Regioselective Addition Reactions of the Organoindium Reagents onto α,β-Unsaturated Ketones†

Phil Ho Lee,* Hyun Kim, Kooyeon Lee, Dong Seomoon, Sundae Kim, Heechul Kim, Hyunseok Kim, Miae Lee, Eunkyong Shim, Seokju Lee, Misook Kim, Mijeong Han, Kwanghyun Noh, and Madabhushi Sridhar

Department of Chemistry, Kangwon National University, Chunchon 200-701, Korea
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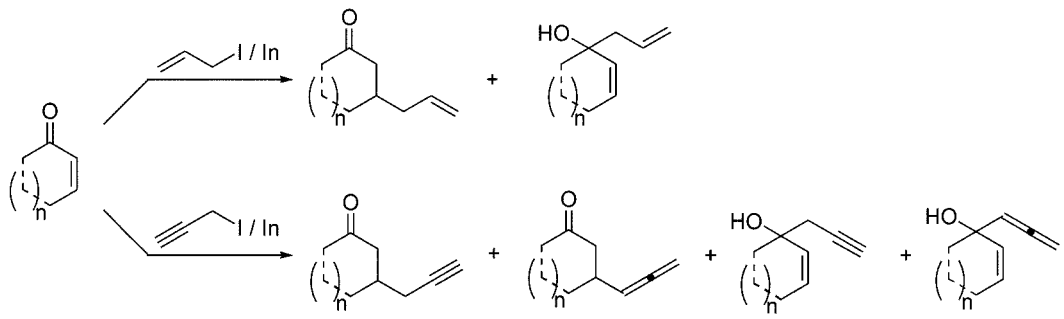
Regioselectivity on the reactions of α,β-enones with organoindium such as *in situ* generated allylindium and allenylindium was systematically studied in the presence of TMSCl as an additive. Treatment of 2-cyclohexen-1-one, carvone, 2-cyclohepten-1-one, and chalcone with allylindium reagent produced 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 1,2-addition products. Indium reagent derived from indium and propargyl bromide in Grignard type gave addition products in good yields, under which the successive addition of α,β-enone and TMSCl were necessary. Although organoindium reagent derived from propargyl bromide produced propargylated compound in Grignard type except 2-cyclohepten-1-one, indium reagent obtained from 1-bromo-2-butyne having γ-methyl group gave allenylated product in Barbier type.

Key Words : Regioselectivity, Conjugate addition, Allylindium, Allenylindium, Additive

Introduction

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 an additive such as copper halides.[1] Our interest in extending the scope of the Michael addition reaction and subsequent application of indium to organic reaction[2] has led us to investigate 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.[3] Reaction of 4-phenyl-3-buten-2-one, which is an unique example of an α,β-enone, with allylindiums regioselectively produced 1,2-addition product.[3] However, there are few reports on the Michael addition reaction of α,β-enones with organoindium reagents.[4] Recently, it was reported that In-mediated allylation to 1,1-dicyano-2-arylethenes gave 1,4-addition products in aqueous media with good yields.[4b] Tetraorganoindate complexes reacted with α,β-enones in a 1,4-addition mode.[4a] The reaction of organoindium reagents with α,β-unsaturated carbonyl compounds, in which two electron withdrawing groups were attached to alkenes, proceeded in a 1,2-addition mode, whereas a 1,4-addition reaction took place with 1,1-dicyano-2-arylethenes, which are extremely electron deficient olefins.[4c] Although a variety of examples of the nucleophilic addition of organoindium reagents to aldehydes and ketones have been reported.[5] regioselectivity of the reaction of the organoindium reagents with α,β-enones was not systematically studied.[4d] Recently, In-mediated propargylation and allenylation to carbonyl compounds were reported.[6] 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 is no example on the In-mediated β-propargylation to α,β-enones.[7] As part of our continuing effort to expand the synthetic utility of indium, we have conducted a systematic investigation on the



Scheme 1

†This paper is dedicated to Professor Yong Hae Kim for his outstanding achievements in organic chemistry.
*Corresponding Author. e-mail: phlee@kangwon.ac.kr

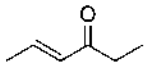
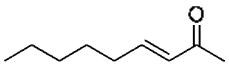
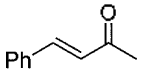
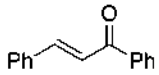
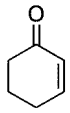
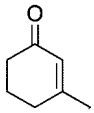
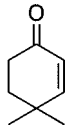
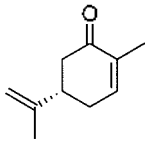
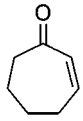
regioselectivity of the organoindium reagents with α,β-enones. The organoindium reagents including allylindium and propargylindium were generated *in situ* (Scheme 1).

Results and Discussion

Reaction of α,β-Enones with *In Situ* Generated Allylindium from Indium and Allyl Iodide. Initial studies were performed with the reaction of 2-cyclohexen-1-one with allylindium. Table 1 summarizes the experimental results and illustrates the efficiency and scope of the present method. The reaction of 2-cyclohexen-1-one occurred regioselectively with allylindium derived from indium and allyl iodide to produce 1,2-addition product in 60% yield (entry 7). Although the catalytic amount of copper iodide was used as an additive, 1,4-addition product was not produced. However, when the catalytic amount of copper iodide in the presence of TMSCl was added, silyl enol ether of 3-allylcyclohexanone was obtained in 44% yield by 1,4-addition of allylindium followed by enolate trapping. Moreover, 2-cyclohexen-1-one was treated with allylindium in the presence of 5 equiv of TMSCl to give 3-allylcyclohexanone in 63% yield. In case of 2-cyclopenten-1-one, 1,2-addition product was afforded in 54% yield even in the presence TMSCl (entry 5). With these results in hands, we could know that reactivity of allylindium is lower than allyl cuprates or Grignard reagents. Subjecting carvone or 2-cyclohepten-1-one to allylindium in the presence of TMSCl gave 1,4-addition products in 70 and 61% yields, respectively (entries 10 and 11), while 2-methylcyclopenten-1-one and 4,4-dimethyl-2-cyclohexen-1-one produced 1,2-addition products even though TMSCl was added (entries 6 and 9). 3-Methyl-2-cyclohexen-1-one did not react with allylindium in the presence of 1 equiv of TMSCl due to steric effect. Increasing amount of TMSCl (5 equiv) yielded a complex mixture of products (entry 8). We next turned our attention to acyclic α,β-enones. Although TMSCl was used as an additive, 1,4-addition products were not obtained but 1,2-addition products were produced in good yields (entries 1, 2 and 3). When TMSCl was used as an additive, yield of 1,2-addition product was increased (entry 2). However, treatment of chalcone with allylindium in the presence of 5 equiv of TMSCl gave the 1,4-addition product in 75% yield (entry 4).

Reaction of α,β-Enones with *In Situ* Generated Organoindium from Indium and Propargyl Bromide. On the bases of allylation results, we studied reaction of 2-cyclohexen-1-one with *in situ* generated organoindium reagent derived from propargyl bromide and indium in the presence of TMSCl. The results are summarized in Table 2. THF was the solvent of choice among the reaction media tested (THF, Et_2O, DME and DMF). Treatment of organoindium reagent with a solution of α,β-enone and TMSCl in THF at 25 °C gave addition product (**1** : **2** = 9 : 1) in 56% yield (entry 1). Reaction proceeded regioselectively to give propargylation product **1** in 45% and 30% yields at 0 °C and −50 °C, respectively (entries 2 and 3). The successive addition of TMSCl and α,β-enone to organoindium reagent gave the desired product (**1** : **2** = 16 : 1) in 68% yield (entry 8). Although addition reaction in Barbier type[8] using 1 equiv of indium and 1.5 equiv of propargyl bromide gave addition products in 49% yield in the presence of 5 equiv of TMSCl (entry 7). 3-propargylcyclohexanone and 3-allenylcyclohexanone were regioselectively obtained in 64% and 4% yields, respectively, in Grignard type[9] at

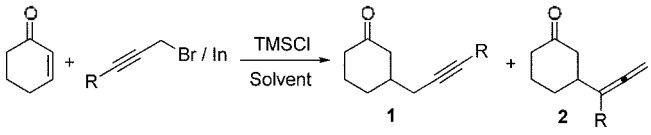
Table 1. Reactions of allylindium with α,β-enones

Entry	α,β-Enone	Conditions[a]	Time (h)	Isolated Yield (%)	
				1, 4	**1, 2**
1		A	0.5		73
		B	0.5		77
2		C		0[b]	
		A[c]	0.5		60
		A	0.5		80
3		A	0.5		61
4		C	0.5		42(25)[d]
		D	0.5	75	
5		A	0.5		54
6		A	0.5		62
7		B/0.1 equiv CuI	1.0	44[e]	
		B[c]/0.1 equiv CuI	1.0		60
		C	0.5	63	
		A[c]	0.5		60
		A	0.5	55	
8		D	24	0[b]	
9		A	0.5		54
10		D	0.5	70 (1.4 : 1)[f]	
11		C	0.5	61	

[a]Stoichiometry of indium, allyl iodide and TMSCl (In : allyl iodide : TMSCl) : A = 2 : 3 : 1, B = 1 : 1.5 : 1, C = 1 : 1.5 : 5, D = 2 : 3 : 5. [b]Messy. [c]TMSCl was not used. [d]The recovered yield of starting material. [e]Silyl enol ether of 3-allylcyclohexanone. [f]The diastereomeric ratio.

25 °C (entry 8). Of the conditions screened, the best results were obtained with organoindium reagent derived from 2 equiv of indium and 3 equiv of propargyl bromide in Grignard type in the presence of 5 equiv of TMSCl at 25 °C, under which 3-propargylcyclohexanone and 3-allenylcyclohexanone were regioselectively obtained in 75% and 6% yields, respectively (entry 10). In case of 1-bromo-2-butyne, *in situ* generated organoindium reagent reacted with 2-cyclohexen-1-one to afford regioselectively 3-(1'-methylallenyl)cyclohexanone in 82% yield in Barbier type (entry 13). However, this reaction did not proceed in Grignard type with LiI used as an additive (entry 11).

Table 2. Reaction optimization

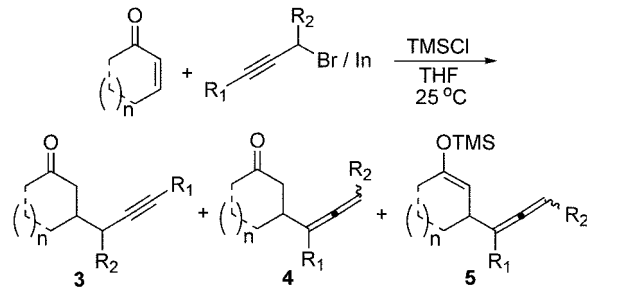


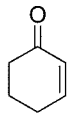
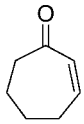
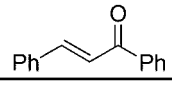
Entry	R	Solvent	Temp (°C)	Isolated Yield (%)[a]
1[b]	H	THF	25	56(9:1)
2[b]	H	THF	0 → 25	45(100:0)
3[b]	H	THF	−50 → 25	30(100:0)
4[b]	H	Et_2O	25	0
5[b]	H	DME	25	0
6[b]	H	DME	25	0
7[c,d]	H	THF	25	49(9:1)
8[c]	H	THF	25	68(16:1)
9[c]	H	THF	25	75[e](18:1)
10[c]	H	THF	25	81[f](13:1)
11[c]	CH_3	THF	25	0[g]
12[c,d]	CH_3	THF	25	73(0:100)
13[c,d]	CH_3	THF	25	82[f](0:100)

[a]Reaction performed in Grignard type in the presence of 1.0 equiv of In, 1.5 equiv of propargyl bromide and 5.0 equiv of TMSCl, unless otherwise noted. Numbers in parentheses are ratio of **1** to **2**. [b]Solution of α,β-enone and TMSCl in solvent were added to indium reagent. [c]α,β-Enone and TMSCl were successively added to a solution of indium reagent. [d]This reaction proceeded as Barbier type reaction. [e]1.5 equiv of In and 2.3 equiv of propargyl bromide were used. [f]2.0 equiv of In and 3.0 equiv of propargyl bromide were used. [g]3 equiv of LiI was used.

With these results in hand, 2-cyclopenten-1-one reacted with organoindium reagent derived from propargyl bromide and indium to give **3** in 49% yield as a major compound (entry 1 in Table 3). When 1-bromo-2-butyne was used, allenylation product **4** was selectively obtained in 37% yield (entry 2). In case of 2-cyclohexen-1-one, no reaction occurred with organoindium reagent derived from 3-bromo-1-butyne having methyl group at α-position (entry 5). 2-Cyclohepten-1-one was treated with organoindium reagent to produce trimethylsilyl enol ether of 3-allenylcycloheptanone in 42% yield in the presence of 2 equiv of TMSCl (entry 6). The use of 5 equiv of TMSCl resulted in messy results. Subjecting chalcone to organoindium reagent gave trimethylsilyl enol ether of 1,3-diphenyl-3-propargyl-1-propanone in 45% yield (entry 7).

Table 3. Reactions of organoindium with α,β-enones



Entry	α,β-Enone	R_1	R_2	Isolated Yield[a] (**3** : **4** : **5**)
1		H	H	49 (11 : 1 : 0)
2[b]		CH_3	H	37 (0 : 1 : 0)
3		H	H	81 (13 : 1 : 0)
4[b]		CH_3	H	82 (0 : 1 : 0)
5		H	CH_3	0
6		H	H	42[c] (0 : 0 : 1)
7		H	H	45[c] (1[d] : 0 : 0)

[a]Reaction performed in the presence of 2.0 equiv of in, 3.0 equiv of propargyl bromide and 5.0 equiv of TMSCl, unless otherwise noted. Numbers in parentheses are ratio of **3**, **4** and **5**. This reaction proceeded as Grignard type reaction. [b]The reaction proceeded as Barbier type reaction. [c]2 equiv of TMSCl was used. [d]Enol silyl ether of ketone was obtained.

In summary, regioselectivity of the reactions of α,β-enones with allylindium reagents was systematically studied in the presence of TMSCl. Ketones such as 2-cyclohexen-1-one, carvone, 2-cycloheptен-1-one and chalcone produced 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 1,2-addition products. Use of TMSCl as an additive caused an increase in yields of addition products. However, excess of TMSCl gave complex mixture of products. Indium reagent derived from 2 equiv of indium and 3 equiv of propargyl bromide in Grignard type gave addition products in good yields, under which the successive addition of TMSCl and enone were necessary. Although organoindium reagent derived from propargyl bromide and indium gave propargylation product except 2-cyclohepten-1-one, organoindium reagent obtained from 1-bromo-2-butyne having γ-methyl group gave allenylation product. Generally, organoindium reagent afforded the desired compound in good yields in Grignard type, while organoindium reagent from 1-bromo-2-butyne having γ-methyl group yielded better results in Barbier type rather than in Grignard type. Although role of TMSCl is not completely understood, it may be explainable in terms of Lewis acidity which activates carbonyl groups.

Experimental Section

Typical Procedure for Addition Reaction Using Allylindium Reagent. To a solution of indium [indium powder (99.99%) purchased from Aldrich Chemical Co.: 115 mg, 1.0 mmol] in THF (3 mL) was added allyl iodide (252.0 mg, 1.5 mmol) under a nitrogen atmosphere at room temperature. After stirred for 1 h, 2-cyclohexen-1-one (96.0 mg, 1.0 mmol) and chlorotrimethylsilane (543.0 mg, 5.0 mmol) was successively added to reaction mixture. After 30 min, the reaction mixture was poured into pH 8.0 buffer solution (10 mL, Na_2HPO_4/NaH_2PO_4) which was pre-cooled at 0 °C. The aqueous layer was extracted with ether (3 × 25 mL) and the combined organic layers were washed with water (20 mL), brine (20 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 20/1) leading to 3-allylcyclohexanone (87 mg, 63%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (ddt, J = 17.83, 10.87, 7.22 Hz, 1H), 5.04 (d, J = 17.83 Hz, 1H), 5.04 (d, J = 10.87 Hz, 1H), 2.44-2.25 (m, 3H), 2.12-1.83 (m, 6H), 1.67-1.60 (m, 1H), 1.41-1.34 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.61, 135.60, 116.70, 47.64, 41.30, 40.71, 38.67, 30.78, 25.05 ppm; IR (film) 3020, 2960, 2900, 1680, 1430, 1410 cm^{-1}; HRMS (EI) calcd for $C_9H_{15}O$ $[M+H]^+$ 139.1123, found 139.1118.

Typical Procedure for Addition Reaction Using Propargylindium Reagent in Grignard Type. To a solution of indium [indium powder (99.99%) purchased from Aldrich Chemical Co.: 230 mg, 2.0 mmol] in THF (3 mL) was added propargyl bromide (357.0 mg, 3.0 mmol) under a nitrogen atmosphere at room temperature. After stirred for 30 min, chlorotrimethylsilane (543.0 mg, 5.0 mmol) and 2-cyclohexen-1-one (96.0 mg, 1.0 mmol) was successively added to reaction mixture. After 2 h, the reaction mixture was poured into pH 7.0 buffer solution (10 mL, K_2HPO_4/KH_2PO_4) which was pre-cooled at 0 °C. The aqueous layer was extracted with ether (3 × 25 mL) and the combined organic layers were washed with water (20 mL), brine (20 mL), dried with $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10/1) leading to 3-propargylcyclohexanone (102 mg, 75%) and 3-allenylcyclohexanone (8 mg, 6%); 3-Propargylcyclohexanone; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.50-2.46 (m, 1H), 2.37-2.35 (m, 1H), 2.31-2.18 (m, 4H), 2.09-2.05 (m, 1H), 2.03 (t, J = 2.70 Hz, 1H), 2.02-1.95 (m, 2H), 1.72-162 (m, 1H), 1.59-1.48 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 211.06, 81.38, 70.49, 47.03, 41.09, 37.76, 30.28, 25.40, 24.86; IR (film): 3290, 2117, 1710 cm^{-1}; 3-Allenylcyclohexanone; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.15 (q, J = 6.28 Hz, 1H), 4.79 (dd, J = 6.71, 3.19 Hz, 2H), 2.51-2.44 (m, 1H), 2.38-2.20 (m, 4H), 2.09-2.04 (m, 1H), 1.99-1.94 (m, 1H), 1.73-1.68 (m, 1H), 1.54-1.48 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 211.02, 207.46, 93.96, 77.13, 47.09, 41.23, 37.12, 31.28, 24.71; IR (film): 2252, 1710, 752 cm^{-1}.

Typical Procedure for Addition Reaction Using Allenylindium Reagent in Barbier Type. To a solution of indium [indium powder (99.99%) purched from Aldrich Chemical Co.: 230 mg, 2.0 mmol] in THF (3 mL) was added 1-bromo-2-butyne (399.0 mg, 3.0 mmol) under a nitrogen atmosphere at room temperature. At once, chlorotrimethylsilane (543.0 mg, 5.0 mmol) and 2-cyclohexen-1-one (96.0 mg, 1.0 mmol) was successively added to reaction mixture. After 2 h, the reaction mixture was poured into pH 7.0 Buffer solution (10 mL, K_2HPO_4/KH_2PO_4) which was pre-cooled at 0 °C. The aqueous layer was extracted with ether (3 × 25 mL) and the combined organic layers were washed with water (20 mL), brine (20 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10/1) leading to 3-(1'-methylallenyl)cyclohexanone (123.2 mg, 82%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.70 (s, 2H), 2.49-2.45 (m, 1H), 2.36-2.30 (m, 2H), 2.27-2.23 (m, 2H), 2.08-1.99 (m, 2H), 1.71 (t, J = 3.13 Hz, 3H), 1.69-1.52 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 211.46, 205.55, 101.524, 76.26, 46.61, 41.36, 41.18, 29.86, 24.88, 17.14; IR (film): 2190, 1712, 750 cm^{-1}.

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8. Barbier type reaction: Propargyl halide and α,β-enone were successively added to a suspension of indium in solvent.
9. Grignard type reaction: After organoindium reagent was prepared from propargyl halide and indium, α,β-enones were added to a solution of organoindium reagent.