

# Ligand effects in selective addition reactions of organoindium reagents with carbonyl compounds<sup>1</sup>

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## Abstract

The reaction of the allyl indium sesquibromide  $(\text{CH}_2=\text{CHCH}_2)_3\text{In}_2\text{Br}_3$  with four equivalents of a bulky lithium alkoxide  $(\text{CH}_3)_3\text{COLi}$  or  $(\text{CH}_3)_3\text{CCH}_2\text{OLi}$  results in modified reagents which show unusual degrees of chemo- and stereoselectivity in reactions with carbonyl compounds. For example, in reactions with cyclohexanone derivatives, 84–93% equatorial attack with preferential formation of the axial alcohols is observed. Chiral aldehydes react in a highly diastereoselective manner. © 1997 Elsevier Science S.A.

*Keywords:* Allylindium reagents; Ligand tuning; Stereoselectivity; Chemoselectivity

## 1. Introduction

Organolithium compounds are the largest class of organometallic reagents used in organic chemistry, ranging from methyllithium to species containing additional functionality (e.g. lithiated nitriles, sulfones, sulfonides, ketones, heterocycles) [1]. The reagents are used in a variety of C–C bond forming reactions, including Grignard-type and aldol additions as well as alkylation reactions. If chemo-, regio- or stereoselectivity is insufficient, transmetalation using a transition metal salt may lead to improvements (metal tuning). We first illustrated this simple principle using titanating agents  $\text{CITiL}_3$  ( $\text{L} = \text{Cl}, \text{OR}, \text{NR}_2$ ) in a wide variety of selective C–C bond forming reactions [2]. Since the ligands L at titanium can be varied at will, a second simple parameter can be adjusted to maximize chemo- and stereoselectivity (ligand tuning), i.e. ligand effects can be introduced into ‘carbanion’ chemistry [2,3]. Since certain synthetic limitations arose, other metal salts were tested in similar stoichiometric reactions (e.g. Zr [4], Ce [5], Cr [6], Fe [7], Yt [8]). Although successful in

a number of cases, ligand effects [3] were seldom studied. This is surprising, since ligand tuning within the above context is such a useful instrument for the practicing organic chemist [2,3,9].

Interest in organoindium reagents [10] in organic chemistry is increasing, especially since the recent discovery that unusual solvents such as water are sometimes compatible with these organometallic reagents [11]. However, essentially nothing is known concerning ligand effects in the addition of organoindium reagents to carbonyl compounds. Here we report our initial efforts in this field using allyl derivatives of In(III) reagents bearing different ligands at the metal. Presently the focus is on applications in synthetic organic chemistry and not on the structure of the reagents prepared in situ.

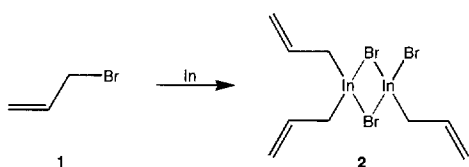
## 2. In situ generation and reactions of allylindium reagents

Rather than transmetalating allyllithium with In(III) salts, allyl bromide **1** was first reacted with indium powder with formation of the structurally not well defined allylindium sesquibromide **2** [12]. Accordingly, a suspension of indium in dry THF was reacted with **1**

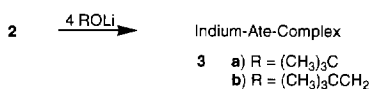
<sup>\*</sup> Corresponding author.

<sup>1</sup> Dedicated to Professor Dr. Gottfried Huttner on the occasion of his 60th birthday.

at room temperature, leading to an exothermic process and dissolution of the metal within 0.5 h.



Compound **2** offers the opportunity to study ligand effects. Since it was known that it reacts with alkyl-lithium reagents to form ate complexes [13], lithium alkoxides were used in the present study to modify the reagent [14]. In doing so, four equivalents of ROLi were added to the THF solution of **2** with formation of ate complexes **3**. No attempt was made to characterize the modified reagents.



The first model reaction to be studied was the diastereoselective addition to 4-*tert*-butylcyclohexanone **4** with formation of a mixture of the axial and equatorial alcohol **5** and **6** respectively. Table 1 summarizes the results and includes previous data concerning other allylmetal reagents [15]. Whereas allylmagnesium bromide reacts essentially stereorandomly (**5:6** = 45:55), all of the indium reagents show a preference for the axial alcohol via equatorial attack. Upon going from **2** to **3b** the ratio of diastereomers **5:6** increases from 82:18 to 90:10. This is the highest selectivity in favor of the axial alcohol **5** known to date. The result is of synthetic significance, especially in view of the fact that the allyltitanium reagent CH<sub>2</sub>=CHCH<sub>2</sub>Ti(NEt<sub>2</sub>)<sub>3</sub> results in the reversal of diastereoselectivity (**5:6** = 20:80) [15]. The methods are thus synthetically complementary. The reason for the switch in diastereoselectivity is not easily pin-pointed. Axial attack leading to the equatorial alcohol **6** is believed to be hindered by 1,3-diaxial interactions with bulky reagents [16]. This may be the

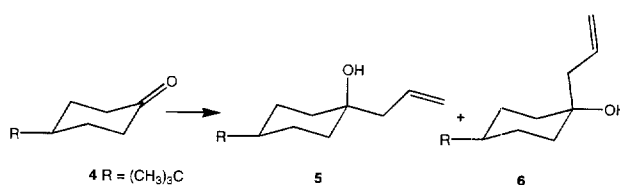
Table 1  
Stereoselective addition of allylmetal reagents to ketone **4**

Reagent	Conversion <sup>a</sup> (%)	<b>5:6</b>
CH <sub>2</sub> =CHCH <sub>2</sub> MgCl	> 90	45:55
CH <sub>2</sub> =CHCH <sub>2</sub> Ti(NEt <sub>2</sub> ) <sub>3</sub>	> 95	20:80
<b>2</b>	85	82:18
<b>3a</b>	80	80:20
<b>3b</b>	99 <sup>b</sup>	90:10

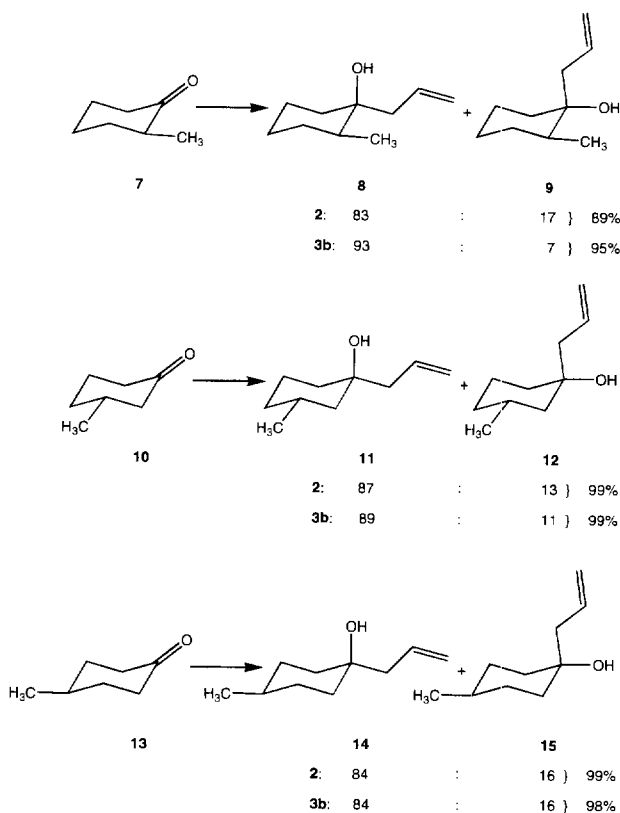
<sup>a</sup> Determined by GC analysis.

<sup>b</sup> Yield of isolated product on preparative scale: 85% [14].

case in the indium reagents, especially in the reaction of **3b**.

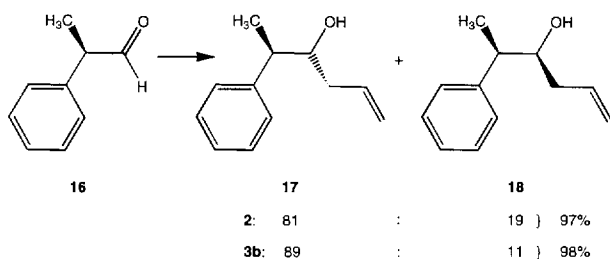


Preferential equatorial attack was also observed in the case of the methyl-substituted substrates **7**, **10** and **13**. Other allylmetal reagents also show a preference for equatorial attack, but the degree of diastereoselectivity is lower [16].

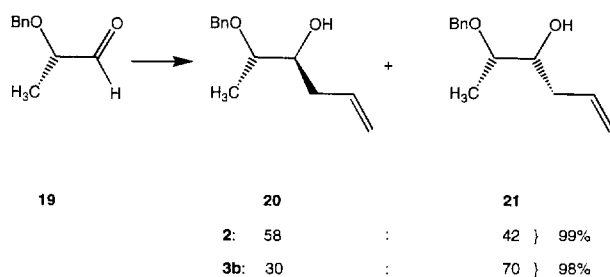


In a model reaction designed to test Cram-selectivity [17], 2-phenylpropanal **16** was reacted with the indium reagents. The addition of allyl metal reagents to **16** is known to be difficult in a diastereoselective manner [15,18]. For example, CH<sub>2</sub>=CHCH<sub>2</sub>MgX delivers a 2:1 ratio of the Cram and anti-Cram products [15,18]. The addition of CH<sub>2</sub>=CHCH<sub>2</sub>Ti(NEt<sub>2</sub>)<sub>3</sub> leads to a 93:7 product ratio, albeit at -120 °C [15]. Thus, the 89% Cram-selectivity achieved in the present study using reagent **3b** at a more convenient temperature (-78 °C

→ + 22 °C) is an acceptable synthetic result. Here again, modification of **2** by alkoxy ligands increases selectivity.

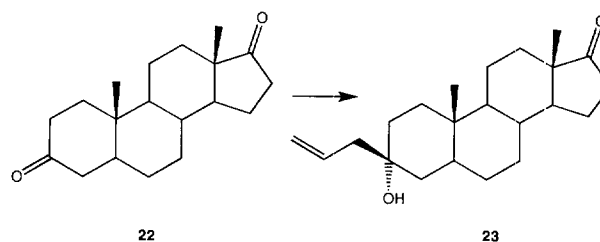


The problem of chelation vs. non-chelation control is relevant in the case of chiral alkoxy aldehydes such as **19** [19]. Whereas chelation control is fairly easy to achieve using the proper Lewis acidic reagents (e.g.  $\text{TiCl}_4/\text{CH}_2=\text{CHCH}_2\text{SiMe}_3$ ) [19,20], non-chelation control remains a challenge. Classical reagents such as  $\text{CH}_2=\text{CHCH}_2\text{MgX}$  or  $\text{CH}_2=\text{CHCH}_2\text{Li}$  react essentially stereorandomly. In the present case the direction of diastereoselectivity is ligand-dependent. **2** shows a slight preference for chelation control, whereas **3b** results in 70% non-chelation control in favor of adduct **21**. Apparently, the more basic reagent prefers not to form intermediate Cram-chelates with the substrate **19**. It is interesting to compare these results with those of Paquette and Mitzel [21], who reacted similar chiral  $\alpha$ -alkoxy aldehydes with an allylindium reagent prepared from indium powder and allyl bromide in water. In this reaction medium the carbonyl addition reactions proceed with 60–79% non-chelation control.



All of the allylindium reagents (**2**, **3a,b**) react > 99% aldehyde-selectively in the presence of ketone functionality [14]. A greater challenge is the chemo- and stereoselective addition to diketones such as androstane **22**. Whereas  $\text{CH}_2=\text{CHCH}_2\text{MgCl}$  is known to attack the two ketone sites indiscriminately, the titanium ate complex  $\text{CH}_2=\text{CHCH}_2\text{Ti}(\text{OiPr})_4\text{MgCl}$  reacts solely at

the 3-position, although in a non-stereoselective manner (53:47 diastereomer mixture) [22]. In the present study, reagent **3b** turned out to be 100% chemoselective, diastereoselectivity amounting to 86% in favor of the axial alcohol **23**. Thus, reagent **3b** is superior to other allyl metal compounds tested in this situation. It is likely that this reagent behaves chemoselectively in reactions with other diketones having two different carbonyl sites.



In summary, allylindium compounds are useful chemo- and stereoselective reagents in carbonyl addition reactions. Modification of the sesquibromide **2** by bulky alkoxy ligands increases selectivity. The results demonstrate that studies directed toward metal and ligand tuning in stoichiometric reactions with carbonyl compounds constitute a rewarding task. Investigations concerning the structure of the ligand-modified reagents remain to be carried out.

### 3. Experimental part

#### 3.1. General remarks

All reactions were carried out in dry flasks under an atmosphere of argon. THF was dried according to standard procedures and distilled from magnesium anthracene. For the purpose of product identification, all relevant compounds were prepared by independent syntheses according to known literature procedures. Diastereomer ratios were determined by standard gas chromatography using a Siemens Sichromat instrument (30 m CW20M or 25 m SE-54 columns, 100–230 °C) in the Department for Chromatography of the Max-Planck-Institut für Kohlenforschung. All chiral carbonyl compounds were used in racemic forms; for simplicity only one enantiomeric form is shown.

#### 3.2. Typical procedure for reagent preparation

To a stirred suspension of 230 mg (2 mmol) indium powder (Aldrich) in 2 ml THF is added via a syringe

362 mg (3 mmol; 260  $\mu$ l) allyl bromide. The indium metal is consumed within 0.5 h in an exothermic reaction, affording a slightly cloudy solution of the sesquibromide **2** which is diluted with 5 ml of THF and cooled to  $-78^\circ\text{C}$ . This solution can be used for carbonyl addition reactions (see below). For alkoxy ligand modification, the solution of 4 mmol of the relevant alcohol (*tert*-butyl or neopentyl alcohol) in 5 ml of THF is first treated with 4 mmol of *n*-butyllithium in a separate flask at  $0^\circ\text{C}$  for 20 min. The lithium alkoxide solution is then transferred to the above solution of the sesquibromide **2** using a steel cannula, resulting in an exothermic reaction. The mixture is stirred for 30 min.

### 3.3. Typical procedure for carbonyl addition reactions

To the allylindium reagents described above is added dropwise a carbonyl compound (2 mmol) in 1 ml of THF at  $-78^\circ\text{C}$ , the mixture being stirred with a magnetic stirrer. After 4 h at  $-78^\circ\text{C}$  the temperature is gradually allowed to reach room temperature and after 14 h the reaction is terminated by treatment with 2 ml of saturated aqueous  $\text{NH}_4\text{Cl}$  solution and diluted with 20 ml of ether. The organic phase is shaken with 20 ml of saturated aqueous  $\text{NaHCO}_3$  solution and the combined aqueous phases are extracted twice with 15 ml of ether. The combined organic phases are washed with 10% aqueous citric acid solution and with  $\text{H}_2\text{O}$ , and finally dried over  $\text{MgSO}_4$ . The mixtures are then analyzed by gas chromatography.

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