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First Nickel-Catalyzed 1,4-Conjugate Additions to α,*β*-Unsaturated Systems Using Triorganoindium Compounds

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Introduction

Organometallic 1,4-conjugate addition to enones is an important means of C−C bond formation in organic synthesis.[1] This reaction was once limited to organocopper chemistry, but now it has been known to be possible with other organometallic compounds through catalysis by metals, nickel especially.[2] In continuance of our research on new applications of organometallics to the 1,4-conjugate addition reaction and others,[3] we report herein a novel, efficient nickel-catalyzed conjugate addition of triorganoindium compounds to α,*β*-unsaturated systems.

Indium has drawn the attention of chemists for many years due to its position in the periodic table, in the same group as boron and aluminum and close to zinc and tin, and to its interesting chemical properties.[4] Nevertheless, the synthetic applications of organoindium compounds are few, are relatively recent,[4] and are limited to (i) the allylation of carbonyls and triple bonds under classical[5] or Barbier conditions (mostly in aqueous media)[6] and (ii) Reformatsky-type reactions.[7] Alkyl organoindium species, as far as we know, have only been used in cross-coupling reactions with chloroalkenes.[8]

Scheme 1

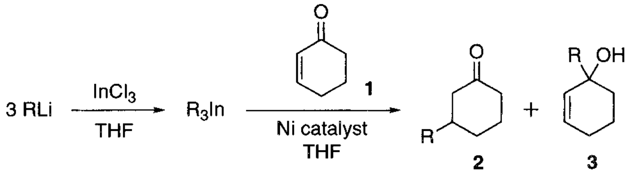

Table 1. Effects of Nickel Complexes on the Conjugate Addition of *n*-Bu$_3$In to 2-Cyclohexen-1-one

		yield (%)[a]		
entry no.	catalyst	**2**[b]	**3**[b]	**1**
1	no catalyst		10	80
2	$Ni(PPh_3)_2Cl_2$	13		80
3	$Ni(acac)_2$	30		60
4	$Ni(PPh_3)_2Cl_2$/DIBALH[c]	16		75
5	$Ni(acac)_2$/DIBALH[d]			95
6	$Ni(PPh_3)_4$[e]	15		82
7	$Ni(COD)_2$[f]	80		

[a] Isolated yields. [b] R = *n*-Bu. [c] Reference 10a. [d] Reference 10b. [e] Reference 11. [f] Reference 12.

Results and Discussion

The 1,4-conjugate addition reaction of organoindium compounds has previously been studied by Araki et al., who reported that triorganoindium compounds are unreactive toward enones but that some tetraalkylindates add in a 1,4-fashion in moderate yields.[9] In our experiments the reactivity of triorganoindium compounds with enones was also low, giving <10% yields of the tertiary alcohol product of the 1,2-addition (Scheme 1); the main component of the reaction mixture was unreacted enone. We found, however, that the reaction is promoted by catalytic amounts of nickel complexes. Table 1 lists the results obtained with various different nickel complexes in the addition of tri-*n*-butylindium to 2-cyclohexen-1-one (**1**).

The commercially available nickel(II) catalysts $Ni(PPh_3)_2Cl_2$ and $Ni(acac)_2$ afforded the 1,4-addition product **2** in yields ≤30%. The results obtained with nickel(0) complexes depended on the source of the latter: when Ni(0) was generated in the reaction medium by reduction with DIBALH[10] (Table 1, entries 4 and 5), most of the enone was recovered and the yields of the 1,4-addition product were lower than 20%. $Ni(PPh_3)_4$[11] proved no better, but a yield of 80% was obtained with $Ni(COD)_2$.[12] The presence of additives such as trimeth-

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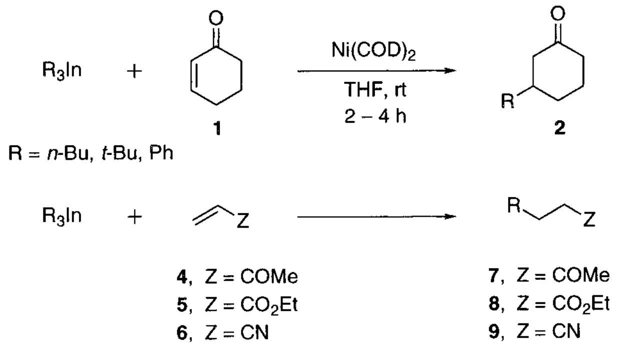
Table 2. Results of 1,4-Addition of Organoindium Compounds to α,β-Unsaturated Systems

entry no.	α,β-unsaturated syst	R in R_3In and product	product	yield (%)[a]
1	**1**	*n*-Bu	**2**	80
2	**4**	*n*-Bu	**7**	81
3	**5**	*n*-Bu	**8**	88
4	**6**	*n*-Bu	**9**	72
5	**1**	*t*-Bu	**2**	81
6	**4**	*t*-Bu	**7**	70
7	**5**	*t*-Bu	**8**	50
8	**1**	Ph	**2**	89
9	**4**	Ph	**7**	71
10	**5**	Ph	**8**	61

[a] Isolated yields.

Scheme 2



ylsilyl chloride[13] as well as the nickel catalyst did not improve the 1,4-addition in any case, the corresponding silyl enol ether being obtained without modification of the yield of 1,4-addition product.

To explore the scope of the reaction, we applied it to the addition of a variety of alkyl and aryl groups to various α,β-unsaturated systems. Since organocopper compounds have important limitations for the addition of tertiary and aryl groups to enones,[1b] these were the first reactions investigated. The organoindium compounds were prepared from commercially available organolithium compounds by transmetalation with $InCl_3$. We found that tri-*tert*-butylindium reacts efficiently with enones (Table 2, entries 5 and 6) under $Ni(COD)_2$ catalysis, affording the desired conjugate addition products in yields similar to these obtained with tri-*n*-butylindium. Triphenylindium (Table 2, entries 8 and 9) also reacted efficiently, under these conditions, affording the 1,4-addition products in good yields (71−89%).

In the presence of 10% of $Ni(COD)_2$, the reactions of tri-*n*-butylindium with ethyl acrylate (**5**) and acrylonitrile (**6**) in THF at room temperature also afforded the corresponding conjugate addition products in good yields (88% and 72% respectively; Scheme 2). Other organoindium compounds (t-Bu_3In and Ph_3In) afforded lower yields when reacted with ethyl acrylate (50% and 61%, respectively) but were nevertheless still more reactive than other organometallics toward these non-enone α,β-unsaturated systems.[1]

The mechanism of the reaction remains unclear. It has been suggested[14] that oxidative addition of a low-valent nickel species to an enone affords a π-allyl complex. Transfer of the group to be added from indium to nickel, followed by reductive elimination of the catalyst, would afford an indium enolate that would be protonated during workup.

In conclusion, we have developed a novel, efficient, nickel-catalyzed 1,4-conjugate addition of triorganoindium compounds to α,β-unsaturated systems. This method can be used as an alternative to the use of other organometallics to add both alkyl and aryl groups to a variety of α,β-unsaturated systems in good yields. The catalyst of choice is $Ni(COD)_2$. Studies of other applications of organoindium compounds in 1,4-conjugate addition and carbon−carbon bond-forming reactions are in progress.

Experimental Section

General Considerations. All reactions were conducted in flame-dried glassware under a positive pressure of argon. Tetrahydrofuran (THF) was dried by distillation from the sodium ketyl of benzophenone. Thin-layer chromatography was effected on silica gel 60 F_{254} (layer thickness 0.2 mm), and components were located by observation under UV light and/or by treatment of the plates with a phosphomolybdic acid reagent followed by heating. Flash chromatography was performed on silica gel 60 (230−400 mesh) by Still's method.[15] 2-Cyclohexen-1-one, methyl vinyl ketone, ethyl acrylate, acrylonitrile, and 1,5-cyclooctadiene were purified, immediately before use, by distillation at room temperature in a high-vacuum line and were trapped at −78 °C in a dry ice−acetone bath. Organolithium reagents and DIBALH were used after titration by known procedures.[16]

Nickel Complexes. $Ni(PPh_3)_4$ was prepared following the procedure of Negishi and Baba:[11] a 25 mL round-bottomed flask charged with a stir bar and $Ni(acac)_2$ (30 mg, 0.1 mmol) was dried under high vacuum with a heat gun. After the mixture was cooled and a positive argon pressure was established, dry THF (4 mL) and PPh_3 (110 mg, 0.4 mmol) were successively added. To the resulting light green solution was added a solution of DIBALH in toluene (0.070 mL, 0.1 mmol, 1.5 M) over a 10 min period, yielding a dark brown solution which was stirred for 1 h at room temperature and directly used.

$Ni(COD)_2$ was prepared according to the method of Krysan and Mackenzie:[12] a 10 mL round-bottomed flask with a stir bar charged with $Ni(acac)_2$ (26 mg, 0.1 mmol) was dried under high vacuum with a heat gun. After the mixture was cooled and a positive argon pressure was established, dry THF (2 mL) and 1,5-cyclooctadiene (0.050 mL, 0.4 mmol) were successively added. The resulting mixture was cooled to −78 °C, and a solution of DIBALH in toluene (0.170 mL, 0.25 mmol, 1.5 M) was slowly added over a 15 min period. The resulting reddish brown solution was stirred for 1 h at the same temperature and then stirred for 1 h at 0 °C and used immediately.

Other nickel complexes are available commercially and were used after drying over P_2O_5 overnight.

General Procedure for the Conjugate Addition Reaction. A 25 mL round-bottomed flask with a stir bar was charged with $InCl_3$ (1.3 mmol) and dried under vacuum with a heat gun. After the mixture was cooled and a positive argon pressure was established, dry THF (7 mL) was added. The resulting solution was cooled to −78 °C, and a solution of RLi (3.6 mmol, 1.0−2.5 M in hexanes or Et_2O) was slowly added (15−30 min). After the mixture was stirred for 30 min, the cooling bath was removed, the reaction mixture was warmed to room temperature, and a solution of the olefin (1 mmol) and $Ni(COD)_2$ (0.1 mmol) in dry THF (5 mL) was added. The resulting brown-black mixture was stirred for 2−4 h and the reaction quenched by addition of drops

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of MeOH. The mixture was concentrated in vacuo, and aqueous HCl (5%, 10 mL) was added. Extraction with Et_2O (2 × 15 mL) gave an organic phase which was washed with saturated aqueous $NaHCO_3$ (15 mL) and brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography to afford, after concentration and high-vacuum drying, the conjugate addition product in 50−89% yield as a colorless liquid.

Compounds Prepared. The products prepared are already known: 3-*n*-butylcyclohexanone (**2**, R = *n*-Bu),[17] 3-*tert*-butylcyclohexanone (**2**, R = *t*-Bu),[17] 5,5-dimethyl-2-hexanone (**7**, R = *t*-Bu),[18] ethyl 4,4-dimethylpentanoate (**8**, R = *t*-Bu),[19] 3-phenylcyclohexanone (**2**, R = Ph),[20] ethyl 3-phenylpropanoate (**8**, R = Ph).[21] 2-Octanone (**7**, R = *n*-Bu), ethyl heptanoate (**8**, R = *n*-Bu), heptanenitrile (**9**, R = *n*-Bu), and 4-phenyl-2-butanone (**7**, R = Ph) are commercially available.

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Supporting Information Available: Text giving NMR data and figures giving NMR spectra for the compounds prepared (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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