Regiocontrolled Addition of Carbonyl Compounds with Allylic Indium Generated by Hydroindation of 1,3-Dienes

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Received 30 January 2008

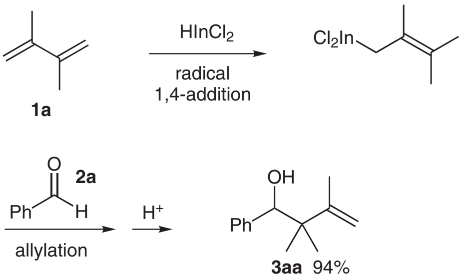
Abstract: Allylic indiums, generated by a conjugate hydroindation of 1,3-dienes by $HInCl_2$, reacted with carbonyl compounds in a one-pot treatment. Both γ- and α-adducts can be obtained depending upon the conditions used.

Key words: allylation, hydrides, indium, ketones, regioselectivity

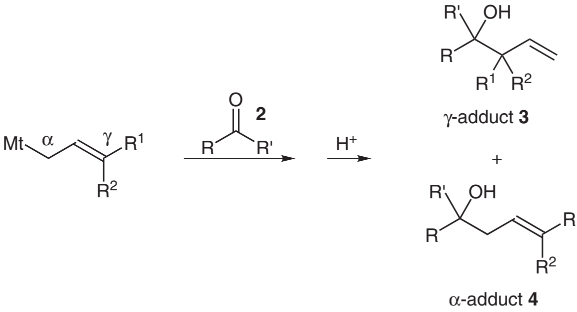
A great deal of attention has been paid to the generation of allylic metals and their reactions with various electrophiles.[1] In particular, the generation and reactions of polysubstituted allylic metals are an important subject, which can lead to tertiary or quaternary carbon centers. Transmetalation using allylic metals such as the Grignard reagent, however, is not appropriate because of low availability of the polysubstituted precursors.[1a,2] One of the practical method for the generation of polysubstituted allylic metals is the hydrometallation of 1,3-diene derivatives.[3] This method provides an atom-economical system and affords various allylic metal species. In this context, we recently reported the generation of allylic indiums by hydroindation of 1,3-dienes and their subsequent addition to carbonyl compounds and imines (Scheme 1).[4] This procedure has significant advantages in that it does not require a radical initiator for the radical pathway, nor a Lewis acid for the ionic reaction pathway. Allylic indium reagents also have been recognized because of their tolerance of water.[5]

The regioselective addition of substituted allylic metals to carbonyl compounds is very important for organic synthesis (Scheme 2). In general, γ-adducts **3** were predominantly obtained.[1] The selective synthesis of α-adducts **4** remains as a subject of current interest. Although there are some reports about α-adducts **4** in the addition to aldehydes, reactions using ketones as electrophiles are rare.[6,7]

Herein, we wish to report the regiocontrolled allylation of various ketones starting with the hydroindation of 1,3-dienes mediated by $HInCl_2$. Noteworthy is the fact that both γ- and α-adducts can be obtained depending on the conditions used. To the best of our knowledge, this is the first example of α-allylation resulting from hydrometallation of 1,3-dienes.



Scheme 1



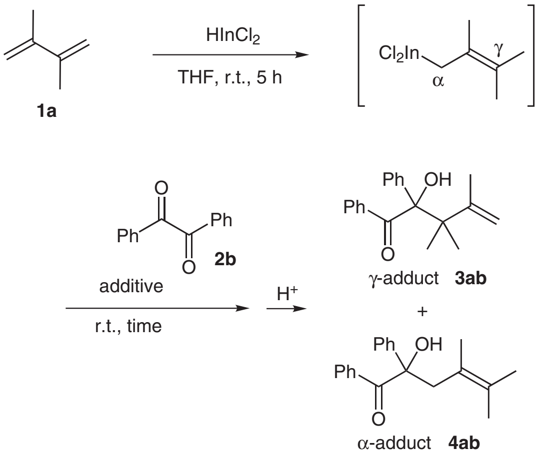
Scheme 2

Initially, the experiment focused on the allylation of benzil (**2b**), which has a higher reactivity than a simple ketone due to its electron-withdrawing group. To generate $HInCl_2$, the $InCl_3$–Bu_3SnH system was used.[8] After the reaction at room temperature for 14 hours, α-adduct **4ab** was obtained (Table 1, entry 1).[9,10] As we have previously reported,[4] no α-adducts had been obtained in the reaction of simple ketones. When the reaction period was reduced from 14 hours to three minutes and one minute, respectively, the formation of small amounts of γ-adduct **3ab** was detected (entries 2 and 3). These results suggest that the γ-adduct was transformed into the α-adduct under mild conditions. To obtain the γ-adduct **3ab**, the reaction was performed in the presence of a small amount of water which effectively trapped the generated indium alkoxide to give the desired γ-adduct **3ab** selectively in an 85% yield (entry 5). The addition of methanol instead of water gave only moderate yield (entry 4).

As regiocontrolled formation of γ- and α-adducts was achieved, we tried to expand to various carbonyl compounds under several conditions (Table 2). The reaction of methyl benzoylformate (**2c**) at room temperature gave

SYNLETT 2008, No. 9, pp 1407–1411
Advanced online publication: 07.05.2008
DOI: 10.1055/s-2008-1072753; Art ID: U00808ST

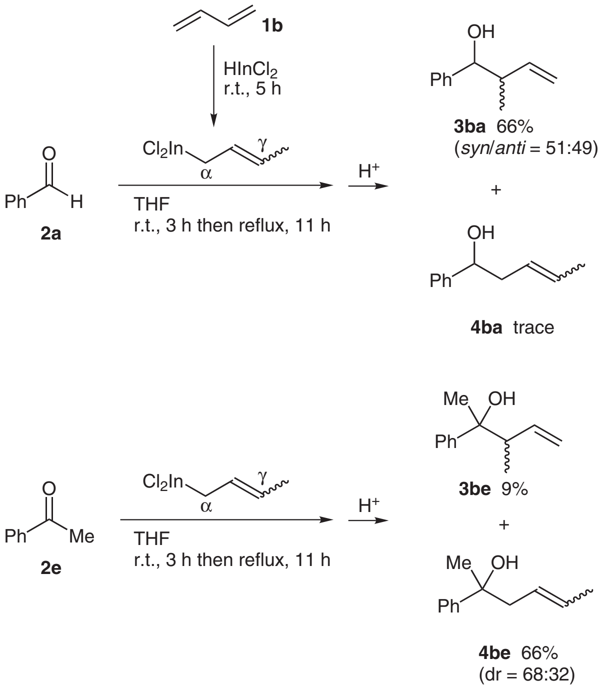
Table 1 Allylation of Benzil by 2,3-Dimethyl-1,3-butadiene and Effect of Additives[a]



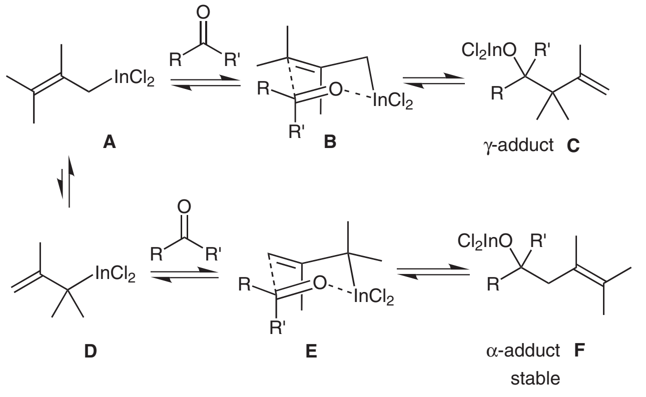
Entry	Time	Additive	Yield (%)	
			3ab	4ab
1	14 h	–	0	89
2	3 min	–	26	14
3	1 min	–	14	0
4	17 h	MeOH (2 mmol)	29	49
5	17 h	H_2O (2 mmol)	85	8

[a] $HInCl_2$ was generated by $InCl_3/Bu_3SnH$ system. Allylic indium was generated from the reaction of diene **1a** (4 mmol) with $HInCl_2$ (2 mmol) in THF (2 mL) at r.t. for 5 h. Benzil (**2b**, 1 mmol) was used.

only γ-adduct **3ac** in a quantitative yield (entry 1). After the reaction at room temperature, heating the mixture gave α-adduct **4ac** exclusively in 90% yield (entry 2). The reaction of 2-methoxyacetophenone (**2d**) afforded the both isomers, **3ad** and **4ad** in the similar treatment to the case of benzil (**2b**), thus the addition of water gave **3ad** (entries 3 and 4). A simple ketone, acetophenone (**2e**) also afforded α-adduct **4ae** in a 66% yield under heating conditions (entry 6). 2′-Methoxyacetophenone (**2f**), which is less electrophilic than acetophenone (**2e**), gave only 6% of γ-adduct at room temperature, and selectively produced α-adduct **4af** in 77% yield by heating (entries 7 and 8). The regiocontrolled addition to α-haloketone **2g** also was successful (entries 9 and 10). In contrast, in the case of 2-hydroxyacetophenone (**2h**), heating resulted in low yield of α-adduct **4ah** (entries 11 and 12). Aliphatic ketones showed somewhat lower reactivity; ketone **2i** gave γ- and α-adduct in 28% and 46% yields, respectively, and aliphatic diketone **2j** gave no α-adduct at all (entries 13–16). Interestingly, this procedure could be applied to aldehydes. Under the heating conditions, α-adducts **4aa** and **4ak** were obtained from **2a** and **2k**, respectively (entries 17–20). However, primary aliphatic aldehyde **2l** gave no α-adduct in which no transformation of γ-adduct took place even under heating conditions (entries 21 and 22).



Scheme 3 *Reagents and conditions*: $HInCl_2$ was generated by $InCl_3–Bu_3SnH$ system. Allylic indium was generated from the reaction of diene **1b** (4 mmol) with $HInCl_2$ (2 mmol) in THF (2 mL) at r.t. for 5 h. Carbonyl compound (1 mmol) was used.

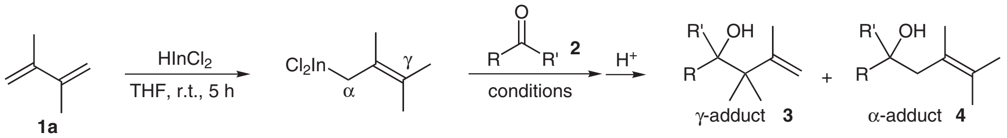


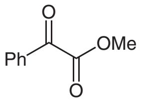
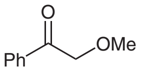
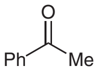
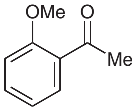
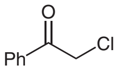
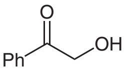
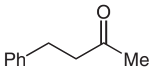
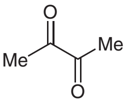
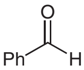
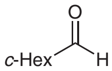
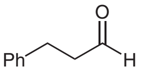
Scheme 4 A plausible mechanism of α-allylation

Next, allylation using 1,3-butadiene (**1b**) was examined. The reaction of benzaldehyde (**2a**) gave only γ-adduct **3ba** in 66% even under heating conditions (Scheme 3), while the reaction of acetophenone (**2e**) afforded the desired α-adduct **4be** in moderate yield.

On the basis of these results, a plausible reaction mechanism is shown in Scheme 4, in which all steps are in equilibrium.[7a] Initially, allylic indium **A** which is generated by conjugate hydroindation adds to the carbonyl compound at the γ-carbon to give kinetically controlled indium alkoxide **C** (γ-adduct). Then, thermodynamically stable α-adduct **F** is formed from the reaction with allylic indium **D**, which is generated via retroreaction from the γ-adduct **C** under the heating conditions. In the case of benzil (**2b**) and 2-methoxyacetophenone (**2d**), the fast retroreaction

Table 2 Regioselective Allylation Using 2,3-Dimethyl-1,3-butadiene[a]



Entry	Carbonyl compound		Conditions	Yield (%)			
				3		4	
1		**2c**	r.t., 3 h	**3ac**	>99	**4ac**	0
2		**2c**	r.t., 19 h then reflux, 3 h	**3ac**	0	**4ac**	90
3[b]		**2d**	r.t., 14 h	**3ad**	90	**4ad**	0
4		**2d**	r.t., 12 h	**3ad**	7	**4ad**	71
5[c]		**2e**	r.t., 16 h	**3ae**	50	**4ae**	0
6		**2e**	r.t., 3 h then reflux, 20 h	**3ae**	11	**4ae**	66
7		**2f**	r.t., 16 h	**3af**	6	**4af**	0
8		**2f**	r.t., 3 h then reflux, 14 h	**3af**	trace	**4af**	77
9[d]		**2g**	r.t., 13 h	**3ag**	69	**4ag**	0
10		**2g**	r.t., 16 h then reflux, 2 h	**3ag**	0	**4ag**	43
11		**2h**	r.t., 3 h	**3ah**	68	**4ah**	0
12		**2h**	r.t., 3 h then reflux, 3 h	**3ah**	0	**4ah**	12
13		**2i**	r.t., 16 h	**3ai**	28	**4ai**	0
14		**2i**	r.t., 3 h then reflux, 13 h	**3ai**	0	**4ai**	46
15		**2j**	r.t., 14 h	**3aj**	46	**4aj**	0
16		**2j**	r.t., 3 h then reflux, 13 h	**3aj**	trace	**4aj**	0
17		**2a**	r.t., 3 h	**3aa**	94	**4aa**	0
18		**2a**	r.t., 16 h then reflux, 20 h	**3aa**	2	**4aa**	87
19		**2k**	r.t., 3 h	**3ak**	71	**4ak**	2
20		**2k**	r.t., 3 h then reflux, 13 h	**3ak**	0	**4ak**	63
21		**2l**	r.t., 3 h	**3al**	88	**4al**	0
22		**2l**	r.t., 3 h then reflux, 48 h	**3al**	66	**4al**	0

[a] $HInCl_2$ was generated by $InCl_3$–Bu_3SnH system. Allylic indium was generated from the reaction of diene **1a** (4 mmol) with $HInCl_2$ (2 mmol) in THF (2 mL) at r.t. for 5 h. Carbonyl compound (1 mmol) was used.

[b] H_2O (2 mmol) was added before addition of ketone **2d**.

[c] $HInCl_2$ (3 mmol) and THF (3 mL) were used.

[d] $HInCl_2$ (3 mmol) and THF (3 mL) were used. H_2O (3 mmol) was added before addition of ketone **2g**.

requires the effective trap of the γ-adduct **C** by water. The reason is not clear, but intramolecular coordination in **C** may promote the retroreaction.[11]

In summary, polysubstituted allylic indiums generated by the hydroindation of 1,3-dienes can add to various carbonyl compounds including ketones to furnish γ-adduct regioselectively. In this reaction system, retroreaction was easily promoted by intramolecular coordination or heating to achieve the transformation from γ-adduct into thermodynamically stable α-adduct. Further applications and detailed mechanism of the presented reactions are under consideration.

Acknowledgment

This research has been supported by JSPS Research Fellowships for Young Scientists, and by the Grant-in-Aid for Scientific Research on Priority Areas (459 and 460) from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and by the JFE 21st Foundation and the Nihonshouken Foundation.

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(9) **Typical Procedure**
A 10 mL round-bottom flask charged with $InCl_3$ (2.0 mmol) was dried by heating to 110 °C under reduced pressure (1 mmHg) for 1 h. After the nitrogen was filled, THF (2 mL) was added to dissolve $InCl_3$. To the mixture was added Bu_3SnH (2.0 mmol) at –78 °C. The mixture was then stirred for 10 min to prepare dichloroindium hydride ($HInCl_2$). After the solution was warmed up to r.t., 2,3-dimethyl-1,3-butadiene (**1a**, 4.0 mmol) was added and the resulting mixture was stirred for 5 h. Then benzil (**2b**, 1.0 mmol) was added and stirred for 14 h. The resulting mixture was quenched by aq 1 N HCl (5 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layer was treated with aq NH_4F and then the precipitate was filtered to remove the tin compound. The filtrate was extracted with Et_2O and dried over $MgSO_4$. Concentration followed by silica gel column chromatography eluting with hexane–EtOAc (90:10) afforded **4ab** as a solid.

(10) **Analytical and Spectroscopic Data of Selected Compounds**
Compound **3ab**: mp 65–66 °C. IR (KBr): 3494 (OH), 1685 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.67–7.59$ (m, 4 H), 7.37–7.23 (m, 6 H), 5.12 (s, 1 H), 5.02 (s, 1 H), 3.52 (s, 1 H), 1.56 (s, 3 H), 1.46 (s, 3 H), 1.23 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 203.43$, 151.81, 138.62, 138.42, 131.38, 129.46, 127.79, 127.62, 127.56, 127.15, 115.61, 83.54, 49.37, 24.49, 24.15, 22.85. MS (CI): *m/z* = 295 (70) [M^+ + 1], 278 (22), 277 (100), 212 (20), 211 (86), 105(34). HRMS (CI, +0.9 mmu): *m/z* calcd for $C_{20}H_{23}O_2$: 295.1698; found: 295.1707 [M^+ + 1].
Compound **4ab**: mp 88–89 °C. IR (KBr): 3498 (OH), 1670 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.89–7.79$ (m, 2 H), 7.63–7.53 (m, 2 H), 7.43–7.25 (m, 6 H), 3.63 (s, 1 H), 3.40 (d, *J* = 13.8 Hz, 1 H), 2.96 (d, *J* = 13.8 Hz, 1 H), 1.66 (s, 3 H), 1.61 (s, 3 H), 1.39 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 201.39$, 143.14, 135.29, 132.61, 132.35, 130.32, 128.69, 127.89, 127.54, 125.11, 122.84, 81.80, 44.66, 21.22, 21.02, 19.74. MS (CI): *m/z* = 295 (67) [M^+ + 1], 278 (22), 277 (100). HRMS (CI, +0.5 mmu): *m/z* calcd for $C_{20}H_{23}O_2$: 295.1698; found: 295.1703 [M^+ + 1].
Compound **4ac**: IR (neat): 3514 (OH), 1732 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.65$ (d, *J* = 8.0 Hz, 2 H), 7.35 (dd, *J* = 8.0, 7.5 Hz, 2 H), 7.29 (d, *J* = 7.5 Hz, 1 H), 3.74 (s, 3 H), 3.50 (s, 1 H), 3.10 (d, *J* = 13.8 Hz, 1 H), 2.87 (d, *J* = 13.8 Hz, 1 H), 1.68 (s, 6 H), 1.60 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 175.59$, 142.20, 131.19, 128.08, 127.58, 125.64, 122.15, 78.00, 52.91, 44.71, 21.11, 21.00, 19.48. MS (EI, 70 eV): *m/z* = 248 (1) [M^+], 105 (100), 84 (39), 77 (23). HRMS (EI, +0.2 mmu): *m/z* calcd for $C_{15}H_{20}O_3$: 248.1412; found: 248.1414 [M^+].
Compound **4ad**: IR (neat): 3564 (OH) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.44$ (d, *J* = 8.0 Hz, 2 H), 7.31 (dd, *J* = 8.0, 7.2 Hz, 2 H), 7.23 (t, *J* = 7.2 Hz, 1 H), 3.67 (d, *J* = 9.3 Hz, 1 H), 3.57 (d, *J* = 9.3 Hz, 1 H), 3.37 (s, 3 H), 2.78 (s, 1 H), 2.75 (d, *J* = 13.8 Hz, 1 H), 2.47 (d, *J* = 13.8 Hz, 1

H), 1.61 (s, 3 H), 1.53 (s, 3 H), 1.41 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.12, 129.66, 127.85, 126.61, 125.33, 123.35, 79.10, 76.51, 59.35, 44.15, 20.92, 20.78, 20.41. MS (CI): *m/z* = 235 (1) [M^+ + 1], 217 (100), 151 (32). HRMS (CI, –0.2 mmu): *m/z* calcd for $C_{15}H_{23}O_2$: 235.1698; found: 235.1696 [M^+ + 1].

(11) Although we tried the reaction of simple acetophenone (**2e**) with diene **1a** in the presence of equimolar amount of Lewis basic additives such as Ph_3P and HMPA, only a small amount of α-adduct **4ae** was obtained at r.t. So we think that intramolecular coordination is more important than intermolecular coordination by ligand.