the stereoselectivity was dramatically reversed to that of the alcoholic **1a** and carboxylic substrates **1b**; allylindium added *trans* with respect to the acetoxymethyl group. At elevated temperature, a ring-opening of the resulting cyclopropylindium species took place with an elimination of the acetoxy group to yield (*Z*)-hepta-1,3,6-triene (**17**) (eq. 2). The *Z*-geometry of **17**, confirmed by NOE experiments, supports again a *syn*-addition mode of the allylindium. The *trans*-selectivity was also observed for cyclopropenecarboxylate **1d**, and the selectivity increased with increasing the solvent polarity and the reaction temperature (entries 12 and 13). 1,2-Disubstituted cyclopropenes **1e** and **1f** resisted to allylindation, giving poor yields (20-27%) of the cyclopropane products **8** - **10** together with considerable amounts of the ring-opening products **13** - **16** (entries 14-18).[6] Nevertheless, a complete

syn-addition mode regarding the allylic group and indium as well as a *cis*-addition to the hydroxymethyl group were again confirmed.



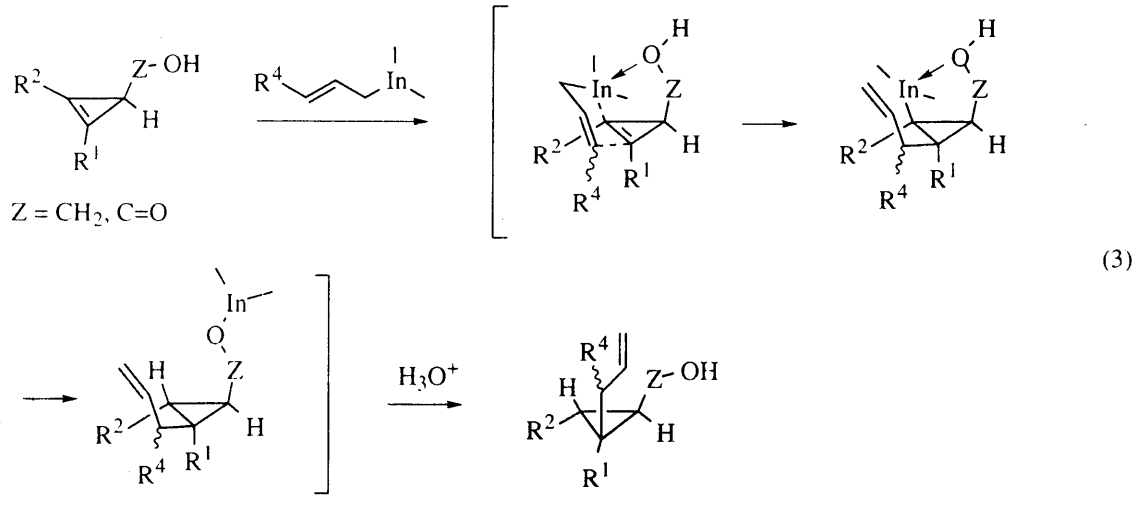
17 R = *n*-C_6H_{13} (2)

The relative reactivities of **1a** and **1c** were compared by a competition experiment. An equimolar mixture of **1a** and **1c** was subjected to allylindation in THF with a limited amount of allylindium sesquiiodide. The product mixture was found to contain **2** (64% yield) and unreacted **1c** (73% recovery), and **6** was not formed at all, thus demonstrating the highly enhanced reactivity of **1a**.

The observed high *cis*-stereoselectivity in the allylindation of the carboxyl- and hydroxymethyl-bearing cyclopropenes can be best explained by the intramolecular coordination of the hydroxyl oxygen to the indium atom (eq. 3). By the chelation with the allylic indium reagent, the chelators direct the reagent stereoselectively *cis*. Steric interaction is considered to be an important factor to determine the regioselectivity. The sterically demanding indium atom is expected to couple with the less substituted carbon atom of the two alkenic carbons and the γ-terminus of the allyl group is extruded to the other carbon, thus a new carbon-carbon bond is formed regioselectively at the more substituted double bond carbon via the tricyclic transition state. The enhanced reactivity of **1a** compared with **1c** is consistent with the fact that the involvement of a chelated intermediate lowers the transition state energy, consequently resulting in rapid conversion to the product.[7] More co-ordinative solvents such as water and DMF are considered to compete with the intramolecular chelation, accordingly decreasing the reaction rate and the *cis*-selectivity of the allylindation. Although similar acceleration and stereoselection based on a hydroxyl-chelation were observed in the

allylindation of alkynols[2] and allenols[3] as well as the allylation of hydroxyaldehydes, [8] examples based on the chelation of a carboxylic acid group are quite limited.[9]

In summary, it has been shown that the substituent on the cyclopropene C^3-carbon plays an important role in determining the stereoselectivity of allylindation: the carboxyl and hydroxymethyl groups facilitate a high *cis*-addition based on the chelation, whereas the ester group directs a *trans*-addition owing to the steric interaction with incoming allylindium reagents. The starting cyclopropene derivatives used in this work are easily accessible via the transition metal catalysed reaction of diazoacetates with alkynes.[10] Therefore, the present allylindation of cyclopropenes provides a convenient method for the stereodivergent synthesis of substituted cyclopropanes.



(3)

Table. Allylindation of Cyclopropenes[a]

Entry	Cyclopropene	R^4	Conditions	Product(s) (Yield/%)	*cis*:*trans*[b]
1	**1a**	H	THF, 0-5 ℃	**2** (85)	95:5
2		H	THF, r.t.	**2** (95)	93:7
3		H	DMF, r.t.	**2** (74)	85:15
4[c]		H	H_2O, r.t.	**2** (30), (25)[d]	45:55
5		Me	THF, r.t.	**3**[e] (63), **11** (5)	92:8
6		Ph	DMF, 100 ℃	**4**[f] (59), **12** (5)	78:22
7	**1b**	H	THF, rfx.	**5** (81)	100:0
8[c]		H	DMF, 100 ℃	**5** (70)	89:11
9	**1c**	H	THF, r.t.	**6** (66)	0:100
10		H	DMF, r.t.	**6** (42) (10)[d]	0:100
11		H	DMF, 100 ℃	**6** (25), **2** (16), **17** (36)	0:100[g]
12	**1d**	H	THF, rfx.	**7** (63)	26:74
13		H	DMF, 100 ℃	**7** (50) (19)[d]	3:97
14	**1e**	H	THF, r.t.	**8** (21), **13** (49)	100:0
15		Me	THF, r.t.	**9**[h] (22), **14** (27)	100:0
16	**1f**	H	THF, r.t.	**10** (20), **15** (42)	100:0
17		H	DMF, 100 ℃	**10** (27), **15** (28)	100:0
18		Ph	DMF, 90 ℃	**16** (43)	----

[a] All reactions were carried out for 3-4 h unless otherwise noted. [b] *Cis*:*trans* refers to the relation between R^3 and the allyl group introduced in the cyclopropane product. [c] Reaction time ca. 20 h. [d] Recovery of the starting substrate. [e] Diastereomeric ratios 91:9 (*cis*-isomers) and 71:29 (*trans*-isomers). [f] Diastereomeric ratios 76:24 (*cis*-isomers) and 68:32 (*trans*-isomers). [g] Ratio of compound **6**. [h] Diastereomeric ratio 89:11.

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EXPERIMENTAL SECTION

The following reaction (entry 7, Table) represents a general procedure: To a solution of allylindium sesquiiodide, prepared from indium powder (172 mg, 1.5 mmol) and allyl iodide (0.20 mL, 2.3 mmol) in THF (3.0 mL), was added 1-hexylcyclopropene-3-carboxylic acid (**1b**) (168 mg, 1.0 mmol), and the mixture was heated under reflux for 4 h. The reaction mixture was allowed to cool down to room temperature and quenched by the addition of diluted hydrochloric acid. The product was extracted with dichloromethane and the extracts were washed with brine and then dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel using CH_2Cl_2-hexane (1:1) as eluent to give **5** (169 mg, 81%).

t-2-Hexyl-r-1-(hydroxymethyl)-c-2-(2-propenyl)cyclopropane (**2**): colorless oil IR (neat): 3340, 3080, 2930, 2850, 1640, 1462, 1438, 1410, 1376, 1148, 1024, 1008, 910, 734, 720 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.18 (t, J = 4.8 Hz, 1H), 0.53 (dd, J = 8.7, 4.8 Hz, 1H), 0.87 (t, J = 6.6 Hz, 3H), 0.95 - 1.04 (m, 1H), 1.15 - 1.43 (m, 10H), 1.59 (s, 1H), 2.05 (dd, J = 15.0, 7.7 Hz, 1H), 2.22 (dd, J = 15.0, 6.1 Hz, 1H), 3.53 (dd, J = 11.6, 8.7 Hz, 1H), 3.74 (dd, J = 11.6, 6.5 Hz, 1H), 5.06 (d, J = 10.0 Hz, 1H), 5.08 (d, J = 17.4, 1H), 5.80-6.00 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 16.4, 22.6, 24.1, 25.6, 26.0, 29.4, 31.8, 35.2, 37.2, 63.4, 115.8, 137.0. Anal. Calcd. for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.27; H, 12.16. The corresponding stereoisomer, ***c*-2-Hexyl-*r*-1-(hydroxymethyl)-*t*-2-(2-propenyl)cyclopropane** was prepared by the hydrolysis of **6**: colorless oil, IR (neat): 3350, 3100, 2950, 2880, 1642, 1466, 1416, 1380, 1158, 1030, 916 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.17 (t, J = 4.8 Hz, 1H), 0.55 (dd, J = 8.6, 4.8 Hz, 1H), 0.88 (t, J = 6.6 Hz, 3H), 0.94 - 1.04 (m, 1H), 1.18 - 1.43 (m, 10H), 1.43 (s, 1H), 1.88 (dd, J = 14.4, 6.8 Hz, 1H), 2.12 (dd, J = 14.4, 7.2 Hz, 1H), 3.63 (m, 2H), 5.02, (d, J = 11.3 Hz, 1H), 5.04 (d, J = 16.6 Hz, 1H), 5.68 - 5.89 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1,

16.2, 22.6, 24.2, 25.7, 26.8, 29.7, 30.8, 31.8, 41.5, 63.4, 116.2, 136.2. Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 78.82; H, 12.63.

***t*-2-Hexyl-*r*-1-(hydroxymethyl)-*c*-2-(1-methyl-2-propenyl)cyclopropane (3):** colorless oil; IR (neat): 3340, 3080, 2920, 2850, 1632, 1450, 1406, 1370, 1024, 906, 728 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.11 (dd, J = 5.7, 4.7 Hz, 1H), 0.59 (dd, J = 8.8, 4.7 Hz, 1H), 0.87 (t, J = 6.5 Hz, 3H), 0.94 - 1.07 (m, 1H), 1.08 - 1.49 (m, 10 H), 1.14 (d, J = 7.1 Hz, 3H), 1.54 (s, 1H), 1.90 (quin, J = 7.1 Hz, 1 H), 3.59 (dd, J = 11.8, 8.8 Hz, 1H), 3.77 (dd, J = 11.8, 6.3 Hz, 1H), 5.02, (d, J = 13.1 Hz, 1H), 5.03 (d, J = 15.7 Hz, 1H), 6.06 (ddd, J = 15.7, 13.1, 7.1 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 16.1, 17.2, 22.6, 26.1, 26.9, 28.6, 29.9, 31.8, 32.7, 41.3, 63.1, 113.3, 143.5. Anal. Calcd for $C_{14}H_{26}O$: C, 79.94; H, 12.46. Found: C, 79.14; H,12.31.

2-Hexyl-1-(hydroxymethyl)-2-(1-phenyl-2-propenyl)cyclopropane (4): (mixture of diastereomers), colorless oil; IR (neat): 3350, 3060, 2940, 2860, 1636, 1600, 1496, 1450, 1030, 1002, 918, 732, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 0.16, 0.19, 0.35, 0.51 (each t, J = 5.5 Hz, total 1H), 0.57 - 0.88 (m, 5H), 1.09 - 1.65 (m, 11H), 3.16, 3.20, 3.48 (each d, J = 8.6 Hz, total 1H), 3.58 - 3.91 (m, 2H), 4.96 - 5.33 (m, 2H), 5.76 - 6.48 (m, 1H), 7.19 - 7.34 (m, 5H). Anal. Calcd for $C_{19}H_{28}O$: C, 83.77; H, 10.36. Found: C, 83.51; H,10.18.

***c*-2-Allyl-*t*-2-hexyl-*r*-1-cyclopropane carboxylic acid (5):** colorless oil; IR (neat): 3050, 2900, 2850, 1685, 1630, 1442, 1420, 1280, 1218, 982, 904 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.87 (t, J = 5.3 Hz, 3H), 0.96 (dd, J = 7.9, 4.5 Hz, 1H), 1.13 - 1.37 (m, 11H), 1.52 (dd, J = 7.9, 5.5 Hz, 1H), 2.08-2.37 (m, 2H), 5.00 - 5.09 (m, 2H), 5.64 - 5.84 (m, 1H), 11.5 - 12.0 (bs, 1H); ^{14}C NMR (50 MHz, $CDCl_3$): δ 14.0, 21.3, 22.6, 25.5, 26.0, 29.3 (overlapped two peaks), 31.8, 33.5, 37.0, 116.5, 135.7, 179.4. Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.29; H, 10.48. Found: C, 74.16; H,10.40.

***c*-2-hexyl-*t*-2-(2-propenyl)-*r*-1-cyclopropylmethyl acetate (6)**: colorless oil, IR (neat): 3080, 2940, 2860, 1740, 1640, 1456, 1372, 1240, 1034, 914, 736 cm^{-1}; ^1H NMR

(200 MHz, $CDCl_3$): 0.20 (t, J=4.9 Hz, 1H), 0.59 (dd, J = 8.6, 4.9 Hz, 1H), 0.88 (t, J = 6.4 Hz, 3H), 0.94 - 1.07 (m, 1H), 1.19 - 1.43 (m, 10H), 1.93 (dd, J = 14.5, 6.9 Hz, 1H), 2.00 - 2.11 (m, 1H), 2.06 (s, 3H), 3.98 (dd, J = 11.7, 8.4 Hz, 1H), 4.17 (dd, J = 11.7, 7.2 Hz, 1 H), 5.02, (d, J = 10.5 Hz, 1H), 5.03 (d, J = 16.8 Hz, 1H), 5.66 - 5.86 (m, 1 H); ^{14}C NMR (50 MHz, $CDCl_3$): δ 14.0, 16.5, 21.0, 21.6, 22.6, 24.1, 26.6, 29.6, 31.0, 31.8, 41.3, 65.4, 116.1, 136.0, 171.2. Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.11; H,10.92.

Ethyl *c*-2-hexyl-*t*-2-(2-propenyl)cyclopropane-*r*-1-carboxylate (7): colorless oil, IR (neat): 3080, 2955, 2930, 2855, 1724, 1640, 1454, 1400, 1262, 1170, 1096, 1044, 992, 916, 842, 804 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.84 - 0.92 (m, 4H), 1.07 (dd, J = 5.5, 4.8, 1H), 1.18 - 1.33 (m, 8H), 1.26 (t, J = 7.1, 3 Hz), 1.40 - 1.57 (m, 2H), 1.52 (dd, J = 8.0, 5.5 Hz, 1H), 2.01 (dd, J = 14.4, 7.0 Hz, 1H), 2.19 (dd, J = 14.4, 7.0 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 5.06 (d, J = 11.8 Hz, 1H), 5.07 (d, J = 14.1 Hz, 1H), 5.65 - 5.86 (*m*, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 14.3, 19.7, 22.6, 25.2, 26.6, 29.3 (overlapped two peaks), 30.4, 31.8, 33.5, 40.9, 60.2, 117.0, 135.1, 172.7. Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.34; H, 11.04.

***r*-1-(Hydroxymethyl)-*t*-2,*t*-3-dimethyl-*c*-2-(2-propenyl) cyclopropane (8)**: colorless oil, IR (neat): 3360, 3100, 3000, 2950, 2900, 1642, 1450, 1390, 1114, 1064, 1022, 1010, 918, 738 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.42 - 0.64 (m, 2H), 1.05 (s, 3H), 1.07 (d, J = 6.6 Hz, 3H), 1.56 (s, 1H), 2.00 (dd, J = 14.8, 7.6 Hz, 1H), 2.19 (dd, J = 14.8, 6.1 Hz, 1H), 3.51 (dd, J = 11.6, 8.5 Hz, 1H), 3.74 (dd, J = 11.6, 6.2 Hz, 1H), 5.06, (d, J = 11.5 Hz, 1H), 5.08 (d, J = 15.7 Hz, 1H), 5.80 - 6.01 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.4, 18.7, 22.3, 23.6, 34.1, 40.3, 63.6, 115.8, 137.2. Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 75.58; H, 11.34.

***r*-1-(Hydroxymethyl)-*t*-2,*t*-3-dimethyl-*c*-2-(1-methyl-2-propenyl)cyclopropane[4b] (9)**: colorless oil, (major isomer) IR (neat): 3380, 3080, 2960,

2870, 1632, 1450, 1382, 1016, 998, 906, 730 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.43 (quin, J = 6.1 Hz, 1H), 0.62 (ddd, J = 9.0, 6.3, 6.1 Hz, 1H), 0.95 (s, 3 H), 1.06 (d, J = 6.1 Hz, 3H), 1.07 (d, J = 6.9 Hz, 3H), 1.62 (s, 1H), 1.78 (quin, J = 6.9 Hz, 1H), 3.53 (dd, J = 11.8, 9.0 Hz, 1H), 3.75 (dd, J = 11.8, 6.3 Hz, 1H), 5.02, (d, J = 15.8 Hz, 1H), 5.03 (d, J = 11.9 Hz, 1H), 6.02 (ddd, J = 15.8, 11.9, 6.9 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.3, 14.1, 17.1, 22.4, 28.2, 35.8, 42.5, 63.2, 113.6, 143.0.

***t*-2,*t*-3-Diethyl-*r*-1-(hydroxymethyl)-*c*-2-(2-propenyl)cyclopropane[4b](10)**: colorless oil, IR (neat): 3350, 3080, 2960, 2930, 2870, 1638, 1460, 1372, 1112, 1020, 904 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.45 (dt, J = 7.1, 5.7 Hz, 1H), 0.61 (ddd, J = 8.8, 6.5, 5.7 Hz, 1H), 0.94 (t, J = 7.3 Hz, 3H), 0.96 (t, J = 7.3 Hz, 3H), 1.17 (s, 1H), 1.14 - 1.54 (m, 4H), 2.10 (bd, J = 7.3 Hz, 2H), 3.52 (dd, J = 11.7, 8.8 Hz, 1H), 3.74 (dd, J = 11.7, 6.5 Hz, 1H), 5.05, (d, J = 10.0 Hz, 1H), 5.06 (d, J = 17.2 Hz, 1H), 5.75 - 5.95 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 10.9, 14.4, 21.6, 24.3, 29.4, 31.6, 32.5, 36.1, 63.4, 115.7, 137.0.

3-Methyl-6-methylene-1-dodecen-4-ol (11): colorless oil, IR (neat): 3340, 3080, 2930, 2860, 1636, 1456, 1374, 1100, 1040, 1000, 910 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, J = 6.8, 3H), 1.08 (d, J = 6.9, 3H), 1.26 - 1.43 (m, 8H), 1.63 (s, 1H), 1.95 - 2.10 (m, 3H), 2.11 - 2.33 (m, 2H), 3.54 - 3.63 (m, 1H), 4.84 (s, 1H), 4.88 (s, 1H), 5.04 - 5.13 (m, 2H), 5.73 - 5.92 (m, 1H).

6-Methylene-3-phenyl-1-dodecen-4-ol (12): colorless oil, IR (neat): 3470, 3080, 3040, 2930, 2850, 1634, 1598, 1490, 1450, 1374, 1060, 914, 758, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.82 - 0.91 (m, 3H), 1.23 - 1.40 (m, 8H), 1.57 (s, 1H), 1.95 - 2.45 (m, 4H), 3.24 - 3.39 (m, 1H), 3.90 - 4.05 (m, 1H), 4.81 - 4.88 (m, 2H), 5.10 - 5.24 (m, 2H), 6.00 - 6.28 (m, 1H), 7.19 - 7.38 (m, 5H).

6-Methyl-1,6-octadien-4-ol (13): colorless oil, IR (neat): 3420, 3090, 3000, 2950, 1644, 1438, 1382, 1052, 1000, 918, 816 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.62 (d, J = 6.4 Hz, 3H), 1.64 (s, 4H), 2.05 (dd, J = 13.3, 9.0 Hz, 1H), 2.16 - 2.28 (m, 3H), 3.69 - 3.82

(m, 1H), 5.11 (d, J = 11.3 Hz, 1H), 5.12 (d, J = 16.4 Hz, 1H), 5.27 - 5.39 (m, 1H), 5.76 - 5.96 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.5, 15.7, 41.4, 47.3, 68.0, 117.5, 122.4, 132.6, 135.0. Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.93; H, 11.69.

3,6-Dimethyl-1,6-octadien-4-ol (14): colorless oil, IR (neat): 3340, 3060, 2960, 2920, 1632, 1450, 1378, 1260, 996, 908, 800 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.05 (d, J = 6.9 Hz, 3H), 1.60 (d, J = 5.9 Hz, 3H), 1.62 (s, 3H), 1.65 (s, 1H), 1.88 - 2.04 (m, 1H), 2.14 - 2.30 (m, 2H), 3.50 - 3.58 (m, 1H), 5.02 - 5.11 (m, 2H), 5.27 - 5.36 (m, 1H), 5.72 - 5.91 (m, 1H).

6-Ethyl-1,6-nonadien-4-ol (15): colorless oil, IR (neat): 3420, 3090, 2970, 2940, 2880, 1640, 1458, 1434, 1060, 998, 910 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.97 (t, J = 7.5 Hz, 3H), 0.98 (t, J = 7.6 Hz, 3H), 1.84 (s, 1H), 1.90 - 2.32 (m, 8H), 3.65 - 3.80 (m, 1H), 5.08 - 5.26 (m, 3H), 5.77 - 5.98 (m, 1H). Anal. Calcd for $C_{11}H_{20}O$: C, 78.78; H, 11.86. Found: C, 78.51; H, 11.98.

6-Ethyl-3-phenyl-1,6-nonadien-4-ol (16): colorless oil, IR (neat): 3480, 3040, 2980, 2940, 2880, 1608, 1496, 1452, 1062, 1000, 910, 760, 734, 702 cm^{-1}; ^{1}H (200 MHz, $CDCl_3$): δ 0.87 (t, J = 7.5 Hz, 3H), 0.94 (t, J = 7.5 Hz, 3H), 1.70 (s, 1H), 1.80 - 2.23 (m, 6 H), 3.29 (m, 1H), 3.91 (m, 1H), 5.09 - 5.23 (m, 3H), 6.00 - 6.29 (m, 1H), 7.19 - 7.36 (m, 5 H). Anal. Calcd for $C_{17}H_{24}O$: C, 83.44; H, 9.94. Found: C, 83.55; H, 9.90.

4-Hexyl-1,3,6-heptatriene (17): colorless oil, IR (neat): 3090, 2930, 2860, 1638, 1454, 1416, 1378, 1260, 984, 898, 804, 734, 660 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, J = 6.5 Hz, 3H), 1.23 - 1.48 (m, 8H), 2.05 (t, J = 7.3 Hz, 2H), 2.91 (d, J = 6.4 Hz, 2H), 4.97 - 5.17 (m, 4H), 5.79 (ddt, J = 17.1, 10.1, 6.4 Hz, 1H), 5.91 (d, J = 10.6 Hz, 1H), 6.58 (dt, J = 16.6, 10.6 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 22.6, 27.9, 29.1, 31.8, 35.3, 37.2, 115.2, 115.4, 126.2, 133.1, 136.0, 141.3; Anal. Calcd for $C_{13}H_{22}$: C, 87.56; H, 12.44 Found: C, 87.80; H, 12.18.

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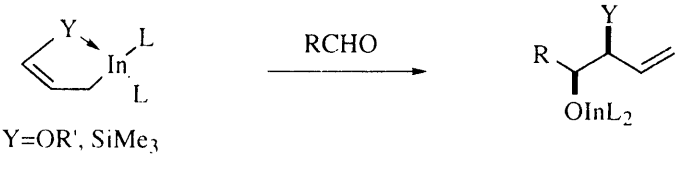
CHAPTER 5

Preparation of γ-Heterosubstituted Allylindium Reagents and Their Reactions with Carbonyl Compounds

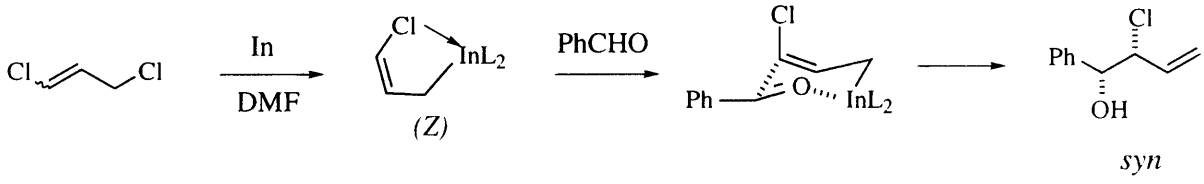
Summary

γ-Heteroatom substituted allylindium reagents were prepared and their reactions with carbonyl compounds were examined. γ-Alkoxyallylindium reagents were prepared by treating the corresponding γ-alkoxyallyllithium with indium trichloride, and reacted with benzaldehyde to give *vic*-diol mono-ethers in high yields with good *syn*-selectivity. γ-(Trimethylsilyl)allylindium and α,γ-disubstituted allylindium reagents were also prepared *via* transmetallation with the corresponding allyllithium. α,γ-Disubstituted allylindium reagents were prepared and their reaction with aldehydes was also examined.



Introduction

In the previous chapter we described that γ-chloroallylindium can be prepared by the reaction of 1,3- or 3,3-dichloropropene with metallic indium in the presence of lithium iodide and that it gives chlorohydrin in good yield with high *syn*-selectivity upon the reaction with benzaldehyde. The indium-mediated reaction of 1,3-dibromopropene with benzaldehyde gave *cis*-2-phenyl-3-vinyloxirane, which is considered to come from the corresponding *syn*-bromohydrin. Based on these results, we postulated the formation of five-memberd chelated ring. Presumably, the halogen atom on γ-chloro- and γ-bromoallylindium reagents coordinate to indium atom leading to *Z*-isomer which give *syn*-selectivity on the reaction of aldehyde (Scheme 1).



Scheme 1

In order to investigate the coordinative ability of other γ-substitient, we have carried out the reaction of γ-oxgenated allylindium reagents with aldehyde. As further examples of γ-heterosubstituted allylindium reagents, γ-(trimethylsilyl)allylindium reagents have also been prepared and their reactions with carbonyl compounds have been investigated.

Results and Discussion

Reaction of γ-alkoxyallylindium reagents with aldehydes. The γ-methoxyallylindium reagent was prepared in THF by deprotonation of allyl methyl ether (**1a**) with *s*-butyllithium, followed by transmetallation with indium trichloride. Addition of benzaldehyde to this reagent afforded the corresponding diol mono-ether **2a** in high yields (Table 1). We first investigated the effect of the ratio allyllithium/$InCl_3$. The best result was obtained with the ratio of allyllithium:$InCl_3$ = 3:1. When the ratio of $InCl_3$ was increased, the yield and *syn*-selectivity were decreased (entries 1, 3, and 5). In each case, the addition of TMEDA improved the yield and *syn*-selectivity (entries 2, 4, and 6). The addition of methanol or water prior to the reaction with benzaldehyde did not decrease the yield of **2a** (entries 7 and 8). In order to examine the influence of solvents, THF was removed after the preparation of γ-methoxyallylindium and replaced with other solvents such as H_2O, CH_2Cl_2 and DMF. Although the same product **2a** was obtained in these solvents, both the yields (48, 60, and 52%, respectively) and *syn*-selectivity (*syn*:*anti* = 48:52, 76:24, and 70:30, respectively) were decreased. The reaction with cinnamaldehyde and octanal also gave the corresponding mono-protected *vic*-diols **2b** and **2c** in high yields (entries 9-11). However, the *syn*-selectivity of **2b** was only modest and even the addition of TMEDA slightly improved the *syn*-selectivity (entry 10). With ketones no reaction proceeded. γ-*t*-Butoxyallylindium also reacted with benzaldehyde to afford **2d** *anti*-selectively (entry 12). In an aqueous medium, the diastereoselectivity was diminished (entry 13). γ-Phenoxyallylindium derived from allyl phenyl ether reacted with formalin to give **2e** (entry 14).

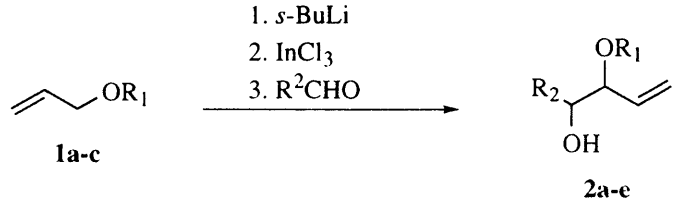
Various γ-alkoxyallylmetal reagents have been used in organic synthesis.[1] Recently, Marshall reported that the reaction of α-alkoxyallylstannane with aldehydes in the presence of

indium trichloride gave mono-protected ***anti***-1,2-diols stereoselectively.[2] In this reaction, α-alkoxyallylstannane is considered to be converted to (*E*)-γ-alkoxyallylindium by means of S_E2' attack of indium trichloride, followed by the coupling with aldehydes *via* a sterically less demanding six-membered transition state leading to the *anti*-products. On the contrary, our reaction of γ-methoxyallylindium prepared by the transmetalation from the corresponding allyllithium provided the mono-protected ***syn***-1,2-diol on the reaction with benzaldehyde. Generally, the *syn/anti* selectivity depends on the geometry of the substituent at the γ-position of allylmetals. The *syn*-selectivity observed in our reaction is considered to come from the *Z*-geometry of γ-methoxyallylindium. During the transmetalation step from γ-methoxyallyllithium which is known to possess the chelated *Z*-geometry,[7e] the geometry is preserved and this gives the opposite *syn*-selectivity to the reaction from α-alkoxyallylstannane. However, other factors such as the differences of the substituents on allylic systems and the reaction conditions (solvent and temperature) have to be taken into account. Indeed, sterically bulky *t*-butoxyallylindium showed *anti*-selectivity (Table 1, entries 12 and 13).

Concerning the coordination of oxygen atom to indium, Paquette reported successful stereoselective syntheses utilizing the coordinative nature of a neighboring oxygen atom.[3] According to the results shown in Table 1, the γ-methoxy group has sufficient coordination ability to indium in organic media. However, the intramolecular coordination to indium becomes less important in aqueous media, owing to the competition with the intermolecular coordination of water. Allylindium compounds are known as water tolerable reagents. In fact, the coupling of γ-alkoxyallylindium with carbonyl compounds proceeded even in aqueous media, though the diastereoselectivity was somewhat diminished. γ-Alkoxyallylindium has now been found to possess typical characteristics of allylic indium reagents in respect of high γ-selectivity and sta-

bility under aqueous conditions.

Table 1. Reaction of γ-alkoxyallylindium Reagent with Carbonyl Compounds [a]

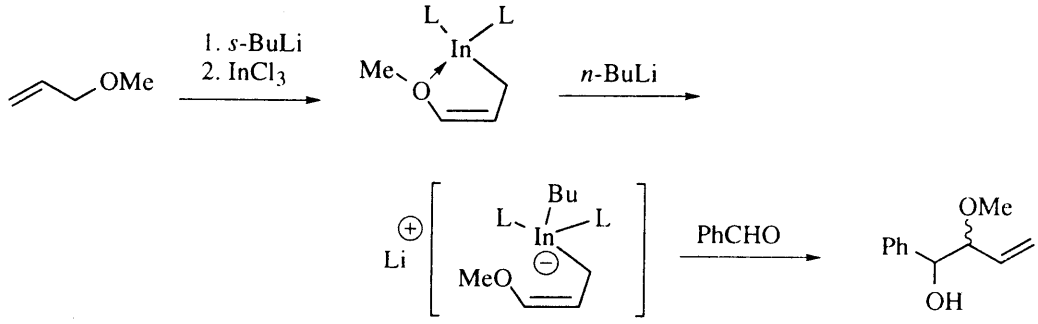


1a-c **2a-e**

Entry	1	R^1	R^2	Molar Ratio 1/$InCl_3$/R^2CHO	2	Yield[b] (%)	*syn*/*anti*[c]
1	**1a**	Me	Ph	1:1:1	**2a**	46	70:30
2[d]	**1a**	Me	Ph	1:1:1	**2a**	55	83:17
3	**1a**	Me	Ph	3:1:1	**2a**	81	87:13
4[d]	**1a**	Me	Ph	3:1:1	**2a**	90	89:11
5	**1a**	Me	Ph	3:3:1	**2a**	55	69:31
6[d]	**1a**	Me	Ph	3:3:1	**2a**	89	88:12
7[e]	**1a**	Me	Ph	3:1:1	**2a**	84	87:13
8[f]	**1a**	Me	Ph	3:1:1	**2a**	80	61:39
9	**1a**	Me	(*E*)-PhCH=CH	3:1:1.5	**2b**	91	50:50
10[d]	**1a**	Me	(*E*)-PhCH=CH	3:1:1.5	**2b**	97	56:44
11	**1a**	Me	$CH_3(CH_2)_6$	3:1:1.5	**2c**	89	82:18
12	**1b**	*t*-Bu	Ph	3:1:1.5	**2d**	65	27:73
13[g]	**1b**	*t*-Bu	Ph	3:1:1.5	**2d**	75	40:60
14	**1c**	Ph	H	3:1:1.5	**2e**	41	-

[a] All reactions were carried out as described in Experimental Section. [b] Based on R^2CHO. [c] Determined by ^1H NMR analysis. [d] TMEDA was added after the preparation of γ-alkoxyallylindium reagent. [e] Methanol (1 equiv.) was added. [f] Excess (70-fold) water was added. [g] In H_2O/THF = 1:1.

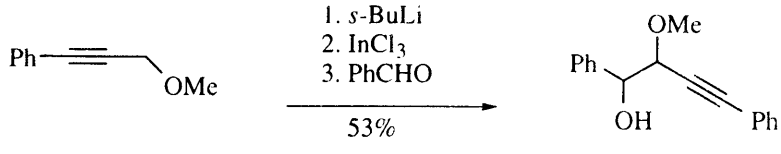
It was possible that γ-methoxyallylindium was converted to the ate complex by the addition of *n*-BuLi. After the preparation of γ-methoxyallylindium reagent, one equivalent of *n*-BuLi was added and then reacted with benzaldehyde (Scheme 2).



Scheme 2

In this reaction, the formation of allylindium ate complex is expected and it may turn to be difficult to be coordinated with γ-oxygen atom because there is any site to receive lone pair in the indium atom on γ-methoxyallylindium reagent. As the results, *Z*-geometry of γ-methoxyallylindium may become loose leading to decrease of the *syn*-selectivity. In fact, while the yield did not changed, the selectivity was decreased.

As a related study, α-methoxy substituted phenylpropargylindium reagent was prepared and submitted to the reaction of benzaldehyde (Scheme 3). Phenylpropargyl methyl ether was deprotonated by *s*-BuLi and tranmetallated with of $InCl_3$ and reacted with benzaldehyde.

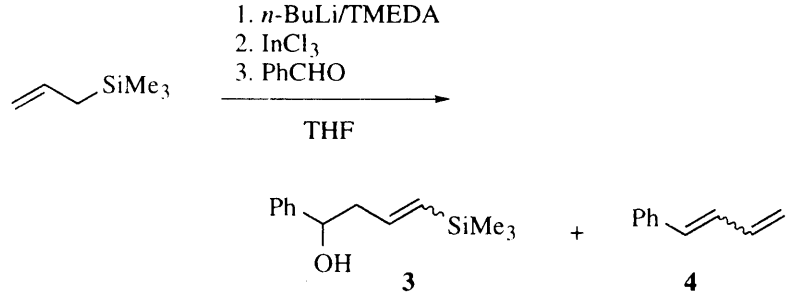


Scheme 3

Although propargyl bromide reacted with aldehyde to give a mixture of homopropagyl- and allenylalcohol under the influence of indium, the organoindium reagent derived from phenylpropargyl methyl ether gave homopropargylalcohol exclusively.

Reaction of γ-trimethylsilyl-substituted allylindium reagents with aldehydes. γ-(Trimethylsilyl)allylindium was prepared by deprotonation of allyltrimethylsilane with *n*-BuLi-TMEDA, followed by the addition of $InCl_3$. The reaction of this indium reagent with benzaldehyde did not proceed selectively, giving a mixture of homoallylic alcohol **3** and (*E*)- and (*Z*)-1-phenylbut-1,3-diene (**4**) (Table 2). Changing the reaction temperature did not improve the regio- and stereoselectivity. 1,3-Diene **4** is considered to arise *via* a Peterson elimination of the initially formed homoallylic alcohol indium salt bearing a *vic*-trimethylsilyl group.

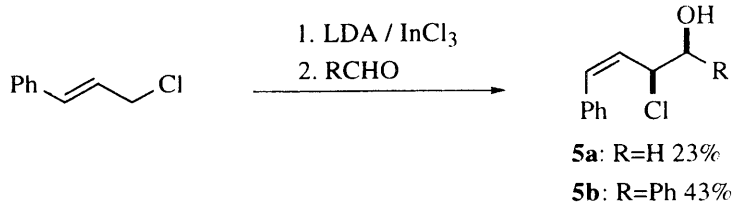
Table 2. Reaction of γ-(Trimethylsilyl)allylindium Reagents with Benzaldehyde [a]



Entry	Conditions	Yield (%)	
		3 (*E*/*Z*)[b]	**4** (*E*/*Z*)[b]
1	-78 °C, 2 h	11 (46:54)	28 (37:63)
2	rfx, 3 h	26 (38:62)	27 (17:83)

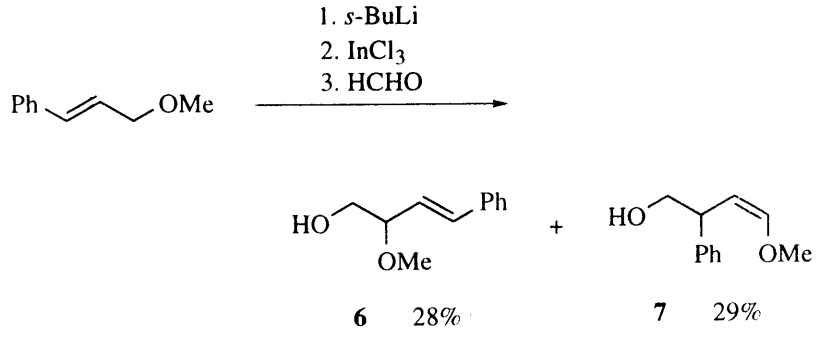
[a] All reactions were conducted as described in Experimental Section. [b] Based on ^1H NMR analysis.

α,γ-Disubstituted allylindium. The α,γ-disubstituted allylindium derived from cinnamyl chloride reacted with formaldehyde and benzaldehyde to give (*Z*)-chlorohydrin **5a** and **5b** highly regio- and diastereoselectively (Scheme 4).



Scheme 4

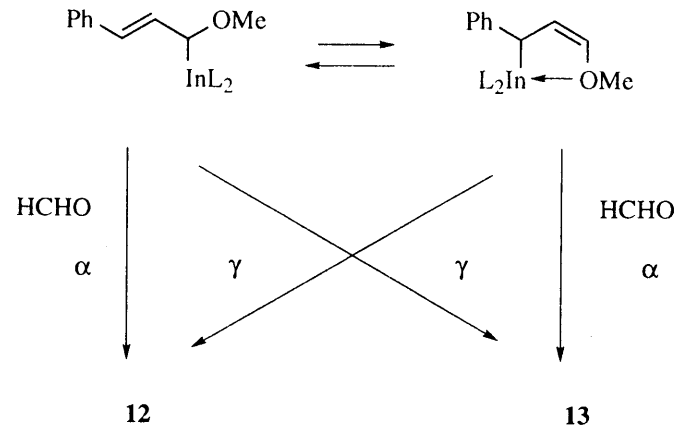
Only *syn*-diastereomer **5b** was formed in the reaction with benzaldehyde. When the α,γ-disubstituted allylindium derived from cinnamyl methyl ether was employed, both the α- and γ-coupling products **6** and **7** were obtained in almost 1:1 ratio (Scheme 5).



Scheme 5

Both cinnamylindium and γ-methoxyallylindium react with aldehydes exclusively at the γ-position to afford the corresponding branched homoallylic alcohols. In the present α,γ-disubstituted case, two allylindium species, namely (*E*)-α-methoxy-γ-phenylallylindium and (*Z*)-γ-methoxy-α-phenylallylindium, are possibly formed through transmetallation (Scheme 6). The former is considered to give vinyl ether **7** *via* the γ-coupling with formalin, the latter provides mono-protected 1,2-diol **6**. Although products **6** and **7** could alternatively be formed *via* the α-coupling of the respective allylindium reagents, examples of α-coupling of allylic indium reagents are rare. On the contrary, the organoindium reagent derived from cinnamyl chloride gave chlorohydrin **5** regioselectively. This fact indicates that the equilibrium of α-

chloro-γ-phenylallylindium and γ-chloro-α-phenylallylindium lies so far to the latter. It is interesting to note that the geometry of the styryl group is opposite between the products from cinnamyl methyl ether and from cinnamyl chloride: mono-protected (*E*)-diol **6** was obtained from cinnamyl methyl ether, whereas (*Z*)-chlorohydrin **5** was formed from cinnamyl chloride.



Scheme 6

EXPERIMENTAL SECTION

All reactions were carried out in dry solvents under argon. Indium powder (99.99%) was obtained from Aldrich Chemical Co. Allyl *t*-butyl ether[4] was prepared according to literature.

Reaction of γ-alkoxyallylindium with carbonyl compounds. The following reaction (Table 1, Entry 4) represents the general procedure.

To a solution of allyl methyl ether (**1a**) (141 μL, 1.5 mmol) in THF (2 mL), *s*-butyllithium in cyclohexane (1.0 M) (1.5 mL, 1.5 mmol) was slowly added at -78 ℃. After stirring for 1 h, a solution of indium trichloride (111 mg, 0.50 mmol) in THF (4 mL) and TMEDA (0.3 mL, 2.0 mmol) was added, and the mixture was kept at this temperature for 0.5 h. Benzaldehyde (51 μL, 0.50 mmol) was added and the reaction was continued for 1 h. The reaction mixture was quenched with diluted hydrochloric acid, and the product was extracted with diethyl ether. The organic extracts were washed with water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography on silica gel (elution with EtOAc:hexane = 1:9 then 2:8) to give **2a**[1f] (80 mg, 90%) as a mixture of diastereomers (*syn*:*anti*=89:11). The *syn*/*anti* ratio was determined based on ^{1}H NMR analysis.[1f]

Methoxy-1-phenylbut-3-ene-1-ol (2a). [1f] IR (neat, cm^{-1}): ^{1}H NMR (200 MHz, $CDCl_3$): *Syn* isomer: 3.37 (s, 3H), 3.62 (t, *J* = 7.8 Hz, 1H), 4.50 (d, *J* = 7.8 Hz, 1H), 5.01-5.21 (m, 2H), 5.53 (ddd, *J* = 14.1, 10.5, 7.3 Hz, 1H), 7.25-7.40 (m, 5H), *Anti* isomer: 4.83 (d, *J* = 4.5 Hz, 1H), 3.32 (s, 3H).

4-Methoxy-1-phenylhexa-1,5-dien-3-ol (2b). IR (neat, cm^{-1}): 3450, 1600, 1444, 1100; ^{1}H NMR (200 MHz, $CDCl_3$) δ Major isomer 2.91 (d, *J* = 2.7 Hz, 1H), 3.35 (s, 3H), 3.49 (t, *J* = 7.6 Hz, 1H), 4.15-4.22 (m, 1H), 5.27-5.38 (m, 2H), 5.60-5.86 (m, 1H), 6.21 (dd, *J* = 16.0, 6.1 Hz, 1H), 6.63 (d, *J* = 16.0 Hz, 1H), 7.18-7.42 (m, 5H); Minor isomer 2.39 (d, *J* = 5.4 Hz, 1H), 3.70 (dd, *J* = 7.7, 4.0 Hz, 1H), 4.33-4.39 (m, 1H), 6.15 (dd, *J* =

16.0, 6.6 Hz, 1H), 6.68 (d, J = 16.0 Hz, 1H); MS (CI) *m/z* 187 (M+H-H_2O, 100%), 155 (30); HRMS (CI) Anal. Calcd for $C_{13}H_{15}O$ (M+H-H_2O) 187.1123, found 187.1125. Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.89. Found: C, 75.33, H, 7.81.

3-Methoxyundec-1-en-4-ol (2c). IR (neat, cm^{-1}) 3450, 1450, 1100; ^1H NMR (200 MHz, $CDCl_3$) δ Major isomer 0.82-0.89 (m, 3H), 1.15-1.50 (m, 12H), 2.15 (br. s, 1H), 3.30 (s, 3H), 3.49 (dd, J = 8.5, 3.7 Hz, 1H), 3.62-3.72 (m, 1H), 5.22-5.38 (m, 2H), 5.76 (ddd, J = 17.1, 10.5, 8.0 Hz, 1H); Minor isomer 5.52-5.65 (m, 1H); Anal. Calcd for $C_{12}H_{24}O_2$: C, 71.94; H, 12.08. Found: C, 71.30, H, 12.18.

2,2-Dimethy-4-methoxy-hex-5-en-3-ol (2d). [5] IR (neat, cm^{-1}): 3450, 2980, 2380, 1454, 1388, 1364, 1198, 1110, 1052, 1020, 920, 780, 700; ^1H NMR (200 MHz, $CDCl_3$): δ Major (*anti*); δ 1.20 (s, 9H), 3.98 (t, J = 7.0 Hz, 1H), 4.36 (d, J = 7.4 Hz, 1H), 4.97-5.09 (m, 2H), 5.63-5.80 (m, 1H), 7.26-7.38 (m, 5H). Minor (*syn*); 1.14 (s, 9H), 4.08-4.14 (m, 1H), 4.66 (d, J = 5.0 Hz, 1H), 5.11-5.24 (m, 2H), 5.63-5.80 (m, 1H), 7.26-7.38 (m, 5H).

2-Phenoxybut-3-en-1-ol (2e). [6] IR (neat, cm^{-1}): 3300, 2930, 1598, 1492, 1408, 1240, 1172, 1044, 932, 752, 690; ^1H NMR (200 MHz, $CDCl_3$): δ 7.20-7.33 (m, 3H), 6.90-7.00 (m, 2H), 5.85 (ddd, J = 17.5, 10.6, 5.9 Hz, 1H), 5.29-5.43 (m, 2H), 4.73-4.81 (m, 1H), 3.78 (d, J = 5.8 Hz, 2H), 1.8-2.1 (br s. 1H).

The reaction of methoxy substituted phenylpropargylindium reagent with benzaldehyde (Scheme 3). To a solution of 3-meyhoxy-1-phenylprop-1-yne (122 mg, 0.84 mmol) in THF (2 mL) *s*-BuLi (1.0 M in cyclohexane, 0.8 mL, o.8 mmol) was added at –78 °C. The mixture was stirred for 10 min and then a solution of $InCl_3$ (94 mg, 0.42 mmol) in THF (4 mL) was added and stirred for another 10 min. Benzaldehyde (30 μL, 0.30 mmol) was added and the reaction mixture was warmed to rt. The reaction was continued for 2 days. The mixture was quenched with diluted HCl, the product was extracted with ether. The ether

layer was washed with water, brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the product was purified by column chromatography on silica gel (elution with EtOAc:hexane = 1:9 to 2:8) to give 1,4-diphenyl-2-methoxyprop-3-yn-1-ol (34 mg, 47%) as a mixture of diastereomer (56:44).

1,4-Diphenyl-2-methoxyprop-3-yn-1-ol..[7] IR (neat, cm^{-1}): 3450, 2940, 1700, 1598, 1490, 1450, 1384, 1320, 1200, 1100, 758, 698; ^1H NMR (200 MHz, $CDCl_3$): δ Major 2.81 (br. s. 1H, OH), 3.52 (s, 3H, OMe), 4.37 (d, *J* = 4.1 Hz, 1H, C*H*OMe), 4.94-4.98 (m, 1H, C*H*OH), 7.20-7.55 (m, 10H, Ph×2), Minor 3.21 (br. s. 1H, OH), 3.58 (s, 3H, OMe), 4.17 (d, *J* = 8.3 Hz, 1H, C*H*OMe), 4.80 (d, *J* = 8.3 Hz, 1H, C*H*OH).

Reaction of γ-(trimethylsilyl)allylindium with benzaldehyde (Table 2, entry 2). To a solution of allyltrimethylsilane (238 μL, 1.5 mmol) in a mixture of dry THF (5 mL) and TMEDA (0.30 mL, 2.0 mmol), *n*-BuLi (1.6 M in hexane, 0.90 mL, 1.5 mmol) was added at -78 °C. After stirring for 30 min, a solution of indium trichloride (111 mg, 0.50 mmol) in THF (5 mL) was added and the mixture was stirred for additional 10 min. Benzaldehyde (156 μL, 1 5 mmol) was added and reaction mixture was heated at reflux for 3 h. The reaction mixture was quenched with saturated aqueous ammonium chloride and extracted with diethyl ether. The extracts were washed with water and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (elution with dichloromethane) to give **3**[1d] (86 mg, 26%) and **4**[8] (53 mg, 27%).

Reaction of the α,γ-disubstituted allylindium reagent derived from cinnamyl chloride (Scheme 4). To a suspension of indium trichloride (283 mg, 1.3 mmol) and cinnamyl chloride (303 μL, 2.2 mmol) in THF (4 mL), freshly prepared LDA (2.2 mmol) in THF (4 mL) was added dropwise at -78 °C. The suspension was stirred at -78 °C for 0.5 h, and benzaldehyde (103 μL, 1.0 mmol) was added. The mixture was gradually warmed to room temperature during 2 h and stirred overnight at room temperature. The reaction mixture was

quenched with saturated aqueous ammonium chloride, the product was extracted with ether, washed with water, and dried over Na_2SO_4. The solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (elution with EtOAc:hexane = 1:9) to give **5b** (112 mg, 43%) as a single diastereomer. Similarly, coupling with formalin (37 wt.%, 1.0 mL, 13 mmol) gave **5a**[9] in 23% yield (based on the cinnamyl chloride).

(Z)-2-Chloro-1-phenyl-4-phenylbut-3-en-1-ol (5b). IR (neat, cm^{-1}) 3350, 1630, 1498, 1456; ^1H NMR (200 MHz, $CDCl_3$) δ 2.09 (d, J = 3.2 Hz, 1H), 4.26 (dd, J = 9.3, 6.1 Hz, 1H), 4.97 (dd, J = 6.1, 3.2 Hz, 1H), 6.20 (d, J = 7.5 Hz, 1H), 6.31 (dd, J = 9.3, 7.5 Hz, 1H), 7.1-7.3 (m, 10H); Anal. Calcd for $C_{16}H_{15}ClO$: C, 74.27; H, 5.84. Found: C, 74.54, H. 5.84.

Reaction of α,γ-disubstituted allylindium reagent derived from cinnamyl methyl ether (Scheme 5). To a solution of cinnamyl methyl ether (148 μL, 1.0 mmol) in THF (2 mL), *s*-butyllithium in cyclohexane (1.0 M) (1.0 mL, 1.0 mmol) was slowly added at -78 ℃. After stirring for 30 min at this temperature, a solution of indium trichloride (90 mg, 0.4 mmol) in THF (2 mL) was added and the mixture was kept at this temperature for 1 h. Formalin (37 wt.%, 0.5 mL, 6.5 mmol) was added and the reaction was continued overnight at room temperature. The reaction mixture was quenched with diluted hydrochloric acid and the products were extracted with ether. The organic extracts were washed with water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography on silica gel (elution with EtOAc:hexane = 1:9 then 2:8) to give **6**[21] (50 mg, 28%) and **7** (52 mg, 29%).

(E)-2-Methoxy-4-phenylbut-3-en-1-ol (6).[10] ^1H NMR (200 MHz, $CDCl_3$): δ 1.8 (br.s, 1H), 3.40 (s, 3H), 3.63-3.67 (m, 2H),. 3.84-3.95 (m, 1H), 6.05 (dd, J = 16.1, 7.8 Hz, 1H), 6.66 (d, J = 16.1, 7.8 Hz, 1H), 7.20-7.45 (m, 5H).

(Z)-4-Methoxy-2-phenylbut-3-en-1-ol (7). IR (neat, cm^{-1}) 3400, 1664, 1498, 1112; ^1H NMR (200 MHz, $CDCl_3$) δ 1.73 (t, J = 6.5 Hz, 1H), 3.63 (s, 3H), 3.68-3.82 (m, 2H), 3.91-4.04 (m, 1H), 4.57 (dd, J = 9.0, 6.4 Hz, 1H), 6.08 (dd, J = 6.4, 1.0 Hz, 1H), 7.15-7.45 (m, 5H); Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.99, H, 8.02.

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CONCLUSIONS

In this thesis, the following novel reactions involving indium were described. 1) Preparation and reaction of α-halo organoindium reagents (Chapter 1). 2) Application of intra- and intermolecular coordinative ability of allylindium reagents (Chapter 2, 4 and 5). 3) Preparation and reaction of γ-vinyl or ethynyl substituted allylindium reagents (Chapter 4). 4) Preparation and reaction of allylic *gem*-diindium compound (Chapter 1 and 2).

α-Halo organoindium reagents were prepared from *gem*-dihalides and indium reacted with electron-deficient olefins and carbonyl compounds to give mainly cyclopropenes and oxiranes respectively. γ-Halo- and γ-alkoxyallylindium reagents were prepared by the transmetaltion of the corresponding allylic lithium compounds with $InCl_3$, or by the oxidative addition of indium toward 3,3-, 1,3-dichloropropene or 1,3-dibromopropene. These reagents coupled with carbonyl compounds at the γ-carbon to give the corresponding homoallylic alcohols *syn*-selectively. This selectivity was considered to come from *Z*-form of γ-substituted allylindium reagents because of the coordination of γ-substituent to indium atom. Concerning coordination of oxygen to indium, the allylindation of cyclopropenols showed the strong ability of intermolecular coordination between allylindium and hydroxymethyl group on the cyclopropenes, which realized the highly stereo-controlled allylindation. Pentadieny- and enynylindium reagents were prepared from the corresponding allylic halides and coupled with aldehydes at the γ-position exclusively. On treatment with indium, 1-phenyl-3,3-dichloropropene, 1,3-dibromopropene or 3-bromo-1-iodopropene gave the allylic *gem*-diindium reagents. Only few examples of allylic *gem*-dimetallic species are hitherto known such as zinc[1] and tin compounds.[2] The diindium species described in this thesis is expected to be synthetically versatile, and adds a new entry to this interesting family of organodimetallic reagents.

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LIST OF ORAL PRESENTATIONS

1. The 68th Annual meeting of the Chemical Society of Japan, Nagoya (1994.10)
Indium-mediated Reaction of 1,3-Dichloropropene with Carbonyl Compounds.

2. The 70th Annual meeting of the Chemical Society of Japan, Tokyo (1996.3)
Indium-mediated Reaction of 1,3-Dibromopropene with Aldehydes.

3. The 27th Chubu Chemical Related Society, Nagoya (1996.10)
Indium Mediated-reaction of 1,3-Bibromopropene or 1,3,3-Tribromopropene with Aldehydes.

4. The 74th Annual meeting of the Chemical Society of Japan, Tokyo (1997.3)
Regioselective Coupling Reaction of 2,4-Pentadinylindium with Aldehydes.

5. The 74th Annual meeting of the Chemical Society of Japan, Kyoto (1998.3)
Reaction of γ-Alkoxyallylindium Reagents with Carbonyl Compounds.

6. Fifth International Symposium on Carbanion Chemistry (ISCC-5) (1998.8)
γ-Heterosubstituted Allylindium and Diindium Reagents

7. The 75th Annual meeting of the Chemical Society of Japan, Matsuyama (1998.9)
Reaction of γ-Heterosubstituted Allylindium Reagents with Carbonyl Compounds.

LIST OF PUBLICATIONS

(1) Reaction of α-Halo Organoindium Reagents with Carbonyl Compounds and Electron-deficient Alkenes
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(2) Indium-mediated Reaction of 1,3-Dichloro- and 1,3-Dibromopropene with Carbonyl Compounds. Generation of Novel 3,3-Diindiopropene
Araki, S.; Hirashita, T.; Shimizu, H.; Yamamura, H.; Kawai M,; Butsugan Y. *Tetrahedron Lett.* **1996**, *37*, 8417-8420.

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J. Org. Chem. in press.