# Account

## Indium and Gallium-Mediated Addition Reactions†

**Phil Ho Lee**

*National Research Laboratory of Catalytic Organic Reaction, Department of Chemistry, Kangwon National University, Chunchon 200-701, Korea. E-mail: phlee@kangwon.ac.kr*
*Received October 31, 2006*

Indium and gallium have emerged as useful metals in organic synthesis as a result of its intriguing chemical properties of reactivity, selectivity, and low toxicity. Although indium belongs to a main metal in group 13, its first ionization potential energy is very low and stable in $H_2O$ and $O_2$. Therefore, indium-mediated organic reactions are of our current interest. On the basis of these properties of indium, many efficient indium-mediated organic reactions have been recently developed, such as the addition reactions of allylindium to carbonyl and iminium groups, the indium-mediated synthesis of 2-(2-hydroxyethyl)homoallenylsilanes, the indium-mediated allylation of keto esters with allyl halides, sonochemical Reformatsky reaction using indium, the indium-mediated selective introduction of allenyl and propargyl groups at C-4 position of 2-azetidinones, the indium-mediated Michael addition and Hosomi-Sakurai reactions, the indium-mediated $\beta$-allylation, $\beta$-propargylation and $\beta$-allenylation onto $\alpha,\beta$-unsaturated ketones, the highly efficient 1,4-addition of 1,3-diesters to conjugated enones by indium and TMSCl, and the intramolecular carboindation reactions. Also, we found gallium-mediated organic reactions such as addition reactions of propargylgallium to carbonyl group and regioselective allylgallation of terminal alkynes.

**Key Words :** Indium, Gallium, Addition reaction, Carboindation, Carbogallation

### Introduction

Recently, indium and gallium have emerged as useful metals in organic synthesis because of their intriguing chemical properties of reactivity, selectivity, and low toxicity.[1] Although indium belongs to a main metal in group 13, its first ionization potential energy is very low like that of sodium and lithium. However, indium is very stable in $H_2O$ and $O_2$ contrary to sodium and lithium. Indium toxicity is very low although it is a heavy main metal. Therefore, indium-mediated organic reactions are of current interest. On the basis of these properties of indium, efficient indium-mediated organic reactions have been developed and applied in environment-friendly organic reactions.[1] Generally, allyl- and propargyl-metal (indium and gallium) are prepared *in situ* from the reaction of metal with allyl and propargyl halides, respectively. Their first synthetic applications have been found in allylation reactions of carbonyl compounds and their derivatives under aqueous and anhydrous Barbier conditions.[2] Especially, indium has now demonstrated itself as the metal of choice in performing many of these reactions. A variety of *in situ* generated organoindium reagents such as allylindiums, propargylindiums, and allenylindiums are of considerable value for regioselective and stereoselective allylation, propargylation, and allenylation of various carbonyl and imine compounds that produce the corresponding alcohols and amines.[1] Therefore, indium-mediated Barbier-type allylation, allenylation, and propargylation of carbonyl compounds in organic and aqueous media have been studied extensively. In addition, a range of indium-mediated organic reactions have been found useful for Reformatsky reactions.[3] Michael addition reactions,[4] cross-coupling reactions,[5] allylic substitution reactions,[6] and the intermolecular addition of organoindium and organogallium reagents to C-C multiple bonds and nitriles.[7] This account describes our recent findings in addition reactions of *in situ* generated

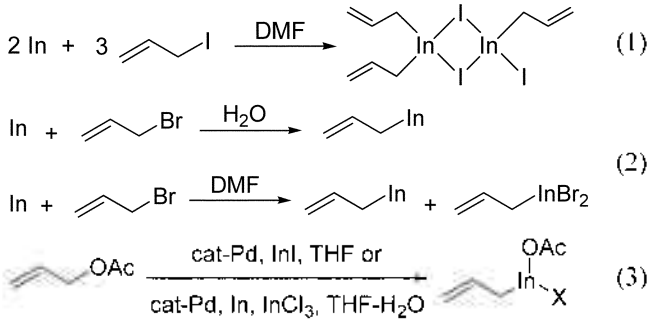
†This paper is dedicated to Professor Chang Kiu Lee on his 60th birthday.

**Phil Ho Lee** was born in Chunchonsi, Kangwondo in 1961. He received his B.S. (1984) degree *summa cum laude* in Chemistry at Kangwon National University, M.S. (1996) and Ph. D. (1989) degree in Chemistry at KAIST under the supervision of Professor S. Kim. He worked for Professor B. M. Trost as a post-doctoral research fellow for two years (1989-1991) at Stanford University. In 1991, he joined the faculty of organic chemistry at Kangwon National University, where he is presently Professor of Chemistry. He was a visiting professor (1996 and 2004) at the department of chemistry, Montana State University. He is director of the National Research Laboratory of Catalytic Organic Reaction (http://indium.kangwon.ac.kr) (2006-present). He has received Presidential Award of Republic of Korea (1984), Excellent Professor Award from President of Kangwon National University (2005), Kangwondo Culture Award (2006), and Chang Sae Hee Award (2006). His current research interests include new synthetic methods involving cross-coupling reactions using indium and transition metal, organic reactions using organoindium and allene, catalytic organic reactions using gold, and $\beta$-lactam chemistry.

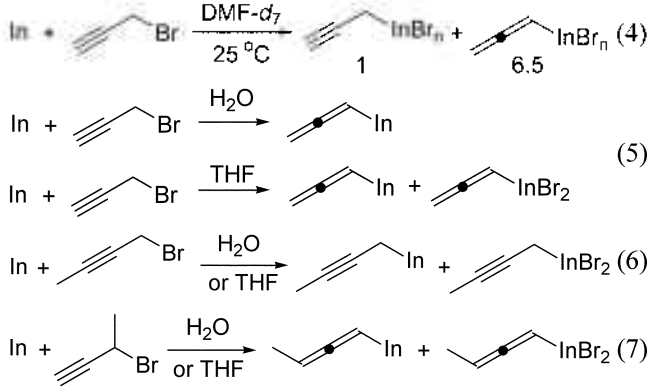
organoindium and organogallium reagents derived from the group 13 metals (indium and gallium) and allyl halides and propargyl halides with a variety of electrophiles.

## Preparation of Organoindium Reagents

Indium can be used in radical reaction and reduction, and it can be used as a Lewis acid to mediate a variety of organic reactions. Organoindium reagents can also be used to addition, substitution, and cross-coupling reactions as nucleophiles. In 1988, Butsugan *et al.* prepared allylic indium sesquihalide from the reaction of 2 equiv of indium with 3 equiv of allyl iodide in DMF (eq. 1).[2] However, Chan *et al.* proved in 1999 that this structure is wrong. He found that reaction of indium with allyl bromide produces allylindium in water (eq. 2).[8] However, this reaction in DMF gives the mixture of allylindium and allylindium dibromide. Araki and Kim developed an efficient synthetic method for *in situ* generated allylindium derived from allyl acetate (eq. 3).[9]




In 2002, we found that the reaction of indium with propargyl bromide gave the mixture of propargylindium and allenylindium (eq. 4) in DMF-$d_7$ at room temperature (ratio of these two reagents; 1:6.5).[10] On the basis of this result, Chan found that the reaction of indium with propargyl bromide produced allenylindium in water.[11] But, this reaction in THF gave the mixture of allenylindium and allenylindium dibromide (eq. 5). Also, the reaction of indium bromide with propargyl bromide gave allenylindium dibromide in THF. Contrary to propargyl bromide, the reaction of indium with 4-bromo-2-butyne gave propargylindium and propargylindium dibromide (eq. 6). In the case of 3-bromo-1-butyne, allenylindium and allenylindium dibromide were produced (eq. 7).



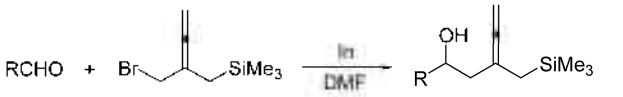

## Indium-Mediated Organic Reactions

### Addition Reactions of Allylindium to Carbonyl and Iminium Groups.

**Indium-Mediated Synthesis of 2-(2-Hydroxyethyl)-homoallenylsilanes:** Allyl metal-mediated C-C bond formation is one of the fundamental processes in organic synthesis.[12] Although allyl metal-mediated allylation of a variety of aldehydes and ketones received much attention, much less attention has been paid to homoallenylation of carbonyl compounds. As part of our continuing effort to synthesize 2-methyl-3-trimethylsilylmethyl dihydrofuran derivatives from homoallenyl alcohols, we needed versatile methods to prepare 2-(2-hydroxyethyl)homoallenylsilanes.[13] To the best of our knowledge, none of methods that are based on the synthesis of 2-(2-hydroxyethyl)allylsilanes has been applied to the synthesis of 2-(2-hydroxyethyl)homoallenylsilanes. Addition of organometallic reagents derived from the halomethylhomoallenylsilanes on aldehydes or ketones could be used to produce 2-(2-hydroxyethyl)homoallenylsilane. However, it was not possible to prepare the corresponding Grignard reagents from halomethylhomoallenylsilianes. In addition, Grignard reagents must be employed in excess in the reactions with electrophiles having any acidic hydrogens. Therefore, we decided to take advantage of indium-mediated allylations, and here, we demonstrate the indium-mediated homoallenylation of aldehydes and ketones.[13,14]

Homoallenylindium reagents *in situ* generated from the reaction of indium with 4-bromo-3-[(trimethylsilyl)methyl]-1,2-butadiene reacted with a variety of aldehydes in DMF to produce 2-(2-hydroxyethyl)homoallenylsilanes in good to excellent yields at room temperature (Table 1). The 2- or 3-hydroxybenzaldehyde that contained labile hydrogen reacted with homoallenylindium reagents to provide homoallenylsilanes. In the case of 4-formylbenzoic acid, the desired compound was produced in 88% yield. However, appli-

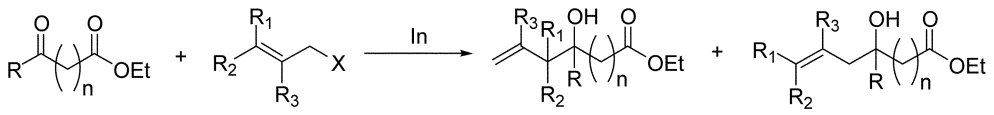
**Table 1.** Indium-Mediated Homoallenylation of Aldehydes

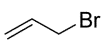
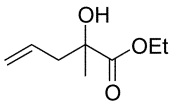
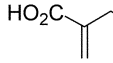
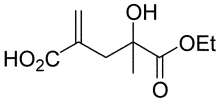
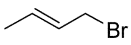
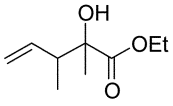
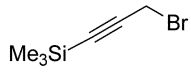
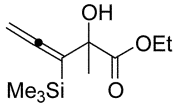
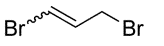
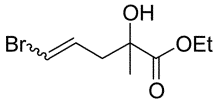
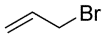
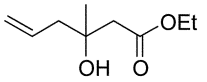
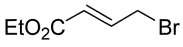
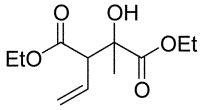
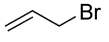
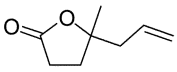



| entry | R | yield (%)[a] | entry | R | yield (%)[a] |
|---|---|---|---|---|---|
| 1 | Me | 98 | 11 | 4-Cl-$C_6H_4$ | 86 |
| 2 | *n*-Bu | 84 | 12 | 2-$NO_2$-$C_6H_4$ | 82 |
| 3 | *iso*-Pro | 77 | 13 | 4-MeO-$C_6H_4$ | 64 |
| 4 | $C_6H_{11}$ | 54 | 14 | 2,6-$(MeO)_2$-$C_6H_3$ | 71 |
| 5 | $PhCH_2$ | 67 | 15 | 2-HO-$C_6H_4$ | 89 |
| 6 | $PhCH_2CH_2$ | 61 | 16 | 3-HO-$C_6H_4$ | 86 |
| 7 | PhCH=CH | 47 | 17 | 4-$HO_2C$-$C_6H_4$ | 79 |
| 8 | Ph | 92 | 18 | 2-$C_4H_3O$ | 71 |
| 9 | 4-Me-$C_6H_4$ | 60 | 19 | 2-$C_4H_3S$ | 69 |
| 10 | 2-Br-$C_6H_4$ | 77 | | | |

[a]All reactions were carried out with indium reagent derived from an equimolar mixture of indium and homoallenylsilane in DMF at room temperature.

**Table 2.** Reaction of Keto Esters with a Variety of Allyl Halides Using Indium



| entry | allyl halide | product | yield (%) | entry | allyl halide | product | yield (%) |
|---|---|---|---|---|---|---|---|
| 1 |  |  | 90[a,b] | 5 |  |  | 67[f] |
| 2 |  |  | 79[b](1.2:1)[c] | 6 |  |  | 72[b] |
| 3 |  |  | 61[a](1.2:1)[d] | 9 |  |  | 98[a] |
| 4 |  |  | 85[e](100:0)[c] | 10 |  |  | 89[a] |

[a]Solvent: MeOH:0.1 N HCl=1:4. [b]Solvent: THF:$H_2O$=1:4. [c]Diastereomeric ratios which were determined by $^1$H NMR integration ratio of methyl groups of $\alpha$-position. [d]*cis trans* ratio and configuration of 1,3-dibromo-1-propene was retained. [e]Solvent: MeOH:0.2 N HCl=1:4. [f]Solvent: $H_2O$.

cation of the present method was restricted to ketones.

**Indium-Mediated Allylation of Keto Esters with Allyl Halides:** The metal-mediated addition of allyl halides to aldehydes or ketones is one of the fundamental reactions in C-C bond formations, and it has become a well established method for the synthesis of homoallylic alcohols.[12,15] Reactions of carbonyl compounds with allyl- and crotyl-metal reagents have been widely investigated.[16] Recently, it has been reported that indium-mediated allylation of carbonyl compounds in aqueous media affords the corresponding homoallylic alcohols.[1] These reactions in aqueous media are of especial interest because they offer the possibility of environmentally benign reaction conditions by reducing the burden of organic solvent disposal. Although numerous examples on the indium-mediated allylation in aqueous media of aldehydes and ketones have been reported,[17] as far as we are aware, no systematic studies of the chemoselective allylation into $\alpha$-keto esters have been published.

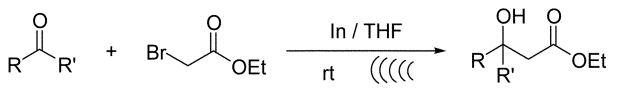
The chemoselective reactions of 1,n-dicarbonyl compounds with allyl halides using indium were investigated. $\alpha$-Keto-esters such as ethyl pyruvate, ethyl 3-methyl-2-oxobutyrate, and ethyl benzoyl formate reacted with a variety of allyl halides in the presence of indium to afford $\alpha$-hydroxy-$\gamma,\delta$-unsaturated carbonyl compounds in good to excellent yields in MeOH/HCl at 25 °C (Table 2). For the allyl bromide, the presence of various substituents at $\alpha$- or $\gamma$-position exhibited little effects on both the reaction rates and yields. Ethyl acetoacetate or ethyl levulinate was treated with allylindium reagent to give hydroxy unsaturated carbonyl compounds in good yield. These results mean that both reactivity and selectivity are independent of the distance between carbonyl groups. The 2,3-butanedione or 1-phenyl-1,2-propanedione reacted with allylindium, producing monoallylation compounds as major products.[18]

**Sonochemical Reformatsky Reaction Using Indium:** Reformatsky reaction, which is regarded as one of the most fundamental reactions in C-C bond formations, is the reaction of a carbonyl compound with $\alpha$-haloester in the presence of zinc metal to furnish $\beta$-hydroxyesters.[19] The products are one of the most important intermediates in organic synthesis.[20] Recently, several modified Reformatsky reactions using other metals have been reported.[21] Although the application of ultrasound has been reported for zinc metal, promoters such as iodine and potassium iodide were needed sometimes to obtain the desired products in good yields.[22] Our interests in extending the scope of the Reformatsky reaction and subsequent application of indium metal to modern organic synthesis have led us to investigate indium mediated Reformatsky reaction.[23]

The sonochemical Reformatsky reaction of aldehydes or ketones with ethyl bromoacetate in the presence of indium afforded $\beta$-hydroxyesters in good to excellent yields under mild conditions (Table 3). Aldehydes having acidic hydrogens such as 2- or 3-hydroxybenzaldehyde reacted with ethyl bromoacetate to provide the desired compounds with the same efficiency. In the case of ethyl 2-bromopropanoate and ethyl 2-bromo-2-methylpropanoate, the desired products were obtained in good yields. The reaction of aldehyde with indium reagent in the presence of ketone group proceeded chemoselectively.

**Indium-Mediated Selective Introduction of Allenyl and Propargyl Groups at C-4 Position of 2-Azetidinones:** Since 2-azetidinone nucleus has been used the central building block of $\beta$-lactam antibiotics, the functionalzation of the 2-azetidinone framework is pivotal for the development of new $\beta$-lactam antibitics.[24] The selective introduction

**Table 3**. Preparation of β-Hydeoxyesters by In-Mediated Reactions of Carbonyl Compounds with Ethyl Bromoacetate




| entry | R | R' | yield (%)[a] | entry | R | R' | yield (%)[a] |
|---|---|---|---|---|---|---|---|
| 1 | *n*-Bu | H | 95 | 6 | 2-$NO_2$-$C_6H_4$ | H | 85 |
| 2 | *iso*-Pr | H | 91 | 7 | 2-HO-$C_6H_4$ | H | 93 |
| 3 | Ph | H | 97 | 8 | 2-$C_4H_3S$ | H | 90 |
| 4 | 3-Br-$C_6H_4$ | H | 91 | 9 | -$(CH_2)_5$- | | 82 |
| 5 | 2,6-$(MeO)_2$-$C_6H_3$ | H | 90 | 10 | 4-Me-$C_6H_4$ | Me | 88 |

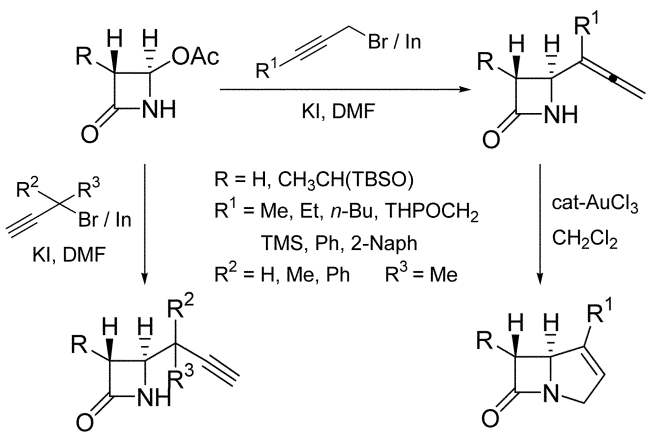
[a]Sonications were carried out at room temperature in a Fisher Scientific ultrasonic cleaner bath, which delivered a 43 kHz wave, with a fixed electrical power of 435 Watts.

of ethynyl,[25] allyl,[26] allenyl,[27] and propargyl[28] groups at C-4 position of 2-azetidinones is an especially intriguing and fundamental problem in the field of carbapenem syntheses because further functionalization of these groups has high potentials for the construction of the bicyclic nucleus.[29] Although a variety of allylations at C-4 position of 4-acetoxy-2-azetidinone have been reported,[20] the methods of selective nucleophilic allenylation or propargylation are relatively few.[27] Moreover, adjusting the regioselectivity of the reaction of propargyl metals with 4-acetoxy-2-azetidinones toward the synthesis of either 4-allenyl or 4-propargyl-2-azetidinones remains a formidable challenge to date.

The reaction of 4-acteoxy-2-azetidinones with organoindium reagents *in situ* generated from indium and γ-substituted propargyl bromides in the presence of KI in DMF selectively produced 4-allenyl-2-azetidinones in good to excellent yields (Scheme 1). The α-substituted propargyl bromides and indium selectively gave 4-propargyl-2-azetidinones. The 4-(1'-substituted allenyl)-2-azetidinones were treated with 5 mol % $AuCl_3$ in $CH_2Cl_2$ to produce bicyclic β-lactams in good yields.[30]

**Indium-Mediated Michael Addition and Hosomi-Sakurai Reactions.**

**Regioselectivity of the Reactions of the Organoindium**

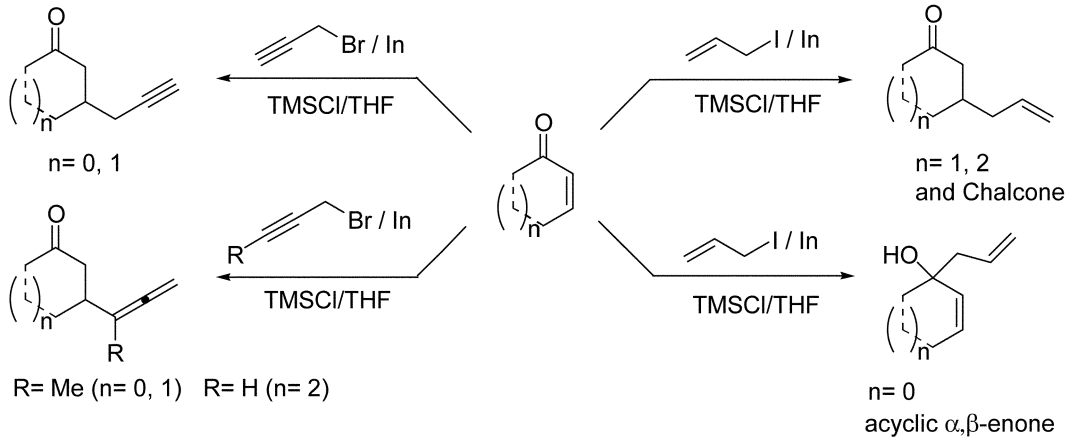



**Scheme 1**

**with α,β-Unsaturated Ketones:** The addition reaction of organometallic reagents with α,β-enones is one of the powerful methods for C-C bond formation. Michael addition reaction has been normally achieved by using organocopper and organomagnesium reagents in the presence of additives such as copper halides.[31] Our interest in extending the scope of the Michael addition reaction and subsequent application of indium to organic reaction[32] has led us to investigate the reaction of organoindium reagents with α,β-enones. Generally, organoindium reagents reacted with α,β-enals to afford 1,2-addition products in good yields.[33] The reaction of 4-phenyl-3-buten-2-one, which is an unique example of α,β-enone, with allylindiums produced a regioselective 1,2-addition product.[17,33] However, there are few reports on the Michael addition reaction of α,β-enones with organoindium reagents.[4] Recently, it has been reported that indium-mediated allylation to 1,1-dicyano-2-arylethenes gives 1,4-addition products in aqueous media with good yields.[4a] Tetraorganoindate complexes react with α,β-enones in 1,4-addition mode.[4c] The reaction of organoindium reagents with α,β-unsaturated carbonyl compounds, in which two electron withdrawing groups were attached to alkenes, proceed in 1,2-addition mode, whereas 1,4-addition reaction took place with 1,1-dicyano-2-arylethenes, which are extremely electron deficient olefins.[4d] Although a variety of examples of the nucleophilic addition of organoindium reagents to aldehydes and ketones have been reported,[34] regioselectivity of the reaction of the organoindium reagents with α,β-enones has not been systematically studied. Recently, indium-mediated propargylation and allenylation to carbonyl compounds has been reported.[35] However, 1,4-propargylation and allenylation onto α,β-enones are very difficult because 1,2-addition mode of propargyl or allenyl group is a major process. In addition, there has been no example on the indium-mediated β-propargylation to α,β-enones.[36]

Regioselectivity on the reactions of α,β-enones with organoindiums such as *in situ* generated allylindium and allenylindium was systematically studied in the presence of TMSCl as an additive. The treatment of 2-cyclohexen-1-one, carvone, 2-cyclohepten-1-one, and chalcone with allylindium reagents produced the 1,4-addition products in good yields, while 2-cyclopenten-1-one, 2-methyl-2-cyclopenten-1-one, 4,4-dimethylcyclohexen-1-one, 3-nonen-2-one, 4-hexen-3-one, and 4-phenyl-3-buten-2-one afforded the 1,2-addition products (Scheme 2). Organoindium reagent derived from indium and propargyl bromide in Grignard type gave addition products in good yields, under which the successive addition of α,β-enones and TMSCl were necessary. Although the organoindium reagent derived from propargyl bromide produced the propargylated compound in Grignard type except 2-cyclohepten-1-one, the indium reagent obtained from 1-bromo-2-butyne having γ-methyl group gave the allenylation product in Barbier type.[4f,37]

**The Catalytic Hosomi-Sakurai Reaction:** When $InCl_3$ was added in a stoichiometric amount to a solution of 2-cyclohexen-1-one in $CDCl_3$, the $^1H$ NMR spectrum of the



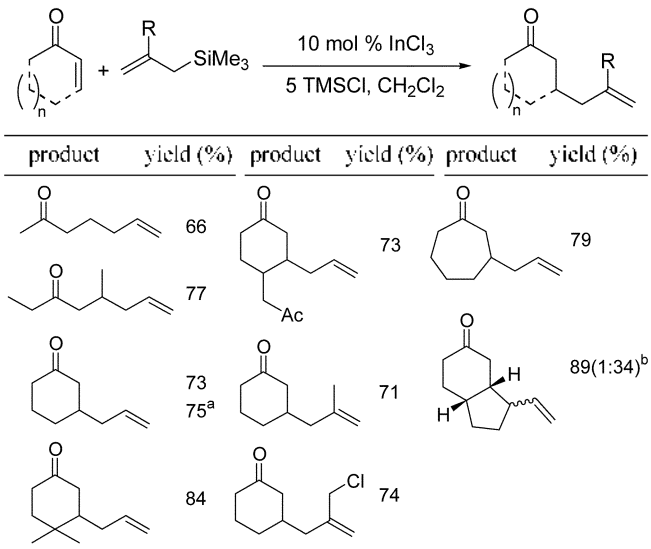

**Scheme 2**

resulting solution exhibited two peaks at 6.16 and 7.13 ppm which corresponds to the $\alpha$- and $\beta$-protons, respectively. Although the chemical shifts of the $\alpha$- and $\beta$-protons were shifted downfield relative to those of 2-cyclohexen-1-one, the $\alpha,\beta$-enone moiety was maintained. In contrast, the $\alpha,\beta$-enone moiety was entirely consumed to produce allylic carbocation species in the presence of stoichiometric amounts of $TiCl_4$ indicating that the titanium complex coordinates to $\alpha,\beta$-enone irreversibly. These results strongly imply that although $InCl_3$ activates 2-cyclohexen-1-one, the extent of the activation is weak enough to have reversible coordination; thus, $InCl_3$ may act as a catalyst in Hosomi-Sakurai reaction (Table 4). Surprisingly, the 1,4-addition product was not produced at all with the catalytic amount of $TiCl_4$ and $AlCl_3$ regardless of the presence of TMSCl.[38]

The conjugate addition of allylsilanes to $\alpha,\beta$-unsaturated carbonyl compounds, referred to as the Hosomi-Sakurai reaction, has been recognized as an efficient method for C-C bond formation.[39] It has played an important role in the area of synthetic organic chemistry.[40] Lewis acids employed in the Hosomi-Sakurai reactions are various, among which $TiCl_4$, $AlCl_3$, and $BF_3{:}OEt_2$ are in general the most effective for the allylations.[39] Recently, indium(III) chloride-mediated Hosomi-Sakurai reactions have been reported.[38,41] Despite the latest development, there is still a strong need for a simple and efficient method for the conjugate allylation of $\alpha,\beta$-enones.

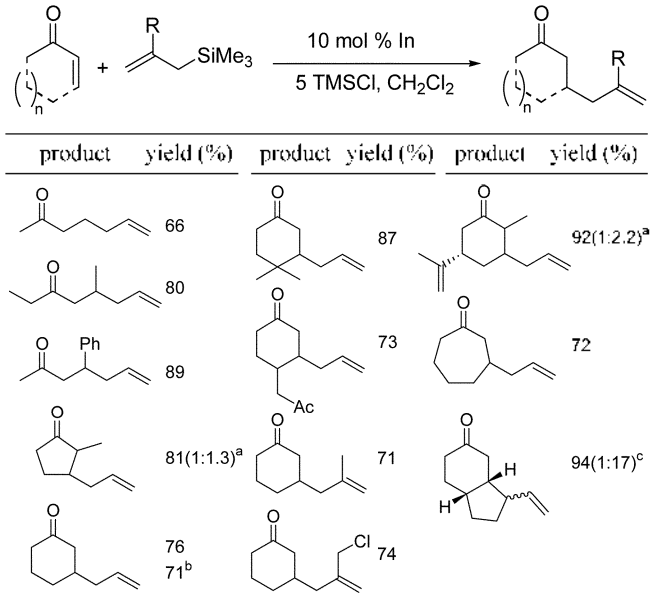
We have demonstrated that a novel indium-mediated strategy can be achieved for 1,4-addition of allyltirmethylsilane to $\alpha,\beta$-enones in dichloromethane in the presence of trimethylsilyl chloride as an additive under mild conditions. The process is simple to conduct and provides a diverse range of 6-oxoalkenes in good yields (Table 5). This protocol is an appealing alternative to the existing Hosomi-Sakurai reaction because of its mild reaction conditions and

**Table 4.** Indium Trichloride-Catalyzed Hosomi-Sakurai Reaction with Allyltrimethylsilane



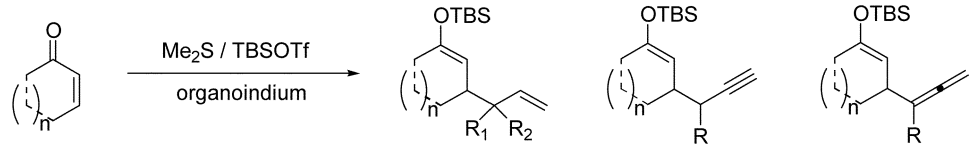

[a]Allylbenzyldimethylsilane was used. [b]Diastereomeric ratio of $\alpha,\beta$. Ratio (*cis:trans*) of starting material=6:1.

**Table 5.** Indium Trichloride-Catalyzed Hosomi-Sakurai Reaction with Allyltrimethylsilane




[a]Allylbenzyldimethylsilane was used. [b]Diastereomeric ratio of $\alpha,\beta$. Ratio (*cis:trans*) of starting material=6:1.

**Table 6.** Indium-Mediated $\beta$-Allylation and $\beta$-Propargylation onto $\alpha,\beta$-Unsaturated Ketones




| entry | halides | product | yield (%)[a] | entry | halides | product | yield (%)[a] |
|---|---|---|---|---|---|---|---|
| 1 | Br | OTBS | 15[b]<br>25[c]<br>0[d]<br>65 | 5 | Br | OTBS | 73[g] |
| 2 | Br[e] | OTBS | 62(1:1)[f] | 6 | Br | OTBS | 86 |
| 3 | Br | OTBS | 61 | 7 | Br | OTBS | 81(1:1.3)[h] |
| 4 | I$\sim$CO$_2$Et | OTBS, CO$_2$Et | 62 | 8 | Br | OTBS | 64[g] |

[a]Reaction performed with 10 equiv of enone, 1.0 equiv of In, 1.5 equiv of propargyl bromide, 1.2 equiv of $Me_2S$ and 1.05 equiv of TBSOTf, unless otherwise notes. [b]Phosphonium salt was used. [c]2-Cyclohexen-1-one:In:allylbromide=1.0:0.67:1.0. [d]$Me_2S$ was not used. [e]Isomeric ratio of crotyl bromide; *cis:trans*=1:5. [f]The ratios in parentheses indicate the diastereomeric ratio. [g]1 Equiv of LiI was used. [h]The ratios in parentheses indicate diastereomeric ratio.

the properties of indium metal being advantageous over other metals.[42]

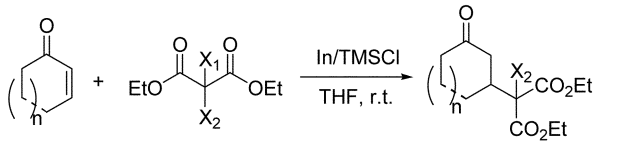
**In-Mediated $\beta$-Allylation, $\beta$-Propargylation, and $\beta$-Allenylation onto $\alpha,\beta$-Unsaturated Ketones:** Michael addition of organometallics to $\alpha,\beta$-unsaturated carbonyl compounds is one of the most useful and important methods. It has been normally achieved by using organocopper and organomagnesium reagents in the presence of additives such as copper halide.[31] Although $\beta$-substituted silyl enol ethers are generally obtained from $\alpha,\beta$-enones by 1,4-addition of organocopper reagents followed by enolate trapping, such procedures are sometimes inconvenient and the requisite reagents are difficult to obtain.[43] Recently, the indium-mediated propargylation or allenylation to carbonyl compounds has been reported.[44] However, 1,4-propargylation and allenylation onto $\alpha,\beta$-unsaturated ketones is very difficult because the 1,2-addition mode of propargyl or allenyl group is a major path. In addition, there is no example of the indium-mediated $\beta$-propargylation to $\alpha,\beta$-unsaturated ketones.[45]

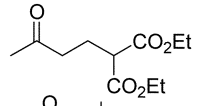
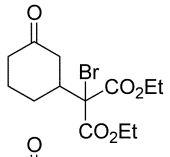
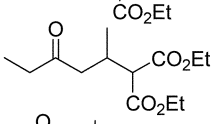
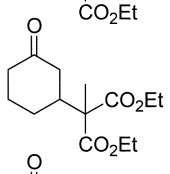
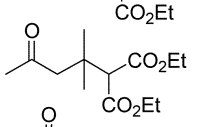
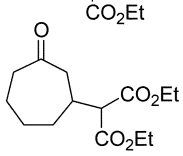
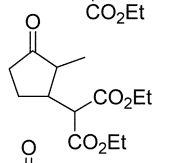
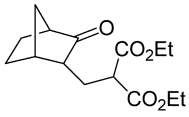
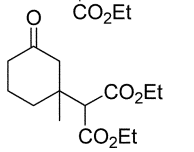
The 3-*tert*-butyldimethylsilyloxyalk-2-enylsulfonium salts, generated *in situ* from the reaction of $\alpha,\beta$-enones with dimethyl sulfide in the presence of TBSOTf, underwent a novel nucleophilic substitution with allylindiums to give silyl enol ethers of $\delta,\varepsilon$-alkenyl ketones in good yields, which correspond to formal Michael addition products (Table 6).[46] In a similar manner, 1,4-propargylation of propargyl-indiums onto the sulfonium salts produced the corresponding silyl enol ethers of $\delta,\varepsilon$-alkynyl ketones in good yields. Organoindium reagents derived from $\gamma$-substituted propargyl bromide and indium afforded the corresponding silyl enol ethers of $\beta$-allenyl ketones in good yields. The reaction proceeded *via* an addition-substitution mechanism involving the formation of allylic sulfonium salts. The presence of the intermediate sulfonium salt was confirmed by the observation of the low temperature $^1$H NMR.

**Highly Efficient 1,4-Addition of 1,3-Diesters to Conjugated Enones by Indium and TMSCl:** The Michael reaction is one of the most efficient methods and has wide applications in organic synthesis.[31,43,47] It is usually carried out with a base as the reagent. However, it suffers from some side reactions such as auto condensations, *bis*-additions, rearrangements, polymerizations, and 1,2-additions in the presence of strong bases. Despite the latest development, there is still strong need for highly efficient and mild methods for the corresponding 1,4-addition of 1,3-diesters to conjugated enones. Although the use of 1.0 equiv of TMSCl produced 1,2-addition product in low yield, we were able to obtain the desired product in 92% yield with 1 equiv of indium and 5 equiv of TMSCl within 30 min at room temperature. Reaction of 2-cyclohexen-1-one with diethyl bromomalonate using 10 mol % of indium and 5 equiv of TMSCl did not proceed. THF was the solvent chosen from several reaction media screened.

Organoindium reagents derived from indium and diethyl bromomalonates were added to a wide range of conjugated enones in a 1,4-fashion in the presence of TMSCl in THF

**Table 7.** Reactions of $\alpha,\beta$-Enones with Organoindium in the Presence of TMSCl




| entry | product | yield (%) | entry | product | yield (%) |
|---|---|---|---|---|---|
| 1 |  | 80 | 6 |  | 84 |
| 2 |  | 92 | 7 |  | 86 |
| 3 |  | 88 | 8 |  | 82 |
| 4 |  | 93 (1:10)[a] | 9 |  | 90 |
| 5 |  | 89 | | | |

[a]Diastereomeric ratio.

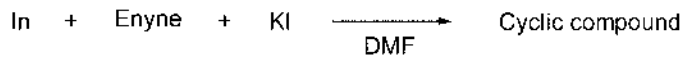
under mild conditions, and the corresponding oxo-1,3-diesters were obtained in good to excellent yields (Table 7).[48]

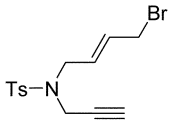
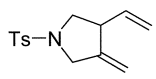
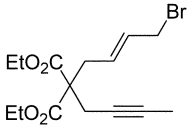
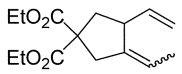
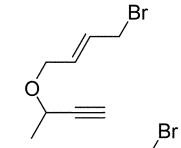
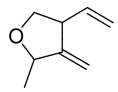
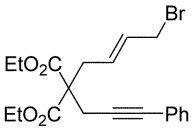
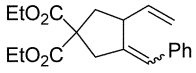
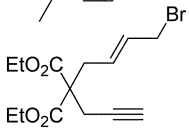
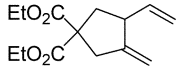
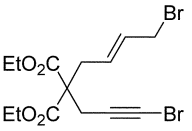
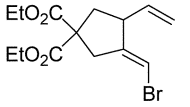
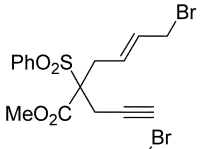
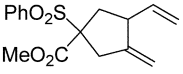
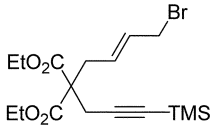
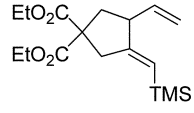
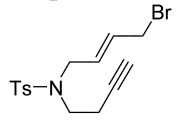
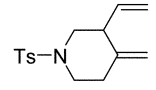
**Intramolecular Carboindation Reactions.** Despite the synthetic usefulness of intermolecular indium-mediated C-C bond formation,[1] the corresponding indium-mediated intramolecular cyclizations are mainly limited to the Pd-In-mediated arylative cyclizations of allenyl carbonyl compounds,[49] intramolecular allylindation of terminal alkynes in aqueous media,[50] cyclizations of tethered propargyl bromides to carbonyl compounds,[51] atom-transfer cyclizations,[52] and cyclizations *via trans*-hydrometallation of alkynes by $InCl_3$ and DIBAL-H.[53] As part of our continuing effort to expand the synthetic utility of organoindium reagents, we found efficient intramolecular cyclizations of 1-bromo-2,7- and 2,8-enynes with indium.[54]

Our initial study focused on the use of *N*-(*E*)-4-bromo-2-butenyl-*N*-propargyl-*p*-toluenesulfonamide. Although the treatment of this compound with 1 equiv of indium did not produce the desired product (25 °C, DMF), heating allyl bromide at 80 °C gave the cyclic compound in 82 % yield. The reaction of *N*-2-butenyl-4-iodo-*N*-propargyl-*p*-toluenesulfonamide with indium gave the desired product in 80% yield (25 °C, 1 h). Addition of 3 equiv of potassium iodide as an additive to allyl bromide gave the best result and afforded the carbocycle in 83% yield (25 °C, 1 h). We believe that KI is involved in the generation of allyl iodide derivatives during the cyclization reaction because the indium-mediated cyclization of allyl bromide did not occur without KI at 25 °C for 1 h.

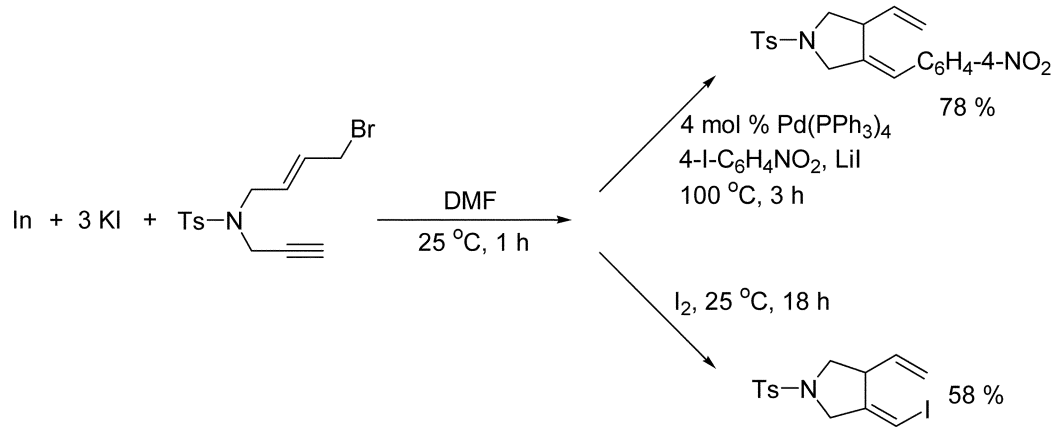
The cyclization of 1-bromo-2,7- and 2,8-enynes mediated by indium in DMF produced five- and six-membered cyclic

**Table 8.** Cyclization of Terminal 1-Bromo-2,7- and 2,8-Enynes Mediated by Indium




| enyne | product | yield (%)[a] | enyne | product | yield (%)[a] |
|---|---|---|---|---|---|
|  |  | 83 |  |  | 60[f] |
|  |  | 95[b] |  |  | 55[g] |
|  |  | 77 |  |  | 45[h] |
|  |  | 76[c] |  |  | 63 |
|  |  | 69[d] | | | |

[a]The reaction performed with 1 equiv of indium and 3 equiv of KI unless otherwise notes. [b]dr=1.3:1. [c]dr=1:2.2. [d]KI was not used. [e]Reaction performed with 1 equiv of indium without KI. [f]dr=1:3. [g]dr=1.1.6. [h]Dehalogenated compound was obtained in 9% yield.




**Scheme 3**

compounds (Table 8). Although KI was a necessary additive in the cyclization of terminal 1-bromo-2,7-enynes to give the desired products at 25 °C, the reactions of terminal 1-bromo-2,8-enynes and internal 1-bromo-2,7-enynes with indium proceeded at 100 °C in DMF without KI. After cyclizations, the subsequent cross-coupling reaction and iodolysis increased the usefulness of this reaction (Scheme 3).

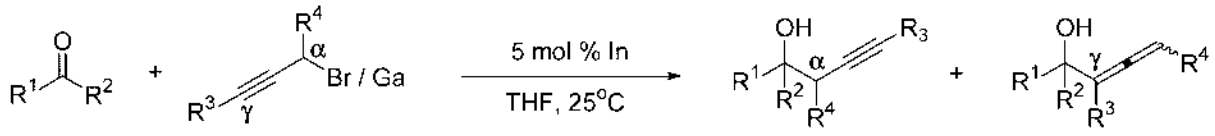
After *N*-(*E*)-4-bromo-2-butenyl-*N*-propargyl-*p*-toluenesulfonamide was treated with indium in the presence of KI in DMF at 25 °C for 1 h, the addition of 4 mol% $Pd(PPh_3)_4$, LiI (3 equiv) and 1-iodo-4-nitrobenzene (3 equiv) to the reaction mixture gave the coupling product in 78% yield. Following the iodolysis (3 equiv $I_2$, 25 °C, 18 h) under the same reaction conditions produced vinyl iodide in 58% yield.

## Gallium-Mediated Organic Reactions

**Addition Reactions of Propargylgallium to Carbonyl Group.** The selective nucleophilic allenylations or propargylations to carbonyl compounds toward the synthesis of either homoallenyl alcohols or homopropargyl alcohols are a very important class of organic transformations.[12,55] To date various methods have been developed on the basis of nucleophilic character of propargylmetals obtained from propargyl halides and metals (Ti, Al, Si, Sc, In, Sn, Zn, Bi, Cd, and Sb).[56] Surprisingly, although organoindium reagents obtained from the reaction of indium with allyl halides, allyl acetates, and propargyl halides have been used extensively in carbonyl addition reactions,[1,57] additions to C-C multiple bonds and nitrile,[58] and cross-coupling reactions,[5] the organogallium reagents prepared from gallium and allyl halides and propargyl halides have not been explored to a great extent.[59] Preparation of allylgalliums *via* direct reduction of allylic bromides using a catalytic amount of indium[60] and selective allene formation[10] using organoindium reagents generated from indium and $\gamma$-substituted propargyl bromides led us to investigate the efficient and regioselective indium-catalyzed addition reactions of propargyl bromides to carbonyl compounds with gallium.[61]

When 3-bromo-1-(trimethylsilyl)-1-propyne was used, the organoindium and organogallium reagents in the presence of 5 mol% of indium gave the same results in yield (81%) and selectivity ($\alpha$-attack). The reactions of organogallium reagents generated from propargyl bromides having substituents at the $\gamma$-position and gallium in the presence of 5 mol% of indium with aldehydes and ketones selectively produced homoallenyl alcohols in good to excellent yields. Treatment of organogallium reagents obtained from propargyl bromides having substituents at the $\alpha$-position and gallium in the presence of 5 mol% of indium with carbonyl compounds selectively afforded homo-propargyl alcohols (Scheme 4).

**Regioselective Allylgallation of Terminal Alkynes.** The carbometalation of C-C multiple bonds is a very important organic transformation.[62] In particular, the development of allylmetalation of simple unactivated alkynes toward the synthesis of 1,4-dienes is valuable in organic syntheses because of the utility of 1,4-dienes and only limited number of allylmetals available for this purpose.[63] To date various allylmetalations have been reported on the basis of nucleophilic character of allylmetals obtained from allyl halides



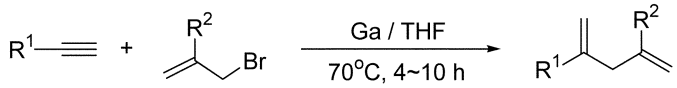

$R^3$= H, $R^4$=H / $R^3$= TMS, $R^4$= H / $R^3$= H, $R^4$= Me
$R^3$= Me, Et, Ph / $R^4$= H
$R^1$ = alkyl, aryl $R^2$ = H, Me

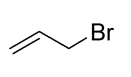
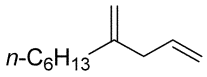
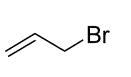
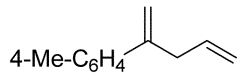
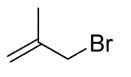
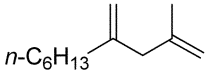
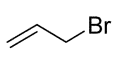
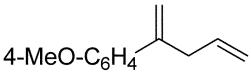
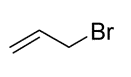
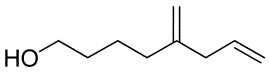
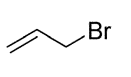
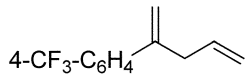
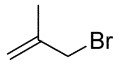
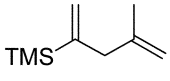
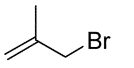
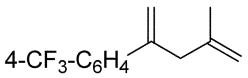
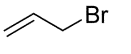
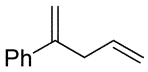
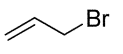
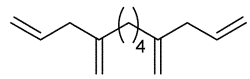
**α-attack major**

**γ-attack major**

**Scheme 4**

**Table 9.** Allylgallation of Terminal Alkynes with Allyl Bromide and Gallium[a]



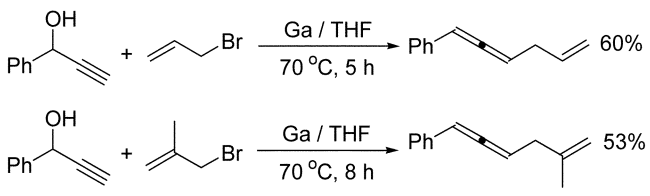

| allyl bromide | product | yield (%)[b] | allyl bromide | product | yield (%)[b] |
|---|---|---|---|---|---|
|  |  | 70 |  |  | 96 |
|  |  | 62 |  |  | 64 |
|  |  | 51 |  |  | 60 |
|  |  | 91[c] |  |  | 53 |
|  |  | 92 |  |  | 67[d] |

[a]Reactions in Grignaed type performed with terminal acetylene (1 mmol), allylic bromide (8.0 mmol), and Ga (2.0 mmol) in THF at 70 °C, unless otherwise noted. [b]Isolated yield. [c]GC yield was obtained on the basis of an internal standard (dodecane). [d]Alkyne (1 mmol), allyl bromede (16 mmol), and Ga (4 mmol) was used.

and metals (Ta, Zr, Zn, Al, Ti, Si, and Sn).[63] Although the organoindium reagents *in situ* generated from the reaction of indium with allyl halides have been used extensively, organogallium reagents have not been explored to a great extent in organic syntheses.[64] We demonstrated an efficient synthesis of 1,4-dienes *via* allylation of alkynes by organogallium reagents.

We first investigated various experimental conditions using phenylacetylene and allyl bromide. Among the reaction conditions examined, the best results were obtained with 2.0 equiv of gallium and 8.0 equiv of allyl bromide in THF at 70 °C for 4 h, which provided 1,4-diene in 95% yield.[65] The reactions of terminal alkynes with allylgallium reagents *in situ* generated from gallium and allyl bromides gave the corresponding 1,4-dienes in good yield *via* Markovnikov addition in THF at 70 °C (Table 9).

Although the allylation of 5-hexyn-1-ol provided 5-methylene-7-octen-1-ol in 51% yield, 1-phenyl-2-propyn-1-ol gave 1-phenyl-1,2,5-hexatriene in 60% yield *via* anti-Markovnikov addition to the triple bond followed by elimination (Scheme 5). This implies that the changes in selectivity for the formation of 1-phenyl-1,2,5-hexatriene *via* the anti-Markovnikov addition in the reaction of 1-phenyl-2-propyn-1-ol were caused by the coordination of the carbinol oxygen to an organogallium intermediate.




**Scheme 5**

## Conclusions

In this account, we have described a number of very useful processes for C-C bond formation using organoindium reagents *in situ* generated from the reaction of indium with allyl halide and propargyl halide, respectively, *via* addition and substitution reactions. We demonstrated efficient addition reactions of allylindium to carbonyl and iminium groups, indium-mediated synthesis of 2-(2-hydroxyethyl)-homoallenylsilanes, indium-mediated allylation of keto esters with allyl halides, and sonochemical Reformatsky reaction using indium. We found the indium-mediated selective introduction of allenyl and propargyl groups at C-4 position of 2-azetidinones, indium-mediated $\beta$-allylation, $\beta$-propargylation and $\beta$-allenylation onto $\alpha,\beta$-unsaturated ketones, and highly efficient 1,4-addition of 1,3-diesters to conjugated enones by indium and TMSCl. Indium-mediated Michael addition and Hosomi-Sakurai reactions were developed, and in this methodology, indium and indium trichloride could be used only in catalytic amounts. Intramolecular carboindation reactions were developed, and the resulting organoindium intermediates could undergo a variety of very useful subsequent transformations to give cyclic compounds. In addition, we found the addition reactions of propargylgallium to carbonyl group and regioselective allylgallation of terminal alkynes. In these methodologies, organoindium reagents were obtained *in situ* from indium and the corresponding halides. The reactions proceeded under relatively mild reaction conditions and tolerated a wide variety of functional groups, thus avoiding the protection-deprotection sequences.

**Acknowledgments.** I thank the graduate students and the postdoctoral research fellows whose names appear in the

references for their hard work, which made this account possible. This work was supported by the National Research Laboratory Program (M10600000203-06J0000-20310), the CMDS at KAIST, and the KOSEF (R01-2006-000-11283-0). The NMR data were obtained from the central instrumental facility in Kangwon National University.

## References


1. (a) Li, C.-J. *Tetrahedron* **1996**, *52*, 5643. (b) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; Wiley: New York, 1997. (c) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023. (d) Li, C.-J.; Chan, T.-H. *Tetrahedron* **1999**, *55*, 11149. (e) Cintas, P. *Synlett* **1995**, 1087. (f) Babu, G.; Perumal, P. T. *Aldrichimica Acta* **2000**, *33*, 16. (g) Araki, S.; Kamei, T.; Hirashita, T.; Yamamura, H.; Kawai, M. *Org. Lett.* **2000**, *2*, 847. (h) Chauhan, K. K.; Frost, C. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3015. (i) Pae, A. N.; Cho, Y. S. *Curr. Org. Chem.* **2002**, *6*, 715. (j) Podlech, J.; Maier, T. C. *Synthesis* **2003**, 633.
2. Araki, S.; Ito, H.; Butsugan, Y. *J. Org. Chem.* **1988**, *53*, 1831.
3. (a) Araki, S.; Ito, H.; Butsugan, Y. *Synth. Commun.* **1988**, *18*, 453. (b) Araki, S.; Katsumura, N.; Kawasaki, K.-I.; Butsugan, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 499.
4. (a) Araki, S.; Shimizu, T.; Jin, S.-J.; Butsugan, Y. *Chem. Commun.* **1991**, 824. (b) Perez, I.; Sestelo, J. P.; Maestro, M. A.; Mourino, A.; Sarandeses, L. A. *J. Org. Chem.* **1998**, *63*, 10074. (c) Wang, L.; Sun, X.; Zhang, Y. *Synth. Commun.* **1998**, *28*, 3263. (d) Araki, S.; Horie, T.; Kato, M.; Hirashita, T.; Yamamura, H.; Kawai, M. *Tetrahedron Lett.* **1999**, *40*, 2331. (e) Lee, P. H.; Ahn, H.; Lee, K.; Sung, S.-Y.; Kim, S. *Tetrahedron Lett.* **2001**, *42*, 37. (f) Lee, P. H.; Seomoon, D.; Lee, K.; Heo, Y. *J. Org. Chem.* **2003**, *68*, 2510.
5. (a) Perez, I.; Sestelo, J. P.; Sarandeses, L. A. *Org. Lett.* **1999**, *1*, 1267. (b) Gelman, D.; Schumann, H.; Blum, J. *Tetrahedron Lett.* **2000**, *41*, 7555. (c) Lee, P. H.; Sung, S.-Y.; Lee, K. *Org. Lett.* **2001**, *3*, 3201. (d) Perez, I.; Sestelo, J. P.; Sarandeses, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 4155. (e) Hirashita, T.; Yamamura, H.; Kawai, M.; Araki, S. *Chem. Commun.* **2001**, 387. (f) Takami, K.; Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K. *Org. Lett.* **2001**, *3*, 1997. (g) Pena, M. A.; Perez, I.; Sestelo, J. P.; Sarandeses, L. A. *Chem. Commun.* **2002**, 2246. (h) Lee, K.; Lee, J.; Lee, P. H. *J. Org. Chem.* **2002**, *67*, 8265. (i) Lee, K.; Seomoon, D.; Lee, P. H. *Angew. Chem. Int. Ed.* **2002**, *41*, 3901. (j) Hirashita, T.; Hayashi, Y.; Mitsui, K.; Araki, S. *J. Org. Chem.* **2003**, *68*, 1309. (k) Lehmann, U.; Awasthi, S.; Minehan, T. *Org. Lett.* **2003**, *5*, 2405. (l) Lee, P. H.; Lee, S. W.; Lee, K. *Org. Lett.* **2003**, *5*, 1103. (m) Pena, M. A.; Sestelo, J. P.; Sarandeses, L. A. *Synthesis* **2003**, 780. (n) Lee, P. H.; Lee, S. W.; Seomoon, D. *Org. Lett.* **2003**, *5*, 4963. (o) Lee, S. W.; Lee, K.; Seomoon, D.; Kim, S.; Kim, H.; Kim, H.; Shim, E.; Lee, M.; Lee, S.; Kim, M.; Lee, P. H. *J. Org. Chem.* **2004**, *69*, 4852.
6. (a) Lee, P. H.; Sung, S.-Y.; Lee, K.; Chang, S. *Synlett* **2001**, 146. (b) Rodriguez, D.; Sestelo, J. P.; Sarandeses, L. A. *J. Org. Chem.* **2003**, *68*, 2518.
7. (a) Ranu, B. C.; Majee, A. *Chem. Commun.* **1997**, 1225. (b) Fujiwara, N.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 2318. (c) Fujiwara, N.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 4095.
8. Chan, T. H.; Yang, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3228.
9. (a) Araki, S.; Kamei, T.; Hirashita, T.; Yamamura, H.; Kawai, M. *Org. Lett.* **2000**, *2*, 847. (b) Jang, T.-S.; Keum, G.; Kang, S. B.; Chung, B. Y.; Kim, Y. *Synthesis* **2003**, 775.
10. Lee, K.; Seomoon, D.; Lee, P. H. *Angew. Chem. Int. Ed.* **2002**, *41*, 3901.
11. Miao, W.; Chung, L. W.; Wu, Y.-D.; Chan, T. H. *J. Am. Chem. Soc.* **2004**, *123*, 13326.
12. Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.
13. 4-Bromo-3-[(trimethylsilyl)methyl]-1,2-butadiene was prepared from monoacetylation and mesylation of 2-butyn-1,4-diol, addition of trimethylsilylmethyl anion, saponification, mesylation followed by Finkelstein reaction. Lee, P. H.; Bang, K.; Ahn, H.; Lee, K. *Bull. Korean Chem. Soc.* **2001**, *22*, 1385.
14. Lee, P. H.; Bang, K.; Lee, K.; Lee, C.-H.; Chang, S. *Tetrahedron Lett.* **2000**, *41*, 7521.
15. Trost, B. M. *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991; p 1.
16. (a) Yamamoto, Y. *Acc. Chem. Res.* **1987**, *20*, 243. (b) Hoffmann, R. W. *Angew. Chem. Int. Ed.* **1982**, *21*, 555.
17. (a) Kim, E.; Gordon, D. M.; Schmid, W.; Whitesides, G. M. *J. Org. Chem.* **1993**, *58*, 5500. (b) Bindra, W. H.; Prenner, R. H.; Schmid, W. *Tetrahedron* **1994**, *50*, 749. (c) Chan, T.-H.; Lee, M.-C. *J. Org. Chem.* **1995**, *60*, 4228. (d) Li, X.-R.; Loh, T.-P. *Tetrahedron: Asymmetry* **1996**, *7*, 1535.
18. (a) Lee, P. H.; Lee, K.; Chang, S. *Synth. Commun.* **2001**, *31*, 3189. (b) Lee, P. H.; Seomoon, D.; Lee, K. *Bull. Korean Chem. Soc.* **2001**, *22*, 1380.
19. (a) Shriner, R. L. *Org. React.* **1946**, *1*, 1. (b) Rathke, M. W. *Org. React.* **1975**, *22*, 423. (c) Gensler, W. J. *Chem. Rev.* **1957**, *57*, 265. (d) Diaper, D. G. M.; Kuksis, A. *Chem. Rev.* **1959**, *59*, 89.
20. (a) Becker, D.; Brodsky, N.; Kalo, I. *J. Org. Chem.* **1978**, *43*, 2557. (b) Barco, A.; Benetti, S.; Pollini, G. P. *J. Org. Chem.* **1980**, *45*, 4776. (c) Klipa, D. K.; Hart, H. *J. Org. Chem.* **1981**, *46*, 2815. (d) West, F. G.; Gunawardena, G. V. *J. Org. Chem.* **1993**, *58*, 5043. (e) Witzemann, J. S.; Nottingham, W. D. *J. Org. Chem.* **1989**, *54*, 3258 and references cited therein.
21. (a) March, J. *Advanced Organic Chemistry*; Wiley: New York, 1992; p 929. (b) Shen, Z.; Zhang, J.; Zou, H.; Yang, M. *Tetrahedron Lett.* **1997**, *38*, 2733. (c) Gabriel, T.; Wessjohann, L. *Tetrahedron Lett.* **1997**, *38*, 1363.
22. (a) Mason, T. J.; Lorimer, J. P. *Sonochemistry: Theory, Applications and Uses of Ultrasound in Chemistry*; Ellis Horwood Limited: Chichester, 1988. (b) Han, B. H.; Boudjouk, P. *J. Org. Chem.* **1982**, *47*, 5030. (c) Nishiyama, T.; Woodhall, J. F.; Lawson, E. N.; Kitching, W. *J. Org. Chem.* **1989**, *54*, 2184.
23. (a) Lee, P. H.; Bang, K.; Lee, K.; Sung, S.-Y.; Chang, S. *Synth. Commun.* **2001**, *31*, 3781. (b) Bang, K.; Lee, K.; Park, Y. K.; Lee, P. H. *Bull. Korean Chem. Soc.* **2002**, *23*, 1272.
24. (a) Manhas, M. S.; Wagle, D. R.; Chiang, J.; Bose, A. K. *Heterocycles* **1988**, *27*, 1755. (b) Georg, G. I. *The Organic Chemistry of β-Lactams*; VCH: New York, 1992. (c) Ojima, I. *Adv. Asym. Synth.* **1995**, *1*, 95. (d) Ojima, I.; Delaloge, F. *Chem. Soc. Rev.* **1997**, *26*, 377. (e) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Amino Acids* **1999**, *16*, 321. (f) Alcaide, B.; Almendros, P.; *Chem. Soc. Rev.* **2001**, *30*, 226. (g) Alcaide, B.; Almendros, P. *Org. Prep. Proced. Int.* **2001**, *33*, 315. (h) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Synlett* **2001**, 1813. (i) Alcaide, B.; Almendros, P. *Synlett* **2002**, 381.
25. Mori, S.; Iwakura, H.; Takechi, S. *Tetrahedron Lett.* **1988**, *29*, 5391.
26. (a) Aratani, M.; Hirai, H.; Sawada, K.; Hashimoto, M. *Heterocycles* **1985**, *23*, 1889. (b) Fliri H.; Mak, C.-P. *J. Org. Chem.* **1985**, *50*, 3438. (c) Fujimoto, K.; Iwano, Y.; Hirai, K. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1363. (d) Blaszczak, L. C.; Armour, H. K.; Hallign, N. G. *Tetrahedron Lett.* **1990**, *31*, 5693. (e) Tarling, C. A.; Holmes, A. B.; Markwell, R. E.; Pearson, N. D. *J. Chem. Soc. Perkin Trans. 1*, **1990**, 1695. (f) Kang, S.-K.; Baik, T.-G.; Jiao, X.-H.; Lee, K.-J.; Lee, C. H. *Synlett* **1999**, 447.
27. (a) Prasad, J. S.; Liebeskind, L. S. *Tetrahedron Lett.* **1988**, *29*, 4253. (b) Prasad, J. S.; Liebeskind, L. S. *Tetrahedron Lett.* **1988**, *29*, 4257.
28. (a) Shibasaki, M.; Nishida, A.; Ikegami, S. *Chem. Commun.* **1982**, 1324. (b) Haruta, J.-I.; Nishi, K.; Kikuchi, K.; Matsuda, S.; Tamura, Y.; Kita, Y. *Chem. Pharm. Bull.* **1989**, *37*, 2338.
29. (a) Kobayashi, T.; Ishida, N.; Hiraoka, T. *Chem. Commun.* **1980**, 736. (b) Hua, D. H.; Verma, A. *Tetrahedron Lett.* **1985**, *26*, 547.
30. Lee, P. H.; Kim, H.; Lee, K.; Kim, M.; Noh, K.; Kim, H. *Angew.*

*Chem. Int. Ed.* **2005**, *44*, 1840.
31. (a) Posner, G. H. *Org. React.* **1972**, *19*, 1. (b) Posner, G. H. *An Introduction to Synthesis Using Organocopper Reagents*; Wiley-Interscience: New York, 1980. (c) Lee, P. H.; Shim, S. C.; Kim, S. *Bull. Korean Chem. Soc.* **1986**, *7*, 425. (d) Lipshutz, B. H. *Synthesis* **1987**, 325. (e) Taylor, R. J. K. *Organocopper Reagents*; Oxford University Press: Oxford, 1994. (f) Lee, P. H.; Park, J.; Lee, K.; Kim, H.-C. *Tetrahedron Lett.* **1999**, *40*, 7109.
32. (a) Lee, P. H.; Sung, S.-Y.; Lee, K. *Org. Lett.* **2001**, *3*, 3201. (b) Lee, P. H.; Sung, S.-Y.; Lee, K.; Chang, S. *Synlett* **2002**, 146. (c) Lee, P. H.; Seomoon, D.; Lee, K. *Org. Lett.* **2005**, *7*, 343. (d) Lee, P. H.; Seomoon, D.; Lee, K.; Kim, S.; Kim, H.; Kim, H.; Shim, E.; Lee, M.; Lee, S.; Kim, M.; Sridhar, M. *Adv. Synth. Catal.* **2004**, *346*, 1641. (e) Lee, P. H.; Shim, E.; Lee, K.; Seomoon, D.; Kim, S. *Bull. Korean Chem. Soc.* **2005**, *26*, 157.
33. (a) Araki, S.; Ito, H.; Katsumura, N.; Butsugan, Y. *J. Organomet. Chem.* **1989**, *369*, 291. (b) Hoppe, H. A.; Lloyd-Jones, G. C.; Murry, M.; Peakman, T. M.; Walsh, K. E. *Angew. Chem. Int. Ed.* **1998**, *37*, 1545. (c) Capps, S. M.; Clarke, T. P.; Charmant, J. P. H.; Hoppe, H. A. F.; Lloyd-Jones, G. C.; Murry, M.; Peakman, T. M.; Stentifold, R. A.; Walsh, K. E.; Worthington, P. A. *Eur. J. Org. Chem.* **2000**, 963.
34. (a) Loh, T.-P.; Ho, D. S.-C.; Chua, G.-L.; Sim, K.-Y. *Synlett* **1997**, 563. (b) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; Wiley: New York, 1997. (c) Loh, T.-P.; Ho, D. S.; Xu, K.-C.; Sim, K.-Y. *Tetrahedron Lett.* **1997**, *38*, 865. (d) Chan, T.-H.; Lu, W. *Tetrahedron Lett.* **1998**, *39*, 8605. (e) Li, C.-J.; Chan, T.-H. *Tetrahedron* **1999**, *55*, 11149.
35. (a) Isaac, M. B.; Chan, T.-H. *Chem. Commun.* **1995**, 1003. (b) Yi, X.-H.; Meng, Y.; Hua, X.-G.; Li, C.-J. *J. Org. Chem.* **1998**, *63*, 7472. (c) Nair, V.; Jayan, C. N.; Ros, S. *Tetrahedron* **2001**, *57*, 9453.
36. For some previously reported examples using other reagent, see (a) Paquette, L. A.; Han, Y.-K. *J. Am. Chem. Soc.* **1981**, *103*, 1831. (b) Corey, E. J.; Rucker, C. *Tetrahedron Lett.* **1982**, *23*, 719. (c) Haruta, J.; Nishi, K.; Matsuda, S.; Akai, S.; Tamura, Y.; Kita, Y. *J. Org. Chem.* **1990**, *55*, 4853. (d) Shibata, I.; Kano, T.; Kanazawa, N.; Fukuoka, S.; Baba, A. *Angew. Chem. Int. Ed.* **2002**, *41*, 1389.
37. Lee, P. H.; Kim, H.; Lee, K.; Seomoon, D.; Kim, S.; Kim, H.; Kim, H.; Lee, M.; Shim, E.; Lee, S.; Kim, M.; Han, M.; Noh, K.; Sridar, M. *Bull. Korean Chem Soc.* **2004**, *25*, 1687.
38. Lee, P. H.; Lee, K.; Sung, S.-Y.; Chang, S. *J. Org. Chem.* **2001**, *66*, 8646.
39. (a) Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 1673. (b) Colvin, E. *Silicon in Organic Synthesis*; Butterworths: London, 1981; p 97. (c) Weber, W. P. *Silicon Reagents for Organic Synthesis*; Springer-Verlag: Berlin, 1983; Vol. 12, p 173. (d) Blumenkopf, T. A.; Heathcock, C. H. *J. Am. Chem. Soc.* **1983**, *105*, 2354. (e) Hosomi, A. *Acc. Chem. Res.* **1988**, *21*, 200. (f) Fleming, I.; Dunogues, J.; Smithers, R. *Org. React.* **1989**, *37*, 57. (g) Langkopf, E.; Schinzer, D. *Chem. Rev.* **1995**, *95*, 1375. (h) Yadav, J. S.; Reddy, B. V. S.; Sadasiv, K.; Satheesh, G. *Tetrahedron Lett.* **2002**, *43*, 9695.
40. (a) Nakamura, H.; Oya, T.; Murai, A. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 929. (b) Schinzer, D.; Feber, K.; Ruppelt, M. *Liebigs. Ann. Chem.* **1992**, 139. (c) Majetich, G.; Song, J.-S.; Leigh, A. J.; Condon, S. M. *J. Org. Chem.* **1993**, *58*, 1030. (d) Kuroda, C.; Inoue, S.; Takemura, R.; Satoh, J. Y. *J. Chem. Soc., Perkin Trans.1* **1994**, 521.
41. (a) Onishi, Y.; Ito, T.; Yasuda, M.; Baba, A. *Tetrahedron* **2002**, *58*, 8227. (b) Onishi, Y.; Ito, T.; Yasuda, M.; Baba, A. *Eur. J. Org. Chem.* **2002**, 1578.
42. Lee, P. H.; Seomoon, D.; Kim, S.; Nagaiah, K.; Damle, S. V.; Lee, K. *Synthesis* **2003**, 2189.
43. (a) Taylor, R. J. K. *Synthesis* **1985**, 364. (b) Hulce, M. *Org. React.* **1990**, *38*, 225. (c) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992. (d) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135.
44. (a) Isaac, M. B.; Chan, T.-H. *Chem. Commun.* **1995**, 1003. (b) Yi, X.-H.; Meng, Y.; Hua, X.-G.; Li, C.-J. *J. Org. Chem.* **1998**, *63*, 7472. (c) Nair, V.; Jayan, C. N.; Ros, S. *Tetrahedron* **2001**, *57*, 9453.
45. For some previously reported examples using other reagent, see (a) Paquette, L. A.; Han, Y.-K. *J. Am. Chem. Soc.* **1981**, *103*, 1831. (b) Corey, E. J.; Rucker, C. *Tetrahedron Lett.* **1982**, *23*, 719. (c) Haruta, J.; Nishi, K.; Matsuda, S.; Akai, S.; Tamura, Y.; Kita, Y. *J. Org. Chem.* **1990**, *55*, 4853. (d) Shibata, I.; Kano, T.; Kanazawa, N.; Fukuoka, S.; Baba, A. *Angew. Chem. Int. Ed.* **2002**, *41*, 1389.
46. (a) Lee, P. H.; Lee, K.; Kim, S. *Org. Lett.* **2001**, *3*, 3205. (b) Lee, K.; Kim, H.; Miura, T.; Kiyota, K.; Kusama, H.; Kim, S.; Iwasawa, N.; Lee, P. H. *J. Am. Chem. Soc.* **2003**, *125*, 9682. (c) Iwasawa, N.; Miura, T.; Kiyota, K.; Kusama, H.; Lee, K.; Lee, P. H. *Org. Lett.* **2002**, *4*, 4463. (d) Miura, T.; Kiyota, K.; Kusama, H.; Lee, K.; Kim, H.; Kim, S.; Lee, P. H.; Iwasawa, N. *Org. Lett.* **2003**, *5*, 1725.
47. (a) Bergman, E. D.; Ginsburg, D.; Pappo, R. *Org. React.* **1959**, *10*, 179. (b) Hulce, M. *Org. React.* **1990**, *38*, 225. (c) Taylor, R. J. K. *Organocopper Reagents*; Oxford University Press: Oxford, **1994**.
48. Lee, P. H.; Seomoon, D.; Lee, K.; Heo, Y. *J. Org. Chem.* **2003**, *68*, 2510.
49. Kang, S.-K.; Lee, S.-W.; Jung, J.; Lim, Y. *J. Org. Chem.* **2002**, *67*, 4376.
50. (a) Salter, M. M.; Sardo-Infiri, S. *Synlett* **2002**, 2068. (b) Nair, V.; Ros, S.; Jayan, C. N.; Pillai, B. S. *Tetrahedron* **2004**, *60*, 1959.
51. Kang, H.-Y.; Kim, Y.-T.; Yu, Y.-K.; Cha, J. W.; Cho, Y. S.; Koh, H. Y. *Synlett* **2004**, 45.
52. Yanada, R.; Nishimori, N.; Matsumura, A.; Fujii, N.; Takemoto, Y. *Tetrahedron Lett.* **2002**, *43*, 4585.
53. Takami, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2002**, *4*, 2993.
54. Lee, P. H.; Kim, S.; Lee, K.; Seomoon, D.; Kim, H.; Lee, S.; Kim, M.; Han, M.; Noh, K.; Livinghouse, T. *Org. Lett.* **2004**, *6*, 4825.
55. (a) Panek, J. S. In *Comprehensive Organic Synthesis*; Schreiber, S. L., Ed.; Pergamon: Oxford, 1991; Vol 1. p 595 (b) Yamamoto, H. In *Comprehensive Organic Synthesis*; Heathcock, C. H., Ed.; Pergamon Press: Oxford, 1991; Vol 2, Chapter 1.3, pp 81-98 (c) Yamaguchi, M. In *Main Group Metals in Organic Synthesis*; Yamamoto, H.; Oshima, K., Eds.; Wiley-VCH: Weinheim, 2004; Vol 1, pp 307-322.
56. (a) Denmark, S. E.; Wynn, T. *J. Am. Chem. Soc.* **2001**, *123*, 6199. (b) Evans, D. A.; Sweeney, Z. K.; Rovis, T.; Tedrow, J. S. *J. Am. Chem. Soc.* **2001**, *123*, 12095. (c) Reddy, L. R.; Gais, H.-J.; Woo, C.-W.; Raabe, G. *J. Am. Chem. Soc.* **2002**, *124*, 10427. (d) Miao, W.; Chung, L. W.; Wu, Y. D.; Chan, T. H. *J. Am. Chem. Soc.* **2004**, *126*, 13326.
57. Hirashita, T.; Kambe, S.; Tsuji, H.; Omori, H.; Araki, S. *J. Org. Chem.* **2004**, *69*, 5054.
58. (a) Ranu, B. C.; Majee, A. *Chem. Commun.* **1997**, 1225. (b) Fujiwara, N.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 2318. (c) Fujiwara, N.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 4095.
59. (a) Nair, V.; Ros, S.; Jayan, C. N.; Pillai, B. S. *Tetrahedron* **2004**, *60*, 1959. (b) Yamaguchi M. In *Main Group Metals in Organic Synthesis*; Yamamoto, H.; Oshima, K., Eds.; Wiley-VCH: Weinheim, 2004; Vol 1, pp 307-322. (c) Andrew, P. C.; Peatt, A. C.; Raston, C. L. *Tetrahedron Lett.* **2004**, *45*, 243.
60. Takai, K.; Ikawa, Y. *Org. Lett.* **2002**, *4*, 1727.
61. Lee, P. H.; Kim, H.; Lee, K. *Adv. Synth. Catal.* **2005**, *347*, 1219.
62. (a) Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841. (b) Negishi, E. *Pure Appl. Chem.* **1981**, *53*, 2333. (c) Oppolzer, W. *Angew. Chem. Int. Ed.* **1989**, *28*, 38. (d) Knochel, P. *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol 4, p 865. (e) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (f) Knochel, P. *Comprehensive Organometallic Chemistry II*; Able, E. W.; Stone, F. G. A.;

Wilkinson, G., Eds.; Pergamon Press: Oxford, 1995; Vol 11, p 159.
63. (a) Chatani, N.; Amishiro, N.; Morii, T.; Yamashita, T.; Murai, S. *J. Org. Chem.* **1995**, *60*, 1834. (b) Takai, K.; Yamada, M.; Odaka, H.; Utimoto, K.; Fujii, T.; Furukawa, I. *Chem. Lett.* **1995**, 315. (c) Yeon, S. H.; Han, J. S.; Hong, E.; Do, Y.; Jung, I. N. *J. Organomet. Chem.* **1995**, *499*, 159. (d) Asao, N.; Matsukawa, Y.; Yamamoto, Y. *Chem. Commun.* **1996**, 1513. (e) Asao, N.; Yoshikawa, E.; Yamamoto, Y. *J. Org. Chem.* **1996**, *61*, 4874.
64. (a) Araki, S.; Ito, H.; Butsugan, Y. *Appl. Organomet. Chem.* **1988**, *2*, 475. (b) Yamaguchi, M.; Sotokawa, T.; Hirama, M. *Chem. Commun.* **1997**, 743. (c) Tsuji, T.; Usugi, S.-I.; Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K. *Chem. Lett.* **2002**, 2. (d) Nair, V.; Ros, S.; Jayan, C. N.; Pillai, B. S. *Tetrahedron* **2004**, *60*, 1959. (e) Yamaguchi, M. *Main Group Metals in Organic Synthesis*; Yamamoto, H.; Oshima, K., Eds.; Wiley-VCH: Weinheim, 2004; Vol 1, pp 307-322. (f) Andrew, P. C.; Peatt, A. C.; Raston, C. L. *Tetrahedron Lett.* **2004**, *45*, 243.
65. Lee, P. H.; Heo, Y.; Seomoon, D.; Kim, S.; Lee, K. *Chem. Commun.* **2005**, 1874.